Use of Intravenous Heparin by North American Neurologists
Do the Data Matter?
Ahmad Al-Sadat, MD; Mohammad Sunbulli, MD; Seemant Chaturvedi, MD

Background and Purpose—Our aim was to determine current usage patterns of intravenous heparin for patients with acute ischemic stroke.

Methods—A survey was undertaken of 280 neurologists from the United States and 270 neurologists from Canada. Brief vignettes were presented for the following 5 scenarios: stroke in evolution, atrial fibrillation-related stroke (A FIB), vertebrobasilar stroke, carotid territory stroke, and multiple transient ischemic attacks. The effect of medicolegal factors was also ascertained. Statistical comparisons were done with chi-squared testing.

Results—US neurologists were significantly more likely than Canadian neurologists to use intravenous heparin for patients with stroke in evolution (51% versus 33%, \(P<0.001\)), vertebrobasilar stroke (30% versus 8%, \(P<0.001\)), carotid territory stroke (31% versus 4%, \(P<0.001\)), and multiple transient ischemic attacks (47% versus 9%, \(P<0.001\)). The vast majority of US and Canadian neurologists would use intravenous heparin for acute stroke patients with A FIB (88% and 84%, respectively). US neurologists more often cited medicolegal factors as a potential influence on the decision-making process than Canadian neurologists (33% versus 10%, \(P<0.001\)).

Conclusions—In several clinical scenarios, US neurologists were significantly more likely than Canadian neurologists to use intravenous heparin. Fears regarding medicolegal consequences may partially explain the treatment disparity. Despite the publication of 4 clinical trials, which have not shown any long-term benefit for patients with acute stroke and A FIB (International Stroke Trial, Heparin in Acute Embolic Stroke Trial) or cardioembolic stroke (Trial of Org 10172 in Acute Stroke Treatment, the Tinzaparin in Acute Ischemic Stroke Trial), both US and Canadian neurologists would use intravenous heparin in large numbers for this condition. Further studies are warranted to investigate the lack of impact of “negative” studies on clinician behavior. (Stroke. 2002;33:1574-1577.)

Key Words: heparin ■ heparin, low-molecular-weight ■ heparinoids ■ jurisprudence ■ stroke, acute ischemic

Intravenous heparin was introduced in the treatment of acute ischemic stroke by Hedenius in 1941.\(^1\) Since then its use has been an area of great controversy among neurologists. Approximately 1 decade ago there were some small clinical trials that did not support the use of heparin,\(^2,3\) whereas other authorities concluded that heparin has a role in some types of stroke such as cardioembolic stroke and stroke in evolution (SIE).\(^4-7\) With these controversial data, most neurologists at that time felt that there was a need for further clinical investigation to evaluate the role of heparin in acute ischemic stroke.\(^8\)

The 1994 American Heart Association guidelines did not give a clear recommendation on the use of intravenous heparin. These guidelines mentioned that “Until more data are available, the use of heparin remains a matter of preference of the treating physician. It should be understood that the use of heparin (or the lack of its administration) may not alter the outcome of a patient with ischemic stroke.”\(^9\) Since the 1994 American Heart Association guidelines, there have been 6 major clinical trials pertaining to the use of heparin, low-molecular-weight heparin, or heparinoids in patients with acute stroke.\(^10-15\) Five of these six studies did not show clear benefit associated with the early use of heparin or related compounds in patients with acute stroke.

We sought to obtain updated information regarding the practices of US and Canadian neurologists with regard to acute heparin use. Our hypothesis was that US neurologists would use heparin more frequently and that medicolegal factors would affect US physicians more than Canadian neurologists.

Subjects and Methods
A survey was taken of 280 neurologists from the United States and 270 neurologists from Canada. All were active members of the American Academy of Neurology. A systematic sample of names was chosen from the 2000–2001 American Academy of Neurology.
likely than Canadian neurologists to use intravenous heparin evolution (SIE): US neurologists were significantly more inclined to use intravenous heparin for CAR (31% versus 8%, \( P < 0.001 \).) (3) Vertebrobasilar stroke (VB): US neurologists were significantly more likely than Canadian neurologists to use intravenous heparin for patients with VB (30% versus 8%, \( P < 0.001 \).) (4) Carotid territory stroke (CAR): US neurologists were significantly more likely than Canadian neurologists to use intravenous heparin for patients with CAR (31% versus 4%, \( P < 0.001 \).) (5) Multiple transient ischemic attacks (TIAs): US neurologists were significantly more likely than Canadian neurologists to use intravenous heparin for patients with multiple TIAs (47% versus 9%, \( P < 0.001 \).) The effect of medicolegal factors is shown in Table 3. US neurologists more often cited medicolegal factors as a potential influence in the decision-making for the use of intravenous heparin than Canadian neurologists (33% of US neurologists responded with “always,” “frequently,” or “sometimes” versus 10% of the Canadian neurologists, \( P < 0.001 \).) The greatest degree of uncertainty (determined by responding to the question “would you use intravenous heparin” as “maybe”) was found for SIE, for which 35% of US and 25% of Canadian neurologists responded with “maybe.” There was no significant heterogeneity in the responses to the questions based on the number of years that the neurologist was in practice.

**Discussion**

Our study demonstrates that in 4 of 5 common clinical scenarios (SIE, CAR, VB, and multiple TIAs), US neurologists were significantly more inclined to use intravenous anticoagulation compared with their Canadian counterparts. This type of practice variation has been previously demonstrated in other aspects of cerebrovascular disease. The use of carotid endarterectomy is much higher in the US than in Canada.17 For the specific scenario of carotid endarterectomy

<table>
<thead>
<tr>
<th>Case vignettes</th>
<th>US neurologists</th>
<th>Canada neurologists</th>
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<tr>
<td>1. A 70-year-old man is admitted to your service at 3:00 PM with mild right facial weakness and mild word-finding difficulty. He is placed on aspirin. At 9:00 PM, you are called by the nurse because he has increased right-sided weakness with 3/5 strength in the right arm and leg and moderate dysphasia. Head CT is negative. Patient is in sinus rhythm with BP 140/80. Would you use IV heparin? (Yes, no, or maybe).</td>
<td>Yes, 51%</td>
<td>No, 14%</td>
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<td>2. A 70-year-old woman is admitted with mild expressive dysphasia and mild right hemiparesis, which began 6 hours ago. She has a history of atrial fibrillation that was treated with aspirin. She continues to be in atrial fibrillation in the emergency room. BP is 140/80. Head CT is negative. Would you use IV heparin? (Yes, no, or maybe).</td>
<td>Yes, 35%</td>
<td>No, 42%</td>
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<tr>
<td>3. A 70-year-old man with a history of HTN, DM, and smoking is admitted with a new onset of vertigo, ataxia, and diplopia, which began 6 hours ago. BP is 140/80. Head CT is negative. He is in a sinus rhythm, and he was not on an antplatelet agent previously. Would you use IV heparin? (Yes, no, or maybe).</td>
<td>Yes, 51%</td>
<td>No, 42%</td>
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<td>4. A 70-year-old woman is admitted with new onset dysphasia and mild right-sided weakness, which began 6 hours ago. She is in sinus rhythm with BP 140/80. Head CT is negative. She has a history of DM and smoking, and you hear a left carotid bruit. She was not on an antplatelet agent previously. Would you use IV heparin? (Yes, no, or maybe).</td>
<td>Yes, 35%</td>
<td>No, 42%</td>
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<td>5. A 70-year-old man is admitted with 2 episodes of transient visual loss in the right eye over the past 2 days, each lasting for 5 minutes. He has a history of DM and smoking. He is in a sinus rhythm. BP is 140/80. Head CT is negative. He was not on an antplatelet agent previously. Would you use IV heparin? (Yes, no, or maybe).</td>
<td>Yes, 51%</td>
<td>No, 42%</td>
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**Results**

One hundred thirteen (40%) of the US neurologists and one hundred thirty-seven (51%) of the Canadian neurologists returned a completed survey. The results are shown in Table 2.

The results can be summarized as follows: (1) Stroke in evolution (SIE): US neurologists were significantly more likely than Canadian neurologists to use intravenous heparin for patients with SIE (51% versus 33%, \( P < 0.001 \)). (2) Atrial fibrillation-related stroke (A FIB): The vast majority of US and Canadian neurologists would use intravenous heparin for an acute stroke in a patient with A FIB (88% and 84%, respectively). (3) Vertebrobasilar stroke (VB): US neurologists were significantly more likely than Canadian neurologists to use intravenous heparin for patients with VB (30% versus 8%, \( P < 0.001 \)). (4) Carotid territory stroke (CAR): US neurologists were significantly more likely than Canadian neurologists to use intravenous heparin for patients with CAR (31% versus 4%, \( P < 0.001 \)). (5) Multiple transient ischemic attacks (TIAs): US neurologists were significantly more likely than Canadian neurologists to use intravenous heparin for patients with multiple TIAs (47% versus 9%, \( P < 0.001 \)).

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**Discussion**

Our study demonstrates that in 4 of 5 common clinical scenarios (SIE, CAR, VB, and multiple TIAs), US neurologists were significantly more inclined to use intravenous anticoagulation compared with their Canadian counterparts. This type of practice variation has been previously demonstrated in other aspects of cerebrovascular disease. The use of carotid endarterectomy is much higher in the US than in Canada.17 For the specific scenario of carotid endarterectomy
in asymptomatic patients, a previous study found that neurologists from Florida were more likely to refer patients for surgery for asymptomatic carotid stenosis than neurologists from Ontario and Quebec. The reasons underlying the increased tendency of US neurologists to use intravenous heparin are unclear. They may in part be driven by medicolegal considerations. In our study, one third of US neurologists did respond that concerns regarding a lawsuit at least sometimes influenced their selection of acute antithrombotic therapy, compared with only 10% of Canadian neurologists (P<0.001). For the situation of carotid endarterectomy for asymptomatic stenosis mentioned above, in that scenario as well, Florida neurologists were significantly more likely to cite medicolegal concerns as a factor in their decision making than Canadian neurologists (27% versus 3%). Differing features of the legal system in the 2 countries (eg, contingency fees for plaintiffs attorneys in the US) may partly explain the apparent increased concern of American neurologists regarding potential litigation.

The one scenario in which the majority of both US and Canadian neurologists would use intravenous heparin is in the setting of an acute stroke with atrial fibrillation. This practice is not well supported by the recent clinical trials. In the Heparin in Acute Embolic Stroke Trial, use of the low-molecular-weight heparin dalteparin did not improve outcome compared with aspirin. In the International Stroke Trial, the use of subcutaneous heparin did not provide any net benefit among 3169 patients with atrial fibrillation. Finally, in the Trial of Org 10172 in Acute Stroke Treatment and the Tinzaparin in Acute Ischemic Stroke Trial, there was no long-term benefit in patients with acute cardioembolic stroke.

The reasons for the continued popularity of intravenous heparin in the setting of A FIB are unclear. Perhaps the clinicians in our study feel that the clinical trials mentioned above (none of which evaluated intravenous unfractionated heparin) are not directly applicable to their patients. Some investigators have suggested that unfractionated heparin may have unique biological properties, including anti-inflammatory effects, which may still make it valuable for patients with acute ischemic stroke. A new study of intravenous, dose-adjusted, unfractionated heparin has been launched in Europe, which will provide important information on the potential efficacy of unfractionated heparin in acute cardioembolic stroke. Intravenous heparin might also be popular in stroke patients with atrial fibrillation as a transitional therapy for long-term warfarin.

In terms of other surveys conducted before the recent clinical trials, a 1988 survey of 219 US neurologists found that heparin was quite popular for the prevention of recurrent cardiogenic emboli (82% believed heparin was indicated in this setting). Anderson surveyed a group of neurologists practicing in Greater Metropolitan Minneapolis-St. Paul, Minnesota in 1988 and 1991 regarding use of intravenous heparin, using clinical vignettes for patients with SIE, TIA, CAR, and VB, and cardioembolic stroke. The results of this study and of our survey are shown in Table 4. The responses in the Minnesota survey were only “yes” or “no,” and therefore, for comparative purposes, we have included in Table 4 the percentage in our study who responded with a definite opinion only (#yes/#yes or no). Using this analysis, we found that US neurologists in our survey are less likely to use intravenous heparin than neurologists surveyed in Minnesota for patients with SIE, VB, CAR, and recurrent TIs. The most significant difference was for VB (75% in 1988 versus 38% in 2001), but the majority of neurologists surveyed in 1991 and 2001 (92% and 94%, respectively) would use intravenous heparin for cardioembolic stroke/A FIB–related stroke. If the practice of neurologists in the Greater Metropolitan Minneapolis-St. Paul area can be extrapolated to the country as a whole, it is possible that US neurologists are using intravenous heparin less frequently in 2001 than in earlier decades. The largely negative recent heparin clinical trials may explain the potential decrease in heparin utilization.

Our study has several limitations, including a moderate response rate (45% total). We cannot exclude potential selection bias in that individuals who chose to respond may have strong opinions on this subject, and this may have skewed the survey results. Because the survey was anonymous, we cannot characterize the nonresponders as to whether they are comparable to the responding group. The incomplete response rate limits our ability to generalize the findings in this study to the broader group of practicing neurologists in the US and Canada. Interestingly, however, we have conducted a companion study using the same survey instrument of neurologists limited to 1 state in the US (to minimize geographic variability), and the results were virtually identical to the results seen in the national sample of US neurologists in the current study (S. Chaturvedi, MD, unpublished data, 2001). This would suggest that the results from the US sample in this study may, in part, be reflective of the practice patterns of most American neurologists.

In conclusion, we found that American neurologists were significantly more likely than Canadian neurologists to use an intravenous anticoagulant in 4 of 5 common clinical neurovascular conditions. This serves as another example of the practice variations among US and Canadian physicians. Future studies should examine whether “negative” studies have the same impact on physician behavior as “positive” trials.

References

| Table 4. Percentage of US Neurologists Who Would Use Intravenous Heparin |
|-----------------|------|------|------|-----|------|
|                 | SIE, % | A FIB/CE, % | VB, % | CAR, % | TIA, % |
| 1988 (Anderson) | 90    | ...    | 75    | 62    | 77    |
| 1991 (Anderson) | 94    | 92     | 74    | 53    | 73    |
| 2001 (current study) | 78    | 94     | 38    | 37    | 58    |
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