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Original Article

Endovascular thrombectomy and medical therapy versus medical therapy alone in acute stroke: A randomized care trial

Naim N. Khoury[a], Tim E. Darsaut[b], Jimmy Ghostine[a], Yan Deschaintre[c], Nicole Daneault[c], André Durocher[c], Sylvain Lanthier[c], Alexandre Y. Pope[c], Céline Odier[c], Louise-Hélène Lebrun[c], François Guilbert[a], Jean-Christophe Gentric[a,d], André Batista[a], Alain Weill[a], Daniel Roy[a], Serge Bracard[e], Jean Raymond[a,*], for the EASI trial collaborators

[a] *Centre hospitalier universitaire de Montréal, Notre-Dame hospital, department of radiology, 1560, Sherbrooke east, Pavilion Simard, suite Z12909, H2L 4M1 Montreal, Quebec, Canada*
[b] *Department of surgery, division of neurosurgery, university of Alberta hospital, Mackenzie health sciences centre, Edmonton, Alberta, Canada (TED)*
[c] *Centre hospitalier universitaire de Montréal, Notre-Dame hospital, department of medicine, division of neurology, 1560, Sherbrooke east, H2L 4M1 Montreal, Quebec, Canada*
[d] *Groupe d'étude de la thrombose en Bretagne Occidentale (GETBO, EA 3878), 29609 Brest cedex, France*
[e] *Service de neuroradiologie diagnostique et thérapeutique, hôpital Central, CHU de Nancy, 54000 Nancy, France*

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ABSTRACT

Background. – Until recently, the benefits of endovascular treatment in stroke were not proven. Care trials have been designed to simultaneously offer yet-to-be validated interventions and verify treatment outcomes. Our aim was to implement a care trial for patients with acute ischemic stroke.
Methods. – The study was offered to all patients considered for endovascular management of acute ischemic stroke in one Canadian hospital. Inclusion criteria were broad: onset of symptoms ≤ 5 h or at any time in the presence of clinical-imaging mismatch and suspected or demonstrated proximal large vessel occlusion. Exclusion criteria were few: established infarction or hemorrhagic transformation of the target symptomatic territory and poor 3-month prognosis. The primary outcome was mRS ≤ 2 at 3 months. Patients were randomly allocated to standard care or standard care plus endovascular treatment. ClinicalTrials.gov: Identifier NCT02157532.
Results. – Seventy-seven patients were recruited in 19 months (March 2013–October 2014) at a single center. Randomized allocation was interrupted when other trials showed the benefits of endovascular therapy. At 3 months, 20 of 40 patients (50.0%; 95% CI: 35%–65%) in the intervention group had reached the primary outcome, compared to 14 of 37 patients (37.8%; 95% CI: 24%–54%) in the control group ($P = 0.36$). Eleven patients in the intervention group died within 3 months compared to 9 patients in the standard care group.
Conclusion. – A care trial was implemented to offer verifiable care to acute stroke patients. This approach offers a promising means to manage clinical dilemmas and guide uncertain practices.

Abbreviations: NIHSS, National institutes of health stroke scale; MCA, Middle cerebral artery; ICA, Internal cerebral artery; ACA, Anterior cerebral artery; CT, Computed tomography; MR, Magnetic resonance; TICI, Thrombolysis in cerebral infarction.

* Corresponding author. Tel.: +1 514 890 8000, ext.: 27235; fax: +1 514 412 7621.
E-mail addresses: naim.khoury@umontreal.ca (N.N. Khoury), tdarsaut@ualberta.ca (T.E. Darsaut), jimmy.ghostine@gmail.com (J. Ghostine), yan.deschaintre.chum@ssss.gouv.qc.ca (Y. Deschaintre), nicole.daneault.chum@ssss.gouv.qc.ca (N. Daneault), andre.p.durocher.chum@ssss.gouv.qc.ca (A. Durocher), sylanthier@gmail.com (S. Lanthier), aypoppe@yahoo.ca (A.Y. Pope), c_odier@hotmail.com (C. Odier), louise-helene.lebrun.chum@ssss.gouv.qc.ca (L.-H. Lebrun), francois.guilbert.chum@ssss.gouv.qc.ca (F. Guilbert), jcgentric@gmail.com (J.-C. Gentric), batista.nchir@gmail.com (A. Batista), alain.weill.chum@ssss.gouv.qc.ca (A. Weill), daniel.roy.chum@ssss.gouv.qc.ca (D. Roy), s.bracard@gmail.com (S. Bracard), jean.raymond@umontreal.ca (J. Raymond).

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Introduction

Until recently, intravenous (i.v.) tissue plasminogen activator (tPA) was the only acute stroke recanalization treatment proven to improve patient outcomes [1,2]. Despite i.v. thrombolysis, patients with severe stroke continued to suffer high mortality (20–25%) and dependency (50%) [3]. While successful vessel recanalization using endovascular treatments was reported in 2012 [4,5], disappointing results from randomized trials of endovascular treatment followed in 2013, showing no clear benefit for patient outcomes [6–8]. Dissatisfied with how we had been practicing interventions without evidence and to improve on the design and conduct of previous trials, we conceived the Endovascular acute stroke intervention (EASI) trial, a pragmatic study of mechanical thrombectomy versus standard care. Unlike other trials, EASI was a care trial [9] with the primary goal to prudently offer patients the opportunity to receive a promising yet unproven treatment. In a care trial, patients are not primarily selected to be participants in a research protocol designed to answer a research question. Rather, the promising but non-validated intervention that clinicians wish to use is regulated by trial methodology, every step of which is designed in the best interest of current patients [9].

EASI was accruing patients at a promising rate when the Steering committee (SC) decided to stop randomized allocation following the release of the Mr Clean trial results in 2014 [10]. Here, we report the use of care trial methods to practice mechanical thrombectomy for acute stroke patients during the period of time when clinical uncertainty was present.

Methods

Study design

The primary aim of the trial was to offer a promising but unproven endovascular intervention for patients with acute ischemic stroke caused by proximal vessel occlusion, while simultaneously protecting patients from the risks involved in using an invasive treatment whose benefit was yet to be established. In this context of uncertainty and until the better option was identified, optimal care was to be offered as a 50% chance of getting the promising treatment, and a 50% chance of getting standard care and thus avoid the potential risks associated with innovative care.

EASI was an investigator-led, randomized care trial comparing clinical outcomes of patients presenting with acute ischemic stroke treated with standard care plus mechanical thrombectomy versus standard care alone. At the time of trial interruption, only one Canadian center was active. The trial was approved by the Institutional review board of the centre hospitalier de l'université de Montréal. The trial is registered at ClinicalTrials.gov: Identifier NCT02157532. The protocol is available at www.clinical-care-trials.org.

Patients

EASI was offered to all patients referred for endovascular treatment of acute ischemic stroke. Inclusion criteria were broad: age $\geq$ 18 years, NIHSS $\geq$ 8, onset of symptoms $\leq$ 5 hours or the presence of clinical-imaging mismatch, and suspected or proven occlusion of the M1 or M2 segments of the MCA, supraclinoid ICA, or basilar artery. Vascular imaging was not mandated in the protocol. The exclusion criteria were: established infarction or haemorrhagic transformation of the target symptomatic territory and co-morbidities associated with a poor 90-day outcome. All patients or representatives signed a standardized informed consent form.

Randomisation and masking

Patients were randomly allocated 1:1 to mechanical thrombectomy plus standard care or standard treatment through a web-based application package (www.medscinet.com). Minimization was used as a method of adaptive stratified sampling with the following criteria: eligibility for IV tPA, less than 3 hours from symptoms onset, and NIHSS $\leq$ 16. Randomization could be performed during i.v. thrombolysis (when appropriate), or within 5 hours from the time of symptoms onset, without waiting for clinical response to i.v. tPA; the goal was achieving thrombectomy as quickly as possible by 6 hours from stroke onset, which also explains the rationale for inclusion of patients with suspected but not proven proximal vessel occlusion. Patients could also be recruited beyond 5 hours from symptoms onset when clinically judged to have a discrepancy between symptoms and imaging. For example, patients with severe deficit, unknown time of onset and normal or near-normal CT scan were judged to have a clinical-imaging mismatch and hence could be included. For patients allocated to thrombectomy, a simultaneous second randomization was conducted in the event that a tandem lesion (severe ipsilateral cervical ICA stenosis or occlusion) was identified during the procedure, allocating patients to treatment or no treatment of the tandem lesion (before or after thrombectomy, at the discretion of the interventionist). There was no masking or blinding.

Procedures

Standard management of the acute ischemic stroke, including i.v. thrombolysis when appropriate, was performed by the treating neurologist, according to local protocols. The thrombectomy procedure was performed under local or general anesthesia (when necessary), using any approved device, according to local practice.

Outcomes

The primary hypothesis of the trial was that endovascular management in addition to standard care would lead to a 15% increase (25% to 40%) in the proportion of patients with a modified Rankin Scale (mRS) score of 0–2 at 90 days, as compared to patients treated with best standard treatment alone (including i.v. thrombolysis if eligible).

The primary efficacy outcome was the proportion of independent patients at 90 days (mRS 0–2). The primary safety outcomes were death at 90 days and symptomatic intracranial hemorrhage (sICH) at 24 hrs. Angiographic reperfusion TICI score [11] and adverse events were collected as secondary imaging and safety outcomes.

Data capture and management were held independently on the secure servers of MedSciNet, ensuring FDA 21 Code of Federal Regulations Part 11, Good clinical practice requirements compliance. Report forms were few and data collected were parsimonious. The registration form included demographics, time of stroke onset, the most severe NIHSS score, and eligibility for IV tPA. The treatment form included the baseline Alberta stroke program early computed tomography score (ASPECTS) and the suspected or demonstrated occlusion site, the time and dose of i.v. tPA administration, and technical parameters of thrombectomy when performed. The next day evaluation form collected data on clinical evolution and imaging findings and the 3-month follow-up form reported the mRS score and patient location. Adverse events and mortality were reported at any time during the trial and automatic notification was sent to the study monitor. All data and outcome measures were collected by routine care personnel in this care trial design and thus, no blinding was involved. Monitoring of data quality was web-based.