ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

www.surgicalneurologyint.com

Surgical Neurology International

Editor-in-Chief: Nancy E. Epstein, MD, Clinical Professor of Neurological Surgery, School of Medicine, State U. of NY at Stony Brook.

SNI: Neurovascular

Editor
Kazuhiro Hongo, MD
Shinshu University, Matsumoto, Japan

SNI
Open Access

Original Article

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

Dimitri Laurent[1], Olgert Bardhi[1], Paul Kubilis[1], Brian Corliss[1], Stephanie Adamczak[1], Ndi Geh[1], William Dodd[1], Sasha Vaziri[1], Katharina Busl[2], W. Christopher Fox[3]

[1]Department of Neurosurgery, Lillian S. Wells, University of Florida, [2]Department of Neurology, University of Florida, Gainesville, [3]Department of Neurosurgery, Mayo Clinic, Jacksonville, Florida, United States.

E-mail: *Dimitri Laurent - dimitri.laurent@neurosurgery.ufl.edu; Olgert Bardhi - olgert@ufl.edu; Paul Kubilis - paul.kubilis@neurosurgery.ufl.edu; Brian Corliss - brianmatthew.corliss@neurosurgery.ufl.edu; Stephanie Adamczak - stephanie.adamczak@neurosurgery.ufl.edu; Ndi Geh - ndi.geh@neurosurgery.ufl.edu; William Dodd - wsdodd@ufl.edu; Sasha Vaziri - sasha.vaziri@neurosurgery.ufl.edu; Katharina Busl - katharina.busl@neurology.ufl.edu; W. Christopher Fox - fox.chris@mayo.edu

***Corresponding author:**
Dimitri Laurent,
Department of Neurosurgery,
Lillian S. Wells, University of Florida, Gainesville, FL 32608, United States.

dimitri.laurent@neurosurgery.ufl.edu

Received : 02 February 2021
Accepted : 29 April 2021
Published : 14 June 2021

DOI
10.25259/SNI_100_2021

Quick Response Code:

ABSTRACT

Background: Spontaneous intracerebral hemorrhage (ICH) is a significant cause of morbidity and mortality worldwide. The development of venous thromboembolism (VTE), including deep venous thrombosis or pulmonary embolism, is correlated with negative outcomes following ICH. Due to the risk of hematoma expansion associated with the use of VTE chemoprophylaxis, there remains significant debate about the optimal timing for its initiation following ICH. We analyzed the risk of early chemoprophylaxis on hematoma expansion following ICH.

Methods: We performed a retrospective analysis of patients presenting with spontaneous ICH at single institution between 2011 and 2018. The rate of hematoma expansion was compared between patients that received early chemoprophylaxis (on admission) and those that received conventional chemoprophylaxis (>24 h).

Results: Data for 235 patients were available for analysis. 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%, $P = 0.5$).

Conclusion: The use of early chemoprophylaxis against venous thromboembolic events following ICH appears safe in our patient population without increasing the risk of hematoma expansion. Given the increased risk of poor outcome in the setting of VTE, early VTE chemoprophylaxis should be considered in patients who present with ICH. Larger, prospective, and randomized studies are necessary to better elucidate the risk of early chemoprophylaxis and potential reduction in venous thromboembolic events.

Keywords: Intracerebral hemorrhage, Deep venous thrombosis, Hematoma expansion, pulmonary embolism, Venous thromboembolism

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,[1] and PE is a leading cause of cardiovascular death in patients with ICH.[4,22] 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 mechanical 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 I61) 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.[13,14] 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 χ^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

test for shift in the early versus late distributions of numeric variables (e.g., initial hematoma volume, and interval hematoma volume). We used logistic regression to estimate odds ratios (ORs) with 90% confidence intervals (CIs) to show the effect of early versus late treatment on binary clinical outcomes. We used linear regression with lognormal errors to estimate the % difference between early versus late median interval hematoma volumes. Within the framework of these outcome models, we carried out TOST equivalence tests to determine if early and late VTE prophylaxis could be declared equivalent within a pre-specified range (e.g., ±5%, ±10%). The equivalence test generates a *P*-value for the null hypothesis that the early VTE prophylaxis outcomes fall outside a pre-specified range bracketing the late treatment outcomes. $P < 0.10$ would indicate equivalence between early and late treatment cohorts.

Because of the observational nature of our study, we also considered the possible influence of confounding on equivalence tests and effect size estimates. To avoid over-fitting our outcome models, we chose to adjust for confounding by developing an early VTE prophylaxis propensity score model. The propensity score model is a multi-predictor logistic regression model incorporating relevant confounders as predictors of a patient's propensity (probability) for assignment to early DVT prophylaxis. The predicted propensity scores are used as inverse weights in the clinical outcome models to adjust for confounding. OR and *P*-values testing OR=1 in the propensity score model indicate the effects of confounders on a patient's propensity to be assigned to early DVT prophylaxis. Effective inverse propensity score (IPS) weighting should balance confounder distributions between cohorts as if the observational study had been conducted as a randomized controlled trial (RCT). We initially considered all pre-treatment variables that had a univariate $P \leq 0.5$ for difference between early and late treatment cohorts. After initially fitting a logistic regression model containing these confounders, we then excluded predictors from the model with $P > 0.5$ and refit a final propensity score model. We used the propensity scores from this model as inverse weights in our outcome models, and contrasted unadjusted equivalence tests and estimated ORs with confounder adjusted tests and estimates generated through IPS weighting.

To put negative findings in proper context, we retrospectively calculated the power our study had to declare equivalence between pre-specified ranges, and the power to detect an OR > 1.5 (or < 0.67). We also estimated the sample sizes needed to detect these characteristics with 80% power and two-sided $\alpha = 0.10$. Finally, we estimated the effect sizes (ORs, % differences) that our study could detect at 80% power. All calculations were performed using SAS Version 9.4 (SAS Institute, Cary NS), R Version 3.5.1 (R Core Team, Vienna, Austria), and PASS Version 16.0.4 (NCSS, LLC. Kaysville, Utah).

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

Table 1: Administration of DVT Prophylaxis.

	<24 h	>24 h	Total
DVT Prophylaxis (heparin)	147 (62.6%)	88 (37.4%)	235
			***P*-value**
Department			
Neurosurgery	61 (41.5%)	15 (17.1%)	<0.0001
Neurology	72 (49.0%)	59 (67.1%)	0.006
Internal Medicine	11 (7.5%)	8 (9.1%)	0.7
Trauma	0 (0.0%)	5 (5.7%)	0.002

Early DVT prophylaxis administered to 147 out of 235 patients. ICH patients admitted to the Neurosurgery Department were more likely to be administered early DVT prophylaxis; late prophylaxis was more likely to be administered by the Neurology and Trauma Departments.
DVT: Deep venous thrombosis

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).

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, 21.8)	10.8 mL (3.1, 27.2)	0.5
ICH 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 χ^2 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

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 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 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 (2.9, 23.5)	11.2 mL (3.6, 27.2)	0.3
Change in hematoma volume from baseline (median [IQR])	0.0 mL (0.0, 0.0)	0.0 mL (0.0, 0.0)	0.5

Comparisons were performed using the χ^2 test or Wilcoxon rank sum test. IQR: Inter-quartile range, PE: Pulmonary embolism, DVT: Deep venous thrombosis

Table 4: Features of the early DVT prophylaxis propensity score model and multivariate confounder balance achieved between early versus late DVT prophylaxis cohorts by IPS weighting.

Early DVT prophylaxis propensity score model			Relative frequencies by PPX timing			
			Unadjusted		IPS-Weighted	
Confounder	**OR**	**OR=1 *P*-value**	**<24 h**	**>24 h**	**<24 h**	**>24 h**
Neurosurgery Department	4.8	<0.0001	41.4%	15.5%	31.8%	33.8%
Eliquis	0.4	0.3	2.3%	3.6%	2.1%	2.1%
Hepatic disease	0.6	0.5	3.8%	8.3%	7.3%	6.3%
COPD	0.5	0.2	7.5%	15.5%	10.0%	10.0%
Thrombocytopenia	0.7	0.5	6.0%	11.9%	9.1%	8.0%
Parietal	2.6	0.06	15.8%	8.3%	12.9%	10.1%
Occipital	0.5	0.4	3.0%	7.1%	5.8%	5.3%
Initial hematoma volume (median)	0.93/+5 mL	0.03	9.1 mL	10.8 mL	8.9 mL	8.2 mL

The propensity score model is a multi-predictor logistic regression model incorporating the listed confounders as predictors of a patient's propensity (probability) for assignment to early DVT prophylaxis. The predicted propensity scores are used as inverse weights in the clinical outcome models to adjust for confounding. ORs and *P*-values testing OR = 1 indicate the effects of confounders on a patient's propensity to be assigned to early DVT prophylaxis. Effective IPS weighting should balance confounder distributions between cohorts as if the observational study had been conducted as a RCT.
IPS: Inverse propensity score, COPD: Chronic obstructive pulmonary disease, DVT: Deep venous thrombosis, OR: Odds Ratio

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 DVT chemoprophylaxis.

Because we observed almost no statistically significant equivalence or effects of early DVT 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 $\alpha = 0.10$). Total sample sizes required to have 80% power to declare equivalence within the ranges specified ranged from 468 to 1079 patients. Minimum ORs (or their inverses) that could be detected with 80% power ranged from 2.1 to 3.1 (2-sided $\alpha = 0.10$). Power to detect an OR > 1.5 (or <0.67) ranged from 20% to 39%. Total sample sizes required to detect an OR > 1.5 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;[6] as such, it is reasonable to conclude that the present study is

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)	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=1 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

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 of 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.

Acknowledgments

We would like to thank Kimberly Foli with her help with obtaining IRB approval.

Declaration of patient consent

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

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Adams HP, Jr., del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, *et al*. Guidelines for the early management of adults with ischemic stroke: A guideline from the American heart association/American stroke association stroke council, clinical cardiology council, cardiovascular radiology and intervention council, and the atherosclerotic peripheral vascular disease and quality of care outcomes in research interdisciplinary working groups: The American academy of neurology affirms the value of this guideline as an educational tool for neurologists. Circulation 2007;115:e478-534.
2. Anderson DR, Morgano GP, Bennett C, Dentali F, Francis CW, Garcia DA, *et al*. American society of hematology 2019 guidelines for management of venous thromboembolism: Prevention of venous thromboembolism in surgical hospitalized patients. Blood Adv 2019;3:3898-944.
3. Andersson T, Söderberg S. Incidence of acute pulmonary embolism, related comorbidities and survival; analysis of a Swedish national cohort. BMC Cardiovasc Disord 2017;17:155.
4. Balami JS, Buchan AM. Complications of intracerebral haemorrhage. Lancet Neurol 2012;11:101-18.
5. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, *et al*. Heart disease and stroke statistics-2018 update: A report from the American heart association. Circulation 2018;137:e67-492.
6. Brouwers HB, Chang Y, Falcone GJ, Cai X, Ayres AM, Battey TW, *et al*. Predicting hematoma expansion after primary intracerebral hemorrhage. JAMA Neurol 2014;71:158-64.
7. Centers for Disease Control and Prevention. Venous thromboembolism in adult hospitalizations United States, 2007-2009. MMWR Morb Mortal Wkly Rep 2012;61:401-4.
8. Collen JF, Jackson JL, Shorr AF, Moores LK. Prevention of venous thromboembolism in neurosurgery: A metaanalysis. Chest 2008;134:237-49.
9. Dennis M, Sandercock P, Reid J, Graham C, Forbes J, Murray G. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): A multicentre randomised controlled trial. Lancet (London, England) 2013;382:516-24.
10. Egleston BL, Uzzo RG, Beck JR, Wong YN. A simple method for evaluating within sample prognostic balance achieved by published comorbidity summary measures. Health Serv Res 2015;50:1179-94.
11. Flibotte JJ, Hagan N, O'Donnell J, Greenberg SM, Rosand J. Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage. Neurology 2004;631059-64.
12. Gregory PC, Kuhlemeier KV. Prevalence of venous thromboembolism in acute hemorrhagic and thromboembolic stroke. Am J Phys Med Rehabil 2003;82:364-9.
13. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, *et al*. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform 2019;95:103208.
14. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform

2009;42:377-81.
15. Hemphill JC 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, *et al*. Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the American heart association/ American stroke association. Stroke 2015;46:2032-60.
16. Iorio A, Agnelli G. Low-molecular-weight and unfractionated heparin for prevention of venous thromboembolism in neurosurgery: A meta-analysis. Arch Intern Med 2000;160:2327-32.
17. Khan NR, Patel PG, Sharpe JP, Lee SL, Sorenson J. Chemical venous thromboembolism prophylaxis in neurosurgical patients: An updated systematic review and meta-analysis. J Neurosurg 2018;129:906-15.
18. Kiphuth IC, Staykov D, Kohrmann M, Struffert T, Richter G, Bardutzky J, *et al*. Early administration of low molecular weight heparin after spontaneous intracerebral hemorrhage. A safety analysis. Cerebrovascular diseases (Basel, Switzerland) 2009;27:146-150.
19. Kothari RU, Brott T, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M, *et al*. The ABCs of measuring intracerebral hemorrhage volumes. Stroke 1996;27:1304-5.
20. Laurent D, Freedman R, Cope L, Sacks P, Abbatematteo J, Kubilis P, *et al*. Impact of extent of resection on incidence of postoperative complications in patients with glioblastoma. Neurosurgery 2020;86:625-30.
21. Nyquist P, Jichici D, Bautista C, Burns J, Chhangani S, DeFilippis M, *et al*. Prophylaxis of venous thrombosis in neurocritical care patients: an executive summary of evidence-based guidelines: A statement for healthcare professionals from the neurocritical care society and society of critical care medicine. Crit Care Med 2017;45:476-9.
22. Ogata T, Yasaka M, Wakugawa Y, Inoue T, Ibayashi S, Okada Y. Deep venous thrombosis after acute intracerebral hemorrhage. J Neurol Sci 2008;272:83-6.
23. Paciaroni M, Agnelli G, Venti M, Alberti A, Acciarresi M, Caso V. Efficacy and safety of anticoagulants in the prevention of venous thromboembolism in patients with acute cerebral hemorrhage: A meta-analysis of controlled studies. J Thromb Haemost 2011;9:893-8.
24. Szekendi MK, Williams MV, Carrier D, Hensley L, Thomas S, Cerese J. The characteristics of patients frequently admitted to academic medical centers in the United States. J Hosp Med 2015;10:563-8.

How to cite this article: Laurent D, Bardhi O, Kubilis P, Corliss B, Adamczak S, Geh N, *et al*. Early chemoprophylaxis for deep venous thrombosis does not increase the risk of hematoma expansion in patients presenting with spontaneous intracerebral hemorrhage. Surg Neurol Int 2021;12:277.