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World Journal of Radiology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.4329/wjr.v5.i12.450

World J Radiol 2013 December 28; 5(12): 450-454
ISSN 1949-8470 (online)

EDITORIAL

Interventional neuroradiology of stroke, still not dead

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Received: May 28, 2013 Revised: November 11, 2013
Accepted: November 15, 2013
Published online: December 28, 2013

Abstract

Since the National Institute of Neurological Disorders and Stroke trial, intravenous thrombolysis has been gaining wide acceptance as the modality of treatment for acute embolic stroke, with a current therapeutic window of up to 4.5 h. Both imaging [with either magnetic resonance imaging (MRI) or computed tomography (CT)] and interventional techniques (thrombolysis and/or thrombectomy) have since improved and provided us with additional imaging of the penumbra using CT or MRI and more advanced thrombolysis or thrombectomy strategies that have been embraced in many centers dealing with patients with acute cerebral ischemia. These techniques, however, have come under scrutiny due to their accrued healthcare costs and have been questioned following major recent studies. These studies basically showed that interventional techniques were not superior to the traditional intravenous thrombolysis techniques and that penumbra imaging could not determine what patients would benefit from more aggressive (*i.e.*, interventional) treatment. We discuss this in the light of the latest developments in both diagnostic and interventional neuroradiology and point out why further studies are needed in order to define the right choices for patients with acute stroke. Indeed, these studies were in part conducted with suboptimal patient recruitment strategies and did not always use the latest interventional techniques available today. So, while these studies may have raised some relevant questions, at the same time, definitive answers have not been given, in our opinion.

Key words: Stroke; Interventional neuroradiology thrombolysis; Magnetic resonance imaging; Computed tomography

Core tip: While intravenous thrombolysis has gained wide acceptance as a major breakthrough for the acute treatment of stroke, interventional and diagnostic neuroradiology tools have also evolved at a very high rate, providing us with very sophisticated techniques to demonstrate brain tissue damage and revascularization techniques. However, these methods have not been evaluated properly until recently and have been adopted quickly by part of the clinical neuroscience community. A number of recent studies question the impact of these techniques.

Pereira VM, Lövblad KO. Interventional neuroradiology of stroke, still not dead. *World J Radiol* 2013; 5(12): 450-454 Available from: URL: http://www.wjgnet.com/1949-8470/full/v5/i12/450.htm DOI: http://dx.doi.org/10.4329/wjr.v5.i12.450

INTERVENTIONAL NEURORADIOLOGY OF STROKE-STILL NOT DEAD

The position of diagnostic neuroradiology and interventional neuroradiology and their role in stroke have been questioned recently by some randomized controlled studies[1-4]. The role and position of imaging in the diagnosis and management of stroke has changed extensively since the 1990s. Overall, stroke and its management have changed drastically: while initially patients were considered to be future candidates for reeducation if they survived, with new advances in the management this perspective has changed considerably. Indeed, the concept of stroke units where these patients were seen with an emphasis on their acute disease has already improved their outcome significantly. Then, thrombolysis was introduced with groundbreaking results following the National Institute of Neurological Disorders and Stroke trials[5-7]; initially this implied a rather strict therapeutic window, as well as the sole intravenous administration of drugs and with the presence of significant potential complications due to treatment, such as hemorrhage. Thus, strict guidelines for the management of patients with stroke have been developed in order to improve management and outcomes[8]. However, during that same decade, the radiological side, both diagnostic and interventional techniques, evolved in ways that were important: in a period of a few years, we additionally had diffusion magnetic resonance imaging (MRI)[9], perfusion computed tomography (CT)[10] and additional interventional procedures, such as local intra-arterial thrombolysis[11], followed by mechanical thrombectomy and stenting[12]. On the one hand, dramatic increases were observed in advances that led to an improved understanding of the acute disease and eventually its treatment. However, while the initial results were encouraging, their use was also more time and money consuming, all without real state of the art validation. For anyone who has been involved in the management, diagnosis and treatment of these patients, it is important to know that we saw advances in a very short period in patients where before nothing was expected. This also caused a shift from stroke being a globally managed disease to one that would be more reasonably treated within specialized stroke units and centers. Thus, in addition to a higher technicality and cost, there was a shift away from the primary gatekeepers, the general practitioners or internists, because if time was more and more brain, it meant that these patients had to have a change in clinical pathway for which not everyone was ready. Therapy was moving fast, while at the same time the scientific evidence was not and this was bound to make the whole system collapse. Fortunately, we are not at that point but the recently published papers in the New England Journal raise some valid points while being inherently flawed.

Interventional neuroradiology, different to medical pharmaceutical treatments, does inherently rely on not being fully standardizable; indeed, in order to obtain a certain level of quality, a certain number of interventions must be performed at the center to assure a good level as well as the whole chain from the arrival at the hospital to the post-operative management. Acute stroke treatment is, in fact, a process that involves different disciplines, divisions and teams at the health network and hospital. High volume centers mean that they are able to bring patients through the detection of stroke, diagnosis and therapeutic steps constantly that imply increased effectiveness over time. If we consider a stroke treatment study, where the acute treatment is evaluated but, in fact, the whole stroke pathway is involved, it is hard to imagine that low volume or inexperienced centers will be able to demonstrate any difference between any kinds of treatment. While a drug such as aspirin can be given by any physician or nurse in a standardized way, this is unfortunately not the case with interventional techniques which, like surgery, rely on expertise (relying on experience and talent) which is also at the same time difficult or impossible to quantify. Thus, to some degree, per se interventional techniques are not best suited to fully randomized studies and are almost always certain to fail. We did read with interest the two recent papers published in the New England Journal of Medicine[13,14] as well as the accompanying editorial[4]. What is worrisome is the potential message that these papers may send out: that interventional therapy as such is a failure in improving outcomes in stroke. The introduction of intravenous thrombolysis was a breakthrough for patients with cerebral ischemia, but clinicians, investigators and patients have been frustrated by the limitations due to the rather limited time window and even associated potential complications if exclusion criteria were not followed. Indeed, even with improved outcomes, a high number of hemorrhagic events have been observed with thrombolysis, forcing many clinicians to look for another alternative therapy that might induce less bleeding. There has also been a striking lack of translation of the knowledge about ischemic events into daily practice due to the failure of any kind of alternative neuroprotective therapy to function clinically. Besides simple intravenous thrombolysis based on the exclusion of other pathologies, many investigators have over the years explored the use of imaging for the detection of still viable tissue and the use of interventional techniques. Anybody who has been confronted with utilizing these methods has been able to see that they have indeed improved patient management to some degree, maybe not to the degree we would like, but at least substantially. A further paper also questioned the use of advanced imaging techniques to help identify patients using penumbra imaging in order to determine what candidates may be best suited for another type of therapy. This is an excellent idea but fails, probably because it did only look at penumbral patterns, whereas when one looks at imaging findings, it is very often important to take all parameters into account and additionally look at the parenchyma (on diffusion weighted imaging or unenhanced CT) and the angiographic appearance of the vessels; indeed, this last factor should not be underappreciated since thrombolysis or thrombectomy target the vessel. However, both CT and MRI have become powerful techniques, at least for the exclusion of hemorrhage and the detection of an early insult[15,16]. Despite the fact that both MR and CT techniques have been able to provide more information than merely the absence or presence of hemorrhage, the main role of imaging is still central to exclude another pathology before initiating treatment. Indeed, one area where the role of neuroimaging has always been more problematic, has been with regard to what we call the penumbra[17,18]. From a theoretical point of view, the penumbra is a state of hypoperfusion associated with synaptic dysfunction but not yet membrane dysfunction[19-22]; thus, this is a state where the neurons are not able to function normally but may recover if flow is recovered. The penumbra that we see on imaging with either MRI[22-37] or CT[38-48] is, due to methodological factors, not a representation of the real penumbra as most people understand it: instead of having a pure metabolic model, we have a model based on hemodynamics and which has limitations whether one uses CT or MRI. The validation of these techniques have been rendered more difficult by the fact that most centers use home-made software that is constantly evolving[49,50] and, while these limitations exist, the technique has been shown to be useful. Indeed, very often, one can demonstrate a larger than expected area of hypoperfusion and sometimes demonstrate other causes that may mimic strokes[51]. Interventional techniques can be time-consuming and prone to potential complications but, if used early on in a setting where the angiography suite is placed ideally close to the emergency room or where the time to puncture can be reduced[52,53], definitely has great value. Indeed, the technique, since it includes angiography with direct luminography of the affected vessel, also allows direct visualization of the thrombus as well as vascular revascularization. Additionally, over the last decade, we have moved from pharmacological local intra-arterial fibrinolysis to more complex interventions requiring stenting and/or clot retrieval systems. The evolution of these techniques that have become more efficient, safer and easier to use has been striking over the last few years. This is unfortunately the period when most of the randomized studies were conducted in centers with low volume or with no significant experience of interventional treatment (we can see this by the recruitment numbers and the techniques and devices used in those studies). Thus, it does not represent the results obtained with current state of the art interventional techniques. These studies are a call to sobriety and show us that we should probably not be too enthusiastic when looking at single patient data compared to larger studies. We are, however, in an era where interventional neuroradiology is trying to become more evidence-based but in order to do so, it has to provide larger series than those presented to date, taking into account the very impressive technological advances we have seen recently, and maybe then more encouraging results can be produced. On the one hand, the studies are not encouraging but they represent the first attempts at investigating interventional stroke therapies with state of the art statistics. What the studies maybe lack in "patient selection criteria", they make up for in study design. Indeed, the recent years or months have seen a shift from aspiration to thrombectomy using stent retrievers with a rapidity that requires that they be taken into account before making a final assessment of the method[4]. The fact that most of the studies, including the recently published randomized ones, put techniques that are completely different into the same basket. Recent studies demonstrated that there are two generations of devices to date and their results are completely different (swift and trevo 2). How can we analyze data using those two generation devices together? Or how can we consider the results of a study using techniques that have not been used on high volume and experienced centers for at least 3-4 years? It is not the fault of those responsible for the studies as they declared they had many issues in order to include high volume centers, to keep a constant and unbiased recruitment, and with many competitive studies. The high volume centers that refused to randomize patients in the past are paying an expensive price now that intra-arterial therapy is being proven. This, in parallel with constant evolution in imaging and post-processing techniques, has made it difficult sometimes to evaluate the situation in the way it still merits before being relegated to history. Thus, efforts should focus on designing further studies involving centers of excellence with a high flow of patients and where time to treatment is reduced to a minimum; then it will be possible to obtain data as homogenous as possible in order to fully appreciate the efficacy of endovascular management of stroke. We feel that, in the worst case, these techniques may be used for a while for more extensive clots but this may be proven wrong if studies are conducted in a more fair way.

Only when new studies have been performed with more relevant study criteria (faster inclusion times, faster time to needle, done in centers with high volumes *etc.*) can we really appreciate the failures and successes of interventional neuroradiology coupled by modern imaging techniques used in a correct way[54]; these paradigms may require using many parameters in order to function correctly[55]. Only then can we avoid being too distracted by the main problem we may still encounter, that the technologies keep evolving in this field faster than the evaluation, thus making validation difficult.

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