Thrombolysis for Acute Stroke in Hemodialysis: International Survey of Expert Opinion

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Summary

Background and objectives Although data are absent, it has been stated that thrombolysis is probably not safe in the treatment of acute stroke in patients undergoing hemodialysis. The objective of this study was for stroke experts to define the range of management concerning thrombolytic treatment of acute stroke in hemodialysis.

Design, setting, participants, & measurements Sixty-five stroke experts in thrombolytic therapy of acute ischemic stroke were queried regarding their personal experience in the use of thrombolysis in hemodialysis patients. Hypothetical case scenarios were presented.

Results Of the 65 stroke experts who were queried, 40 (62%) responded. One-third of the responders had previously treated hemodialysis patients with recombinant tissue-type plasminogen activator (rt-PA). Most favored use of intravenous rt-PA for hemodialysis patients with acute ischemic stroke. When presented with a case of a patient who had recently undergone dialysis with a mildly prolonged activated partial thromboplastin time (aPTT), 50% favored immediate intravenous thrombolysis. Seventy-eight percent of the experts would have considered an intra-arterial approach and would have preferred mechanical clot retrieval to thrombolysis.

Conclusions Despite the acknowledged absence of data and prevalent concerns about bleeding risk, most surveyed experts favored its use. One-third reported treating hemodialysis patients with this therapy. Although these results do not substitute for data, they usefully define the range of current practice of stroke experts.

Introduction

An estimated 1.5 million patients with end-stage renal disease receive chronic hemodialysis worldwide (1). Hemodialysis serves as a multiplier for other vascular risk factors, and stroke rates are substantial, averaging approximately 4% per year with an estimated 60,000 acute ischemic strokes occurring annually among hemodialysis patients (2). Hemodialysis treatment is often complicated by relative hypotension, and although data are limited, a substantial fraction (approximately 30%) of strokes appear to occur during or immediately after hemodialysis (2,3). Most patients receive intravenous heparin at the onset of or during hemodialysis, typically carried out 3 times weekly, and consequently hemodialysis patients with acute stroke are more likely to present to the emergency department with elevated prothrombin times/partial thromboplastin times (4). Even between dialysis treatments, patients are predisposed to bleeding, suspected to be due to uremic platelet dysfunction (5). For these reasons, the benefit and particularly the risk of intravenous thrombolytic therapy given for acute ischemic stroke may hypothetically be different for patients undergoing chronic hemodialysis compared with other patients.

Should hemodialysis patients experiencing acute ischemic stroke be treated with thrombolytic therapy applying the same criteria as for patients without renal failure? Clinical trials testing intravenous recombinant tissue-type plasminogen activator (rt-PA) for acute ischemic stroke did not specifically exclude hemodialysis patients. However, there are no good published data addressing the safety or efficacy of thrombolysis for hemodialysis patients with acute ischemic stroke. A single case report of a hemodialysis patient given intravenous rt-PA reported a good outcome, albeit with asymptomatic hemorrhagic transformation (6). Major guidelines are silent on this issue. Relevant to rt-PA treatment of hemodialysis patients with acute ischemic stroke, major guidelines recommend that the activated partial thromboplastin time (aPTT) must be in the normal range if heparin has been given in the previous 48 hours (7–10). In the absence of better information, we solicited the experience and opinions of 64 experts in thrombolytic therapy of acute stroke.

Materials and Methods
We queried via e-mail 65 experts in thrombolytic therapy of acute ischemic stroke in North America, Europe, Australasia, and Latin America. These experts were identified on the basis of frequent publication on this topic, co-authorship of guideline recommendations, and/or status as regional leaders in stroke treatment. Experts were asked to respond to the following specific queries:

1. Have you treated hemodialysis patients with acute ischemic stroke with intravenous thrombolysis? If so, about how many and please summarize your experience.
2. Do you have any reservations about treatment of hemodialysis patients with acute ischemic stroke with thrombolytic therapy? Do you regard them as any different from other candidates for thrombolysis for acute stroke if they have not received heparin recently?
3. Case #1. A 65-year-old diabetic, hypertensive hemodialysis patient with atrial fibrillation is receiving aspirin 81 mg daily. At the start of hemodialysis, he receives unfractionated heparin 5000 U intravenously. Four hours later, shortly after finishing dialysis, he suddenly develops aphasia and right-sided weakness. You see him 1 hour after symptom onset. National Institute of Health (NIH) stroke scale score is 18, BP is 160/105 mmHg, head CT is unremarkable, and the patient is otherwise eligible for thrombolysis, except the aPTT is slightly prolonged at 47 seconds (normal range up to 35 seconds).
   A. Would you treat immediately with intravenous rt-PA? If not, why not?
   B. Would you administer protamine sulfate to reverse the heparin effect?
   C. Would you wait approximately 2 hours and repeat the aPTT, expecting metabolism of the heparin?
   D. If intra-arterial thrombolysis were available, would it change your approach?
4. Case #2 is the same scenario as Case #1 except the patient does not have atrial fibrillation and develops a pure motor deficit suggestive of a capsular infarct that is fluctuating somewhat, but with an NIH stroke scale score of 4. Would you treat with intravenous rt-PA? If so, please explain.

We collated responses that were submitted within 30 days of the e-mail query. In a few instances, responses were incomplete or reflected misunderstanding; hence, the denominators for frequencies of responses vary slightly.

Results
Of the 65 stroke experts who were queried, 40 (62%) responded within 1 month, with a similar response rate from all regions (35 from North America with 23 responses [66%], 18 from Europe with 11 responses [61%], 5 from Australasia with 3 responses [60%], 7 from Latin America with 3 responses [43%]; Appendix I).

Previous Treatment of Hemodialysis Patients with Intravenous Thrombolysis for Acute Stroke
One-third of experts responded affirmatively that they had previously treated hemodialysis patients, with the average number treated by those responding affirmatively of 5 (range 1 to 15). Anecdotally, one reported a major hemorrhagic complication of intravenous thrombolysis. Of the 63 hemodialysis patients treated with thrombolysis for acute ischemic stroke, 56 were from North America.

Reservations about Treatment of Hemodialysis Patients with Acute Ischemic Stroke with Thrombolytic Therapy
Half of the experts reported reservations (with a similar frequency in all regions; see Table 1) related to concerns about a possibly higher bleeding risk and suspicion of cardiovascular instability. A representative response was “probably different but would treat.” Combining those without reservations and those who would treat despite mild reservations, most respondents favored use of intravenous rt-PA for hemodialysis patients with acute ischemic stroke who met guideline criteria.

Immediate Treatment with Intravenous rt-PA of a Hemodialysis Patient with a Prolonged aPTT
Almost half (17 of 40) of the experts would have treated Case #1, with no evident regional differences (Table 1). Those refraining from immediate treatment cited that recent heparin use with a prolonged aPTT is listed as a contraindication to intravenous thrombolysis in major guidelines. Justification for treatment despite the prolonged aPTT by those who would treat included that “time is brain,” that the aPTT exclusion is not firmly evidence-based, and that an aPTT prolongation of >1.5 the upper limit of normal would be required for exclusion. Of note, only 6% of the experts (n = 2) would consider administering protamine sulfate to reverse the heparin effect before intravenous thrombolysis. Most of the experts (80%) would have treated Case #1 without delaying for 2 hours to repeat the aPTT. The agreement about this approach was 100% among the 11 European experts.

Change in Therapeutic Approach with Availability of Intra-Arterial Thrombolysis
Seventy-eight percent of the experts would have considered an intra-arterial approach if available. Most of those who chose this intervention would have preferred mechanical clot retrieval to thrombolysis with rt-PA.

Treatment If Presentation Was Consistent with a Lacunar Syndrome
As in Case #1, approximately half of the experts would have treated Case #2, whereas the other 50% would have withheld treatment. Typical comments from those who elected not to treat included the good prognosis without treatment combined with suspected increased bleeding risk if hemodialysis patients were given tissue plasminogen activator (tPA). Some experts would have been more or less inclined to treat depending on the specific type of deficits obtained from the same NIH stroke score (i.e., motor versus sensory).

Discussion
Should hemodialysis patients with acute ischemic stroke undergo thrombolysis using the same criteria as for other patients? Major guidelines are silent on this issue, although one warns that “any other condition that could increase the risk of hemorrhage after alteplase administration” is a
Table 1. Summary of responses

<table>
<thead>
<tr>
<th></th>
<th>All (n = 40)</th>
<th>North America (n = 23)</th>
<th>Europe (n = 11)</th>
<th>Australasia (n = 3)</th>
<th>Latin America (n = 3)</th>
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<tr>
<td>Previous thrombolysis of hemodialysis patients</td>
<td>63%</td>
<td>89%</td>
<td>5%</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Bleeding concerns?</td>
<td>Yes 55%</td>
<td>Yes 43%</td>
<td>Yes 64%</td>
<td>Yes 33%</td>
<td>Yes 33%</td>
</tr>
<tr>
<td></td>
<td>No 45%</td>
<td>No 57%</td>
<td>No 36%</td>
<td>No 67%</td>
<td>No 67%</td>
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<tr>
<td>Immediate tPA for Case #1</td>
<td>Yes 46%</td>
<td>Yes 38%</td>
<td>Yes 54%</td>
<td>Yes 67%</td>
<td>Yes 50%</td>
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<tr>
<td></td>
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<td>No 62%</td>
<td>No 46%</td>
<td>No 33%</td>
<td>No 50%</td>
</tr>
<tr>
<td></td>
<td>No response n = 3</td>
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<td>No response n = 1</td>
<td>No response n = 1</td>
<td>No response n = 1</td>
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<tr>
<td>Protamine use in Case #1</td>
<td>Yes 6%</td>
<td>Yes 5%</td>
<td>Yes 18%</td>
<td>Yes 0%</td>
<td>No response n = 1</td>
</tr>
<tr>
<td></td>
<td>No 94%</td>
<td>No 95%</td>
<td>No 82%</td>
<td>No 100%</td>
<td>No response n = 3</td>
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<tr>
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<td>No response n = 1</td>
<td>No response n = 1</td>
<td>No response n = 1</td>
<td>No response n = 3</td>
</tr>
<tr>
<td>Delay tPA in Case #1</td>
<td>Yes 20%</td>
<td>Yes 27%</td>
<td>Yes 0%</td>
<td>Yes 50%</td>
<td>No response n = 3</td>
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<td></td>
<td>No 80%</td>
<td>No 73%</td>
<td>No 100%</td>
<td>No 50%</td>
<td>No response n = 3</td>
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<td></td>
<td>No response n = 5</td>
<td>No response n = 1</td>
<td>No response n = 1</td>
<td>No response n = 1</td>
<td>No response n = 2</td>
</tr>
<tr>
<td>Intra-arterial therapy in Case #1, if available?</td>
<td>Yes 78%</td>
<td>Yes 83%</td>
<td>Yes 73%</td>
<td>Yes 50%</td>
<td>Yes 33%</td>
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<td></td>
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<td>No 50%</td>
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<td>Immediate tPA in Case #2</td>
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<td>Yes 45%</td>
<td>Yes 33%</td>
<td>Yes 67%</td>
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<tr>
<td></td>
<td>No 53%</td>
<td>No 52%</td>
<td>No 55%</td>
<td>No 67%</td>
<td>No 33%</td>
</tr>
</tbody>
</table>

See Materials and Methods for details of queries.
reason for withholding treatment with intravenous rt-PA (8). Three studies have assessed whether renal impairment influences outcomes in patients treated with intravenous rt-PA for acute ischemic stroke (11–13). The two larger studies (12,13) reported renal impairment to be associated with higher rates of symptomatic intracerebral bleeding after rt-PA treatment; this association was independent of other recognized risk factors in the Japanese Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement (SAMURAI) rt-PA registry (13). However, few hemodialysis patients were included in these studies, and results were not reported separately for hemodialysis patients. Concerns about bleeding prompted an editorial opinion that thrombolysis for acute stroke “does not appear to be a safe option in dialysis patients” (14).

Despite specific proscription of intravenous rt-PA use by North American and European guidelines if the patient has received heparin within 48 hours and the aPTT is prolonged, almost 50% of stroke experts favored tPA administration in Case #1 (whose aPTT was moderately prolonged after heparin was given for hemodialysis). This may reflect a general disregard for strict adherence to guidelines by stroke experts, although actual treatment of acute stroke patients with recent heparin/high aPTT appears to be rare (15). The metabolism of unfractionated heparin is relatively rapid after hemodialysis (16), and repeating the aPTT after 1 to 2 hours may be a sensible option for clinicians who are reluctant to violate guideline recommendations, if thrombolysis can still be administered within accepted time restrictions. Several experts commented that “time is brain” in justifying immediate thrombolysis despite the prolongation of the aPTT in Case #1. Of note, the anticoagulant effect of low-molecular-weight heparins is prolonged in hemodialysis patients.

A potential limitation of this survey is the selection of stroke experts and self-selection for responding. The substantial response rate of 60% and generally consistent views from multiple areas of the world may it likely that the survey results are generalizable.

In the absence of adequate data to guide therapy, our goal was to define the range of management by stroke experts concerning thrombolytic treatment of acute stroke in patients undergoing hemodialysis. Despite the acknowledged absence of data and prevalent concerns about bleeding risk, most surveyed experts who responded favored tPA use, and one-third reported treating hemodialysis patients with this therapy. Although these results do not substitute for data, they usefully define the range of current practice of stroke experts.

Appendix I. Stroke Experts Who Contributed Information (Alphabetically)

H. Adams (Iowa City, IA), M. Aguilar (Scottsdale, AZ), G. Albers (Palo Alto, CA), P. Amarenco (Paris, France), D. Anderson (Minneapolis, MN), A. Arauz (Mexico City, Mexico), P. Bath (Nottingham, United Kingdom), O. Benavente (Vancouver, Canada), J. Biller (Chicago, IL), L. Birnbaum (San Antonio, TX), A. Chamorro (Barcelona, Spain), S. Cruz-Flores (St. Louis, MO), S. Davis (Melbourne, Australia), C. Estol (Buenos Aires, Argentina), K. Furie (Boston, MA), N. Gonzales (Houston, TX), J. Grotta (Houston, TX), G. Hankey (Perth, Australia), M. Hill (Calgary, Canada), T. Ingall (Scottsdale, AZ), M. Johnson (Dallas, TX), S.C. Johnston (San Francisco, CA), C. Kase (Boston, MA), S. Kasner (Philadelphia, PA), M. Kaste (Helsinki, Finland), C. Kidwell (Washington, DC), K. Lees (Glasgow, United Kingdom), S. Levine (New York, NY), W. Longstreth (Seattle, WA), H. Lutsep (Portland, OR), B. Norrving (Lund, Sweden), W. Oczkowski (Hamilton, Canada), P. Rothwell (Oxford, United Kingdom), P. Sandercock (Edinburgh, United Kingdom), J. Streifler (Tel Aviv, Israel), J. Tapia (Santiago, Chile), D. Tirschwell (Seattle, WA), K. Toyoda (Osaka, Japan), J. Wardlaw (Edinburgh, United Kingdom), and C. Weimar (Essen, Germany).

Disclosures

None.

References

13. Naganuma M, Koga M, Shiokawa Y, Nakagawa J, Furui E,


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