CHEMICAL OPTIMISATION OF CEREBRAL EMBOLECTOMY: CHOICE STUDY

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1. Abstract

The latest generation of endovascular devices is highly effective in recanalizing large vessel occlusions (LVO) in patients with acute ischemic stroke (AIS) but have more limited capacity to reperfuse the target downstream territory. Indeed, only 37% of patients achieve complete reperfusion of this territory. Mechanical thrombectomy (MT) has shown to increase the likelihood of good outcome, but the benefits were restricted to less than half of the treated patients. Experimentally, thrombolytic therapy effectively reinstitutes the capillary flow and improves outcome, and observational studies and post hoc analyses of clinical trials have shown the relevance of accomplishing complete reperfusion (defined as a modified treatment in cerebral ischemia [mTICI] 3 score) at the end of MT compared to near complete reperfusion (defined as an mTICI 2b score). Therefore, it is important to identify new methods to increase the proportion of mTICI 3 at the end of MT. The value of administering thrombolytic therapy after MT (rescue therapy) is so far unknown. Several reasons would justify the assessment of this new approach.

Our hypothesis sustains that in selected patients, rescue thrombolysis may be an effective add-on therapy after MT to lysis of distal thrombi that prevent complete capillary flow and brain perfusion, thus limiting functional recovery in patients otherwise successfully recanalized.

In accordance with this hypothesis, the main objective of this project is to perform the Chemical Optimization of Cerebral Embolectomy (CHOICE) Trial, a double-blinded, randomized, controlled phase 2b study aimed at evaluating whether rescue intra-arterial (IA) thrombolysis with alteplase is better than placebo to improve the stroke outcomes of patients with an mTICI 2b at the end of MT. As these patients represent a substantial portion of those who currently receive MT, rejection of the null hypothesis of the CHOICE trial could represent a major step forward in the management of patients with AIS and LVO.

2. Results

CHOICE included 121 patients with LVO treated with thrombectomy within 24 hours after stroke onset and all of them had an eTICI angiographic score of 2b50 to 3 at the end of MT. Participants were randomized post-MT to receive intra-arterial alteplase (0.225 mg/kg; maximum dose, 22.5 mg) (n = 61) or placebo (n = 52). The primary outcome was the difference in proportion of disability-free patients on the 90-day (achieving a score of 0 or 1 on the 90-day modified Rankin Scale) and safety outcomes included the rate of symptomatic intracranial hemorrhage (sICH) and death. The proportion of participants with a modified Rankin Scale score of 0 or 1 at 90 days was 59.0% with alteplase and 40.4% with placebo (adjusted risk difference, 18.4%; 95% CI, 0.3%-36.4%; P = 0.047). Reassuringly, the proportion of patients with sICH was 0% with alteplase and 3.8% with placebo (risk difference, −3.8%; 95% CI, −13.2% to 2.5%). Ninety-day mortality was 8% with alteplase and 15% with placebo (risk difference, −7.2%; 95% CI, −19.2% to 4.8%).

In conclusion, the use of adjunct intra-arterial alteplase resulted in a greater likelihood of excellent neurological outcome at 90 days compared with placebo. The study results support the safety of adjunct intra-arterial alteplase in patients with successful reperfusion at the end of thrombectomy, including in patients treated previously with intravenous alteplase.

In a pre-planned nested study of CHOICE, at 48 hours of stroke onset 36 patients also had the infarct expansion ratio (IER) measured on DWI-MRI, the prevalence of hypoperfusion measured on PWI-MRI, and the n-acetylaspartate (NAA) peak relative to total creatine assessed on brain MRI spectroscopy (data submitted for publication). In this predefined subgroup, the proportion of participants with abnormal microvascular perfusion was 24% with IA alteplase, and 58% with placebo; aOR 0.20, 95% CI, 0.04-0.91, P=0.03. IA alteplase reduced the IER [median (IQR) 0.7 (0.5-1.2) vs. 3.2 (1.8-5.7), P=0.01)], and resulted in higher peaks of NAA [median (IQR) 1.13 (0.91-1.36) vs. 1.00 (0.74-1.22), P<0. 0001] compared with placebo. Overall, these findings made it possible to conclude that the use of adjunct IA alteplase also resulted in a significant reduction in the proportion of patients with areas of microvascular hypoperfusion, and the proportion of patients with infarct expansion, as well as improved markers of

neuronal integrity, thus providing ancillary clues to explain the remarkable clinical findings.

3. Relevance with possible future implications

These results may help to change the paradigm of ischemic stroke treatment with the administration of a thrombolytic agent after mechanical thrombectomy. This study provides relevant new information that will change the clinical guidelines for acute ischemic stroke with the ultimate goal of improving the functional outcome of patients. In addition, the findings of the neuroimaging sub-study pre-planned allowed to conclude that the use of adjunct IA alteplase also resulted in a significant reduction in the proportion of patients with areas of microvascular hypoperfusion, and the proportion of patients with infarct expansion, as well as improved markers of neuronal integrity, thus providing ancillary clues to explain the remarkable clinical findings.

If confirmed in the current proposal, the safety and efficacy of the therapy makes IA alteplase a ground breaking compound that could be prescribed to many of the patients admitted into Comprehensive Stroke Centers. CHOICE-2 may assist policy makers in their decisions as it will provide unbiased evidence on the value of rescue IA thrombolysis following MT in patients with acute ischemic stroke. The current availability of the medication worldwide will facilitate an immediate take of the study results in clinical practice which will be incorporated in the Acute Stroke Therapy Guidelines worldwide. CHOICE-2 will have a major health and social impact given the prevalence of the disease under study. The value of adjunct IA thrombolysis to obtain capillary brain reperfusion at the end of MT will also have relevant procedural consequences during MT. Thus, the assertiveness of the endovascular procedure will be tempered, for interventionalists will limit the number of passes to obtain a mTICI3 as they would have evidence of the efficacy of less invasive pharmacologic strategies to ameliorate brain perfusion.

Human neurological disorders represent 24% of all the disability-adjusted lost years (DALYs), and stroke represents 42% of the neurological DALYS. About 1.2 million strokes occur each year in the EU, and about 25% of men and 20% of women can expect to suffer a stroke if they live to be 85 years old. In the EU, stroke accounts for

more than 500,000 deaths each year with about one in ten men (9%) and one in eight women (12%) dying from stroke. In the EU, about 3.7 million DALYs are lost each year due to stroke, representing 6% of total DALYs lost. The economic costs of stroke added up to more than €34bn in the EU in 2006, and approximately 3 to 7% of total health care expenditures in Western countries are spent on stroke. Only in Spain, there are approximately 120,000 new strokes every year and if CHOICE-2 confirms the anticipated results, every year there will be an increase of 900 stroke patients completely free of disability at 3 months. This result would have a major economic impact in Spain, where the mean annual cost of one stroke has been calculated to be €27,711. Informal care refers to care for persons with disabilities that are carried out by relatives, friends, acquaintances or neighbors, often without a contractual agreement or formal payment. It is estimated that informal annual care giving costs are five times larger in patients with mRS 2-5 than patients with mRS 0-1. Therefore, this proposal will have an immediate economic impact on the citizenship. The Stroke Therapy Academic Industry Roundtable (STAIR), a collaboration of medical academia, the healthcare industry and government, considers acceptable for a new neuroprotective therapy to demonstrate an absolute treatment effect size of 2% to 8% compared with placebo. The 14% treatment effect that it is intended to be accomplished in this project speaks for itself of the tremendous impact on health indicators. At last, CHOICE-2 will also address the special needs of other vulnerable groups such as stroke patients older than 80 years-old which are currently excluded from the therapeutic guidelines that arbitrate the use of thrombolytic therapy.

4. Scientific bibliography generated

These remarkable results received enormous national and international media coverage (https://neuronewsinternational.com/improved-neurological-outcomes-alteplase-placebo-choice/) and were recognized as a major contribution at the International Stroke Conference 2022 held in New Orleans during the annual meeting of the American Stroke Association. These results were a trending topic in JAMA (doi:10.1001/ Project Proposal Form, page 20 2022 jama.2022. 2096), and the trial has been recognized as a "Game Changer" in the treatment of acute ischemic stroke. Experts consider that more trials and research are needed, including analysis of imaging endpoint, but if CHOICE is confirmed, we might have a new standard of care

for treating incomplete microvascular reperfusion. Some practitioners might start to use IA tPA for TICI 2 outcomes based on this data alone (https://facultyopinions.com/article/741603169#eval793591698). The Altmetric Score of CHOICE achieved in just 2 months of publication is 338, thus representing top 5% of all research outputs (https://www.altmetric.com/ details/122855908).

Publication of CHOICE Trial results in JAMA:
https://jamanetwork.com/journals/jama/article-abstract/2789098

JAMA editorial on the CHOICE Trial Results:
https://jamanetwork.com/journals/jama/article-abstract/2789101

Altmetric from CHOICE Trial publication:
https://jamanetwork.altmetric.com/details/122855908