

ICU Interventions in Ischemic Stroke Patients Treated Using Liberalized IV-tPA Criteria

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Background and Objective: Current standard practice guidelines recommend ICU admission for ischemic stroke patients treated with intravenous tissue plasminogen activator (IV-tPA). More recently, the trend in stroke care is to broaden eligibility for IV thrombolysis. Two examples are a more liberal inclusion criteria known as SMART criteria (sIV-tPA), and the transfer of patients to comprehensive stroke centers (CSC). The present study characterizes ICU interventions in these patients. Understanding which stroke patients that require ICU-level care may allow for placement of patients in the appropriate level of care at hospital admission. *Methods:* We performed a retrospective review of consecutive transfer and nontransfer sIV-tPA-treated patients admitted to the ICU at a CSC. We evaluated the frequency, timing, and nature of ICU interventions. *Results:* Three hundred and thirty one patients were treated with sIV-tPA and 42% required ICU interventions during ICU admission. Of patients requiring ICU interventions, 98% had an ICU intervention performed in triage, prior to admission. National Institute of Health Stroke Scale score only had a moderate association to requirement of ICU interventions. Neither transferring patients to a CSC nor the number of standard IV-tPA contraindications increased ICU interventions. *Conclusions:* Liberalized IV-tPA administration did not increase ICU interventions. Nearly all patients that required ICU interventions declared this need in triage, prior to ICU admission. This timing of ICU intervention use during triage is highly sensitive for whether a patient will require ongoing ICU-level care during hospital admission. Identifying ICU intervention use in triage may allow for more effective placement of post-IV-tPA patients in the appropriate inpatient care setting, leading to better utilization of scarce ICU resources.

Key Words: Admission decisions—predictors of ICU needs—tissue plasminogen activator—ischemic stroke—intensive care unit
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Introduction

Intravenous tissue plasminogen activator (IV-tPA) is widely considered to be the first-line treatment for acute

ischemic stroke.¹ Nearly all stroke practice guidelines recommend frequent neurochecks and ICU admission post-tPA administration, so one can monitor and treat potential

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tPA-related complications.¹ However, more recent data demonstrated that only 7% of patients without ICU-level interventions at end of tPA administration proceed to develop ICU needs.² This indicates that ICU admission for all tPA-treated patients may be an inefficient utilization of ICU resources.

Recognizing which subset of tPA-treated patients requiring ICU care is an important first step to optimally place patients in an appropriate care setting for hospital admission. A previous study revealed that stroke severity, as defined by the NIH stroke scale, blood pressure, and race are predictors for ICU interventions following IV thrombolysis.² However, this study did not include patients treated with 2 recent advances in acute stroke care, and each advance has increased the patient population eligible for thrombolytic therapy. The first advance is the adoption of a new, more liberal tPA inclusion criteria known as Simplified Management of Acute stroke using Revised Treatment (SMART).³ The SMART criteria establish candidacy for tPA treatment if the patient presents with disabling neurological symptoms and the symptoms are felt to be caused by cerebral ischemia, with a single absolute exclusion criterion of acute intracranial hemorrhage on computed tomography (CT) scan. SMART IV-tPA (sIV-tPA) treated patients have similar favorable functional outcomes with no difference in rates of symptomatic intracranial hemorrhage when compared to patients treated using standard criteria.³ The use of sIV-tPA is not common as evidenced by the low absolute rate (2.4%-7.0%) of IV-tPA administration in all patients presenting within the therapeutic time window.^{4,6} This is likely due to the strict adherence to previously determined relative and absolute thrombolysis exclusion criteria.⁷

The second advance in acute stroke care is the transfer of patients to Comprehensive Stroke Centers (CSC) for advanced multidisciplinary care. In this "drip and ship" model of care, tPA administration is typically completed in the emergency department of a remote hospital, followed by a transfer to a CSC. This model of care is becoming increasingly common and is associated with improved clinical outcomes.⁸⁻¹¹ In addition, many institutions, such as the one in this study, incorporate both advances into the standard care of ischemic stroke patients.

However, the more liberal use of IV-tPA, along with the subsequent transfer of patients during their acute stroke may be perceived to increase complication rates related to tPA-treatment, and result in different ICU requirements relative to patients treated at a single institution with standard tPA criteria. To assess this, in the following study, we characterize the timing, frequency, and nature of ICU interventions of patients treated with sIV-tPA criteria in both transfer and nontransfer patients at a CSC. Since sIV-tPA and the transfer of patients to a CSC have not been demonstrated to lead to an increase in adverse events, we predict that there will be no increase in the frequency of ICU interventions in these patients.³

Methods

Study Design and IRB

Consecutive patients who received sIV-tPA from November 2013 to July 2015 at California Pacific Medical Center (CPMC), a CSC, or at an outside hospital under guidance of CPMC Telestroke program, and then transferred to CPMC were retrospectively identified from the CPMC Stroke Database, as described previously.³ Timing of ICU interventions were categorized to 1 of 2 care phases; the first stage being "triage" defined as the duration prior to ICU admission, such as time spent in the emergency department or in transport. The second stage of ICU interventions occurring in the ICU was categorized as during the "ICU admission." The study was approved and monitored by the Sutter Health IRB and the research was conducted in accordance with IRB-approved protocols.

Individual and Clinical Characteristics

We extracted the following individual characteristics for each patient: age, gender, race, initial systolic and diastolic blood pressure, admission low-density lipoprotein (LDL), and pre-existing medical conditions including hypertension, diabetes, history of atrial fibrillation, and current smoking status. Additionally, for each patient, the following clinical characteristics were determined: Initial National Institute of Health Stroke Scale (NIHSS) score, time from symptom onset to IV-tPA administration, number of standard IV-tPA contraindications (detailed below), and whether the patient received IV-tPA at an outside hospital and was then subsequently transferred to the CSC.

SMART IV-tPA Criteria

As described previously,³ sIV-tPA criteria allow tPA administration to any patient with disabling stroke symptoms with a single absolute exclusion criterion of acute intracranial hemorrhage as identified on the head CT. sIV-tPA criteria therefore permit consideration of thrombolysis candidacy for patients that meet prior standard IV-tPA exclusion criteria, such as, unknown time of symptom onset, symptom duration more than 4.5 hours, age greater than 80 or younger than 18, mild or severe stroke, rapidly resolving symptoms, systemic hemorrhage within 21 or 90 days, dementia, recent surgery within the prior 90 days, or early infarct signs of head CT. The standard IV-tPA exclusion criteria are based on guidelines from the American Heart Association, American Academy of Neurology, and the criteria from the European Cooperative Acute Stroke Study-III, and the National Institute of Neurological Disorders and Stroke trial.^{1,12-15} Specific "standard IV-tPA" absolute and relative exclusion criteria characterized in this study included: symptom duration greater than 4.5 hours before IV-tPA administration, age greater than 80 years, high NIHSS scores greater than 22,

mild NIHSS scores less than 4, occurrence of an intracranial or cardiac injury or intervention in the past three months, and gastrointestinal or genitourinary bleeding within the preceding 21 days.

ICU Intervention Characteristics

For each patient, we determined the use of ICU interventions in triage and during the entire ICU admission of each patient, which was a minimum of 24 hours post-tPA. ICU interventions included greater than 1 IV push of an antihypertensive in 1 hour or requirement of an antihypertensive infusion, use of any IV vasopressor, need for invasive hemodynamic monitoring requiring an arterial line or central venous catheter, continuous rate or rhythm control medication to treat cardiac arrhythmias, use of an insulin infusion, use of invasive or noninvasive ventilation, requirement for close clinical monitoring due to systemic bleeding, symptomatic intracranial hemorrhage (defined as any intracranial hemorrhage on follow-up imaging with associated increase of ≥ 2 points of the NIHSS score), poor mental status (as characterized by rapidly declining Glasgow Coma Scale (GCS) by ≥ 3 points over 30 minutes or $GCS \leq 8$), use of any hyperosmolar therapy, use of any intra-arterial stroke therapy (including mechanical thrombectomy, mechanical aspiration, angioplasty, and intra-arterial tPA), and any neurosurgical intervention.

Data Analysis and Statistics

The primary outcomes were (1) frequency of ICU interventions during "triage" and (2) frequency of ICU interventions during "ICU admission." We compared individual and clinical characteristics of patients that did require ICU interventions to those that did not using parametric *t* test, ANOVA, and Fisher's exact test, with *P* less than .05 considered significant (GraphPad Prism, La Jolla, CA). Odds ratios were derived using 2-sided Fisher's exact test with Baptista-Pike confidence interval calculation. Frequency distribution plotting was used to associate NIHSS to ICU intervention. Cumulative distribution plots were generated using a Best-fit nonlinear Gaussian Curve, modeled by $z = (X - \text{Mean})/SD$ and $Y = N \times \text{zdist}(z)$. Mean is the average of the original distribution, from which the frequency distribution was created, SD is the standard deviation of the original distribution. Unless otherwise noted, data is reported in mean \pm standard deviation.

Results

Patient Characteristics

A total of 331 consecutive transfer and nontransfer patients with symptoms of ischemic stroke were treated with sIV-tPA. Of these 331 patients, 170 patients (51.4%) required ICU interventions at any time point,

whereas 161 patients never required ICU interventions (Table 1). Of all patients treated with sIV-tPA, most demographic and comorbid medical characteristics were not associated with an increased need for an ICU intervention, except for Asian patients (use of ICU interventions: 72.2% in Asians versus 47.0% remainder of patients, *P* = .029).

Timing of ICU Interventions

Of patients requiring ICU interventions at any time: 31 patients required interventions in triage only, 136 patients required interventions in both triage and ICU admission, and 3 patients required interventions only during ICU admission (Fig 1). The use of an ICU intervention during triage yielded a positive predictive value of 81.8% (95% confidence interval: 75.3%-86.9%) that the patient would require an ICU intervention during admission. Conversely, of the 164 patients that did not require ICU interventions in triage, 161 did not require interventions during ICU admission (Fig 1). This yielded a negative predictive value of 98.1% (95% confidence interval: 94.7%-99.5%) that patients not requiring ICU interventions in triage would not need interventions during admission.

Effects of Stroke Severity and Transfer of Patients on ICU Interventions

The mean NIHSS for all patients was 9.9 (SD: 8.5). Higher NIHSS scores were associated with increased use of ICU interventions (NIHSS with ICU interventions 14.2 ± 9.0 versus no ICU interventions 5.3 ± 5.4 ; *P* < .001). To assess the requirement of ICU interventions by stroke severity, we binned the NIH scores to 4-unit bins and calculated the respective odds ratios. There was an increase in odds ratios for ICU interventions with increasing NIHSS scores (Table 2). We then assessed the use of ICU interventions across each NIHSS score. Again, there was a positive linear correlation between NIHSS score and use of ICU interventions, until the NIHSS score was approximately greater than 20, when nearly all patients required ICU interventions (Fig 2A). Extrapolating from our regression analysis, patients with a NIHSS score of 8 had approximately 50% chance of requiring ICU interventions (Fig 2A, dotted line). In our patient population, 27.1% of patients with a NIHSS less than 8 required ICU interventions, and 20.5% of patients with a NIHSS greater than or equal to 8 did not (Fig 2B).

The majority of the patients were transfer patients (*n* = 234, 70.7%). The administration of sIV-tPA and subsequent transfer of patients to the CSC did not change the frequency for ICU interventions (OR 1.2, 95% confidence interval: .7-1.9, *P* = .63). The time to sIV-tPA administration from the last known normal did not change the likelihood that a patient would require an ICU intervention (Table 2).

Table 1. Baseline patient characteristics of SMART Criteria IV-tPA (sIV-tPA) treated stroke patients that required ICU interventions in triage only, in triage and ICU admission*, and those that did not require any ICU intervention

Characteristic	All patients	ICU interventions in triage only	ICU interventions in triage and ICU admission	No ICU interventions in triage and ICU
<i>Patients, n</i>	331	31	139*	161
Age, mean (SD)	69.4 (15.3)	72.9 (18.0)	69.8 (15.0)	68.4 (14.9)
Female, %	42.4%	44.1%	42.0%	42.2%
<i>Medical history, %</i>				
Hypertension	58.9%	61.8%	61.8%	55.9%
Atrial fibrillation	32.1%	35.3%	34.6%	29.4%
LDL mmol/L (SD)	84.7 (34.9)	74.1 (31.8)	85.0 (38.2)	86.7 (32.5)
Diabetes	28.4%	26.5%	30.9%	26.7%
Smoker	12.7%	11.8%	11.8%	13.8%
<i>Race, %</i>				
White	68.9%	73.5%	62.5%	73.3%
Asian	10.9%	11.8%	16.2%	6.3%
Black	6.1%	3.0%	7.4%	5.6%
Hispanic	8.5%	8.8%	8.8%	8.1%

There were no differences in individual characteristics between the groups, except Asian patients required ICU interventions more frequently (all $P > .05$; Asian $P = .029$). Column data represents proportion or percent of the patient group contained in the column header.

*Three of these patients did not require interventions in triage.

Frequency of Specific ICU Interventions by Timing and Stroke Severity

We characterized the timing of each ICU intervention by determining the frequency of each intervention during triage and after admission, in the ICU (Table 3). The most common ICU interventions in triage were blood pressure control and intra-arterial therapy. These interventions were used to safely administer sIV-tPA or to acutely treat large vessel occlusion strokes, respectively. In contrast, the most frequent interventions after admission in the ICU were hyperosmolar therapy, blood pressure control, or ventilatory support. These interventions were focused on the treatment of stroke sequelae. We then further characterized the frequency of each ICU intervention in patients with low (NIHSS < 8) and high

(NIHSS ≥ 8) stroke scores. Blood pressure reduction was the most common ICU intervention in patients with low stroke scores (Fig 3, yellow box), while blood pressure augmentation, intra-arterial therapy, and ICP control were the most common ICU interventions in patients with high NIHSS scores (Fig 3, blue box).

Presence of IV-tPA Contraindications and ICU Interventions

In our patient cohort treated with sIV-tPA, 81.6% had 1 or more standard IV-tPA contraindication. Giving IV-tPA to patients with 1 or more contraindications did not increase the use of ICU interventions compared to patients with no contraindications (Fig 4).

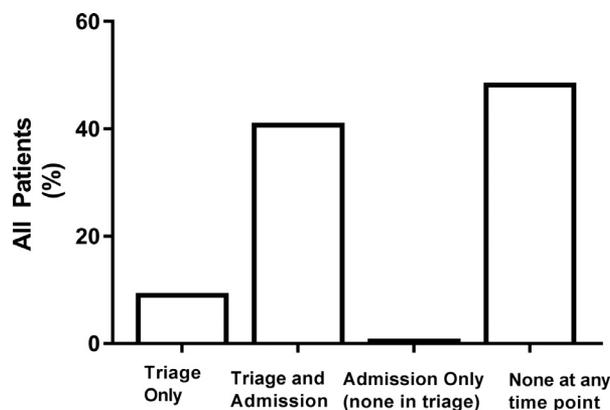


Figure 1. Timing of ICU interventions in SMART criteria IV-tPA (sIV-tPA) treated stroke patients. Shown are the percentage of patients requiring ICU interventions during triage only, during both triage and ICU admission, during ICU admission only, and patients never requiring ICU interventions (n = 31, 136, 3, 161, respectively). Thus, nearly all patients that did not require an ICU intervention in triage (n = 164), did not require an ICU intervention at any time point (n = 161).

Table 2. The effect of clinical stroke severity, as measured by NIHSS score and tPA-treatment characteristics in patients treated with sIV-tPA, on requiring ICU interventions

Characteristic	All patients (n = 331)	OR for an ICU intervention	95% confidence interval
<i>NIH Stroke scale</i>			
NIH ≥ 20	16.9%	13.4*	5.3-31.7
NIH ≥ 16 -<20	8.5%	8.1*	2.8-21.7
NIH ≥ 12 -<16	6.6%	2.7*	1.0-6.9
NIH ≥ 8 -<12	12.4%	1.8	.9-3.7
NIH ≥ 4 -<8	25.7%	.30*	.2-6
NIH 0-<4	29.9%	.20*	.1-4
IV-tPA given at an outside hospital	70.7%	1.2	.7-1.9
<i>Latency of sIV-tPA delivery after last known normal</i>			
<3 hours	66.1%	1.2	.8-1.9
≥ 3 -<4.5 hours	26.0%	.80	.5-1.4
≥ 4.5 hours	7.9%	.80	.4-1.7

*P < .05.

Discussion

We characterized ICU interventions in ischemic stroke patients treated using 2 recent advances in stroke care: sIV-tPA, a more liberalized IV-tPA criteria,³ and transfer to a CSC for advanced multidisciplinary care.⁸⁻¹¹ We found that the use of ICU interventions in triage was closely associated with ongoing needs for ICU interventions during admission. Neither liberal IV-tPA criteria nor the transfer of patients increased the need for ICU interventions. Our Stroke Center's practice includes a comprehensive telestroke evaluation by a Stroke Expert for all

sIV-tPA use at outside facilities, a standard protocol for medical treatment during transport, and close post-tPA monitoring, all of which may mitigate the risk of tPA-related complications.

Although approximately one-half of sIV-tPA-treated patients required ICU interventions, the rate of symptomatic hemorrhage, a presumed tPA-related complication, was low (2.5%), suggestive that the need for ICU interventions was not directly related to tPA complications. Our results indicate that the need for ICU interventions stem from 2 primary factors: strict blood pressure control in *all* tPA-treated patients to decrease the risk of tPA-associated hemorrhage, and the multiorgan compromise and acute stroke treatments typically associated with more severe strokes. Additional evidence to support that ICU needs in tPA-treated patients were not related to tPA-related complications was the timing of ICU needs. In our patients requiring ICU interventions, nearly 80% had such interventions prior to tPA administration while in triage (e.g., antihypertensive pushes to achieve target blood pressures).

Our study used a broader definition of ICU interventions compared to previous studies regarding ICU care in post-tPA patients. For example, in our study, we included the use of 2 or more IV pushes of antihypertensive in 1 hour as an ICU-level intervention. Our more extensive definition identified more patients that require ICU-level care. Indeed, we demonstrated higher rates of ICU interventions among all patients compared to a prior study (51.0% versus 27.5%).² Since most patients that need ICU care during admission require such care in triage, our broader definition of ICU care captured more patients needing ICU interventions early, leading to only a very small number of patients that needed ICU-level care during admission that were not identified in triage (3 of 139

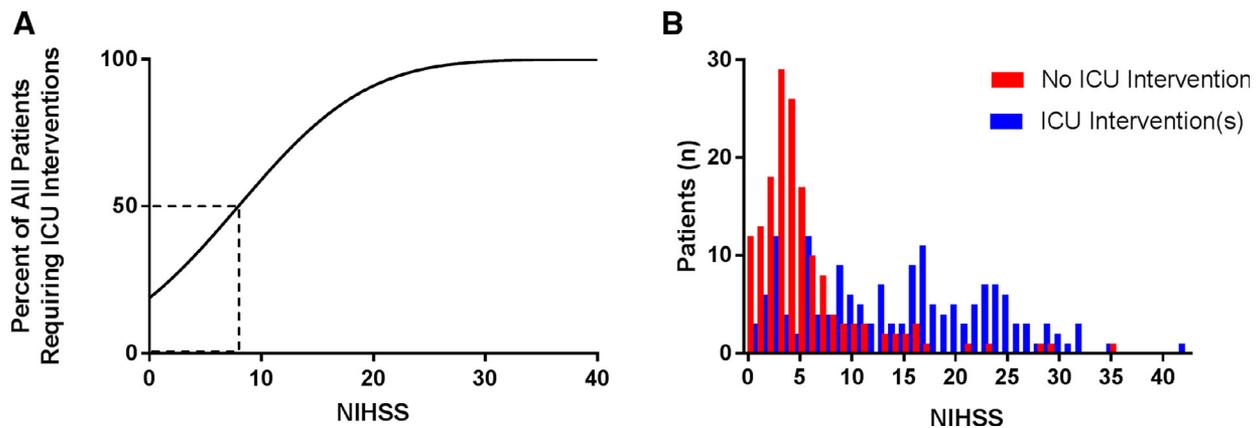


Figure 2. Frequency of ICU interventions required for individual NIHSS scores of sIV-tPA-treated stroke patients. (A) Percent of all patients' NIHSS scores requiring ICU interventions modeled by a Best-fit Gaussian Curve (NIHSS in 4-unit bins, Best-fit: mean 7.9, standard deviation 9.0, Standard error: mean 1.03, SD 1.7, degrees of freedom: 12, $R^2 = .82$). Dotted line at a NIHSS score of 8 is the threshold of where approximately 50% of patients required ICU interventions. (B) Histogram of the number of patients and their use of ICU interventions per each NIHSS score (Red bars: No ICU Intervention, Blue bars: ICU intervention (s)). Color version of figure is available online.

Table 3. Timing and frequency of specific ICU-level interventions in triage versus the ICU admission in all patients treated with sIV-tPA

ICU level intervention	Timing of ICU interventions	
	Triage	ICU admission
> 1 Anti-HTN Push /1 hour	35.3%	5.9%
Anti-HTN gtt	11.4%	19.9%
Close Monitoring	17.5%	6.2%
Vasopressor	13.0%	23.1%
Intra-arterial Therapy	47.1%	.0%
A or C line	12.4%	15.3%
Hyperosmolar therapy	4.7%	27.6%
BIPAP or vent	10.0%	20.0%
NSG intervention	.0%	8.8%
Rate control gtt	.0%	7.6%
ICP monitoring	.0%	4.4%

The frequency of each intervention is represented as the percent of the total 170 patients who required ICU interventions at any time point.

total patients). Thus, our comprehensive definition of ICU interventions confers a key advantage – it allows *timing* of ICU interventions (i.e., present or absent in the triage time period) to serve as the single most effective clinical identifier to predict whether patients will or will not proceed to need ICU-level care. Recognizing this single clinical identifier would yield a clear admission protocol that may be safe and easily followed. This advantage can be observed when comparing to a prior study: we found that

only 1.8% of patients without ICU interventions in triage went on to require such interventions later, lower than previously reported (7.0%), where a stricter definition of ICU interventions was used.²

A previous study demonstrated that higher NIHSS scores correlate to increased frequency of ICU interventions, which was similarly observed in our patients.² Thus, NIHSS score may be considered as a placement tool for the level of hospital care that a post-tPA patient may require. However, using NIHSS alone will likely miss a significant percentage of patients that will require ICU care. Based on our study population, 27% of patients with less severe strokes (NIHSS < 8) required an ICU intervention. Thus, using NIHSS score alone for determining level of subsequent care may miss ICU needs in 1 of every 4 patients with less severe strokes, exposing a significant number of patients triaged to a non-ICU setting of care to potential harm.

Another interesting result is the association of increased ICU interventions in Asians treated with sIV-tPA. Asians were the second most common race in our treated population. In this ethnic subgroup, the NIHSS scores were higher (mean: 14.4 versus 9.9 for all other races). The increase in ICU interventions may be related to the more severe strokes seen in the Asian stroke population. However, more recent data have demonstrated that Asian Americans have higher rates of cardiovascular mortality compared to whites, and Asians are more susceptible to strokes or have more severe strokes compared to Caucasians with comparable risk factors.¹⁶⁻¹⁸ This series of data suggests an intrinsic, genetic predisposition to have worse

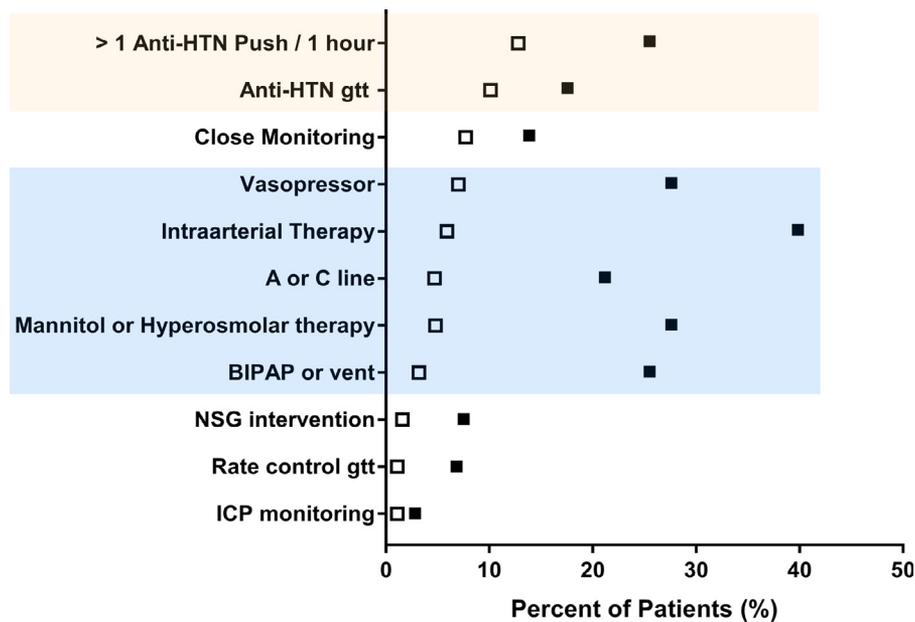


Figure 3. The use of ICU interventions in sIV-tPA treated patients with low (NIHSS < 8, open boxes) and high (NIHSS ≥ 8, closed black boxes) stroke scores. Interventions are arranged ranked order to frequency of use in patients with low stroke scores (open boxes). Interventions in which low and high NIHSS stroke scores had similar frequencies are represented in the yellow-shaded box, whereas interventions significantly more frequent in high NIHSS scores are marked by the blue-shaded box (P < .05). Color version of figure is available online.

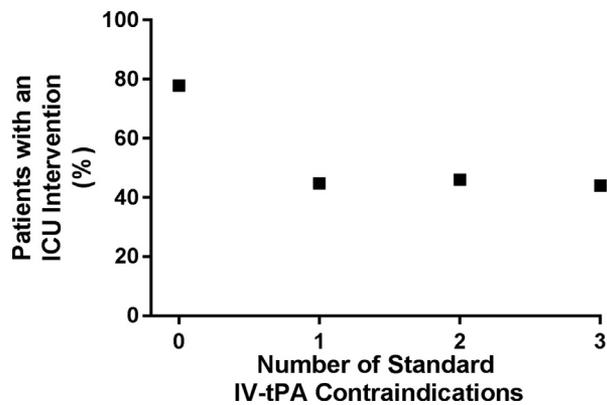


Figure 4. IV-tPA contraindication frequency in sIV-tPA patients and the probability of requiring an ICU level intervention. N for each group of contraindications for all NIHSS scores were: 0 contraindications $n = 63$, 1 contraindication $n = 185$, 2 contraindications $n = 76$, and ≥ 3 contraindications $n = 7$.

clinical outcomes related to stroke and cardiovascular disease, and this may translate to the increased need for ICU-level care during a stroke.

Our study has several limitations. First, stroke care using a liberalized IV-tPA criteria is not established, commonly practiced, standard of care, and our results may not be currently applicable to many healthcare institutions. There is institutional variability on interpretation of thrombolysis exclusion criteria, and recently more providers are interpreting some of the exclusion criteria used here as relative instead of absolute. However, as mentioned below, there is a current trend in acute stroke care to expand the patient population that may benefit from IV thrombolytics. As more research is completed, we expect there will be an increase in the number of patients eligible for IV-thrombolysis as inclusion criteria for therapy becomes more wide-ranging. Second, this was a retrospective study with limited number of patients. Further prospective studies are needed and are currently underway to determine long-term outcomes of post-tPA patients treated in ICU versus non-ICU settings.

The future of stroke treatment and acute stroke care may rapidly change as more patients are considered for treatment with IV thrombolytics.^{3,19,20} Ongoing and future trials (TWIST and TIMELESS) will look at the safety and efficacy of IV thrombolytics given in an extended therapeutic time window. Recent results of DAWN and DEFUSE III revealed that endovascular therapy directed at reperfusion in an extended time window improves long-term functional outcomes and is safe.^{21,22} We expect that similar reperfusion via IV thrombolytics is likely to show comparable benefits. The results of these IV thrombolytic studies may lead to an overall increase in patients receiving thrombolytics for acute stroke care. If current guidelines continue requiring that all ischemic stroke patients receive ICU level of care, this will lead to considerable strain on scarce ICU resources. An essential

first step in developing new treatment protocols that effectively allocate ICU resources is the determination at the time of admission which patients will and will not need ICU-level care.

Conclusions

Liberalized IV-tPA administration and the transfer of patients to a CSC is safe and does not change the frequency of ICU interventions. Nearly all patients requiring ICU interventions during admission declare this need during triage. Thus, timing of ICU interventions by their use in triage informs the required subsequent level of care.

Authors' Contributions

Dr. Murray provided direct patient care, conception and study design, acquisition and analysis of data, drafting the manuscript, and critical manuscript revisions.

Dr. Ke provided direct patient care, conception and study design, acquisition and analysis of data, drafting the manuscript, and critical manuscript revisions.

Dr. Yee provided direct patient care, conception and study design, drafting the manuscript, and critical manuscript revisions.

Dr. Chen provided direct patient care, conception and study design, drafting the manuscript, and critical manuscript revisions.

Dr. Wong provided direct patient care, conception and study design, drafting the manuscript, and critical manuscript revisions.

Ms. Bedenk provided direct patient care, conception and study design, and critical manuscript revisions.

Ms. Fernandes provided direct patient care, conception and study design, and critical manuscript revisions.

Dr. Barazangi provided direct patient care, conception and study design, acquisition and analysis of data, drafting the manuscript, and critical manuscript revisions.

Dr. Tong provided direct patient care, conception and study design, acquisition and analysis of data, drafting the manuscript, and critical manuscript revisions.

Disclosures and Conflicts of Interest

The authors have no conflict of interest to disclose.

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