Perioperative continuation or ultra-early resumption of antithrombotics in elective neurosurgical cranial procedures

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Objective Discontinuation of antithrombotics (AT) prior to elective cranial procedures is common practice, despite the higher risk of thromboembolic complications in these patients. The aim of this study was to investigate the risks and benefits of a new perioperative management protocol of continuation or ultra-early AT resumption in elective cranial procedures.

Methods This study was an analysis of a prospectively collected cohort of patients undergoing elective cranial surgery with (AT group) and without (control group) AT. For extraaxial or shunt surgeries, acetylsalicylic acid (ASA) was continued perioperatively. For intraaxial pathologies, ASA was discontinued 2 days before surgery and resumed on postoperative day 3. All other AT were discontinued according to their pharmacokinetics, and resumed on postoperative day 3 after unremarkable postoperative imaging. Additionally, the authors performed a retrospective analysis of patients with AT who underwent surgery before implementation of this new AT management protocol (historical AT group). Primary and secondary outcomes were the incidence of hemorrhagic and thromboembolic complications within 3 months after surgery.

Results Outcomes of 312 patients were analyzed (83 [27%] in the AT group, 106 [34%] in the control group, and 123 [39%] in the historical AT group). For all 3 patient groups, the most common type of surgery was craniotomy for intraaxial tumors (14 [17%] in the AT group, 28 [26%] in the control group, and 60 [49%] in the historical AT group). The most commonly used AT were ASA (38 [46%] in the AT group and 78 [63%] in the historical AT group), followed by non–vitamin K oral anticoagulants (32 [39%] in the AT group and 18 [15%] in the historical AT group). The total perioperative discontinuation time in the AT group was significantly shorter than in the historical AT group (median of 4 vs 16 days; p < 0.001). The rate of hemorrhagic complications was 4% (95% CI 1–10) (n = 3/83) in the AT group, 6% (95% CI 2–12) (n = 6/106) in the control group, and 7% (95% CI 3–13) (n = 9/123) in the historical AT group (p = 0.5). The rate of thromboembolic complications was 5% (95% CI 1–12) (n = 4/82) in the AT group, 8% (95% CI 3–15) (n = 8/104) in the control group, and 7% (95% CI 3–13) (n = 8/120) in the historical AT group (p = 0.7).

Conclusions The presented perioperative management protocol of continuation or ultra-early resumption of AT in elective cranial procedures does not seem to increase the hemorrhagic risk. Moreover, it appears to potentially protect patients from thromboembolic complications.

Keywords neurosurgery; cranial procedures; antithrombotics; hemorrhagic complications; thromboembolic complications
its cessation. Further studies have demonstrated that 10% of platelet function is recovered per day after discontinuation. Hematological studies have shown that ASA should no longer be recommended for primary prevention. Additionally, we performed a retrospective analysis of patients with AT who underwent elective cranial surgery before implementation of the new perioperative AT management protocol (historical AT group). These patients underwent surgery between 2015 and 2017 and had typically longer perioperative AT discontinuation times.

### Methods

**Informed Consent Statement**

This study was approved by the local ethics board. Patient informed consent was obtained for all surgeries.

**Study Design and Inclusion/Exclusion Criteria**

This study was an analysis of a prospectively collected database of a single-center cohort. All consecutive patients with or without AT (AT group vs control group) undergoing an elective cranial procedure at the University Hospital of Basel, Switzerland, between January 2021 and March 2023 were included. Patients in the AT group were treated according to our new perioperative AT management protocol, which was implemented in January 2021. Patients managed with different perioperative AT protocols were excluded (n = 33). Patients receiving ASA for primary prevention were also excluded, because recent studies have shown that ASA should no longer be recommended for primary prevention. Additionally, we performed a retrospective analysis of patients with AT who underwent elective cranial surgery before implementation of the new perioperative AT management protocol (historical AT group). These patients underwent surgery between 2015 and 2017 and had typically longer perioperative AT discontinuation times.

### Perioperative AT Management Protocol

The detailed perioperative management protocol for the most commonly used AT is presented in Table 1. For extraaxial or shunt surgeries, ASA is continued during the perioperative period. For intraaxial pathologies, ASA is discontinued 2 days before surgery and resumed on postoperative day (POD) 3. All other AT are discontinued preoperatively according to their own pharmacokinetics, and resumed on POD 3. The aim of this study was to analyze the risks and benefits of the abovementioned perioperative AT management protocol in elective cranial procedures.

<table>
<thead>
<tr>
<th>AT</th>
<th>Preop Discontinuation Time (day)</th>
<th>Postop Resumption Time (day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>Craniotomy for extraaxial lesions/TSS</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Craniotomy for intraaxial lesions</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Prasugrel</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Ticagrelor</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>7</td>
</tr>
</tbody>
</table>

Apixaban

- GFR >30 mL/min: 2 | POD 3 |
- GFR ≤30 mL/min: 3 | POD 4 |

Rivaroxaban

- GFR >30 mL/min: 2 | POD 3 |
- GFR ≤30 mL/min: 3 | POD 4 |

Eldoxaban

- GFR >30 mL/min: 2 | POD 3 |
- GFR ≤30 mL/min: 3 | POD 4 |

Dabigatran

- GFR >50 mL/min: 3 | POD 3 |
- GFR 30–50 mL/min: 4 | POD 3 |
- GFR <30 mL/min: 5 | POD 4 |

Heparin

- GFR ≤30 mL/min: 4 hrs | POD 3 |
- GFR >30 mL/min: 1 | POD 3 |

Dabigatran

- GFR >30 mL/min: 3 | POD 3 |
- GFR 30–50 mL/min: 4 | POD 3 |
- GFR <30 mL/min: 5 | POD 4 |

Heparin

- GFR ≤30 mL/min: 4 hrs | POD 3 |
- GFR >30 mL/min: 1 | POD 3 |

Nadroparin

- GFR >30 mL/min: 3 | POD 3 |

Enoxaparin

- GFR >30 mL/min: 3 | POD 3 |

GFR = glomerular filtration rate.

* Information provided for the therapeutic dose of the antithrombotic medication.
Outcome Analysis

The primary outcome was the incidence of postoperative hemorrhagic complications within 3 months. A hemorrhagic complication was defined as a symptomatic bleeding and/or a bleeding requiring surgical revision. The time period of 3 months after surgery was chosen in order to assess late hemorrhagic complications such as a postoperative chronic subdural hematoma. At the 3-month follow-up, a postoperative imaging study was only performed if the surgeon had previously planned a specific radiological follow-up or in cases involving a symptomatic patient.

The secondary outcome was the incidence of perioperative thromboembolic complications occurring from the time of AT discontinuation (or the time of surgery in cases with AT continuation) up to 3 months after surgery. Screening of asymptomatic patients for potential thromboembolic complications was not performed. Diagnostic investigations were only undertaken in cases involving symptomatic patients. Iatrogenic cerebral infarctions were not considered to be thromboembolic complications.

Statistical Analysis

Descriptive data analyses were conducted to summarize the characteristics of the data set. For qualitative data, the number of observations and their respective percentages were reported. For quantitative normally distributed data, the mean and standard deviation were used. For non-normally distributed data, we used the median and range. Univariable logistic regression analyses were performed to assess the association between the type of intervention and each outcome. To investigate differences between the intervention groups, pairwise comparisons using the Tukey method to account for multiple comparisons were conducted. This method enabled direct comparisons between each pair of intervention groups, while maintaining control over the overall error rate. Additionally, univariable and multivariable logistic regression analyses were performed to evaluate potential risk factors for the occurrence of complications. Furthermore, we performed individual logistic regression models with Firth’s bias correction to explore the differences in postoperative complications among the different types of surgery and AT. All models have been corrected for the type of intervention. The results were reported as odds ratios with corresponding 95% confidence intervals and p values. The level of significance was set at 0.05. All analyses were performed with R statistical software (R Core Team, http://www.R-project.org/).

Results

A total of 312 patients were included in the final analysis, consisting of the AT group (n = 83 [26.6%]), the control group (n = 106 [34%]), and the historical AT group (n = 123 [39.4%]). Baseline characteristics are presented in Table 2. The types of surgeries for the different patient groups are presented in Fig. 1. For all 3 patient groups, the most common type of surgery was craniotomy for intraaxial tumors (14 [17%] in the AT group, 28 [26%] in the control group, and 60 [49%] in the historical AT group) (Table 2 and Fig. 1). The types of AT are depicted in Fig. 2. The most commonly used AT were ASA (38 [46%] in the AT group and 78 [63%] in the historical AT group), followed by non–vitamin K oral anticoagulants (NOAC, 32 [39%] in the AT group and 18 [15%] in the historical AT group). In the AT group, AT were discontinued according to the perioperative management protocol presented in Table 1. In the historical AT group, the median preoperative discontinuation time was 7 days (range 0–124) for ASA, 7 days (range 5–9) for other antiplatelet drugs, 5 days (range 1–122) for NOAC, and 7 days (range 0–14) for vitamin K antagonists (VKA). The median postoperative discontinuation time was 8 days (range 1–91) for ASA, 7.5 days (range 5–10) for other antiplatelet drugs, 8.5 days (range 1–108) for NOAC, and 12 days (range 1–31) for VKA. The total perioperative discontinuation time in the AT group was significantly shorter than in the historical AT group (median of 4 vs 16 days; p < 0.001). In the AT group all patients received postoperative imaging, which was typically performed on POD 1 when the AT medication had to be resumed on POD 3. However, some patients had a postoperative imaging session at a later point in time in cases with perioperative ASA continuation (median POD 1, range POD 0–11).

Primary Outcome: Hemorrhagic Complications

The rate of hemorrhagic complications was 3.6% (95% CI 0.8–10.2) (n = 3/83) in the AT group, 5.7% (95% CI 2.1–12) (n = 6/106) in the control group, and 7.3% (95% CI 3.4–13.4) (n = 9/123) in the historical AT group (p = 0.5) (Fig. 3).

Among the 18 patients in the entire cohort with hemorrhagic complications, 6 patients (33.3%) developed a chronic subdural hematoma within 3 months, 4 patients (22.2%) suffered from a postoperative acute subdural hematoma, 4 patients (22.2%) had a postoperative intracerebral hemorrhage, and 4 patients (22.2%) had an epistaxis after transsphenoidal surgery (TSS). All patients with hemorrhagic complications were symptomatic; 8 patients (44.4%) needed surgical revision, 5 patients (27.8%) could be managed conservatively, the 4 patients (22.2%) with epistaxis underwent a bedside intervention (nasal tamponade or silver nitrate application), and 1 patient (5.6%) (85-year-old patient in the control group) died of the hematoma complication.

Secondary Outcome: Thromboembolic Complications

The rate of thromboembolic complications was 4.9% (95% CI 1.3–12) (n = 4/82) in the AT group, 7.7% (95% CI 3.4–14.6) (n = 8/104) in the control group, and 6.7% (95% CI 2.9–12.7) (n = 8/120) in the historical AT group (p = 0.7) (Fig. 4).

Among the 20 patients in the entire cohort with thromboembolic complications, 13 patients (65%) suffered from an ischemic stroke, 3 patients (15%) developed a pulmonary embolism, 2 patients (10%) had a deep venous thrombosis, 1 patient (5%) a sinus venous thrombosis, and 1 patient (5%) had an NSTEMI (non–ST-elevation myocardial infarction).

Potential Predictors of Hemorrhagic and Thromboembolic Complications

We studied potential predictors of hemorrhagic and
thromboembolic complications. In the uni- and multivari-
able logistic regression analysis, a higher international
normalized ratio (INR) and higher intraoperative blood
loss were significantly predictive for hemorrhagic com-
lications (Table 3). In the univariable logistic regression
analysis, lower postoperative hemoglobin levels and vas-
cular surgery were found to be predictive for hemorrhagic
complications (Table 4). The use of heparin was shown to
be a significant predictor for thromboembolic complica-
tions (Table 4).

Discussion
This study suggests that the presented perioperative
management protocol of continuation or ultra-early re-
sumption of AT in elective craniotomies does not seem to
increase the risk for hemorrhagic complications. The fact
that the AT group had the lowest hemorrhagic complica-
tion rate (although without significant difference) might
be random due to the small sample size or potentially be-
cause the surgeons performed extra-meticulous hemosta-
sis knowing that the patients were receiving continuous
AT or would receive AT already on POD 3.

The presented perioperative AT management protocol
appears to potentially protect patients from thromboem-
bolic complications. Indeed, the rate of thromboembolic
complications was the lowest in the AT group. Although
there may be differences between the groups, the current
analysis did not provide enough statistical power to de-
tect them. This potential benefit needs to be further in-
vestigated in a larger patient cohort. In our study, the rate
of thromboembolic complications is probably underesti-
mated because patients were not screened perioperatively with electrocardiography, cardiac troponin measurements, or ultrasound examinations of the legs. For instance, perioperative troponin screening in the setting of noncardiac surgery leads to a PMI incidence ranging from 13% to 16%. PMI is known to be associated with substantial short- and long-term mortality.\textsuperscript{11,12} We recommend that practitioners consider screening tools for thromboembolic complications and use PMI as an outcome parameter for future studies.

For extraaxial or shunt surgeries, ASA was continued during the perioperative period. For intraaxial pathologies we were more cautious and discontinued ASA 2 days before surgery. The rationale for these 2 days of discon-

![FIG. 1. Types of surgery. A: AT group. B: Control group. C: Historical AT group.](image1)

![FIG. 2. Types of AT. Left: AT group. Right: Historical AT group.](image2)
continuation comes from hematological studies stating that 2 days are needed to achieve sufficient hemostasis. \(^{16–18}\) The study by Hanalioglu et al. suggested the safety of ASA continuation in elective craniotomies for brain tumors. \(^{20}\) However, intraaxial tumor location was shown to have a marginal effect (\(p = 0.087\)) on hemorrhagic complications in this study, warranting some caution for intraaxial lesions. \(^{20}\) A meta-analysis by our own research group reinforced the evidence in favor of ASA continuation in elective craniotomies, with a similar hemorrhagic complication rate in the ASA continuation and discontinuation group (3% [95% CI 0.01–0.05] vs 3% [95% CI 0.01–0.09]; \(p = 0.9\)). \(^{19}\) Taken together, it seems that more and more evidence exists for the safety of continuing ASA treatment during elective cranial surgery. In the presented perioperative management protocol, AT other than ASA were discontinued preoperatively according to their own pharmacokinetics, and resumed on POD 3. Because most

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
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<td>AT- / Control- Group</td>
<td>0.619</td>
<td>0.114 - 3.37</td>
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<td>0.475</td>
<td>0.096 - 2.35</td>
<td>0.520</td>
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<td>Control- / Historical AT- Group</td>
<td>0.768</td>
<td>0.214 - 2.75</td>
<td>0.878</td>
</tr>
</tbody>
</table>

**FIG. 3.** Hemorrhagic complication rates. The table within the figure outlines the pairwise post hoc test results of univariable logistic regression between the 3 groups. No significant differences were found.

4.9% 7.7% 6.7%

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
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<tbody>
<tr>
<td>AT- / Control- Group</td>
<td>0.615</td>
<td>0.14 - 2.7</td>
<td>0.722</td>
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<tr>
<td>AT- / Historical AT- Group</td>
<td>0.718</td>
<td>0.164 - 3.14</td>
<td>0.859</td>
</tr>
<tr>
<td>Control- / Historical AT- Group</td>
<td>1.17</td>
<td>0.346 - 3.94</td>
<td>0.953</td>
</tr>
</tbody>
</table>

**FIG. 4.** Thromboembolic complication rates. The table within the figure outlines the pairwise post hoc test results of univariable logistic regression between the 3 groups. No significant differences were found. Although there may be differences between the groups, the current analysis does not provide enough statistical power to detect them.
hemorrhagic complications occur in the first postoperative hours, we believed that the resumption of AT on POD 3 is reasonable. Indeed, the study by Ullmann et al. for tumor and the one by Ebel et al. for vascular surgery showed that shorter preoperative (≤ 5 days) and postoperative (≤ 5 days) discontinuation times are not associated with an increased hemorrhagic risk in comparison to longer discontinuation times. 14,15

To the best of our knowledge, the presented study protocol has the shortest AT postoperative resumption times found in the literature, legitimizing the term ultra-early resumption. Mehta et al. recently conducted a literature review regarding the resumption of therapeutic anticoagulation after elective craniotomy for patients with atrial fibrillation. The authors stratify the patients in three different groups: confident intraoperative hemostasis, tenuous hemostasis and a congestive heart failure, hypertension, age 75 years or older, diabetes, prior stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category (CHA2DS2-VASc) score ≥ 4, and tenuous hemostasis and a CHA2DS2-VASc score < 4. 31 According to the stratification group, the authors recommend resumption of anticoagulation on POD 7, POD 7–10, and POD 10–12, respectively. According to the results of our own study, we believe that a more aggressive protocol with earlier postoperative resumption of AT is warranted.

In the uni- and multivariable logistic regression analysis, a higher INR was predictive for hemorrhagic complications, which is somewhat intuitive and expected (Table 3). A higher intraoperative blood loss was also predictive for hemorrhagic complications in the uni- and multivariable analysis (Table 3). In fact, strongly vascularized lesions cause higher intraoperative blood losses and may lead to a higher postoperative hemorrhagic risk, particularly when the lesion cannot be resected completely. Similarly, lower postoperative hemoglobin levels were found to be predictive for hemorrhagic complications in the univariable analysis (Table 3). In our univariable analysis, vascular surgery was found to be predictive for hemorrhagic complications (Table 4). No clear explanation for this finding could be found—hence caution should be used when interpreting these results, due to the low event rate in our cohort. Hanalioglu et al. did not find any significant predictive factors for hemorrhagic complications in a patient cohort with and without ASA. 20

Concerning thromboembolic complications, the only predictive factor that could be found in the univariable logistic regression analysis was the use of heparin (Table 4). Indeed, a bridging therapy with heparin is only indicated in high-risk patients (e.g., patients with a mechanical heart valve), which explains the higher perioperative thromboembolic risk in those patients. It is well known that patients with meningioma have a higher risk of developing postoperative venous thromboembolisms. 32–34 Our cohort was presumably too small to confirm these results. Others, however, were able to show that male sex, and skull base meningiomas in particular, were independent predictors for thromboembolic complications. 20

**Strengths**

Our study addresses a very relevant topic of daily neu-
rosurgical practice, for which the paucity of evidence leads to heterogeneous and somewhat arbitrary management strategies. We have elaborated a clear and easily applicable perioperative AT management protocol for elective craniotomies and have demonstrated its feasibility in the context of this prospective study. To the best of our knowledge, there are no similar studies defining and analyzing standardized postoperative ultra-early resumption times for various AT. Clearly, further prospective studies from other centers are needed to underline our results.

Limitations
The main limitation of this study is the small sample size of the different patient cohorts (AT, control, and historical AT groups), which precludes us from drawing strong conclusions from the analyzed data. In addition, the compared patient cohorts were relatively heterogeneous. In fact, the historical AT group included only craniotomies for tumor and vascular surgery, whereas the AT and control groups also comprised TSS, shunt, and cranioplasty surgeries. The inclusion of patients with various AT slightly limits the interpretation and generalizability of the study’s results because of the different pharmacological mechanisms of action and risk profiles. The heterogeneity in surgery and AT types potentially resulted in design biases. The lack of blinding of the surgeons to the patient groups potentially led to a performance bias if surgeons performed extra-meticulous hemostasis knowing that the patients were in the AT group. Finally, we advise caution in the interpretation of the uni- and multivariable logistic regression analysis due to the relatively small number of event numbers within our cohort.

Conclusions
The presented perioperative management protocol of continuation or ultra-early resumption of AT in elective cranial procedures does not seem to increase the hemorrhagic risk. Moreover, it appears to potentially protect patients from thromboembolic complications. These findings need to be further investigated in larger patient cohorts.

References


Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Rychen, Soleman. Acquisition of data: Weiger, Ebel, Ullmann. Analysis and interpretation of data: Rychen, Weiger, Ullmann.撰写 and design: Rychen, Soleman. Acquisition of data: Weiger, Ebel, Ullmann. Analysis and interpretation of data: Rychen, Weiger, Halbeisen, Soleman. Drafting the article: Rychen, Weiger. Weiger, Ebel, Mariani, Guzman, Soleman. Approved the final version of the manuscript on behalf of all authors: Rychen. Statistical analysis: Weiger, Halbeisen. Administrative/technical/material support: Mariani, Guzman. Study supervision: Mariani, Soleman.

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