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PROSPECTIVE COHORT STUDY

Dengue Fever in Liver Transplant Recipients: A Report of 3 Cases

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Abstract

Background: The evidence supporting post-endoscopic management of anticoagulation after bleeding is lacking consensus. Many studies favor resumption of agents to mitigate thrombotic risks; however, timing of resumption is also debatable.

Aim: To determine the relation between anticoagulation resumption and bleeding, thrombotic events, and mortality within 90 days after discharge.

Methods: Non-interventional prospective study of all patients in our hospital who were admitted for GI bleeding while on anticoagulation in 2022. The primary outcomes were GI bleeding events, thrombotic events and mortality events within 90 days. We ran a logistic regression analysis to assess correlation between resumption of anticoagulation and primary outcomes. We ran a Mantel-Haenszel analysis between primary outcomes, various bleeding scores to determine a safe timing of resumption in our patient population.

Results: 140 patients met our inclusion criteria. Resumption of anticoagulation was significantly associated with decrease in mortality events while there was no association with bleeding or thrombotic events. Performing an endoscopic evaluation was associated with decrease in mortality events and no association with bleeding or thrombotic events. There was no significant difference in mortality, bleeding or thrombotic events between days of anticoagulation restart.

Conclusion: Resumption of anticoagulation seems to be safe and should be prompt once bleeding is addressed. Performance of endoscopic procedures was associated with decreased mortality even in high-risk patients. Decision and safety of anticoagulation seem to be more dependent on the overall status of the patients after their bleeding events are addressed rather than how it was addressed or how they presented.

Keywords

Anticoagulation, Gastrointestinal bleeding, Mortality, Endoscopy

Introduction

Use of vitamin K antagonists (VKA) and direct oral anticoagulants (DOAC) has increased over the past few decades. Indications for use include prevention of strokes in atrial fibrillation and mechanical valve replacements, as well as prevention and treatment of venous thromboembolism events. Unfortunately, use of anticoagulants can increase bleeding risks. Warfarin was reported by the Food and Drug Administration FDA as one of the top 10 drugs with the largest number of adverse events in the 1990s and 2000s (U.S. Food and Drug Administration, FDA). Rate of hemorrhage was about 3.8% per person-year in patients taking warfarin for atrial fibrillation [1]. The gastrointestinal GI tract was noted in studies to be the most common site of bleeding [2]. Upper GI bleeding appears to be more common than lower GI bleeding [2]. There is a dramatic increase in the use of DOACs with more patients switching from warfarin to DOACs given the decreased need to monitor

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and less interaction with food and other medications. However, there was no significant difference between DOACs and VKAs in the risk of Major GI bleeding [3].

The management of anticoagulation in the setting of GI bleeding requires balancing the thrombotic risk with the hemorrhagic complications. The risk of recurrent GI bleeding after resuming anticoagulation is near 18%, while the thrombotic risks with withholding anticoagulation is around 8%, which makes the decision challenging yet critical.4 The evidence supporting post-endoscopic management of anticoagulation after bleeding is lacking consensus. Many studies favor resumption of agents to mitigate thrombotic risks; however, timing of resumption is also debatable.

The aim of this study is to follow patients who present to our hospital with GI bleeding while on anticoagulation in a prospective fashion. We aim to gather multiple variables that we believe affect the bleeding and thrombosis risks of patients. With this data, we will determine the relation between anticoagulation resumption and bleeding, thrombotic events, and mortality within 90 days after discharge. We will also evaluate the relation between timing of resumption and mentioned outcomes.

Methods

Study design and patient cohort

Non-interventional prospective study of all patients in the Tidal Health system located in Salisbury, Maryland who were admitted for GI bleeding or anemia of GI blood loss while on anticoagulation for various indications in 2022 (January until December). These were collected by following the gastroenterology consultation list on a daily basis. Our cohort included 140 patients who met criteria. We excluded patients with missing data and patients who presented to the emergency department but did not require admission.

Data collection

We first gathered data from multiple variables of interest that in our opinion might affect the bleeding and thrombotic risks in patients. We also collected data on variables that would reflect severity of presentation and might affect the decision regarding anticoagulation resumption. This included data on age, gender, smoking status, comorbidities (Hypertension, diabetes mellitus, chronic kidney disease, chronic liver disease, coronary artery disease, history of cerebrovascular events and congestive heart failure), anticoagulation agent, relevant medications (proton pump inhibitors, antiplatelets agents, aspirin, non-steroidal anti-inflammatory drugs), labs (hemoglobin, platelet level, INR, creatinine, blood urea nitrogen, albumin), vital signs, symptoms on presentation, details of any procedure performed (timing, type of procedure, intervention, location, type of lesion, hemostasis), anticoagulation resumption specifics (timing, agent on restart), and various scores including CHADsVASc, Glascow Blatchford, Oakland and Has-Bled scores for each patient.

Outcome

The primary outcomes were GI bleeding events, thrombotic events (recurrent stroke, deep vein thrombosis, or pulmonary embolism), and mortality events within 90 days of discharge. Our secondary outcomes included resumption of anticoagulation, timing of resuming anticoagulation, and Charlson Comorbidity indices of patients included in the study.

Statistical analysis

We analyzed the data using SPSS application to determine relevant correlations. We first gathered descriptive statistics regarding the incidence of various variables among our general population. Then, we divided our population into two groups; patients who resumed their anticoagulation by the time of discharge versus patients who did not. We compared the two groups using the same variables with the Chi-square analysis for categorical variables and t-test for continuous variables to calculate P-values.

The main bias concern in cohort studies would be confounding bias. To address this, we included all patients who presented to the hospital in 2022. We also ran analysis on different groups of our population to determine significant differences that might affect outcome. We included patients that were provided care by different providers with different approaches. The size of the study was determined by the number of patients who presented in 2022 as we included them all, power analysis was not performed given lack of data to predict our outcome in the literature.

We then ran a logistic regression analysis to assess correlation between resumption of anticoagulation and our primary outcomes (bleeding, thrombotic, and mortality events). We generated 95% confidence intervals along with p-values. A two tailed P-value of < 0.05 was considered significant. We also ran a peripheral analysis using Charlson comorbidity index in our patients and the primary outcomes, performance of procedures, and resumption of anticoagulation to determine any presence of bias in relation to high-risk patients at baseline.

We finally ran a Mantel-Haenszel analysis between primary outcomes, various bleeding scores, and day of resumption of anticoagulation to determine a safe timing of resumption in our patient population.

Results

Baseline characteristics

Our cohort consisted of 140 patients who presented in the year of 2022 with gastrointestinal bleeding or anemia of GI blood loss while on anticoagulation. Mean

age of the population was 73-years-old (range 37-97). 50.7% of patients were males (n = 71) and 64.3% of patients had a smoking history (n = 90). Most of our patients had hypertension (n = 121, 86.4%). 42.8% had chronic kidney disease, (45.7%) had coronary artery disease, 43.5% had diabetes mellitus, and 41% had congestive heart failure. A smaller proportion had a history of strokes (19.3%) and chronic liver disease (7%).

Most of our patients were on Apixaban on presentation (61.4%) followed by Rivaroxaban (20.7%), and Warfarin (10%). 40% of patients were on concurrent proton pump inhibitors. 69.3% of presentations had overt GI bleeding symptoms (melena, hematochezia, hematemesis) and the rest had anemia suspected due to GI blood loss. 63% of patients underwent endoscopic evaluation; however, only half of these procedures included an intervention (33.6%). Overall, there were 25 mortality events in 90 days, 21 GI bleeding events and 8 thrombotic events (stroke, deep vein thrombosis, and pulmonary embolism).

Resumption of anticoagulation

More than half of the patients had their anticoagulation agent restarted by discharge (68.5%). We divided our patient cohort into two groups depending on whether they had their anticoagulation restarted or not. We compared the two groups using the variables collected to assess factors involved in the decision of resuming anticoagulation and to assess impact of these variables on our primary outcomes.

There was no significant difference between the two groups in age, gender, comorbidities, type of anticoagulation, and concurrent medications. There was no difference in procedures performed, interventions taken and laboratory parameters (Table 1).

GI bleeding, thrombotic and mortality events in 90 days

There was no significant correlation between various variables collected and our three primary outcomes

Table 1: Comparison of different variables collected between two groups of patients based on resumption of anticoagulation and their P-values.

Variables	Details	no restart	restart	P-value
Gender (Male)		52%	50%	0.803
Smoking (present)		68%	62.50%	0.515
Alcohol (present)		11.30%	11.40%	0.987
CHF (present)		41%	41.60%	0.933
HTN (present)		84%	87.50%	0.585
DM (present)		45.40%	42.70%	0.761
CLD (present)		9%	6%	0.545
CAD (present)		50%	43.70%	0.491
CVA (present)		18%	19.70%	0.823
CKD (present)		50%	39.50%	0.24
AC on presentation	Warfarin	6.80%	11.40%	0.184
	Eliquis	61.30%	61.40%	
	Xarelto	18.20%	21.80%	
	Dabigatran	2.20%	0%	
	Others	11.40%	7%	
ASA on presentation (present)		25%	29%	0.61
PPI on presentation (present)		47.70%	34.50%	0.206
Procedure	None	41%	35.40%	0.804
	EGD	27.30%	35.40%	
	Colonoscopy	9%	7.30%	
	EGD+Colonoscopy	22.70%	21.80%	
Culprit Lesion	Ulcer	66.00%	57.20%	0.96
	Esophagitis	13.60%	13.50%	
	Variceal bleeding	2.20%	2.00%	
	GAVE	0.00%	1.00%	
	AVM	0.00%	1.00%	
	Hemorrhoids	11.30%	11.50%	
	Diverticular	0.00%	1.00%	

	Malignancy	4.50%	7.30%	
	Dieulafoy	2.20%	3.10%	
	Others	0.00%	2.00%	
Location	Upper	59.00%	54.20%	0.657
	Lower	27.30%	27.00%	
	Small bowel	11.40%	16.60%	
	Unknown	0.00%	2.00%	
Intervention (present)		20.50%	28.10%	0.335
Overt bleeding symptoms (present)		75.00%	66.60%	0.081
Age (mean)		75.8636	72.7917	0.689
GBS (mean)		10.1818	9.7604	0.465
Oakland (mean)		23.12	22.21	0.16
CHADVASc (mean)		4.5143	4.5507	0.345
HASBLED (mean)		3.7273	3.6771	0.982
Hemoglobin on presentation (mean)		7.7000	8.4000	0.244
INR on presentation (mean)		2.3000	2.3000	0.945
Platelets on presentation (mean)		229.0000	239.0000	0.613
Creatinine on presentation (mean)		2.0000	1.7000	0.794
BUN on presentation (mean)		47.0000	37.0000	0.430
Albumin on presentation (mean)		2.9000	2.9000	0.840
SystolicBP on presentation (mean)		123.0000	120.0000	0.440
Heart Rate on presentation (mean)		82.0000	86.0000	0.292

CHF: Congestive Heart Failure; HTN: Hypertension; DM: Diabetes Mellitus; CLD: Chronic Liver Disease; CAD: Coronary Artery Disease; CVA: Cerebrovascular Accident; CKD: Chronic Kidney Disease; AC: Anticoagulation; ASA: Aspirin; PPI: Proton Pump Inhibitor; EGD: Esophagogastroduodenoscopy; GAVE: Gastric Antral Vascular Ectasia; AVM: Arteriovenous Malformation; GBS: Glascow Blatchford Score

Table 2: Correlation between resumption of anticoagulation and our three primary outcomes.

Outcome	P-value (restart/No restart)	Confidence Interval lower	Confidence Interval upper
Mortality	0.001	-0.4	-0.174
Bleeding events	0.188	-0.04	0.215
Thrombosis events	0.689	-0.06	0.1

using linear regression. A minor exception to that was the association found between CKD (p value 0.008, CI 95% 0.05 - 0.363) and hemoglobin (P value 0.017, CI 95% -0.06 - -0.007) with bleeding events.

We ran an analysis to predict the primary outcomes based on resumption of anticoagulation between groups we stratified. Resumption of anticoagulation was significantly associated with decrease in mortality events (P value 0.001, CI 95% -0.04 - -0.174) while there was no association with bleeding or thrombotic events (Table 2).

Primary outcomes were then compared based on the performance of procedures. Performing an endoscopic evaluation was associated with decrease in mortality events (P value 0.025, CI 95% -0.282 - -0.019) and no association with bleeding or thrombotic events.

Charlson comorbidity score and patients with high comorbidity

Charlson comorbidity index can help predict overall prognosis based on age and multiple comorbidities. We calculated Charlson indices to determine high risk patients at baseline. We ran an analysis to see if those baseline risks affected our primary outcomes and decision to perform endoscopy or resume anticoagulation. There was no significant difference between low-risk patients and high-risk patients in the three outcomes mentioned above (Table 3).

Timing of anticoagulation restart

We tried to assess timing of safe resumption of anticoagulation and determine feasibility of predicting this based on multiple scores collected including CHADsVASc, GBS, Oakland, and HAS-BLED scores. This was done using Mantel-Haenszel analysis. The number of patients we had, limited detailed analysis of such outcomes. There was no significant difference in mortality, bleeding or thrombotic events between days of restart stratified based on levels of the four scoring systems. An exception to this was an increase in bleeding events if anticoagulation was restarted after

Table 3: Correlation between Charlson Comorbidity Index and performance of procedures, resumption of anticoagulation and mortality.

Variable	P-value vs Charlson index	Confidence interval lower	Confidence interval upper
Procedure	0.724	-0.048	0.033
Restart of anticoagulation	0.311	-0.05	0.01
Mortality	0.332	-0.016	0.048

Table 4: Mantel-Haenszel analysis between CHADVASc, HAS-BLED, GBS, Oakland scores with timing of anticoagulation resumption and our three primary outcomes.

Day of restart	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
1	0.9	0.28	0.87	0.27	0.449	0.04	0.197	0.59
2	N/A	0.65	0.7	0.53	0.916	0.822	0.29	0.42
3	0.65	N/A	N/A	N/A	N/A	0.833	0.79	0.37
4	0.39	N/A	N/A	N/A	N/A	0.62	0.5	0.32
5	N/A	N/A	N/A	N/A	N/A	0.388	0.09	0.22
6	N/A	N/A	N/A	N/A	N/A	0.08	0.28	0.28
7	N/A	0.59	0.755	0.68	0.342	0.14	0.68	0.34
8	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.15
9	N/A	N/A	N/A	N/A	N/A	0.15	N/A	N/A
10	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
>10	0.5	0.36	0.26	0.36	N/A	0.26	0.36	N/A

(1) CHADVASc vs. thrombotic events; (2) CHADVASc vs. mortality events; (3) HAS-BLED vs. Mortality events; (4) GBS vs. Mortality events; (5) OAKLAND vs. Mortality events; (6) HAS-BLED vs. Bleeding events; (7) GBS vs. Bleeding event; (8) OAKLAND vs. Bleeding events

one day of bleeding in patients with high HAS-BLED scores (Table 4).

We divided restart days into three periods: 1-3 days, 3-7 days, and more than 7 days. We compared between these three periods based on the primary outcomes. No significant difference between various periods and outcomes: Bleeding (P value 0.55, CI 95% -0.03 - 0.02), thrombotic (P value 0.96 CI 95% -0.04 - 0.04), and mortality events (P value 0.59, CI 95% -0.06 - 0.03).

Discussion

Our results were generally consistent with other studies showing safety and a margin of benefit of anticoagulation resumption in terms of mortality. Restarting anticoagulation improved mortality and had no significant impact on bleeding and thrombotic events within 90 days. All included variables were not significantly different between our two groups (patients who resumed anticoagulation versus not) suggesting these variables did not affect the decision for restarting anticoagulation. It also suggests that these two groups are somewhat similar and the mortality benefit is inherent to resumption of anticoagulation. Our study did not show a decrease in thrombotic events; however, this could be due to lack of power as we only had 7 thrombotic events in our cohort.

The decrease in mortality seen in our patients who resumed anticoagulation was also seen in other studies; however, our study did not show any significant increase in rebreeding or decrease in thrombotic events. Qureshi, et al. (2014) showed that mortality was significantly lower in the group where anticoagulation was resumed. This study showed that patients who resumed their agents within 7 days of bleeding had a higher risk of rebreeding. These patients did not have a significant decrease in thrombotic events compared to patients who restarted anticoagulation after 7 days [4]. Wallvik, et al. (2017) showed that specifically related to upper GI bleeding there was a benefit from resuming anticoagulation in lowering thrombotic events and mortality but with increase in recurrent bleeding rates [5]. This was not noted in Patel's study (2018) that included only lower GI bleeding events where no significant benefit in lowering mortality was noted [6] Sengupta, et al. study (2015) followed patients whose anticoagulation's resumption after GI bleeding had lower risk of major thrombotic event, similar risk of re-bleeding and death within 90 days as patients who had their anticoagulation discontinued [7]. Decreased mortality events could be related to a decrease in thrombotic events.

Interestingly, there was also an association with decreased mortality in patients who underwent endoscopic evaluation. We could predict that patients with less comorbidities would be better candidates for procedures and hence better mortality at baseline. However, based on Charlson index comparison between patients who underwent procedures and patients who did not, there was no difference between the two groups. Moreover, there was no association between

performing a procedure and restarting anticoagulation. There seems to be an independent association between procedures and mortality.

As for the timing of resumption, our study did not show a significant difference between chosen periods (less than 3 days, 3-7 days, more than 7 days after stopping). Multiple studies addressed timing of restarting anticoagulation. Qureshi, et al. (2014) study showed no significant increase in bleeding recurrence and no significant increase in thrombotic events if anticoagulation was restated after 7 days of GI bleeding [4]. Witt, et al. (2012) study concluded a similarly high rate of rebleeding if anticoagulation was restarted within the first 7 days after bleeding. This study showed that the death rate was lowest when warfarin therapy was restarted between 15 and 90 days of bleeding. This study concluded that the safest time to restart anticoagulation was around 2 weeks [8].

We tried to include CHADsVASc, HAS-BLED, GBS, and Oakland scores into the timing equation. Although this was limited by the number of patients in our study. These scores did not significantly predict the primary outcomes within 90 days based on timing of restart. An exception to that was that a high HAS-BLED score predicted bleeding on day 1 of restart but not afterwards.

Conclusion

Resumption of anticoagulation in patients hospitalized for GI bleeding while on anticoagulation after their bleeding event is addressed, was associated with a decrease in mortality events within 90 days. Performance of procedures while in the hospital was also independently associated with decreased mortality. Finally, timing of resumption did not correlate with risk of bleeding, thrombotic events nor mortality suggesting safety of resuming agents once signs of bleeding resolved regardless of endoscopic evaluation. Decision and safety of anticoagulation seem to be more dependent on the overall status of the patients after their bleeding events are addressed rather than how it was addressed or how they presented.

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Potential Competing Interest

None declared.

Summary Box

What is already known:

- Resumption of anticoagulation after addressing GI bleeding is based on assessment of risks and benefits of such agents.
- Timing of resumption after bleeding is debatable.

What is new:

- Resumption of anticoagulation is associated with decrease in mortality at 90 days, not associated with increase of bleeding events.
- Performance of endoscopic procedures for bleeding regardless of comorbidities is associated with decrease in mortality independent of restarting anticoagulation.

This study suggests safety of resumption as soon as 2 days after addressing bleeding with or without endoscopy.

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