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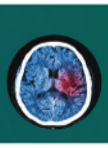

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ORIGINAL ARTICLE

Addressing a real-life problem: treatment with intravenous thrombolysis and mechanical thrombectomy in acute stroke patients with an extended time window beyond 4.5 h based on computed tomography perfusion imaging

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Background and purpose: Acute ischemic stroke treatment with intravenous thrombolysis (IVT) is restricted to a time window of 4.5 h after known or presumed onset. Recently, magnetic resonance imaging-guided treatment decision-making in wake-up stroke (WUS) was shown to be effective. The aim of this study was to determine the safety and outcome of IVT in patients with a time window beyond 4.5 h selected by computed tomography perfusion (CTP) imaging.

Methods: We analyzed all consecutive patients last seen well beyond 4.5 h after stroke onset treated with IVT based on CTP between January 2015 and October 2018. CTP was visually assessed to estimate the mismatch between cerebral blood flow and cerebral blood volume maps. Early infarct signs were documented according to Alberta Stroke Program Early CT Score (ASPECTS). Safety data were obtained for mortality and symptomatic intracerebral hemorrhage (sICH). Follow-up was assessed with the modified Rankin Scale (mRS).

Results: A total of 70 patients fulfilled the inclusion criteria (mean age ± SD 77.6 ± 11.5 years, 50.0% female). Median National Institutes of Health Stroke Scale score on admission was 8.0 [interquartile range (IQR), 4–14]. The most frequent reasons for an extended time window were WUS (60.0%) and delayed hospital admission (27.1%). Median time from last seen well to IVT was 11.4 h. Median ASPECTS was 10 (IQR, 9–10) and CTP mismatch 90% (IQR, 80%–100%). A total of 24 patients (34.3%) underwent additional mechanical thrombectomy. sICH occurred in four patients (5.7%). At follow-up, 49.3% had an mRS score of 0–2 and 22.4% had an mRS score of 0–1.

Conclusions: In patients presenting in an extended time window beyond 4.5 h, IVT treatment with decision-making based on CTP might be a safe procedure. Further evaluation in clinical trials is needed.

Introduction

The burden of acute ischemic stroke remains high despite all recent advances in acute therapy using intravenous thrombolysis (IVT) and mechanical thrombectomy (MT) [1]. Early treatment is associated with better clinical outcome [2,3]. The main reason for withholding IVT is an unknown time of onset and last seen well >4.5 h ago or a proven onset of symptoms >4.5 h ago [4,5]. Therefore, the majority of patients who wake up with stroke symptoms beyond 4.5 h of presumed symptom onset ['wake-up stroke' (WUS)] and

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patients with unknown symptom onset and a last seen well >4.5 h ago do not receive IVT. This is the case in up to 14–27% of acute stroke patients [6,7]. A substantial proportion of strokes that are evident after sleep probably occur within the last few hours before awakening, which would be within the approved time window for IVT [8]. As a result, in a significant proportion of patients effective therapeutic options might be withheld, e.g. in the EXTEND-IA trial, only 13.4% of patients were treated with IVT, mostly because of an extended time window [9]. However, real-world data from the nationwide Austrian Stroke Unit Registry compared in a non-randomized study the safety and efficacy of IVT in WUS and known onset of symptoms in stroke patients. There was no statistical difference regarding clinical outcome and complication rate [10]. These registry data do not fully reveal the selection parameters for IVT in these patients. Different modalities for penumbral imaging that guides patient selection for reperfusion therapy were investigated [6,11–13]. The WAKE-UP trial demonstrated a significantly better functional outcome in patients with extended time window and IVT decision-making guided by diffusion-weighted imaging and fluid-attenuated inversion recovery mismatch in magnetic resonance imaging (MRI) compared with placebo [14]. The recently published EXTEND trial showed a benefit of IVT in an extended time window of up to 9 h after symptom onset and WUS patients using penumbral imaging with MRI or computed tomography perfusion (CTP) [15]. Results of DAWN and DEFUSE 3 trials showed a benefit of MT in patients with an unknown symptom onset, severe stroke and large-vessel occlusion [16,17]. However, in clinical practice, a large number of patients do not receive IVT due to extended time window and unavailability of functional neuroimaging in many hospitals, especially with limited or no access to MRI [18]. Furthermore, MRI is more time-consuming than CTP, which has practical advantages in 24/7 accessibility and fewer practical restrictions compared with MRI. Here, we present a retrospective analysis of prospectively collected data on imaging and clinical outcome of patients treated with IVT in an extended time window of >4.5 h in WUS patients and patients with unknown time of stroke onset and last seen well of >4.5 h ago based on CTP.

Materials and methods

Study population

Between January 2015 and October 2018, all consecutive patients treated with IVT in our tertiary comprehensive stroke center were prospectively collected.

Patients with extended time window were included in cases of: (i) WUS and last seen well >4.5 h ago, (ii) unknown symptom onset with last seen well >4.5 h ago and (iii) known symptom onset >4.5 h ago. Treatment decisions were made by experienced neurologists based on individual patient data, clinically relevant deficits and on the basis of imaging signs of early ischemic damage on non-contrast computed tomography (CT) according to the Alberta Stroke Program Early CT Score (ASPECTS), posterior circulation-ASPECTS and CTP. There was no pre-defined limiting baseline infarct volume. Decision-making for IVT and/or thrombectomy was a clinical decision in every case.

Symptomatic intracerebral hemorrhage (sICH) was defined according to ECASS-3 (any hemorrhage with neurologic deterioration as indicated by an NIHSS score that was 4 points higher than the value at baseline or the lowest value in the first seven days or any hemorrhage leading to death; in addition, the hemorrhage must have been identified as the predominant cause of the neurologic deterioration) [19]. Functional outcome was assessed using the modified Rankin Scale (mRS) either by telephone calls or outpatient visits. Clinical outcome was assumed as excellent if the mRS score was 0–1 and good if the mRS score was 0–2. An independent experienced interventional neuroradiologist rated recanalization success based on final angiograms according to the thrombolysis in cerebral infarction score in anterior circulation. Successful recanalization was defined as thrombolysis in cerebral infarction score of 2b–3 [20].

Imaging data

Each patient underwent initial CT imaging including non-contrast CT, CT angiography (CTA) and CTP. An independent experienced neuroradiologist assessed all images in a blinded and randomized fashion. Between 18 and 36 h after IVT, each patient underwent CT or MRI to rate the extent of an ischemic lesion and to detect intracerebral hemorrhage. White matter disease was identified according to the age-related white matter changes rating scale [21]. All CT examinations were performed using one of the following four CT scanners: SOMATOM Force, a 2 × 192 slice dual-source CT scanner; SOMATOM Definition Flash, a 2 × 128 slice dual-source CT scanner; SOMATOM Definition Edge and SOMATOM Definition AS+, both 128 slice CT scanners (all Siemens Healthcare, Erlangen, Germany). For CTA, 50 mL of iodinated contrast agent was administered intravenously, followed by a saline chaser of 40 mL, both with a flow rate of 5 mL/s. CTA was performed from

the aortic arch to the vertex with 140 and 80-kV tube voltage and attenuation-based tube current modulation (CareDose, Forchheim, Germany). Collimation was 0.6 mm. CTA data were read as source images using syngo.via imaging software (Siemens Healthcare). CTP was obtained with 0.6-mm collimation and 100-mm scan coverage in the z-axis using adaptive spiral scanning. The datasets were acquired continuously over 48 s (32 cycles, one sweep every 1.5 s). Tube voltage and current were 80 kV and 200 mAs, respectively. A total of 35 mL of iodinated contrast agent (400 mg/mL) was administered at a flow rate of 5 mL/s, followed by a saline flush of 40 mL at 5 mL/s. Analysis of CTP was based on the cerebral blood flow (CBF) and cerebral blood volume (CBV) perfusion maps. The CTP deficit according to the ASPECTS topography was assessed for CBF and CBV maps as previously described and used to assess CBF–CBV mismatch [22]. In addition, mismatch was visually assessed in 10% increments as routinely used clinically and as previously described [23].

Statistics

Data were collected and evaluated using Excel (Microsoft, Redmond, WA, USA) spreadsheet software. Statistical analysis was performed using SPSS (IBM, Armonk, NY, USA). Baseline characteristics, periprocedural time and outcome parameters were analyzed. Groups were compared according to the distribution by using *t*-test, Mann–Whitney *U*-test or chi-squared test. Differences were considered significant if $P < 0.05$.

Ethics statement

This study was approved by the local ethics committee (Faculty of Medicine at LMU Munich, project number 17-074) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained.

Results

Of 545 patients treated with IVT from January 2015 to October 2018, 70 patients were included (mean age ± SD 77.6 ± 11.5 years, 50.0% female). Median National Institutes of Health Stroke Scale (NIHSS) score on admission was 8.0 [interquartile range (IQR), 4–14] and median pre-morbid mRS score was 0 (IQR, 0–1). Patients' baseline demographic, clinical and radiological data are summarized in Table 1. The most frequent reason for an extended time window was

Table 1 Baseline characteristics and treatment details

	All patients (n = 70)
Age (years)	77.6 ± 11.5
Sex – female	35 (50)
WUS with last seen well > 4.5 h	42 (60.0)
Onset unknown with last seen well > 4.5 h	9 (12.9)
Delayed hospital admission > 4.5 h	19 (27.1)
Drip and ship	3 (4.3)
pmRS score	0 (0–1.3)
0	37 (52.9)
1	16 (22.9)
2	9 (12.9)
3	4 (5.7)
4	3 (4.3)
5	1 (1.4)
Admission NIHSS score	8.0 (4.0–14.3)
Risk factors	
Arterial hypertension	62 (88.6)
Diabetes mellitus	19 (27.1)
Hypercholesterolemia	14 (20.0)
Current smoking	12 (17.1)
Family history	3 (4.3)
Atrial fibrillation	28 (40.0)
Coronary heart disease	12 (17.1)
Peripheral artery disease	8 (11.4)
CHA_2DS_2-VASC score	6.0 (4.8–7.0)
Length of hospital stay (days)	7 (3.8–12.0)
Admission	
blood pressure, systolic (mmHg)	162.2 ± 24.9 (n = 64)
blood pressure, diastolic (mmHg)	87.2 ± 15.8 (n = 60)
heart rate (bpm)	81.7 ± 15.4 (n = 23)
Anterior circulation stroke	51 (72.9)
Posterior circulation stroke	16 (22.9)
Stroke mimic	3 (4.3)
Etiology	
Cardioembolic	33 (49.3)
Large-vessel occlusion	10 (14.9)
Small-vessel disease	5 (7.5)
Embolic stroke of undetermined source	15 (22.4)
Unknown	4 (6.0)
Stroke mimic	3 (4.3)
IVT	70 (100)
rtPA dosage (/mg)	64.8 ± 12.4
Large-vessel occlusion	42 (60.0)
MT	24 (34.3)

IVT, intravenous thrombolysis; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; pmRS, premorbid modified Rankin Scale; WUS, wake-up stroke. Data are given as n (%), mean ± SD and median (interquartile range). The CHA2DS2-VASc score is a clinical prediction rule for estimating the risk of stroke in patients with non-rheumatic atrial fibrillation used to determine whether or not anticoagulation treatment is required. The CHADS2 score is determined by adding the points that corresponds to the conditions that are present in the patients (C: congestive heart failure—1 point, H: hypertension–1 point, A: Age ≥75 years—1 point, D: diabetes mellitus—1 point, S2: prior stroke, TIA or thromboembolism—2 points). The CHA2DS2-VASc score is a refinement of CHADS2 score and extends the latter by including additional common stroke risk factors (age 65–74, female gender and vascular disease. Furthermore "Age ≥75 years" has extra weight with 2 points). The maximum CHA2DS2-VASc score is 9.

Table 2 Time intervals in treated patients regarding hospital admission, intravenous thrombolysis (IVT) and mechanical thrombectomy (MT)

	All patients (n = 70)
Symptom recognition to door (min)	100.0 (67.8–175.3)
Last seen well to door (min)	639.0 (344.0–863.5)
Symptom recognition to IVT (min)	150.0 (110.0–262.5)
Last seen well to IVT (min)	685.0 (387.5–950.5)
Door to needle (min)	45.0 (38.0–59.5)
MT: Door to groin (min)	92.0 (79.3–110.8)
MT: Symptom recognition to groin (min)	174.5 (154.0–225.8)
MT: Symptom recognition to revascularization (min)	279.0 (203.8–346.5)
MT: Last seen well to revascularization (min)	888.5 (802.0–1318.3)

Data are given as median (interquartile range).

Table 3 Imaging characteristics of patients

	All patients (n = 70)
ASPECTS (data available in n = 53)	10 (9–10)
pc-ASPECTS (data available in n = 17)	10 (9–10)
CTP mismatch %	90 (80–100)
CBF-ASPECTS	6.5 (3–9)
CBV-ASPECTS	9.5 (8–10)
White matter disease	48 (68.6)
Old infarction in CT	26 (37.1)

ASPECTS, Alberta Stroke Program CT Score; CBF, cerebral blood flow; CBV, cerebral blood volume; CT, computed tomography; CTP, computed tomography perfusion; pc-ASPECTS, posterior circulation-ASPECTS. Data are given as n (%) and median (interquartile range).

WUS after awaking from sleep with stroke symptoms (60.0%) followed by delayed hospital admission (27.1%). A total of 75.7% of the patients showed anterior circulation stroke symptoms. Large-vessel occlusion was eminent in 42 patients (60.0%) and 24 patients also received endovascular treatment in addition to IVT. Median time between symptom recognition and hospital admission ('door') was 1.7 h and between last seen well to door was 10.7 h, whereas it was 2.5 and 11.4 h for administration of IVT, respectively (Table 2).

Median ASPECTS and posterior circulation-ASPECTS estimated on plain CT scans were each 10 (IQR, 9–10). On CTP images, median CTP mismatch was 90% (IQR, 80%–100%). Median CBF-ASPECTS was 6.5 (IQR, 3–9) and CBV-ASPECTS was 9.5 (IQR, 8–10) (Table 3). Three patients with stroke mimics were treated in this study (one patient each with vestibular neuropathy, peripheral radial palsy and cerebral venous sinus thrombosis). sICH according to ECASS-3 occurred in four patients (5.7%) and adverse events other than sICH in five patients (7.1%)

Table 4 Peri-procedural and in-hospital complications

	All patients (n = 70)
IVT, adverse events[a]	5 (7.1)
IVT, angioedema[a]	1
IVT, other bleeding[a]	4
MT – successful revascularization TICI 2b/3[b]	19 (79.2)
MT – TICI[b]	
TICI 0	2 (8.3)
TICI 1	2 (8.3)
TICI 2a	1 (4.2)
TICI 2b	9 (37.5)
TICI 3	10 (41.7)
MT – peri-procedural complications (groin hematoma)[b]	2 (8.3)
sICH (ECASS-3)[a]	4 (5.7)2 WUS patients 2 delayed hospital admission
ICH[a]	
HI1	4
HI2	1
PH1	3
PH2	2
ICH remotely	
SAH	4

ICH, intracerebral hemorrhage; IVT, intravenous thrombolysis; MT, mechanical thrombectomy; SAH, subarachnoid hemorrhage; sICH, symptomatic intracerebral hemorrhage; TICI, thrombolysis in cerebral infarction; WUS, wake-up stroke. Data are given as n (%). ECASS-3, any hemorrhage with neurologic deterioration as indicated by an NIHSS score that was 4 points higher than the value at baseline or the lowest value in the first seven days or any hemorrhage leading to death; in addition, the hemorrhage must have been identified as the predominant cause of the neurologic deterioration [19]. HI1, hemorrhagic infarction defined as small petechiae along the margins of the infarct; HI2, as more confluent petechiae within the infarcted area, but without space-occupying effect. PH1, parenchymatous hematoma was defined as a clot not exceeding 30% of the infarcted area with some mild space-occupying effect; PH2, represented dense blood clot(s) exceeding 30% of the infarct volume with significant space-occupying effect [24]. [a]Data available in n = 70 patients. [b]Data available in n = 24 patients undergoing MT.

(Table 4). In-hospital mortality was 11.4%. Median NIHSS score at discharge was 3.0, which was significantly different from NIHSS score at admission ($P < 0.001$). There was a good clinical outcome at 3-month follow-up in 49.3% and excellent clinical outcome in 22.4% of patients. Median mRS score at 3 months was 3 (IQR, 2–5) (Fig. 1). Regarding patients who underwent MT (n = 24), excellent clinical outcome was achieved in two patients (8.3%) and good clinical outcome in seven patients (29.2%).

Discussion

The aim of this study was to show real-life data in patients treated with IVT and MT beyond the

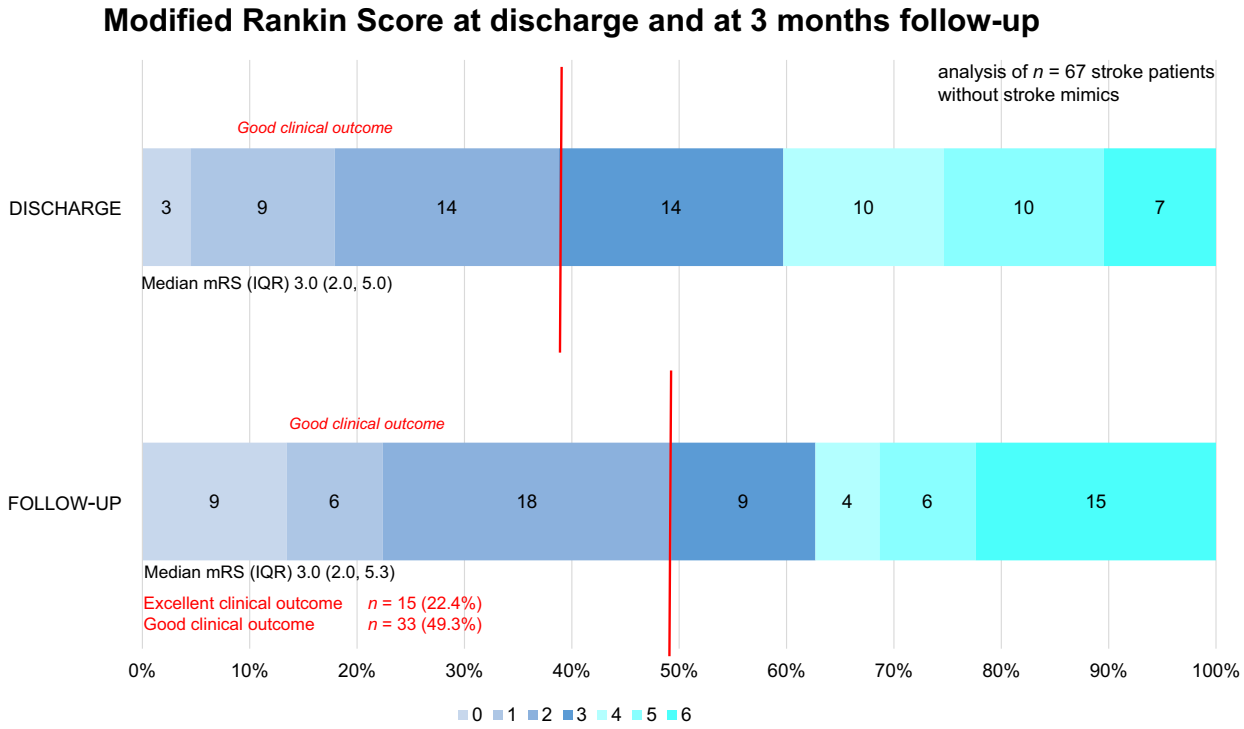

Figure 1 Functional outcome at discharge and at 3-month follow-up. IQR, interquartile range; mRS, modified Rankin Scale. Data available in $n = 70$. [Colour figure can be viewed at wileyonlinelibrary.com]

established time window of 4.5 h with decision-making based on CTP. The main findings of this study are as follows.

First, in patients with unknown onset, last seen well of >4.5 h ago and an extended time window of >4.5 h, patient selection for IVT, potentially in conjunction with MT, can be safely performed based on CTP. Median last seen well to hospital admission and to IVT were 10.7 and 11.4 h, respectively. With respect to time intervals, our study represents a different study population compared with the EXTEND trial with a median time from stroke onset to hospital arrival of about 5.0 h and time from stroke onset to IVT of about 7.0 h [15].

Secondly, the complication rate, especially regarding sICH, does not exceed that in the approved time window <4.5 h for IVT after appropriate patient selection with CTP. In the current study, sICH according to ECASS-3 was observed in 5.7%, which is in line with the sICH rate of 5.2% reported in clinical trials. In the pooled analysis of ECASS, ATLANTIS, NINDS and EPITHET trials, parenchymal hemorrhage was seen in 5.2% [25]. Compared with this, the WAKE-UP trial showed a rate of sICH of 2% [14], whereas in the EXTEND trial sICH occurred in 6.2% [15]. Data from the Austrian Stroke Unit Registry comparing WUS with stroke patients with known symptom onset presented a rate of sICH of 4.1% [10].

Thirdly, this patient group can benefit from reperfusion therapy. Median NIHSS score at discharge was significantly different from NIHSS score on admission. Good clinical outcome at follow-up was seen in 49.3% and excellent clinical outcome in 22.4% of patients. These results are within the range of the nationwide Austrian Stroke Unit Registry reporting 51.9% good outcome at 3 months. In our study, 42 patients (60%) suffered from large-vessel occlusion and 24 of these underwent MT with successful recanalization in 19 patients and good clinical outcome in 29.2%. Therefore, these real-life data regarding MT in combination with IVT showed a lower rate of good outcome than in DAWN and DEFUSE 3 trials with good clinical outcome in 49% and 45%, respectively [16,17]. However, in our study, we could only present a small number of MT cases overall and, in these trials, patients treated with thrombectomy following strict inclusion criteria.

In our study, we found that selected patients within an extended time window beyond 4.5 h and treatment with IVT (and MT) showed good clinical outcome and no increase of adverse events, especially sICH. Precise criteria of patient selection could contribute to

identifying those patients who can still benefit from off-label IVT beyond the accepted time window of 4.5 h.

However, our study has some limitations. The data describe only a single-center experience. Therefore, treatment decisions were performed according to in-house standards. Moreover, the study, although including consecutive patients, is of an observational character. Our study population represents only moderate strokes with a median NIHSS score of 8 and with significant penumbra. Thus, results cannot be transferred to patients with other clinical and imaging parameters. Due to the lack of a control group we cannot make any conclusions about the efficacy of IVT/MT in these selected patients. The examined patient group is not completely homogenous. In 27.1% of patients the time window was certainly longer than 4.5 h (known onset, delayed hospital admission), the rest of the patients had WUS or unknown symptom onset with a last seen well of >4.5 h ago. Here, of course, stroke symptom onset could have occurred within the permitted time window of 4.5 h. The strongest limitation is the lack of comparison group and the treated patients cannot be compared with the untreated patients.

Conclusions

In conclusion, among patients with an unknown and extended time window and CTP findings consistent with a small ischemic core, treatment with IVT seems feasible and safe and may be effective. Therefore, functional imaging including CTP may help to extend the number of patients with acute stroke who can benefit from further treatment. Randomized prospective comparisons of CTP- and MRI-based approaches are therefore needed.

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Disclosure of conflicts of interest

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