Transcranial Laser Therapy and Infarct Volume

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Background and Purpose—Two randomized trials suggested that transcranial laser therapy (TLT) may benefit patients with acute ischemic stroke, although efficacy has not been confirmed. Supportive proof of concept could be demonstrated if TLT reduces the volume of cortical infarction.

Methods—The NeuroThera Efficacy and Safety Trial-2 (NEST-2) was a randomized trial of TLT versus sham in patients with acute ischemic stroke treated within 24 hours of onset. Infarct volumes were measured quantitatively and semiquantitatively on all protocol-required computed tomography (or MRI, if clinically indicated) scans performed on day 5 (±2). Two approaches assessed treatment effects on cortex: (1) indirectly, by analyzing total infarct volume among patients with clinical presentations suggesting cortical involvement; and (2) directly, by assessing the cortical Alberta Stroke Program Early CT Score (cASPECTS) components (M1-M6, anterior, posterior) on a 0- to 8-point modified scale.

Results—A total of 640 subjects had scans (576 computed tomography, 64 MRI) on day 5. The reliability of ASPECTS (intraclass correlation coefficient=0.85) and cASPECTS (intraclass correlation coefficient=0.82) was excellent, and total ASPECTS was correlated with total infarct volume (r=0.71). In the overall study population, there was no impact of TLT on total infarct volume (P=0.30), total ASPECTS (P=0.85), or cASPECTS (P=0.89). Similarly, no effect was seen in any of the following prespecified subgroups selected to indicate cortical involvement: baseline National Institutes of Health Stroke Scale score >10, Oxfordshire Total Anterior Circulation Syndrome, subjects with aphasia or extinction at baseline, or subjects with radiographic involvement of cortex.

Conclusions—TLT was not associated with a reduction in overall or cortical infarct volume as measured on computed tomography in the subacute phase. (Stroke. 2013;44:00-00.)

Transcranial laser therapy (TLT) is being tested as a therapy for patients with acute ischemic stroke. The NeuroThera Efficacy and Safety Trials, NEST-1 and NEST-2, demonstrated that TLT was safe. NEST-1, with 120 subjects, showed a significant clinical treatment benefit, whereas NEST-2, with 660 subjects, indicated a trend suggesting a possible benefit.1,2 Pooled analysis of these 2 trials showed that 41% of patients treated with TLT had a good outcome (modified Rankin Scale score ≤2) compared with 32% of those treated with sham (P=0.003; odds ratio, 1.67; 95% confidence interval, 1.19–2.35).1,3

The exact mechanisms of the treatment effect are unknown. A leading concept is that infrared energy increases ATP in the brain and stimulates (or prevents) apoptotic cascades in mitochondria.4 The depth of brain penetration and putative therapeutic effect is also uncertain, but it is likely a few centimeters; therefore, superficial cerebral cortex is most likely to benefit from this intervention. We hypothesized that TLT would be most likely to have a measureable effect on cortical infarction. We analyzed the NEST-2 data to determine whether TLT impacted cortical infarct volumes as well as total infarct volumes in subjects with probable cortical involvement.

NEST-2 was a double-blind, sham-controlled, 1:1 randomized, clinical trial in which 660 patients were enrolled at 57 centers in 4 countries. Patients were eligible if they were 40 to 90 years of age, had a clinical diagnosis of acute ischemic stroke with a baseline National Institutes of Health Stroke Scale (NIHSS) score of 7 to 22, had no evidence of cerebral hemorrhage, had not received thrombolytic therapy, and provided informed consent. Initiation of treatment had to occur within 24 hours after stroke onset. Full inclusion and exclusion criteria are detailed in the primary report of this trial.2 Subjects were randomly assigned to receive either TLT or sham. All subjects received standard medical management throughout the trial.

Clinical assessments, including the NIHSS and modified Rankin Scale, were performed at baseline and day 90. Neuroimaging was performed at baseline and day 5 (±2). Total infarct volumes were measured quantitatively using Alice software (Hayden Image Processing Solutions). Total infarct volumes also were assessed semiquantitatively using the Alberta Stroke Program Early CT Score (ASPECTS) on all protocol-required computed tomography (CT) scans (or MRI, if clinically indicated) performed on day 5 (±2). All scans were interpreted for ASPECTS by 2 independent raters who were blinded to treatment allocation. If the 2 raters disagreed by >1 point, then a third rater scored the scan, and the average score was used.

Our primary aim was to determine the impact of TLT on cortical infarct volume, but there are no automated quantitative methods to measure this parameter, and manual tracing is not possible when the...
gray–white boundaries are distorted by infarction. Therefore, we used a combination of approaches to assess cortex. The quantitative, but indirect, approach used total infarct volumes in prespecified subgroups selected with the following clinical or radiographic evidence of cortical involvement: patients with baseline NIHSS score >10, aphasia or extinction on the NIHSS at baseline; Oxfordshire Total Anterior Circulation Syndrome; or radiographic involvement of cortex. The semiquantitative direct approach used the cortical components of the ASPECTS score (M1-M6, anterior, posterior; 1 point each) on a 0- to 8-point modified cortical ASPECTS scale (cASPECTS).

Statistical analysis compared TLT with sham using nonparametric linear regression based on ranks because total infarct volumes, ASPECTS, and cASPECTS were not normally distributed. Analyses were adjusted for hemisphere and for race because skin color could be related to absorption of infrared laser. Inter-rater reliability was assessed using intraclass correlation coefficients.

**Results**

A total of 640 subjects had scans (576 CT, 64 MRI) performed on day 5 that were available for analysis. The inter-rater reliability of both ASPECTS (intra-class correlation coefficient, 0.85; 95% confidence interval, 0.83–0.87) and cASPECTS (intra-class correlation coefficient, 0.82; 95% confidence interval, 0.79–0.84) was excellent. Total ASPECTS was highly correlated with total infarct volume (r=0.71).

The TLT and sham groups had similar total infarct volume (TLT median 22.5 mL [interquartile range, 1.5–94.1] versus sham 25.4 mL [1.4–76.7]), total ASPECTS (TLT median 7 [5.8–8.5] versus sham 7 [4.5–8.5]), and cASPECTS (TLT median 6 [4.5–7.5] versus sham 6 [4.5–7.5]). In the overall study population, there was no impact of TLT on total infarct volume (P=0.30), total ASPECTS (P=0.85), or cASPECTS (P=0.89).

Similarly, no effect was seen in any of the following prespecified subgroups selected to indicate cortical involvement: baseline NIHSS score >10, Oxfordshire Total Anterior Circulation Syndrome, subjects with aphasia or extinction at baseline, or subjects with radiographic involvement of cortex (Table).

**Discussion**

TLT aims to deliver near-infrared energy to cells to stimulate cytochrome c oxidase in mitochondria, which has been shown in preclinical experiments to increase cellular energy, to inhibit subsequent apoptosis, and to improve neurological outcomes after cerebral infarction. Other potential mechanisms of action remain to be elucidated. The NEST-1 and NEST-2 trials suggested trends in favor of clinical benefit, but our analysis was unable to demonstrate a favorable effect on cortical infarction.

Analysis of surrogate markers may support the primary clinical outcome of a trial, and previous studies have demonstrated that infarct volume measured in the first few days after onset is strongly associated with clinical outcomes at 90 days. Furthermore, such markers often offer greater statistical power as well as assessment of the pathophysiology and proof of concept.

We found that TLT within 24 hours after stroke onset was not associated with a reduction in overall infarct volume or cortical infarct size as measured in the subacute phase. Furthermore, there was no impact on infarct volume in any subgroup with likely cortical involvement. These results do not reflect the trends observed in the clinical trials and do not support the concept that TLT is more likely to benefit cortex compared with deeper structures.

Strengths of our study include systematic blinded review of scans performed at a standardized time after stroke onset. Weaknesses include the predominant use of CT rather than MRI, because the latter is both more sensitive and specific for assessment of acute infarction, and small differences could have been missed. The ASPECTS system was designed primarily for the assessment of early CT scans but seemed to have face validity for assessment of infarct size even at later times, and it was found to have inter-rater reliability and criterion validity compared with quantitative infarct volumes in this analysis. The modification of ASPECTS for semiquantitative assessment of cortical infarction was a novel strategy that should be considered exploratory.

**Disclosures**

Drs Kasner, Walker, Shi, and Streeter are consultants to Photothera.

**References**


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