Stroke risk related to intentional discontinuation of antithrombotic therapy for invasive procedures

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OBJECTIVE Antithrombotic medications pose a challenge for conducting surgical or invasive procedures, because their discontinuation is required to avoid postprocedural hemorrhagic complications but potentially increases the ischemic risk for the patient. This study aimed to estimate the increased risk of developing cerebral ischemic events during hospitalization requiring discontinuation of antithrombotic therapy.

METHODS This investigation was a single-center retrospective observational study. Clinical data in patients scheduled for admission between January 1, 2021, and December 31, 2022, were collected. Patients requiring discontinuation of antithrombotic therapy were identified by referring to the admission database. Patients who developed cerebral ischemia were identified by referring to the institution’s stroke center database.

RESULTS Seven hundred ninety-six patients scheduled for nonneurosurgical procedures and 39 scheduled for neurosurgical procedures underwent discontinuation of antithrombotic therapy. Anticoagulation therapy was prescribed in 40.0%, and antiplatelet therapy was prescribed in 69.1% of the patients. A total of 9.2% of the entire cohort of patients were receiving both anticoagulation and antiplatelet therapy. Bridging therapy was administered in 20.9% of nonneurosurgical patients. No ischemic event was observed in the patients undergoing neurosurgical procedures. Among the entire cohort, 3 patients encountered some kind of thrombotic event—2 of which were cerebral ischemia—accounting for an incidence of 0.24%, which was significantly higher than incidental in-hospital stroke unrelated to discontinuation of antithrombotic therapy (p = 0.04). Patients undergoing both anticoagulation and antiplatelet therapy harbored a significantly higher risk for cerebral ischemia related to discontinuation of antithrombotic therapy (p < 0.0001).

CONCLUSIONS Discontinuing antithrombotic therapy during hospitalization for elective invasive procedures—including neurosurgical procedures—entailed a relatively small risk of developing cerebral ischemic events, but the risk was significantly higher compared to hospitalized patients without discontinuation of antithrombotic therapy.

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KEYWORDS antithrombotic therapy; stroke; bridging therapy

ANTITHROMBOTIC therapy includes anticoagulants and antiplatelet agents, which are indicated for preventing cardiovascular or cerebrovascular diseases.¹⁻⁴ Antithrombotic medications are currently more and more frequently prescribed in Japan due to its rapidly aging population.³ This trend poses a challenge for conducting surgical or invasive procedures, because discontinuation of these agents is required to avoid postprocedural hemorrhagic complications while potentially increasing the ischemic risk for the patient. Although a meta-analysis suggests no disadvantage of discontinuing antiplatelet therapy during the perioperative period, the general risk of discontinuing antithrombotic therapy for surgery-related hospitalization is not fully understood.⁶ The role of bridging therapy using low-molecular-weight heparin is also debatable, with some randomized clinical trials showing...
the noninferiority of a perioperative nonbridging strategy versus a bridging strategy in patients with atrial fibrillation.7–10

Although there is no nationwide documentation, nearly all academic medical institutions in Japan now strictly demand consideration of the discontinuation of antithrombotic therapy when conducting surgical procedures under general anesthesia. Thus, it is necessary to elucidate the actual ischemic risks involved in discontinuation of antithrombotic therapy from a medical safety standpoint. In order to ensure patient safety, medications of all patients scheduled for admission to our institution are centrally reviewed and registered before hospitalization, and antithrombotic therapy is discontinued for those preparing for elective surgery under general anesthesia. By taking advantage of our admission registration database, this study aimed to estimate the increased risk of developing cerebral ischemic events during hospitalization requiring discontinuation of antithrombotic therapy and to further identify any factor contributing to developing cerebral ischemic events.

Methods

Patient Cohort

This investigation was a single-center, retrospective, observational study approved by the institutional review board at our institution. Written informed consent was waived. We collected and analyzed information on all patients scheduled for admission between January 1, 2021, and December 31, 2022, to Asahikawa Medical University Hospital, who are required to check in at the Asahikawa Medical University Hospital Admission Center. Thus, emergency patients were excluded from the analysis. Furthermore, emergency and elective neurological cases were searched during the same period, because neurosurgeons decided to continue or discontinue antithrombotic drugs before referring the patients to the admission center. Patients who developed cerebral ischemia were identified by referring to the Asahikawa Medical University Hospital’s stroke center database and defined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.11 The presentation of neurological symptoms identified all patients with cerebral ischemia, and no patients with radiological stroke (silent stroke) were included, because the primary goal of the study was to elucidate the disadvantage of discontinuation of antithrombotic therapy from a patient’s perspective. Given that patients could undergo multiple surgeries, we used patient-level data for analysis.

Protocol for Discontinuation of Antithrombotic Therapy

The institutional protocol for discontinuation of antithrombotic therapy basically follows published guidelines.12,13 Direct oral anticoagulants (DOAC) and warfarin are discontinued approximately 1–3 and 3–5 days, respectively, before surgery. Antiplatelet therapy such as aspirin, clopidogrel, cilostazol, prasugrel, and ticlopidine are discontinued approximately 7–14, 7–14, 2, 14, and 7–14 days before surgery, respectively. Heparin or cilostazol bridging therapy was allowed according to each physician’s independent decision. Heparin bridging therapy usually consists of 200U/kg/24 hrs of intravenous low-molecular-weight heparin administration during discontinuation of antithrombotic therapy. Cilostazol bridging therapy, on the other hand, usually consists of 200 mg/day of oral cilostazol administration during discontinuation of antithrombotic therapy. Although there was no strict institutional guideline for resuming antithrombotic therapy, antithrombotic drugs were restarted approximately 1–3 days after surgery.

Statistical Analysis

Statistical analysis was performed using Prism 9 for macOS (GraphPad Software). Fisher’s exact test was used for analyzing contingency tables, and multiple linear regression was used for multivariate analysis. A p value of less than 0.05 was considered statistically significant.

Results

Characteristics of Patients Undergoing Discontinuation of Antithrombotic Therapy for Nonneurosurgical Procedures

Seven hundred ninety-six patients scheduled for nonneurosurgical procedures underwent discontinuation of antithrombotic therapy. Detailed patient characteristics are listed in Table 1 and Supplementary Data 1. In summary, the patient age was 72.7 ± 8.7 years (mean ± SD), and 220 patients (27.6%) were female. A total of 607 patients (76.3%), 457 patients (57.4%), and 413 patients (51.9%) had hypertension, hyperlipidemia, and valve/coronary artery diseases as preexisting conditions, respectively. On the other hand, cerebral disease was identified as a preexisting condition in 233 patients (29.3%). Major reasons for antithrombotic therapy were valve disease/atrial fibrillation (34.5%), coronary artery disease (30.9%), and previous stroke (30.4%). Patients were mainly asked to discontinue antithrombotic therapy due to scheduled elective surgery (70.9%) and gastrointestinal endoscopy (18.0%).

Characteristics of Antithrombotic and Bridging Therapy for Nonneurosurgical Procedures

Characteristics of antithrombotic and bridging therapy are listed in Table 2. Anticoagulation therapy was prescribed in 40% of the patients, with 80% of them receiving DOAC. On the other hand, antiplatelet therapy was prescribed in 69.1% of the patients, with more than half (57%) receiving aspirin. Of the entire cohort of patients, 9.2% were under both anticoagulation and antiplatelet therapy. Bridging therapy, either by heparin or cilostazol, was performed in 20.9% of the patients.

Characteristics of Patients Undergoing Discontinuation of Antithrombotic Therapy for Neurosurgical Procedures

During the time of the survey, there were 557 neurosurgical procedures, and 323 procedures were elective. Seventy-seven cases were receiving antithrombotic therapy, and 39 underwent discontinuation of antithrombotic therapy. Those who did not undergo discontinuation of antithrombotic therapy were mostly receiving endovascular treatments. Detailed patient characteristics are listed in
Table 3 and Supplementary Data 2. In summary, the mean patient age (± SD) was 71.5 ± 9.7 years, and 11 patients (28.2%) were female. Twenty-eight (71.8%) and 24 (61.5%) patients had hypertension and hyperlipidemia as preexisting conditions, respectively. Cerebral disease was identified as a preexisting condition in 8 patients (20.5%). Major reasons for antithrombotic therapy were previous stroke (38.5%) and coronary artery disease (33.3%). More than half of the patients were asked to discontinue antithrombotic therapy due to elective craniotomy (53.8%).

Characteristics of Antithrombotic and Bridging Therapy for Neurosurgical Procedures

Characteristics of antithrombotic and bridging therapy are listed in Table 4. Anticoagulation therapy was prescribed in 28.2% of the patients, with 91% of them receiving DOAC. On the other hand, antiplatelet therapy was prescribed in 71.8% of the patients, with clopidogrel leading the frequency of prescriptions (38.5%). No patients
Preoperative management was carefully done, as can be seen in Supplementary Data 2.

**Thrombotic Event During Discontinuation of Antithrombotic Therapy and its Risk Factor**

There was no thrombotic event for patients undergoing neurosurgical procedures (Supplementary Data 2). When we expand into the entire surveyed cohort, 3 patients encountered some kind of thrombotic event related to discontinuing antithrombotic therapy during hospitalization or right after discharge, 2 of which were cerebral ischemia—accounting for an incidence of 0.24% (Tables 5 and 6). The in-hospital cerebral ischemic event was unrelated to the discontinuation of antithrombotic therapy and was observed in 6 of 18,368 patients, with 4 of the events presumably related to postoperative surgical complication (Tables 5 and 6, and Supplementary Data 3; incidence rate = 0.03%). The cerebral ischemic event occurred significantly more frequently for patients undergoing antithrombotic therapy (p = 0.04, Fisher’s exact test). Both univariate (data not shown) and multivariate linear regression models revealed that patients under both anticoagulation and antiplatelet therapy possessed significantly higher risk for cerebral ischemia related to discontinuation of antithrombotic therapy (p < 0.0001, Table 7). The introduction of bridging therapy did not reduce the risk of ischemic events related to discontinuation of antithrombotic therapy. The invasiveness of the nonneurosurgical procedure also did not correlate with the risk of cerebral ischemic events (p = 0.51, linear regression analysis).

**Discussion**

The current study aimed to elucidate the real-world frequency and risk of developing cerebral ischemic events related to discontinuing antithrombotic therapy during hospitalization for elective invasive procedures. We showed that the frequency of cerebral ischemic complications associated with discontinuing antithrombotic therapy is as low as 0.24% for nonneurosurgical procedures. Furthermore, our patients did not experience any symptomatic ischemic complications for neurosurgical procedures. The current guideline for antithrombotic therapy for coronary artery disease recommends discontinuing antithrombotic

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**TABLE 4. Characteristics of ATT and bridging therapy for elective neurosurgical procedures**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation therapy</td>
<td>11</td>
<td>28.2</td>
</tr>
<tr>
<td>DOAC</td>
<td>10</td>
<td>25.6</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1</td>
<td>2.6</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>28</td>
<td>71.8</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>15</td>
<td>38.5</td>
</tr>
<tr>
<td>Aspirin</td>
<td>12</td>
<td>30.8</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>8</td>
<td>20.5</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>1</td>
<td>2.6</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Both anticoagulation &amp; antiplatelet therapy</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Values are expressed as the case count.

**TABLE 5. Characteristics of patients having any thrombotic event during hospitalization**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age in Yrs</th>
<th>Sex</th>
<th>ATT</th>
<th>Reason for ATT</th>
<th>Preexisting Condition</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>279</td>
<td>60</td>
<td>M</td>
<td>Warfarin, clopidogrel</td>
<td>Valve disease/AF, previous stroke</td>
<td>HTN, HL, DM, AF, VC, Ce</td>
<td>Cerebral embolism during hospitalization for elective surgery.</td>
</tr>
<tr>
<td>300</td>
<td>70</td>
<td>M</td>
<td>Warfarin, aspirin</td>
<td>Valve disease/AF, coronary artery disease</td>
<td>HTN, VC</td>
<td>Warfarin continued w/ cilostazol substituted for aspirin for polypectomy, &amp; patient was discharged. However, warfarin was discontinued due to postprocedural bleeding at outpatient consultation, &amp; patient subsequently had a cerebral infarction.</td>
</tr>
<tr>
<td>985</td>
<td>55</td>
<td>F</td>
<td>Aspirin</td>
<td>Unknown</td>
<td>HTN, DM, VC</td>
<td>Acute myocardial infarction during hospitalization for elective surgery.</td>
</tr>
<tr>
<td>NA</td>
<td>76</td>
<td>F</td>
<td>None</td>
<td>HTN</td>
<td>DM</td>
<td>Stroke after elective cardiac surgery.</td>
</tr>
<tr>
<td>NA</td>
<td>72</td>
<td>M</td>
<td>None</td>
<td>NA</td>
<td>HTN, AF, cancer</td>
<td>Stroke after elective thoracic surgery.</td>
</tr>
<tr>
<td>NA</td>
<td>66</td>
<td>M</td>
<td>None</td>
<td>NA</td>
<td>HTN, aortic dissection</td>
<td>Stroke after elective cardiac surgery.</td>
</tr>
<tr>
<td>NA</td>
<td>77</td>
<td>M</td>
<td>None</td>
<td>NA</td>
<td>HTN, chronic heart failure</td>
<td>Stroke after elective cardiac surgery.</td>
</tr>
<tr>
<td>NA</td>
<td>71</td>
<td>F</td>
<td>None</td>
<td>NA</td>
<td>HL, cancer</td>
<td>De novo stroke, most likely a lacuna infarction.</td>
</tr>
<tr>
<td>855</td>
<td>76</td>
<td>F</td>
<td>None</td>
<td>NA</td>
<td>HL, cancer</td>
<td>Stroke probably due to Trousseau syndrome.</td>
</tr>
</tbody>
</table>

Ce = cerebral disease; NA = not available.
Case number refers to patient ID in the supplementary data.

**TABLE 6. In-hospital stroke occurrence**

<table>
<thead>
<tr>
<th>Variable</th>
<th>During Discontinuation of ATT*</th>
<th>Unrelated to Discontinuation of ATT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>No stroke</td>
<td>833</td>
<td>18,368</td>
</tr>
<tr>
<td>Stroke frequency</td>
<td>0.24%</td>
<td>0.03%</td>
</tr>
</tbody>
</table>

*Statistically significant at p = 0.04; calculated using Fisher’s exact test.
therapy depending on individual perioperative bleeding and thrombotic risks.12,14,15 However, most elective noncardiac surgeries or treatments requiring general anesthesia or those targeting deep-seated lesions demand discontinuation of antithrombotic therapy due to the fear of postoperative hemorrhagic complications.

Although the rationale for continuing or discontinuing antithrombotic therapy during the perioperative period has mainly been established by looking into the risks associated with coronary artery disease,16,17 its risk has not been thoroughly investigated, instead focusing on cerebral ischemic complications.6 Although the frequency of cerebral ischemic events related to discontinuing antithrombotic therapy was relatively low, it was significantly higher than that seen for hospitalized patients not requiring discontinuation of antithrombotic therapy (Table 6). This could result from multiple causes, given that patients requiring antithrombotic therapy harbor numerous risk factors that can lead to cerebral ischemia. Nonetheless, clinicians should be aware of a 10-fold increased risk of developing cerebral ischemic events for patients requiring discontinuation of antithrombotic therapy. We would also like to emphasize that the observed extremely low frequency of cerebral ischemic complications for neurosurgical procedures could be the product of meticulous management of antithrombotic therapy discontinuation by neurosurgeons (Supplementary Data 2). Our investigation also revealed that patients receiving both anticoagulant and antiplatelet therapy harbor a significantly higher risk of developing cerebral ischemic events, which could be a valuable observation helping clinicians and patients to understand the overall risk associated with the treatment. Notably, patients receiving anticoagulant therapy showed a stronger correlation with cerebral ischemic development than those receiving antiplatelet therapy (Table 7; p = 0.08 vs 0.34).

Perioperative bridging therapy with unfractionated heparin is commonly used to counteract the risk associated with discontinuing antithrombotic therapy.9,10 According to the evidence established from clinical trials, however, the advantage of bridging therapy is under suspicion. It was shown that bridging therapy increased the risk of hemorrhagic complications while not reducing the risk of thromboembolism.7 Despite these negative findings, 20.9% of the patients in our study received heparin or cilostazol bridging therapy (Table 2). Due to the small number of patients who developed some kind of thrombotic complication among the entire cohort, we could not determine with certainty the benefit of bridging therapy. It should be noted, however, that one of the two-stroke patients was receiving bridging therapy during discontinuation of antithrombotic therapy (Table 5, case 300), which could align with previous findings demonstrating minimal protective benefit of bridging therapy.

We should note several limitations regarding this investigation. First, this was a single-center retrospective study with a limited number of patients who developed positive findings (i.e., cerebral ischemic event). Thus, the statistical power is limited, and the multivariate linear regression analysis results should be interpreted with great caution. Second, the clinical backgrounds of the analyzed patients were heterogeneous. Ideally, the risks associated with discontinuing antithrombotic therapy should be determined according to the treatment categories. Despite these limitations, our findings should still hold value to those involved in treating patients under similar circumstances, and should provide data for proposing future clinical trials.

Conclusions

Discontinuing antithrombotic therapy during hospitalization for elective invasive procedures—including neurosurgical procedures—entailed a relatively small risk of developing cerebral ischemic events, but the risk was significantly higher compared to hospitalized patients without discontinuation of antithrombotic therapy. Patients receiving both anticoagulant and antiplatelet therapy were significantly associated with a higher risk of developing cerebral ischemia related to discontinuation of antithrombotic therapy.

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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: Kinoshita, Mitsui, Fujiya, Furukawa. Acquisition of data: Kinoshita, Mitsui, Sawada. Analysis and interpretation of data: Kinoshita, Mitsui. Drafting the article: Kinoshita, Mitsui, Fujiya. Critically revising the article: Kinoshita, Sawada, Fujiya, Furukawa. Reviewed submitted version of manuscript: Kinoshita, Mitsui, Sawada, Furukawa. Approved the final version of the manuscript on behalf of all authors: Kinoshita. Statistical analysis: Kinoshita, Mitsui. Administrative/technical/material support: Kinoshita, Fujiya. Study supervision: Kinoshita.

**Supplemental Information**

Online-Only Content

Supplemental material is available online.


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