Early chemoprophylaxis for deep venous thrombosis does not increase the risk of hematoma expansion in patients presenting with spontaneous intracerebral hemorrhage

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INTRODUCTION

Spontaneous intracerebral hemorrhage (ICH) is a significant cause of morbidity and mortality worldwide, with an estimated annual incidence of 300,000–600,000/year in the United States.
alone.\(^5\) Despite improving mortality rates as modern therapies develop, morbidity, and functional outcomes in patients with ICH remain poor.\(^5\) The development of venous thromboembolism (VTE), including deep venous thrombosis (DVT) or pulmonary embolism (PE), is correlated with negative outcomes following ICH,\(^10\) and PE is a leading cause of cardiovascular death in patients with ICH.\(^11,22\) Hemorrhagic stroke is an independent risk factor for the development of VTE, with estimated incidences of about 2% for DVT and 0.5% for PE.\(^12\)

Preventive strategies to reduce the incidence of VTE include early mobilization, the use of intermittent lower extremity compression devices, and chemoprophylaxis in the form of unfractionated heparin (UFH) or low-molecular weight heparin (LMWH).\(^9,15\) Due to the fear of hematoma expansion associated with the use of VTE chemoprophylaxis, there remains significant debate about the optimal timing for its initiation following ICH.\(^11,18\) The American Heart Association (AHA) and American Stroke Association (ASA) provide Class IIb recommendations for the timing of chemoprophylaxis initiation following ICH: 1–4 days from the outset of hemorrhage after the documentation of cessation of bleeding.\(^15\) The most recent guidelines by the Society of Critical Care Medicine and Neurocritical Care Society suggest to initiate chemical DVT prophylaxis within 48 h of admission in case of clinical stability.\(^21\) A meta-analysis evaluating timing on VTE prophylaxis commencement suggests that initiation of chemoprophylaxis at or after 24 h after hemorrhagic stroke, but within the 1st week, does not portend an increased risk for hematoma expansion.\(^23\)

Given the uncertainty of these recommendations pertaining to the optimal time point of initiation of chemical VTE prophylaxis, there is marked variability in practice. In our neurosurgical practice, we adapted a practice standardizing early initiation of chemical DVT prophylaxis, often at the time of admission. This practice is done in an attempt to mitigate the negative effect of VTE on outcomes in patients suffering from ICH. At present, there is no great evidence on the safety profile of early administration of VTE in ICH patients. In this study, we report our findings of this practice. We hypothesized that the risk of hemorrhagic expansion is low, and outweighed by the possible benefit of reducing the incidence of VTE. The aims of this study were threefold: (1) determine the safety profile of early VTE prophylaxis in patients who present to the hospital with spontaneous ICH; (2) determine the risk of hematoma expansion in early implementation of LMWH/UFH as compared to delayed administration; and (3) determine the difference in incidence of DVT/PE in those patients who received early LMWH/UFH as compared to delayed administration.

**MATERIALS AND METHODS**

**Patient selection**

The University of Florida Institutional Review Board (IRB) approved the study protocol before patient enrollment (IRB # 201801414). We queried the hospital billing database to identify patients who were admitted with non-traumatic ICH (ICD 161) between January 1, 2011, and December 31, 2018. Adult patients (age 18 and older) who had been treated at our institution for spontaneous ICH during the study timeframe were retrospectively enrolled under a full waiver of informed consent. Patients were excluded if they had no interval computed tomography (CT) scan available for review, or underwent limitations of care including comfort measures on initial evaluation.

**Data acquisition**

Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Florida.\(^1,14\) Data collected included patient demographics, hematoma volume at admission, hematoma location, interval hematoma volume (hematoma volume at first follow-up surveillance imaging), modified ranking score (mRS) at admission, mRS at 30 days, mRS at 90 days, date of mortality if applicable, history of prior anticoagulant use, DVT/PE present on admission, comorbidities (hypertension [HTN] diabetes mellitus, smoking status, history of DVT/PE, atrial fibrillation, and hypercoagulable state), active use of antiplatelets or anticoagulants (aspirin, clopidogrel, ticagrelor, prasugrel, warfarin, apixaban, and rivaroxaban), initial international normalized ratio (INR), prothrombin time, activated partial thromboplastin time, platelet count, and admitting service.

Early initiation of chemoprophylaxis was defined as initiation on admission to our institution, with the first dose administered within 24 h of admission. VTE chemoprophylaxis was considered “conventional” if the first dose was administered 24–72 h after admission. Hematoma volumes were calculated based on CT scans using the ABC/2 method.\(^19\) Radiology reports were queried to evaluate for hematoma expansion. If the report documented stable hematoma volume, the interval hematoma volume was assumed to be identical to the initial hematoma volume. If the report documented a change in hematoma volume, interval hematoma volumes were calculated by a single reviewer (D.L.).

**Statistical analysis**

We used the \(\chi^2\) test or Fisher exact test to perform univariate comparisons of proportions between early and late VTE prophylaxis cohorts. We used the Wilcoxon rank sum test to
RESULTS

Administration of early and late DVT prophylaxis

Data for 235 patients were available for analysis. 217 patients had complete confounder and outcome data; and 146 patients had complete data for 90-day mRS > 2.

Of those 235 patients, 62.6% (n = 147) were administered early DVT chemoprophylaxis and 37.4% (n = 88) received conventional chemoprophylaxis [Table 1]. Patients admitted to the neurosurgery service were more likely to be administered early chemoprophylaxis (P < 0.0001). Conventional chemoprophylaxis was more likely to be administered by the neurology (P = 0.006) and trauma (P = 0.002) services [Table 1].

Pre-prophylaxis anticoagulant therapy, comorbidity, presenting features, and ICH location

Univariate comparison of pre-prophylaxis rates of anticoagulant use, comorbidities, presenting features, and ICH location between early and late DVT prophylaxis cohorts is displayed in [Table 2]. Only the percentage of patients with COPD differed significantly between patients assigned to early (8.2%) versus late (17.1%) prophylaxis (P = 0.04). Non-significant pre-treatment variables demonstrating mild to moderate imbalance between early and late prophylaxis cohorts included Plavix use (early 12%, late 8%), Eliquis use (early 2% and late 5%), HTN (early 88% and late 92%), hepatic disease (early 3% and late 8%), thrombocytopenia (early 6% and late 11%), INR > 1.4 (early 15% and late 20%), parietal location (early 15% and late 8%), and occipital location (early 4% and late 7%).

There was no standardized mechanism for obtaining surveillance imaging. Imaging was obtained at the discretion of the treating physician. On average, interval non-contrast
CT head was obtained 1.57 days (SD 1.59) after admission, with a range of 1–14 days.

Clinical outcomes – Univariate analysis

Univariate comparisons of the clinical outcomes between early and late DVT prophylaxis cohorts are displayed in [Table 3]. Eleven patients (7.5%) in the early prophylaxis cohort and seven patients (8.0%) in the conventional prophylaxis cohort developed VTE ($P = 0.9$). Hematoma expansion also did not differ significantly (early 19%, conventional 23%, $P = 0.5$). None of the remaining outcome percentages or interval hematoma volume distributions differed significantly between early and late treatment cohorts: interval hematoma volume ($P = 0.3$); 30-day modified Rankin Score > 2 ($P = 0.5$); and 90-day modified Rankin Score > 2 ($P = 0.1$).

Clinical outcomes – Adjustment for confounders

We identified the variables in [Tables 1 and 2] (admitting department and pre-treatment variables) with $P \leq 0.5$ for univariate comparison between early and late DVT prophylaxis. We considered these variables as potential confounders of the effect of early DVT prophylaxis on clinical outcomes. We initially included them in our propensity score model as predictors of a patient’s propensity to be assigned to early DVT prophylaxis (an indicator for neurology admissions was excluded because of its strong inverse correlation with neurosurgery admissions; and an indicator for trauma admissions was excluded because of low frequencies). After fitting the initial propensity score model, we removed any confounder with $P > 0.5$ for testing $OR = 1$. The ORs and $P$-values testing OR=1 for the remaining confounders are displayed in [Table 4]. Admission to neurosurgery ($OR = 5.2; P < 0.0001$) and parietal ICH location ($OR = 2.7; P = 0.06$) most greatly increased a patient’s propensity to be assigned to early prophylaxis. A patient’s propensity for early prophylaxis decreased with increasing initial hematoma volume ($OR = 0.93/5\text{ mL increase}; P = 0.03$). [Table 4] also displays the confounder balance achieved between early and late DVT prophylaxis cohorts using the predicted propensity scores (probabilities) as inverse weights. Effective IPS weighting should balance confounder distributions between cohorts as if the observational study had been conducted as a randomized clinical trial (RCT). Balance of percentages and means between early and late cohorts is greatly improved with IPS weighting across all confounders.

[Table 5] displays the unadjusted and confounder-adjusted prevalence, median interval volumes, ORs, and % differences between medians for clinical outcomes, contrasting the effect of early versus late DVT prophylaxis. Unadjusted prevalence

Table 2: Association of pre-treatment anticoagulant therapy, comorbidity, presenting features, and ICH location with the assignment of early versus late DVT Prophylaxis.

| DVT Prophylaxis | <24 h | >24 h | P-value |
|-----------------|-------|-------|---------|
| Medication      |       |       |         |
| Aspirin         | 67 (45.6%) | 37 (42.1%) | 0.6 |
| Plavix          | 18 (12.2%) | 7 (8.0%) | 0.3 |
| Coumadin        | 17 (11.6%) | 12 (13.6%) | 0.6 |
| Eliquis         | 3 (2.0%) | 4 (4.6%) | 0.4 |
| Xarelto         | 1 (0.7%) | 2 (2.3%) | 0.6 |
| Comorbidities   |       |       |         |
| CAD             | 24 (16.3%) | 15 (17.1%) | 0.9 |
| Diabetes mellitus | 57 (38.8%) | 32 (36.4%) | 0.7 |
| Hypertension    | 130 (88.4%) | 81 (92.1%) | 0.4 |
| Hepatic disease | 5 (3.4%) | 7 (8.1%) | 0.1 |
| COPD            | 12 (8.2%) | 15 (17.1%) | 0.04 |
| Atrial fibrillation | 33 (22.5%) | 22 (25.0%) | 0.7 |
| Presenting features |     |       |         |
| GCS motor<5     | 16 (11.1%) | 8 (9.1%) | 0.6 |
| Thrombocytopenia | 8 (5.5%) | 10 (11.4%) | 0.4 |
| INR>1.4         | 22 (15.1%) | 17 (19.5%) | 0.1 |
| Premorbid mRS>2 | 13 (10.0%) | 9 (11.3%) | 0.8 |
| Initial hematoma volume (median [IQR]) | 9.1 mL (3.3, 10.8 mL) | 21.8 (3.1, 27.2) | 0.5 |
| Location        |       |       |         |
| Frontal         | 18 (12.4%) | 13 (14.8%) | 0.6 |
| Parietal        | 22 (15.2%) | 7 (8.0%) | 0.1 |
| Occipital       | 6 (4.1%) | 6 (6.8%) | 0.4 |
| Temporal        | 17 (11.7%) | 11 (12.5%) | 0.9 |

Comparisons were performed using the χ² test, Fisher exact test, or Wilcoxon rank sum test. Median and interquartile range are displayed for Initial Hematoma Volume.

ICH: Intra-cranial hemorrhage, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, GCS: Glasgow Coma Scale, INR: International normalized ratio, mRS: modified rankin score, IQR: Inter-quartile range, DVT: Deep venous thrombosis

Table 3: Univariate comparison of clinical outcomes between patients receiving early (<24 h post-ICH) versus late (>24 h post-ICH) DVT Prophylaxis.

| Clinical outcome | DVT Prophylaxis | <24 h | >24 h | P-value |
|------------------|-----------------|-------|-------|---------|
| Developed DVT/PE | 11 (7.5%) | 7 (8.0%) | 0.9 |
| Hematoma expansion | 26 (19.3%) | 19 (22.9%) | 0.5 |
| 30-day mRS>2     | 94 (66.7%) | 53 (62.4%) | 0.5 |
| 90-day mRS>2     | 48 (54.6%) | 33 (54.1%) | 1.0 |
| Interval hematoma volume (median [IQR]) | 9.4 mL | 11.2 mL | 0.3 |
| Change in hematoma volume from baseline (median [IQR]) | 0.0 mL | 0.0 mL | 0.5 |

Comparisons were performed using the χ² test or Wilcoxon rank sum test. IQR: Inter-quartile range, PE: Pulmonary embolism, DVT: Deep venous thrombosis

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and median interval volumes were similar to those listed in [Table 3]. Equivalence test P-values to determine if the outcomes for early DVT prophylaxis fell within the equivalence ranges specified in [Table 5] were all non-significant (P > 0.10).

Consistent with the univariate comparisons from [Table 3], none of the unadjusted early versus late ORs or % differences differed significantly from 1 to 0, respectively [Table 5]. Confounder-adjusted estimates of prevalence, median interval volume, ORs and % differences shifted minimally relative to corresponding unadjusted point estimates, but these adjusted effects of early versus late DVT prophylaxis remained non-significant. Adjusted ORs for binary clinical outcomes included DVT/PE development (OR = 1.2; P = 0.8), hematoma expansion (OR = 0.7; P = 0.3), 30-day mRS > 2 (OR = 1.5; P = 0.2), and 90-day mRS > 2 (OR = 1.1; P = 0.8). The adjusted % difference between early and late median interval hematoma volume was −27% (P = 0.2, suggesting that on average there was a trend for the hematoma volume to be less on surveillance CT scans in patients who had received early DTV chemoprophylaxis.

Because we observed almost no statistically significant equivalence or effects of early DTV prophylaxis on clinical outcomes relative to late prophylaxis, we retrospectively determined the power our sample sizes had to declare equivalence within the ranges specified in [Table 5]. Depending on the prevalence or standard deviation of the outcome, power to declare equivalence within the ranges specified ranged from 0.01% to 38% (2-sided α = 0.10). Total sample sizes required to have 80% power to declare equivalence ranged from 1033 to 2129 patients.

These calculations suggest that our study was inadequately powered to declare equivalence between early and late DVT prophylaxis as they influence clinical outcomes. With regard to detecting positive or negative effects of early DVT prophylaxis relative to late treatment, our study had adequate power to detect relatively large effects. However, our study was sufficiently powered to demonstrate equivalence in numeric values (median interval hematoma volume and median change in hematoma volume from baseline). When adjusting for confounders, our study was sufficiently powered to demonstrate equivalence of an interval hematoma volume of 4.7 mL or greater and a change in hematoma volume of within 1.1 mL between patients receiving early and conventional DVT chemoprophylaxis.

**DISCUSSION**

In the present study, we demonstrated that in this patient population there was no significant risk of early administration of VTE chemoprophylaxis on hematoma expansion following ICH. More specifically, our study was sufficiently powered to suggest equivalence of about one milliliters of volumetric expansion between patients receiving early and conventional VTE prophylaxis. Furthermore, our study was sufficiently powered to suggest total volumetric equivalence of ICH between early and conventional VTE prophylaxis groups within 5 mL. The previous studies have defined hematoma expansion as greater than six milliliters[10] as such, it is reasonable to conclude that the present study is...
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**Table 5: Unadjusted and confounder-adjusted ORs and % differences between medians for clinical outcomes, contrasting the effects of early versus late DVT prophylaxis.**

| Binary clinical outcome | Confounder adjustment | <24 h | >24 h | Min. Signif. equivalence range P<0.10 | Early versus Late OR (95% CI) | OR=1 P-value |
|-------------------------|-----------------------|-------|-------|-------------------------------------|-------------------------------|-------------|
| Developed DVT/PE        | Unadjusted            | 7.5%  | 8.3%  | ±6%                                 | 0.9 (0.3 – 2.5)              | 0.08        |
|                         | IPS-weighted          | 7.6%  | 6.6%  | ±8%                                 | 1.2 (0.4 – 3.4)              | 0.8         |
| Hematoma expansion      | Unadjusted            | 19.5% | 23.3% | ±10%                                | 0.8 (0.4 – 1.6)              | 0.5         |
|                         | IPS-weighted          | 19.7% | 26.9% | ±14%                                | 0.7 (0.3 – 1.4)              | 0.3         |
| 30-day mRS>2            | Unadjusted            | 66.2% | 62.7% | ±12%                                | 1.2 (0.7 – 2.1)              | 0.6         |
|                         | IPS-weighted          | 68.6% | 59.2% | ±18%                                | 1.5 (0.9 – 2.6)              | 0.2         |
| 90-day mRS>2            | Unadjusted            | 54.0% | 54.2% | ±12%                                | 1.0 (0.5 – 1.9)              | 0.9         |
|                         | IPS-weighted          | 53.6% | 51.6% | ±14%                                | 1.1 (0.5 – 2.3)              | 0.8         |

| Numeric clinical outcome | Confounder adjustment | <24 h | >24 h | Min. Signif. Equivalence Range P<0.10 | Early versus Late % Difference (95% CI) | % Diff=0 P-value |
|--------------------------|-----------------------|-------|-------|-------------------------------------|------------------------------------------|-----------------|
| Interval hematoma volume (median) | Unadjusted            | 7.3 mL | 10.3 mL | ±4.9 mL                               | -29% (−55%, +10%)                       | 0.1             |
|                         | IPS-weighted          | 7.4 mL | 10.0 mL | ±4.7 mL                               | -27% (−54%, +17%)                       | 0.2             |
| Change in hematoma volume from baseline (median) | Unadjusted            | +0.2 mL | +0.9 mL | ±0.2 mL                               | -6% (−24%, +16%)                        | 0.6             |
|                         | IPS-weighted          | +0.4 mL | +2.6 mL | ±1.1 mL                               | -18% (−50%, +34%)                       | 0.4             |

n=217 patients available with complete confounder and outcome data; n=146 patients with complete data for 90-day mRS>2 outcome. ORs and 95% CIs were estimated using logistic regression; % differences between medians with 95% CIs were estimated using linear regression with lognormal errors. The OR=p and % difference~0 P-values test whether the estimated ORs differ from 1 or the % differences differ from 0. IPS weighting was used to adjust for confounding [Table 4]. The equivalence test tests the hypothesis that the early and late DVT prophylaxis outcomes fall within pre-specified equivalence ranges. The minimum significant equivalence ranges listed in the table are the narrowest ranges that would result in the declaration of equivalence between early and late DVT prophylaxis outcomes at a significance level of α=0.10. IPS: Inverse propensity score, DVT: Deep venous thrombosis, PE: Pulmonary embolism, OR: Odds Ratio, CI: Confidence interval

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sufficiently powered to demonstrate equivalence in the rate of hematoma expansion between both groups. Presenting hematoma volume and use of coumadin are positive factors associated with hematoma expansion.[6] In the present study population, there was no significant difference between these two confounders in patients who received early versus conventional timing of VTE prophylaxis. Due to the retrospective study design, any baseline differences between groups were controlled for using propensity scoring analysis.[10]

Hemorrhagic stroke is an independent risk factor for the development of venous thromboembolic events, with an estimated incidence of about 2%.[12] Beyond its effect on patient morbidity and mortality, these events are now tracked by regulatory agencies such as the Agency for Healthcare Research and Quality and the Center for Medicare and Medicaid Services as a quality metric to serve as a point of comparison between clinicians and between hospitals.[20] Annual costs related to VTE are estimated to be upwards of 30 billion dollars.[7] Early mobilization, the use of intermittent pneumatic compression devices and chemoprophylaxis is accepted measures to reduce the occurrence of DVT/PE.[9] Enthusiasm for early chemoprophylaxis to reduce the rate of VTE events following ICH is tempered by the fear of potentiating hematoma expansion, and resultant neurologic deficit, increased requirements for ICU care, and increased length of stay. Currently accepted guidelines recommend the implementation of anticoagulation as early as 24 h following ICH, following documentation of stable hematoma.[15] There is significant equipoise amongst clinicians as to the ideal time to initiate VTE prophylaxis following neurosurgical procedures, though some meta-analyses argue for its safe use in neurosurgical patients.[8,16,17] However, the 2019 recommendations put forth by the American Society of Hematology recommend against VTE chemoprophylaxis for patients undergoing major neurosurgical procedures.[2]

The present study suggests that early chemoprophylaxis, that is, within 24 h of admission does not result in worse outcomes. Our departmental practice of early chemoprophylaxis is unique even within our institution and was instituted due to the high overall morbidity index in our tertiary care center patient population, as evidenced by a rate of symptomatic thromboembolism at 8%, which is greater than the estimated incidence of 2% patients presenting with hemorrhagic stroke.[12] Our findings show that early chemoprophylaxis did not result in an increased rate of hematoma expansion in this patient population. The rate of symptomatic thromboembolic events was similar between both groups, about 8%. Cardiovascular disease is one of the greatest risk factors associated with the development of VTE.[3] About 90% of patients in the current study presented with comorbid HTN. As an academic medical center, the patients presenting to our institution are increasingly complex and are more likely to have multiple chronic conditions and be uninsured.[24] It is our belief that our patients are at increased risk of developing...
VTE, which is consistent with the relatively high rate of VTE encountered in the present study. We, therefore, elected to devise a treatment protocol with the early implementation of VTE prophylaxis.

CONCLUSION

The use of early UFH or LMWH for prophylaxis against venous thromboembolic events following ICH appears safe in our patient population without increasing the risk of hematoma expansion. Our study is sufficiently powered to demonstrate equivalence of the risk of hematoma expansion between early and conventional chemoprophylaxis. Larger, prospective, and randomized studies are necessary to better elucidate the risk of early chemoprophylaxis and potential reduction in venous thromboembolic events. This would help clarify the external validity of the results of our single institution, retrospective study.

Limitations

Our study is limited by sample size, precluding our ability to draw conclusions on clinical outcome as related to rate of venous thromboembolic events and functional independence as determined by Modified Rankin Scale. Due to the retrospective nature of this study, there was no standardized mechanism to screen patients for DVT/PE. As such, the incidence of DVT/PE is the result of investigative studies ordered by the treating physician on the suspicion of a thromboembolic event. Clinically silent VTE events are unaccounted for. Furthermore, the retrospective nature of this study does not provide a standardized protocol for surveillance cranial imaging. In an attempt to mitigate biases inherent to the study design, we performed propensity matching; therefore, any effect is unlikely to be related to differences in patient comorbidities between the early and conventional VTE chemoprophylaxis groups.

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Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Conflicts of interest

There are no conflicts of interest.

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