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ORIGINAL

The Italian Study of Pharmacological Treatment of Acute Stroke in the Elderly (SPASE)-I Group*

SPASE-I: a multicenter observational study on pharmacological treatment of acute stroke in the elderly

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Abstract We investigated the clinical outcome and current therapeutic management of ischemic stroke in elderly patients in different neurological wards throughout Italy. Twelve centers in 10 Italian regions were involved. The clinical and instrumental data were prospectively collected for 335 patients 65 years or older, presenting in a 12-month period. At the multivariate analysis, death was associated with the presence of total anterior circulation infarct and the use of antiedema agents. Stroke-related disability was related to female sex, unified stroke scale (USS) scores at entry and mini-mental state examination (MMSE) scores at the 1-month follow-up. The majority of patients (70%) received antiplatelets to prevent stroke recurrence. Very elderly (≥80 years) patients had worse presentation and prognosis than less elderly stroke victims (<80 years). Age played an important role in the therapeutic approach to stroke: while antiplatelets were widely used, oral anticoagulants were underused even when specifically indicated.

Key words Elderly • Stroke outcome • Therapy

M. Altieri (✉)
Department of Neurology
La Sapienza University of Rome
Viale dell'Università 30, I-00185 Rome, Italy

*Members listed at end of paper

Introduction

The life expectancy in developed countries has risen so dramatically over recent decades that more than a quarter of people over the age of 65 years can now expect to live until they are 90 [1]. Since Italy has one of the lowest birth rates in the world and one of the longest life expectancies, the proportion of elderly people in the population is quickly increasing. The prevalence rate of stroke among people aged 65–84 years is about 6%, and is expected to increase rapidly [2]. A major target of medical research during the last years has thus been disease prevention and health care in elderly subjects.

The aim of our study was to investigate current clinical and therapeutic management of cerebral ischemia in elderly patients in different neurological wards throughout Italy. In particular, we investigated whether age per se influenced the therapeutic approach to acute stroke in the very old (≥80 years) to limit the direct effects of cerebral ischemia, to control risk factors and to prevent stroke recurrences.

Patients and methods

Study of Pharmacological Treatment of Acute Stroke in the Elderly (SPASE)-I is an observational multicenter study on pharmacological treatment of acute stroke in people aged 65 years or more. The study involved 12 centers in 10 Italian regions: Piedmont, Veneto, Friuli Venezia Giulia, Abruzzo, Marches, Tuscany, Umbria, Latium, Campania, and Sicily. The study's population base consisted of those patients aged 65 years or more presenting with ischemic stroke at the 12 participating centers during the 1-year period between January 1998 and December 1998.

After an initial workshop of the study investigators, stroke-specific questionnaires were prepared, and information was collected prospectively by the co-ordinating center (Rome) and entered into a computerized database. Patients were evaluated during the acute phase and 1 month after stroke.

Medical history concerning the following risk factors and pre-stroke health status was obtained: age, gender, body temperature at

admission, history of arterial hypertension, atrial fibrillation (AF), smoking habit, alcohol consumption, dyslipidemia, diabetes mellitus and previous strokes or transient ischemic attacks (TIA). At entry, neurological status was assessed by means of the unified stroke scale (USS) [3] and stroke was classified according to the Oxford criteria [4].

All patients underwent computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, duplex sonognaphy of neck vessels, while echocardiography was performed on patients in whom medical history and physical examination findings were considered insufficient to rule out an underlying heart disease.

Stroke outcome at 1 month was evaluated by means of USS [3] and the Barthel Index (BI) [5]. Patients were considered to have a bad outcome if the BI score was <75 [6]. Cognitive performance at discharge was assessed by means of the mini mental state examination (MMSE) [7]. A MMSE score of <24 indicated cognitive impairment [8].

Pharmacological treatment during hospitalization was classified as follows: antithrombotics (antiplatelets, anticoagulants), brain antiedema agents, antihypertensives, hypoglycemic drugs and antibiotics.

Statistical analyses

Clinical features and therapeutic approach to stroke patients aged 80 years and over were compared with those of patients less than 80 years.

The differences in the frequency of categorical variables were analyzed using the χ^2 test and crude odds ratios (ORs) with 95% confidence intervals (CIs). Student's *t*-test for independent samples was used for continuous variables.

Linear regression analysis was performed for continuous variables. Stepwise forward logistic models were used to evaluate the independent contribution of variables with a p value of <0.05. The statistical analysis was divided into two phases. In the first phase, logistic regression analysis was performed to identify the best independent predictors of death and clinical outcome in three different models. The first model assessed the contribution of vascular risk factors, the second model that of clinical variables, and the third model the use of drugs. In the second phase, the variables with a p value <0.05 were included in a general model. Moreover, multiple linear regression analysis was performed on continuous variables with the same two-phase approach to identify the best predictors of death and outcome at discharge. All analyses were performed using STATA software (release 4.0, College Station, Texas).

Results

During the 12-month study period, 359 patients met the study's entry criteria. Of these, 24 patients were excluded because of incomplete data. Therefore, there were 335 patients available for study. Overall, the patients had a mean age of 79 ± 7 years (range, 65–98 years); 173 (52%) of the patients were female.

The patients were then stratified into two groups according to age: ≤80 years and >80 years (Table 1). The mean age in the younger group was 72.6±4.2 years, while that of the older group was 85.7±3.7 years. In the older group of stroke patients, 65.6% were female, whereas there was a male predominance (64.5%) in the younger groups (p<0.001). The prevalences of a history of hypertension, dyslipidemia, diabetes and previous stroke or TIA were similar in the two age groups (Table 1). Alcohol intake was more frequent among patients <80 years, but the difference did not reach statistical significance. The proportion of patients who had a history of AF was significantly higher in the older group of patients (p<0.05). Conversely, younger patients were more frequently smokers (p<0.001).

On admission, a total anterior circulation infarct (TACI) was more frequent in the older group of patients (p<0.001), while a posterior circulation infarct (POCI) was more common in the younger patients (p<0.05, Table 1). Mean USS

Table 1 Prevalence of risks factors and clinical characteristics of the 355 patients with ischemic stroke at admission, by age group. Values are numbers (percentages) of patients in each group, unless otherwise indicated

	<80 years (n=155)	≥80 years (n=180)	*p* value
Risk factor			
Female gender	55 (35.5)	118 (65.6)	<0.001
Hypertension	(59.1)	112 (62.2)	NS
Atrial fibrillation	37 (23.9)	69 (38.3)	<0.05
Smoking habit	(37.7)	21 (11.7)	<0.001
Alcohol consumption	(18.2)	20 (11.1)	NS
Dyslipidemia	81 (45.0)	48 (26.7)	NS
Diabetes	(26.3)	(23.6)	NS
Previous stroke or TIA	102 (65.9)	126 (70.0)	NS
Clinical characteristics			
TACI	7 (4.6)	34 (19)	<0.001
POCI	22 (14.6)	12 (6.8)	<0.05
USS score[a]	20.8 (8.4)	15.5 (9.2)	<0.001
Fever	9 (5.8)	13 (7.2)	NS

[a] Values are means (SD)

TIA, transient ischemic attack; *NS*, not significant; *TACI*, total anterior circulation infarct; *POCI*, posterior circulation infarct; *USS*, unified stroke scale

scores at entry were 15.4±9.2 in patients ≥80 years, and 20.8±8.4 in younger patients ($p<0.001$). Fever on admission was observed more frequently in the older group of patients, although this difference did not reach statistical significance.

During hospitalization the majority of patients (70.0%) received antiplatelet agents to prevent recurrence of stroke, while 10.1% received oral anticoagulants. No antithrombolic therapy was administered in 20.0% of patients, the majority of whom were aged ≥ 80 years ($p<0.05$). Among the 106 patients with AF, only 23 (21.7%) received oral anticoagulants, with no statistically significant difference between age groups. To prevent deep venous thrombosis, 39.6% of patients received subcutaneous heparin at a dosage of 5000 IU every 12 hours.

The group of older patients more frequently received antibiotics and antiedema agents, while younger patients more frequently received anticoagulants and antihypertensive drugs (Table 2). No statistically significance was found between the two groups with respect to hypoglycemic drugs and antiplatelets.

The 30-day case fatality rate was 29.8% in patients ≥ 80 years and 7.3% in patients ≥80 years ($p<0.001$). Mortality in the older group of patients was significantly higher among patients who had had previous TIA or strokes (35.2% vs. 6.2%; $p<0.001$).

At the 1-month follow-up, the mean USS score was 21.8±8.6 among patients ≥80 years, and 24.9±7.5 among patients <80 years ($p=0.001$), while the BI score was 47.6±34.3 in the older group of patients, and 65.3±34.0 in the younger patients. Overall, more than twice as many younger patients had a good outcome, defined as BI >75 (48.6% vs. 23.2%; $p<0.001$). On the MMSE, which was performed only in 174 patients, younger patients showed significantly higher scores 17.4±11.2 vs. 9.3±10.2, $p<0.001$). Patients who did not undergo MMSE evaluation were older ($p<0.001$), presented a more severe outcome ($p<0.001$) and a higher rate of early death ($p<0.001$) in comparison with those who underwent this evaluation.

Independent predictors of death and disability at 1 month were analysed using multivariate models (Tables 3, 4).

Discussion

This study was observational, non-interventional and designed to facilitate recruitment not specifically within a "trial-sponsored" framework, in order to obtain a picture of the current situation in Italian stroke wards.

There were significant differences between very old and younger patients in the risk factor profile and stroke severity, both at onset and during hospitalization. In terms of outcome, advanced age in the univariate analysis was associated with a higher in-hospital case-fatality rate. Moreover, older patients were more disabled 1 month after stroke.

Table 2 Drugs administered during hospitalization, according to age group

Drug administered	<80 years (n=155)	≥80 years (n=180)	*p* value
Antiplatelet agents	112 (73.2)	123 (68.3)	NS
Oral anticoagulants	21 (13.7)	13 (7.2)	0.05
Subcutaneous heparin	37 (24.2)	53 (29.4)	NS
Antibiotics	41 (26.8)	80 (44.4)	<0.001
Hypoglycemic drugs	40 (26.1)	38 (21.1)	NS
Antihypertensive drugs	76 (49.7)	63 (35.0)	<0.05
Antiedema agents	48 (29.4)	80 (44.4)	<0.05

Table 3 Predictors of death at discharge: logistic regression alalysis with stepwise selection of variables

Variable	OR	95% CI	*p* value
Age	11.3	0.21–581	NS
Atrial fibrillation	2.53	0.54–11.7	NS
USS score at entry	0.96	0.87–1	NS
MMSE score at 1 month	0.6	0.14–2.53	NS
TACI	14.7	2.4–91.2	<0.05
Antibiotics	5.4	0.9–33	NS
Antiedema agents	8.4	1.3–55.5	<0.05
Antihypertensive drugs	0.03	0.003–0.3	<0.05

USS, unified stroke scale; *MMSE*, mini-mental state examination; *TACI*, total anterior circulation infarct

Table 4 Predictors of disability at discharge, evaluated by the Barthel index score: multiple linear regression analysis with stepwise selection of variables

Variable	B	SE	*p* value
Age	0.31	0.40	NS
Female gender	8.11	3.22	<0.05
USS score at entry	2.30	0.23	<0.001
MMSE score at 1 month	0.56	0.17	<0.001
Right hemispheric infarction	-7.11	3.15	<0.05
Antibiotics	-7.88	4.01	<0.05
Antiedema agents	7.85	4.04	NS
Antihypertensive drugs	1.64	3.11	NS

B, slope of the regression line; *SE*, standard error of the B coefficient

However, age did not have an independent significant influence on stroke-related disability and mortality when severity of stroke was also considered. This finding suggests that, regardless of the age of patients, the influence of the initial severity of stroke, and in particular the presence of a major dominant hemispheric stroke syndrome, was so great that the independent influence of age per se disappeared in the logistic regression model when these factors were considered. This observation also applies to the independent influence of antiedema agents on death. Unfortunately, as the range of CIs in our study was very wide, this finding should be interpreted with caution even if it is in accordance with previous studies [2, 9].

Age might negatively influence stroke outcome by acting as a “cofactor”. In fact very old patients have, when compared with younger ones, poorer daily living activity functions before stroke, lower motivation to recover and a higher comorbidity [10]. In this regard, Asplund et al. [11] argued that very high age per se has little impact on short-term survival. Therefore, clinical decision-making in very old patients with stroke should be based on the same prognostic indicators as in younger stroke patients.

This does not seem to be the current attitude in the therapeutic management of elderly patients. The high percentage of very old patients who did not receive any antithrombotic treatment probably reflects the reluctance of the physician of using potentially dangerous medication in this group of patients. This view is supported by the extremely low use of anticoagulants in patients over 80 years of age in our study.

AF probably provides the best example of physicians’ unwillingness to use anticoagulation in elderly people. Several randomized controlled studies have shown that oral anticoagulants reduce the overall risk of stroke in patients with AF by 68% without significantly raising the rate of hemorrhagic complications [12–15]. Nevertheless, many recent retrospective analyses have reported that anticoagulation is underused in patients with AF in clinical practice, and this is even more evident in the very old [16–21]. Cohen et al. [19] found that only 37.2% of patients with AF aged 80 years or over received warfarin. In our study, this percentage was even lower (21.7%). This is in complete disagreement with data in the literature indicating that the risk of embolic events increases considerably in patients who are > 75 years old or have other vascular risk factors such as a recent TIA or stroke, hypertension and diabetes [12, 21]. This discrepancy can be ascribed to both physician and patient factors [19–20, 22]. In our study, the low number of patients treated with anticoagulants seems to be mainly physician-related, and may reflect either an underestimation of the magnitude of the relative risk reduction achievable by risk factor management [14], or the belief that prevention in the very old is more dangerous than the risk of stroke recurrence itself. In fact, prevention of further events in severe acute stroke might be seen as a secondary and remote problem. By contrast, we underline that in our study mortality was significantly higher among patients who had suffered from previous cerebrovascular events. Moreover, this underuse might reflect the fact that whether or not these drugs increase the bleeding risk in this subgroup of patients remains a matter of debate. In this regard, the influence of well-known authors on this scarce utilization of anticoagulation should not be underestimated, if not co-agreed [23–25]. Patient-related factors may include individual preferences regarding treatment options and various cultural, intellectual and technical inconveniences associated with frequent visits to the clinic [21, 26].

Unfortunately, in this study, a low number of patients underwent MMSE. This may have affected the precision of our estimates, although probably not sufficiently to distort the trends of differences observed between the two age groups. Since the incidence of cognitive decline is known to increase with age, the high frequency of low MMSE scores might be related to the age of our patients. Furthermore, it is possible that some of our patients were already cognitively impaired before the stroke or that the MMSE was performed too soon after the stroke, when the "acute" effects of the ischemic lesion were still present. According to previous studies, cognitive impairment was independently related to severe disability [27, 28].

In conclusion, our data confirm that very elderly people have a worse presentation and prognosis than less elderly old stroke victims. However, outcome is influenced more by the neurological status at entry than by age itself. On the other hand, age seems to play an important role in the therapeutic approach to stroke. The therapy of choice to prevent stroke recurrence in the very old is antiplatelet agents, while anticoagulants are underused even when a specific and well-known risk factor for stroke recurrence, such as AF, is present.

Sommario *SPASE-I è uno studio osservazionale multicentrico italiano volto ad investigare l'outcome ed il trattamento farmacologico dell'ictus acuto nei pazienti anziani (>65 anni) affetti da ischemia cerebrale. Lo studio ha coinvolto 12 centri neurologici uniformemente distribuiti nel territorio italiano; per ciascun paziente sono stati raccolti dati anamnestici e clinici secondo una procedura standardizzata. Nel periodo di un anno sono stati reclutati 335 pazienti. All'analisi multivariata la mortalità risultava essere significativamente associata con la presenza di un infarto totale della circolazione anteriore (TACI) e l'uso di agenti antiedemigeni durante il ricovero. La disabilità era invece correlata con il sesso femminile, un basso punteggio alla unified stroke scale (USS) all'ingresso, ed alla mini-mental state examination (MMSE) dopo 1 mese. Durante il ricovero il 70% dei pazienti è stato trattato con farmaci antiaggreganti mentre gli anticoagulanti sono stati scarsamente utilizzati.*

SPASE-I investigators and committee members

Chairman, G.L. Lenzi, Department of Neurology, La Sapienza University of Rome, Rome, Italy

Steering committee, V. Di Piero, M. Altieri, N. Vanacore, Department of Neurology, La Sapienza University of Rome, Rome, Italy

Study participants, R. Bella, G. Pennisi, Department of Neurological Sciences, University of Catania; G. Orlandi, L. Murri, Department of Neurological Sciences, University of Pisa; M. Baldassarre, C. Marini, A. Carolei, Department of Neurology, University of L'Aquila; G. Cardaioli, V. Gallai, Department of Neurological Sciences, University of Perugia; L. De Zanche, M. Turrin, Monselice Hospital, Monselice (PD); R. Manara, G. Meneghetti, Department of Neurological Sciences, University of Padua; G. Carlucci, D. Inzitari, Department of Neurological and Psychiatric Sciences, University of Florence; F. Chiodograndi, Stroke Unit, Neurological Clinic Ospedale Maggiore, Trieste; G. Lagalla, L. Provinciali, Neurorehabilitation Clinic, Department of Neurological and Motor Sciences, Umberto I Hospital, Ancona; R. Mutani, Department of Neurology, University of Turin, Turin; L. Lavorgna, P.B. Carrieri, Department of Neurological Sciences, Federico II University of Naples, Italy.

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