Subtherapeutic International Normalized Ratio in Warfarin-Treated Patients Increases the Risk for Symptomatic Intracerebral Hemorrhage After Intravenous Thrombolysis

Raymond C.S. Seet, MD; Yi Zhang, MD; S. Arthur Moore, MD; Eelco F. Wijdicks, MD, PhD; Alejandro A. Rabinstein, MD

Background and Purpose—There is uncertainty whether warfarin-treated patients (despite international normalized ratio <1.7) have increased risks of symptomatic intracerebral hemorrhage after intravenous thrombolysis.

Methods—Vascular risk factors, stroke subtype, and outcome measures were compared between warfarin- and nonwarfarin-treated patients undergoing acute thrombolysis within 3 hours of symptom onset.

Results—From 212 patients (mean age, 74±14 years; 50% men) studied, 14 (6.5%) had prior warfarin use. After adjusting for age, baseline National Institutes of Health Stroke Scale, and stroke subtype, warfarin-treated patients had significantly increased risks of developing symptomatic intracerebral hemorrhage (adjusted OR, 14.7; 95% CI, 1.3 to 54.3). A trend for poorer stroke recovery and increased mortality was observed in warfarin-treated patients on univariate, but not on multivariable, analyses.

Conclusions—Warfarin-treated patients with stroke have increased risks of symptomatic intracerebral hemorrhage after thrombolytic treatment. These data raise safety concerns of thrombolytic treatment in warfarin-treated patients with subtherapeutic international normalized ratio. (Stroke. 2011;42:00-00.)

Key Words: INR ■ intracerebral hemorrhage ■ ischemic stroke ■ warfarin

A pproximately 1 in 10 patients eligible for recombinant tissue-type plasminogen activator (rtPA) treatment had prior warfarin use. However, clinical trials and treatment guidelines differ in their enrollment of warfarin-treated patients for rtPA treatment. The National Institute of Neurological Disorders and Stroke and all 3 European Cooperative Acute Stroke Study (ECAS) trials excluded warfarin-treated patients from study enrollment, whereas the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study and the postmarketing study of rtPA (Standard Treatment With Alteplase to Reverse Stroke Study [STAR]) included such patients. The current American Heart Association guidelines consider warfarin-treated patients eligible for rtPA treatment if they present within 3 hours of symptom onset with international normalized ratio (INR) ≤1.7. In Europe, patients with prior warfarin use are excluded from the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST).

Current data on the safety of warfarin-treated patients with subtherapeutic INR undergoing rtPA treatment are conflicting. One study indicated increased symptomatic intracerebral hemorrhage (ICH) risks, whereas another suggested the risks to be unchanged. These studies, however, did not assess the confounding effects of blood pressure control after rtPA treatment and stroke subtype. The purpose of this study is to evaluate the frequency of symptomatic ICH among rtPA-treated patients with stroke with prior warfarin use and to investigate whether blood pressure control (before and after rtPA treatment) may account for the differences in hemorrhagic risks.

Methods and Materials

Between April 2006 and September 2010, consecutive rtPA-treated patients with acute ischemic stroke who presented within 3 hours of symptom onset at St Marys Hospital, Mayo Clinic, Rochester, MN, were studied. Patients who underwent primary or adjunctive endovascular treatments due to contraindication to or after intravenous rtPA were excluded. Warfarin use was defined as the consumption of warfarin 5 days before stroke onset. The current American Heart Association guidelines consider warfarin-treated patients eligible for rtPA treatment if they present within 3 hours of symptom onset with international normalized ratio (INR) ≤1.7. In Europe, patients with prior warfarin use are excluded from the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST).

Current data on the safety of warfarin-treated patients with subtherapeutic INR undergoing rtPA treatment are conflicting. One study indicated increased symptomatic intracerebral hemorrhage (ICH) risks, whereas another suggested the risks to be unchanged. These studies, however, did not assess the confounding effects of blood pressure control after rtPA treatment and stroke subtype. The purpose of this study is to evaluate the frequency of symptomatic ICH among rtPA-treated patients with stroke with prior warfarin use and to investigate whether blood pressure control (before and after rtPA treatment) may account for the differences in hemorrhagic risks.
and minimum BP. Antihypertensive treatment was recorded. The presence of ICH was classified according to the European–Australian Acute Stroke Study (ECASS) criteria and symptomatic ICH was defined by hemorrhagic transformation with at least a 4-point increment in National Institutes of Health Stroke Scale score. Poor functional recovery was considered when 3-month modified Rankin scale score was ≥3. The study protocol was approved by the Mayo Clinic Institutional Review Board.

**Results**

From 248 patients who received thrombolysis, 36 patients (who underwent endovascular procedures) were excluded. Mean age (SD) of the remaining 212 patients was 74.1 (14.1) years; median baseline National Institutes of Health Stroke Scale score, 13.4 (interquartile range, 10.2 to 16.4), and mean onset-to-treatment time with rtPA 142 (56) minutes (Table 1). BP measurements and antihypertensive use (at baseline and 24 hours post-rtPA) did not differ between warfarin and nonwarfarin patients (data not shown). Fourteen patients (6.5%) had consumed warfarin before rtPA treatment, of whom 5 (36%) had baseline INR <1.1. Among warfarin-treated patients, baseline INR levels did not differ between those with and without symptomatic ICH (median INR, 1.1 versus 1.2; P=0.937).

Sixteen patients developed symptomatic ICH. Symptomatic ICH occurred in 36% of warfarin-treated patients and 6% of nonwarfarin patients. After adjusting for baseline National Institutes of Health Stroke Scale, mean arterial pressure, and stroke subtype, warfarin-treated patients had 5-fold increased incidence of symptomatic ICH compared with nonwarfarin patients (adjusted OR, 14.7; 95% CI, 1.3 to 54.3; Table 2). Among patients with atrial fibrillation, the incidence of symptomatic ICH was higher in warfarin-treated compared with nonwarfarin patients (40% versus 8%, P=0.034). Similarly, patients with cardioembolic stroke on warfarin treatment had a higher incidence of symptomatic ICH compared with those without (39% versus 4%, P<0.001).

**Discussion**

We observed a significant increase in the incidence of symptomatic ICH among rtPA-treated patients with prior warfarin use, an association that is independent of BP control and stroke etiology. Our findings are in agreement with those of a previous study but differed from another study that included younger patients and those undergoing endovascular treatments.

Consistent with previous observations, symptomatic ICH occurred in warfarin-treated patients who presented with normal or near-normal baseline INR and these INR levels did not differ between those who developed symptomatic ICH and those who did not. It is not known whether baseline INR accurately reflects the subsequent anticoagulant effects of warfarin in the presence of exogenous rtPA and whether warfarin could interact with other hemostatic factors, resulting in an excess of hemorrhagic events. In warfarin-treated patients with subtherapeutic INR, caution should be exercised when making treatment decisions based on baseline INR alone. Future studies should consider serial measurements of INR during treatment.
INR, tPA antigen, and endogenous fibrinolysis inhibitors (eg, plasminogen activator inhibitor) to elucidate the excess in hemorrhagic risks.

Despite including a relatively small number of patients from a single referral center, we highlight serious safety concerns of rtPA in warfarin-treated patients with stroke.

Disclosures

None.

References

Subtherapeutic International Normalized Ratio in Warfarin-Treated Patients Increases the Risk for Symptomatic Intracerebral Hemorrhage After Intravenous Thrombolysis
Raymond C.S. Seet, Yi Zhang, S. Arthur Moore, Eelco F. Wijdicks and Alejandro A. Rabinstein

Stroke. published online June 9, 2011; Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2011/06/09/STROKEAHA.111.614214

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2013/10/08/STROKEAHA.111.614214.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
Abstract 11

와파린 치료 중인 환자에서 치료 범위 이하의 INR은 정맥내 혈전용해술 후 증상성 뇌내출혈의 위험을 높인다

Subtherapeutic International Normalized Ratio in Warfarin-Treated Patients Increases the Risk for Symptomatic Intracerebral Hemorrhage After Intravenous Thrombolysis

Raymond C.S. Seet, MD; Yi Zhang, MD; S. Arthur Moore, MD; Eelco F. Wijdicks, MD, PhD; Alejandro A. Rabinstein, MD

(Stroke. 2011;42:2333-2335.)

Key Words: INR • intracerebral hemorrhage • ischemic stroke • warfarin

배경과 목적
와파린 치료 중인 환자에서 (국제표준화비율(international normalized ratio, INR) 1.7 미만의 경우에) 정맥내 혈전용해술 후 증상성 뇌내출혈(symptomatic intracerebral hemorrhage)의 위험이 증가하는지는 불확실하다.

방법
증상 발생 3시간 이내에 혈전용해술을 받은 환자들에서 와파린 치료군과 비lesi름 군 환자들 사이의 현관 위험인지, 뇌증 중 아형과 결과들을 비교하였다.

결과
212명(평균 나이, 74±14세; 50% 남성)의 대상 환자들 중 14명 (6.5%)이 이전에 와파린을 복용하던 환자였다. 나이, 기저 NIH 뇌졸중도, 뇌졸중 아형을 보정하였을 때, 와파린 치료 중인 환자에서 증상성 뇌내출혈의 발생 위험이 유의하게 증가하였다 (보정 교차비[adjusted OR], 14.7; 95% CI, 1.3~54.3). 단변량 분석에서는 와파린 치료 중인 환자에서 뇌졸중 확장이 뚜렷하고 사망률이 증가하는 경향이 있었으나, 다변량 분석에서는 그렇지 않았다.

결론
와파린 치료 중재 뇌졸중이 발생한 환자에서 혈전용해술 후 증상성 뇌내출혈 위험이 높았다. 이러한 결과는 치료 범위 이하의 INR을 가진 와파린 치료 환자에서의 혈전용해술의 안전성에 대한 우려를 높인다.

Table 2. Odds Ratios (95% CIs)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Unadjusted</th>
<th>( P )</th>
<th>Adjusted*</th>
<th>( P )</th>
<th>Adjusted†</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any intracerebral hemorrhage</td>
<td>4.61 (1.49–14.3)</td>
<td>0.004</td>
<td>5.29 (0.98–19.5)</td>
<td>0.054</td>
<td>5.49 (0.92–33.6)</td>
<td>0.094</td>
</tr>
<tr>
<td>Symptomatic intracerebral hemorrhage</td>
<td>6.67 (2.52–15.5)</td>
<td>&lt;0.001</td>
<td>9.17 (2.32–24.4)</td>
<td>0.025</td>
<td>14.7 (1.3–54.3)</td>
<td>0.044</td>
</tr>
<tr>
<td>Poor functional recovery</td>
<td>2.76 (0.84–9.09)</td>
<td>0.083</td>
<td>3.42 (0.75–15.6)</td>
<td>0.112</td>
<td>3.25 (0.71–14.9)</td>
<td>0.130</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>2.37 (0.75–7.46)</td>
<td>0.131</td>
<td>1.90 (0.42–8.62)</td>
<td>0.404</td>
<td>1.41 (0.44–9.17)</td>
<td>0.370</td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale; CI, confidence interval.
*Adjusted for age and baseline NIHSS.
†Adjusted for age, baseline NIHSS and stroke subtype.