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Contemporary Trends in the Treatment of Mild Ischemic Stroke with Intravenous Thrombolysis: Paul Coverdell National Acute Stroke Program

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Abstract

Background: Presentation with mild symptoms is a common reason for intravenous thrombolysis (IVT) nonuse among acute ischemic stroke (AIS) patients. We examined the impact of IVT on the outcomes of mild AIS over time.

Methods: Using the Paul Coverdell National Stroke Program data, we examined trends in IVT utilization from 2010 to 2019 among AIS patients presenting with National Institutes of Health Stroke Scale (NIHSS) scores ≥ 5 . Outcomes adjudicated included rates of discharge to home and ability to ambulate independently at discharge. We used generalized estimating equation models to examine the effect of IVT on outcomes of AIS patients presenting with mild symptoms and calculated adjusted odds ratio (AOR) with 95% confidence intervals (CI).

Results: During the study period, 346,762 patients presented with mild AIS symptoms. Approximately 6.2% were treated with IVT. IVT utilization trends increased from 3.7% in 2010 to 7.7% in 2019 ($p < 0.001$). Patients treated with IVT had higher median NIHSS scores upon presentation (IVT 3 [2, 4] vs. no IVT 2 [0, 3]). Rates of discharge to home (AOR 2.06, 95% CI: 1.99–2.13) and ability to ambulate at time of discharge (AOR 1.82, 95% CI: 1.76–1.89) were higher among those treated with IVT.

Conclusion: There was an increased trend in IVT utilization among AIS patients presenting with mild symptoms. Utilization of IVT increased the odds of being discharged to home and the ability to ambulate at discharge independently in patients with mild stroke.

Keywords

Mild stroke; Outcomes; Stroke; Thrombolysis

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Author Contributions

Each author has made substantial contribution to this article, revised the article, and gave final approval of this article for submission to this journal.

Statement of Ethics

Data utilized in this study were from a deidentified database.

Conflict of Interest Statement

G.A. has nothing to disclose. X.T. has nothing to disclose. S.M.C.K. has nothing to disclose. M.G.G. has nothing to disclose.

Background

A majority of patients with acute ischemic stroke (AIS) present with mild neurological symptoms upon initial presentation [1–3]. Mild stroke has previously been defined as low scores on the National Institutes of Health Stroke Scale (NIHSS) [4, 5]. However, up to 30% of these AIS patients presenting with mild symptoms have functional disability at 90 days after the stroke [1–3, 6, 7]. This is likely because low NIHSS scores do not necessarily exclude disabling symptoms, such as aphasia, hemianopsia, and monoparesis [6, 8]. Timely utilization of intravenous thrombolysis (IVT) for AIS is an evidence-based recommendation among patients who present within 4.5 h of symptom onset in an effort to reduce chances of permanent disability [9]. However, presentation with mild stroke symptoms is the most commonly cited reason for nonuse of IVT among patients who are otherwise eligible based on time of presentation [1, 2, 4, 7, 8]. We examine the most recent trends and factors associated with IVT utilization among AIS patients presenting with mild stroke symptoms.

Methods

Our study population included patients admitted with AIS presenting with mild stroke symptoms from 2010 to 2019 within the Paul Coverdell National Acute Stroke Program (PCNASP). The PCNASP is supported by the Centers for Disease Control and Prevention (CDC) and is an ongoing acute stroke quality improvement program that provides feedback to states in order to improve quality of care for patients across the stroke care continuum. Within our study period, hospitals in 12 states (Arkansas, California, Georgia, Iowa, Massachusetts, Michigan, Minnesota, New York, North Carolina, Ohio, Washington, and Wisconsin) participated in the PCNASP. Hospital participation within each state is voluntary. Trained abstractors from participating hospitals collected detailed information on stroke and transient ischemic attack admissions concurrent with admission or soon after hospital discharge using standard data definitions provided by the CDC [10, 11]. This study was approved by the CDC Institutional Review Board (#5373).

We estimated IVT utilization as the percent of AIS admissions with mild stroke severity. Mild stroke severity was defined as NIHSS scores ≤ 5 based on previous studies [1, 2, 6, 7]. Demographic information of patients included in the study comprised age, sex, and race/ethnicity. Baseline clinical characteristics of patients studied included stroke severity upon presentation (as defined by the NIHSS score), ambulatory status prior to stroke, history of a previous stroke, hypertension, dyslipidemia, coronary artery disease, heart failure, diabetes mellitus, atrial fibrillation, or current tobacco use. Insurance status information was also collected and included private, Medicaid, Medicare, or no insurance/self-pay. We compared outcomes of patients receiving IVT to those who did not receive IVT. Favorable outcomes were defined as rates of discharge to home and ability to ambulate independently at time of discharge. Adverse outcome measures included rates of symptomatic intracranial hemorrhage (sICH), life-threatening or serious systemic hemorrhage, or in-hospital death.

Statistics were expressed as means with standard error, medians with interquartile range, and frequency (percentages). Categorical variables were compared between groups using 2-tailed Fisher's exact or χ^2 tests. Continuous variables were compared using the Wilcoxon-

Mann-Whitney rank or Kruskal-Wallis tests. We examined trends of IVT utilization across the study period based on the Cochran-Armitage test. To account for the clustering of patients within hospitals, generalized estimating equations (GEE) were used to assess the association between the outcomes (discharge to home and ability to ambulate independently at discharge) and the effect of IVT among ischemic stroke patients presenting with mild symptoms who received IVT. In GEE multivariable modeling using unstructured correlation structure, we included age, sex, race/ethnicity, arrival by emergency medical services, insurance status, NIHSS score, prior stroke, medical history of hypertension, dyslipidemia, MI/CAD, heart failure, diabetes, atrial fibrillation, and current smoker. Because patients were clustered within hospitals, to provide appropriate estimates of the standard errors, the hospital was treated as a cluster variable in the model. Adjusted odds ratios (AOR) were obtained, along with 95% confidence intervals (CI), and a p value <0.01 was considered statistically significant. All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA).

Results

From 2010 to 2019, there were 346,762 AIS patients presenting with mild stroke symptoms (NIHSS ≥ 5) reported from 670 participating hospitals in PCNASP (Table 1). There were 21,648 patients (median age 67 [57, 77] years, 45.3% women) who received IVT, and 325,114 patients (median age 70 [60, 80] years, 47.1% women) who did not receive IVT. Emergency medical service (EMS) utilization was higher among patients who received IVT (IVT 59.2% vs. no IVT 36.7%). Patients treated with IVT had higher median NIHSS scores upon presentation (IVT 3 [2, 4] vs. no IVT 2 [0, 3]). Patients who did not receive IVT had higher proportions of comorbidities (Table 1). The proportion of patients able to ambulate at time of discharge was higher among those who received IVT (IVT 65.7% vs. no IVT 62.0%; AOR 1.82 [95% CI: 1.76–1.89], Table 2). The proportion of patients discharged to home was higher among those treated with IVT (IVT 69.0% vs. no IVT 62.7%; AOR 2.06 [95% CI: 1.99–2.13]). Among those who received IVT, the proportion of patients with sICH was 2.0% and with life-threatening or serious systemic hemorrhage was 0.8%.

We observed an increased trend in IVT utilization for mild AIS from 2010 to 2019 ($p < 0.001$, Table 3). Younger patients were more likely to receive IVT for mild stroke symptoms when compared to those aged 85 years or older (Table 4). Women were less likely to receive IVT. We did observe racial/ethnic variations in IVT utilization. Hispanic patients were more likely (AOR 1.10 [95% CI: 1.03–1.19]) but non-Hispanic Black patients were less likely (AOR 0.71 [95% CI: 0.68–0.74]) to receive IVT for mild stroke when compared to non-Hispanic White patients. Patients arriving by EMS were much more likely to receive IVT for mild stroke symptoms as compared to those who arrived by a private vehicle (AOR 2.55 [95% CI: 2.47–2.62]). Patients with lower NIHSS scores were less likely to receive IVT than those presenting with NIHSS scores of 5 (Table 4). Patients with Medicare (AOR 0.78 [95% CI: 0.75–0.81]) and Medicaid (AOR 0.66 [95% CI: 0.62–0.70]) and those without insurance (AOR 0.62 [95% CI: 0.58–0.67]) were less likely to receive IVT for mild stroke symptoms than those with private insurance. Patients with prior stroke, hypertension, heart failure, diabetes, atrial fibrillation, and who are current smokers were less likely to receive IVT compared to their counterparts.

Discussion

We report increasing IVT utilization among patients presenting with mild stroke symptoms from 2010 to 2019. This is concurrent with the overall increase in IVT utilization among all AIS patients regardless of contraindications [12]. Most recently, it has been estimated that patients presenting with mild symptoms account for approximately 4 out of 10 patients treated with IVT [13]. Adverse events including sICH and life-threatening or serious systemic hemorrhage in our analysis were low and consistent with other studies [3, 8]. The PRISMS (Potential of rTPA for Ischemic Strokes With Mild Symptoms) study concluded that among patients with minor nondisabling AIS, treatment with IVT compared to aspirin did not increase the likelihood of long-term favorable functional outcome [1]. Therefore, our observed trend suggests that IVT utilization among mild strokes may be related to perceived disabling symptoms.

Patients presenting with an NIHSS score of 0–4 were less likely to receive IVT as compared to those presenting with NIHSS scores of 5, with the lower adjusted odds of receiving IVT with decreases in NIHSS scores. Levine and colleagues [4] contend that several criteria used for exclusion from IVT in clinical trials, including presentation with mild stroke symptoms, were not based on actual data or operationally defined for use in clinical practice. Even further, Martin-Schild and colleagues [14] maintain that while NIHSS scores can correlate with infarct size, clinical severity, and long-term outcomes, they are weighted heavily toward deficits caused by the anterior circulation. The NIHSS does not capture some ischemic stroke syndromes, often those within the posterior circulation that can be disabling [14].

While patients with mild stroke symptoms who receive IVT had a higher chance of being discharged home and ambulating independently in our study, a noticeable proportion were not able to be discharged directly home or ambulate independently, even with IVT. Our results are similar to Saber and colleagues [13], who reported that IVT increased the chances of being discharged home. However, our findings also support those reported by others that despite low NIHSS scores, a noticeable minority of patients were unable to be discharged home despite IVT utilization [3, 7, 15]. This may be the result of low NIHSS scores but with deficits that include aphasia, hemianopsia, or monoparesis [6, 8]. Further, patients presenting with NIHSS scores of 0 can still have observed neurological deficits, including truncal ataxia, decreased visual acuity, and memory impairments, that can contribute to long-term disability [14]. Patients who present with mild deficits may develop neurological worsening or complications associated with their medical comorbidities that can increase the risk of long-term disability [1, 2, 15].

Racial/ethnic disparities are observed in all aspects of stroke care [16]. In an urban population study, Hsia and colleagues [17] reported that Black patients were one-third less likely than White patients to receive IVT. Contributing factors to this lower likelihood of utilization affecting Black patients include a higher chance of fulfilling exclusion criteria and a lower chance of presenting within the therapeutic time window [17]. In addition, Mendelson and colleagues [16] found that over 7% of eligible AIS patients refused IVT, many of whom were Black patients and independently accounted for lower rates of IVT among Black patients. These factors may have contributed to our observed lower odds of

IVT among non-Hispanic Black patients presenting with mild stroke in our study. Using administrative data, investigators have reported decreased IVT utilization rates among Black and Hispanic patients when compared to White patients [13, 18]. However, we found that Hispanic patients presenting with mild stroke symptoms were more likely to receive IVT as compared to non-Hispanic White patients. Addressing social determinants of health may help impact racial/ethnic disparities in stroke outcomes [19].

Younger patients were more likely to receive IVT for mild symptoms with the highest magnitude of IVT utilization among those aged 18–54 years. Investigators recently reported that younger patients were more likely to be treated with IVT, which was likely related to fewer comorbidities and more comfort in treating younger patients with perceived lower risk of sICH [3, 20]. Dodds and colleagues [20] also reported that despite higher likelihood of IVT utilization among younger patients, these patients did experience longer door to needle times. This in part could be related to lower utilization rates of EMS among younger patients [21]. We found that arriving to hospitals by EMS increased the likelihood of IVT utilization for mild strokes; EMS arrival to the hospital can increase the efficiencies in stroke workup, including faster stroke team activation and image acquisition times that can lead to faster door to needle times [21].

Medicare and Medicaid beneficiaries and those without insurance or self-pay were less likely to receive IVT than those with private insurance for mild stroke. Medicaid beneficiaries, who are low income by definition, and those without insurance or who are self-pay may delay seeking care due to mild symptoms in hopes that they do not need medical attention that would result in hospitalization costs [22]. Seeking medical attention as soon as possible should be encouraged based on Levine and colleagues' [4] analysis in which they concluded that the chances of complete resolution of stroke symptoms (thereby resulting in a diagnosis of transient ischemic attack) is <2% per hour after symptoms persist for at least 1 h beyond onset. Further disparities based on insurance status for the treatment of mild stroke should be explored.

Important strengths of our study include the large number of patients and the multistate data from a variety of hospitals collected during regular care delivery. The PCNASP does not collect NIHSS subitem scores; therefore, we are unaware of what presenting symptoms prompted IVT utilization or exclusion from IVT. We did not determine if patients were excluded from IVT due to mild stroke symptoms as multiple reasons can be selected in our database to exclude patients from IVT, which could lead to confirmatory bias in our study. In the absence of large vessel occlusion data, we did not study the impact of intra-arterial treatment of mild strokes. Reporting bias may exist since participation in PCNASP is voluntary, but participating hospitals make an effort to abstract all stroke cases in order to minimize this bias [23]. A formal outcome scale was not available in our study to ascertain long-term disability, such as the 90-day modified Rankin Scale score, but it has been shown that discharge destination can act as a surrogate for standard outcome scales and be highly predictive in determining rates of death and disability [24, 25].

Conclusion

We found an increasing trend in IVT utilization among patients presenting with mild symptoms from 2010 to 2019. Younger patients and those who arrived at the hospital via EMS were most likely to receive IVT. Utilization of IVT increased odds of discharge to home and the ability to ambulate at discharge independently. Future nationwide trends could be informative, and continued public health efforts in improving emergent stroke treatments and promoting timely practice changes in hospitals are recommended.

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Data Availability Statement

All data generated and analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Table 1. Baseline and clinical characteristics associated with IVT utilization among patients presenting with mild stroke symptoms, 2010–2019

Variables	IVT	No IVT	<i>p</i> value
<i>N</i> (%)	21,648 (6.2)	325,114 (93.8)	
Median [IQR] age, years	67 (57, 77)	70 (60, 80)	<0.0001
Age in groups <i>n</i> (%), years			
18–54	4,333 (20.0)	49,956 (15.4)	<0.001
55–64	4,835 (22.3)	67,428 (20.7)	<0.001
65–74	5,570 (25.7)	81,499 (25.1)	0.030
75–84	4,537 (21.0)	76,787 (23.6)	<0.001
85+	2,373 (11.0)	49,444 (15.2)	<0.001
Women, <i>n</i> (%)	9,810 (45.3)	153,180 (47.1)	<0.001
Race, <i>n</i> (%)			
Non-Hispanic White	15,898 (73.4)	236,396 (72.7)	0.020
Non-Hispanic Black	3,196 (14.8)	55,822 (17.2)	<0.001
Hispanic	938 (4.3)	11,772 (3.6)	<0.001
Other race	1,616 (7.5)	21,124 (6.5)	<0.001
Insurance, <i>n</i> (%)			
Medicaid	1,572 (7.3)	24,642 (7.6)	0.087
Medicare	12,038 (55.6)	201,286 (61.9)	<0.001
Private	7,142 (33.0)	84,056 (25.9)	<0.001
Self-pay/no insurance	896 (4.1)	15,130 (4.7)	<0.001
Arrival by EMS, <i>n</i> (%)	12,817 (59.2)	119,342 (36.7)	<0.001
Median [IQR] NIHSS score	3 (2–4)	2 (0–3)	<0.001
NIHSS score in groups, <i>n</i> (%)			
0	1,155 (5.3)	85,391 (26.3)	<0.001
1	2,235 (10.3)	68,159 (21.0)	<0.001
2	3,817 (17.6)	61,832 (19.0)	<0.001
3	4,702 (21.7)	46,436 (14.3)	<0.001
4	5,177 (23.9)	36,272 (11.2)	<0.001
5	4,562 (21.1)	27,024 (8.3)	<0.001

Variables	IVT	No IVT	p value
Past medical history, <i>n</i> (%)			
Prior stroke	3,777 (17.4)	75,504 (23.2)	<0.001
Hypertension	14,986 (69.2)	247,336 (76.1)	<0.001
Dyslipidemia	10,179 (47.0)	163,551 (50.3)	<0.001
MICAD	4,490 (20.7)	74,733 (23.0)	<0.001
Heart failure	1,482 (6.8)	27,350 (8.4)	<0.001
Diabetes mellitus	5,835 (27.0)	112,054 (34.5)	<0.001
Atrial fibrillation	2,596 (12.0)	49,885 (15.3)	<0.001
Current smoker	4,069 (18.8)	66,624 (20.5)	<0.001
Able to ambulate independently prior to event, <i>n</i> (%)	19,775 (91.3)	294,779 (90.7)	<0.001
Outcomes			
Able to ambulate independently at discharge	14,213 (65.7)	201,583 (62.0)	<0.001
Discharge to home	14,947 (69.0)	203,885 (62.7)	<0.001
In-hospital death	273 (1.3)	2,716 (0.8)	<0.001
Symptomatic ICH	438 (2.0)	NA	NA
Life-threatening or serious systemic hemorrhage	66 (0.3)	NA	NA

ICH, intracranial hemorrhage; IVT, intravenous thrombolysis; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale.

Table 2.

Effect of IVT utilization for mild stroke symptoms on outcomes, 2010–2019

	OR (95% CI)	AOR (95% CI)*
Discharge to home	1.33 (1.29, 1.37)	2.06 (1.99, 2.13)
Ability to ambulate independently at discharge	1.30 (1.26, 1.35)	1.82 (1.76, 1.89)

IVT, intravenous thrombolysis.

* Adjusted by age, sex, race/ethnicity, arrival by emergency medical services, insurance status, National Institutes of Health Stroke Scale score, prior stroke, and medical history of hypertension, dyslipidemia, MI/CAD, heart failure, diabetes, atrial fibrillation, and current smoker.

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Table 3.

Trends in IVT utilization by year among patients presenting with mild stroke symptoms (2010–2019)

	2010 (N = 10,843)	2011 (N = 14,241)	2012 (N = 16,925)	2013 (N = 27,629)	2014 (N = 34,987)	2015 (N = 36,890)	2016 (N = 40,397)	2017 (N = 47,629)	2018 (N = 56,839)	2019 (N = 60,382)	p value for trend
Use of IVT (%)	400 (3.7)	538 (3.8)	653 (3.9)	1,335 (4.8)	1,696 (4.9)	2,042 (5.5)	2,610 (6.5)	3,383 (7.1)	4,363 (7.7)	4,628 (7.7)	<0.001

IVT, intravenous thrombolysis.

Table 4.

Factors associated with IVT utilization for mild stroke symptoms, 2010–2019

	OR (95% CI)	AOR (95% CI)*
Age		
18–54 years	1.81 (1.72, 1.90)	2.73 (2.56, 2.92)
55–64 years	1.49 (1.42, 1.57)	2.13 (2.01, 2.27)
65–74 years	1.42 (1.36, 1.50)	2.03 (1.92, 2.14)
75–84 years	1.23 (1.17, 1.30)	1.54 (1.46, 1.62)
85 years	Ref	Ref
Sex		
Women	0.93 (0.90, 0.96)	0.97 (0.94, 0.99)
Men	Ref	Ref
Race/ethnicity		
Non-Hispanic Black	0.85 (0.82, 0.89)	0.71 (0.68, 0.74)
Hispanic	1.18 (1.11, 1.27)	1.13 (1.05, 1.21)
Others	1.14 (1.08, 1.20)	1.05 (0.99, 1.11)
Non-Hispanic White	Ref	Ref
Arrival by EMS		
Yes	2.50 (2.43, 2.57)	2.55 (2.47, 2.62)
No	Ref	Ref
NIHSS score		
0	0.08 (0.075, 0.086)	0.08 (0.07, 0.08)
1	0.19 (0.18, 0.20)	0.19 (0.18, 0.20)
2	0.37 (0.35, 0.38)	0.37 (0.35, 0.39)
3	0.60 (0.57, 0.63)	0.61 (0.58, 0.63)
4	0.85 (0.81, 0.88)	0.85 (0.82, 0.89)
5	Ref	Ref
Insurance status		
Medicare	0.70 (0.68, 0.73)	0.66 (0.62, 0.70)
Medicaid	0.75 (0.71, 0.79)	0.78 (0.75, 0.81)
None/self-pay	0.70 (0.65, 0.75)	0.62 (0.58, 0.67)
Private	Ref	Ref
Prior stroke		
Yes	0.70 (0.67, 0.72)	0.64 (0.62, 0.67)
No	Ref	Ref
Hypertension		
Yes	0.71 (0.69, 0.73)	0.80 (0.77, 0.83)
No	Ref	Ref
Dyslipidemia		
Yes	0.88 (0.85, 0.90)	1.10 (1.07, 1.13)
No	Ref	Ref
MI/CAD		

	OR (95% CI)	AOR (95% CI)*
Yes	0.88 (0.85, 0.91)	1.02 (0.99, 1.06)
No	Ref	Ref
Heart failure		
Yes	0.80 (0.76, 0.84)	0.89 (0.84, 0.94)
No	Ref	Ref
Diabetes mellitus		
Yes	0.70 (0.68, 0.72)	0.67 (0.65, 0.70)
No	Ref	Ref
Atrial fibrillation		
Yes	0.75 (0.72, 0.78)	0.75 (0.72, 0.78)
No	Ref	Ref
Current smoker		
Yes	0.90 (0.87, 0.93)	0.70 (0.67, 0.72)
No	Ref	Ref

EMS, emergency medical services; MI/CAD, myocardial infarction/coronary artery disease; NIHSS, National Institutes of Health Stroke Scale.

* Adjusted by age, sex, race/ethnicity, arrival by EMS, insurance status; NIHSS, prior stroke, and medical history of hypertension, dyslipidemia, MI/CAD, heart failure, diabetes, atrial fibrillation, and current smoker.