Intravenous fibrinolysis plus endovascular thrombectomy versus direct endovascular thrombectomy for anterior circulation acute ischemic stroke: clinical and infarct volume results.

CURRENT STATUS: ACCEPTED

Massimo Gamba
Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia Unità Operativa Medicina del Lavoro Igiene Tossicologia e Prevenzione Occupazion

Corresponding Author

Nicola Gilberti
Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

Enrico Premi
Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

Angelo Costa
Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

Michele Frigerio
Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

Dikran Mardighian
Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

Veronica Vergani
Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

Raffaella Spezi
Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

Ilenia Delrio
Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

Andrea Morotti
Fondazione IRCCS Policlinico San Matteo

Loris Poli
Università degli Studi di Brescia
Valeria De Giuli
Università degli Studi di Brescia

Filomena Caria
Università degli Studi di Brescia

Alessandro Pezzini
Università degli Studi di Brescia

Roberto Gasparotti
Università degli Studi di Brescia

Alessandro Padovani
Università degli Studi di Brescia

Mauro Magoni
Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

DOI:
10.21203/rs.2.482/v1

SUBJECT AREAS
Internal Medicine Specialties

KEYWORDS
ischemic stroke, intravenous thrombolysis, endovascular therapy, combined therapy, large vessels occlusion
Abstract

Background and Purpose

Endovascular therapy (ET) is the standard of care for anterior circulation acute ischemic stroke (AIS) caused by large vessel occlusion (LVO). The role of adjunctive intravenous thrombolysis (IVT) in these patients is still unclear. The present study aims to test whether IVT plus ET (CoT, combined therapy) provides additional benefits over direct ET for anterior circulation AIS by LVO.

Methods

We performed a single center retrospective observational study of patients with AIS caused by anterior circulation LVO, referred to our center between January 2014 and January 2017 and treated with ET. The patients were divided in 2 groups based on the treatment they received: CoT and, if IVT contraindicated, direct ET. We compared functional recovery (modified Rankin at 3-months follow-up), recanalization rate (thrombolysis in cerebral infarction TICI score) and time, early follow-up infarct volume (EFIV) (for recanalized patients only) as well as safety profile, defined as symptomatic intracerebral hemorrhage (sICH) and 3-month mortality, between groups.

Results

145 subjects were included in the study, 70 in direct ET group and 75 in CoT group. Patients who received CoT presented more frequently a functional independence at 3-months follow-up compared to patients who received direct ET (mRS score 0-1: 48.5% vs 18.6%; P<0.001. mRS score 0-2: 67.1% vs 37.3%; P<0.001), higher first-pass success rate (62.7% vs 38.6%, P<0.05), higher recanalization rate (84.3% vs 65.3%; P=0.009) and, in recanalized subjects, smaller EFIV (16.4ml vs 62.3ml; P=0.003). The safety profile was similar for the 2 groups. In multivariable regression analysis, low baseline NIHSS score (P<0.05), vessel recanalization (P=0.05) and CoT (P=0.03) were independent predictors of
3-month favorable outcome.

Conclusions

CoT appears more effective than ET alone for anterior circulation AIS with LVO, with similar safety profile.

Background

Endovascular therapy (ET) represents the standard of care for anterior circulation acute ischemic stroke (AIS) due to large vessel occlusion (LVO) [1-3]. It remains unclear whether intravenous thrombolysis preceding ET provides additional benefit compared to direct ET. The administration of IVT may have important drawbacks such as potential risk of bleeding, delay in beginning of ET and clot fragmentation leading to distal arterial embolism. [4]. Recent observational studies showed conflicting results on this clinically important topic [4-10].

The goal of our study was to compare CoT versus ET in a real world single center cohort of AIS patients with LVO, exploring the safety profile of these two treatments and comparing their effect on radiological and functional outcomes [11, 12].

Methods

Subjects. single-center retrospective observational study. All AIS patients referring to our center (Stroke Unit, Neurologia Vascolare, ASST “Spedali Civili”, Brescia, Italy) between January 2014 and January 2017 were screened for the study. Subjects with anterior circulation AIS due to LVO and fulfilling AHA/ASA criteria for ET [3] were included in the analysis. LVO was diagnosed by computed tomography angiography as an occlusion involving intracranial terminal internal carotid artery (tICA) and/or M1–proximal M2 tracts of middle cerebral artery (MCA). Patients fulfilling criteria for IVT and ET were allocated to
CoT group while subjects with IVT exclusion criteria were included in ET group [13].

Patients with CoT received intravenous full-dose rtPA (0.9 mg/kg) followed by ET, with groin puncture performed at the same time of rtPA bolus or as soon as possible during IVT infusion. Patients with undetermined time of symptoms onset and those with ET performed after complete rtPA administration were excluded. Written informed consent was obtained by patients or relatives. All the procedures of the study conformed to the Helsinki Declaration.

Demographics, vascular risk factors, laboratory exams, imaging findings and vital signs were collected. Stroke etiology, according to Trial of ORG 10172 in acute stroke treatment (TOAST) criteria [14], was assessed. All patients underwent a baseline brain computed tomography (CT) with Alberta Stroke Program Early Computed Tomography Score (ASPECTS) evaluation [15] and a follow up brain CT at 2-4 days from onset. Baseline National Institute of Health Stroke Scale (NIHSS) were recorded. The number of passes during ET have been recorded as well and the recanalization degree has been assessed on digital subtraction angiography (DSA) according to TICI criteria; Good recanalization was defined as TICI grade 2b or 3 [16].

The main safety outcomes of interest were: symptomatic intracranial hemorrhage (sICH) defined as deterioration in NIHSS ≥ 4 associated with evidence of any intracerebral hemorrhage on follow-up non-contrast cerebral CT, according to European Cooperative Acute Stroke Study II (ECASS II) [17] and mortality at 3 months follow up.

Cerebral Infarct Volume Measurement

The Cerebral Infarct Volume (CIV) of all recanalized patients were manually delineated by one experienced neurologist (N.G.) on early follow-up brain CT scan (at 2-4 days after stroke). The infarct volume was delineated section-by-section by using ITK-SNAP 2.2.0 (http://www.itksnap.org/pmwiki/pmwiki.php). Observer was blinded to all clinical
information and outcome [11, 12, 18].

**Interventional procedures.**

All procedures were performed under conscious sedation on a biplane angiography (Axiom Artis, Siemens, Erlangen, Germany) avoiding general anesthesia, if possible. Endovascular procedures consisted in thrombectomy with stent retrievers (Solitaire stent-Ev3 Inc. and Trevo stent-Stryker) or thromboaspiration (Penumbra 5 Max, Penumbra, Alameda, California, USA).

**Statistical Analysis.**

Univariate comparisons between the groups were made using Pearson's chi-squared test for categorical variables, the Mann-Whitney U test or Wilcoxon rank sum test for continuous variables. We assessed both clinical (mRS at 90 days) and neuroradiological outcome (early follow-up Infarct Volume - EFIV - at 2-4 days CT scan, in well recanalized cases). Independent predictors of the outcomes of interest were explored with a multivariable forward stepwise binary logistic regression model. Variables known to be predictive of clinical outcome from the literature were entered into the initial model. SPSS package (v. 17.0, Chicago, IL, USA) was used for the analyses and p values < 0.05 were considered statistically significant

**Results**

A total of 2248 AIS patients referred to our Hospital were screened and 145 subjects met the inclusion criteria of our study (70 in CoT and 75 in direct ET group). There was no significant difference between groups regarding age, gender, blood pressure, blood glucose, coronary disease, hypercholesterolemia and antithrombotic medications before stroke.

Stroke subgroups according to TOAST criteria, baseline NIHSS, ASPECTS scores and occluded vessel were also similar between the two groups (Table 1). Table 2 summarizes
the causes of exclusion from IVT. Time-to-groin puncture and time-to-recanalization were similar in the 2 groups. Recanalization rate was significantly higher in CoT group (84.3% vs 65.3%; P=0.009), as well as first-pass success rate (62.7% vs 38.6%, P<0.05). CoT group presented a significantly higher functional independence rate at 3-months follow-up (mRS score 0-1: 48.5% vs 18.6%; P<0.001. mRS score 0-2: 67.1% vs 37.3%; P<0.001).

In recanalized subjects, EFIV was significantly smaller in the CoT group (16.4ml vs 62.3ml; P=0.003). Safety outcome measures were similar between the two groups (Table 3).

In multivariable analysis, CoT was independently associated with higher odds of favorable functional outcome (OR, 3.75; 95% CI, 1.09-12.85; P=0.03). Other predictors of good outcome were lower baseline NIHSS (OR, 0.73; 95% CI,0.62-0.86; P<0.05), and vessel recanalization (OR, 7.30; 95% CI, 0.60-88.62; P=0.05) (Table 4).

Discussion

Randomized clinical trials (RCTs) have definitively proven the effectiveness of endovascular approach for anterior circulation AIS with LVO [3]. In this scenario, the role of adjunctive IVT before ET remains unclear and the currently available evidence on this topic is inconclusive [4-10]. The main of our study is the independent association between CoT and favorable outcome, compared with direct ET. A higher rate of vessel recanalization and lower infarct volume at follow-up CT seem the plausible biological mechanisms mediating the beneficial effect of CoT on outcome. Maintenance of an optimal microvascular perfusion downstream to the arterial occlusion, may also explain the positive association between CoT and favorable outcome [18].

Our findings therefore support the use administration of IVT before ET in eligible patients, in line with the recommendations of the American Heart Association / American Stroke Association guidelines [3].

The possible reduction of EFIV supports the hypothesis of a direct effect of rtPA treatment on
potentially salvageable brain tissue. Moreover determination of EFIV may represent a valid outcome measure for future clinical trials, potentially having a higher inter-observer reliability compared to clinical assessment alone with the mRS [11, 12]. The possible suggested mechanisms of action of adjunctive rtPA may be explained by a twofold effect: i) a favorable impact on endovascular procedure as suggested by the higher recanalization and higher first-pass success rates in CoT patients [9] and, ii) an effectiveness of systemic rtPA on preserving microvascular perfusion in downstream to the arterial occlusion, therefore improving benefit of large vessel recanalization [18]. Finally, another interesting result of our study is the lack of association between tPA and intracranial bleeding. This may have relevant implications for clinical practice, highlighting that tPA treatment in eligible patients should not be withheld for the fear of intracranial hemorrhage. Some limitations should be considered in the interpretation of our findings such as relatively small sample size obtained from a single center retrospective analysis, non-randomized comparison, potential risk of confounding by indication due to treatment allocation bias (subjects included in the ET group mostly consisted of patients with contraindications for IVT), lack of advanced neuroimaging-based patients’ selection. While taking them into full consideration, our data seems to confirm a favorable role of rtPA in improving clinical and neuroradiological outcome of patients treated by endovascular mechanical thrombectomy for a large vessel occlusion stroke.

Conclusions

The study confirms the safety and beneficial effect of CoT for anterior circulation AIS with LVO compared to direct ET. Coupling EFIV and mRS at 90 days assessment may represent a more reliable and possibly more powerful tool to be used in future clinical trials [11, 12].
Declarations

Ethics approval and consent to participate: ethical approval was not sought for this study because it was a retrospective study, as defined by local ethics committee (Spedali Civili Ethics Committee, Spedali Civili Hospital, Piazzale Spedali Civili, 1, 25123, Brescia, Italy). Written informed consent was obtained (by patients (if she/he was mentally-competent) or by the next of kin in all the remaining cases (i.e. hemiparesis, aphasia). The consent was obtained for medical/interventional treatment for life-threatening condition (i.e. ischemic stroke) as well as for research purpose.

Consent for publication: Not applicable.

Availability of data and materials: request of data (anonymized dataset) can be done directly to the Corresponding Author (Dr. Massimo Gamba, massimo.gamba@asst-spedralicivili.it).

Competing interests: Dr Andrea Morotti is Associated Editor of BMC Neurology; The other Authors declare that there is no competing interest.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors’ contributions:

MG: study design, data acquisition, data interpretation, manuscript writing.

NG: data acquisition, data analysis, data interpretation, manuscript writing.

EP: data acquisition, data analysis, data interpretation, manuscript writing

AC: data acquisition, data interpretation, manuscript drafting

MF: data acquisition, data interpretation, manuscript drafting

DM: data acquisition, data interpretation, manuscript drafting

VV: data acquisition, data interpretation, manuscript drafting

RS: data acquisition, data interpretation, manuscript drafting
ID: data acquisition, data interpretation, manuscript drafting
AM: data acquisition, data analysis, data interpretation, manuscript writing
LP: data acquisition, data interpretation, manuscript drafting
VDG: data acquisition, data interpretation, manuscript drafting
FC: data acquisition, data interpretation, manuscript drafting
AP: data acquisition, data interpretation, manuscript drafting
RG: data acquisition, data interpretation, manuscript drafting
AP: data acquisition, data interpretation, manuscript drafting
MG: data acquisition, data interpretation, manuscript drafting
All authors: i) approved the submitted version, ii) agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.
Acknowledgments: We would like to thank all participants to the study and their families.

List Of Abbreviations

Endovascular therapy (ET)
acute ischemic stroke (AIS)
large vessel occlusion (LVO)
recombinant tissue-plasminogen activator (rTPA)
intravenous thrombolysis (IVT)
Combined therapy (CoT)
Computed tomography (CT)
Trial of ORG 10172 in acute stroke treatment (TOAST)
thrombolysis in cerebral infarction (TICI)
early follow-up infarct volume (EFIV)
symptomatic intracerebral hemorrhage (sICH)
terminal internal carotid artery (tICA)
middle cerebral artery (MCA)
Alberta stroke program early ct score (ASPECTS)
modified Rankin Scale (mRS)
Randomized clinical trials (RCTs)
National Institute Of Health Stroke Scale (NIHSS)
Digital subtraction angiography (DSA)
Cerebral infarct volume (CIV)
European Cooperative Acute Stroke Study II (ECASS)

References
1. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, Yavagal DR, Ribo M, Cognard C, Hanel RA et al: Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct The New England journal of medicine 2018, 378(1):11-21.

2. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, McTaggart RA, Torbey MT, Kim-Tenser M, Leslie-Mazwi Tet al: Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging 2018, 378(8):708-718.

3. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J,
Brown M, Demaerschalk BM, Hoh Bet et al: 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association Stroke 2018, 49(3):e46-e110.

4. Leker RR, Pikis S, Gomori JM, Cohen JE: Is Bridging Necessary? A Pilot Study of Bridging versus Primary Stentriever-Based Endovascular Reperfusion in Large Anterior Circulation Strokes. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2015, 24(6):1163-1167.

5. Tsivgoulis G, Katsanos AH, Mavridis D, Alexandrov AW, Magoufis G, Arthur A, Caso V, Schellinger PD, Alexandrov AV: Endovascular thrombectomy with or without systemic thrombolysis? Therapeutic advances in neurological disorders 2017, 10(3):151-160.

6. Coutinho JM, Liebeskind DS, Slater LA, Nogueira RG, Clark W, Davalos A, Bonafe A, Jahan R, Fischer U, Gralla Jet al: Combined Intravenous Thrombolysis and Thrombectomy vs Thrombectomy Alone for Acute Ischemic Stroke: A Pooled Analysis of the SWIFT and STAR Studies. JAMA neurology 2017, 74(3):268-274.

7. Abilleira S, Ribera A, Cardona P, Rubiera M, Lopez-Cancio E, Amaro S, Rodriguez-Campello A, Camps-Renom P, Canovas D, de Miquel MAet al: Outcomes After Direct Thrombectomy or Combined Intravenous and Endovascular Treatment Are Not Different Stroke 2017, 48(2):375-378.

8. Merlino G, Sponza M, Petralia B, Vit A, Gavrilovic V, Pellegrin A, Rana M, Cancelli I, Naliato S, Lorenzut Set al: Short and long-term outcomes after combined intravenous thrombolysis and mechanical thrombectomy versus direct mechanical thrombectomy: a prospective single-center study. Journal of thrombosis and thrombolysis 2017, 44(2):203-209.
9. Mistry EA, Mistry AM, Nakawah MO, Chitale RV, James RF, Volpi JJ, Fusco MR: Mechanical Thrombectomy Outcomes With and Without Intravenous Thrombolysis in Stroke Patients: A Meta-Analysis. *Stroke* 2017, 48(9):2450-2456.

10. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota B et al: Randomized assessment of rapid endovascular treatment of ischemic stroke. *The New England journal of medicine* 2015, 372(11):1019-1030.

11. Yushkevich PA, Piven J, Hazlett HC, Smith RG, Ho S, Gee JC, Gerig G: User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. *NeuroImage* 2006, 31(3):1116-1128.

12. Ernst M, Boers AMM, Aigner A, Berkhemer OA, Yoo AJ, Roos YB, Dippel DWJ, van der Lugt A, van Oostenbrugge RJ, van Zwam WH et al: Association of Computed Tomography Ischemic Lesion Location With Functional Outcome in Acute Large Vessel Occlusion Ischemic Stroke. *Stroke* 2017, 48(9):2426-2433.

13. Wahlgren N, Ahmed N, Davalos A, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Kuelkens S, Larrue V et al: Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet (London, England)* 2007, 369(9558):275-282.

14. Barber PA, Demchuk AM, Zhang J, Buchan AM: Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. *Lancet (London, England)* 2000, 355(9216):1670-1674.

15. Higashida RT, Furlan AJ, Roberts H, Tomsick T, Connors B, Barr J, Dillon W, Warach S,
Broderick J, Tilley Bet al: Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke Stroke 2003, 34(8):e109-137.

16. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE, 3rd: Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment Stroke 1993, 24(1):35-41.

17. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, Larrue V, Bluhmki E, Davis S, Donnan Get al: Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators Lancet (London, England) 1998, 352(9136):1245-1251.

18. Desilles JP, Loyau S, Syvannarath V, Gonzalez-Valcarcel J, Cantier M, Louedec L, Lapergue B, Amarenco P, Ajzenberg N, Jandrot-Perrus Met al: Alteplase Reduces Downstream Microvascular Thrombosis and Improves the Benefit of Large Artery Recanalization in Stroke. Stroke 2015, 46(11):3241-3248.

Tables

Table 1. Baseline characteristics of the patients.

Due to technical limitations, Table 1 is only available as a download in the supplemental files section.

Table 2. Causes of IVT exclusion in patients with AIS
### Causes of IVT exclusion, (%)

| Cause                                         | %   |
|-----------------------------------------------|-----|
| Anticoagulant therapy                         | 28.6|
| Brain or systemic lesions at risk of bleeding | 14.3|
| Possible placement of vascular stent          | 11.4|
| Onset > 4.5 hours                             | 14.3|
| Major trauma                                  | 7.1 |
| Recent surgery                                | 4.3 |
| Other reasons                                 | 20.0|

IVT: intravenous thrombolysis.

**Table 3. Details of Procedural, Clinical, and Safety Outcomes.**
| Variables                                                                 | CoT (n=70) | Direct ET (n=75) | P Value |
|--------------------------------------------------------------------------|------------|------------------|---------|
| Time from symptoms onset to needle, Mean (SD), min                       | 156.1 (37.6) | n.a              | n.a     |
| Time from symptoms onset to groin puncture, Mean (SD), min              | 194.1 (59.9) | 204.8 (60.4)     | 0.322   |
| Time from symptoms onset to recanalization, Mean (SD), min              | 245.9 (75.8) | 245.1 (58.6)     | 0.952   |
| TICI 2b or 3 reperfusion, n (%)                                          | 59 (84.3)  | 49 (65.3)        | 0.0091  |
| Rates of first-pass success, %                                          | 62.7       | 38.6             | <0.051  |
| sICH, n (%)                                                              | 7 (10.0)   | 8 (10.6)         | 0.871   |
| Cerebral infarct Volume, Mean (SD), ml                                   | 16.4 (25.3) | 62.3 (81.7)      | 0.0032  |

Outcome at 90 days

| mRS score of 0-1, n (%)                                                  | 34 (48.5)  | 14 (18.6)        | <0.0011 |
| mRS score of 0-2, n (%)                                                  | 47 (67.1)  | 28 (37.3)        | <0.0011 |
| Mortality, n (%)                                                         | 5 (7.1)    | 11 (14.6)        | 0.151   |

1 Pearson's chi-squared test; 2 Mann-Whitney test for unpaired groups; CoT: combined therapy; ET: endovascular therapy.; SD: standard deviation; ICH: intracerebral hemorrhage; mRS: modified Rankin Scale; TICI: thrombolysis in cerebral infarction grading scale.
Table 4. Multivariate analysis.
### Variables

| Variables                                      | $P$ value | OR (95% CI)    |
|-----------------------------------------------|-----------|----------------|
| Baseline NIHSS                                | <0.05     | 0.73 (0.62-0.86) |
| ASPECTS score                                 | 0.07      | 0.59 (0.33-1.05) |
| TICI 2b or 3 reperfusion                      | 0.05      | 7.30 (0.60-88.62) |
| CoT treatment                                 | 0.03      | 3.75 (1.09-12.85) |
| MCA M2 vs. M1 segment                         | 0.15      | 3.04 (0.66-14.05) |
| tICA vs. MCA M1 segment                       | 0.25      | 0.33 (0.05-2.20) |
| Time from symptoms onset to recanalization    | 0.11      | 0.99 (0.98-1.00) |
| First-pass success                            | 0.15      | 0.41 (0.12-1.37) |

Forward stepwise logistic regression with dependent variable good clinical outcome (MrS score at 90 days: 0-1). NIHSS: National Institute of Health Stroke Scale; TICI: thrombolysis in cerebral infarction grading scale; MCA: middle cerebral artery; tICA: terminal internal carotid artery; OR: odd ratio. mRS: modified Rankin Scale; ASPECTS: Alberta Stroke Program Early Computed Tomography Score; CoT: combined therapy.

**Supplementary Files**

This is a list of supplementary files associated with the primary manuscript. Click to download.

Table 1.jpg