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Outcomes of trauma patients on chronic antithrombotic therapies in a trauma center in a rural state

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ABSTRACT

Objective: The number of trauma patients presenting with chronic antithrombotic therapy is on the rise. The risk of hemorrhage, the leading cause of death in trauma patients, increases for those on such therapy. This study sought to compare the clinical outcomes of patients on warfarin, direct oral anticoagulants (DOAC), or antiplatelet agents.

Methods: A retrospective cohort analysis was conducted on adult patients admitted to a Level 1 trauma center with pre-admission antithrombotic therapy. Patients were divided into those on warfarin, DOACs, and antiplatelet agents. The primary outcomes measured were hospital mortality, total blood products received, hospital length of stay (LOS), and ICU LOS.

Results: 738 patients were included in the study: 191 (26 %) warfarin, 260 (35 %) DOACs, and 287 (39 %) antiplatelet. There were no differences in the demographic variables between study groups. The Injury Severity Score (ISS) was similar across the three groups as well as blood product usage, reversal agent usage, and mean hospital stay. Multivariable regression showed patients with pre-admission antiplatelet usage were more likely to have a shorter ICU LOS than those on warfarin ($p = 0.048$).

Conclusion: Blood product and reversal agent use was similar between patients on warfarin, DOACs, or antiplatelet agents. Patients on antiplatelet agents had a shorter ICU stay than the warfarin group, the only significant difference observed. Our results indicate similar safety profiles of antithrombotic medications in a generic trauma population, likely due to institutional protocols to increase responsiveness and immediate availability of resources when the patient has known anticoagulation.

Introduction

The use of anticoagulation, especially direct oral anticoagulants (DOACs), has increased in recent years [1,2], likely due to increased prescribing for venous thromboembolism and stroke prophylaxis per current guidelines [3]. Since DOACs require less monitoring than warfarin, they have become more popular, especially in the setting of atrial fibrillation [4]. As a result of this increased use and an aging population, a greater proportion of trauma patients present while on anticoagulant therapy.

The relationship between anticoagulant use and worse clinical outcomes has been observed in patients admitted to the ICU with acute bleeding, including trauma patients [5]. Other studies have detailed the clinical risks and increased rate of surgery seen with warfarin, DOACs, and antiplatelet therapies [5–9]. However, few studies have compared the outcomes for these three categories of blood-thinning agents. In addition, most studies limit the inclusion criteria to specific traumatic events, such as traumatic brain injury or massive hemorrhagic events. The studies described above also delineate the need for further investigation of larger populations, comparison of all anticoagulants, and updated data with the changing patterns of anticoagulation use and aging population.

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The objective of this study was to describe and compare outcomes of all adult trauma patients on pre-injury anticoagulation at the only adult Level I trauma center in a rural state. In particular, we sought to compare clinical outcomes of patients receiving either warfarin, DOACs, or antiplatelet therapies.

Methods

Study design

Statistical analysis

Descriptive statistics were tabulated for each group, including mean and standard deviation for continuous variables. Data was not assessed for normality as healthcare data is assumed to be non-normally distributed. However, per accepted practice, *t*-test and chi-square analysis were utilized for this large healthcare cohort. ANOVA and Chi-square tests were used to determine differences between the group means and proportions. A generalized linear model (Poisson Family, log link) was performed to determine the relationship between subgroups and length of ICU and hospital stays, while including age, race, sex, ISS, van Walraven score, and blood products to control for other factors known to affect patient outcomes. All statistical analyses were conducted in Stata 15 (College Station, TX: StataCorp LLC.) using a significance level of 0.05.

Results

Demographics

During the study period, there were a total of 9373 trauma admissions of whom 738 (7.9 %) were receiving an anticoagulation agent at the time of admission: warfarin ($n = 191$, 25.88 %), DOACs ($n = 260$, 35.23 %), and antiplatelet agents ($n = 287$, 38.89 %). Demographic data are displayed in Table 1. When comparing the three antithrombotic groups, there were no significant differences in sex, race, van Walraven Comorbidity Score, or ISS. Similarly, no significant differences were observed in the total ICU stay and total hospital stay. However, age varied significantly across the three groups ($p = 0.005$).

Blood utilization

In terms of blood product usage, the proportion of patients who received any blood products varied significantly between the DOAC (8.1 %), warfarin (15.2 %), and antiplatelet (14.6 %) groups ($p = 0.028$, Table 1). While the proportion of patients who received PRBC ($p = 0.994$) did not vary significantly among the three groups, the proportion of patients who received FFP was greater in the warfarin group ($p = 0.003$), and the proportion of patient who received platelets ($p = <0.001$) was greater in the antiplatelet group. However, among patients who received blood products, there were no differences in the number of units received among study groups (Table 2). In addition to blood products, reversal agent use was considered for each of the groups. Statistical analysis showed no significant difference in the number of patients receiving reversal agents ($p = 0.246$, Table 1). Furthermore, there were no patients that received both reversal agents and blood products.

Table 1
Demographics of the Warfarin, DOAC, and Antiplatelet Groups.

	Total	Warfarin	DOACs	Antiplatelets	p-value
	$n = 738$	$n = 191$	$n = 260$	$n = 287$	
Male, n (%)	383 (51.90)	105 (54.97)	126 (48.46)	152 (52.96)	0.353
Age, years	72.31 ± 13.22	73.68 ± 13.45	73.49 ± 13.22	70.33 ± 12.87	0.005
Race, n (%)					0.554
White	599 (81.50)	156 (81.68)	215 (82.69)	228 (79.44)	
Black	122 (16.60)	29 (15.18)	41 (15.77)	52 (18.12)	
Other	14 (1.90)	6 (3.14)	4 (1.54)	4 (1.39)	
ISS, n (%)					0.565
1 - 8	304 (46.63)	85 (44.50)	105 (40.38)	114 (39.72)	
9 - 15	204 (31.29)	49 (25.65)	78 (30.00)	77 (26.83)	
>15	144 (22.09)	36 (18.85)	45 (17.31)	63 (21.95)	
van Walraven Score	10.82 ± 10.61	10.04 ± 10.23	11.58 ± 10.64	10.66 ± 10.83	0.297
Received Blood Product(s), n (%)					
PRBC	42 (5.69)	11 (5.76)	15 (5.77)	16 (5.57)	0.994
FFP	47 (6.37)	22 (11.52)	12 (4.62)	13 (4.53)	0.003
Platelets	37 (5.01)	1 (0.52)	8 (3.08)	28 (9.76)	< 0.001
Any Blood Product	92 (12.47)	29 (15.18)	21 (8.08)	42 (14.63)	0.028
Received Reversal Agent, n (%)	38 (5.15)	14 (7.33)	10 (3.85)	14 (4.88)	0.246
Total ICU Stay, days	1.20 ± 2.78	1.21 ± 2.84	1.08 ± 2.62	1.30 ± 2.88	0.672
Total Hospital Stay, days	4.26 ± 4.42	4.15 ± 4.12	4.32 ± 4.67	4.28 ± 4.40	0.919
Mortality, n (%)	29 (3.93)	8 (4.19)	8 (3.08)	13 (4.53)	0.634

Table 1. Values are presented as mean ± SD unless indicated otherwise. DOACs – direct oral anticoagulants; ISS – injury severity score; PRBC – packed red blood cells; FFP – fresh frozen plasma; ICU – intensive care unit.

This study was a retrospective cohort analysis using electronic medical record data from the Arkansas Clinical Data Repository (AR-CDR) from 2015 to 2020. The AR-CDR database is an institutional database only including data from the single Level 1 trauma center in a rural state. The Institutional Review Board deemed this study as non-human subjects research (IRB #261,966). All trauma patients 18-years-old or older who were admitted to our adult Level I trauma center were included in the original query. Rural state was defined as a larger proportion of the population living in rural counties as compared to the overall U.S. population. As of 2021, 41 % of Arkansans lived in rural counties, considerably higher than the national average of 19 % [10]. Database records for pre-admission antithrombotic therapy were used to exclude patients who were not taking anticoagulation prior to admission as well as those receiving multiple categories of anticoagulation therapy. The final cohort only included patients on antithrombotic therapy, divided into three groups based on the category of medication. These categories included warfarin, direct-acting oral anticoagulants (DOACs), and antiplatelet agents (excluding aspirin) alone. Demographic and clinical data were collected, along with blood product utilization and use of reversal agents. The reversal agents used in this study included vitamin K, recombinant factor Xa, idarucizumab, prothrombin complex concentrate (PCC), desmopressin, and tranexamic acid. Furthermore, the von Walraven Score, a weighted summary score of the Elixhauser Comorbidity Index [11], was used to describe each group. ISS was broken into three categories: 1–8, 9–15, and >15. If a patient received RBCs, plasma, or platelets, they were classified as having received blood products. The primary outcomes measured were hospital mortality, total blood products received, length of ICU stay, and length of hospital stay.

Table 2
Blood Product Utilization.

Characteristic	Warfarin	DOACs	Antiplatelets	p-value
Blood Products				
PRBC	1.64 ± 1.012	2.67 ± 2.66	2.25 ± 1.77	0.445
FFP	2.18 ± 1.40	3.50 ± 4.01	2.77 ± 2.05	0.337
Platelets	2	1.88 ± 0.99	1.54 ± 0.79	0.546

Table 2. Values are presented as mean ± SD unless indicated otherwise. DOACs – direct oral anticoagulants; PRBC – packed red blood cells; FFP – fresh frozen plasma; ISS – injury severity score.

Mortality and length of stay

There was a small percentage of patients (between 2.9 and 4.4 %) in each anticoagulant group that died in the hospital, but there was no significant difference between groups. In a regression analysis, every year increase in age had a higher likelihood of having a shorter ICU length of stay (LOS) ($p = 0.003$), whereas every unit increase in ISS ($p = <0.001$) or von Walraven Comorbidity Score ($p = <0.001$) had a greater likelihood of a longer ICU LOS (Table 3). Compared to white patients, patients of other races ($p = 0.012$) had a higher chance of having a shorter ICU LOS, as did patients on antiplatelets compared to patients on warfarin ($p = 0.048$, Table 3). Compared to patients who did not receive any blood products, patients who received any blood products ($p = <0.001$) had a higher chance of having a longer ICU LOS (Table 3). In a similar analysis for hospital LOS, a higher ISS ($p = <0.001$) or van Walraven comorbidity score ($p = <0.001$) were associated with a higher likelihood of having a longer hospital LOS (Table 4). Similar to ICU LOS analysis, Black ($p = 0.011$) and patients of other races ($p = 0.044$) were associated with a higher chance of having a shorter hospital LOS when compared to White patients, as did male patients ($p = 0.007$) when compared to female patients (Table 4). Compared to patients who did not receive any blood products, patients who received blood products ($p = <0.001$) had a higher chance of having a longer hospital LOS (Table 4).

Discussion

We found that 7.9 % of trauma admissions to the only adult Level I trauma center in a rural state were patients on chronic antithrombotic therapy at the time of admission. There were no significant differences in routine clinical outcomes between patients on warfarin, DOACs, or antiplatelet therapy, other than patients on antiplatelet medications had a tendency towards a shorter ICU LOS compared to patients on warfarin or DOACs. Furthermore, there was no significant difference in mortality, overall blood product usage, and reversal agent usage between the three groups of anticoagulants. These results indicate similar trauma outcomes for these groups of medications.

Table 3
Generalized Linear Model for Length of ICU Stay.

Characteristic	Coefficient	95 % CI		p-value
Age	−0.010	−0.016	−0.003	0.003
Race				
Black	−0.156	−0.365	0.053	0.143
Other	−1.259	−2.246	−0.271	0.012
Anticoagulants				
DOACs	−0.138	−0.327	0.051	0.152
Antiplatelets	−0.185	−0.368	−0.002	0.048
ISS				
9–15	0.713	0.467	0.959	<0.001
>15	2.279	2.065	2.494	<0.001
Any Blood Products	0.333	0.167	0.500	<0.001
Male	−0.022	−0.172	0.129	0.778
van Walraven Score	0.029	0.023	0.035	<0.001

Table 3. ICU – intensive care unit; DOACs – direct oral anticoagulants; ISS – injury severity score; CI = confidence interval. Referent groups: Race- White; Anticoagulants- Warfarin; ISS- ISS 1–8.

Table 4
Generalized Linear Model for Length of Hospital Stay.

Characteristic	Coefficient	95 % CI		p-value
Age	−0.002	−0.006	0.001	0.124
Race				
Black	−0.145	−0.256	−0.033	0.011
Other	−0.349	−0.689	−0.009	0.044
Anticoagulants				
DOACs	< 0.001	−0.099	0.010	0.995
Antiplatelets	−0.054	−0.151	0.044	0.283
ISS				
9–15	0.367	0.272	0.461	<0.001
>15	0.837	0.737	0.936	<0.001
Any Blood Products	0.315	0.215	0.415	<0.001
Male	−0.107	−0.185	−0.029	0.007
van Walraven Score	0.023	0.020	0.026	<0.001

Table 4. DOACs – direct oral anticoagulants; ISS – injury severity score. CI= confidence interval. Referent groups: Race- White; Anticoagulants- Warfarin; ISS- ISS 1–8.

A previous study by Bonville et al. described the prevalence of warfarin use as increasing to 4 % in 2006 [7]. A similar study by Ganetsky showed a combined prevalence of warfarin and DOACs of 5.8 % between 2010 and 2014. Our prevalence is in a similar range as these studies but falls on the lower end with 2.1 % prevalence of warfarin and 5.1 % combined prevalence. The Ganetsky study would also suggest that the elderly mean age for our population would be more consistent with a higher prevalence of antithrombotic use [1,12]. An overall prevalence of antithrombotic use was reported as 11.2 or 13.3 % in two different papers [7,9], both values higher than the 7.9 % observed in this study. Therefore, there is a lower rate of prescription of any antithrombotic in our population. A possible explanation for the lower chronic antithrombotic use could be a lack of insurance and access to primary care in the state. Rural areas have a disproportionate lack of access to health insurance [13]. Furthermore, fewer healthcare professionals reside and practice in rural areas, decreasing access to primary care providers who may prescribe antithrombotics [14].

Our study population shows a relatively equal use distribution for the three groups of antithrombotics. In similar studies, there is a different distribution of these groups. In several studies over the last decade, antiplatelets comprised 50–70 % of antithrombotic therapy, while warfarin represented less than 20 % and DOACs less than 10 % [7,15,16]. Furthermore, when warfarin and DOACs are compared directly, warfarin typically makes up 60–70 % of the population [3,5]. A new study in March of 2023 found that DOACs have begun to overtake all other forms of anticoagulation, making up around 90 % of anticoagulation use for deep vein thrombosis (DVT) prophylaxis [17]. The difference between our study population and these studies may denote a difference in prescription practices. The use of more warfarin and less DOACs could be due to lack of access in rural areas or higher cost. It may also simply reflect a difference in the age of the study population compared to previous literature.

Several studies have compared some combinations of the three antithrombotic groups described in our study. Two studies in 2011 and 2015 looked at traumatic brain injury (TBI) patients on pre-injury anticoagulation. They found preinjury warfarin was an independent risk factor for in-hospital mortality, increased the risk of intracranial hemorrhages (ICH), and increased the need for neurosurgical intervention for ICH, but it was not associated with increased LOS. The same studies found no association between antiplatelets and the same outcomes [7,15]. Three further studies compared blood transfusions, mortality outcomes and LOS for warfarin and DOACs. Nishimura et al. found a higher rate of mortality and FFP use in the warfarin group as compared to DOACs [18]. The study from 2020 found increased mortality and LOS for any anticoagulation, with both outcomes being higher for warfarin as compared to DOACs [5]. The 2017 study described a

similar rate of blood transfusion for warfarin and DOACs, while DOAC patients received more tranexamic acid (TXA) and warfarin patients received more prothrombin complex concentrates (PCC). Furthermore, warfarin was found to result in greater mortality than DOACs [3]. A final study in 2020 compared the outcomes of mortality or hospice for elderly TBI patients in warfarin, DOACs, antiplatelets, and no antithrombotics. It showed that warfarin and DOACs increased mortality or hospice outcomes, while antiplatelets showed no increased risk of these outcomes [16].

At our institution, a protocol is used in order to direct care of patients with pre-injury anticoagulation. A detailed history is taken from the patient if possible and the electronic medical record is utilized to determine anticoagulation use. Patients determined to be on anticoagulation receive a CT scan within 30 min and STAT labs (INR, ROTEM, PFA, and P2Y12) are drawn. Lab values along with clinical judgement is used to determine severity of bleeding, directing the use of blood products and reversal agents. For DOACs, the major reversal agent is PCC with the exception of idarucizumab for dabigatran. Reversal of warfarin use includes vitamin K administration along with PCC. Patients taking antiplatelet therapy are treated with platelets or desmopressin, depending on clinician judgement. Finally, FFP, aminocaproic acid, and tranexamic acid all may be employed at clinician discretion for patients with serious bleeding.

Since blood product use is associated with clinical and laboratory determination of serious bleeding, blood product use functioned as an indirect measure of bleeding complications in this study. Our findings indicate patients on warfarin or platelets received significantly more FFP or platelets than the other anticoagulants, respectively. These trends are to be expected as these blood products are indicated in the reversal protocol for the aforementioned anticoagulants. Some have questioned the use of platelets to treat acute hemorrhage in patients on antiplatelet therapy, but that is beyond the scope of this paper [19]. We also found that patients taking DOACs needed fewer blood products overall. The lack of significant difference in reversal agent use between the three classes of anticoagulants shows a consistency in their use. The use of blood products and reversal agents have shown benefits in patients on pre-injury anticoagulants. Specifically, the use of platelets and desmopressin have shown benefit in patients taking antiplatelet medications [20,21]. Furthermore, idarucizumab, recombinant factor Xa, and PCC have all shown benefit in patients taking DOACs [22]. Finally, it has long been known that PCC and vitamin K are effective reversals for warfarin therapy [23]. The consistent use of the reversal agents is most likely a result of the institutional protocol, which uses reversal agents and blood products in an evidence-based manner.

There are limitations to consider with this study. An important population to consider in trauma populations is the combined use of DOACs with antiplatelet agents. The rise of anticoagulation prescriptions has made this combination not rare. Our study intentionally excludes this population in order to study the individual effects that each anticoagulant may have on trauma outcomes. With this in mind, the results may not be generalizable to all patients on anticoagulation, specifically those on multi-drug anticoagulation. A further limitation to this study is the lack of separation of blood product usage in the reversal protocol from blood product usage given due to active bleeding. Future research could specify the indication for blood product usage in order to elucidate more specific trends. This study does not flesh out the use of ROTEM data for indication of reversal agent and blood product usage. A future direction for research would be to describe the utilization of ROTEM in this way. The population studied herein is from a single institution in a rural state, and thus may not exhibit generalizability to other larger, urban centers. Finally, the possible changes over time in reversal agent policy both nationally and institutionally was not taken into account in this study.

Our study describes a profile of warfarin, DOACs, and antiplatelets that has little difference in outcome in a general population of trauma patients. Although our data show a shortened ICU stay for patients on antiplatelets, there is an overall similarity in outcome for the three groups. Our institutional protocol for patients with chronic anticoagulation may explain these results. At our institution, there is a "leveling up" of trauma response when a patient is known to be on antithrombotic treatment. Any patient receiving anticoagulation and over the age of 65 are considered a level 2 trauma, requiring the presence of a trauma attending physician and chief resident within 15 min. As discussed previously, blood products and reversal agents are then given based on clinician judgement, lab values, and the standardized institutional protocol for reversal. This treatment protocol may account for similar safety of the three classes of drugs at our institution.

Conclusion

Our study showed that 7.9 % of trauma admissions in a Level I trauma center were patients on chronic antithrombotic therapies. We found no significant differences in routine clinical outcomes between patients on warfarin and DOACs, and only found a shorter length of ICU stay for antiplatelets versus warfarin. These results indicate a similar safety profile for these groups of medications in a generic trauma population. The varying risk profiles of antithrombotic therapies are likely more pronounced in high-risk categories such as traumatic brain injury, which other studies have previously explored. Institutional safeguards, such as leveling up when treating a patient on antithrombotic therapy, likely contribute to similar outcomes among therapeutic groups.

Author contributions

HJ and HC conceived of the presented idea. KP and ZM helped gain regulatory approval and retrieved data. RR, SL, and SB performed the analytic calculations. BM took the lead in drafting the manuscript with the assistance of MK, KK, JM, and AB. All authors discussed the results and reviewed and edited the final manuscript.

Disclosures

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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