Original Research Article

Ischemic stroke and periprocedural discontinuation of antithrombotic agents: A single center retrospective chart review

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Abstract

Objective: To investigate the relationship between periprocedural discontinuation of antithrombotics and the occurrence of ischemic stroke in a regional stroke center.
Methods: This is a retrospective chart review that examined 517 patients presenting to a regional stroke center with radiographically and/or clinically confirmed ischemic stroke. Prescription of oral antithrombotics at time of stroke and discontinuation for any cause were recorded.
Results: Of the 36 patients who had their antithrombotic therapy interrupted, six patients with periprocedural discontinuation and subsequent ischemic stroke (within 30 days) were identified. These patients received anticoagulation therapy with factor Xa inhibitors, direct thrombin inhibitors, or warfarin prior to discontinuation. Adverse bleeding events were identified as the most common reason for discontinuation, followed by non-adherence to medication regimen.
Conclusion: Although the quantity of patients presenting with ischemic stroke following periprocedural anticoagulation interruption was significantly lower than hypothesized, this project nonetheless identifies the need for greater examination into clinician adherence with anticoagulation guidelines and reasons for patient non-compliance.

Keywords: Perioperative; periprocedural; antithrombotic; ischemic stroke

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Introduction and literature review

Antithrombotics are important for primary and secondary stroke prevention

In patients diagnosed with their first ischemic stroke, longitudinal studies have identified an increased risk of recurrent ischemic stroke, particularly in the subsequent years following the initial incident (1,2). In Ontario, Edwards et al. observed an approximate five-fold increase in incidence of ischemic stroke in the five years following the first transient ischemic attack (TIA) or ischemic stroke, when compared with matched controls (3). Together, these studies underscore the importance of secondary prevention in ischemic stroke.

Indeed, the necessity for secondary prophylactic medical therapy in such scenarios is reflected in the most recent Canadian Stroke Best Practice Recommendations for the Secondary Prevention of Stroke and the American Heart Association/American Stroke Association guidelines for secondary prevention of stroke (4,5). Antithrombotic medications are first-line therapy in these patients and are used to great clinical effect. A meta-analysis of over 15,000 randomized patients demonstrated a significantly decreased incidence of recurrent ischemic stroke at 12 weeks following the initial ischemic insult when treated with aspirin, an antiplatelet therapy (6). Clopidogrel, also an antiplatelet therapy, has been shown to provide a further reduction in incidence of ischemic stroke; however, the clot-reduction benefits of clopidogrel come at the cost of a higher risk of major hemorrhage (7). Anticoagulants, such as factor X inhibitors (e.g., apixaban or rivaroxaban), direct thrombin inhibitors (e.g., argatroban or dabigatran), or vitamin K antagonists (e.g., warfarin) are used in the primary prevention of stroke in high-risk patients with atrial fibrillation, as determined by validated evaluation tools (8,9). More recently, the COMPASS trial demonstrated an additional role for rivaroxaban in the secondary prevention of ischemic stroke (10). Overall, the benefits of antithrombotic therapy cannot be understated; however, it should be noted that antithrombotic therapies carry a non-negligible risk of increased bleeding events that must be weighed in careful consideration with each individual patient.

Adherence to periprocedural management of antiplatelet and anticoagulant guidelines can be unpredictable

Thrombosis Canada provides extensive clinical guides which outline appropriate management of antiplatelets and anticoagulants in the periprocedural period. Within these guides, surgical procedures are stratified as either low, moderate, or high risk, depending on the probability of associated adverse bleeding. These stratifications assist in determining the length of time for which an antithrombotic agent should be held pre- and post-operatively, and are based on current best evidence (11). To highlight the incorporation of the most up to date literature within the guidelines, one can examine the nuances of direct oral anticoagulant (DOAC) discontinuation in the perioperative period. The guidelines partly base this information on a sub-study of the RE-LY trial,

which showed that the use of bridging anticoagulation during interruption of dabigatran or warfarin increased major bleeding events, but had no significant effect in decreasing stroke or thromboembolism (12). Moreover, a study by Douketis et al. found very low rates of perioperative arterial thromboembolism, ranging from 0.16-0.60% depending on the specific DOAC, when standardized management measures were appropriately followed (13).

Despite the availability of these evidence-based guidelines, perioperative management of antithrombotic medications can vary based on practitioner and healthcare site. These variations appear to be present during both the pre- and post-operative periods, theoretically increasing the risk of procedural bleeds as well as thromboembolic events (1-5). This lack of adherence may be partially attributed to an inadequacy in the guidelines themselves in providing clear direction for clinical gray areas, a concept which is especially true in the periprocedural setting. To highlight the nuance and the complex nature of the guidelines—which can increase the rates of non-adherence or misinterpretation—one can take the example of the perioperative management of aspirin. Thrombosis Canada outlines the management for low and high-risk patients, and the guidelines suggest discontinuing the medication seven to 10 days prior to the procedure if there is a high risk of bleeding (11). However, in addition to these two classifications, patients with coronary stents are classified and managed differently, and often require both hematology and cardiology specialist consultation in order to manage their perioperative anticoagulant dosages (11). Other disciplines within which this heterogeneity exists includes dermatology and interventional pain management (14,15).

This lack of adherence may also be due to suboptimal understanding of treatment guidelines or adverse consequences by the patient population. While not specifically studying periprocedural outcomes, Borne et al. examined adherence patterns in a population of patients treated with preventative anticoagulation due to atrial fibrillation. They found that more than 25% of their sample displayed suboptimal adherence and that this was associated with an increased risk of ischemic stroke (16). Overall, these studies demonstrate a need for further investigations into guideline adherence and interventions at the level of the clinician and the patient to minimize both cerebrovascular accidents and major bleeds.

Discontinuation of antithrombotics may increase risk for cerebrovascular accident (CVA)

While there is robust evidence to prove that inadequate interruption of anticoagulants puts patients at risk of adverse bleeding outcomes, it is also important to consider whether there is an increased risk of ischemic stroke with prolonged interruption. For instance, one group of researchers studied the incidence of anticoagulant interruption amongst patients with atrial fibrillation undergoing secondary stroke prevention. In a sample of over 3,000 patients, they found that stroke recurrence occurred in four percent of patients whose dosing schedule was interrupted, with the most common reason for interruption being patient non-compliance (17). When specifically considering perioperative management of oral anticoagulation, subsequent CVA risk may be related to higher-

risk procedures, as defined by Thrombosis Canada, due to the lengthier interruption that these entail. In the BRUISE CONTROL-2 study of over 600 anticoagulated patients undergoing cardiac device implantation, a low-risk procedure, researchers found that ischemic stroke was a very uncommon complication and that there was no difference between continuous versus interrupted groups (18). In contrast, Kaatz et al. studied risk of post-operative stroke in patients treated for chronic atrial fibrillation undergoing high-risk surgeries, such as abdominal, lung, neurologic, orthopedic, and urologic operations. They found that the 30-day risk of stroke was two times higher than that of individuals without underlying atrial fibrillation who were not anticoagulated (19).

Overall, there is evidence in the literature to support the idea that periprocedural withdrawal of anticoagulant and antiplatelet medications is associated with an increased risk of subsequent ischemic stroke. Broderick et al. studied all patients presenting at a single hospital system with acute ischemic stroke and found that 5.2% of these patients had associated interruption of antithrombotic agents, including warfarin, low molecular weight heparin, aspirin, and clopidogrel (22). While this does represent a considerable proportion of strokes, it is important to recognize that these results are representative of a single geographic region and must be studied further. Currently, there is more emphasis, both academically and clinically, placed on risk of adverse bleeding associated with anticoagulation and surgery; the risk of ischemic stroke with interruption of anticoagulation is another important factor that must be seriously considered.

Why is this study needed now?

While there has been considerable improvement in the prevention and treatment of stroke over the years, CVAs remain the third leading cause of death in Canada (20). Moreover, the Economic Burden of Ischemic Stroke study examined a cohort of 232 ischemic stroke patients across 12 Canadian stroke centres and estimated an average annual cost of $74,353 CAD per ischemic stroke (21). Given the substantial morbidity, mortality, and financial burden of ischemic stroke, preventative measures should be emphasized and optimized. One avenue for optimization lies in the often-inconsistent perioperative management of antithrombotics. This study seeks to identify the proportion of ischemic strokes associated with antithrombotic discontinuation, whether due to preprocedural discontinuation or patient non-adherence, in a Canadian mixed community/academic stroke center. To the authors' knowledge, this question has not been explored previously in this setting. The information gathered from this study can also be used to guide future quality improvement projects as needed.

Purpose

The primary purpose of this study is to examine the incidence of CVAs associated with periprocedural discontinuation of antithrombotic medications; this will be accomplished by performing a chart review of all patients with ischemic strokes who presented to the Greater Niagara General Hospital (GNGH), the centralized stroke centre within the Niagara Health

System, in 2019. We will assess the severity of these strokes as determined by the initial National Institute of Health Stroke Scale (NIHSS) score and modified Rankin Score at 90 days post-infarct.

This study aims to address the following clinical research question: in adult patients diagnosed with ischemic stroke, is there an association between recent cessation of antithrombotic therapy and ischemic stroke occurrence? The primary outcome of interest is to identify the proportion of ischemic strokes occurring within 30 days of antithrombotic agent discontinuation within a larger cohort of ischemic stroke patients. A secondary objective would be to identify and categorize the reasons for antithrombotic agent discontinuation in these patients.

In all patients, the following baseline characteristics will be recorded: age and sex; history of previous stroke, atrial fibrillation, current smoking status, dyslipidemia, hypertension, and diabetes mellitus; initial NIHSS score and pre/post-stroke Modified Rankin score; investigations including initial INR and the presence of CT findings for ischemic stroke; and, if relevant, the date and type of procedure and the date and time of oral antithrombotic interruption and reinstatement.

Methods

This study will be a single-centre retrospective chart review examining all strokes presenting to the GNGH in 2019. To be included in the current study, patients must have presented to GNGH with a discharge diagnosis of acute ischemic stroke. Hemorrhagic strokes were excluded from the study, but patients with hemorrhagic transformation of an acute ischemic infarct were still considered. TIAs were also excluded from this study, as determined by negative CT head and resolving focal neurologic deficits without intervention within 24 hours of presentation.

Data extraction procedures

Hamilton Integrated Research Ethics Board approval was obtained to access patient charts for the cohort admitted to the GNGH during 2019. Meditech electronic medical records were used to access patient data primarily extracted from consult notes for inpatient visits provided by the internal medicine and neurology services. Discharge notes were also checked to confirm the discharge diagnosis of ischemic stroke confirmed radiographically. NIHSS scores were calculated for the initial presentation by reviewers trained and certified in NIHSS scoring. Relevant data were extracted by four independent reviewers. Analysis was primarily performed by deriving descriptive statistics using excel functions, to mimic the design and procedures employed by previous studies in the field (22).

Results

Descriptive statistics and baseline characteristics

The total patient sample (n) of individuals presenting with ischemic stroke to the GNGH in 2019 included 517 patients; the mean age of the sample was 74 years with a median of 77 years (range 33 - 98 years). The sample consisted of 282 (55% of the total sample size) males and 235 (45%) females. Baseline characteristics and comorbidities are recorded in Table 1.

Less than half of the patients (n=218, 42%) were on antithrombotic therapy prior to their stroke, including antiplatelets (n=134, 26%) and anticoagulants (n=84, 16%). Thirty-six (7%) patients had their antithrombotic therapy interrupted, and, of these, only 10 (1.9%) experienced ischemic stroke within 30 days of discontinuation.

Table 1. Baseline characteristics and comorbidities of adults before ischemic stroke

Patient Characteristics		**N (%)**
Sex	Male	282 (55%)
	Female	235 (45%)
Comorbidities	Previous CVA	209 (40%)
	Atrial fibrillation	142 (27%)
	Dyslipidemia	248 (48%)
	Hypertension	383 (74%)
	Diabetes mellitus	145 (28%)
	Chronic kidney disease	43 (8%)
	Smoking history	179 (35%)
Neuroimaging confirmed	Yes	414 (80%)
	No	103 (20%)
	TOTAL SAMPLE	517

Median age = 77 years
Median initial NIHSS = 4

Reasons for antithrombotic therapy interruption

Of the 36 patients who had their antithrombotic therapy interrupted, only six (1.2%) were interrupted for periprocedural reasons. In order of decreasing proportion, the reasons cited for discontinuation included adverse bleeding event (n=15, 2.9%), non-adherence to medication regimen (n=13, 2.5%), perioperative/periprocedural (n=6, 1.2%), and the presence of contraindications (n=2, 0.4%).

The patients for whom antithrombotics were discontinued due to adverse bleeding events were categorized by whether they suffered a major or minor bleeding event; major bleeding events included internal bleeding events, including intracerebral hemorrhage and gastrointestinal

bleeding, subdural hemorrhage resulting from fall or trauma, as well as bleeding from varicose veins requiring transfusion. Minor events included bruising, hematuria and rectal bleeds, and minor post-op bleeding complications.

Non-adherence was the second largest reason for discontinuation, affecting 13 patients; the medications that were not adhered to included apixaban (n=5), clopidogrel (n=1), aspirin (n=5), and dabigatran (n=2). Patients with contraindications included patients with worsening renal function and pelvic fracture with high risk of bleeding events on antithrombotics.

Perioperative / periprocedural discontinuation

There were six (1.2%) patients who had their therapy interrupted due to perioperative or periprocedural guidelines. Table 2 outlines the surgical procedures and agents interrupted.

Table 2. Periprocedural/perioperative discontinuation of antithrombotics in adults before ischemic stroke

Patient	Surgery	Associated risk	Antithrombotic	Number of days between interruption and ischemic event
1	Lipoma removal	Moderate	Dabigatran	1-5
2	Open reduction internal fixation of radius	Moderate	Apixaban	1-5
3	Circumcision	Low	Apixaban	1-5
4	Colonoscopy	Low	Rivaroxaban	6-10
5	Tooth extraction	Low	Apixaban	6-10
6	Cardiac catheterization	Low	Warfarin	6-10

Antithrombotic interruption and temporal relation to ischemic stroke

Of the 36 patients for whom antithrombotic therapy was discontinued, only 10 (1.9%) experienced ischemic stroke within 30 days. Data on the respective time intervals corresponding to the reason for discontinuation for these 10 patients are included in Table 3. Patients discontinued from DOACs and vitamin K antagonists experienced ischemic stroke within the first half of the 30-day periprocedural time frame (one to 14 days). One patient discontinued from antiplatelets experienced stroke within the second half of the periprocedural period (15-30 days).

Table 3. Reasons for discontinuation and antithrombotic agents for ischemic stroke in 30 days

Timing of stroke	Reason for discontinuation	Antithrombotic agent	Number of patients
Within 1-5 days	Perioperative or periprocedural	Dabigatran	1
		Apixaban	2
	GI bleed	Dabigatran	1
Within 6-10 days	Perioperative or periprocedural	Rivaroxaban	1
		Apixaban	1
		Warfarin	1
Within 11-14 days	GI bleed	Apixaban	1
Within 15-30 days	Bruising	Aspirin	1
	Contraindication	Aspirin	1

Discussion

The use of antithrombotics is critical to primary and secondary stroke prevention; however, adherence to appropriate antithrombotic guidelines can be unpredictable due to several factors. Identifying these variables can provide avenues for quality improvement interventions to better optimize adherence to clinical guidelines and avoid unnecessary antithrombotic discontinuation which increases risk for CVA.

In this study, we retrospectively reviewed patient charts to describe the incidence of ischemic strokes associated with periprocedural antithrombotic discontinuation in a Canadian community stroke center. From our sample cohort, we found six patients (1.2%) with periprocedural antithrombotic discontinuation, a significantly lower incidence than was found in a similar previous study of 5.2% (22). This difference in findings can potentially be accounted for due to our significantly lower sample size as well as possible geographical differences of medical profiles and presence of risk factors in the sample population. Our results revealed non-operative adverse bleeding events as the primary reason for patient antithrombotic discontinuation, with patient non-adherence being the second most common; both are well-established reasons for discontinuation consistent with previous literature (16,17).

There are some limitations within the methodological design of the study, including the previously cited low sample size, resulting in a significantly lower incidence of patients with perioperative and all-cause discontinuation of antithrombotics than was hypothesized. The small sample size can likely be attributed to the largely community-based nature of the hospital from which patients were recruited and the lack of collaboration with other stroke centers in the region, as has been done in previous studies. The team also encountered many obstacles in gathering patient charts and evaluating them for inclusion in the study, including erroneous medical identification numbers, identification numbers which either did not match to an existing file or led to a duplicated file, and unclear/inadequate reporting around the timelines of discontinuation; these

unfortunate instances resulted in approximately 30 otherwise valid charts being excluded from the study, further limiting the sample size.

The results of this study establish a preliminary foundation of knowledge around antithrombotic management in patients presenting with risk factors for ischemic stroke within the local region for future research studies to build upon. Some additional avenues of exploration can include: investigating the rationale behind different types of adverse bleeding events (e.g., major / minor) associated with antithrombotic discontinuation, expanding the study population time frame to better visualize the population of patients with perioperative antithrombotic discontinuation, and, finally, analyzing barriers behind patient non-adherence to antithrombotic therapy for the potential implementation of quality improvement interventions. Further areas of analysis which could be considered for this patient population include examining instances where clinician decisions regarding periprocedural and perioperative management do not adhere with the established guidelines and delving into the reasons for these non-adherences.

Conclusion

This single-center retrospective chart review examined the association between periprocedural antithrombotic discontinuation and the development of ischemic stroke within a 30-day time frame. The study was based upon the findings of previous literature citing significant association between periprocedural discontinuation and ischemic stroke, with 5.2% of all ischemic strokes studied having been attributed to peri-procedural interruption (22). Our study revealed a much lower rate of 1.2%; an inadequate sample size and the small-scale community nature of the setting were identified as contributing factors. Nevertheless, the study identified a notable number of patients who experienced ischemic stroke after discontinuation of their antithrombotics for a wider variety of factors than have previously been identified, including adverse bleeding events, patient non-adherence to therapy, and contraindications. These findings indicate the need for further study into clinician adherence to antithrombotic guidelines, and understanding patterns of inappropriate discontinuation in patients on primary or secondary prophylactic therapy.

Conflict of interest

There are no conflicts of interest to disclose.

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