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Intra-Arterial Thrombolysis for Acute Ischemic Stroke in Octogenarians

Marie-Luise Mono[a] Lorenz Romagna[a] Simon Jung[a] Marcel Arnold[a] Aekaterini Galimanis[a] Urs Fischer[a] Adrian Kohler[a] Pietro Ballinari[a] Caspar Brekenfeld[b] Jan Gralla[b] Gerhard Schroth[b] Heinrich P. Mattle[a] Krassen Nedeltchev[a]

Departments of [a]Neurology and [b]Neuroradiology, Inselspital, University Hospital and University of Bern, Bern, Switzerland

Key Words
Acute ischemic stroke · Intra-arterial thrombolysis, outcome · Octogenarians · Complications

Abstract
Background: It is unclear whether octogenarians benefit from intra-arterial thrombolysis (IAT) for the treatment of acute ischemic stroke (AIS). The aim of the present study was to compare baseline characteristics, clinical outcome and complications of patients aged ≥80 with those of patients aged <80 years. ***Methods:*** Forty-three octogenarians and 524 younger patients with AIS were treated with IAT. The modified Rankin scale (mRS) score was used to assess 3-month outcome. ***Results:*** There was a female preponderance among octogenarians (63 vs. 37%, p = 0.015). Stroke severity, occlusion site, and time from stroke onset to IAT did not differ between the groups. Good recanalization (TIMI 2–3) was achieved in 65% of older and in 71% of younger patients (p = 0.449). Rates of symptomatic intracranial hemorrhage (ICH) were 6% in patients <80 years and 2% in octogenarians (p = 0.292). Favorable outcome (mRS 0–2) was less frequent among octogenarians (28 vs. 46%, p = 0.019), while mortality was higher (40 vs. 22%, p = 0.008). Octogenarians died more often from extracerebral complications than younger patients (59 vs. 27%, p = 0.008). ***Conclusions:*** Compared with younger patients, octogenarians did not have a significantly increased risk of symptomatic ICH after IAT. Although favorable outcome was less frequent and mortality rates were higher, IAT appeared to be safe in octogenarians. It seems reasonable to include octogenarians in randomized clinical trials to assess the balance of risk and benefit of IAT in this patient group.

Introduction

The risk of stroke is strongly age-related [1, 2]. Advancing age is associated with increased mortality [3, 4] and more severe disability from stroke [5, 6]. Current demographic trends indicate that vascular events in octogenarians will increase by about 280% until the middle of this century [7]. Therefore, advances in acute ischemic stroke (AIS) treatment in the very elderly are urgently needed.

While several studies have examined the use of intravenous recombinant tissue plasminogen activator (rtPA) in this population [5, 8–11], data regarding the safety and efficacy of intra-arterial thrombolysis (IAT) in octogenarians are limited [12–15]. In the largest comparative studies of AIS patients who received IAT, recanalization and hemorrhagic rates did not differ between octogenar-

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Gerhard Schroth, MD
University Hospital and University of Bern
Institute of Diagnostic and Interventional Neuroradiology
Freiburgstrasse 10, CH–3010 (Bern)
Tel. +41 32 632 2654, E-Mail gerhard.schroth@insel.ch

ians and younger individuals [12]. However, the mortality rate was higher and outcome was poorer in the elderly.

The aim of this single-center series of AIS patients who were treated with IAT was to compare baseline characteristics, clinical outcome and complications in patients aged ≥80 years with those in younger patients.

Patients and Methods

Patients

Prospectively collected data of 576 AIS patients who underwent IAT at our stroke center from January 2000 to October 2009 were included in this retrospective analysis. Forty-three of the patients were ≥80 years old. Some aspects of these patients have been reported previously [16, 17]. Baseline investigations included a neurological and physical examination, assessment of stroke severity using the National Institute of Health Stroke Scale (NIHSS), routine blood analysis, 12-lead ECG and brain imaging with MRI or CT. IAT was considered if: (1) the patient presented with AIS in a 6-hour window, (2) the NIHSS on admission was more than 4 points, except for isolated severe aphasia or complete hemianopsia, and (3) the prestroke modified Rankin scale (mRS) was ≤2. Treatment beyond the 6-hour window was performed when there was evidence of substantial salvageable penumbra tissue on multimodal imaging. The site of vessel occlusion was determined by diagnostic angiography. All patients or their family members consented to thrombolytic treatment. The TOAST classification was used to define stroke etiology [18].

Clinical outcome measures were mortality and mRS score, dichotomized into favorable (mRS 0–2) and unfavorable (mRS 3–6) at 3 months. The mRS was assessed by clinical investigations or structured telephone interviews with the patients, their families and/or their treating physician. Follow-up data was available for all but 3 patients aged <80 years.

The study protocol was approved by our institutional review board.

Thrombolytic and Antithrombotic Treatment

Details of the technique used for IAT have been described elsewhere [16, 17, 19]. Patients received one of the following treatments: (1) intra-arterial urokinase at a dosage from 500,000 to 1,250,000 IU; (2) combined intravenous thrombolysis/IAT with rtPA started within 3 h (within 4.5 h since October 2008) at a dose of 0.6 mg/kg (15% as a bolus, the remainder over 40 min) and followed by intra-arterial urokinase up to a maximum of 500,000 IU); (3) intra-arterial urokinase up to 1,250,000 IU in combination with mechanical recanalization techniques such as aspiration, clot retrieval, angioplasty and stenting, or (4) mechanical recanalization alone. Time from symptom onset to thrombolysis and the method of thrombolysis were analyzed. An interventional neuroradiologist who was blinded to the clinical outcome classified the collaterals semiquantitively into 'poor' and 'good' according to previously published criteria [16, 17, 19]. The degree of vessel recanalization was dichotomized into 'poor' (Thrombolysis in Myocardial Infarction, TIMI 0–1) and 'good' (TIMI 2–3) [20].

Identification and Classification of Intracranial Hemorrhage

Brain MRI or CT was routinely performed within 24 h after thrombolysis or in case of clinical deterioration. Intracranial hemorrhage (ICH) was classified as 'symptomatic' if it led to a 4-point increase in the NIHSS score or death [21, 22], otherwise intracranial bleedings were defined as asymptomatic ICH.

Risk Factors

We assessed the history of coronary artery disease, atrial fibrillation, transient ischemic attack or ischemic stroke and the presence of hypertension (treated hypertension or systolic and diastolic blood pressure >140 mm Hg and >90 mm Hg, measured on two different occasions), diabetes mellitus (symptoms of diabetes plus random blood glucose concentration >11 mmol/l or fasting glucose >7 mmol/l), current cigarette smoking, hypercholesterolemia (total venous plasma cholesterol concentration >5 mmol/l) and family history of cerebrovascular events.

Statistical Analysis

Patients were divided into two groups: age ≥80 years and <80 years. For comparisons χ^2, Mann-Whitney test and Student's t test were used. To determine whether age, considered as a continuous variable, was an independent predictor for outcome (nonfavorable outcome of mRS >2) and for death, a multivariate logistic regression analysis with bootstrap estimates was performed including all variables with probability values <0.1 in univariate analysis. A probability value of $p < 0.05$ was considered significant.

Results

Baseline clinical and radiologic characteristics are summarized in table 1. Treatment variables are given in table 2.

Good recanalization rates (TIMI 2–3) were achieved in 65% of the octogenarians and in 71% of their younger counterparts (p = 0.489).

At 3 months, 28% of the octogenarians and 46% of the younger patients achieved a favorable outcome (mRS 0–2, p = 0.019, fig. 1). Complete recovery (mRS 0) was equally frequent in the two groups (7% in octogenarians, 8% in younger patients). Mortality was higher in octogenarians compared to younger patients (40 vs. 22%, p = 0.008). Octogenarians died more often from extracerebral complications such as pulmonary embolism, pneumonia, cardiac failure, or ischemic colitis than younger patients (59 vs. 27%, p = 0.008).

In multivariate analysis, age as a continuous variable was an independent predictor of nonfavorable outcome at 3 months (mRS >2) along with NIHSS at admission, diabetes mellitus, time from symptom onset, symptomatic and asymptomatic ICH, and mechanical thrombolysis (table 3). Age as a continuous variable was also an in-

Table 1. Baseline data of 567 patients treated by IAT from 2000 to October 2009

Demographic and clinical characteristics	Patients <80 years (n = 524)	Patients ≥80 years (n = 43)	p value
Mean age, years (SD)	62 (13)	82 (2)	
Female sex, n (%)	228 (27)	27 (63)	**0.015**
Vascular risk factors, n (%)			
Arterial hypertension	308 (59)	36 (84)	**0.001**
Smoking	126 (24)	1 (2)	**0.001**
Diabetes mellitus	73 (14)	9 (21)	0.212
Hypercholesterolemia	262 (50)	22 (51)	0.912
Coronary artery disease	89 (17)	13 (30)	**0.03**
Atrial fibrillation, n (%)	150 (29)	19 (46)	**0.018**
Prior stroke/TIA, n (%)	92 (18)	10 (23)	0.353
Mean NIHSS at admission, median (range)	15 (2–36)	17 (3–36)	0.306
Antithrombotic treatment at baseline, n (%)	170 (32)	19 (44)	0.130
Antiplatelets	131 (30)	18 (42)	**0.016**
Anticoagulants	29 (6)	1 (2)	0.366
Antiplatelets/anticoagulants	10 (2)	0 (0)	0.361
Etiology, n (%)			
Cardioembolic	234 (45)	18 (42)	0.723
Large artery disease	90 (17)	8 (19)	0.812
Small artery disease	1 (<1)	0 (0)	0.774
Other defined etiology	61 (12)	5 (12)	0.998
Unknown etiology	138 (26)	12 (28)	0.858
Site of vessel occlusion, n (%)			
Extracranial ICA	60 (11)	5 (12)	0.713
Intracranial ICA	71 (14)	2 (5)	0.089
Intracranial and extracranial ICA	20 (4)	2 (5)	0.142
Middle cerebral artery	299 (57)	31 (72)	0.055
M1 segment	199 (38)	22 (51)	0.088
M2 segment	66 (13)	8 (19)	0.261
M3/4 segment	34 (6)	1 (2)	0.276
Anterior cerebral artery	6 (1)	0 (0)	0.565
A1 segment	2 (0.5)	0 (0)	0.685
A2 segment	2 (0.5)	0 (0)	0.685
Posterior cerebral artery	9 (2)	0 (0)	0.386
P1 segment	5 (1)	0 (0)	0.520
P2 segment	4 (1)	0 (0)	0.565
Vertebrobasilar arteries	81 (15)	5 (12)	0.501

SD = Standard deviation; TIA = transient ischemic attack; ICA = internal carotid artery.

dependent predictor of mortality along with NIHSS at admission, symptomatic ICH, poor collaterals on cerebral angiography and time from symptom onset (table 4).

Frequencies of hemorrhagic complications are shown in table 5. The rates of symptomatic ICH were similar in both groups. Fatal symptomatic ICH occurred in 1 patient from the older group and in 24 patients from the younger group. Nine symptomatic ICH survivors from the younger group had a nonfavorable outcome (mRS >2).

Discussion

The growing proportion of octogenarians among the potential candidates for thrombolysis creates medical-ethical dilemmas. Very old patients have been underrepresented in randomized controlled trials (RCTs) on thrombolysis, thus narrowing the basis for evidence-driven decisions [22–25]. On the one hand, it appears reasonable that thrombolysis, which has proved to be efficacious in younger stroke patients, would also work for oc-

Table 2. Treatment variables of IAT in 567 patients

Variable	Patients <80 years (n = 524)	Patients ≥80 years (n = 43)	p value
General anesthesia, n (%)	199 (38)	17 (40)	0.840
Mean time ± SD from symptom onset to start of IAT, min	295 ± 107	317 ± 194	0.973
Start of treatment >6 h from symptom onset, n (%)	79 (15)	9 (21)	0.308
Start of treatment 6–8 h from symptom onset	65 (12)	8 (19)	0.444
Start of treatment >8 h from symptom onset	14 (3)	1 (2)	0.892
Treatment regimen, n (%)			
Intra-arterial urokinase only	278 (54)	24 (56)	0.927
Urokinase with mechanical recanalization techniques	159 (30)	15 (35)	0.535
Mechanical recanalization alone	75 (14)	4 (9)	0.782
Combined intravenous thrombolysis/IAT (tPA and urokinase)	12 (2)	0 (0)	0.316
Good collateral status, n (%)	408 (78)	31 (72)	0.345

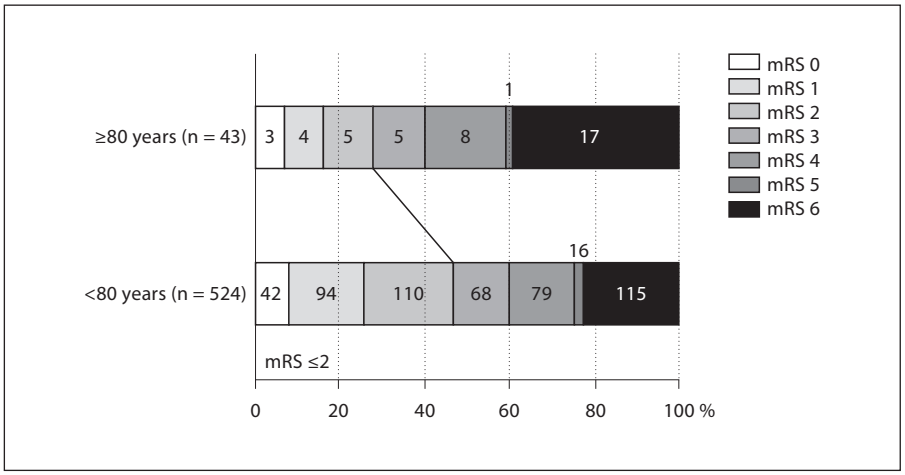

Fig. 1. Three-month outcome of patients ≥80 years in comparison to patients <80 years. The figures in the bar indicate the number of patients with a given mRS at the 3-month follow-up. Patients <80 years achieved more frequently a favorable outcome (mRS 0–2) than octogenarians (p = 0.019).

togenarians. The fact that clinical outcome in the elderly is rather poor without thrombolysis [11, 26, 27] has motivated its use in selected patients [5, 8–13]. On the other hand, thrombolysis has the potential to do harm because of ICH. Treatment decisions are even more difficult, when the uncertain benefit-risk ratio is balanced against the rising health care expenditures for the aged.

Until evidence from RCTs is available, comparisons with younger patients may provide the basis for realistic expectations in both patients and physicians.

In this large series, there was no difference in the recanalization and ICH rates between octogenarians and younger patients. In octogenarians, the proportion of patients with good functional outcome was lower and mortality rate was higher than in their younger counterparts.

Recanalization rates (TIMI 2–3) in our study are in line with the results of the PROACT II trial and several previous IAT case series [12, 13, 28]. Four studies have specifically examined recanalization in the very old. They reported recanalization rates of 62–79% in patients aged ≥80 years, which is in line with the results of our study [12–15]. Contrary to the results of Qureshi et al. [14], the recanalization rates did not differ between octogenarians and younger patients in the series of Kim et al. [12], Pundik et al. [13] and Mazighi et al. [15], which is in accordance with our findings.

Exclusion of very old patients from some large RCTs was mainly based on concerns regarding symptomatic ICH. Cerebral amyloid angiopathy, leukoaraiosis or impaired ability to clear the thrombolytic agents are considered risk factors that are very common among the

Table 3. Multivariate predictors of a nonfavorable outcome (mRS >2) at 3 months with age as a continuous variable

	Odds ratio	95% CI	p value
Age (per year)	1.032	1.015–1.049	0.000
NIHSS at admission	1.121	1.083–1.161	0.000
Time from symptom onset to treatment	1.002	1.000–1.004	0.027
Asymptomatic ICH	1.692	1.003–2.853	0.004
Symptomatic ICH	exp(21.301)	exp(20.838)–exp(21.807)[a]	0.001[a]
Diabetes mellitus	3.037	1.638–5.630	0.000
Mechanical thrombolysis	2.156	1.399–3.320	0.000

[a] Bootstrap 95% confidence interval (CI) and p value based on 1,000 samples (there was not a single good outcome for patients with symptomatic ICH).

Table 4. Multivariate predictors of death at 3 months with age as a continuous variable

	Odds ratio	95% CI	p value
Age (per year)	1.067	1.043–1.092	0.000
NIHSS at admission	1.100	1.063–1.130	0.000
Time from symptom onset to treatment	1.003	1.001–1.005	0.015
Symptomatic ICH	18.555	7.040–48.900	0.000
Poor collaterals on angiography	0.634	0.450–0.893	0.009

Table 5. Frequency of hemorrhage after IAT in 567 patients

	Patients <80 years (n = 524)	Patients ≥80 years (n = 43)	p value
ICH, n (%)	129 (25)	11 (26)	0.680
Asymptomatic ICH	98 (19)	10 (23)	0.720
Symptomatic ICH	33 (6)	1 (2)	0.292
Systemic hemorrhage, n (%)	5 (1)	1 (2)	0.398

elderly [29, 30]. Nevertheless, two systematic reviews of patients who were treated with intravenous thrombolysis showed similar rates of symptomatic ICH in octogenarians and in younger patients [9, 31]. Similarly, the risk of asymptomatic ICH after intravenous thrombolysis was not increased by advancing age in other studies [8, 10, 11, 13]. Little is known about the safety of IAT in octogenarians. In our series, the frequency of both symptomatic and asymptomatic ICH did not differ between octogenarians and younger patients. This is consistent with the results of Kim et al. [12] and Qureshi et al. [14], who found similar ICH rates in octogenarians and in younger patients. Quite the opposite, Mazighi et al. [15] found an increased rate of asymptomatic but not symptomatic ICH in patients ≥80 years treated by an intravenous thrombolysis-IAT approach in comparison to patients <80 years. Furthermore, the risk of ICH was not influenced by age in the PROACT II trial, though this study was not designed to specifically examine patients ≥80 years [28]. Other studies found NIHSS score, platelet count, serum glucose levels on admission, time to recanalization, but not age to predict hemorrhage following IAT [32, 33].

In our series, favorable outcome at 3 months was less frequent in octogenarians than in younger patients (28 vs. 46%). Furthermore, mortality rate was higher in patients aged ≥80 years. Our results corroborate the findings of previous studies assessing the efficacy of IAT [12, 14, 15] and intravenous thrombolysis [5, 8–11, 13] for the treatment of AIS in octogenarians. These studies emphasize the importance of age as a strong independent predictor of clinical outcome after ischemic stroke.

Stroke mortality rates increase with advancing age due to significant comorbidity in older patients [4, 34]. In our study, octogenarians suffered more often from hypertension, atrial fibrillation and coronary artery disease than younger patients. The European BIOMED study included 1,358 stroke patients aged 80 years and older. The 45% mortality rates reported in this nonthrombolysis study are similar to the 40% mortality in our series [6]. Data from the Virtual International Stroke Trials Archives and the SITS-ISTR (Safe Implementation of Treatment in Stroke – International Stroke Thrombolysis Registry) showed no excess in mortality when octogenarians receiving intravenous thrombolysis were compared with nonthrombolyzed patients of the same age. Furthermore, age was associated with poorer outcome but the association between thrombolysis treatment and improved outcome was maintained in very elderly people [11].

Our study has several limitations. The decision to perform IAT was at the discretion of the treating physician and selection bias cannot be ruled out. The higher prevalence of vascular risk factors and comorbidities might have obscured the effect of thrombolysis in

octogenarians. Furthermore, the use of general anesthesia in 40% of the octogenarians might have contributed to a worse outcome because general anesthesia in the elderly is generally associated with more complications due to the higher prevalence of comorbidities. The results regarding bleeding complications must also be interpreted with caution because of the relatively small sample size of octogenarians in our study. Only 1 patient among the very elderly suffered a symptomatic ICH. Furthermore, 15.5% of our patients were treated beyond the 6-hour window, and 2.6% even beyond the 8-hour window, hence the results cannot be strictly compared to trials where all patients were treated within the predefined time window. The treatment approaches that we used were somewhat heterogeneous, especially for mechanical thrombectomy devices, although they did not differ between the groups.

In conclusion, compared with younger patients, octogenarians did not have an increased risk of symptomatic ICH after IAT. Although a favorable outcome was less frequent and mortality rates were higher, IAT appeared to be safe in the very elderly. There is an urgent need to include octogenarians in RCTs. However, as long as results of such trials are lacking, IAT should be considered as a treatment option for appropriately selected older patients with AIS.

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