UNIVERSITE DE LAUSANNE - FACULTE DE BIOLOGIE ET DE MEDECINE

Département de Radiologie Médicale

Is intracerebral Haemorrhage a Time-Dependent Phenomenon after Successful Combined Intravenous and Intra-Arterial Therapy?

THESE

préparée sous la direction du Professeur Reto Meuli

et présentée à la Faculté de biologie et de médecine de l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

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"Is intracerebral haemorrhage a time-dependent phenomenon after successful combined intravenous and intra-arterial therapy?"

Enjeu et contexte de la recherche:
Le temps entre le début des symptômes et la désobstruction artérielle avec rétablissement de la perfusion cérébrale (temps de recanalisation ou TDR) a récemment émergé comme un facteur pronostique essentiel dans la prise en charge de l'AVC ischémique aigu. Plus le TDR est court, plus le pronostic fonctionnel est favorable. Il est établi qu'au delà de 4.5 heures après le début des symptômes, le traitement standard de fibrinolyse au rtPA par voie intraveineuse (IV) n'améliore pas le pronostic et qu'il augmente même le risque de transformation hémorragique. En revanche, on ignore à ce jour si le TDR détermine le risque d'hémorragie cérébrale étant donné que le TDR ne peut pas être mesuré précisément avec le traitement IV conventionnel seul. Nous avons donc cherché à déterminer si le TDR influençait le risque de survenue et le volume d'hémorragie cérébrale en combinant au traitement IV le traitement intra-artériel (IA) – aussi appelé endovasculaire – afin de précisément mesurer le TDR.

Méthodes:
Sur la base d'un registre prospectif, nous avons inclus 157 patients consécutifs victimes d'un AVC ischémique aigü sur obstruction artérielle démontrée puis recanalisée avec succès (score TIMI 2 ou 3) par traitement IV-IA combiné entre Avril 2007 et Octobre 2011. L'outcome primaire était toute hémorragie cérébrale dans les 24 heures suivant le traitement. Les outcomes secondaires étaient l'identification des hémorragies symptomatiques (augmentation du score déficitaire neurologique NIHSS de 4 points ou plus) et la détermination du volume d'hémorragie basé sur la méthode ABC/2.

Résultats:
Nous avons observé 26% d'hémorragies cérébrales dans notre échantillon (n = 33), avec un taux d'hémorragie symptomatique de 5,5% (n = 7). Le volume médian d'hémorragie était de 0,8 ml. Le TDR était augmenté de manière hautement significative chez les patients avec hémorragie (médiane = 260 min; intervalle interquartile (IQR) = 230 à 306) comparé au TDR chez les patients sans hémorragie (médiane = 226 min; IQR = 200-281, p = 0,008). Le TDR moyen atteignait 300 minutes chez les patients avec hémorragie symptomatique (intervalle interquartile = 276-401, p = 0,004). Après analyses multivariées avec ajustement pour les facteurs potentiels de confusion de survenue d'hémorragie, les différences restaient significatives (p ajusté pour l'hémorragie = 0,04 ; p ajusté pour l'hémorragie symptomatique = 0,002). Nous n'avons pas trouvé de corrélation entre le TDR et le volume d'hémorragie (r = 0,16, p = 0,33).

Conclusion:
Le TDR influence le taux mais pas le volume d'hémorragie cérébrale et semble être un prédicteur significatif d'hémorragie symptomatique après recanalisation IV-IA combinée efficace.

Perspectives et implications cliniques:
Afin de minimiser le risque de saignement et favoriser un bon pronostic fonctionnel, l'objectif de reperfusion angiographique doit être atteint dans les 4,5 heures suivant l'apparition des symptômes même si le traitement endovasculaire permet de prolonger la fenêtre thérapeutique jusqu'à 6 heures après le début des symptômes.

Stroke
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Brief Report

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:XXX–XXX.)**

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.[1] 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) thrombolysis, 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 Stroke[1]—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,[2] starting with 0.6 mg/kg IV rt-PA, followed by 0.3 mg/kg IA rt-PA when occlusion persisted on the baseline 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.

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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 reproductibility.

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 χ^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 measurement; 95% confidence interval was calculated using bootstrap resampling method with 10 000 replications. Spearman's correlation coefficients (*r*) between ICH volume and ORT were calculated whenever applicable. Statistical testing was done at the 2-tailed α level of 0.05. Data were analyzed with the SAS software package, release 9.3 (SAS Institute, Cary, NC).

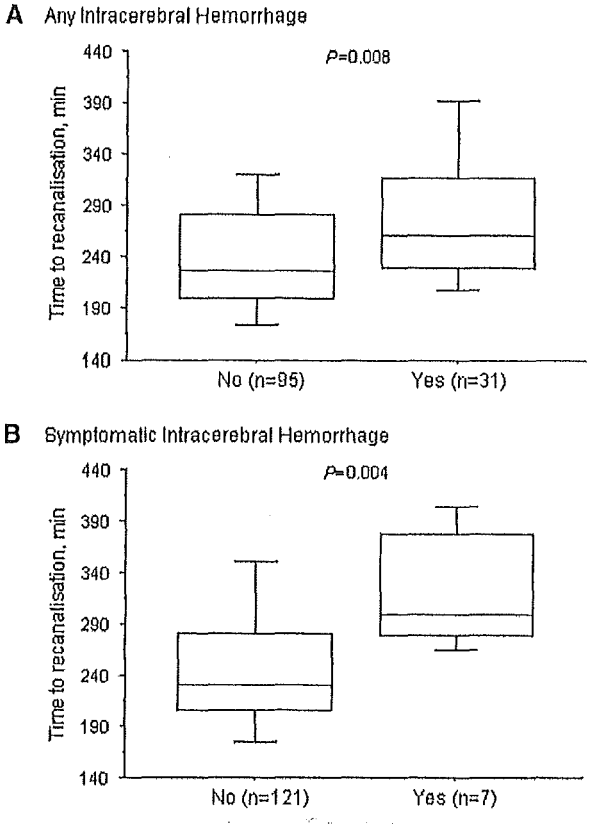

Figure 1. Distribution of time to successful recanalization in patients with and without intracerebral hemorrhage. Boxes show the 25th, 50th, and 75th and whiskers the 5th and 95th percentiles. Probability values calculated with the Mann–Whitney *U* test.

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). Parenchyal 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

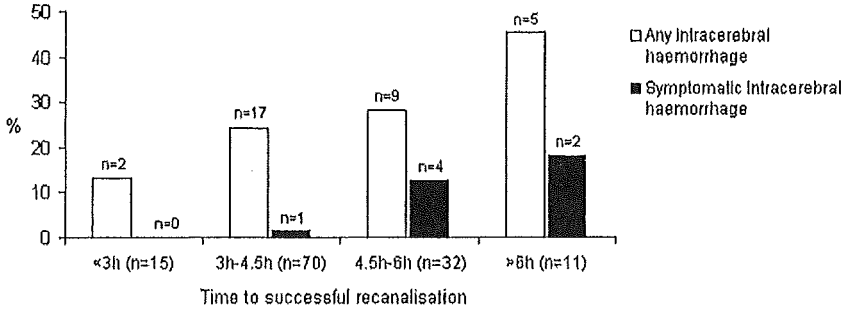

Figure 2. Risk of intracerebral hemorrhage according to time to successful angiographic reperfusion.

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),[9] 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[2] 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[2,4] 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[5] or IMS[10] (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,[11] accurate distinction requires either dual-energy CT[12] 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,[13] 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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SUPPLEMENTAL MATERIAL

Supplemental Table

TABLE S1. Baseline Characteristics in Patients With and Without Intracerebral Hemorrhage

	Overall	Any Intracerebral Haemorrhage		
	(n=128)	No (n=95)	Yes (n=33)	*P*
Age, y, mean ± SD	68.3 (17.1)	67.2 (16.6)	71.4 (18.4)	0.23
Men	51.6 (66)	51.6 (49)	51.5 (17)	1.00
Medical history				
Hypertension	50.8 (65)	50.5 (48)	51.5 (17)	0.92
Diabetes	10.9 (14)	11.6 (11)	9.1 (3)	1.00
Hypercholesterolemia	28.1 (36)	29.5 (28)	24.2 (8)	0.56
Current or former smokers	36.7 (47)	36.8 (35)	36.4 (12)	0.96
Antithrombotic medication	34.4 (44)	31.6 (30)	42.4 (14)	0.26
Clinical and biological markers				
Platelets, G/L count, mean ± SD	238 ± 81	242 ± 84	226 ± 72	0.35
Blood glucose level, mg/dL, median (IQR)	119 (101-148)	117 (99-146)	119 (101-156)	0.54
SBP, mmHg, mean ± SD	148 ± 22	147 ± 22	149 ± 21	0.80
DBP, mmHg, mean ± SD	80 ± 15	80 ± 16	80 ± 13	0.98
NIHSS score, median (IQR)	16 (10-20)	14 (9-19)	18 (15-22)	0.004
Cardioembolic etiology	60.2 (77)	55.8 (53)	72.7 (24)	0.09
ICA occlusion (isolated or with tandem MCA)	22.6 (29)	17.9 (17)	36.4 (12)	0.029
OTT, min, median (IQR)	135 (103-169)	132 (95-167)	147 (110-170)	0.31

Values expressed as percentage (no.) unless otherwise specified. SD indicates standard deviation; IQR, interquartile range; ICA, internal carotid artery; MCA, middle cerebral artery; OTT, onset to treatment time.