Editorial

Cerebrovascular Diseases

Cerebrovasc Dis 2007;23:83–84
DOI: 10.1159/000097042

Published online: November 15, 2006

Symptomatic Intracranial Hemorrhage after Thrombolysis

Martin Köhrmann Peter D. Schellinger

Department of Neurology, University Hospital of Erlangen, Erlangen, Germany

Symptomatic intracranial hemorrhage (sICH) is the most feared complication after systemic thrombolysis for acute ischemic stroke. The respect for this complication has hampered the propagation of this life-saving and disability-reducing therapy and has led to the fact that even a decade after the approval of recombinant tissue plasminogen activator (rtPA) thrombolysis is still widely underused. Singular cases of devastating hemorrhages lead to continuing doubts of safety and efficacy of a – for neurologists unusually aggressive – therapy even after the benefit and safety of this therapy have been repeatedly shown in numerous studies. Therefore establishing predictors for occurrence of thrombolysis-related sICH is an important objective.

In this issue of *Cerebrovascular Diseases* Marti-Fabregas et al. present a study in which they examined 347 patients treated with rtPA in 7 Spanish university hospitals from 1999 to 2004 [1]. They analyzed the frequency of thrombolysis-related bleeding complications and examined the predictive value of different clinical, radiological and laboratory data for occurrence of sICH. With only 8 cases (2.3%), the frequency of sICH was very low in their study. Logistic regression analysis for predictors of sICH yielded two very interesting results worth taking a closer look at.

The first predictor – early ischemic changes (EIC) on CT – is a topic of ongoing controversies. While EIC have been an exclusion criterion for some studies, others, most prominently the NINDS trial, only used CT for exclusion of hemorrhage. First of all it has to be noted that different types of EIC have different pathophysiological equivalents. While it is believed that hypoattenuating brain tissue represents irreversible damage, it has recently been suggested that sulcal effacement without hypodensity corresponds to increased blood flow or cerebral blood volume and is therefore a marker for reperfusion rather than tissue damage. It is therefore highly questionable to analyze those signs together. Furthermore the evidence for a predictive value of EIC in the 3-hour time window is thin at best. Reanalyses of the data from the NINDS trial did not show a higher risk for bleeding complications in patients with EIC [2, 3]. The same is true for the 3-hour European-Australian Acute Stroke Study (ECASS) II population [4]. Still most experts agree that patients with extended hypoattenuation should not be treated. The main problem with EIC is that they are very difficult to read and have a poor sensitivity and interrater agreement [5]. At present we still do not succeed in treating enough patients based on the simple protocol given by the NINDS trial. Adding the uncertainty and the mystery of EIC has seriously impaired the implementation of thrombolysis over the years. The NINDS trial as well as clinical practice demonstrate that treatment based on the sole exclusion of hemorrhage works. Once we achieve a broader use of this simple yet effective protocol, it will be time to improve on this fundament.

The second predictor identified by the authors is deviation from the treatment protocol. While this has been shown to be a risk factor in previous studies too [6–8], we believe that there are two completely different types of deviation that need to be discussed separately. First there are the 'unintentional' deviations such as screening mistakes, dosing of the thrombolytic agent and deviations from general handling and treatment algorithms, e.g. blood pressure control. These are the kind of deviations that clearly need to be avoided, and it has been shown that

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1015–9770/07/0233–0083$23.50/0

Accessible online at:
www.karger.com/ced

Dr. Martin Köhrmann
Neurologische Universitätsklinik, Schwabachanlage 6
DE–91054 Erlangen (Germany)
Tel. +49 9131 853 4508, Fax +49 9131 853 4510
E-Mail martin.koehrmann@neuro.imed.uni-erlangen.de

experience with thrombolysis leads to improved safety and better results, presumably by minimizing these 'mistakes' [8]. However it is important to notice that there is another group of 'intentional' deviations from the protocol, e.g. treatment of patients >80 years old, patients with diabetes and previous stroke or treatment beyond 3 h, even if only by minutes, accounting for a sizeable proportion of deviations in clinical practice as well as in the present study. One has to bear in mind that these are deviations the clinician is fully aware of at the time of treatment. Of course those deviations could easily be minimized as demanded by the authors. However do we really want that? In these cases we actively choose to disregard those deviations and accept a lower risk-benefit ratio than for the classical candidate. Approval guidelines always aim for the maximum of treatment safety, but is it really justifiable to exclude a patient from the only available treatment just because he or she is a diabetic and had a previous stroke or just turned 80 one week before? There is no good data available on the treatment of diabetics with previous strokes. However treating octogenarians is a good example of a common 'intentional' deviation. Although there are no specific randomized trials, the NINDS trial did not exclude those patients, and many recent studies examine thrombolysis in older patients [9, 10]. The majority of these studies show a mildly though mostly not significantly increased risk for sICH. However if the alternative is not to treat the patients who are naturally at a higher risk for worse outcome and death after stroke, most experts find this deviation and a maybe somewhat higher risk acceptable. This demonstrates that deviations from a protocol might not always be a bad thing, even if they exhibit higher complication rates. Intense research is also under way to 'deviate' from the time window for thrombolysis [11]. Based on these considerations we strongly feel that 'unintentional' and 'intentional' deviations need to be considered as two different entities and should therefore also be analyzed separately in future studies regarding the safety of thrombolysis.

Even almost a decade after the landmark trials we are still at a stage were we have to fight for a wider implementation of thrombolysis. And while finding predictors for complications is an important research field, the main message conveyed in numerous studies and again in the present study by Marti-Fabregas et al. is: the treatment of acute ischemic stroke using rtPA is safe in clinical practice. So *treat*!

'We plan on getting out there and doing it right.' *Axl Rose, Guns n' Roses*

References

1 Martí-Fàbregas J, Bravo Y, Cocho D, Martí-Vilalta J-L, Díaz-Manera J, San Román L, Puig M, Blanco M, Castellanos M, Millán M, Roquer J, Obach V, Maestre J: Frequency and predictors of symptomatic intracerebral hemorrhage in patients with ischemic stroke treated with recombinant tissue plasminogen activator outside clinical trials. Cerebrovasc Dis 2007;23:85–90.

2 Patel SC, Levine SR, Tilley BC, Grotta JC, Lu M, Frankel M, Haley EC Jr, Brott TG, Broderick JP, Horowitz S, Lyden PD, Lewandowski CA, Marler JR, Welch KM: Lack of clinical significance of early ischemic changes on computed tomography in acute stroke. JAMA 2001;286:2830–2838.

3 Demchuk AM, Hill MD, Barber PA, Silver B, Patel SC, Levine SR: Importance of early ischemic computed tomography changes using ASPECTS in NINDS rtPA Stroke Study. Stroke 2005;36:2110–2115.

4 Dzialowski I, Hill MD, Coutts SB, Demchuk AM, Kent DM, Wunderlich O, von Kummer R: Extent of early ischemic changes on computed tomography (CT) before thrombolysis: prognostic value of the Alberta Stroke Program Early CT Score in ECASS II. Stroke 2006;37:973–978.

5 Grotta JC, Chiu D, Lu M, Patel S, Levine SR, Tilley BC, Brott TG, Haley EC Jr, Lyden PD, Kothari R, Frankel M, Lewandowski CA, Libman R, Kwiatkowski T, Broderick JP, Marler JR, Corrigan J, Huff S, Mitsias P, Talati S, Tanne D: Agreement and variability in the interpretation of early CT changes in stroke patients qualifying for intravenous rtPA therapy. Stroke 1999;30:1528–1533.

6 Katzan IL, Furlan AJ, Lloyd LE, Frank JI, Harper DL, Hinchey JA, Hammel JP, Qu A, Sila CA: Use of tissue-type plasminogen activator for acute ischemic stroke: the Cleveland area experience. JAMA 2000;283:1151–1158.

7 Tanne D, Bates VE, Verro P, Kasner SE, Binder JR, Patel SC, Mansbach HH, Daley S, Schultz LR, Karanjia PN, Scott P, Dayno JM, Vereczkey-Porter K, Benesch C, Book D, Coplin WM, Dulli D, Levine SR; the t-PA Stroke Survey Group: Initial clinical experience with IV tissue plasminogen activator for acute ischemic stroke: a multicenter survey. Neurology 1999;53:424–427.

8 Heuschmann PU, Kolominsky-Rabas PL, Roether J, Misselwitz B, Lowitzsch K, Heidrich J, Hermanek P, Leffmann C, Sitzer M, Biegler M, Buecker-Nott HJ, Berger K: Predictors of in-hospital mortality in patients with acute ischemic stroke treated with thrombolytic therapy. JAMA 2004;292:1831–1838.

9 Engelter ST, Reichhart M, Sekoranja L, Georgiadis D, Baumann A, Weder B, Müller F, Lüthy R, Arnold M, Michel P, Mattle HP, Tettenborn B, Hungerbühler HJ, Baumgartner RW, Sztajzel R, Bogousslavsky J, Lyrer PA: Thrombolysis in stroke patients aged 80 years and older: Swiss survey of IV thrombolysis. Neurology 2005;65:1795–1798.

10 Berrouschot J, Rother J, Glahn J, Kucinski T, Fiehler J, Thomalla G: Outcome and severe hemorrhagic complications of intravenous thrombolysis with tissue plasminogen activator in very old (> or = 80 years) stroke patients. Stroke 2005;36:2421–2425.

11 Kohrmann M, Juttler E, Fiebach JB, Huttner HB, Siebert S, Schwark C, Ringleb PA, Schellinger PD, Hacke W: MRI versus CT-based thrombolysis treatment within and beyond the 3 h time window after stroke onset: a cohort study. Lancet Neurol 2006;5:661–667.