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A Single Center Retrospective Analysis of Door-to-Needle Times of Anticoagulation Reversal Agents in Intracranial Hemorrhage

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Abstract

Objective: Anticoagulant associated intracranial hemorrhage (AA-ICrH) accounts for 10-25% of all intracranial hemorrhages. Being on anticoagulation at the time of the event of hemorrhage more than doubles the risk of hematoma expansion and mortality. Despite the rapid onset of action of the new anticoagulation reversal agents no guidelines for target times to treatment have been established. We evaluated anticoagulation reversal treatment times among patients with AA-ICrH presenting to a single large community hospital with institutional target times established in 2018.

Methods: Retrospective chart review was performed for all AA-ICrH treated with reversal agents in Sarasota Memorial Hospital Comprehensive Stroke Center, Sarasota, Florida, between 2018-2021. Clinical and non-clinical variables were collected. Predictors with $p<0.20$ in the univariate analysis were investigated further in a multivariable model.

Results: We identified 164 patients, 60 % male, 94% Caucasian. FXa inhibitors were used among 67%, warfarin 29% and dabigatran 4%. Half the cohort was treated with andexanet, 46% with PCC and 4% with idarucizumab. Most arrived via emergency medical services (EMS), 74%, transfers from other facilities, 11%, and walk-ins, 15%. Overall, 70% arrived <6 hours from symptom onset, 54% and 20% were treated under trauma alert (TA) and stroke alert (SA) protocols, respectively. Overall median [IQR] door-to-needle (DTN) and CT -to-needle (CTN) times (minutes) were 102 [69-181] and 75 [55-112], respectively. However, DTN was faster for SA, 65 [52-99], followed by TA 96 [70-160], $p<0.001$. DTN ≤90 minutes was seen in 42% of all cohort but in 73% of SA and 48% of TA. CTN ≤60 minutes was achieved in 36% overall, but in 62% of SA and 36% of TA. SA and TA protocols ($p<0.001$), and arrival by EMS ($p=0.02$) were independent predictors of faster DTN times.

Conclusions: Similar to ischemic strokes, treatment under SA or TA protocols and arrival by EMS were associated with significantly faster DTN times for anticoagulation reversal therapies in patients presenting with AA-ICrH. Our institution's proposed target times for DTN ≤90 and CTN ≤60 minutes for >75% of all treated AA-ICrH remained unmet during the study period. Increased awareness and tracking of DTN metric may help achieve timely anticoagulation reversal in AA-ICrH.

INTRODUCTION

Anticoagulation-associated intracranial hemorrhages (AA-ICrH) comprise 10% to 25% of all intracranial hemorrhages (ICrH) [1-4]. ICrH associated with the use of anticoagulants results in worse outcomes than spontaneous ICrH in non-anticoagulated individuals [5,6]. Compared to spontaneous ICrH, anticoagulation at the time of ICrH more than doubles hematoma expansion and mortality risk [7,8]. For several decades Vitamin K dependent anticoagulant coumadin (warfarin) was used for treatment and prevention of thromboembolic cerebral events, however, currently non-vitamin K oral anticoagulants (NOAC) are more commonly prescribed [9]. Although NOAC are noted to have a lower risk of intracerebral hemorrhages and fatal bleeding, the annual risk of ICrH remains between 0.23 and 0.5% [10,11]. Baseline hematoma volume and ICrH expansion are major determinants of poor outcomes with most expansion occurring in the first 3 hours from symptom onset [7,12,13]. Hematoma expansion stands out as one of the few potentially modifiable variables and its early control could mitigate the secondary brain injury and facilitate subsequent therapeutic approaches. The current approved antidotes,

i.e., prothrombin complex concentrate (PCC) for warfarin, idarucizumab for dabigatran and andexanet alfa for apixaban or rivaroxaban, reverse the anticoagulation effect within minutes, potentially abating the rate of hematoma expansion [14-16]. Rapid identification of intracerebral hemorrhages, especially for the patient population on anticoagulation therapy, and fast administration of an anticoagulant antidote could be a key step for improving patient outcomes. Unlike intravenous thrombolysis, no generally accepted guidelines for arrival/door-to-needle (DTN) time targets have been established for the administration of anticoagulant reversal agents in the setting of AA-ICrH. We evaluated the current DTN times for anticoagulant reversal use among AA-ICrH in a four-year retrospective sample in a single large community medical center with institutional target times established in mid-2018.

MATERIAL AND METHODS

A structured, retrospective chart review was performed on all consecutive AA-ICrH treated with approved reversal agents between 2018 and 2021 (four years) in Sarasota Memorial Hospital Comprehensive Stroke Center (SMHCSC), Sarasota, Florida- a 900 bed community medical center. In the third quarter of 2018 SMHCSC started collecting DTN times for the use of approved and specific anticoagulation reversals in AA-ICrH treatment as a stroke program quality metric. We established two institutional time targets: 1) Overall median DTN time target <90 minutes, and 2) Treatment of ≥ 75% of AA-ICrH under 90 minutes from arrival. The primary objective of this study was two-fold: i) To describe the DTN times in all AA-ICrH treated with reversal agents in SMHCSC, during a four-year period following our institution's formulary adoption of the last approved specific anticoagulation reversal agent in 2018, andexanet alfa, ii) To establish the proportion of patients with AA-ICrH treated with reversal agents within 90 minutes from Emergency Department (ED) arrival. Secondary objectives were: i) To explore covariates associated with faster DTN times for anticoagulation reversal agents in AA-ICrH, ii) To describe the CT-to-needle (CTN) times for reversal agents in AA-ICrH and iii) To describe the four-year temporal trend of DTN times for anticoagulation reversal agents in AA-ICrH in SMHCSC.

For the purpose of this study, AA-ICrH was defined as intracranial hemorrhage in any of the intracranial compartments (intracerebral, intraventricular, subdural, epidural or subarachnoid) occurring in patients taking oral anticoagulants at the time of the ICrH diagnosis. Patient inclusion criteria comprised: 1) Age ≥18 years old, 2) Patients must have been on oral anticoagulants at the time of the ICrH index event including warfarin, apixaban, rivaroxaban, edoxaban or dabigabtran AND received one or more of the following reversal therapies: any prothrombin complex concentrate (PCC), andexanet alfa or idarucizumab, 3) Traumatic or non-traumatic (spontaneous) ICrH, 4) History of concomitant antiplatelet was allowed. Exclusion criteria included: 1) Patients with ICrH not taking oral anticoagulants at the time of the index event, 2) AA-ICrH who did not receive any of the approved reversal therapies outlined above and 3) AA-ICrH due to heparin, lovenox, or any other parenteral anticoagulant.

Data Collection

Structured data collection was performed by trained research assistants using a HIPPA compliant encrypted database (REDCap, Vanderbilt University, Nashville, TN). In addition to collecting the type of approved reversal agent (Prothrombin complex concentrate, idarucizumab, andexanet) used and the date/time of first dose administration, we collected sociodemographic, clinical, laboratory, radiological data at the time of patient's presentation, patient's disposition at discharge and inpatient mortality. Specifically, Electronic Health Records were searched for mode of arrival, emergency department triage protocol, time of symptom onset, time from last dose of oral factor Xa inhibitor, time to head imaging, Glasgow coma scale [GCS], blood pressure at presentation, concomitant antiplatelet treatments, albumin level <3.0 g/dL, creatinine and creatinine clearance and international normalized ratio [INR].

Data abstractors were trained using a library of definitions. We periodically monitored data collection and provided feedback to the data abstractors during and after data collection and entry. Because of the retrospective design of chart review without any investigational intervention, our local Institutional Review Board waived the need for informed consent.

Statistical Methods

Descriptive statistics to characterize the sample are reported in terms of frequencies and percentages for categorical measures, and means, standard deviations, medians and quartiles for continuous measures. Yearly interval trends of median DTN times were plotted by categorical variables of interest. Kruskal-Wallis test was used to compare median DTN and CTN times among groups. To improve the asymptotic normality of DTN time the natural log transformation was applied. Bivariate general linear regression models were used to identify potential predictors of the transformed time measures. Predictors with $p<0.20$ were investigated further in a multivariable model and manual backward stepwise selection procedure was used to arrive at a final prediction model for the transformed DTN time. Results are reported in terms of model-adjusted means and 95% confidence intervals, exponentiated in order to report geometric means in the original time units. Significance was defined at $p<0.05$, and statistical analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc., Cary NC).

RESULTS

Baseline characteristics are described in Table 1. Out of a total of 164 patients identified during the study period 60% were male and 94% Caucasian. The most common indication for being anticoagulated was atrial fibrillation, 79%. Most patients were on apixaban or rivaroxaban, 48% and 18%, respectively, followed by warfarin, 29%. Only 7 patients were taking dabigatran. Just

over half the cohort, 54%, arrived to the emergency department and were treated under trauma alert (TA) protocol and 20% under stroke alert (SA) protocol; 3 patients were treated under concomitant trauma and stroke alert protocols. Emergency Medical Services (EMS) transported 74% of the patients and 11% were transfers from an outside institution (7% transferred by land and 4% transferred by air), whereas 15% of study patients presented as 'walk-ins' through triage. Over two thirds of patients, 70% (109/155), presented to the ED within 6 hours from the onset of symptoms with most of them, 88% (96/109), arriving within 3 hours from the onset of symptoms. Only 18% of the cohort arrived 18 hours after from the onset of symptoms or time was unknown. The overall DTN and CTN median times were 102 min (IQ 69-181) and 75 min (55-112), respectively [Table 1]. Order-to-needle median time was 36 min (30-45). The overall proportion of patients with DTN times under 90 minutes from arrival was only 42%. However, treatment time discrepancies among the triage subgroups in the emergency department were noticeably different. Whereas 73% of patients treated under a stroke alert pathway received the anticoagulation reversal agent within 90 minutes, 48% of patients under the trauma alert pathway, 13% of patients treated under regular emergency department pathway and 6% of 'walk-in' patients received the anticoagulation reversal agent within 90 minutes from arrival [Figure 1]. Treatment time under 60 minutes from arrival was seen in only 16% of all study patients. Again, more patients treated under a stroke alert pathway, 40%, received the anticoagulation reversal agent within 60 minutes from arrival to the ED in contrast to only 14% patients treated under the trauma alert pathway, 7% of patients treated under regular emergency department pathway, and none of the 'walk-in' (triage) patients [Figure 1].

Treatment time for the segment CTN under 60 minutes was seen in only 36% of all study patients. However, 62% of stroke alert patients received the anticoagulation reversal agent within 60 minutes from the diagnostic scan in contrast to 36% patients treated under the trauma alert pathway, 22% of patients treated under regular emergency department pathway, and only 7% of the 'walk-in' (triage) patients [Figure 2].

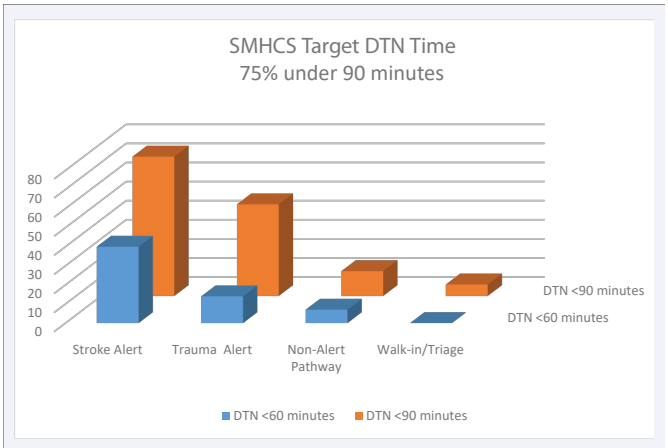

Figure 1 SMHCS Target DTN Time

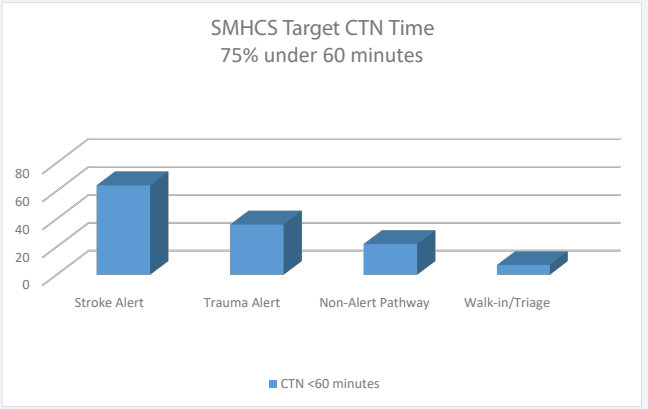

Figure 2 SMHCS Target CTN Time

The bivariate analysis showed no significant differences in the median times of DTN or CTN by gender, ethnicity, anticoagulant type or reversal agent type [Table 1]. There was nearly a 50-50 split between use of andexanet alpha and PCC. Within the 76 PCC treatments, 48 patients were on warfarin and 28 patients on FXa-inhibitors [Table 1]. Mode of arrival to diagnosis of the AA-ICrH yielded significant differences in the DTN and CTN times [Table 1]. Median DTN and CTN times were shorter among patients arriving to the emergency department by local EMS, 98 (69-160) and 70 (54-110) minutes, respectively; compared to patients arriving through triage 204 (144-262) and 88 (66-130) minutes, respectively. Although numbers were small, not unexpectedly DTN and CTN times were fastest for patients transferred by air 50 (43-70) and 24 minutes (only one patient had CT on arrival to our institution and before treatment), respectively. Treatment pathway subgroups in the emergency department also revealed significant time differences. Patients treated under a stroke alert pathway had the shortest DTN times, 65 (52-99) minutes, compared to trauma alert pathway, 96 (70-160) minutes, regular treatment pathway, 148 (104-218), and triage or "walk-in" patients, 221 (159-268) minutes. Significant differences, albeit within a narrower time spread, were observed in the CTN times, stroke alert pathway 55 (43-71) minutes, trauma alert pathway, 80 (55-121) minutes, regular pathway, 84 (62-122), and triage, 114 (67-130) minutes [Table 1]. Time from symptom onset to arrival and clinical severity at presentation had statistically significant trends [Table 1]. Shorter times from symptom onset to arrival between 0-6 hours were associated with faster DTN and CTN times, compared to progressively slower times for patients presenting 6-18 and >18 hours after onset of symptoms, respectively. Similarly, worse clinical severity at presentation, GCS <12, was associated with shorter DTN, and CTN compared to DTN and CTN times among patients with less severe clinical condition at presentation, i.e. CGS 12-14 and GCS of 15 [Table 1].

In the multivariable analysis, stroke alert and trauma alert pathways, as well as arrival mode were independent predictors of faster DTN times after adjusting for time from symptom onset, GCS, and reversal agent type [Table 2]. The adjusted geometric mean for patients treated under stroke alert pathway was 51.6

Table 1: Baseline Characteristics; Bivariate Analysis

		DTN		CTN	
	N (%)	Median (IQR)	p value	Median (IQR)	p value
Overall	164	102 (69-181)		75 (55-112)	
Gender					
• Male	99 (60)	110 (69-186)	0.39	81 (57-111)	0.09
• Female	65 (40)	96 (70-155)		65 (51-112)	
Ethnicity					
• Caucasian	154 (94)	103 (69-182)	0.63	73 (55-112)	0.53
• A-American	3 (2)	111 (98-318)		84 (81-172)	
• Hispanic	4 (2)	81 (61-129)		52 (44-95)	
• Other	3 (2)	99 (75-220)		85 (54-106)	
Anticoagulant					
• Fxa inhibitors	109 (67)	99 (72-167)	0.35	81 (56-122)	0.28
• Warfarin	48 (29)	113 (68-186)		70 (53-106)	
• Dabigatran	7 (4)	57 (31-210)		57 (38-137)	
Reversal Agent					
• Andexanet alfa	81 (49)	97 (72-160)	0.56	82 (57-121)	0.28
• PCC	76 (46)	---		---	
- Fxa inhibitors	28 (17)	110 (62-185)		71 (43-129)	
- Warfarin	48 (29)	113 (68-186)		70 (53-106)	
• Idarucizumab	7 (4)	57 (31-210)		57 (38-137)	
Arrival Mode					
• Direct EMS	122 (74)	98 (69-160)	<0.001	70 (54-110)	<0.053
• Triage	24 (15)	204 (144-262)		88 (66-130)	
• Transfer- Land	12 (7)	96 (63-120)		81 (47-94)	
• Transfer- Air	6 (4)	50 (43-70)		24 (24-24)	
ED Protocol					
• Stroke Alert	33 (20)	65 (52-99)	<0.001	55 (43-71)	<0.001
• Trauma Alert	88 (54)	96 (70-160)		80 (55-121)	
• Other	30 (18)	148 (104-218)		84 (62-122)	
• Triage	16 (10)	221 (159-268)		114 (67-130)	
Symptom onset to ED arrival**					
• <6 hrs	109 (70)	86 (67-145)	0.003*	68 (53-107)	0.40*
• 6-18 hrs	18 (11)	113 (85-172)		87 (56-112)	
• 18+ hrs	28 (18)	192 (116-228)		88 (64-136)	
GCS					
• <12	30 (18)	81 (54-136)	0.049*	67 (40-105)	0.11*
• 12-14	51 (31)	99 (75-186)		81 (59-111)	
• 15	83 (51)	114 (70-197)		72 (54-129)	

* Trend test p value
** 9 observations missing

Table 2: Multivariable Analysis of Predictors of faster Door-to-Needle times. Adjusted Stroke Alert, Trauma Alert and Arrival Mode geometric means.

	Geometric Mean Minutes	(95% CI)*	Adjusted p-value
Stroke Alert	5	(39 – 68)	<0.001
No Stroke Alert	103	(86 – 125)	
Trauma Alert	64	(50 – 82)	0.021
No Trauma Alert	83	(68 – 101)	
Transfer by Air	34	(22 – 54)	<0.001
Transfer by Land	79	(56 – 113)	
EMS	95	(79 – 114)	
Walk-ins (triage)	109	(83 – 144)	

** Adjusted by time from symptom onset, GCS and reversal agent*

minutes or twice as fast as non-stroke alert pathway patients, 103.3 minutes (p<0.001). Similarly, the adjusted geometric mean for patients treated under the trauma alert pathway was 64.4 minutes compared to non-trauma alert patients, 82.8 minutes (p=0.021). Treatment for patients arriving to the ED by EMS resulted in faster adjusted times, fastest for air transfers, 34.4 minutes, followed by land transfers, 79.3 minutes, and local EMS transports, 95.2 minutes (p<0.001). These times stand in clear contrast with the adjusted geometric means of 109.4 minutes of the walk-in patients.

Inpatient mortality was 13%, while 27% were discharged home and 19% went to inpatient rehabilitation. The overall hospital and intensive care unit (ICU) median length of stay were 3.7 and 1.8 days, respectively. No association with faster DTN was observed. Over the 4-year study period we did not observe any distinct temporal trends by subgroups of treatment pathway, mode of arrival, type of anticoagulant or reversal agent for DTN or CTN times. Overall, during the COVID pandemic years 2019-2020 we observed a worsening of DTN and CTN for all subgroups with mixed improvement of times in 2021.

DISCUSSION

Intracranial hemorrhage is a disabling and life-threatening condition with high risk for early mortality, as such, it merits fast diagnosis and treatment, particularly when associated with anticoagulation [17]. Anticoagulation increases hematoma expansion and the most recent AHA/ASA guidelines for the management of patients spontaneous AA-ICrH recommend that "anticoagulation should be stopped immediately and rapid reversal of anticoagulation should be performed as soon as possible after diagnosis of spontaneous intracranial hemorrhage to improve survival." [18]. We showed that our overall median time of 102 minutes from arrival to the emergency department to initiation of anticoagulation reversal treatment, i.e., DTN time, for all AA-ICrH presenting to SMHCSC over a four-year study period fell short of our institution's DTN time target <90 minutes. Similarly, the proportion of AA-ICrH treated under 90 minutes from arrival, 41%, did not reach our aim to treat at least 75% of AA-ICrH under 90 minutes from arrival. However, among AA-ICrH treated via a SA pathway the DTN median time was significantly shorter, 65 minutes, and met our time target time [Table 1]. Furthermore, with 55 minutes this SA subgroup also met our institutional CTN time under 60 minutes [Table 1]. Most noticeable, the adjusted stroke alert DTN time was twice as fast as non-stroke alert treated patients [Table 2]. In contrast, in SMHCSC the unadjusted DTN time for intravenous thrombolysis in ischemic stroke during the same four-year study period was in 37 minutes. The adjusted trauma alerts and transfer median times were also within our target, while arrival via local EMS adjusted DTN time was close at 95 minutes [Table 2]. To our knowledge, this is the first study to report shorter DTN times for reversal agents in AA-ICrH associated to these acute stroke treatment pathways and mode of arrival to emergency departments. As a certified Comprehensive Stroke Center and Level II Trauma Center since 2015, more than two thirds of patients in our institution were treated under a stroke alert or trauma alert pathway and 85% arrived by EMS. Our findings suggest that similar to treatments in acute ischemic stroke, the treatment time reductions obtained by implementing urgent treatment pathways are also attainable in the acute treatment of AA -ICrH paradigm [19,20]. Establishing time targets for use of anticoagulation reversal agents as part of our program quality metrics helped us achieve faster DTN and CTN times than most previously reported [21-24]. The largest retrospective observational study of hospitalized patients across 354 institutions in the United States between 2018 and 2022, who were administered andexanet alfa or 4-factor PCC for rivaroxaban- or apixaban associated major bleeding (intracranial or gastrointestinal) showed a median DTN of 2.5 hours (1.2-6.4) and 2.3 hours (1.2-5.7) for andexanet and PCC use, respectively [25]. An earlier case series review of warfarin-related ICH reported significant delay from arrival to administration of PCC, median 3.6 hours, and median CTN was 2.7 hours [18]. In a previous study implementing an improved care bundle process that included anticoagulation reversal median DTN times improved to 105.5 minutes during the post-implementation phase [22]. A retrospective review between 2013 and 2018 of all warfarin associated ICH in a large tertiary center in New Zealand, reported a median DTN to any first reversal agent (vitamin K included) of 174 minutes and specifically for PCC of 183 minutes [23]. In the same time period, median DTN for intravenous thrombolysis in ischemic strokes was 52 minutes [23]. The Canadian PCC Registry was implemented shortly after the approval of PCC therapy in 2008 and of 141 consecutive patients with anticoagulant-associated ICH for the subsequent two years, 107 received PCC therapy. The median DTN- and CT-to-PCC treatment times were 213 and 100 minutes, respectively [24].

The SA treatment pathway is directly influenced by the treatment targets and initiatives established by stroke programs. Our findings point to the value of establishing specific time target driven processes to help achieve timely DTN times among SA patients that may translate into better clinical outcomes as suggested by the limited number of studies available. In spite the data paucity, improved survival with faster anticoagulation reversal treatment is suggested by earlier studies [21,25-28]. Specifically, in a case series review of warfarin-related ICrH, there were significant delays before administration of reversal therapy (mean, 3.3 hours from CT to PCC, 4.8 hours from arrival to reversal agent). Lower mortality was observed among patients who received PCC within 2 hours from presentation to the ED compare to those who received PCC between 2-4 hours and >4 hours after arrival [21]. The benefit in survival with early therapy may be, to a great extent, associated with less hematoma expansion. In effect, with a similar time from onset to baseline CT, the INCH trial showed that shorter treatment times and normalization of INR (≤1.2) was associated with less hematoma expansion [28]. The study authors suggest that "the inability to rapidly antagonize anticoagulation effectively increases the risk of hematoma expansion and early death [28]. More recently, a retrospective observational study of hospitalized patients who were administered andexanet alfa or 4-factor PCC for

rivaroxaban- or apixaban associated major bleeding showed that among the subgroup of 1283 ICrH, longer door-to-reversal administration time was associated with higher mortality risk, with an adjusted odds ratio for time ≥ 30 minutes of 2.46 (95% CI 1.12-6.22) [29]. Further controlled studies are needed to evaluate the impact that timely DTN may have on survival and neurologic disability. ANNEXA-I trial, a randomized, controlled study comparing treatment with andexanet alfa and standard of therapy in FXa inhibitor-associated ICrH may provide valuable information on the timeliness of reversal therapies, hemostatic efficacy and neurological outcome (ANNEXA-I NCT03661528) [30]. In patients with spontaneous ICH, a substudy of the FAST trial suggested that faster achievement of hemostatic efficacy with recombinant activated factor VII may be associated with better outcomes and less hematoma expansion [31].

The presence of anticoagulation at the time of ICrH more than doubles the risk for hematoma expansion and mortality [7,32]. The natural history of hematoma expansion following intracerebral hemorrhage is a steeply time-dependent process. While most of the hematoma expansion occurs in the first three hours after the hemorrhage onset, the odds of hematoma expansion taper over several hours before it plateaus [7]. Further, earlier studies suggest that the time to hematoma stabilization is also prolonged by the presence of anticoagulation [4,12]. The advent of rapid reversal of anticoagulation with the new specific approved antidotes for NOACs- less than 5 minutes after end of initial bolus- and normalization of INR within 30 minutes in a majority of patients treated with PCCs, opens the opportunity to assess the scale to which faster reversal of anticoagulation modifies hematoma expansion and clinical outcomes [33-35]. Meantime, these observations accentuate the need for rapid DTN processes to reverse the anticoagulation effect in acute treatment of AA-ICrH. Whether the therapeutic approach is medical, or a combination of medical and surgical treatment, patients with AA-ICrH first require a rapid reversal of anticoagulation. To be effective, hemostasis must be restored as early as possible after the onset of the hemorrhage event. Therefore, while further controlled studies become available, it seems reasonable for stroke centers to devote attention to achieving a timely DTN process for anticoagulation reversal agents in AA-ICrH. As a certified comprehensive stroke center with several years of experience trimming the target DTN times for intravenous thrombolysis in ischemic stroke, we are of the opinion that until new data is available, a 90-minute DTN time in ≥75% of AA-ICrH is a reasonable target. Similarly, we considered that 60 minutes CTN is reasonable until further data becomes available.

CTN makes up for an important time segment of the DTN therapeutic window, and once a diagnostic CT confirms the presence of an ICrH in a patient on anticoagulation, one expects a fast treatment to reverse the anticoagulation effect regardless of patient subgroup category. Interestingly, albeit a narrower spread between patient subgroups we still saw substantially slower CTN times among patients not treated under stroke or trauma alert pathways [Table 1]. With only 33% of patients with CTN time under 60 minutes our stroke program is working diligently to identify the barriers to a faster CTN segment and develop corrective measures to optimize these times. Two previous studies showed improvements in their CTN times after correcting process barriers. A UK center removed hematology pre-approval for PCC order, moved PCC stock to the ED and introduced point-of-care INR testing, which showed a reduction in the median CTN from 127 to 58 minutes [36]. By implementing a pharmacist driven protocol for PCC dosing, preparation, and delivery one US center was able to halve CTN median times from 70 to 35 minutes [37]. Noteworthy, few other studies have managed to obtain CT to treatment time under 60 minutes [38]. In a randomized, controlled trial of fresh frozen plasma versus prothrombin complex concentrate (PCC) in patients with warfarin-related major bleeding, the average time from CT to treatment was 59 minutes in the PCC study arm [28]. Similarly, the mean time from baseline CT to treatment was 51 ± 17 minutes in the recombinant activated factor VII for acute ICH trial [39,40]. In our program we consider that an initial CTN target of ≥75% of AA-ICrH treated under 60 minutes is therefore reasonable.

Our study set out to describe door to needle times for anticoagulant reversal administration in AA-ICrH in the setting of a large community hospital functioning as a comprehensive stroke center. Despite the significant body of work that informs thrombolytic administration guidelines for the treatment of ischemic stroke, few studies have attempted to examine timeframes for procoagulant administration. Our analysis was performed in an attempt to understand what our current door-to-needle times were and what predicted shorter or longer times to administration. Hematoma expansion is one of the few modifiable risk factors of poor outcome following an ICrH. The earlier diagnostic imaging occurs and the faster treatment begins, the greater chance to re-establish hemostasis and consequently mitigate or halt hematoma growth and hopefully improve survival. With the new rapid acting anticoagulation reversal agents our disproportionate attention to the DTN process for AA-ICrH compare to ischemic stroke merits rectification. Following the establishment of specific time driven targets in 2018, these 4-year results have sharpened our stroke program awareness and impetus to achieve even better DTN times for future anticoagulation reversal treatments across all subgroups of AA-ICrH presenting to SMHCSC and not only those under stroke alert pathway or arriving by EMS. We hope our study observations encourage other stroke centers to raise awareness on this issue and consider implementing quality metrics to assess the timely use of anticoagulation reversal in AA-ICrH. In this effort, we welcome the timely GWTG 2023 update including metrics on anticoagulant reversal agents, as well as the CODE ICH initiative [39,40]. These initiatives and other future studies are needed in order to help close the gap in our understanding of the barriers that keep us from achieving timely DTN processes for faster delivery of anticoagulation reversals, as well as to identify covariates associated to faster DTN and clinical outcomes.

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