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Thrombolysis for Ischemic Stroke in Patients Aged 90 Years or Older

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1. Introduction

Currently, i.v. thrombolysis with recombinant tissue plasminogen activator (r-TPA) in acute ischemic stroke is approved in Europe only for patients 80 y.o. or younger, but data from the literature do suggest that patients older than 80 might also benefit from it (Sanossian and Ovbiagele, 2009). These older patients do have a worse outcome than younger ones, a finding that seems to be due to worse baseline prognostic factors, but they are not more prone to r-TPA -induced haemorrhage than younger ones (Engelter et al., 2006; Toni et al., 2008). Based on these considerations, a randomized clinical trial of i.v. r-TPA vs. usual care in acute stroke in patients older than 80 years is currently under way in Italy.

Even lesser data are available for stroke patients older than 90 years. Recently, it has been suggested that these patients may not benefit significantly from i.v. r-TPA, despite the fact that this treatment appeared reasonably safe in this age range, too (Mateen et al., 2009; Mishra et al., 2010).

We are reporting our experience with i.v. r-TPA in patients 90 year old or older in acute ischemic stroke.

2. Patients and results

We treated with i.v. r-TPA for acute stroke 6 patients (1male, 5 females). Median age was 92.5 y.o. (range 90-95). In all cases a CT scan had ruled out haemorrhagic stroke, and there were none of the exclusion criteria of the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST (Wahlgren et al., 2007)), apart from age and (in some cases, see below) elapsed time from onset of stroke. Specifically, all patient were in good neurological conditions before stroke. Modified Rankin Scale (mRS) before stroke was 0 or 1 in all cases, except in one 91 y.o. female where it was 3 due to severe hip arthrosis (no pre-existing neurological deficit). Risk factors were none (in 2 patients), hypertension (3 patients), previous minor stroke more than 3 months before the index one (2 patients), atrial fibrillation (2 patients), diabetes (1 patient). No patient had cognitive impairment.

In all cases a written informed consent was obtained either from the patient through a witness (n = 3) or from a first degree relative (n = 3).

The median National Institute of Health Stroke Scale (NIHSS) on presentation was 17.5 (range 3-21). It should be noted that that in the single case where NIHSS was less than 6, the symptoms included aphasia, a condition that is considered to be very disabling, thus worth the risk of thrombolysis (Kohrmann et al., 2009). All strokes were in the carotid arteries territory. Stroke was due to cardiac emboli in 3 cases and to large vessel disease in 2 cases; the remaining case was a lacunar stroke in the basal ganglia area. Median stroke-to-hospital time was 84.50′ (range 32′-102′). Upon their arrival into the Emergency Room the advanced age of these patients caused them to be initially excluded from thrombolytic treatment, therefore they were not handled in the rapid way that prospective r-TPA patients are usually treated. Only later the consulting stroke neurologist considered thrombolysis as an option. Thus, in-hospital times were rather slow. Median door-to-CT time was 82′ (range 39′-147′), median CT-to-treatment time was 49.5′ (range 15′-110′). Median door-to-treatment time was 150.5′ (range 80′-215′). Median time from stroke onset to thrombolysis ("stroke-to-needle" time) was 210′ (range 177′-273′).

Four patients received the standard r-TPA dose of 0.9 mg/Kg i.v., 10% of which was administered as an initial bolus, followed by the remaining 90% over 1h. One 94 y.o. patient received the lower dose of 0.67 mg/Kg i.v. (10% as a bolus, 90% in 1h) because in the Emergency Room she had already been given 500 mg acetyl-salicylic acid i.v. in the belief that she was not a candidate to thrombolysis. This same patient suffered shortly after thrombolysis a traumatic clavicle fracture, after which a major bleeding, requiring transfusion, occurred around the site of fracture. In another 91 y.o. patient r-TPA infusion was stopped after 25′ (when about 50% of the full dose had been administered) because of headache and a minor gingival bleeding. It should be noted that minor gingival bleeding occurred during drug infusion in another 91 y.o. patient who nevertheless went on to receive the full standard dose of r-TPA with no other harmful consequences. No bleeding was observed in the other patients.

No symptomatic intracranial haemorrhage occurred in any patient. In 1 patient a haemorrhagic transformation of the stroke (categorized HI2 according to ECASS III classification (Hacke et al., 2008)) was seen at the 24 hours follow-up CT scan, in all other cases no bleeding was observed at routine 24 hours follow-up CT scan.

In 3 patients transcranial ultrasound examination was carried out both before and immediately after thrombolysis. In all these cases occlusion of the middle cerebral artery was found, graded 0 (1 case) or 2 (2 cases) according to the TIBI classification (Demchuk et al., 2001). In all these cases improvement of flow to a TIBI 3 score was noted after thrombolysis. It should be noted that these are the 3 patients that showed good outcome at the 3-months follow up (mRS=0-1). In one of the 3 cases where ultrasound examination could not be carried out, a dense middle cerebral artery sign (Launes and Ketonen, 1987) was found upon non-contrast CT scan before thrombolysis. This patient showed an almost full recovery of motor function at the end of tPA infusion, that was followed by worsening 1 hour after. A CT scan right after the second worsening ruled out any intracranial bleeding. We interpret these findings as r-TPA -induced recanalization followed by early restenosis.

Figure 1 shows the NIHSS score before thrombolysis and at various times after it. As it can be seen, both patients with milder symptoms (NIHSS=3 and 6, respectively) had very

good outcome (NIHSS=1 and 0, respectively, after 7 days). Of the 4 patients with more severe symptoms, 1 had very good improvement (NIHSS=1 after 7 days – this is the lady who received 0.67 mg/Kg because she had already received 500 mg ASA), the other 3 had minimal or no improvement. Of the latter 3 ones, 1 is the lady whose treatment was aborted because of gingival bleeding, and the other 2 are the patients who later died (see below).

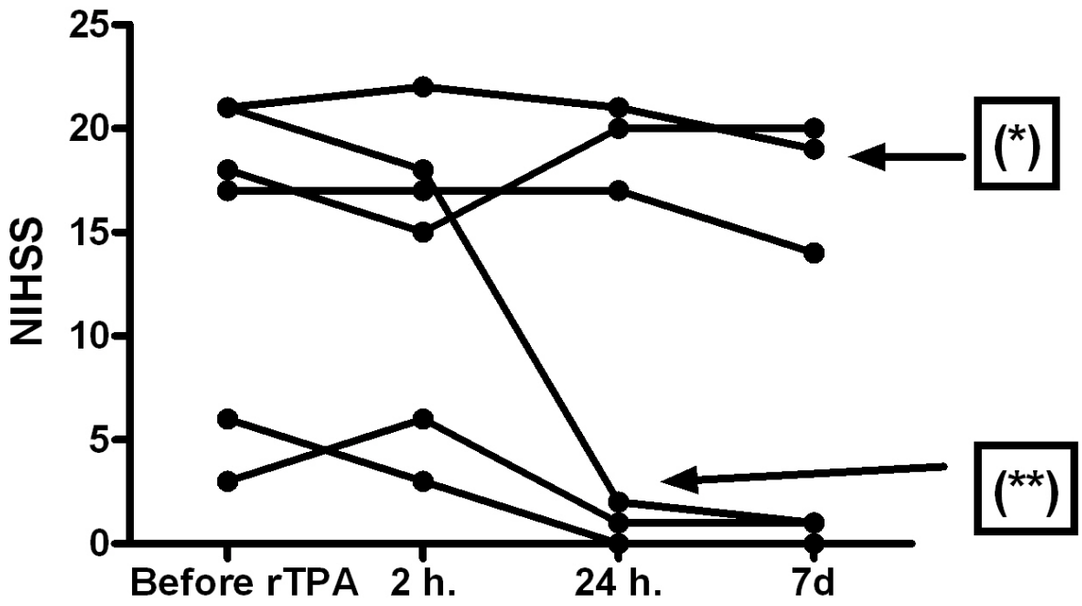

Fig. 1. NIHSS score before thrombolysis and 2 hours, 24 hours and 7 days after it in each patient. One asterisk indicates the patient in whom treatment was aborted before of gingival bleeding after 25', when approximately 50% of the full rTPA dose had been received. Two asterisks indicate the patient to whom the reduced rTPA dose of 0.67 mg/Kg was administered because she had already received 500 mg ASA i.v.

Figure 2 shows the score on the modified Rankin Scale (mRS) (Farrell et al., 1991) before stroke as well as 7 days and 3 months afterwards (note that mRS=6 was added to the original mRS, indicating death (Mateen et al., 2009)). As it can be seen, 2 patients died (14 and 16 days after thrombolysis, respectively), both of cardiac failure (acute pulmonary oedema). Neither one had significantly improved after thrombolysis (see above). One more patient was left with moderately severe disability (mRS=4) and 3 patients showed very good outcome (mRS=0-1).

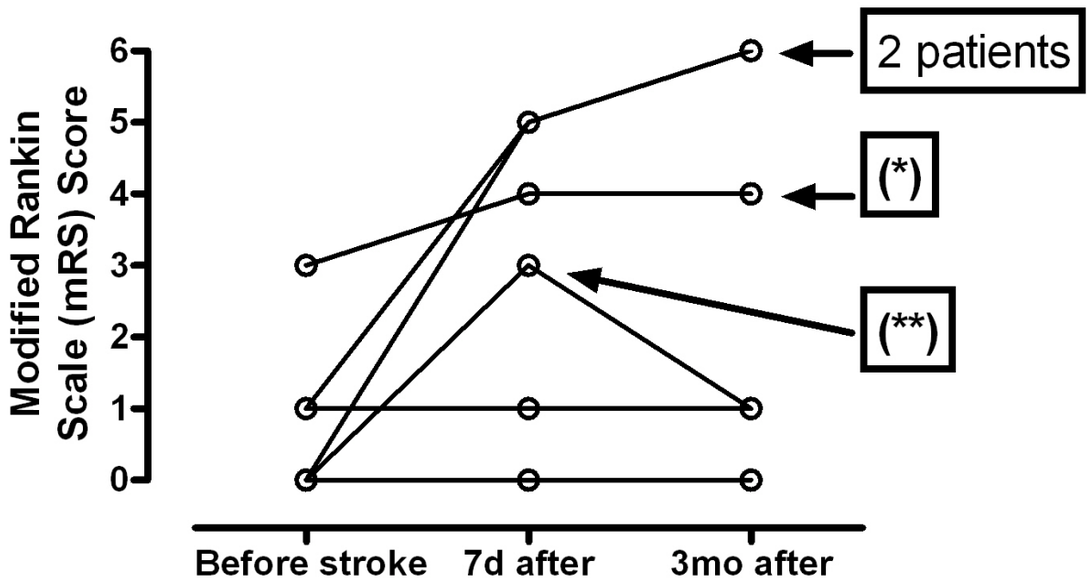

Fig. 2. mRS score before stroke, 7 days and 3 months after it in each patient. One asterisk indicates the patient in whom treatment was aborted before of gingival bleeding after 25', when approximately 50% of the full rTPA dose had been received. Two asterisks indicate the patient to whom the reduced rTPA dose of 0.67 mg/Kg was administered because she had already received 500 mg ASA i.v.

3. Discussion

The present report has the obvious limitation of being retrospective, nevertheless we believe that it has some interest given the extreme paucity of literature reports on thrombolysis in 90 y.o. patients or older. To the best of our knowledge, so far only one such report exists in the literature (Mateen et al., 2009), while another recently published paper reports a comparison between two different databases (Mishra et al., 2010). Our findings are in agreement with those report, as far as they confirm that i.v. thrombolysis with r-TPA is reasonably safe in these patients. In our patients no treatment-related worsening occurred, and no intracranial symptomatic haemorrhage was observed. Retrospectively, abortion of therapy upon gingival bleeding may have been excessive (in the other case of minor gingival bleeding the full dose was still given with no harm). Death occurred in two of the three unimproved cases 14 and 16 days after thrombolysis because of cardiac failure, unrelated to treatment. Three out of six patients improved upon thrombolysis. Although this finding is obviously encouraging, randomized clinical trials are needed to reach firm conclusions that may be applied to the general population of 90 y.o. patients or older. Finally, we note that our patients were not handled rapidly by hospital personnel because it was initially believed that their old age should have ruled out thrombolysis. This resulted in a significant delay of treatment (see above), that has probably reduced the chances of good outcome in our patients (Lees et al., 2010). This finding strongly suggests that stroke therapy is a complex

issue, one that, whenever possible, should be managed by stroke physicians having specific competence and experience.

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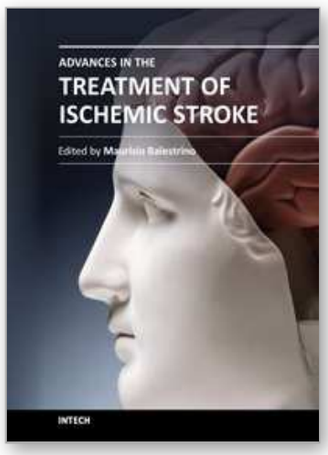

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In recent years research on ischemic stroke has developed powerful therapeutic tools. The novel frontiers of stem cells therapy and of hypothermia have been explored, and novel brain repair mechanisms have been discovered. Limits to intravenous thrombolysis have been advanced and powerful endovascular tools have been put at the clinicians' disposal. Surgical decompression in malignant stroke has significantly improved the prognosis of this often fatal condition. This book includes contributions from scientists active in this innovative research. Stroke physicians, students, nurses and technicians will hopefully use it as a tool of continuing medical education to update their knowledge in this rapidly changing field.

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