Thrombolysis Following Heparin Reversal With Protamine Sulfate in Acute Ischemic Stroke: Case Series and Literature Review

Tamra Ranasinghe, MD,* Traci Mays,† Jeff Quedado, Pharm D,‡ and Amelia Adcock, MD§

Introduction: Administering intravenous IV tissue plasminogen activator (tPA) is the recommended standard of care in acute ischemic stroke (AIS), although it is not recommended to administer intravenous thrombolysis with tPA following heparin reversal with protamine sulfate in patients with AIS. *Methods:* We describe a case series of three patients and the most comprehensive literature review published to date in this specific subset of AIS patients undergoing thrombolysis following heparin reversal with protamine sulfate. The literature review was based on a scoping review methodology performed on four databases; PubMed, CINAHL, Web of Science, and Cochrane Library. All sources were searched from the inauguration of the database until February 2019. A total of six articles involving eight patients were identified. *Results:* The primary safety outcome of no symptomatic intracranial hemorrhage (sICH) was met in all eleven patients, although only seven cases had a good functional outcome at 3 months. *Conclusions:* In appropriately selected AIS patients, coagulopathy correction appears to be safe from an sICH standpoint and may be beneficial. However, given the potential for bias with observational databases, case reports and case series, extreme caution is warranted in applying these results to routine clinical practice.

Key Words: Acute ischemic stroke—heparin reversal—protamine sulfate—IV tPA—thrombolysis—symptomatic intracranial hemorrhage—case series, literature review

Introduction

Administration of IV tissue plasminogen activator (tPA) is the recommended standard of care in acute ischemic stroke (AIS). Currently, a conservative estimate reports that 3.4%-5.2% of AIS patients in the United States receive tPA.[1] Several exclusionary criteria render a large majority (95%) of AIS patients ineligible for medical therapy. Current guidelines exclude intravenous thrombolysis (IVT) in heparinized patients with an activated partial thromboplastin time (aPTT) greater than 40 seconds.[2] Therapeutic heparin is commonly used during hospitalization for many indications, including non-ST elevation myocardial infarction, atrial fibrillation and several cardiac procedures.

Since the number of cardiac procedures performed continues to increase each year, with more than 2 million cardiac catheterizations performed annually in the United States,[3] AIS is a possible complication and can be catastrophic.[4] Incidence of stroke following percutaneous coronary intervention ranges from .30% to .40% [5-7] regardless of routine peri-procedure heparinization. Increased atherosclerotic burden, advanced age, triple vessel disease, prior stroke, and the presence of intracoronary thrombus are independent predictors of cerebrovascular events following cardiac catherization.[8]

From the *Department of Neurology, West Virginia University, Morgantown, West Virginia; †Health Science Library, West Virginia University, Morgantown, West Virginia; ‡Department of Pharmacy, West Virginia University, Morgantown, West Virginia; and §Department of Neurology, West Virginia University, Morgantown, West Virginia.

Received March 22, 2019; revision received June 23, 2019; accepted June 27, 2019.

Address correspondence to Tamra Ranasinghe, MD, Department of Neurology, West Virginia University, 1 Medical Center Drive, Room #1310 HSC, Morgantown, WV 26506. E-mail: tamrar@gmail.com.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.06.041

Intravenous protamine sulfate can rapidly (~5 minutes) reverse the anticoagulant effects of heparin. Protamine sulfate is an alkaline protein molecule with a large positive charge that neutralizes heparin by forming a stable salt. Although it is biologically possible to reverse heparin with protamine prior to tPA administration, the general lack of data precludes formal recommendation in support of this approach. However, protamine is widely used to neutralize heparin during carotid endarterectomies (CEA). A meta-analysis involving 10,621 patients concluded that the use of protamine following CEA is associated with reduction in bleeding complications without increasing major thrombotic outcomes, including stroke, myocardial infarction, or death.[9] Further, the use of protamine to reverse the effects of heparin after cryoballoon ablation of atrial fibrillation appears to be safe, with no increase of thromboembolic risk.[10]

Our comprehensive literature review found limited evidence in the neurological literature of thrombolysis following heparin reversal in AIS patients. In what follows, we describe three cases treated with IV tPA following heparin reversal with protamine sulfate at our own institution.

Methods

Study Selection

This case study series with a literature review was based on the methods outlined by Arksey and O'Malley for a scoping review,[11] which include six iterative steps: (1) identifying the research question; (2) searching for relevant studies; (3) selecting the studies; (4) charting the data; (5) collating, summarizing, and reporting the results; and (6) consulting with stakeholders to inform or validate findings. While step 6 is optional, as the key stakeholders, the authors held multiple consultations throughout the research process. The authors did not consult acute ischemic stroke stakeholders during this research. A scoping review methodology was selected because it allows for expansive questions and a range of research types in exploring a topic of interest. This methodology aids in determining gaps in the current knowledge base, which will help guide future research in the field.

To identify studies relevant to this research question, a systematic search of four databases (PubMed, CINAHL, Web of Science, and Cochrane Library) as well as reference lists of included studies was conducted. Three authors performed the search for potentially relevant articles using a preplanned comprehensive and reproducible search strategy, applying the terms "heparin reversal," "protamine," "tissue plasminogen activator," "acute ischemic stroke," "thrombolytic therapy," "stroke," "tPA," "thrombolysis," and "reversal." The search terms and subject headings were modeled after the search used in PubMed and adjusted according to different database interfaces. The study selection process was conducted in two stages. In the first stage, articles were selected based on title and abstract; in the second, based on the full text. To survey as broad a knowledge base as possible, the authors resolved to include all peer-reviewed published literature. All sources were searched from the inauguration of the database until February 2019. Searches were restricted to English language articles. All references were imported into Endnote.

Inclusion and Exclusion Criteria

Once the searches were complete, the inclusion criteria were applied by two authors (T.R. and A.A.). The following criteria were: (1) adults (18 or over), (2) diagnosis of acute ischemic stroke, (3) therapeutic heparin reversal with protamine sulfate, (4) administration of IV tPA and (5) after the year of 1995. The studies excluded using the following criteria: (1) children, (2) adolescent, (3) patients on novel anti-coagulants, (4) large stroke (over 1/3 of brain involvement), (5) intracranial hemorrhages on presentation and (6) studies on animal models.

The first author (T.R.) identified the general information (including title, journal, authors, year, excluded or included, reason for exclusion, heparin used, reverse with protamine used, IV tPA administration stroke diagnosis, and complications experienced) to capture specific features in each article. These features were charted to provide a full description of each study. The studies that did not use anticoagulation with heparin, that did not reverse heparin with IV protamine sulfate, and that did not use thrombolysis with IV tPA were excluded. Data was observed inductively. Each article was independently reviewed following the systematic application of the inclusion and exclusion criteria. Any disagreement between reviewers was resolved by consensus. The following findings comprise the result of this process.

Outcome Measure

Primary outcome was safety, defined as symptomatic intracranial hemorrhage (sICH). sICH was defined as "any computed tomography (CT)-documented hemorrhage that was temporally related to deterioration in the patient's clinical condition in the judgment of the clinical investigator."[12] Additional outcomes included good functional outcome and mortality at 3 months. Good functional outcome was defined as modified Ranking Score (mRS) of 0-2.

Results

The flow of studies through the process is shown in the PRISMA 2009 flow diagram (Diagram 1). The final number of studies included in this literature review was 36. The summary of data extraction is provided in

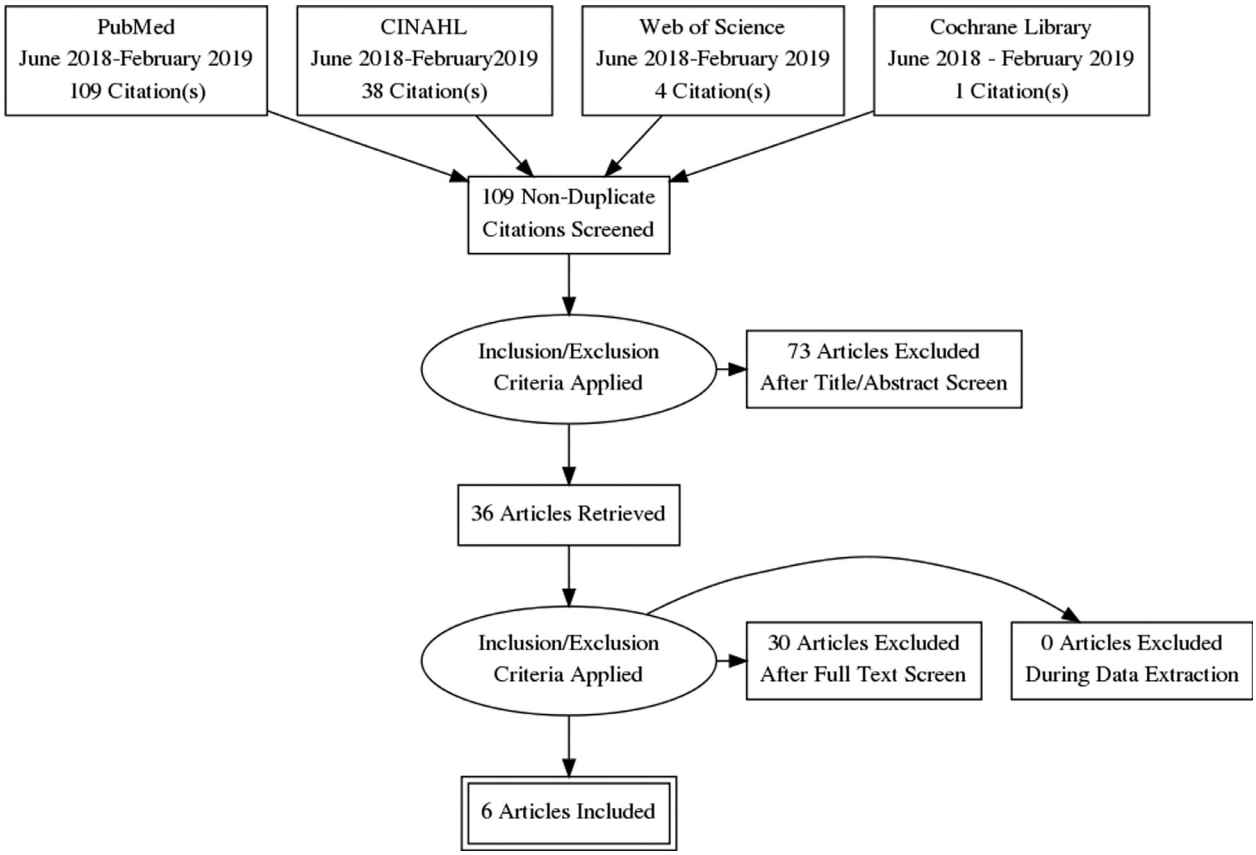

Diagram 1. *PRISMA 2009 flow diagram, demonstrating the flow process data extraction.*

supplementary data (see Appendix). Reports describing an acute ischemic stroke, where heparin was reversed with protamine and IV tPA was administered, were identified in a total of six articles involving eight patients. The six articles included five case reports (Fontaine et al,[13] Danoun et al,[14] Bereczki et al,[15] Safouris et al,[16] Warner et al[17]) and one case series of three patients (Guevara et al[18]).

All three patients in our case series (cases #1-3 on Table 1) developed AIS while on therapeutic heparin with an aPTT > 40 seconds. ICH was excluded by a noncontrasted CT scan. Following a detailed risk-benefit discussion, heparin was reversed with IV protamine sulfate 50 mg. Following the normalization of the serum aPTT levels (<40 seconds), IV tPA (.9 mg/kg) was administered. All three patients or their families acknowledged the risks of receiving IV tPA off-label.

Case #1 presented with the unusual systemic thrombotic complication of an ischemic limb affecting his right lower extremity. A revascularization attempt was unsuccessful, and the patient was scheduled for an amputation when he developed acute left-sided weakness while on a heparin drip. Following thrombolysis with IV tPA, brain imaging demonstrated an asymptomatic petechial hemorrhage. The patient underwent a right lower extremity amputation while inpatient and was discharged on warfarin for atrial fibrillation. At the 3-month follow-up visit, he had no residual stroke symptoms.

On presentation, case #2 had a baseline mRS of 2, stemming from a recent history of myxedema coma. Following IV tPA, her right-sided flaccidity improved, and she was able to move against gravity. Two days later, she developed wide complex tachycardia, requiring cardioversion, and acute hypercapnic respiratory failure, requiring intubation. During her medically complicated inpatient stay of 3 weeks, she required ventilator support twice secondary to *Haemophilus influenza* pneumonia in the setting of restrictive lung disease, obstructive sleep apnea, tracheomalacia, and congestive heart failure. She was discharged to a long-term acute care hospital (LTACH) with a tracheostomy and percutaneous endoscopic gastrostomy tube in place.

Approximately halfway into the IV tPA infusion in case #3, the patient became aphasic and her neurological status acutely worsened. IV tPA infusion was halted, and a repeat CT head and angiogram indicated a new left M1 thrombus. Alberta Stroke Program Early CT score was 10. The patient was intubated as she was unable to protect her airway and taken for mechanical thrombectomy. She was re-perfused with a thrombolysis in cerebral infarction score of 2B. Over the next several days, she remained minimally responsive on mechanical ventilation and continuous renal replacement therapy, and ultimately discharged with a percutaneous endoscopic gastrostomy tube/tracheostomy to a LTACH.

Discussion

None of the 11 AIS patients in our systemic review and case series (Table 1) developed sICH after undergoing thrombolysis following heparin reversal with protamine sulfate. Subsequent imaging demonstrated asymptomatic petechial hemorrhage in two patients. This evidence suggests that it may be safe for heparinized AIS patients to receive IV tPA following heparin reversal with protamine. Seven out of eleven patients had a good functional outcome (mRs 0-2) at their follow-up appointments. Three patients (including case #2) did not achieve acceptable functional outcomes (described as mRS 3 or worse) on follow-up, and one patient (case #3) died several weeks after being discharged. Case #2's long-term outcome was unknown, as she was discharged to an LTACH in another state. Her mRS was 2 on presentation and 5 on discharge, the difference attributed to respiratory complications. Case #3 is the only patient reported as deceased on follow-up. She experienced a new left MCA M1 segment thrombus while on the tPA infusion drip after heparin was reversed with protamine. This development could be due to a possible transient hypercoagulable state following coagulopathy correction in the setting of TAVR procedure or recurrent thromboembolic phenomenon from her atrial fibrillation. Instances of thrombosis in operated internal carotid arteries in CEA patients following heparin reversal with protamine have been reported.[19]

In addition to transient prothrombotic consequences inherent to any coagulopathy correction, protamine sulfate's possible effects are complex. Protamine sulfate is a positively charged polypeptide with anticoagulant properties. When protamine is given in the presence of heparin (strongly acidic and negatively charged), a stable salt is formed, and the anticoagulant activity of both drugs is nullified. Protamine has a short onset of action (~5 minutes) and elimination of half-life (~7 minutes). The half-life of heparin (~90 minutes) means that timing of protamine administration in patients depends upon the timing of heparin exposure. Given these significant variables, it is conceivable that excess protamine (a positively charged protein) could gain access to the cerebral microenvironment via endocytosis at the negatively charged blood brain barrier.[20] Further, protamine should not be considered entirely benign, as it may result in hypotension, bradycardia, and bronchoconstriction. Administration via slow intravenous push (not to exceed 50 mg/min, 10 minutes) can minimize these effects.[21]

All three cases treated at our facility demonstrated a perfusion mismatch on CT perfusion study corresponding to their deficits on exam. Perfusion mismatch with an increase in time to peak and decrease in blood volume is highly concerning for evolving AIS. None of the other previously published literature included in this review describes a perfusion mismatch in its reports. Given the high stakes medical decision-making in this subset of AIS, advanced imaging that indicates salvageable tissue is significant when considering the use of off-label IVT.

Three patients described by Guevara et al received a reduced dose of .6 mg/kg of IV tPA with the rationale of possibly reducing ICH risk. A systemic review and meta-analysis on low dose versus standard dose of IV tPA in AIS demonstrated a comparable improvement of neurological function and reduced incidence of sICH with the use of low-dose tPA (by National Institute of Neurological Disorders and Stroke definition: OR = .71, 95% CI .57-.89; P = .003).[22] However, caution should be exercised before reducing IVT dose in populations at elevated risk for sICH, as both the Enhanced Control of Hypertension and Thrombolysis Stroke (ENCHANTED) trial[23] and an observational study of octogenarians[24] published earlier this year found worse functional outcomes in the low-dose groups even though sICH was reduced.

In these complicated cases, four possible treatment paradigms are available to the managing physician. (1) Exclude AIS patients from thrombolysis with a recent history of heparin use and aPTT > 40 seconds. (2) Wait for the aPTT to normalize; if under 4.5 hours from symptom onset, proceed with thrombolysis. (3) Proceed with thrombolysis with elevated aPTT > 40 seconds. (4) Reverse heparin with protamine sulfate. Once the aPTT normalizes, administer IV tPA.

Treatment paradigm (1) is the current 2018 American Heart Association guideline's recommendation for the early management of patients with AIS. The safety and efficacy of IV tPA for AIS patients with platelets less than 100,000/mm^3, INR > 1.7, aPTT > 40 seconds, or PT > 15 seconds is unknown; therefore, IV alteplase should not be administered.[2] Strength of recommendation is Class III: Harm, and the level of evidence is consensus of expert opinion based on clinical experience. We agree that IV tPA should not be offered to heparinized patients (with an aPPT > 40 seconds) who present with a large vessel occlusion and are mechanical thrombectomy (MT) candidates. This subgroup of patients should proceed directly to MT. The following paradigms (2, 3 and 4) should therefore only be considered in heparinized non-MT candidates.

The apparent biological half-life of unfractionated heparin is approximately 90 minutes. Given the relatively short half-life of heparin, paradigm (2) can be considered reasonable. Kulairi et al described a 39-year-old male, who developed left-sided hemiparesis with a National Institute of Health Stroke Scale of 9 following an elective cardiac catherization.[25] His initial aPTT was higher than the upper limit due to recent heparin use. Repeat aPTT 1 hour later normalized, and the patient received IV tPA within the recommended thrombolysis time window (exact time not specified in the case report). Follow-up MRI brain demonstrated a right anterior parietal lobe infarct, and he was discharged with an National Institute of Health Stroke Scale of 1. Although this case demonstrates a good functional outcome, it is well established that time delays

Table 1. *Reported Cases of Thrombolysis Following Heparin Reversal With Protamine Sulfate in Acute Ischemic Stroke*

Cases	Age	Sex	Vascular Comorbidities	Reason for Anticoagulation with Heparin	Initial NIH SS	Initial CT Brain	CTA intracranial and extracranial vessels	Perfusion Mismatch	Initial aPTT	Protamine Sulfate	Repeat aPTT	tPA Dose mg/kg	Time in minutes LSN to tPA	Follow up Brain Imaging	ICH	sICH	mRS at 3-month follow up
Case #1	73	M	HTN, HLD, Afib	Afib & right leg ischemia	6	Unremarkable	Unremarkable	Right parietal lobe	65.3	50 mg	31	.90	177	MRI: Right parietal infarct	Right Parietal HI1	No	2 (due to right BKA, no residual stroke symptoms)
Case #2	66	F	HTN, HLD, CAD, CHF, CKD	NSTEMI & coronary angiogram	18	Loss of gray-white matter in left occipito-temporal region	left PCA P2 occlusion	Left Parieto-occpital lobe	62.1	50 mg	30	.90	218	MRI: left PCA, thalamic and temporal lobe infarct	Neg	No	no show
Case #3	79	F	HTN, HLD, Afib, CAD s/p CABG x5, OSA, CKD, DM, Severe AS	TVAR procedure	21	Unremarkable	Right P1-2 junction occlusion	Right occpital lobe	46.5	50 mg	32.3	.90 discontinued halfway	171	MRI: Large L MCA and right PCA infarcts	Left basal ganglia HI1	No	6
Fontaine G.V. et al.[13]	73	M	HTN, HLD, CAD s/p 4 stents, CHF, DM	NSTEMI & coronary angiogram	12	Unremarkable	Unremarkable	unremarkable	110	40 mg	26	.90	152	MRI: Right pontine and right cerebellar infarcts	Neg	No	3
Danoun O. et al.[14]	52	F	N/R	Coronary angiogram	16	Unremarkable	N/R	N/R	51.4	25 mg	25	N/R (likely .90)	94	MRI: Left thalamic infarct	Neg	No	0
Warner D.S. et al.[15]	87	M	HTN, HLD, CAD, DM	Coronary angiogram	4	Unremarkable	Unremarkable	N/R	181	40 mg	normal	N/R (likely .90)	265	MRI: No infarct	Neg	No	0 (on discharge)
Guevara C. et al.[16]	68	F	HTN, CAD	Coronary angiogram	12	Unremarkable	N/R	N/R	N/R	50 mg	26.1	.60	190	CT: unremarkable	Neg	No	0
Guevara C. et al.[16]	61	F	HTN, Smoker	Coronary angiogram	11	Unremarkble	N/R	N/R	N/R	50 mg	12.5	.60	164	CT: Left parietal lobe infarct	Neg	No	1 (at 2 months)
Guevara C. et al.[16]	67	F	HTN, Smoker, severe valvular AS	Coronary angiogram	8	Unremarkable	N/R	N/R	90	50 mg	24.7	.60	270	CT: Unremarkable	Neg	No	1
Bereczki J. et al.[17]	70	M	AFIB, diffuse hypokinesis with inferoseptal akinesis on cardiac echo	Afib	9	Unremarkable	N/R	N/R	N/R	6000 IU	N/R	.90	~180	CT: unremarkable	Neg	No	1
Safouris A. et al.[18]	66	M	Afib	Afib	26	MRI brain: left MCA infarct	N/R	N/R	59	N/R	35	N/R (likely .90)	125	MRI: Left MCA infarct	Neg	No	3

Afib, atrial fibrillation; AS, aortic stenosis; BKA, below the knee amputation; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, chronic heart failure; CKD, chronic kidney disease; DM, diabetes mellitus; HI1, hemorrhagic infarction type 1; HLD, hyperlipidemia; HTN, hypertension; NR, not reported; NSTEMI, non ST elevation myocardial infarction; MCA, middle cerebral artery; OSA, obstructive sleep apnea; PCA, posterior cerebral artery; TAVR, transfemoral transcatheter aortic valve replacement; The repeat CT angiogram demonstrated a new left MCA M1 segment occlusion, and she was taken for mechanical thrombectomy.

in IV tPA administration increase the risk of ICH and decrease the probability of good functional outcomes.[26] Hence, given the "Time is Brain" paradigm of stroke theory of relativity, is it reasonable to wait for spontaneous normalization of aPTT prior to considering thrombolysis in AIS patients?

Regarding paradigm (3), Demaerschalk et al reviewed 164 patients who received IV tPA with prolonged aPTT (>39 seconds). Six out of 164 patients (4.3%) subsequently developed sICH[27]; all were from the Virtual International Stroke Trial Archive. This analysis showed a favorable outcome among IV tPA treated patients with prolonged aPTT (OR, 1.57; 95% CI, 1.02-2.41).[28] A multicenter retrospective cohort study of consecutive stroke cases postcatheterization found 7/66 (11%) were treated with IVT and 2/7 (29%) had a prolonged aPTT (>40 seconds) at the time of treatment.[29] Within this cohort of patients, functional outcome improved in the treated group, and no difference in mortality or sICH was observed. None of these patients underwent correction of coagulopathy prior to IVT. However, given the paucity of data, the review group still recommends against thrombolysis with IV tPA in AIS patients with aPTT greater than 40 seconds.[27]

Our case series and the literature review describe the final paradigm (4). All 11 patients *(*Table 1*)* with AIS received thrombolysis following heparin reversal with protamine sulfate. All 11 met the primary safety outcome of no sICH observed. Three did not meet the secondary long-term functional outcome, and one patient was lost to follow up. Two patients had asymptomatic hemorrhagic transformation categorized as hemorrhagic infarction (HI1). HI1 is defined as small petechiae within the margins of the infarction. Correcting coagulopathies within the time window for IVT has also become a reality with the development of reversal agents for some of the novel anticoagulants. Several cases of successful thrombolysis following dabigatran reversal with Idarucizumab have been reported.[30-32] The neurological symptoms significantly improved in these patients without evidence of hemorrhagic conversion. However, no definitive conclusions can be drawn regarding the safety and efficacy of IVT following coagulopathy correction.

Reliable data is lacking, possibly due to its observational nature, which poses high risk for publication and selection bias. An extensive risk-benefit discussion with the patient and family is thus crucial before considering off-label use of IV tPA following heparin reversal with protamine.

Conclusion

We believe this literature review of the specific subset of AIS patients undergoing thrombolysis following heparin reversal with protamine sulfate is the most comprehensive to date. The primary safety outcome (no sICH) was met in all 11 patients. IV tPA following heparin reversal in appropriately selected AIS patients appears to be safe from an sICH standpoint and may be beneficial. In light of the potential for bias with observational databases, case reports and case series, extreme caution is warranted in applying these results to routine clinical practice. Rather, we suggest that thrombolysis may still be considered in AIS patients on therapeutic heparin who are not candidates for MT. Physicians must still exercise discretion with an individualized patient-centered approach. Larger prospective, randomized studies are needed. We propose expanding the Addressing Real-world Anticoagulant Management Issues in Stroke registry[33] to include heparinized patents with longer follow-up data to better understand the relative risk-benefit ratio of heparin reversal prior to thrombolysis.

Conflict of Interest

No conflict of interest by the authors.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.06.041.

References

1. Adeoye O, Hornung R, Khatri P, et al. Recombinant tissue-type plasminogen activator use for ischemic stroke in the United States: a doubling of treatment rates over the course of 5 years. Stroke. 2011;42:1952-1955. https://doi.org/10.1161/STROKEAHA.110.612358.
2. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2018 Mar;49:e46-e110.
3. National Center for Health Statistics. 1999 National Hospital Discharge Survey: Annual Summary With Detailed Diagnosis and Procedure Data. Washington, DC: US Dept of Health and Human Services; September 2001 No. 151. DHHS publication (PHS) 2001-1722.
4. Sirker A, Kwok CS, Kotronias R, et al. Influence of access site choice for cardiac catheterization on risk of adverse neurological events: a systematic review and meta-analysis. Am Heart J 2016;181:107-119.
5. Fuchs S, Stabile E, Kinnaird TD, et al. Stroke complicating percutaneous coronary interventions: incidence, predictors, and prognostic implications. Circulation 2002;106:86-91.
6. Dukkipati S, O'Neill WW, Harjai KJ, et al. Characteristics of cerebrovascular accidents after percutaneous coronary interventions. J Am Coll Cardiol 2004;43:1161-1167.
7. Hoffman SJ, Holmes Jr. DR, Rabinstein AA, et al. Trends, predictors, and outcomes of cerebrovascular events related to percutaneous coronary intervention: a 16-year single-center experience. JACC Cardiovasc Interv 2011;4:415-422.
8. Korn-Lubetzki I, Farkash R, Pachino RM, et al. Incidence and risk factors of cerebrovascular events following cardiac catheterization. J Am Heart Assoc. 2013;2:e000413.

https://doi.org/10.1161/JAHA.113.000413. Published 2013 Dec 19.
9. Newhall KA, Saunders EC, Larson RJ, et al. Use of protamine for anticoagulation during carotid endarterectomy: a meta-analysis. JAMA Surg 2016 Mar;151:247-255. https://doi.org/10.1001/jamasurg.2015.3592. Review.
10. Conte G, de Asmundis C, Baltogiannis G, et al. Periprocedural outcomes of prophylactic protamine administration for reversal of heparin after cryoballoon ablation of atrial fibrillation. J Interv Card Electrophysiol 2014 Nov;41:129-134. https://doi.org/10.1007/s10840-014-9922-y.
11. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005 Feb;8:19-32.
12. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581-1587.
13. Fontaine GV, Smith SM. Alteplase for acute ischemic stroke after heparin reversal with protamine: a case report and review. Pharmacotherapy 2017 Oct;37:e103-e106.
14. Danoun O, Sachar P, Rajamani K. Thrombolysis for acute ischemic stroke after protamine reversal of heparin. Am J Ther 2018 Sep/Oct;25:e552-e554.
15. Bereczki Jr. D, Simony Z, Szakacs Z, et al. Systemic thrombolysis in acute stroke after protamine-reversal of anticoagulation with low-molecular-weight heparin. Arch Neurosci October 01, 2016;3:e35202.
16. Safouris A, Massaut J, Triantafyllou N, et al. Safety of IV thrombolysis in an acute stroke patient anticoagulated with unfractioned heparin. J Neurol 2013 Nov;260:2911-2912.
17. Warner DS, Schwartz BG, Babygirija R, et al. Thrombolysis after protamine reversal of heparin for acute ischemic stroke after cardiac catheterization: case report and literature review. Neurologist 2018 Nov;23:194-196.
18. Guevara C, Quijada A, Rosas C, et al. Acute ischemic stroke after cardiac catheterization: the protamine low-dose recombinant tissue plasminogen activator pathway. Blood Coagul Fibrinolysis 2017 Apr;28:261-263.
19. Fearn S, Parry A, Picton A, et al. Should heparin be reversed after carotid endarterectomy? A randomised prospective trial. Eur J Vasc Endovasc Surg. 1997 Apr;13:394-397.
20. He Q, Liu J, Liang J, et al. Towards improvements for penetrating the blood−brain barrier—recent progress from a material and pharmaceutical perspective. Cells 2018;7:24. https://doi.org/10.3390/cells7040024.
21. Simon EM, Streitz MJ, Sessions DJ, et al. Anticoagulation reversal. Emerg Med Clin North Am 2018 Aug;36:585-601. https://doi.org/10.1016/j.emc.2018.04.014.
22. Cheng JW, Zhang X, Cheng L, et al. Low-dose tissue plasminogen activator in acute ischemic stroke: a systematic review and meta-analysis. J Stroke Cerebrovasc Dis 2018 Feb;27:381-390.
23. Anderson CS, Robinson T, Lindley RI, et al. Low-dose versus standard-dose intravenous alteplase in acute ischemic stroke. N Engl J Med. 2016;374:2313-2323.
24. Chao AC, Han K, Lin SF, et al. Low-dose versus standard-dose intravenous alteplase for octogenerian acute ischemic stroke patients: a multicenter prospective cohort study. J Neurol Sci 2019 Jan 29;399:76-81. https://doi.org/10.1016/j.jns.2019.01.047.
25. Kulairi Z, Deol N, Tolly R, et al. Is intravenous heparin a contraindication for TPA in ischemic stroke? Case Rep Neurol Med. 2017;2017:9280961.
26. Lees KR, Emberson J, Blackwell L, et al. Effects of alteplase for acute stroke on the distribution of functional outcomes: a pooled analysis of 9 trials. Stroke 2016;47:2373-2379.
27. Demaerschalk BM, Kleindorfer DO, Adeoye OM, et al. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2016;47:581-641.
28. Frank B, Grotta JC, Alexandrov AV, et al. Thrombolysis in stroke despite contraindications or warnings? Stroke 2013;44:727-733. https://doi.org/10.1161/STROKEAHA.112.674622.
29. Khatri P, Taylor RA, Palumbo V, et al. The safety and efficacy of thrombolysis for strokes after cardiac catheterization. J Am Coll Cardiol 2008;51:906-911.
30. Berrouschot J, Stoll A, Hogh T, et al. Intravenous thrombolysis with recombinant tissue-type plasminogen activator in a stroke patient receiving dabigatran anticoagulant after antagonization with idarucizumab. Stroke 2016;47:1936-1938.
31. Ohya Y, Makihara N, Wakisaka K, et al. Thrombolytic therapy in severe cardioembolic stroke after reversal of dabigatran with idarucizumab: case report and literature review. J Stroke Cerebrovasc Dis 2018 Jul;27:e128-e131.
32. Schafer N, Muller A, Wullner U. Systemic thrombolysis for ischemic stroke after antagonizing dabigatran with idarucizumab a case report. J Stroke Cerebrovasc Dis 2016;25:e126-e127.
33. Xian Y, Hernandez AF, Harding T, et al. Acute management of stroke patients taking non-vitamin K antagonist oral anticoagulants Addressing Real-world Anticoagulant Management Issues in Stroke (ARAMIS) Registry: design and rationale. Am Heart J 2016 Dec;182:28-35.