Prospective Endovascular Treatment in Acute Ischemic Stroke Evaluating Non-Contrast Head CT versus CT Perfusion (PLEASE No CTP)

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Abstract

Background: Studies have shown a lack of agreement of computed tomography perfusion (CTP) in the selection of acute ischemic stroke (AIS) patients for endovascular treatment. Purpose: To demonstrate whether non-contrast computed tomography (CT) within 8 h of symptom onset is comparable to CTP imaging. Methods: Prospective study of consecutive anterior circulation AIS patients with a National Institute of Health Stroke Scale (NIHSS) score > 7 presenting within 8 h of symptom onset with endovascular treatment. All patients had non-contrast CT, CT angiography, and CTP. The neuro-interventionalist was blinded to the results of the CTP and based the treatment decision using the Alberta Stroke Program Early CT score (ASPECTS). Baseline demographics, co-morbidities, and baseline NIHSS scores were collected. Outcomes were modified Rankin scale (mRS) score at discharge and in-hospital mortality. Good outcomes were defined as a mRS score of 0–2. Results: 283 AIS patients were screened for the trial, and 119 were enrolled. The remaining patients were excluded for: posterior circulation stroke, no CTP performed, could not obtain consent, and NIHSS score < 7. Mean NIHSS score at admission was 16.8 ± 3, and mean ASPECTS was 8.4 ± 1.4. There was no statistically significant correlation with CTP penumbra and good outcomes: 50 versus 47.8% with no penumbra present (p = 0.85). In patients without evidence of CTP penumabra, there was 22.5% mortality compared to 22.1% mortality in patients with a CTP penumbra. If ASPECTS ≥7, 64.6% had good outcome versus 13.3% if ASPECTS <7 (p < 0.001). Patients with an AS-
PECTS \( \geq 7 \) had 10% mortality versus 51.4% in patients with an ASPECTS < 7 \( (p < 0.001) \). **Conclusions:** CTP penumbra did not identify patients who would benefit from endovascular treatment when patients were selected with non-contrast CT ASPECTS \( \geq 7 \). There is no correlation of CTP penumbra with good outcomes or mortality. Larger prospective trials are warranted to justify the use of CTP within 6 h of symptom onset.

**Introduction**

Endovascular thrombectomy is the standard of care when treating an acute ischemic stroke (AIS) patient with anterior circulation large-vessel occlusion within 6 h of symptom onset \[1–5\]. Non-contrast head computed tomography (NCCT) excludes an intracranial hemorrhage (ICH) and allows for the determination of the Alberta Stroke Program Early CT score (ASPECTS) \[6, 7\]. CT angiography (CTA) is performed to evaluate for a large-vessel occlusion. The role of CT perfusion (CTP) for the selection of an AIS patient for endovascular treatment is unclear within the first 6 h of symptom onset.

CTP provides the measure of brain tissue blood perfusion and delivers data such as penumbra and infarct core while providing more sensitive, specific, and accurate imaging than NCCT \[8\]. The addition of CTP did not increase short-term favorable outcomes among patients with AIS within 6 h of symptom onset in a retrospective study \[9\]. CTP has not been validated for use in the diagnosis of penumbra and identification of patients appropriate for endovascular treatment within 6 h of symptom onset.

The 2018 American Heart Association/American Stroke Association guidelines recognize additional imaging, beyond CT and CTA or MRI and magnetic resonance angiography such as perfusion studies for selecting patients for mechanical thrombectomy in < 6 h, is not recommended \[10\]. The aim of this study was to demonstrate that NCCT within 8 h of the onset of an anterior circulation AIS is comparable to CTP imaging and to determine a correlation between CTP penumbra and favorable outcomes and/or mortality.

**Methods**

A prospective study, between March 2011 and July 2015, was conducted on consecutive anterior circulation AIS patients who underwent endovascular treatment at the University of Minnesota, USA, and Valley Baptist Medical Center, Harlingen, TX, USA. Patients selected for endovascular treatment at the two stroke centers presented with a National Institute of Health Stroke Scale (NIHSS) score \( \geq 7 \) and were treated within 8 h of symptom onset. The study was approved by the local Institutional Review Board at each participating hospital, and written informed consent was obtained from the patients’ family or power of attorney.

All patients underwent NCCT to identify an ICH, cerebral edema, sulcal effacement, dense vessel sign, focal parenchymal hypodensity, or an infarction greater than 1/3 of the middle cerebral artery vascular territory and the ASPECTS. CTA and CTP scans were also performed on all ischemic stroke patients who had an NIHSS score \( \geq 7 \). The operators were blinded to the results of the CTP and based their decision on treatment solely using the ASPECTS. Most perfusion scans were performed on the Phillips 64-slice CT scanner. Maps obtained by the Phillips 64 (Phillips Medical Systems, Cleveland, OH, USA) were generated using both gaussian fit and single-value deconvolution methods using Vitrea software (Vital Images), yielding the following perfusion parameters: mean transit time (MTT), regional cerebral blood flow (CBF), and regional cerebral blood volume (CBV).

CBF, CBV, and MTT are parameters calculated by post-processing software. MTT is the average amount of time it takes blood to transit through a given volume of brain and is measured in seconds. CBV is defined as the volume of flowing blood for a given volume of brain and is measured in units of milliliters of blood per 100 g of brain. CBF is defined as the volume of flowing blood moving through a given volume of brain in a
specific amount of time and is measured in units of milliliters per 100 g of brain per minute [11]. At the completion of the study, the CTP studies were analyzed for penumbra defined by a preserved regional CBV, decreased regional CBF, and increased MTT in ≥20% of the affected region [8, 12].

Baseline demographics, presence of cardiovascular risk factors, time between symptom onset and endovascular intervention, and hemorrhage type were documented and analyzed. Additionally, NIHSS scores were recorded at admission, 24 h after treatment, and at discharge, along with modified Rankin Scale (mRS) scores at discharge and in-hospital mortality. NCCT or MRI was also conducted 24 h after treatment as well as after any neurological decline in the patient. Favorable functional outcome was defined as a mRS score of 0–2 at discharge.

Symptomatic ICH was defined as: NCCT-documented ICH either in the area of stroke and related to neurological deterioration (≥4-point decline on NIHSS from previous assessment) or in a different vascular territory with neurological deficits within 24 h of treatment. Early neurological improvement was documented as improvement of ≥4 points on NIHSS or NIHSS score = 0 at 24 h after treatment. Favorable functional outcome was defined as a mRS score of 0–2 at discharge.

Results

A total of 283 AIS patients were screened for the trial over the duration of the study. Of the 283 screened, 119 AIS patients (mean age ± SD: 70 ± 15 years; n = 59 [50%] women) were enrolled in the study; the remaining were excluded for the following reasons: posterior circulation stroke, no CTP performed, no consent obtained, and an NIHSS score < 7. Please refer to Table 1 for patient demographics, risk factors, and endovascular treatment characteristics. The average (±SD) NIHSS score at admission was 16.8 ± 3, and the mean (±SD) ASPECTS was 8.4 (±1.4).

Prior to endovascular treatment, intravenous recombinant tissue plasminogen activator was administered to 44 (37%) of the patients. Favorable outcome (mRS score of 0–2 at discharge) was observed in 53 (44.5%) patients that underwent endovascular treatment. Median time interval between symptom onset and recanalization was 260 min (131–496 min). Median time interval between hospital arrival and recanalization was 159 min (57–360 min). Median time interval between hospital arrival and groin puncture was 109 min (18–293 min).

There was no statistically significant correlation between CTP penumbra and good outcomes: 50% with penumbra present versus 47.8% with penumbra absent (p = 0.85). Patients with no evidence of CTP penumbra had a 22.6% mortality compared to 22.1% mortality in patients with CTP penumbra present (see Table 2). Patients with an ASPECTS ≥7 demonstrated 64.6% good outcome compared to 13.3% with an ASPECTS < 7 (p < 0.001).

Mortality for patients with ASPECTS ≥7 was 10%, while patients with ASPECTS < 7 had 51.4% mortality (p < 0.001) (see Table 3).

Discussion

A CTP penumbra did not identify patients who would benefit from endovascular treatment when selected with NCCT ASPECTS ≥7 within 8 h of symptom onset. ASPECTS ≥7 was significant in correlation to a good outcome, but there was no statistically significant correlation of CTP penumbra with good outcome or mortality. The majority of the patients included in the study were treated within 6 h from their symptom onset. There is no good published data to support the use of CTP or MR perfusion within 6 h of symptom onset to triage AIS patients for endovascular mechanical thrombectomy; however, the DAWN [13] and DEFUSE 3 [14] trials demonstrated the clinical benefit for CT/MR perfusion in patient’s presenting after 6 h from symptom onset.
A previously published study demonstrated no significant difference among factors which could predict a distinction in the clinical outcomes of patients selected based on CTP or standard endovascular treatment based on time interval from symptom onset to presentation time and NCCT [9]. Similar to this study, the CTP-guided patients were not found to have an increased clinical benefit compared to the time-guided patients pertaining to functional outcome, early neurological improvement, ICH, and in-hospital mortality.

In this study, the CTP penumbra was initially determined through subjective interpretation of the brain perfusion maps that indicate the MTT, CBF, and CBV; however, we started to use the RAPID CTP penumbra software as it became available. The automated software
improved CTP interpretation because the results are quantifiable. Austein et al. [15] conducted a study to determine the accuracy of different commercial CTP software packages from Philips, Siemens, and RAPID to predict the final infarct volume after mechanical thrombectomy. The study identified significant differences between the 3 CTP packages in the predictive accuracy of final infarct volume after mechanical thrombectomy. The RAPID software provided the highest precision and good accuracy, superior to the software from Philips and Siemens [15].

The Dutch acute stroke study (DUST) reported that the assessment of ischemia in any region of the brain, including the middle cerebral artery territory, was much easier and more reliable with CTP than with either NCCT or CTA [16]. However, while patient characteristics and NCCT measures were significantly predictive for poor clinical outcomes, adding CTA and CTP predictors did not increase the prognostic value. The primary outcome measure of the study was poor clinical outcome (defined as a mRS score of 3–6) after 90 days. Poor clinical outcome at 90 days occurred in 501 patients (36%). The basic model, based on NCCT and patient characteristics, was highly predictive of clinical outcome and had an AUC value of 0.84. The addition of CTA and CTP measures to the basic model did not improve the outcome predictive value (AUC value = 0.85). The study concluded that individually, CTA and CTP were strong predictors of clinical outcome, but in addition to patient characteristics and NCCT, they presented only limited additional prognostic value.

There is a significant inter-rater variability in the interpretation of CTP. A previous retrospective study evaluated the agreement among stroke specialists in selecting stroke patients for endovascular treatment based on CT and CTP imaging interpretation [17]. CT images and CTP data were interpreted independently by stroke specialists to decide if a patient was an appropriate candidate to undergo endovascular treatment. Intra-rater agreement, which indicates variability within the same subject’s response on treatment decision based on CT versus CTP scan, demonstrated poor agreement. The inter-rater agreement to treat with endovascular treatment based on CT scans had moderate variability (75% observed agreement), while there was substantial variability (59% observed agreement) among decisions based on the interpretation of CTP scans. Furthermore, analysis also showed that subjects who initially chose to treat a patient based on CT scan chose otherwise based on CTP findings of the same patient (occurred 8.2 times in 25 patients). The study concludes there is a significant lack of agreement in regards to treatment decisions based on CTP changes, even among stroke specialists.

Time interval between symptom onset and administration of intravenous recombinant tissue plasminogen activator is inversely related to good outcomes. This emphasizes the importance to consider factors which may cause delays in endovascular reperfusion therapies. Sheth et al. [18] suggests that the use of advanced neuroimaging modalities, such as CTP, is associated with significant delays in initiating endovascular therapy. Patients selected with NCCT had significantly lower times to groin puncture (61 min) in comparison to patients selected with CTP (114 min) [18]. Furthermore, patients selected with CTP did not demonstrate any significant improvement in hemorrhage rates, final infarct size, or improved clinical outcome when compared to patients selected with NCCT.

Understanding the size of the established infarct is critical in selecting AIS patients for mechanical thrombectomy. NCCT ASPECTS and RAPID CTP ischemic core volume have been used to measure the size of established infarcts. Studies have shown that a NCCT ASPECTS is highly predictive of outcome, whereas studies have also demonstrated that ASPECTS is more accurately determined by CTP in comparison to NCCT or CTA [19–21]. Haussen et al. [22] demonstrated significant variability of RAPID CTP-derived ischemic core volumes within specific ASPECTS grades and a lack of strong correlation between them. The study suggests a package approach of NCCT and CTP to evaluate patients for selection to outline
patients who may not benefit and avoid eliminating those who may benefit from endovascular treatments.

There are limitations to acquiring and interpreting CTP imaging in this study. Multi-slice CT scanners provide 2–4 cm of coverage per acquisition, which does not necessarily allow the evaluation of the exact perfusion deficit volumes if they exceed the volume studied [8]. The variation in reconstruction of CTP images and qualitative interpretation of salvageable tissue may cause the selection of a relatively heterogeneous population, resulting in the inclusion of patients with limited salvageable tissue; which may obscure the benefit of endovascular treatment. False-negatives and uninterpretable imaging can be obtained when using CTP imaging largely due to a patient’s low cardiac output, inappropriate timing of the bolus administration, contrast extravasation in the subcutaneous tissue, patient movement, and operator inexperience [21].

**Conclusion**

A CTP penumbra did not identify patients who would benefit from endovascular treatment, whereas a NCCT ASPECTS \( \geq 7 \) had a significant correlation to good outcome. In our study, the presence of a CTP penumbra in AIS patients treated using an endovascular approach within 6 h of symptom onset did not provide an additional benefit when compared to the information obtained from a NCCT.

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