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Ambulatory Status Protects Against Venous Thromboembolism in Acute Mild Ischemic Stroke Patients

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Abstract

Introduction—Ischemic stroke patients are at high risk (up to 18%) for venous thromboembolism. We conducted a retrospective cross-sectional study to understand the predictors of acute post-mild ischemic stroke patient's ambulatory status and its relationship with venous thromboembolism, hospital length of stay, and in-hospital mortality.

Methods—We identified 522 patients between February 2006 and May 2014 and collected data about patient demographics, admission NIHSS, venous thromboembolism prophylaxis, ambulatory status, diagnosis of venous thromboembolism, and hospital outcomes (length of stay, mortality). Chi-square tests, t-test and Wilcoxon Ranks Sum tests, and binary logistic regression were used for statistical analysis as appropriate.

Results—A total of 61 (11.7%), 48 (9.2%), and 23 (4.4%) mild ischemic stroke patients developed venous thromboembolism, deep venous thrombosis, and pulmonary embolism, respectively. During hospitalization, 281 (53.8%) patients were ambulatory. Independent predictors of in-hospital ambulation were being married (OR 1.64, 95% CI 1.10–2.49), being non-religious (OR 2.19, 95% CI 1.34–3.62), admission NIHSS (per unit decrease in NIHSS; OR 1.62, 95% CI 1.39–1.91), and non-usage of mechanical venous thromboembolism prophylaxis (OR 1.62, 95% CI 1.02–2.61). After adjusting for confounders, ambulatory patients had lower rates of venous thromboembolism (OR 0.47, 95% CI 0.25–0.89), deep venous thrombosis (OR 0.36, 95%

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Conflicts of Interest
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CI 0.17–0.73), prolonged length of hospital stay (OR 0.24, 95% CI 0.16–0.37), and mortality (OR 0.43, 95% CI 0.21–0.84).

Conclusions—Our findings suggest that for hospitalized acute mild ischemic stroke patients, ambulatory status is an independent predictor of venous thromboembolism (specifically deep venous thrombosis), hospital length of stay, and in-hospital mortality.

Keywords

Ischemic stroke; ambulation; ambulatory status; venous thromboembolism; deep vein thrombosis; pulmonary embolism; protection; odds ratio

Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE), characterized as venous thromboembolisms (VTE), are major preventable post-stroke complications leading to prolonged hospital stay and increased in-hospital mortality. [1] Prophylaxis against VTEs encompass pharmacological (unfractionated heparin, low-molecular weight heparin) and non-pharmacological treatments (pneumatic compression devices, repetitive electrical stimulation, ambulation). [2] Among the myriad of VTE risk factors, non-ambulatory status is a major concern for stroke patients. [3] A magnetic resonance direct thrombus imaging study by Kelly and colleagues identified non-ambulatory stroke patients as being at high risk for developing VTE. [4] With over 50% of stroke patients unable to walk immediately after stroke, [5, 6] ambulation may be a key factor in preventing post-stroke VTE.

However, ambulation during hospitalization may be underutilized as a VTE prophylaxis. Recent work showed that over 93% of hospitalized acute stroke patients are sedentary, [7] even though these patients had physician clearance to ambulate. Although there is current work underway for determining whether early mobilization should be conducted during acute stroke, [8] there is limited information concerning the relationship between in-hospital ambulation and the rates of post- mild stroke VTE during index hospitalization.

We conducted a retrospective cross-sectional study to determine if ambulation has a protective benefit against VTEs in acute mild stroke patients admitted to an academic medical center. We hypothesized that ambulatory acute stroke patients would have lower rates of VTE, DVT, and PE compared to non-ambulatory patients. Our secondary aims were to identify predictors of in-hospital ambulation and study the effect of ambulation on patient’s length of hospital stay and in-hospital mortality.

Methods

We conducted a retrospective analysis of consecutive acute stroke patients who were admitted to the University of Kansas Hospital (UKH) between February 2006 and May 2014. This duration corresponds to the amount of time the Get with the Guidelines-Stroke (GWTGS) [9] initiative has been in use at UKH. The GWTGS is a quality improvement program voluntarily used in hospitals. University of Kansas Medical Center’s (KUMC) Institutional Review Board (IRB) approved the study.

We included patients with age more than 18 years and a diagnosis of acute mild ischemic stroke (defined as National Institutes of Health Stroke Scale (NIHSS) score less than 5) confirmed by neuroimaging (CT or MRI head). Patients without recorded NIHSS and with no match of medical records in the Healthcare Enterprise Repository for Ontological Narration (HERON) database were excluded.

KUMC established an i2b2 based HERON database, a clinical data repository derived from electronic medical records providing electronic access to all patients' clinical, laboratory, and nursing flowsheets. The HERON database is designed to integrate clinical and biomedical data for translational resource purposes, and is used for a variety of research purposes ranging from clinical trials to retrospective studies. [10] Data was obtained from the combination of the GWTGS database and the HERON database. Data included patient demographics, medical history, admission NIHSS, mechanical VTE prophylaxis (intermittent pneumatic compression device or venous foot pumps), chemical VTE prophylaxis (low dose unfractionated heparin, low molecular weight heparin, or warfarin), VTE, DVT, PE, in-hospital mortality, length of hospitalization (based on the median value of 3 days, this data point was dichotomized as normal (less than equal to 3 days) or prolonged (more than 3 days)), and ambulatory status (ambulated with physical therapy and without assistance) during hospitalization (yes/no). Right and left leg weakness was assessed based on the leg weakness component of the NIHSS. A score of 0 was considered no weakness, and a score of 1 or 2 was considered weakness.

Statistical Analysis

Data was analyzed using JMP version 11 (SAS Institute Inc.) for Windows. For univariate analysis, continuous variables were summarized using their mean and standard deviations or median and interquartile range, and categorical variables were summarized using their frequency counts and percentages. For univariable analysis, chi-square tests were used to test for associations between categorical covariates. Based on whether the normality assumption was valid or not, we used t-test or Wilcoxon Rank Sum test to compare continuous variables between ambulatory and non-ambulatory groups. All significant variables ($p<0.10$) from the univariable analysis were further assessed via binary multivariable logistic regression. We fit six separate regression models for the following outcomes; in-hospital ambulation, DVT and/or PE, DVT without PE, and PE without DVT, length of stay, and mortality. Odds ratios along with their corresponding 95% confidence intervals (CI) are presented to measure the effect size of ambulation on odds of having a VTE during hospitalization, as well as the odds of length of stay and mortality. A p-value below 0.05 was considered statistically significant.

Results

A total of 1908 acute ischemic stroke patients were admitted at UKH between February 2006 and May 2014. Seventy-seven percent (1474/1908) of these had a documented NIHSS in the GWTGS database. Fifty-three percent (781/1474) of patients had NIHSS less than 5. Sixty-seven percent (522/781) of patients were matched correctly to their flowsheet data in HERON which made our final study cohort.

Participant characteristics and comparisons between ambulatory and non-ambulatory patients are presented in Table-1. There were 281 (53.8%) ambulatory patients and 241 (46.2%) non-ambulatory patients.

In univariable analysis, ambulatory patients were younger than non-ambulatory patients (62.2 years vs 65.1 years, p value= 0.01). Ambulatory patients also were more likely to be married (55.2% vs 43.6%, p= 0.008), non-religious (27.8% vs 16.6%, p=0.002), and had a prior normal ambulatory status (99.6% vs 97.4%) as compare to non-ambulatory patients. There was no significant difference between the two groups in terms of sex, body mass index, and race. Medical co-morbidities were also similar between two groups except that coronary artery disease was less often seen in the ambulatory group (22.4% vs 32.4%, p= 0.01) as compare to the non-ambulatory group. Stroke severity as measured by NIHSS was milder in the ambulatory group than the non-ambulatory group (1.5 vs 2.3, p= <0.0001). Ambulatory group had less often left (5.3% vs 14.1%, p= 0.0006) or right (5.0% vs 9.1%, p= 0.06) leg weakness than non-ambulatory group. There was no difference in chemical VTE prophylaxis between the two groups. There was a trend towards less mechanical VTE prophylaxis in the ambulatory group (70.8%) as compare to the non-ambulatory group (77.6%) (p= 0.08).

In multivariable analysis (Table-2), we found being married (OR 1.64, 95% CI 1.10–2.49), being non-religious (OR 2.19, 95% CI 1.34–3.62), having lower admission NIHSS (per unit change in NIHSS; OR 1.62, 95% CI 1.39–1.91), and absence of mechanical VTE prophylaxis (OR 1.62, 95% CI 1.02–2.61) as independent predictors of in-hospital ambulation (model-1). In this model, we adjusted for all other significant predictors of univariable analysis (age, race, overweight, baseline ambulation, and history of coronary artery disease).

Outcome comparison of ambulatory and non-ambulatory mild ischemic stroke patients

A total of 61 (11.7%, 95% CI 9.2–14.7), 48 (9.2%, 95% CI 7.0–12.0), and 23 (4.4%, 95% CI 3.0–6.5) patients developed VTE, DVT, and PE, respectively. Ten patients had both DVT and PE. In univariable analysis, comparing to non-ambulatory group, ambulatory group had less rate of VTE (7.5% vs 16.6%, p= 0.001), DVT (5.3% vs 13.7%, p= 0.001), and PE (3.2% vs 5.8%, p= 0.15). Ambulatory group had less mortality (6.8% vs 20.8%, p<0.0001) and shorter length of stay (LOS more than 3 days in 27.8% in the ambulatory vs 63.1% in non-ambulatory group, p<0.0001) than the non-ambulatory group.

In multivariable analysis (Table-3), ambulatory patients had lower rates of VTE (OR 0.47, 95% CI 0.25–0.89; model-2) and DVT (OR 0.36, 95% CI 0.17–0.73; model-3) adjusting for all significant predictors of univariable analysis (age, race, marriage, religious inclination, overweight, baseline ambulation, history of coronary artery disease, admission NIHSS, and mechanical VTE prophylaxis). The ambulatory group did not have significantly lower rates of PE (OR 0.88, 95% CI 0.33–2.37; model-4) after adjusting all the predictors. Race was not included in model-4 as there were not enough cases (5 or more) of PE sub-classified by ambulation status in each race group.

In a second model (Table-3), we studied the effect of ambulation on patients' length of stay and in-hospital mortality. In the multivariable analysis, adjusting for all significant predictors of univariable analysis (age, race, marriage, religious inclination, overweight, baseline ambulation, history of coronary artery disease, admission NIHSS, in-hospital mechanical VTE prophylaxis, and in-hospital venous thromboembolism) prolonged length of stay (OR 0.24, 95% CI 0.16–0.37; model-5) and mortality (OR 0.43, 95% CI 0.21–0.84; model-6) were noted to be lower in the ambulatory group.

Discussion

To our knowledge, this is the largest cross-sectional study to investigate the relationship of ambulatory status with rate of VTE in MIS patients. Our findings are important as we showed that even in the mild stroke patients, in-hospital ambulation leads to lower rates of VTE, reduced length of stay, and less mortality as compared to sedentary patients, controlling for potential confounders. Although we found a protective effect of ambulation on VTE and DVT, we did not see that effect on PE, which could be due to the low event rate of PE in our group. Venous thromboembolism is one of the preventable in-hospital conditions defined by the Centers for Medicare and Medicaid Service. [11] Although stroke related VTE is not currently affected by the reimbursement, it is vital to improve care of our patients to prevent these conditions.

Recent work by Stecker and colleagues [12] using their GWTGS database suggested that hospital ambulatory status may be related to a lower rate of VTE development in univariate analysis but not in a multivariable model. They had a smaller sample size of 33 VTE events (1.3%) which could have been their limiting factor in identifying ambulation as a protective factor in a multivariable model. The VTE rate of 1–3% may be underdiagnosed in the GWTGS database as it is dependent on manual chart review. [12, 13] The DVT rate in ischemic stroke patients may vary from 1% to 18% depending on the screening methods, symptomatic or asymptomatic DVT, inclusion of transient ischemic attacks in study cohort, stroke severity, timing of DVT assessment, and use of chemical prophylaxis. [4, 14–16] Our study used the HERON database, enabling us to reduce chances of missing VTE diagnosis as HERON provided discharge diagnosis of VTE using physician documentation and also billing data. Hence, using HERON is more accurate and time efficient than manual chart review. Our rate of DVT (9.2%) was similar to previously reported rates of 8–9% DVT in this population. [14, 15] Kong et al found lower d-dimer levels in ambulatory stroke patients (OR: 0.47, 95% CI 0.30–0.72), which further strengthens our hypothesis that ambulation leads to lower VTE rates. [15]

We identified being married, being non-religious, lower admission NIHSS, and absence of mechanical VTE prophylaxis as significant independent predictors of in-hospital ambulation. A study from the members of the MacArthur Successful Aging cohort identified marriage to be protective against age-related decline in productive activities similar to our cohort. [17] Only 13% of stroke patients were found to be active within the first 2 weeks of acute stroke, and they were alone > 60% of the time. [18] A spouse is generally an involved caregiver which may translate into increased motivation for enhanced activity level. It is not clear why non-religious people would be more likely to ambulate than religious stroke patients. It may be related to the sense of independence, freedom, and inner peace in non-religious patients leading to more motivation to ambulate. [19] Stroke severity, especially lower extremity weakness, has been previously reported to be a predictor of walking recovery after an acute stroke similar to our study. [20] Although mechanical VTE prophylaxis (intermittent pneumatic compression device or venous foot pumps) is one of the mainstays for VTE prophylaxis in stroke patients, it also acts as a mechanical restraint keeping people in a bed or chair. We have noticed that it restricts patients' mobility in and out of the bed, making it more harmful for patients who are at low risk for VTE and are able to ambulate.

There is an urgent need for using post-stroke in-hospital ambulation as a VTE prophylaxis measure because over 93% of hospitalized acute stroke patients were found to be sedentary. [7] This is surprising, as ambulation is perceived to be safe by stroke professionals. This perception is based on a survey of 202 professionals in Australia where 40% of respondents favored mobilizing ischemic stroke patients within 24 hours of stroke onset. The majority of the respondents believed that ambulation improves patients' motor and cognitive outcome and reduces risk of depression. [21] In our center, we involve physical therapists for assessing acute ischemic stroke patients' ambulation from the first day of hospitalization. Physical therapists or patients' bedside nurse get them out of bed after the first 24 hours, depending on their ability to bear weight and amount of assistance required. We also use mechanical VTE prophylaxis (intermittent pneumatic compression device or venous foot pumps) or chemical VTE prophylaxis (low dose unfractionated heparin, low molecular weight heparin, or warfarin) for most of our patients. Few patients who are fully ambulatory and do not meet criteria for being high risk VTE patients are not on any chemical or mechanical VTE prophylaxis. [22]

Limitations of our study include the retrospective nature of data collection. Although the HERON database [10] is well structured and reduces the potential for missing data, it also relies on coding and diagnosis by several different healthcare providers, which can lead to potential measurement bias. We did not capture whether the DVT, PE, or VTE seen in our patients was clinically significant or just asymptomatic, nor do we have information on what type of DVT screening was used to determine incidence of DVT. Further, the GWTGS database does not account for whether chemical prophylaxis, mechanical prophylaxis or compression stockings were used. The exact timing and amount of ambulation for each individual patient was also not captured which may also be a potential confounder for VTE prevention. The amount of ambulation may be an important factor in post-stroke rehabilitation care as there is no consensus as to what the appropriate dose or timing of ambulation is needed to mitigate post-stroke complications. [23] A prospective observational study of timing (since stroke onset), type (standing on the bedside, with or without assistance), amount (how many minutes a day), and duration of ambulation in acute stroke patients is much needed to overcome these potential barriers.

Conclusion

Our study showed that hospitalized mild ischemic stroke patients are at a high risk for VTE, and in-hospital ambulation in these patients is related to lower VTE rate, length of hospital stay, and in-hospital mortality. Future, prospective observational studies are needed to confirm our findings, to understand the barriers in ambulation of acute stroke patients, and to understand the timing, type, amount, and duration of post-stroke ambulation to improve clinical outcomes for our patients.

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Table-1

Univariable Analysis of Mild Ischemic Stroke Patients

	Total (n = 522)	Ambulatory (n = 281)	Non-ambulatory (n = 241)	*p*-value
Demographics				
Age, mean (SD), years	66.0 (13.2)	62.2 (13.0)	65.1 (14.1)	0.01
Sex, F:M	247:275	127:154	120:121	0.29
Body mass index, mean (SD), kg*m^{-2}	29.4 (6.5)	29.4 (6.0)	29.4 (7.1)	0.99
Race, n (%)[b]				0.07
Black	114 (21.8)	51 (18.2)	63 (26.1)	
White	351 (67.2)	200 (71.2)	151 (62.7)	
Other	57 (10.9)	30 (10.7)	27 (11.2)	
Married at time of stroke, n (%)	260 (49.8)	155 (55.2)	105 (43.6)	0.008
Non-religious, n (%)	118 (22.6)	78 (27.8)	40 (16.6)	0.002
Prior normal ambulation	506 (98.6)	279 (99.6)	227 (97.4)	0.03
Medical History, n (%)				
Atrial fibrillation and/or flutter	64 (12.3)	31 (11.0)	33 (13.7)	0.36
Coronary artery disease	141 (27.0)	63 (22.4)	78 (32.4)	0.01
Carotid stenosis	28 (5.4)	12 (4.3)	16 (6.6)	0.23
Diabetes Mellitus	170 (32.6)	90 (32.0)	80 (33.2)	0.78
Dyslipidemia	251 (48.1)	130 (46.3)	121 (50.2)	0.37
Hypertension	417 (80.0)	226 (80.4)	191 (79.3)	0.74
Prior Stroke or TIA	128 (24.5)	68 (24.2)	60 (24.9)	0.85
Overweight (BMI>25)	349/488 (71.5)	198/264 (75.0)	151/224 (67.4)	0.06
Smoker	162 (31.0)	92 (32.7)	70 (29.1)	0.36
NIHSS, total (SD)	1.9 (1.3)	1.5 (1.2)	2.3 (1.3)	< 0.0001
Right Leg weakness, n (%)	36 (6.9)	14 (5.0)	22 (9.1)	0.06
Left Leg weakness, n (%)	49 (9.3)	15 (5.3)	34 (14.1)	0.0006
VTE prophylaxis, mechanical	386 (74.0)	199 (70.8)	187 (77.6)	0.08
VTE prophylaxis, chemical	371 (71.1)	202 (71.9)	169 (70.1)	0.66
Outcomes, n (%)				
VTE	61 (11.7)	21 (7.5)	40 (16.6)	0.001
DVT	48 (9.2)	15 (5.3)	33 (13.7)	0.001
PE	23 (4.4)	9 (3.2)	14 (5.8)	0.15
Prolonged length of stay (>3 days)	230 (44)	78 (27.8)	152 (63.1)	< 0.0001
Mortality	69 (13.2)	19 (6.8)	50 (20.8)	< 0.0001

Abbreviations: DVT = deep vein thrombosis; IQR= Interquartile Range; NIHSS = National Institutes of Health Stroke Scale; PE = pulmonary embolism; VTE = venous thromboembolism.

Table-2

Multivariable Analysis*: The Effect of Patient's Characteristics on In-Hospital Ambulation in Mild Ischemic Stroke Patients

Predictors of in-hospital ambulation	Odds Ratio	95% Confidence Interval
Married	1.64	1.10–2.49
Non-religious	2.19	1.34–3.62
Lower NIHSS (per unit change)	1.62	1.39–1.91
No mechanical VTE prophylaxis	1.62	1.02–2.61

*The model was adjusted for age, race, overweight, baseline ambulatory status, and history of coronary artery disease (significant predicators from univariable analysis).

Table-3

Multivariable Analysis: The Effect of Ambulation on In-Hospital Outcomes in Mild Ischemic Stroke Patients

In-Hospital Outcome	Odds Ratio	95% Confidence Interval
Venous thromboembolism *	0.47	0.25–0.89
Deep venous thrombosis *	0.36	0.17–0.73
Pulmonary embolism **	0.88	0.33–2.37
Length of stay more than 3 days ***	0.24	0.16–0.37
In-hospital mortality ***	0.43	0.21–0.84

* These models were adjusted for age, race, marriage, religious inclination, overweight, baseline ambulation, history of coronary artery disease, admission NIHSS, and mechanical VTE prophylaxis.

** This model was adjusted for age, marriage, religious inclination, overweight, baseline ambulation, history of coronary artery disease, admission NIHSS, and mechanical VTE prophylaxis.

*** These models were adjusted for age, race, marriage, religious inclination, overweight, baseline ambulation, history of coronary artery disease, admission NIHSS, in-hospital mechanical VTE prophylaxis, and in-hospital venous thromboembolism.