European Journal of Radiology 91 (2017) 82–87

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Outcome of patients with proximal vessel occlusion of the anterior circulation and DWI-PWI mismatch is time-dependent

Sibu Mundiyanapurath[a,*], Sascha Diatschuk[b], Sarah Loebel[c], Johannes Pfaff[c], Mirko Pham[c,d], Markus Alfred Möhlenbruch[c], Wolfgang Wick[a,e], Martin Bendszus[c], Peter A. Ringleb[a,1], Alexander Radbruch[b,c,1]

[a] Department of Neurology, University Hospital Heidelberg, Heidelberg, Germany
[b] German Cancer Research Centre, Department of Radiology, Heidelberg, Germany
[c] Department of Neuroradiology, University Hospital Heidelberg, Heidelberg, Germany
[d] Institute for Diagnostic and Interventional Neuroradiology, University Hospital Würzburg, Germany
[e] CCU Neurooncology, German Cancer Consortium (DKTK) & German Cancer Research Centre (DKFZ), Heidelberg, Germany

ARTICLE INFO

Keywords:
Ischemic stroke
Endovascular therapy
Magnetic resonance perfusion
Mismatch
Penumbra
Symptom onset-to-treatment time

ABSTRACT

Background and purpose: Patients with ischemic stroke and large vessel occlusion are assumed to benefit from endovascular therapy (ET) independent of the symptom onset-to-treatment time (OTT) if they present with a mismatch of diffusion- and perfusion-weighted imaging (DWI-PWI mismatch). We aimed at studying the influence of OTT on clinical outcome in these patients.

Methods: Retrospective database review in a tertiary care university hospital. All patients presented with proximal vessel occlusion of the anterior circulation and DWI-PWI mismatch. Primary outcome was the influence of OTT on modified Rankin scale (mRS) score three months after treatment, dichotomized in favourable (0–2) and unfavourable outcome (3–6). Secondary outcome was the effect of OTT on the shift of the mRS score. Patients treated within an early time window (< 340 min) and a late time window (≥ 340 min) were compared.

Results: 139 patients were included. The rate of favourable outcome was significantly higher in patients who were treated in an early compared to those treated in a late time window (31 [49%] vs. 20 patients [27%], p = 0.005). Adjusted multivariate logistic regression revealed that late treatment was an independent negative predictor of favourable outcome (odds ratio 0.39, confidence interval [0.18–0.84]; p = 0.016). A shift towards higher mRS scores for late treatment was evident (p = 0.015). In sensitivity analysis, OTT remained an independent predictor when evaluated as continuous variable. These findings were confirmed in patients with a comparable DWI-PWI mismatch according to the definitions from large trials (DEFUSE 2, DEFUSE 3, SWIFT-PRIME, EXTEND-IA).

Conclusion: Outcome of patients with comparable DWI-PWI mismatch is time-dependent.

1. Introduction

Until recently, the only proven acute stroke therapy was IV thrombolysis (IVT) with alteplase. Within the last year several trials have shown the benefit of additional endovascular therapy (ET) using stent retriever devices [1]. Rates of relevant reperfusion ranging from 59 to 88% were achieved in a median symptom-onset-to-angiography time extending from 200 min to 269 min [2]. The maximum time in which a patient will still benefit from ET is unclear. Results from the large ET trials suggest that attempting reperfusion after around 7 h may be futile [3].

MRI including perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI) has the capability to differentiate hypoperfused from ischemic tissue in acute stroke patients [4]. Frequently, the time to the maximum of the residue curve (T_{max}) is used to identify hypoperfused tissue. A threshold between Tmax > 4 s or > 6 s seems

Abbreviations: CI, confidence interval; CT, computed tomography; DWI, diffusion-weighted imaging; ET, endovascular therapy; mRS, modified Rankin Scale; ICA, internal carotid artery; NIHSS, National Institute of Health stroke scale; OR, odds ratio; OTT, symptom-onset-to-treatment time; PWI, perfusion-weighted imaging; Tmax, time to the maximum of the residue curve

* Corresponding author at: Department of Neurology, Im Neuenheimer Feld 400, 69120, Heidelberg, Germany.
E-mail address: sibu.mundiyanapurath@med.uni-heidelberg.de (S. Mundiyanapurath).
[1] Department of Neurology, Im Neuenheimer Feld 400, 69120, Heidelberg, Germany.

http://dx.doi.org/10.1016/j.ejrad.2017.03.016
Received 22 December 2016; Received in revised form 15 March 2017; Accepted 24 March 2017

to differentiate benign oligemia from critically hypoperfused tissue [5,6]. The mismatch between critically hypoperfused tissue and the diffusion restricted and therefore irreversibly damaged lesion defines the salvageable tissue or the penumbra [6]. Selecting patients based on their DWI-PWI mismatch might help to choose the patients who will benefit from ET even if they arrive in a late symptom-onset-to-treatment time (OTT) [7,8]. One of the studies analysing the effect of DWI-PWI mismatch in patients undergoing endovascular therapy was the DEFUSE 2 trial [8]. It included 99 patients with anterior circulation stroke. The authors found that the odds ratio for a favourable outcome was markedly higher in patients with target mismatch than in patients that did not have a target mismatch (OR 8.8 (95% CI 2·7–29·0) vs. 0.2 (0.0–1.6)). The definition of a target mismatch can be found in the online-only Appendix table A3.

The question whether a mismatch in an early time window has the same prognostic value as a mismatch in a late time window has not been studied in detail before. One study found that the outcome of patients with stroke undergoing ET with a mismatch according to the target mismatch definition of the DEFUSE 2 trial did not change depending on the time window [9]. The aim of the current study was to investigate the clinical outcome of patients with DWI-PWI mismatch, who have been treated with ET in an early or late time window. We wanted to know whether the OTT influences outcome despite the fact that there is a similar amount of salvageable tissue at baseline.

2. Methods

Approval by the local ethics committee was obtained for this study (statement S-330/2012). Due to the retrospective character of the analysis, requirement of subsequent informed written consent was waived.

2.1. Patient selection

We identified all consecutive patients between 2009 and 2014 with acute ischemic stroke due to internal carotid artery (ICA) occlusion, middle cerebral artery (MCA) occlusion or the combination thereof, who were treated with ET after MRI including DWI and PWI of sufficient quality. Experienced neuroradiologists, blinded to the clinical course and to this analysis, found an insufficient quality impeding interpretation in 16 PWI and in one DWI. These 17 cases were excluded from the analysis. All patients had a proximal vessel occlusion and a DWI-PWI mismatch (ratio of $T_{max>}$ 4 s lesion volume and DWI lesion volume > 1.2, infarct core < 100 ml, minimum perfusion lesion volume of 20 ml). To exclude an effect of the threshold we use at our hospital, we studied the mismatch ratios (hypoperfused tissue divided by infarcted tissue) for both the $T_{max>}$ 4 s and the $T_{max>}$ 6 s threshold. In addition, to compare our population to those of other large trials (DEFUSE 2, DEFUSE 3, SWIFT-PRIME, EXTEND-IA), we applied their mismatch definitions [8,10–12] to the MRI of our patients. Symptom-onset-to-treatment time was used as primary time measure as published before [3]. Symptom onset in patients with unknown symptom-onset time but defined last-seen-well time was calculated as described previously [13]. The threshold between early and late time window was defined according to the median of the population. Patients with unknown symptom-onset and unknown last-seen-well time were classified as late time window. Follow-up-interviews of the patients, relatives or a treating physician to determine mRS at day 90 were performed by an experienced neurologist blinded to this analysis. As in previous stroke trials [8], the primary outcome favourable outcome was defined as mRS 0–2 (reflecting the ability to live independently) and unfavourable outcome as mRS 3–6. In the large stroke trials on endovascular therapy, patients with a premorbid mRS of > 2 were excluded as many used the mRS as primary outcome. In everyday clinical practice however, it sometimes seems unethical to withhold an effective treatment from a patient with a premorbid mRS > 2 as their outcome without recanalization is mostly poor. Therefore, as an off-label treatment based on clinical experience, some patients in our study with a premorbid mRS of greater than 2 were also treated (7 with mRS 3, 4 with mRS 4). Those with a premorbid mRS of 3 were defined to have a favourable outcome if they had an unchanged mRS at day 90 (n = 3). All patients with a premorbid mRS of 4 had a mRS of 5 or 6, which was declared as unfavourable outcome. A shift of the mRS between patients treated in an early and a late time window was defined as secondary outcome. Symptomatic intracerebral haemorrhage (ICH) was defined according to ECASS-II definition [14].

2.2. Image acquisition and analysis

T_{max} maps were calculated automatically using Olea-Sphere software (Olea Medical, La Ciotat, France). DWI lesions were segmented automatically replicating a previously published algorithm [15] with in-house software created with MATLAB (MathWorks, Natick, MA, USA). Automated volumetric measurements of all maps were performed using software created with MATLAB. Final infarct volume was assessed on non-contrast CT by two authors (SM, AR). Disagreement by more than ten per cent was solved by consensus reading. All images were checked for artefacts using ITK-SNAP (www.itksnap.org) [16] by two authors separately and blinded to the clinical course. Maps with grouped values of $T_{max>}$ 4s/6s/8s/10 s were created with MATLAB. Perfusion images were co-registrated to T2-images to facilitate artefact correction using statistical parametric mapping (SPM; www.fil.ion.ucl.ac.uk/spm). Details on image acquisition and further information on image analysis can be found in the online-only appendix.

Reperfusion was scored using modified Thrombolysis In Cerebral Infarction (mTICI) scores [17] by two experienced vascular neurologists and two neuroradiologists (SM, PAR, JP, MP). Relevant reperfusion was defined as TICI 2b and 3. Disagreements were solved by consensus reading.

2.3. Statistical analysis

Microsoft Excel version 2010 and IBM SPSS version 22 were used to conduct the statistical analyses. Univariate analysis was performed using the Mann-Whitney-U test or Chi-square/Fisher exact test depending on the level of measurement. Shift analysis was performed using the Cochran-Mantel-Haenszel test. Multivariate analysis was run with binary logistic regression. Variable selection was performed using the backward elimination method based on likelihood-ratio tests where variables were removed if the related *p*-value fell above 0.10. The alpha-level was determined to be 0.05. Two-sided *p*-values are reported throughout.

3. Results

139 patients were included in the study. The median NIHSS on admission was 18 (interquartile range: IQR 15–21), 136 (98%) patients were treated with stent-retrievers and the median symptom-onset-to-treatment time was 340 min (IQR 226–488). Regarding the patients who were not treated with stent-retrievers, 2 (1%) were treated with aspiration alone and 1 (1%) patient received intraarterial alteplase alone. Further baseline variable are listed in Table 1.

Three months mRS score was available for all patients. 51 (37%) had a favourable outcome. Symptomatic ICH occurred in 10 patients (7.3%) while any ICH on imaging was found in 54 patients (39%). Relevant reperfusion was achieved in 97 patients (70%).

3.1. Clinical outcome in relation to the time to treatment

Comparing the patients treated in an early to those treated in a late time window, there were no significant differences regarding risk factors, the rate of relevant reperfusion, the rate of ICH, the DWI lesion