The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke

Olvert A. Berkhemer, M.D., Puck S.S. Fransen, M.D., Debbie Beumer, M.D., Lucie A. van den Berg, M.D., Hester F. Lingsma, Ph.D., Albert J. Yoo, M.D., Wouter J. Schonewille, M.D., Jan Albert Vos, M.D., Ph.D., Paul J. Nederkoorn, M.D., Ph.D., Marieke J.H. Wermer, M.D., Ph.D., Marianne A.A. van Walderveen, M.D., Ph.D., Julie Staals, M.D., Ph.D., Jeannette Hofmeijer, M.D., Ph.D., Jacques A. van Oostayen, M.D., Ph.D., Geert J. Lycklama à Nijeholt, M.D., Ph.D., Jelis Boiten, M.D., Ph.D., Patrick A. Brouwer, M.D., Bart J. Emmer, M.D., Ph.D., Sebastiaan F. de Bruijn, M.D., Ph.D., Lukas C. van Dijk, M.D., L. Jaap Kappelle, M.D., Ph.D., Rob H. Lo, M.D., Ewoud J. van Dijk, M.D., Ph.D., Joost de Vries, M.D., Ph.D., Paul L.M. de Kort, M.D., Ph.D., Willem Jan J. van Rooij, M.D., Ph.D., Jan S.P. van den Berg, M.D., Ph.D., Boudewijn A.A.M. van Hasselt, M.D., Leo A.M. Aerden, M.D., Ph.D., René J. Dallinga, M.D., Marieke C. Visser, M.D., Ph.D., Joseph C.J. Bot, M.D., Ph.D., Patrick C. Vroomen, M D., Ph.D., Omid Eshghi, M.D., Tobien H.C.M.L. Schreuder, M.D., Roel J.J. Heijboer, M.D., Koos Keizer, M.D., Ph.D., Alexander V. Tielbeek, M.D., Ph.D., Heleen M. den Hertog, M.D., Ph.D., Dick G. Gerrits, M.D., Renske M. van den Berg-Vos, M.D., Ph.D., Giorgos B. Karas, M.D., Ewout W. Steyerberg, M.D., Ph.D., H. Zwenneke Flach, M.D., Henk A. Marquering, Ph.D., Marieke E.S. Sprengers, M.D., Ph.D., Sjoerd F.M. Jenniskens, M.D., Ph.D., Ludo F.M. Beenen, M.D., René van den Berg, M.D., Ph.D., Peter J. Koudstaal, M.D., Ph.D., Wim H. van Zwam, M.D., Ph.D., Yvo B.W.E.M. Roos, M.D., Ph.D., Aad van der Lugt, M.D., Ph.D., Robert J. van Oostenbrugge, M.D., Ph.D., Charles B.L.M. Majoie, M.D., Ph.D., and Diederik W.J. Dippel, M.D., Ph.D. for the MR CLEAN Investigators

N Engl J Med 2015; 372:11-20 | January 1, 2015 | DOI: 10.1056/NEJMoa1411587

Comments open through January 7, 2015

Share:

Abstract

In patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion, intraarterial treatment is highly effective for emergency revascularization. However, proof of a beneficial effect on functional outcome is lacking.

We randomly assigned eligible patients to either intraarterial treatment plus usual care or usual care alone. Eligible patients had a proximal arterial occlusion in the anterior cerebral circulation that was confirmed on vessel imaging and that could be treated intraarterially within 6 hours after symptom onset. The primary outcome was the modified Rankin scale score at 90 days; this categorical scale measures functional outcome, with scores ranging from 0 (no symptoms) to 6 (death). The treatment effect was estimated with ordinal logistic regression as a common odds ratio, adjusted for prespecified prognostic factors. The adjusted common odds ratio measured the likelihood that intraarterial treatment would lead to lower modified Rankin scores, as compared with usual care alone (shift analysis).

We enrolled 500 patients at 16 medical centers in the Netherlands (233 assigned to intraarterial treatment and 267 to usual care alone). The mean age was 65 years (range, 23 to 96), and 445 patients (89.0%) were treated with intravenous alteplase before randomization. Retrievable stents were used in 190 of the 233 patients (81.5%) assigned to intraarterial treatment. The adjusted common odds ratio was 1.67 (95% confidence interval [CI], 1.21 to 2.30). There was an absolute difference of 13.5 percentage points (95% CI, 5.9 to 21.2) in the rate of functional independence (modified Rankin score, 0 to 2) in favor of the intervention (32.6% vs. 19.1%). There were no significant differences in mortality or the occurrence of symptomatic intracerebral hemorrhage.

In patients with acute ischemic stroke caused by a proximal intracranial occlusion of the anterior circulation, intraarterial treatment administered within 6 hours after stroke onset was effective and safe. (Funded by the Dutch Heart Foundation and others; MR CLEAN Netherlands Trial Registry number, NTR1804, and Current Controlled Trials number, ISRCTN10888758.)

Article

Intravenous alteplase administered within 4.5 hours after symptom onset is the only reperfusion therapy with proven efficacy in patients with acute ischemic stroke.[1] However, well-recognized limitations of this therapy include the narrow therapeutic time window and contraindications such as recent surgery, coagulation abnormalities, and a history of intracranial hemorrhage.[2] Moreover, intravenous alteplase appears to be much less effective at opening proximal occlusions of the major intracranial arteries, which account for more than one third of cases of acute anterior-circulation stroke.[3,4] Early recanalization after intravenous alteplase is seen in only about one third of patients with an occlusion of the internal-carotid-artery terminus,[5] and the prognosis without revascularization is generally poor for such patients.[6] For these reasons, intraarterial treatment is regarded as a potentially important component of the therapeutic armamentarium.

Table 1. Baseline Characteristics of the 500 Patients.*

Characteristic	Intervention (N=233)	Control (N=267)
Age — yr		
Median	65.8	65.7
Interquartile range	54.5–76.0	55.5–76.4
Male sex — no. (%)	135 (57.9)	157 (58.8)
NIHSS score†		
Median (interquartile range)	17 (14–21)	18 (14–22)
Range	3–30	4–38
Location of stroke in left hemisphere — no. (%)	116 (49.8)	153 (57.3)
History of ischemic stroke — no. (%)	29 (12.4)	25 (9.4)
Atrial fibrillation — no. (%)	66 (28.3)	69 (25.8)
Diabetes mellitus — no. (%)	34 (14.6)	34 (12.7)
Prestroke modified Rankin scale score — no. (%)‡		
0	190 (81.5)	214 (80.1)
1	21 (9.0)	29 (10.9)
2	12 (5.2)	13 (4.9)
>2	10 (4.3)	11 (4.1)
Systolic blood pressure — mm Hg§	146±26.0	145±24.4
Treatment with IV alteplase — no. (%)	203 (87.1)	242 (90.6)
Time from stroke onset to start of IV alteplase — min		
Median	85	87
Interquartile range	67–110	65–116
ASPECTS — median (interquartile range)¶	9 (7–10)	9 (8–10)
Intracranial arterial occlusion — no./total no. (%)‖		
Intracranial ICA	1/233 (0.4)	3/266 (1.1)
ICA with involvement of the M1 middle cerebral artery segment	59/233 (25.3)	75/266 (28.2)
M1 middle cerebral artery segment	154/233 (66.1)	165/266 (62.0)
M2 middle cerebral artery segment	18/233 (7.7)	21/266 (7.9)
A1 or A2 anterior cerebral artery segment	1/233 (0.4)	2/266 (0.8)
Extracranial ICA occlusion — no./total no. (%)‖**	75/233 (32.2)	70/266 (26.3)
Time from stroke onset to randomization — min††		
Median	204	196
Interquartile range	152–251	149–266
Time from stroke onset to groin puncture — min		
Median	260	NA
Interquartile range	210–313	

* The intervention group was assigned to intraarterial treatment plus usual care, and the control group was assigned to usual care alone. Plus–minus values are means ±SD. ICA denotes internal carotid artery, IV intravenous, and NA not applicable.

† Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficits. The NIHSS is a 15-item scale, and values for 30 of the 7500 items were missing (0.4%). The highest number of missing items for a single patient was 6.

‡ Scores on the modified Rankin scale of functional disability range from 0 (no symptoms) to 6 (death). A score of 2 or less indicates functional independence.

§ Data on systolic blood pressure at baseline were missing for one patient assigned to the control group.

¶ The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is a measure of the extent of stroke. Scores ranges from 0 to 10, with higher scores indicating fewer early ischemic changes. Scores were not available for four patients assigned to the control group: noncontrast computed tomography was not performed in one patient, and three patients had strokes in the territory of the anterior cerebral artery.

‖ Vessel imaging was not performed in one patient in the control group, so the level of occlusion was not known.

** Extracranial ICA occlusions were reported by local investigators.

†† Data were missing for two patients in the intervention group.

| − | ▲ | + | Fullscreen |

Table 1. Baseline Characteristics of the 500 Patients.