Is Intracerebral Hemorrhage a Time-Dependent Phenomenon After Successful Combined Intravenous and Intra-Arterial Therapy?

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Background and Purpose—Onset-to-reperfusion time (ORT) has recently emerged as an essential prognostic factor in acute ischemic stroke therapy. Although favorable outcome is associated with reduced ORT, it remains unclear whether intracranial bleeding depends on ORT. We therefore sought to determine whether ORT influenced the risk and volume of intracerebral hemorrhage (ICH) after combined intravenous and intra-arterial therapy.

Methods—Based on our prospective registry, we included 157 consecutive acute ischemic stroke patients successfully recanalized with combined intravenous and intra-arterial therapy between April 2007 and October 2011. Primary outcome was any ICH within 24 hours posttreatment. Secondary outcomes included occurrence of symptomatic ICH (sICH) and ICH volume measured with the ABC/2.

Results—Any ICH occurred in 26% of the study sample (n=33). sICH occurred in 5.5% (n=7). Median ICH volume was 0.8 mL. ORT was increased in patients with ICH (median=260 minutes; interquartile range=230–306) compared with patients without ICH (median=226 minutes; interquartile range=200–281; P=0.008). In the setting of sICH, ORT reached a median of 300 minutes (interquartile range=276–401; P=0.004). The difference remained significant after adjustment for potential confounding factors (adjusted P=0.045 for ICH; adjusted P=0.002 for sICH). There was no correlation between ICH volume and ORT (r=0.16; P=0.33).

Conclusions—ORT influences the rate but not the volume of ICH and appears to be a critical predictor of symptomatic hemorrhage after successful combined intravenous and intra-arterial therapy. To minimize the risk of bleeding, revascularization should be achieved within 4.5 hours of stroke onset. (Stroke. 2013;44:806–808.)

Key Words: endovascular procedures ■ stroke ■ thrombolysis, therapeutic

Successful recanalization is a powerful predictor of favorable outcome after acute ischemic stroke.1–3 Furthermore, favorable outcome is directly linked to onset-to-reperfusion time (ORT).2,4 Intravenous (IV) alteplase studies have shown no clear relationship between intracranial hemorrhage (ICH) and onset to treatment time.2,4 Assessing ORT with IV–recombinant tissue plasminogen activator (rt-PA) alone, however, is more difficult than with endovascular therapy because arterial patency cannot be as accurately monitored. ICH after intra-arterial (IA) thrombolyis, on the other hand, is associated with an 80% to 86% rate of disability or mortality in certain series.5,6 Because it remains unclear whether ICH depends on ORT after combined IV-IA therapy, we sought to determine whether ORT influenced the occurrence and extent of ICH.

Methods Patients presenting with acute ischemic stroke between April 2007 and October 2011 were identified from our prospective registry. IV thrombolysis (0.9 mg/kg rt-PA) was administered within 4.5 hours of stroke onset when no arterial occlusion was identified, as recommended by the National Institute of Neurological Disorders and Stroke1—unless the patient presented with impaired consciousness, ICH or infarction >1/3 middle cerebral artery territory on CT or MR. In case of arterial occlusion, combined IV–IA thrombolysis was performed,7 starting with 0.6 mg/kg IV rt-PA, followed by 0.3 mg/kg IA rt-PA when occlusion persisted on the baseline

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angiogram. Additional mechanical thrombectomy was performed if IA rt-PA failed.

The Ethics Committee of the Ambroise-Paré Hospital approved the research protocol. Informed consent was obtained from all patients or legal substitute.

Data Collection and Definitions
Data were prospectively collected using a structured questionnaire. Revascularization was assessed during IA therapy and graded by two staff members (E.M. and M.M.) using the Thrombolysis In Myocardial Infarction (TIMI) scale.\(^7\) Time between treatment initiation and symptom onset—or patient last seen normal—was recorded, as well as ORT.

All patients were controlled with CT or MRI 24 hours after treatment onset to rule out ICH, which was considered symptomatic (sICH) whenever National Institutes of Health Stroke Scale (NIHSS) scores increased by ≥4. A neuroradiologist (P.M.) blinded to all clinical data retrospectively reviewed all follow-up imaging and evaluated ICH volumes using the ABC/2 method.\(^8\) A second reader (M.M.) provided an independent assessment of ICH volumes to assess interobserver reproducibility.

Outcomes
Primary outcome was any ICH. Secondary outcomes were ICH volume and percentage of sICH.

Statistical Analysis
Bivariate comparisons between patients with and without ICH were made using \(\chi^2\) tests for categorical variables (or Fisher exact test when the expected cell frequency was <5) and Student \(t\) test for continuous variables or the Mann–Whitney \(U\) test for skewed distribution. Nonparametric analysis of covariance was used to adjust for group differences between ORT and ICH (NIHSS admission score and occlusion site) and to assess heterogeneity across recanalization grades, site of arterial occlusion (internal carotid artery [ICA] versus other), and patients treated ± mechanical thrombectomy. Intraclass correlation coefficient was calculated to assess the agreement in the 2 ICH volume measurements; 95% confidence interval was calculated using bootstrap resampling method with 10000 replications. Spearman's correlation coefficients (\(r\)) between ICH volume and ORT were calculated whenever applicable. Statistical testing was done at the 2-tailed \(\alpha\) level of 0.05. Data were analyzed with the SAS software package, release 9.3 (SAS Institute, Cary, NC).

Results
During the 4-year study period, 157 consecutive acute ischemic stroke patients were treated with a combined IV-IA rt-PA approach—with additional mechanical thrombectomy in 44 patients. Of these, 29 (18%) with unsuccessful recanalization (TIMI 0–1) were excluded; 8 (28%) had ICH. Of the 128 patients included (TIMI 2–3), any ICH occurred in 33 cases (25.8%; 95% confidence interval, 17.8–33.8), with no significant difference among TIMI grades (21% in the 86 patients with TIMI 3 versus 36% in the 42 patients with TIMI 2, \(P=0.07\)). Patients with ICH had significantly higher NIHSS admission scores and a higher proportion of ICA occlusions (see Table I in the online-only Data Supplement).

Time-to-Recanalization and Risk of Intracerebral Hemorrhage
ORT was significantly prolonged in patients with ICH compared with those without (Figure 1). Median ORT (interquartile range) was 260 (230–306) versus 226 (200–281) minutes, respectively (\(P=0.008\)). No heterogeneity was found across recanalization grades, among patients with and without ICA occlusion or those needing additional mechanical thrombectomy (all \(P\) for heterogeneity >0.10). After adjusting for NIHSS score and ICA occlusion, ORT remained significantly higher in patients with ICH (\(P=0.045\)). It was even greater in patients with sICH (\(n=7\)) compared with those without or asymptomatic ICH: 300 (276–401) versus 230 (206–281) min, respectively (crude/adjusted \(P=0.004/0.002\)). Figure 2 shows the crude rate of ICH after categorizing ORT into 4 groups (<3 h, 3–4.5 h, 4.5–6 h, >6 h).

Time-to-Recanalization and Intracerebral Hemorrhage Volume
ICH volume could be measured in all but 3 patients who either had subarachnoid (\(n=1\)) or petechial (\(n=2\)) hemorrhagic foci. The interobserver agreement for ICH volume was good with an Intraclass correlation coefficient of 0.81 (Bootstrap 95%CI, 0.64–0.90). Parenchymal hemorrhage occurred in the deep middle cerebral artery territory alone in 17 (57%), lobar territory alone in 8 (26%), both territories in 3 (10%), and in the brain stem in 2 (7%). Median ICH volume was 0.8 mL (interquartile range, 0.3–2.2 mL; range, 0.02–300 mL). There was no correlation between ICH volume and ORT (\(r=0.18\); \(P=0.34\)).

Discussion
Our data show that ORT is an independent predictor of ICH after IV/IA thrombolysis. Kidwell et al\(^6\) previously...
identified the main independent predictors of ICH after IA therapy (ie, higher NIHSS scores at admission, prolonged ORT, low platelet count, and hyperglycemia). Compared with that study—which included 89 patients treated with IV or IA alteplase or urokinase—our series excluded the use of urokinase, focusing on 128 consecutive patients recanalized with IV/IA alteplase only. Although a recent study evaluating 623 acute ischemic stroke patients demonstrated that collateral supply appears to be a powerful predictor of sICH (2.6% versus 10.2% with or without collaterals, respectively), this analysis was not conducted in the present study, because a full-vessel angiography was typically omitted to achieve shorter time-to-recanalization.

The major IV-alteplase trials showed no relationship between increased onset to treatment time and major ICH but suffered from a lack of precise ORT monitoring. Our results indicate that increased ORT appears to correlate with sICH but not with ICH volume. The favorable outcome associated with reduced ORT in other IV/IA trials may thus largely reflect a lower incidence of sICH, regardless of the size of ICH. 5.5% of our patients experienced sICH—less than in other IA thrombolysis trials such as PROACT II or IMS (9% to 11%). This may relate to the acceptable IV-therapeutic window from which all our patients initially benefitted.

Our study had other limitations. First, the contrast staining on CT images in the subacute stage after recanalization may lead to an overestimation of ICH. Although another control CT beyond 48h might show decreased attenuation favoring contrast staining in questionable cases, accurate distinction requires either dual-energy CT or MR. Secondly, our sample size was too small to draw definite conclusions; larger studies are warranted to validate our findings and evaluate other sICH predictors, such as collaterals. Thirdly, advanced perfusion/diffusion studies were not used to evaluate the infarct-to-penumbra ratio. Although carefully selected patients may benefit from reperfusion independently of stroke duration, we restricted our criteria to those most widely accepted.

Summary
ORT influences the rate but not the volume of ICH and appears to be a critical predictor of symptomatic hemorrhage after successful combined IV-IA therapy. To minimize the risk of bleeding, revascularization should be achieved within 4.5 hours of stroke onset.

Disclosures
None.

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静脈内投与と動脈内投与の併用療法成功後の脳内出血は時間依存現象か？

Is Intracerebral Hemorrhage a Time-Dependent Phenomenon After Successful Combined Intravenous and Intra-Arterial Therapy?

Pascal J. Mosimann, MD; Gaia Sirimarco, MD; Elena Mesequer, MD; Jean-Michel Serfaty, MD; Jean-Pierre Laissy, MD; Julien Labreuche, BST; Bertrand Lapergue, MD; Jaime Gonzalez-Valcarcel, MD; Philippa C. Lavallée, MD; Lucie Cabrejo, MD; Celine Guidoux, MD; Isabelle F. Klein, MD, PhD; Jean-Marc Olivot, MD, PhD; Elisa Schouman-Claeys, MD; Pierre Amarenco, MD; Mikael Mazighi, MD, PhD

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背景および目的：急性虚血性脳卒中の治療に不可欠の予後因子として発症から再灌流までの時間（ORT）が最近、取り上げられるようになってきた。良好な転帰はORTの短縮と関連しているが、頭蓋内出血とORTの関係はまだ明らかになっていない。そこで我々は、静脈内投与と動脈内投与の併用療法後の脳内出血（ICH）の発症リスクと出血量にORTが影響を及ぼすかどうかについて調べた。

方法：我々の前向き登録研究に基づき、2007年4月から2011年10月までの期間において、急性虚血性脳卒中患者で静脈内投与と動脈内投与の併用療法で再開通した連続症例157例を含めた。主要評価項目は、治療後24時間以内的ICHの発症とした。副次的評価項目は、症候性ICH（sICH）の発症とABC/2で測定した出血量とした。

結果：被験者の26％（n = 33）が何らかのICHを発症し、5.5％（n = 7）がsICHを発症した。ICHの出血量の中央値は0.8 mLであった。ORTはICHを発症しなかった患者（中央値 = 226分、四分位範囲 = 200〜281）よりも発症した患者（中央値 = 260分、四分位範囲 = 230〜306）の方が長かった（p = 0.008）。sICHでは、ORTの中間値は300分に達した（四分位範囲 = 276〜401、p = 0.004）。潜在的交絡因子で調整した後も有意差が認められた（ICHの調整p値 = 0.045、sICHの調整p値 = 0.002）。ICHの出血量とORTには相関はなかった（r = 0.16、p = 0.33）。

結論：ORTはICH発症率に影響を及ぼすが、ICHの出血量には影響しない。静脈内投与と動脈内投与の併用療法成功後は、ORTが症候性脳内出血の重要な予測因子と考えられる。出血のリスクを最小限に抑えるためには脳卒中の発症から4.5時間以内に血行を再建しなければならない。

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