Neuroradiology 58.5 (2016): 487–493

DOI: 10.1007/s00234-016-1652-7

Alberta Stroke Program Early CT Score applied to CT angiography source images is a strong predictor of futile recanalization in acute ischemic stroke

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Abstract

Introduction Reliable predictors of poor clinical outcome despite successful revascularization might help select patients with acute ischemic stroke for thrombectomy. We sought to determine whether baseline Alberta Stroke Program Early CT Score (ASPECTS) applied to CT angiography source images (CTA-SI) is useful in predicting futile recanalization. Methods Data are from the FUN-TPA study registry (ClinicalTrials.gov; NCT02164357) including patients with acute ischemic stroke due to proximal arterial occlusion in anterior circulation, undergoing reperfusion therapies. Baseline non-contrast CT and CTA-SI-ASPECTS, timelapse to image acquisition, occurrence, and timing of recanalization were recorded. Outcome measures were NIHSS at 24 h, symptomatic intracranial hemorrhage, modified Rankin scale score, and mortality at 90 days. Futile recanalization was defined when successful recanalization was associated with poor functional outcome (death or disability). Results Included were 110 patients, baseline NIHSS 17 (IQR 12; 20), treated with intravenous thrombolysis (IVT; 45 %), primary mechanical thrombectomy (MT; 16 %), or combined IVT+MT (39 %). Recanalization rate was 71 %,

median delay of 287 min (225; 357). Recanalization was futile in 28 % of cases. In an adjusted model, baseline CTA-SI-ASPECTS was inversely related to the odds of futile recanalization (OR 0.5; 95 % CI 0.3–0.7), whereas NCCT-ASPECTS was not (OR 0.8; 95 % CI 0.5–1.2). A score ≤5 in CTA-SIASPECTS was the best cut-off to predict futile recanalization (sensitivity 35 %; specificity 97 %; positive predictive value 86 %; negative predictive value 77 %).
Conclusions CTA-SI-ASPECTS strongly predicts futile recanalization and could be a valuable tool for treatment decisions regarding the indication of revascularization therapies.
Keywords Ischemic stroke . CT-angiography .

Introduction

Early recanalization of the occluded vessel is crucial in improving the prognosis of acute ischemic stroke. However, despite achieving successful and prompt recanalization, intravenous thrombolysis (IVT) or mechanical thrombectomy (MT) fail to improve outcomes in a subset of patients; rates of futile recanalization occurring in up to 50 % of cases. Factors such as older age, high initial NIHSS score, and longer delay to treatment have been identified as predictors of futile recanalization [1, 2]. The Alberta Stroke Program Early CT Score (ASPECTS) [3] from baseline non-contrast CT (NCCT) is a predictor of outcome; scores 0 to 4 being proposed as a marker of futile recanalization [4, 5]. However, the usefulness of this score for treatment decisions has been debated as it has modest inter-rater reliability, and the majority of recent trials of MT excluded patients with poorer baseline ASPECTS score [6]. ASPECTS on CT angiography source images (CTA-SIASPECTS) has been shown to be a more accurate predictor of outcome and final infarct volume in acute ischemic stroke [7, 8]. CTA is recommended for the assessment of site of occlusion and vessel anatomy of acute stroke patients who are potential candidates for endovascular treatment [9], CTA data being available in the majority of these patients during their initial evaluation. The aim of this study is to assess whether baseline CTA-SI-ASPECTS might help predict response to treatment and can reliably predict futile recanalization in patients undergoing reperfusion therapies; the intention being to find a reliable tool for treatment decision making.

Materials and methods

Cohort data were from the FUN-TPA study registry (ClinicalTrials.gov; NCT02164357). This is a prospective, observational, multicentered study designed to assess the safety of primary MT using stent retrievers, compared to a standard IVT or IVT+MT, for patients with acute ischemic stroke due to proximal intracranial artery occlusion. Initiation of treatment (whatever IVTor primary MT) is needed to be within 4.5 h from symptom onset. Assessment of recanalization by transcranial Doppler, CTA, or angiography (the latter in patients undergoing MT) was mandatory within the first 6 h.

The study received the approval of the Ethics Committees of all the participating centers and was authorized by the Spanish Agency for Drugs and Health Products (Agencia Española de Medicamentos y Productos Sanitarios; AEMPS). Patients provided written informed consent to participation in the study.

Included in this current sub-study were consecutive patients with intracranial vessel occlusion confirmed prior to any treatment by CTA in which ASPECTS scoring was available.

Patients received standard IVT or primary MT as first choice when there were any contraindications for IVT and were considered for MT after IVT if arterial occlusion persisted within the time window of opportunity.

All diagnostic and therapeutic procedures were performed according to clinical protocols that follow current guidelines, adhered to by all the participating stroke centers [10, 11]. Our protocol did not include imaging selection criteria based on multimodal imaging (such as CT perfusion or MRI). Patients with signs of extensive lesions on baseline NCCT were excluded from treatment.

Image acquisition On admission, NCCT and CTA were obtained on a 64-slice spiral CT scanner using standardized protocols. CTAwas performed following injection of a bolus (50–60 mL) of contrast medium (4 mL/s) in an antebrachial vein. An automated system for image acquisition triggered by the appearance of contrast in the ascending aorta was used (Sure Start, Toshiba).

Acquisition was performed by slicing every 0.5 mm to permit subsequent multidimensional image reconstruction. Area of coverage spanned from the aortic arch to the vertex.

Imaging parameters for the aims of the study were measured retrospectively by independent neuroradiologists experienced in the interpretation of CTscans in acute stroke. These investigators were blinded with respect to patient clinical data (except for the side of neurological involvement) and to outcomes.
The data collected included the following: demographics, risk factors, clinical severity on admission according to the National Institute of Health Stroke Scale (NIHSS), site of occlusion, treatment received, time lapse from symptom onset to diagnostic, and therapeutic procedures, recanalization achieved (or not) and time lapse to recanalization, when applicable.
Vessel occlusion or recanalizationwas defined according to the thrombolysis in brain ischemia (TIBI) grading system [12], using transcranial ultrasound assessment, and according to the thrombolysis in cerebral infarction (TICI) grading system in angiography [13]. Successful recanalization was considered as TIBI 4 or 5 and TICI 2b or 3.
Early ischemic changes such as focal hypo-attenuation, loss of gray-white matter differentiation, and sulci effacement were quantified using the ASPECTS scoring [3] in baseline NCCT. In CTA-SI, regions of diminished contrast enhancement of the parenchyma relative to the contralateral hemisphere were scored as abnormal [7]. Absence of vessel enhancement in the affected areas was also taken into account.
Outcome measures were symptomatic intracerebral hemorrhage (SICH), defined as a parenchymal hemorrhage associated with a neurological deterioration of ≥4 points from the lowest NIHSS from baseline, or leading to death, NIHSS at 24 h, mRS score, and mortality at 90 days. Good outcome was considered when independence was achieved (mRS 0–2).
Futile recanalization was considered when successful recanalization was obtained, but there was a poor outcome at 90 days (i.e., mRS was 3–6). Since the pre-specified inclusion criteria imply severe deficit, recovery of ability to walk without assistance, despite partial dependency (i.e., mRS score 3), can be considered as an acceptable outcome. As such, a secondary analysis was performed taking mRS scores of 4–6 as poor outcomes.
Data analyses

Data are expressed as median and the inter-quartile ranges (IQRs) for continuous variables, or as absolute and relative frequencies for categorical variables. NCCT-ASPECTS and CTA-SI-ASPECTS as a function of time from symptom onset to CT acquisition are graphically displayed as scatter plots. Univariate comparisons between futile and useful recanalization were made using the Fisher exact test for categorical variables and the Mann-Whitney U test for continuous variables.

The relationships of radiological parameters and clinical data vs. outcomes and futile recanalization were analyzed with univariate and multivariate backward stepwise logistic regression models. Variables considered in the multivariate models were NCCT-ASPECTS as well as CTI-SI-ASPECTS, those identified as prognostic factors in previous studies—age, baseline NIHSS, site of occlusion, time lapse to recanalization—and those that were significant in the univariate comparisons.

The AUROC curve was used to evaluate the discriminative function of the model; the optimum cut-off point being that which had maximum specificity (Sp) plus sensitivity (Se). All analyses were performed with the Stata/SE 12.1 statistical package (StataCorp LP, USA).

Results

Between May 2012 and May 2014, we recorded data from 110 patients who fulfilled all the inclusion criteria. Sites of occlusion were as follows: intracranial internal carotid artery (ICA) 9 (8 %), bifurcation of the ICA (T-thrombus) 16 (14.5 %), M1 segment of the middle cerebral artery (MCA) 58 (53 %), and MCA-M2 segment 22 (20 %).

There were five (4.5 %) cervical ICA and M1 segment tandem occlusions. Data on NCCT-ASPECTS were available from 105 patients and CTA-SI-ASPECTS from 77 patients. IVT was administered in 92 patients. All these patients were monitored for recanalization within 6 h from symptom onset, as pre-specified, and 65 of them did not achieve recanalization: 43 had MT following IVT, 9 were excluded for MT due to radiological signs of established lesion in a second CT scan, and 13 due to medical contraindications or technical difficulties associated with the procedure. Primary MT was performed in 18 patients due to contraindications for IVT. Characteristics of the cohort are summarized in

Table 1. NCCT-ASPECTS and CTA-SI-ASPECTS per site of occlusion are summarized in Table 2. NCCT-ASPECTS decreased when there were longer delays from symptom onset to image acquisition, while CTASI-ASPECTS remained more stable along this time course(Fig. 1).
Recanalization was achieved in 78/110 patients (71 %); 28/ 92 (30 %) after IVT and 50/61 (82 %) after MT; 35/43 (81 %) after combined IVT+MTand 15/18 (83 %) after primary MT.
Recanalization rate per site of occlusion was 5/9 (56 %) for ICA, 9/16 (56 %) for carotid T-occlusion, 44/58 (76 %) for M1, 15/22 (78 %) for M2, and 5/5 (100 %) for tandem occlusions.
Recanalization was the main predictor of good outcome. Comparisons of patients who achieved recanalization with those who did not indicated the following: the NIHSS at 24 h was 4 (IQR 1; 9) vs. 17 (IQR 9; 19), p = 0.0001; mRS at 3 months was 2 (IQR 0; 3) vs. 3 (IQR 1; 5), p = 0.009; mortality at 90 days was 6 vs. 22 %, p =0.019; and intracranial symptomatic hemorrhage was 1 vs. 6 %, p= 0.28, respectively.
After adjustment for baseline NIHSS score and age, the odds ratio for good outcome (mRS 0–2) was 4.3 (95 % CI 1.6–11.4; p= 0.003) for patients who achieved recanalization compared with those who did not. CTA-SI-ASPECTS was an independent predictor of good outcome only in patients who achieved recanalization (OR 2.1; 95 % CI 1.3–3.4; p=0.001) but was not in patients who did not achieve recanalization (OR 1.4; 95 % CI 0.9–2.2; p =0.14). NCCT-ASPECTS was not a predictor of outcome in our study.
Despite successful recanalization, 22 patients (28 %) had a poor outcome (mRS 3–6): 6/27 patients (22 %) treated with IVT, 6/15 treated with MT (40 %), and 10/35 who received IVT +MT (29 %). Differences in clinical and radiological characteristics between patients with good vs. poor outcomes post-recanalization are summarized in Table 3. Futile recanalization rate was higher among patients with more severe occlusions: 2/5 (40 %) ICA, 6/9 (67 %) T-thrombus, 2/5 (40 %) tandem occlusions, 10/43 (23 %) M1, and 2/15 (13 %) M2. Multivariate logistic regression analyses showed that CTISI-ASPECTS was an independent predictor of futile recanalization (OR 0.5; 95 % CI 0.3–0.7; p=0.001), while NCCTASPECTS was not (OR 0.8; 95 % CI 0.5–1.2; p=0.3).With

an AUCROC curve of 0.66 (95 % CI 0.55–0.78), our data define an CTA-SI-ASPECTS cut-off point ≤5 to predict futile recanalization, with Se of 0.35 (95 % CI 0.14–0.62) and Sp of 0.97 (95 % CI 0.86–0.99) and with positive predictive value (PPV) and negative predictive value (NPV) of CTA-SIASPECTS ≤5 of 86 % (95 % CI 42–99.6) and 77 % (95 % CI 62–88), respectively. Figure 2 shows the optimal AUCROC.

Eleven patients (14 %) scored 4–6 in the mRS: 2/27 patients treated with IVT (7 %), 4/15 treated with MT (27 %), and 5/35 who received IVT+MT (14 %). Considering this score as a criteria for futile recanalization, CTA-SIASPECTS was indeed a better predictor (OR 0.3; 95 % CI 0.15–0.7; p = 0.002). With an AUCROC curve of 0.79 (95 %CI 0.63–0.95), the best cut-off point was again a score ≤5, with Se of 0.60 (95 % CI 0.26–0.88), Sp of 0.98 (95 % CI 0.88–0.99), PPVof 86%(95%CI 42–99.6), and NPVof 92% (95 % CI 80–98).

Discussion

Our study identified CTA-SI-ASPECTS as an independent predictor of dependency or death despite successful recanalization, i.e., for every point of increase in CTA-SI-ASPECTS, the odds of poor outcome (mRS >2) decreases 50 %. Our data identify a score ≤5 as the best predictive value to forecast futile recanalization. MT has been proven to significantly increase the odds of good outcome in patients with stroke due to proximal intracranial artery occlusions [14–19]. However, some patients may not benefit from treatment, the rate of futility being high after MT, especially in cases of larger vessel occlusion. Given the high costs of the resources required, it would be important to identify the subset of patients who would not benefit from recanalization, in order to avoid unnecessary procedures in circumstances such as protracted time lapse from symptom onset, existence of comorbidities, or any other in which the indication of treatment may be doubtful.

Clinical prognostic factors such as older age, higherNIHSS score, and longer delay between symptom onset and treatment, proposed as markers of futile recanalization [1, 2], are not sufficiently discriminatory for treatment decisions. Hence, reliable indicators of high probability of futility of treatment are necessary in order to facilitate decision-making at the time of patient admission. The recently published studies EXTEND-IA [15], ESCAPE [16], and SWIFT-

PRIME [18] demonstrated that the selection of patients for MTon the basis of imaging criteria helps improve the odds of good outcomes.

However, the benefits of additional imaging, such as CT-perfusion, diffusion- and perfusion-weighted MRI, or multiphase CTA, beyond NCCTand CTA or MRI and MRA for selecting patients for endovascular treatment, are not clear [9]. Our results suggest that CTA-SI-ASPECTS on baseline CT study could help in making the decision to discard the option of MT since the likelihood of success is very low in patients considered as at-risk of futile recanalization using the criterion based on CTA-SI-ASPECTS ≤5. Lower sensitivity of this cutoff point implies that a number of patients that will not benefit from treatment would not be correctly identified, but the high specificity indicates that few patients would be falsely classified as at-risk of futile recanalization, thus preventing exclusion from treatment of patients that may benefit. The sensitivity and the predictive values of CTA-SI-ASPECTS ≤5 increase when considering mRS score of 4–6 as poor outcome; this being a more conservative approach taking into account that achieving mRS 0–3 could be a good outcome in patients suffering from severe strokes. This criterion prevents the exclusion of patients who might obtain some benefit from reperfusion, on the basis of imaging criteria. NCCT-ASPECTS has also been proposed as a marker of futile recanalization [4, 5]. In our study, NCCT-ASPECTS did not appear to be an independent predictor of outcome.

This can be explained, partially, by the majority of our patients having a baseline score ≥7. Our data are in accordance with previous studies that demonstrated that CTA-SI-ASPECTS detects irreversible damage and predicts final infarct extent and neurological outcome with more accuracy than NCCT-ASPECTS [7, 8]. Our results suggest that CTA-SI-ASPECTS is also superior in predicting the futility of recanalization since it is more sensitive in detecting early irreversible damage. NCCT-ASPECTS semiquantitatively measures the extent of early ischemic changes. The hypo-attenuation observed in NCCT in ischemic stroke depends on tissue water content and is, thus, a measure of cytotoxic edema in the ischemic brain, which increases linearly with time. Hence, NCCT-ASPECTS would be higher the shorter the delay from symptom onset to CT

image acquisition and, as shown in our study, would decrease along with time because the ensuing changes are more evident [20].
Thus, higher NCCT-ASPECTS scores do not necessarily exclude irreversible damage, especially in the very early phase of infarction if there is a short time lapse from symptom onset to image acquisition. Conversely, CTA-SI-ASPECTS detects regions of the brain with hypo-attenuation due to longer delays, or severe reduction in contrast medium arriving in the ischemic brain, i.e., due to reduced cerebral blood flow (CBF) and, as such, being an indicator of leptomeningeal collateral circulation status and a marker of the degree of perfusion at the tissue level [21]. Studies have suggested that patients with adequate collateral flow as assessed by CTA are likely to do better after MT [16, 22, 23]; collateral supply being responsible for tissue viability. Our study is in agreement with these data: lower CTA-SI-ASPECTS were observed in patients with larger vessel occlusions (such as carotid T-thrombus) in which collateral blood supply through the circle of Willis is more severely jeopardized and are associated with poorer outcomes after reperfusion. Since collateral status does not depend on time, but more on the individual and the site of occlusion, this explains the observation that CTA-SI-ASPECTS appears to be less reliant on delay between symptom onset and image acquisition and having a better prognostic value, especially at shorter time lapses from stroke onset. Thus, CTA-SIASPECTS could be a useful tool to estimate collateral status, and a reliable marker of tissue resilience to the ischemic insult.
The procedure uses a commonly applied CT scoring system which is familiar to most clinical practitioners. Dynamic CTA techniques such as multiphase CTA are more accurate for the evaluation of collateral status than a single snap shot CTA in the arterial phase, since it can detect very delayed pial vessel enhancement [6]. In this regard, tandem carotid occlusions or severe stenosis (>70 %) may impact on CTA-SI-ASPECTS in such a way that the scoring would be reduced due, potentially, to the hemodynamic effect on regional cerebral blood flow.
This is a limitation of this first pass CTA technique in that the reduction of collateral supply may be overestimated. Dynamic CTA techniques may help to

avoid this type of bias. The number of patients with tandem occlusions in our study was too small to address this issue.

It has been suggested that CTA-SI could be a useful tool for estimating ischemic core since both CTA-SIASPECTS and cerebral blood volume (CBV) ASPECTS, in CT-perfusion maps, correlate with final NCCT-ASPECTS at 24 h [24]; CTA-SI-ASPECTS showing the highest sensitivity and specificity for predicting final infarct. However, CTA-SI (like other radiological markers) does not reflect all the dynamic processes of ischemic injury and may include areas of irreversible damage as well as penumbra. As such, the role of imaging-based criteria (CTA, CT-perfusion, diffusion MRI) to select patients for reperfusion therapies is still to be determined and is an evolving area of clinical investigation.

Our study has some limitations. Firstly, the futility rate in our series of patients is quite low compared to previous reports. This could be due to our strict inclusion criteria and narrow selection of patients as well as the short delay to recanalization. This might miss identifying other possible predictors of futile recanalization.

Conversely, it reinforces the hypothesis that better selection of patients would increase efficiency of recanalization therapies. Secondly, image scoring was not centralized, and several investigators were responsible for NCCT-ASPECTS as well as CTA-SI-ASPECTS. This could have introduced some variability in scoring. However, the setting resembles clinical practice in which intra- and inter-observer reliability has been shown to be substantial for both scores [25, 26].

Conclusions

The data from our study indicate that a score for CTASI-ASPECTS between 0 and 5 is strongly predictive of futile recanalization. This would help select-out patients from the application of MT in cases of doubtful benefit.

However, so as not to miss suitable patients who may benefit from reperfusion after MT, the CTA-SIASPECTS score should be combined with other prognostic factors in the decision-making process. Further studies are needed to establish the role of CTA-SI together with other radiological tools in the selection of stroke patients for reperfusion therapies

Acknowledgments

We thank Alfonso Muriel, PhD (Department of Clinical Biostatistics of the University Hospital Ramón y Cajal, Madrid, Spain), for expert statistical analyses. Editorial assistance was by Peter R. Turner of Tscimed.com. This study received funding from Fundación Mutua Madrileña.

Compliance with ethical standards

We declare that all studies have been approved by the Ethics Committees of the hospitals in which patients were recruited (Hospital Universitario Ramón y Cajal; Hospital Universitario La Paz; Hospital Universitario Gregorio Marañón; Hospital Universitario 12 de Octubre) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that all patients gave informed consent prior to inclusion in this study.

Conflict of interest

We declare that we have no conflict of interest.

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