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Intravenous rtPA versus mechanical thrombectomy in acute ischemic stroke: A historical cohort in Joinville, Brazil

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ABSTRACT

Groundbreaking results concerning ischemic stroke (IS) hyperacute treatment worldwide were published in 2014 and 2015. We aimed to compare functional status after 3 months in patients treated with intra-arterial thrombectomy (IAT) and those treated with intravenous thrombolysis (IVT) alone in Joinville, Brazil.

From the Joinville Stroke Registry, we extracted and compared all consecutive IVT patients treated with r-tPA within 4.5 h in the period 2009–2011 versus all consecutive IAT treated within 6 h with the Solitaire FR device plus IVT in the period 2012–2014.

We registered 82 patients in the IVT group and 31 patients in the IAT group. At hospital admission, patients in the IAT group were significantly younger ($p < 0.001$), had a higher educational level ($p = 0.001$), had a slightly higher prevalence of atrial fibrillation ($p = 0.057$) and had more severe strokes measured by the NIH stroke scale ($p = 0.011$). After 90 days, 45% of patients in the IAT group and 27% in the IVT group were independent (0–1 points) according to the modified Rankin scale (adjusted odds ratio: 4.53; 95% CI: 1.22 to 16.75). Symptomatic hemorrhage was diagnosed in 10% of patients in both groups ($p = 1.0$). The 90-day case-fatality was 39% (32/82) in the IVT group and 26% (8/31) in the IAT group ($p = 0.27$). In this small cohort, a greater rate of functional independence was achieved in patients treated with IAT plus IVT, compared with patients treated with IVT lysis alone. Our "real-world" findings are consistent with results of controlled, randomized clinical trials.

1. Introduction

In December 2014 and during 2015, a landmark was set in the contemporary treatment of ischemic stroke (IS) when the results of MR CLEAN (Multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands), ESCAPE (Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke), EXTEND IA (A multicenter, randomized, controlled study to investigate EXtending the time for Thrombolysis in Emergency Neurological Deficits with Intra-Arterial therapy), SWIFTPRIME (Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke) and REVASCAT (Thrombectomy within 8 h after symptom onset in ischemic stroke) trials framed a new landscape for neurologists worldwide [1–5].

However, similarly to the new paradigm of care introduced by the relevance of stroke units in 1993, the evidence of effectiveness of mechanical endovascular treatment translates into huge challenges for IS care, particularly in low- and middle-income (LMIC) countries [6]. For example, in 2013, only 82 stroke centers, including 45 public hospitals had recombinant tissue-type plasminogen activator (r-tPA) in their emergency units [7], which means that less than 2% of all Brazilian hospitals (6700) according to National Registration of Health Establishments. How many stroke centers are prepared to implement these new approaches? How much infrastructure do we need in our programs to teach new skills required for endovascular treatment, for stroke and neuroradiology residents? Moreover, its well known that the findings of randomized clinical trials are quite distinct from the "real world" even in well structured settings [8].

Joinville is an industrial city located in Southern Brazil [9]. In the last Brazilian census (2010), the Joinville population included 515,288 inhabitants in an area of 1130 km^2 [9]. The city has two stroke centers,

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three general hospitals (with computed tomography — CT — available 24 h/d, 7 d/wk), and 1 public rehabilitation care facility, totaling 1078 beds [9]. Since 2005, stroke patients have been transported by the national emergency medical service [Serviço de Atendimento Móvel de Urgência (SAMU)] [10], which uses a standard checklist based on the Cincinnati Stroke Scale [11].

The intravenous thrombolysis and first stroke unit in the country started to function in Joinville in 1997 [12,13]. From 2005 until 2011, the adjusted incidence of thrombolysis for IS increased significantly from 1.4 (95% CI 0.6–2.9) in 2005 to 9.8 (7.3–12.9) per 100,000 in 2011 [12]. Results of the five main clinical trials of endovascular treatment for acute IS, published in 2014 and 2015, indicated that further improvements in outcome could be achieved by intra-arterial thrombectomy (IAT) as an add-on treatment to patients undergoing intravenous thrombolysis (IVT) or to patients not eligible for this intervention. In these studies, rates of functional independence (mRS score: 0–2) at 3 months ranged from 33% to 71% in patients treated with IAT ± IVT, compared with 19% to 40% of patients in the groups treated with usual care, which included IVT up to 4.5 h after IS [1–5]. Whether similar results can be obtained in a developing country is still unknown.

After 2011, our team started rescue IAT when the patient with IS presented NIHSS above 10 points, in 6 h time window, with cervical and cranial angiotomography defining a vascular occlusion site. Therefore, we aimed to compare functional status after 3 months between patients with IS who underwent IAT plus intravenous r-tPA versus intravenous thrombolysis (IVT) alone in Joinville, Brazil, using a historical cohort design. We hypothesized that the outcomes of patients treated with IAT + IVT would be better than those of patients treated with IVT alone.

2. Material and methods

2.1. The Joinville population registry

Cohort data were retrospectively extracted from the Joinville Stroke Registry. The Joinvile Stroke Registry is an ongoing population-based stroke data bank started in 2005 and supported by law since 2013 [14]. The registry uses the ideal methodology proposed by Sudlow and Warlow [15] as well as the Stroke-Steps modular program proposed by the WHO (first step for all hospital cases, second step for checking of death certificates and third step to ascertain mild events) [16]. The detailed methods of cohort recruitment have been described elsewhere [17].

After having obtained written informed consent from all patients or their relatives, the Joinville Stroke Register research nurses recorded the biochemical, electrocardiographic and radiological results. A neurologist was responsible for the NIH and ASPECTS scores [18,19], OCSP and TOAST classifications [20,21]. Baseline demographic data, risk factors, and length of stay were also registered. Local ethics committees approved the use of patients' retrospective data.

2.2. Groups

We specifically assessed performance of IVT, IAT and usual care in patients included in the Joinville Stroke Registry between 2009–2011 and 2012–2014. From 2009 to 2011, IVT was performed with intravenous r-tPA within 4.5 h time-window criteria (ECASS III) [22]. From 2012 until 2014, patients eligible for IVT were treated with both IVT and endovascular catheterization with a Solitaire FR device, up to 6 h after symptom onset [23]. We compared outcomes from two groups of patients within two time periods: patients treated with IVT alone from 2009 to 2011 ($Group_{IVT}$); patients treated with IVT + IAT from 2012 to 2014 ($Group_{IVT+IAT}$). In addition, in order to evaluate whether outcomes within the two study periods would be influenced by possible differences in usual care, we compared outcomes from patients treated with usual care (no thrombolysis), not included in the IVT group from 2009 to 2011 or IAT plus IVT from 2012 to 2014, using the same inclusion criteria.

2.3. Evaluation of outcomes

Functional independence was evaluated using the mRS, which ranges from 0 (no symptoms) to 6 (death) [24]. mRS scores were assessed at one month (face to face) and at 90 days (by telephone), by interviewers who were blinded to patient groups [24].

2.4. IVT protocol

The routine of stroke thrombolysis and stroke investigation followed the guidelines proposed by the Brazilian Society of Cerebrovascular Diseases [25]. The same protocol, based on the National Institute of Neurological Disorders and Stroke (NINDS) trial [26], was used in all of the centers that admitted IS patients in the acute phase. Clinical severity was measured by the NIH stroke scale (NIHSS) [20]. Following a concise clinical and neurological examination by a neurologist, a head CT was performed and eligibility for thrombolytic treatment was determined. The time of onset of symptoms, the interval between hospital arrival (door time) and the interval between hospital arrival and onset of tPA bolus infusion (needle time) were registered. To evaluate the extension of ischemic lesions in CT, we used the ASPECTS (Alberta Stroke Program Early CT score) [21]. A second CT was performed within 48 h after admission to ascertain intracerebral hemorrhage (ICH) in all patients who received r-tPA. CTs were also performed at any time, if clinical deterioration occurred. Symptomatic ICH was diagnosed if there was any neurological clinical worsening or NIH decline ≥4, and a parenchymal hematoma type 2 in the control brain CT as proposed in ECASS II [27,28]. A neuroradiologist (PSCM) reviewed all imaging results.

2.5. IVT + IAT protocol

The following criteria were used for administration of IAT in addition to IVT: age ≥18 years, NIHSS >10, non-lacunar syndrome or partial anterior cerebral infarction according to OCSP classification or small artery occlusion (SAO) according to TOAST classification. The OCSP classification assigns an ischaemic stroke subtype according to clinical signs and symptoms, modified where appropriate by the site and size of the underlying infarction on brain imaging. Whilst this method does not distinguish CE from LAA stroke, it does allow separate categorization of lacunar strokes (mainly presumed to be due to SAO). All endovascular procedures were performed by the same neuroradiology team (PSCM, HA and PW), who have followed a guideline for endovascular ischemic stroke intervention [29]. Time of groin puncture and time of vascular reperfusion were registered. Patients who awoke with stroke symptoms were excluded from the symptom-to-door time calculation.

IV r-tPA was started inside the CT room (0.9 mg/kg) and the patient was transferred to the angiography suite. IAT was performed via a femoral artery approach. For the anterior circulation, an 8F Corail ballon-guided catheter (Balt) was placed in the internal carotid artery. For posterior circulation an 6F Chaperon catheter (Microvention) was navigated to vertebral artery. Using the combination of a 0.014 microguide-wire and a 0.021-inch Rebar microcatheter (Medtronic), the occlusion site was accessed and the stent retriever Solitaire (Medtronic) was deployed. After 5 min, the ballon of the guiding catheter was inflated, the stent retriever and the micro catheter were pulled back together through the ballon-guided catheter, during continuous manual aspiration to reverse the flow inside the catheter. A control angiogram was performed to determine the immediate reperfusion status. Arterial patency in preprocedure, post thrombectomy, and post procedure angiograms were classified by the modified Thrombolysis in Cerebral Infarction (mTICI) scores [30]. This system classifies revascularization in 5 grades: grade 0, no perfusion; grade 1, perfusion past the