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Stroke- on- Awakening: Safety of CT-CTA Based Selection for Reperfusion Therapy

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ABSTRACT: ***Background:*** We studied the safety of use of acute reperfusion therapies in patients with stroke- on- awakening using a computed tomographic angiography (CTA) based large vessel occlusion-good scan paradigm in clinical routine. ***Methods:*** The CTA database of the Calgary stroke program was reviewed for the period January 2003-March 2010. Patients with stroke-on-awakening with large artery occlusions on CTA, who received conservative, IV thrombolytic and/or endovascular treatment at discretion of the attending stroke neurologist were analyzed. Time of onset was defined by the time last seen or known to be normal. Baseline non-contrast CT scan (NCCT) Alberta Stroke Program Early CT Score (ASPECTS) > 7 was considered a good scan. Hemorrhage was defined on follow-up brain imaging using ECASS 3 criteria. Independence (mRS≤2) at three months was considered a good clinical outcome. Standard descriptive statistics and multivariable analysis were done. ***Results:*** Among 532 patients with large artery occlusions, 70 patients with stroke-on-awakening (13.1%) were identified. The median age was 69.5 (IQR 24) and 41 (58.6%) were female; 41 (58.6%) received anti-platelets only and 29 (41.4%) received thrombolytic treatment [IV-12 (17.1%), IV/IA-12 (17.1%) and IA-5(7.1%)]. Unadjusted analysis showed that baseline NCCT ASPECTS ≤ 7 (p=0.002) and higher NIHSS scores (p=0.018) were associated with worse outcomes. There were no PH2 hemorrhages in the IV thrombolytic or endovascular treated group. Functional outcome was not different by treatment. ***Conclusion:*** When carefully selected using CT –CTA, by a good scan (ASPECTS > 7) occlusion paradigm, acute reperfusion therapies in patients with stroke-on-awakening can be performed safely in clinical routine.

RÉSUMÉ: Accident vasculaire cérébral constaté au réveil : sécurité de la sélection des patients par CT-CTA pour le traitement de reperfusion. ***Contexte :*** Nous avons étudié la sécurité de l'utilisation des thérapies de reperfusion en phase aiguë, chez les patients présentant un accident vasculaire cérébral (AVC) au réveil, au moyen de l'angiographie par tomodensitométrie (AT) basée sur le paradigme du scan démontrant la présence d'occlusion de gros vaisseaux en pratique clinique. ***Méthodes :*** La période de janvier 2003 à mars 2010 de la base de données AT du programme d'AVC de Calgary a été revue. Les dossiers des patients présentant un AVC au réveil, qui avaient des occlusions de grosses artères à l'AT et qui ont reçu un traitement conservateur, un traitement thrombolytique IV et/ou un traitement endovasculaire à la discrétion du neurologue traitant, ont été analysés. Le moment de l'apparition de l'AVC était défini comme le moment où le patient avait été vu ou était connu comme ayant été normal pour la dernière fois. Un score >7 au CT scan sans contraste (CTSC) selon l'échelle Alberta Stroke Program Early CT Score (ASPECTS) était considéré comme un bon scan. L'hémorragie était identifiée à l'imagerie du cerveau effectuée au cours du suivi au moyen des critères ECASS3. L'autonomie (mRS ≤ 2) 3 mois après l'événement était considérée comme une bonne issue clinique. Nous avons utilisé des méthodes standards de statistique descriptive ainsi que l'analyse multivariée. ***Résultats :*** Parmi les 532 patients qui présentaient une occlusion d'une grosse artère, nous avons identifié 70 patients ayant présenté un AVC au réveil (13,1%). L'âge médian des patients était 69,5 ans (écart interquartile 24) et 41 (58,6%) étaient des femmes ; 41 (58,6%) ont reçu seulement un anti-plaquettaire et 29 (41,4%) ont reçu un traitement thrombolytique [IV-12 (17,1%), IV/IA-12 (17,1%) et IA-5 (7,1%)]. L'analyse sans ajustement des données a montré qu'un score ASPECTS au CTSC ≤ 7 (p = 00,2) et des scores plus élevés au NIHSS p = 0,018) étaient associés à une issue moins favorable. Il n'y a eu aucune hémorragie parenchymateuse de type PH2 chez les patients ayant reçu un traitement thrombolytique IV ou dans le groupe ayant subi un traitement endovasculaire. L'issue fonctionnelle n'était pas différente selon le traitement reçu. ***Conclusion :*** En pratique clinique, quand les patients sont bien choisis au moyen du CT–CTA (score ASPECTS >7), les thérapies de reperfusion chez les patients présentant un AVC au réveil peuvent être administrées de façon sécuritaire en phase aiguë de l'AVC.

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Approximately, 10–27% of all acute ischemic strokes (AIS) occur during sleep, with the patients or relatives becoming aware of their neurological deficits on awakening.[1-4] No consensus exists on acute treatment of stroke-on-awakening. Because stroke onset is timed from the time last seen well, typically the evening prior, most patients with stroke-on-awakening therefore fall outside a standard 4.5 hour (hr) time window, precluding thrombolysis.

A surrogate measure of time from stroke onset may be defined using imaging as a biomarker. The idea that there is a tissue-window of salvageable brain among stroke-on-awakening patients is a corollary of the diffusion-perfusion mismatch hypothesis. There is only one computed tomography (CT) based trial (AbESTT-2 Trial) to date, which examined the effect of treatment with abciximab on outcomes among patients with stroke–on–awakening; the trial had to be terminated prematurely due to an increased incidence of intracranial hemorrhage in the treatment arm.[5] Planned clinical trials will examine the issue of use of thrombolytic therapy in patients with stroke on awakening: (WAKE-UP - NCT01525290 and EXTEND - NCT01580839).

It is known that there is an increased risk of symptomatic intracranial hemorrhage (ICH) secondary to thrombolysis as time from onset elapses.[6,7] Because no definitive trials have been completed in this patient population there is a complete lack of data on efficacy; tests of efficacy are predicated on demonstrated safety. Thus, currently the primary concern with treating stroke-on-awakening patients is safety defined by the risk of hemorrhage. Patients with a small core of established infarction have the lowest risk of hemorrhage.[8] Others have used multimodal MR imaging or CT perfusion imaging to define candidates for thrombolysis outside of proven treatment windows.[9] We believe that a simpler CT-based paradigm may be used to treat selected patients. We previously conducted a formal pilot study of the use of non-contrast CT and CT angiography (CTA) to define a thrombolysis population in patients with stroke-on-awakening. In that study, we have used a 'good-scan-occlusion' model for selecting such patients, defined by CT and CT angiography (NCCT ASPECTS > 7 and evidence of occlusion on CTA).[10] We report our experience in clinical routine on the safety of acute treatment in patients with stroke-on-awakening and the factors predicting outcomes for conservative, IV thrombolytic and endovascular treatment among patients with stroke-on-awakening.

Methods

The CT angiography (CTA) database of the Calgary stroke program, which is approved for research use by the conjoint human research ethics board at university of Calgary, was reviewed for the period Jan03-Mar10. The CTA database includes information on patients who came to Emergency department at Foothills Medical Center with symptoms of stroke/minor stroke/transient ischemic attack (TIA). Patients with stroke-on-awakening with proximal vessel large artery occlusions in anterior and posterior circulations and who were treated in clinical routine (not within a cohort study or randomized controlled trial (RCT)) were analyzed. Patients with suspected small vessel ischemic disease or no occlusion on baseline CTA were excluded. The time of onset was defined when the patient was last seen or known to be normal. Baseline demographic and clinical data were collected for all patients. Stroke-on-awakening was defined as stroke-related deficits that were noticed first on awakening. Patients were treated at the discretion of the attending neurologist of the day. Patients who received IV thrombolysis (0.9 mg/kg tPA) and/or endovascular treatment (MERCI retriever, PENUMBRA stroke system) were treated according to the good-scan-occlusion paradigm as judged by the attending stroke neurologist. The off label nature and additional risk was explained to the patient's relatives or legally authorized decision maker. Patients not thrombolysed were treated conservatively with antiplatelet therapy and stroke unit care. Blood pressure was managed according to the Canadian Best-Practice Guidelines.[11]

Standard non-helical NCCT was performed on a multi-slice scanner (GE Medical Systems, Fairfield, CT, USA or Siemens Medical Solutions, Erlangen, Germany) using 120 kV, 170 mAs with 5-mm slice thickness. Non-contrast CT was followed immediately by CTA with a helical scan technique from arch to vertex. Follow-up imaging was performed on all patients within 24 hours from the first CT scan (for those patients who were treated with thrombolytic therapy) to a maximum of seven days after the initial CT scans. The CT scans were reviewed independently by three reviewers to achieve a consensus score.[12] ASPECTS was used to score early ischemic change in patients with anterior circulation stroke.[13] NCCT scans with ASPECTS >7 were labeled as good scans. Hemorrhage was defined on follow-up brain imaging using ECASS 3 criteria.[14] Among those who were treated with endovascular therapy, cerebral angiogram was used to document recanalization. Where possible, the remaining thrombolysed patients were investigated with MRA within 48 hours to determine recanalization.

The primary outcome was safety, defined as symptomatic ICH according to the ECASS-3 definition.[14] Secondary outcome was a modified Rankin's score (mRS) less than or equal to 2 at three months. Standard descriptive statistics are used to report the data. We used conventional levels of significance at alpha of 0.05 and all tests were two-tailed. To explore predictors of our secondary outcome, a multivariable generalized linear model with log link and binomial distribution was developed to assess predictors of outcome. Only main effects were assessed in the multivariable model.

Results

Among 532 patients with large artery occlusions, 70 patients (41 female) with stroke-on-awakening (13.1%) were identified. The median age was 69.5 (IQR 24); mean time from last seen normal to admission was 542 minutes (min) (SD 212 min). Forty-one patients (59%) received conservative treatment with anti-platelets only, 29 (41%) received thrombolytic treatment [IV-12 (17%), IV/IA-12 (17%) and IA-5 (7%)]. (Table 1) The mean time from last seen normal to thrombolytic treatments was 516 min (SD ± 160.2)). Stroke severity was similar between thrombolysed and non-thrombolysed subjects. Baseline ASPECT score was interpreted in real time as favorable in all thrombolysed subjects but on retrospective central review was less than or equal to 7 in half the subjects. Baseline ASPECTS score was lower in the non-thrombolysed cohort. Asymptomatic ICH was observed in 3/41 (7%) patients in the conservatively

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Table 1: Comparison of baseline characteristics of patients with large artery occlusions presenting with stroke-on-awakening with those with known time of onset

	Occlusions- Non stroke on wakening (n=462)	Conservative treatment (n=41)	Thrombolysis (n=29)	P
Age (median, IQR)	67(31)	74 (21)	68 (23)	0.33
Sex – Female	52%	59%	59%	1.00
Hypertension	61%	66%	62%	0.80
Diabetes mellitus	22%	17%	10%	0.50
Atrial fibrillation	31%	44%	34%	0.29
High cholesterol	30%	15%	31%	0.14
Anti-platelet treatment	48%	49%	59%	0.47
Current smoker	39%	46%	45%	1.00
Baseline NIHSS	11(9)	13 (11)	14 (11)	1.00
Baseline ASPECTS	7 (3.5)	6 (3.5)	7 (3.5)	1.00
Baseline ASPECTS > 7	48%	29%	78%	0.26
Onset-to-admission time (SD)	148 (92) min	540 (140) min	526 (112) min	1.00
Onset-to-IV tPA (n=15)	---	---	516 (160) min	
Recanalization [IV+IA/IA]	---	---	11/17(65%)	
[IV]			3/7 (43%)	
HMCAS	41%	32%	45%	0.31
Site of occlusion				
	M1-MCA		49%	28%
M2-MCA		27%	17%	
M1-MCA + ICA		12%	17%	
M2-MCA + ICA		5%	7%	
M3-MCA		2%	0%	
ACA		2%	0%	
BA		2%	31%	

IQR = interquartile range; ASPECTS = Alberta Stroke Program Early CT score; IV = intravenous; tPA = tissue plasminogen activator; HMCAS = hyper dense middle cerebral artery sign; MCA = middle cerebral artery; ACA = anterior cerebral artery; BA = basilar artery

treated group and 3 patients (10%) in the thrombolytic group [1(IV thrombolysis), 1(IV+IA), 1(IA)]. One patient (2.4%) had a symptomatic hemorrhage (PH2) in the conservative treatment group. Good outcomes occurred in 14/29 (48%) patients treated with thrombolytic therapy as compared to 17/41 (42%) treated conservatively (p=0.806). Unadjusted analysis showed that baseline NCCT ASPECTS <=7 (p=0.002) and higher national Institutes of Health Stroke Scale (NIHSS) scores (p=0.018) were associated with worse outcomes. Thrombolysis did not predict independent outcome. (Table 2) In a multivariable model, baseline NCCT ASPECTS >7 (RR 2.9 CI_{95} 1.6-5.1), prior anti-platelet medication use (RR 1.7 CI_{95} 1.1-2.9) and age (RR 0.99 per year, CI_{95} 0.97-0.998) were predictors of good outcome.

Discussion

Our study highlights the safety of a CT–based paradigm for thrombolytic treatment in clinical routine among patients with stroke-on-awakening and confirms the findings of our previous pilot study.[10] The low hemorrhage rate is likely due to patient selection and is concordant with a MR based study in patients with stroke on awakening treated with thrombolytic therapy using a DWI-FLAIR volume difference paradigm.[15,16]

Despite the absence of treatment guidelines in this sub-group of patients, there does exist a common and growing understanding that a substantial number stroke-on-awakening patients may have salvageable brain tissue, enough to warrant reperfusion therapies.[17-19] All the major tPA trials have used NCCT as the primary imaging modality to select patients for

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Table 2: Comparison of complications and outcomes of patients with Stroke-on-awakening treated conservatively and with thrombolytic therapy.

	Conservative treatment (n=41)	Thrombolysis (n=29)	P
PH1	2%	0%	1.00
PH2	2%	0%	
HI1	7%	0%	
HI2	2%	3%	
mRS (median)	3 (1.5)	3 (2)	0.27
24h NIHSS	10.5 (15.5)	10 (13)	0.65
mRS 0-2	41%	48%	0.80
mRS 0-1	24%	24%	1.00
Death	7%	24%	0.08
FU ASPECTS	6 (3)	6 (2.5)	0.79
Outcomes (excluding Basilar occlusions)			0.27
mRS 0-2	12(60%)	9 (45%)	
Death	2(10%)	4(20%)	

PH = parenchymal hemorrhage; HI = hemorrhagic infarction; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; ASPECTS = Alberta Stroke Program Early CT score

treatment.[14,20-23] Although MR-based imaging has superior sensitivity and specificity compared to CT[24], a CT and CTA-based approach may be enough. The lack of MR availability in majority of centers, the duration of imaging and feasibility concerns impair more widespread use of MR for stroke.[22,23,25-29] Further, it is increasingly clear that there is a significant time trade off to intensive multimodal imaging.[30]

ASPECTS is an useful scoring tool to detect early ischemic changes on NCCT brain in patients with middle cerebral artery territory stroke because it is easy to access, learn and interpret. An ASPECTS of 4 or less corresponds well with the 1/3rd MCA rule and[31] at a threshold of ASPECTS <8, endovascular therapy is not likely to improve average outcomes.[31,32] ASPECTS score is prognostically relevant but requires high quality, usually non-helically acquired, imaging with careful review of the images. Further it is useful only in patients with stroke involving anterior circulation.[12] Similarly CTA is prognostically relevant, helpful in planning endovascular therapy and confirms a logical target for thrombolytic therapy. It also requires high quality acquisition, careful timing of the intravenous contrast injection and may be limited to those patients without renal impairment.[33,34] In the present study, the decision to treat these patients was primarily based on imaging findings with ASPECTS>7 together with a proximal vessel occlusion. We conclude that these patients can be safely treated with thrombolytic therapy but cannot assess efficacy in this single cohort design.

One-third of our patients had posterior circulation occlusions and anecdotally, it is believed that these patients have a longer relevant time window for thrombolysis. Although the usefulness of the good scan-occlusion model is not as applicable among patients with posterior circulation stroke due to inability to estimate early ischemic change well with CT alone, our results nevertheless confirm the safety of the CT-based approach in these patients.

Patient selection likely explains the lack of difference in outcomes. (Table 1) However, we also consider that patients in late or undefined time windows have a different natural history than those in the usual 4.5 hr window. Indeed, in the ECASS2 and ECASS3 trials, patients had lower average severity of stroke measured on the NIHSS score compared to the NINDS tPA trial where patients were treated much earlier after stroke onset.[14,20] Consequently, the placebo groups in both of the ECASS trials fared much better than in the NINDS tPA Stroke trial. Perhaps because of collateral circulation or differences in tissue susceptibility, these later time-window patients may do well without thrombolysis. Randomized data are needed to answer this question.

This is a retrospective study with inherent limitations of this study design. We did not assess patients with non-visualized occlusion such as small vessel ischemic disease. The numbers of patients is small in the reperfusion therapy arm and the results are not adjusted to show the effect of early recanalization and leptomeningeal collateral status, which are important parameters for tissue salvage. Outcomes were assessed in clinical routine and unblinded to patient treatment and patients who received recanalization therapies (IV+IV/IA+IA) were lumped into one group. We were unable to obtain glucose levels on all the patients and therefore did not assess this variable as a modifier of outcome; in prior studies it has been shown to be important.[35] Thrombolytic and endovascular treatment in patients with stroke on awakening selected using a CT-based paradigm, are potentially safe using a good scan-occlusion paradigm and the hypothesis that thrombolytic therapy is helpful in these patients is worthwhile to test in a clinical trial.

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Statement of Authorship

SB wrote the primary draft of this manuscript. Data were analyzed and collected by SB, RB, NS and MDH. All authors provided editorial input on the final manuscript. MDH provided overall authorship and responsibility as the senior author.

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