ERASER

A Thrombectomy Study With Predictive Analytics End Point

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Background and Purpose—Using a novel study design with virtual comparators based on predictive modeling, we investigated whether next-generation mechanical thrombectomy devices improve outcomes in patients with ischemic stroke. We hypothesized that this new study design shows that a next-generation mechanical thrombectomy system is superior to intravenous tPA (tissue-type plasminogen activator) therapy (IVT) alone.

Methods—ERASER (Eric Acute Stroke Recanalization) was an investigator-initiated, prospective, multicenter, single-arm (virtual 2-arm) study that evaluated the effectiveness of a new recanalization device together with a specific intermediate catheter (Embolus Retriever with Interlinked Cages/SOFIA, Microvention) in stroke patients with internal carotid artery or middle cerebral artery occlusions. The primary end point was the volume of saved tissue. Volume of saved tissue was defined as the difference of actual infarct volume and brain volume predicted to develop infarction using a machine learning model based on data from intravenous tPA therapy patients.

Results—Eighty-one patients were enrolled. The median patient age was 71 years (interquartile range, 61–77). National Institutes of Health Stroke Scale score was 14 (interquartile range, 12–18). The actual infarct volume was smaller than predicted by the intravenous tPA therapy model, with a median volume of saved tissue of 50 mL (interquartile range, 19–103; $P<0.0001$). Good clinical outcome (modified Rankin Scale, 0–2 at 90 days) was observed in 48 out of 69 (70%). The recanalization rate (Thrombolysis in Cerebral Infarction 2b/3) was 95%.

Conclusions—ERASER is the first mechanical thrombectomy study with a primary end point based on predictive analytics enabling intraindividual virtual comparisons. The next-generation mechanical thrombectomy method resulted in smaller infarcts than predicted after intravenous tPA therapy alone and showed a high rate of good clinical outcome. The novel study design with virtual comparisons is promising for further application and testing in the neurovascular arena.

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The Embolus Retriever with Interlinked Cages (ERIC) is an innovative retrieval system for mechanical thrombectomy (MT) in patients with stroke with large vessel occlusions. Initial retrospective studies were indicative of good efficacy and a favorable safety profile.[1] To further build on these analyses, the ERASER study (Eric Acute Stroke Recanalization) was designed to prospectively evaluate its effectiveness together with a specific intermediate catheter (ERIC/SOFIA, Microvention, Aliso Viejo, CA) by means of modeling based on baseline clinical and imaging data.[2]

The key idea was to compare within the same patient the predicted outcome of alternative therapy based on pretherapeutic variables, with the actual observed outcome following MT (virtual 2-arm study). We hypothesized this new study design shows that these next-generation MT devices improve tissue outcomes when compared with intravenous tPA (tissue-type plasminogen activator) therapy (IVT) alone.

Methods

ERASER was an investigator-initiated, prospective, multicenter, virtual controlled, open-label, single-arm (virtual 2-arm) study.

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External monitoring was conducted by an independent contract research organization (CTC North, Hamburg, Germany). Image data transmission, quality management, image analysis, and data storage were provided by Eppdata (Eppdata, Hamburg, Germany). The study was performed in accordance with Good Clinical Practice. ERASER was conducted in 10 centers throughout Germany and Switzerland. ERASER was approved by the leading ethics committee of Hamburg, Germany. The data that support the findings of this study are available from the corresponding author on reasonable request.

The primary end point was the volume of saved tissue (VOST). VOST was defined as the difference of actual infarct volume and the brain volume predicted to develop infarction using a high-level machine learning model trained based on data from a historical cohort treated with IVT.[2]

Patients with symptoms of acute ischemic stroke and occlusion of the internal carotid artery or middle cerebral artery were enrolled. Other key inclusion criteria were age ≥18 years, informed consent, National Institutes of Health Stroke Scale score of 8–25, prestroke modified Rankin Scale 0–1, and eligibility for IVT. A SOFIA catheter was either used for primary aspiration at the discretion of the interventionalist or as an intermediate catheter to deliver the ERIC as primary recanalization device.

Patients additionally fulfilling the following prespecified imaging criteria were included in the ERASER+ subgroup: computed tomography (CT) perfusion at <4.5 hours, M1-occlusion, IVT, and follow-up CT <30 hours (±12 hours). Key exclusion criteria were recanalization in baseline angiography or an Alberta Stroke Program Early CT Score of ≤6. Clinical and neurological assessments were completed at baseline and after treatment at 30 hours poststroke and at 90 days.

Image Data

An imaging core laboratory performed qualitative and semiquantitative assessments of all available image data to confirm occlusion and determine the Alberta Stroke Program Early CT Score at baseline. Infarct volumes were segmented by 2 independent readers in follow-up noncontrast CT or on fluid-attenuated inversion recovery/T2-weighted magnetic resonance imaging. Successful recanalization was defined as Thrombolysis in Cerebral Infarction 2b or better.

Predictive Modeling

For extraction of the training set for the simulation of the infarct volume after IVT, the follow-up images of historical IVT patients fulfilling the ERASER+ criteria were registered to the corresponding pretreatment CT perfusion dataset. The normalized perfusion parameters (cerebral blood flow, cerebral blood volume, mean transit time, and time to the maximum of the residue function) were extracted for each voxel of the follow-up lesion, as well as an equal number of surviving voxels, randomly sampled from the ipsilateral hemisphere (Figure 1). These features were enriched by age, sex, baseline-National Institutes of Health Stroke Scale, and time from onset to imaging. The parameters for all patients of the training group were then combined into a final training set and used to generate a predictive model using a random forest classifier of 100 decision trees with 60% random sampling. The classifier was used to predict the tissue outcome and compared with the real MT-based lesion volume for each ERASER+ patient.

Results

Eighty-one patients were enrolled from April 2015 to April 2017. One patient was excluded because another stent-retriever was used as an initial device (Table I in the online-only Data Supplement).

The recanalization rate was 76 out of 80 (95% Thrombolysis in Cerebral Infarction 2b/3). Clinical outcome data were available in 69 out of 80 patients. Good clinical outcome was observed in 48 out of 69 patients (70% 0–2 at 90 days). Mortality was 7 out of 80 (9%). Bail out procedures with devices other than ERIC were conducted in 10 out of 80 (13%).

Forty-one patients qualified for the ERASER+ cohort and were used for the analysis of the primary end point (VOST). Reasons for exclusion were vessel occlusions other than M1 (n=6), Alberta Stroke Program Early CT Score <7 in noncontrast CT (n=5), unavailable CT perfusion source data or a cerebral blood volume-decrease with Alberta Stroke Program Early CT Score<7 (n=26), and onset to image >4.5 hours (n=2).

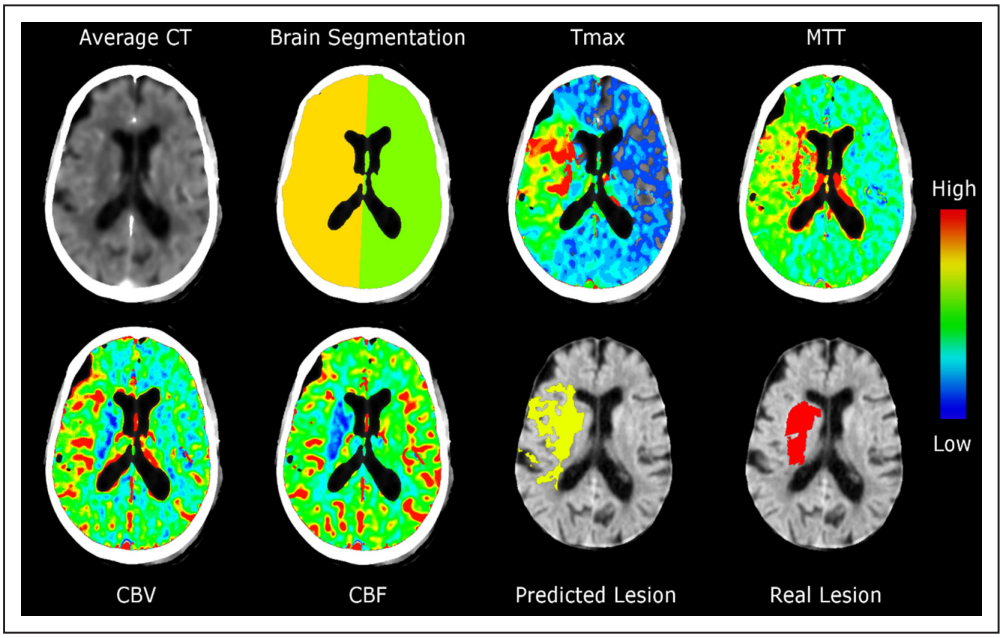

Figure 1. The image shows the average computed tomography (CT) from the perfusion maps before contrast arrival, the segmented brain hemispheres, and the normalized perfusion parameter maps. The predicted lesion extent based on these maps is marked in yellow, and the actually delineated infarct on follow-up is shown in red. CBF indicates cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time; and Tmax, time to the maximum of the residue function.

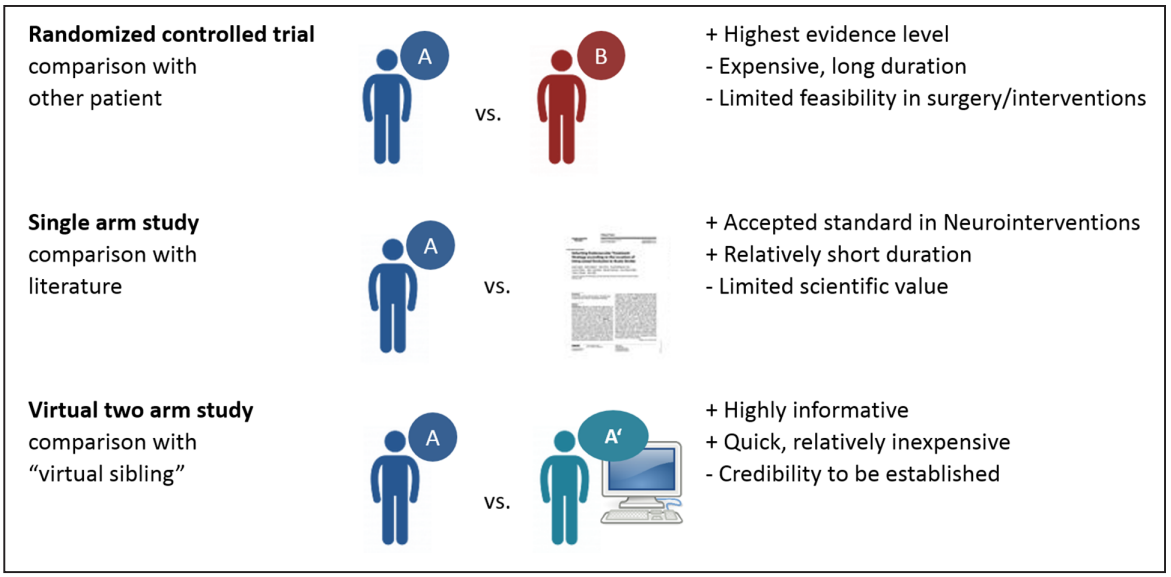

Figure 2. Schematic illustration of the traditional trial designs compared with the virtual 2-arm study, such as ERASER.

The median infarct volume in the ERASER+ cohort at 30 hours was 5 mL (interquartile range, 2–15 mL) compared with a median predicted infarct volume after IVT only therapy of 58 mL (36–110 mL). When determined on a subject level, the median VOST was 50 mL (19–100 mL, $P<0.0001$). The observed infarct volume was larger than the predicted volume in 4 out of 41 (10%; range, 2–35 mL).

Discussion

In this prospective, virtual controlled study, next-generation MT devices improved tissue outcomes compared with simulated IVT. The difference between the predicted and actual infarct volumes resulted in a VOST of 50 mL, which is in agreement with the known higher therapy efficacy of combined IVT and MT in patients with large vessel occlusion.[3]

Computer simulations, although widely used in complex, mission-critical areas, such as aircraft or nuclear power plant safety, are rarely employed in clinical trials. Recently, a large working group consisting of members from a variety of backgrounds suggested that in silico trials might be valuable to refine and complement traditional clinical trials.[4] To date, although contributing to this development, ERASER represents only an early pilot study. To further strengthen this paradigm, considerable efforts are required, in particular, to standardize image acquisition.

High recanalization rates are associated with good outcome and have been used as a surrogate marker for clinical MT efficacy.[5] However, this association may not necessarily hold true in the individual patient. Based on logical pathophysiological reasoning, one could assume that recanalization leads to tissue reperfusion, which limits infarct volume, which in turn limits clinical deficit. Infarct volume, and therefore VOST, should be more closely related to clinical outcome than recanalization/reperfusion.

We applied predictive analytics to correct for individual tissue prognosis before enrollment for evaluating the final infarct and, thus, the therapy effect. In this study, we compared the predicted tissue outcome (infarct volume) following an alternative therapy regime (based on pretherapeutic variables) with the actual infarct volume after MT, all within the same individual (Figure 2). This aspect is advantageous in that it limits the heterogeneity between patients.

The rate of good clinical outcome in ERASER was relatively high and is presumably subject to ascertainment bias because of missing values. However, the rate of good outcome would be 60% even if all patients with missing values were considered poor outcome. This observation could be explained by the high recanalization rate and the strict inclusion criteria.

A major limitation of ERASER is the selection of the control group. Instead of comparing ERIC/SOFIA with the current gold standard (MT+IVT), we compared the ERASER+ cohort with patients treated with a historical standard (IVT only). Other limitations include a higher mean National Institutes of Health Stroke Scale score in the training cohort, lack of CT perfusion standardization, and the relatively small sample size. Furthermore, there are other potential sources of bias throughout the entire process, from selection of the training data to the statistical comparison between the results of virtual and real treatment. Strengths include imaging evaluation by an independent core laboratory and independent external monitoring.

Conclusions

ERASER represents a pilot study with the primary end point based on predictive analytics, enabling a comparison with a virtual control group. The ERIC/SOFIA device resulted in a high rate of good clinical outcome and recanalization and significantly smaller infarct volumes than predicted after IVT alone. The major challenge for in silico trials is to develop methods to increase credibility in the scientific community.

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Financial support was provided by Microvention (Aliso Viejo, CA). The funder had no influence on study design, data analysis, interpretation, and article writing.

Disclosures

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References

1. Gruber P, Zeller S, Garcia-Esperon C, Berberat J, Anon J, Diepers M, et al. Embolus retriever with interlinked cages versus other stent retrievers in acute ischemic stroke: an observational comparative study. *J Neurointerv Surg.* 2018;10:e31. doi: 10.1136/neurintsurg-2018-013838
2. Siemonsen S, Forkert ND, Bernhardt M, Thomalla G, Bendszus M, Fiehler J. Eric acute stroke recanalization: a study using predictive analytics to assess a new device for mechanical thrombectomy. *Int J Stroke.* 2017;12:659–666. doi: 10.1177/1747493017700661
3. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al; HERMES Collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* 2016;387:1723–1731. doi: 10.1016/S0140-6736(16)00163-X
4. Viceconti M, Henney A, Morley-Fletcher E. In silico clinical trials: how computer simulation will transform the biomedical industry. Research and Technological Development Roadmap, Avicenna Consortium, Brussels Jan 2016. doi: 10.13140/RG.2.1.2756.6164
5. Liebeskind D, Jovin T, Majoie C, Mitchell P, van der Lugt A, Menon B, et al. eTICI reperfusion: defining success in endovascular stroke therapy [published online September 7, 2018]. *J Neurointerv Surg*. https://jnis.bmj.com/content/early/2018/09/06/neurintsurg-2018–014127. Accessed March 7, 2019.