Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editors' note: Comparative safety and efficacy of combined IVT and MT with direct MT in large vessel occlusion

In their multicenter observational study titled "Comparative safety and efficacy of combined IVT and MT with direct MT in large vessel occlusion," Goyal et al. found that IV thrombolysis (IVT) before mechanical thrombectomy (MT) was associated with higher odds of functional independence at 3 months. Ganesh et al. propose that this may be related to a lower risk of infarction in unrelated vascular territories among patients pretreated with IVT. Further, Ganesh et al. note that an important minority of patients selected for thrombectomy may not achieve successful recanalization; therefore IVT may be the only chance to facilitate reperfusion. LeCouffe et al.—who represent the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN)–NO IV Investigators and are prospectively evaluating the benefit of IVT before MT—address the importance of blood pressure and coagulopathy as confounders. These unmeasured variables might have influenced the propensity matching in this investigation. In response to these comments, Goyal et al. acknowledge the limitations of observational studies where unmeasured, but important, clinical variables may not be captured during data acquisition. Ultimately, the superiority of combination IVT + MT over MT alone may not be confirmed until the results of ongoing prospective clinical trials are published.

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Reader response: Comparative safety and efficacy of combined IVT and MT with direct MT in large vessel occlusion

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We support the findings of Goyal et al.,[1] which showed that IV thrombolysis pretreatment improves outcomes in patients with large vessel occlusion (LVO) undergoing mechanical thrombectomy. We agree that reasons may include protection from infarct in new territory (INT) in thrombolysis recipients,[2] as suggested in a post hoc analysis of the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial.[3] We propose that INT should be systematically studied as a secondary outcome in any trials of combined thrombolysis/thrombectomy vs thrombectomy alone to further clarify this issue.

In addition, thrombectomy, despite its elegance, is simply not successful in a meaningful minority of cases. In the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke trials (HERMES) collaboration trials, 29% of thrombectomy recipients did not achieve successful revascularization (modified Thrombolysis in Cerebral Infarction 2b/3).[4] Pretreatment thrombolysis takes on paramount importance in this scenario, which cannot be predicted when thrombolysis is being contemplated. Furthermore, a smaller proportion of patients with LVO

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will reperfuse with thrombolysis alone en route to angiography. These patients may stand to benefit the most from early treatment and should not be denied that chance.

However, given the low recanalization rates with thrombolysis in ICA occlusions, it is worth examining if this subgroup had the same outcome differences as the full cohort, as examined in another recent study.[5]

1. Goyal N, Tsivgoulis G, Frei D, et al. Comparative safety and efficacy of combined IVT and MT with direct MT in large vessel occlusion. Neurology 2018;90:e1274-e1282.
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4. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016;387:1723–1731.
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Reader response: Comparative safety and efficacy of combined IVT and MT with direct MT in large vessel occlusion

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In their article, Goyal et al.[1] questioned the added benefit of IV thrombolysis (IVT) prior to mechanical thrombectomy (MT) in patients with ischemic stroke and a large vessel occlusion. As we await the results of ongoing randomized trials (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands [MR CLEAN–NO IV], ISRCTN80619088; Bridging Thrombolysis Versus Direct Mechanical Thrombectomy in Acute Ischemic Stroke [SWIFT DIRECT], NCT03192332; Direct Intra-arterial Thrombectomy in Order to Revascularize AIS Patients With Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals [DIRECT-MT], NCT03469206), we must rely on observational data with adequate adjustment for potential confounding variables to estimate the value of IVT in MT-eligible patients.[2] Goyal et al.[1] rightfully stated that no statistical method can completely adjust for allocation bias. However, current American Heart Association guidelines state that a blood pressure above 185/110 mm Hg and impaired hemostasis (direct oral anticoagulant use or international normalized ratio >1.7) are contraindications for IVT.[3] These variables have also been associated with worse outcomes[4] and, therefore, are true confounders. Much to our surprise, data on baseline blood pressure and hemostasis were not reported in by Goyal et al.,[1] and it does not appear that these variables were used in the propensity score matching. We invite the authors to comment on why information on baseline blood pressure and hemostasis was not reported and how this may have affected their results.

1. Goyal N, Tsivgoulis G, Frei D, et al. Comparative safety and efficacy of combined IVT and MT with direct MT in large vessel occlusion. Neurology 2018;90:e1274–e1282.
2. Lee PH. Should we adjust for a confounder if empirical and theoretical criteria yield contradictory results? A simulation study. Sci Rep 2014;4:6085.
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4. Linfante I, Starosciak AK, Walker GR, et al. Predictors of poor outcome despite recanalization: a multiple regression analysis of the NASA registry. J Neurointerv Surg 2016;8:224–229.

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Author response: Comparative safety and efficacy of combined IVT and MT with direct MT in large vessel occlusion

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We thank Ganesh et al. for reading and commenting on our article on the comparative safety and efficacy of combined IV thrombolysis (IVT) and mechanical thrombectomy (MT) with direct MT in patients with emergent large vessel occlusion (ELVO).[1] We agree that IVT pretreatment can protect from infarct in new territory (INT), and may account for improved outcomes observed in the combination therapy (IVT + MT) group. Data on INT were not collected in our cohort. However, INT should be evaluated as one of the outcomes variables in future MT trials. We are also in support of another point made by Ganesh et al. about the recanalization rates with IVT alone. According to a recently published meta-analysis, roughly 1 of 10 patients with ELVO achieve successful recanalization with IVT pretreatment alone, negating the need for additional endovascular reperfusion therapy.[2] Although this rate is low, pretreatment with IVT appears to be important. Finally, we followed the suggestion of Ganesh et al. and compared outcomes (safety and efficacy) between direct MT (dMT) and combination therapy in the subgroup of patients with intracranial ICA occlusions. We failed to document any differences in the safety and efficacy outcomes between the 2 groups, but the small number of patients with ICA occlusions (n = 29), corresponding to 9% of the total matched cohort, needs to be taken into account in the interpretation of this subgroup analysis.

We also thank LeCouffe et al. for reading and commenting on our article.[1] In our study, the data on pretreatment anticoagulation use and blood pressure were not collected; therefore, these variables were not included in the propensity score matching. The majority of patients treated with dMT in our cohort had relative contraindications to IVT,[1] including pretreatment with oral anticoagulation and uncontrolled blood pressure levels. This could have led to a treatment allocation bias affecting the results of our study. Nevertheless, it should be noted that several recent studies showed that MT is equally safe and effective in patients pretreated with anticoagulants compared to those without prior anticoagulation use.[3,4] Also, the rate of spontaneous ICH was not increased in the dMT subgroup compared to combination therapy and does not account for the worse functional outcomes (shift in modified Rankin Scale scores) and higher mortality rates that we documented in the dMT group in our matched analyses. Finally, we agree with LeCouffe et al. that we need to wait for the results of ongoing randomized controlled clinical trials to get definitive answers on the utility of IVT pretreatment in patient with ELVO receiving MT. Until these trials' data are available, IVT should be offered to all tissue plasminogen activator–eligible ELVO patients treated with MT as advocated by current international recommendations.[5] Thus, we wish to clarify that our study does not question the utility of IVT pretreatment in patients with ELVO receiving MT.

1. Goyal N, Tsivgoulis G, Frei D, et al. Comparative safety and efficacy of combined IVT and MT with direct MT in large vessel occlusion. Neurology 2018;90:e1274-e1282.
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