Intern Emerg Med (2013) 8:653–654
DOI 10.1007/s11739-013-0987-x

DEBATE

Italian guidelines on thrombolysis indications in ischaemic stroke have been revised after IST 3 trial and Cochrane Review: PROS

Stefano Ricci · Silvia Cenciarelli · Tatiana Mazzoli

Received: 10 June 2013 / Accepted: 30 July 2013 / Published online: 23 August 2013

On 26th, 27th and 28th October 2012, a group of Italian neurologists and stroke physicians met in Vibo Valentia, to discuss the implications of IST 3 and updated Cochrane Systematic Review results on thrombolysis in acute ischaemic stroke [1, 2]. After careful examination of all the available evidence, some modifications of the current Italian guidelines were agreed to, which are as follows:

Recommendation, Grade A: treatment with rt-PA (0.9 mg/kg) is indicated within 4.5 h from the beginning of symptoms of an ischaemic stroke, without any age limit. Treatment must be started as soon as possible after the stroke onset.

Synthesis: both the IST 3 trial and Cochrane Systematic Review suggest that treatment could be effective up to 6 h. Single patient data meta-analysis of all rt-PA trials (which is ongoing) will offer a clarification of the possible interaction among age, severity and onset to treatment time.

Text: exclusion criteria for thrombolysis: third criterium "severe stroke clinically (i.e. National Institute for Health Stroke Scale >25) or by neuroimaging". Note: this criterium should be abandoned after IST 3 results.

Why were these important statements decided? The results of IST 3 are to be carefully analysed, and put in the context of the whole evidence on rt-PA treatment for cerebral ischaemia. IST 3 was a no profit, clinicians driven trial, with the aim of clarifying whether a promising therapy could be given to almost all the patients admitted to Stroke Units, despite age and severity of the neurological deficit. The randomisation was based on the uncertainty principle, a well-known concept, successfully used in many previous relevant large trials (i.e. IST, CLOTS, FOOD, ECST), that produces a high degree of external validity of the results. The trial was based on the PROBE (prospective, randomised, open blinded endpoint) method (after the first 300 patients were randomized in a blind fashion), which is the best available system to combine both correct methodology and feasibility of the study [3]. Central blind follow-up was secured, and this way to obtain outcome information has been validated many years prior [4, 5] and is the same used in many previous and current studies.

As happens in many large trials, IST 3 lasted several years, during which new pieces of knowledge were made available in the field of stroke medicine, and of course they should have been taken into account by the IST 3 group. In fact, the original IST 3 protocol stated that the primary outcome was a dichotomized end point, based on Oxford Handicap Scale (OHS) at 6 months [that can be considered as the modified Rankin Scale (mRS)]: 0–2 vs 3–6, aiming at a 4 % absolute reduction of worse prognosis. However, when results of ECASS 3 [6] became available, it was clear that different dichotomizations could lead to different results: in fact, ECASS 3 results were not statistically significant when considering 0–2 vs 3–6 cut off, but definitely positive when considering 0–1 vs 2–6 cut off, and this very result prompted a modification of the European Guidelines, which was widely accepted by the stroke community (time limit moved from 3 to 4.5 h). As a matter of fact, ECASS 2 had given a statistically not significant result when considering 0–1 vs 2–6 cut off, but was significant if 0–2 vs 3–6 was taken into account. Therefore, we decided to add the 0–1 vs 2–6 endpoint to our outcome measures, to make our results comparable with those already produced. In the meantime, increasing evidence had become available on a new way to analyze stroke

S. Ricci (✉) · S. Cenciarelli · T. Mazzoli
UO Neurologia, USL Umbria 1, Centro di Coordinamento IST 3 per l' Italia, Ospedali di Città di Castello e Branca, Città di Castello, Italy
e-mail: stefano.ricci@uslumbria1.it

outcome (the ordinal shift analysis, OSA) which was able to give value to any single improvement along the whole mRS [7, 8]. The OSA makes it possible to see whether a putative patient, who if treated in the control group would end up with a mRS of (say) 4, could improve with treatment to 3, which is clinically an important achievement, but which is lost with the usual dichotomization. Furthermore, the statistical power increases with OSA. Therefore, this type of analysis was added to the protocol. The whole statistical plan was published well in advance [9], when no outcome data were known to anyone, to ensure the perfect validity of the procedure.

When the results were presented, it was clear that the absolute improvement of 4 % at 6 months was not reached, and therefore it was obvious that the difference in the dichotomized end point 0–2 vs 3–6 was not conventionally statistically significant. However, both the 0–1 vs 2–6 dichotomization and the OSA gave clear-cut, statistically significant results: just to summarise: treatment gave a 27 % higher probability of a good outcome. It was also clear that age and severity were not (as someone could think) related to a worse effect of rt-PA, but instead older patients and those with severe strokes seemed to benefit most. To summarise, for every 1,000 treated patients, there were 29 more with favourable outcome, and in patients older than 80, 38 more were alive and independent (80 if treated within 3 h). The updated Cochrane systematic review confirmed these results, leaving space for a possible effect beyond 4.5 h. There was no effect on 6-month mortality; in fact, mortality increased within the first week, but decreased from 7 days to 6 months, and therefore the whole effect was neutral. Haemorrhages were increased by treatment, but, interestingly, applying the 'Cochrane' definition of Symptomatic Intracerebral Haemorrhage (SICH), the 7 % IST-3 frequency is comparable with the 7.3 % SITS registry of 6,483 patients treated within licence in routine clinical practice.

The above summarised results were used to update the Italian guidelines, according to the suggested "implication for practice" (European Stroke Conference, Lisbon 2012): (1) consider thrombolytic treatment for a wider variety of patients, particularly those aged over 80 years and with more severe strokes. (2) Reinforce their efforts to increase the proportion of ischaemic strokes treated <3 h. (3) Have greater confidence that mortality is not increased by treatment. In fact, most European guidelines were modified according to these suggestions, and thrombolysis is now much more widely used.

Recently, follow-up data of IST 3 at 18 months were published, which confirmed the positive effect of thrombolysis: in fact, the dichotomized outcome 0–2 vs 3–6 gave this time a significant result, and obviously the effect was even more favourable with OSA [10].

While waiting for the results of single patient data meta-analysis, we confirm here that, from the practical point of view of a stroke clinician—and despite some formal criticism we have received [11]—the new indications of Italian guidelines are to be followed (and indeed they are, as far as we can say); to quote again Leys and Chardonnier [12], "the role of stroke and emergency physicians is now not to identify patients who will be given rt-PA, but to identify the few who will not".

Conflict of interest None.

References

1. The IST-3 collaborative group (2012) The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. Lancet 379:2352–2363
2. Wardlaw J, Murray V, Berge E, Del Zoppo G, Sandercock P, Lindley R, Cohen G (2012) Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. Lancet 379:2364–2372
3. Sandercock P, Lindley R, Wardlaw J, Dennis M, Lewis S, Venables G, Kobayashi A, Czlonkowska A, Berge E, Slot KB, Murray V, Peeters A, Hankey G, Matz K, Brainin M, Ricci S, Celani MG, Righetti E, Cantisani T, Gubitz G, Phillips S, Arauz A, Prasad K, Correia M, Lyrer P, IST-3 collaborative group (2008) The third international stroke trial (IST-3) of thrombolysis for acute ischaemic stroke. Trials 9:37
4. Shinar D, Gross CR, Bronstein KS, Licata-Gehr EE, Eden DT, Cabrera AR, Fishman IG, Roth AA, Barwick JA, Kunitz SC (1987) Reliability of the activities of daily living scale and its use in telephone interview. Arch Phys Med Rehabil 68:723–728
5. Candelise L, Pinardi G, Aritzu E, Musicco M (1994) Telephone interview for stroke outcome assessment. Cerebrovasc Dis 4:341–343
6. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, Von Kummer R, Wahlgren N, Toni D, ECASS Investigators (2008) Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 359:1317–1329
7. Saver J (2007) Novel end point analytic techniques and interpreting shifts across the entire range of outcome scales in acute stroke trials. Stroke 38:3055–3062
8. Bath PMW, Lees KR, Schellinger PD, Altman H, Bland M, Hogg C, Howard G, Saver JL (2012) Statistical analysis of the primary outcome in acute stroke trials. Stroke 43:1171–1178
9. IST 3 Collaborative Group (2012) Statistical analysis plan for the third International Stroke Trial (IST-3); part of a 'thread' of reports of the trial. Int J Stroke 7:186–187
10. The IST-3 collaborative group. Effects of thrombolysis with recombinant tissue plasminogen activator for acute ischaemic stroke on long term outcomes in the third international stroke trial (IST-3): a randomised controlled trial. Lancet Neurol, Early Online Publication, 21 June 2013
11. Del Medico M, Bonura A (2013) Can we extend thrombolysis indications for acute ischaemic stroke? The IST-3 study. Intern Emerg Med 8:261–262
12. Leys D, Cordonnier C (2012) rt-PA for ischaemic stroke: what will the next question be? Lancet 379:2320–2321