LONG-TERM EVALUATION OF NEUROLOGICAL IMPAIRMENT SCALES AFTER ISCHEMIC STROKE IN TYPE 2 DIABETIC CAUCASIANS

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Abstract

Background

Until now, there is no data regarding long-term predictive ability of stroke impairment scales in diabetic patients. The aim of this prospective study was to evaluate and compare National Institutes of Health Stroke Scale (NIHSS), Orpington Prognostic Scale (OPS), and Scandinavian Stroke Scale (SSS) in predicting outcome of type 2 diabetic patients after ischemic stroke.

Methods

Two-hundred and eighty-eight diabetic patients with ischemic stroke comprised the study population. Baseline neurological evaluation was performed on admission using the NIHSS, OPS and SSS. End points were recurrence of stroke or death within the year following the initial attack.

Results:

Significant correlation between NIHSS and OPS ($r=0.89$, $p<0.001$), between NIHSS and SSS ($r=-0.92$, $p<0.001$) and between OPS and SSS ($r=-0.9$, $p<0.001$) was

observed. Baseline NIHSS (OR=1.14, $p=0.032$), SSS (OR=0.88, $p=0.009$) and OPS (OR=2.46, $p=0.012$) were identified as significant predictors of recurrence of stroke or death after major cardiovascular disease risk adjustment such as tobacco smoking, obesity, history of hypertension and atrial fibrillation. Major strokes as defined by OPS (OR=31.6, $p<0.001$) and NIHSS (OR=28.1, $p<0.001$) predicted significantly recurrence of stroke or death 12 months following the initial episode.

Conclusions:

Baseline NIHSS, SSS and OPS are significant predictors of recurrence of stroke or death within the year following the initial attack after adjustment for major cardiovascular disease risk factors. OPS severity index might represent the most accurate tool in identifying long-term prognosis of ischemic stroke diabetic Caucasian patients.

Introduction

Stroke is a leading cause of long-term disability in the developed countries. In the United States approximately 795,000 people annually experience a new or recurrent stroke (RS), out of which 135,000 are fatal

(1), while self-sufficiency is preserved only in 26% of survivors (2). Additionally, of all annual strokes approximately 610,000 are first attacks, whereas 185,000 are recurrent episodes (3).

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Diabetes is an independent risk factor for ischemic stroke (IS) (4). Studies have shown that diabetes doubles the risk of a new episode and worsens the prognosis in stroke patients (5,6). Additionally, stress hyperglycemia belongs to the impaired glucose tolerance disorders commonly seen after acute stroke and is associated with worse functional outcome in non-diabetic stroke patients (7).

Recording the neurological disabilities of IS patients is time consuming and challenging for the clinician. Therefore, impairment stroke scales have been developed to evaluate the neurologic status, the severity, and the short-term functional outcome of stroke patients. The National Institutes of Health Stroke Scale (NIHSS), the Orpington Prognostic Scale (OPS) and the Scandinavian Stroke Scale (SSS) are commonly used scales available for clinical practice and research (8-10). The NIHSS comprises a 13-item assessment of neurological function including level of consciousness, language, neglect, visual-field loss, extraocular movements, motor strength, ataxia, dysarthria, and sensory loss. Its scores range from 0 to 42 (0 indicates patient with no neurological deficits and 42 a fully impaired patient). OPS's score of motor deficit in arms, proprioception, balance, and cognition, ranges from 1.6 to 6.8 (1.6 represents a fully independent patient in physical functioning and 6.8 a severely deficient patient), while SSS assesses consciousness, extraocular movement, motor strength, orientation, dysarthria, sensory loss and balance. Its scores range from 58 indicating no mental or functional impairment, to 0 indicating full neurological injuries.

Until now, there is no data regarding long-term predictive ability of impairment scales in IS diabetic patients. Therefore, the aim of the present study was to evaluate the relationship between these stroke scales and compare their ability to predict RS or death within 12 months following the initial episode of stroke in diabetic patients.

Materials and methods

This single center, prospective study was conducted in a 480-bed tertiary hospital with 32,000 admissions annually. The study population consisted of 383 consecutive type 2 diabetic Caucasian patients with primary IS who were admitted between January 2008 and September 2010. The research protocol was approved by the hospital's ethics committee, while participation to the study was voluntary and all patients or next of kin gave informed consent.

In our study, acute stroke and its recurrence was defined according to the World Health Organization

criteria as "of rapid onset and of vascular origin reflecting a focal disturbance of cerebral function, excluding isolated impairments of higher function and persisting longer than 24 hours" and were confirmed by a brain computed tomography (CT) (11). Categorization of IS subtypes was made according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) which includes five categories: 1) large-artery atherosclerosis, 2) cardioembolism, 3) small-artery occlusion (lacune), 4) stroke of other determined etiology and 5) stroke of undetermined etiology (12). All patients underwent thorough diagnostic evaluation including complete medical history for cardiovascular disease (CVD) such as tobacco smoking, obesity, history of hypertension or atrial fibrillation, clinical characteristics and subtype of the stroke, full blood count and blood biochemistry, electrocardiography, brain CT and, in selected patients, spinal tap with cerebrospinal fluid analysis. Comatose patients, patients with hemorrhagic stroke, tumors, or other conditions mimicking at presentation thrombotic stroke or transient ischemic attacks (TIA) were excluded from the study (Fig. 1).

Baseline NIHSS, SSS, and OPS were recorded in each patient by 2 specialists independently at admission and were assessed again after 24 hours in order to exclude TIA and to reconfirm the scores. Their performance was externally certified blindly to allocation by another examiner. It was important to define that stroke severity will not progress after 24 hours and will be similar to its onset. For this reason all patients with onset symptoms more than 6 hours to their examination were excluded from the study. Minor stroke was defined as NIHSS ≤ 13 or SSS > 25 , while major stroke

Figure 1. Inclusion and exclusion study criteria of the study.

Figure 2. Matrix scatter chart between baseline NIH stroke scale, baseline SSS and baseline OPS. Linear relationship between baseline measurement of scales is highlighted by the diagonal straight line, indicating strong correlation ($r \geq 0.80$ or $r \leq -0.80$). *NIHSS = National Institutes of Health Stroke Scale, †SSS = Scandinavian Stroke Scale, ‡OPS = Orpington Prognostic Scale.

as NIHSS > 13 or SSS ≤ 25. According to the OPS, IS was defined as minor with a score < 3.2, as moderate with a score 3.2 to 5.2, and as major with a score > 5.2 (13–15). All stroke scales were evaluated for their ability to predict the end-points of our study which were RS or death due to any cause within one year following the initial attack.

Severity adjustment for diabetes was made by excluding patients with long-term complications due to diabetes as retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joints; and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction. In our patients, glycosylated hemoglobin (HbA1c) was tested every 3 months and a value below the upper limit of normal local equivalent of 6.5% for a Diabetes Control and Complications Trial–traceable assay was required in order to ensure optimal post-stroke recovery. For the same reason, treatment with antihypertensive, antilipidemic and antiplatelet agents were also monitored. At a 3 month-interval, the patients were reevaluated for survival or recurrence of stroke confirmed by brain CT. Surviving patients were examined clinically and plasma HbA1c was measured in order to ensure acceptable diabetes control during recovery. Of the 383 diabetic IS patients that were evaluated, 63 were excluded due to abnormal diabetes control, 18 due to late arrival to the hospital and 14 due to incomplete follow-up. Also,

patients not able to be contacted in these time intervals were categorized as lost to follow up.

Descriptive statistics were used to analyze demographics, medical history, prior functional status, stroke characteristics, neurological scores, severity of impairment and outcome. Values were expressed as means ± the standard deviation (continuous variables) or as percentages of the group from which they were derived (categorical variables). Continuous variables were compared by the Student t-test. Categorical variables were evaluated by the Pearson Chi-Square test or Fisher's exact test as appropriate. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of any association that emerged. Evaluation of the linear relationship between NIHSS, OPS and SSS was calculated using Spearman's rank correlation coefficient. Logistic regression analysis was conducted in order to identify how accurately the neurological scales predict new IS or death. Scales were assessed in a continuous manner. Although the sum of OPS list item is ordinal in nature, it has been disputed that in some cases ordinal-level data may be treated as interval-level data without serious problem (16). The goodness of fit of the models was tested by Hosmer and Lemeshow test. Statistically significant values were considered for $p \leq 0.05$. Statistical analyses were performed with the SPSS statistical software (version 17; SPSS Inc., Chicago, IL)

Table 1. Baseline characteristics of the study population (n=288).

	n	%	Mean±SD
Age (years)			75.64 ± 7.38
Sex, male	135	46.9	
female	153	53.1	
Major CVD‡ risk			
Hypertension	238	82.6	
Obesity	43	14.9	
Tobacco smoking	50	17.4	
Atrial Fibrillation	42	14.6	
Glycemic indices			
Admission plasma glucose (mg/dl)			153.5 ± 41.9
Glycosylated Hemoglobin (%)			8.58 ± 1.68
Stroke subtype			
Large-artery atherosclerosis	37	12.8	
Cardioembolism	32	11.1	
Small-artery occlusion (lacune)	192	66.7	
Stroke of other determined etiology	10	3.5	
Stroke of undetermined etiology	17	5.9	
Impairment scales			
Baseline NIHSS£			15.2 ± 10.1
Baseline SSS†			32.1 ± 14.2
Baseline OPS‡			3.9 ± 1.4
Severity			
Baseline NIHSS£ > 13	119	41.3	
> 13	84	39.6	
Baseline SSS† ≤ 25	96	33.3	
Baseline OPS‡ > 5.2	81	28.1	

‡Cardiovascular Disease, £National Institutes of Health Stroke Scale, †Scandinavian Stroke Scale, ‡Orpington Prognostic Scale. Values were expressed as medians, mean ± the standard deviation (continuous variables) or as frequencies and percentages of the group from which they were derived (categorical variables).

Results

Two-hundred and eighty-eight IS diabetic patients, 135 (46.9%) males and 153 (53.1%) females, comprised the final study population. Mean values for NIHSS, SSS, and OPS were 15.2 ± 10.1, 32.1 ± 14.2 and 3.9 ± 1.4 respectively (Table 1). Twelve months after the initial stroke, 142 out of 288 (49.3%) IS diabetic patients, 70 (24.3%) men (OR=1.21 95% CI:0.76-1.92, p=0.417) and 72 (25%) women (OR=0.82 95% CI:0.51-1.31, p=0.471), suffered RS or died. In particular, RS occurred in 59 (20.5%) patients, 29 (10.1%) women (OR=0.81 95% CI:0.46-1.46, p=0.493) and 30 (10.4%) men (OR=1.22 95% CI:0.68-2.16, p=0.493), while 83 (28.8%) patients, 43 (14.9%) women (OR=0.92 95% CI:0.55-1.54, p=0.776) and 40 (13.9%) men (OR=1.07 95% CI:0.64-1.79, p=0.776) died.

Analysis of factors associated with study's end points within the 12 months following the initial episode did not show significantly gender outcome differences. Of all patients who suffered RS or died, 70 (49.3%) were males (OR=1.21, 95% CI: 0.76-1.92, p=0.417). Diabetic patients with history of hypertension (OR=3.36, 95% CI: 1.7-6.65, p<0.001) or atrial fibrillation (OR=2.99, 95% CI: 1.46-6.11, p=0.002) had significantly higher odds for RS or death, but there was no difference for obese (OR=1.36, 95% CI: 0.71-2.61, p=0.355) or patients that used to smoke tobacco (OR=1.68, 95% CI: 0.91-3.13, p=0.096). Patients with elevated admission plasma glucose (APG) (128.4 ± 29.8 / 179.2 ± 36.6, p<0.001) and HbA1c (8 ± 1.52 / 9.18 ± 1.64, p<0.001) had significantly higher frequencies of RS or death (Table 2).

Lacunar strokes were the commonest TOAST subtypes followed by large-artery atherosclerosis and

Table 2. Analysis of factors associated with recurrence of stroke or death within the 12 months following the initial attack.

Variables	No Recurrence of Stroke or Death	Recurrence of Stroke or Death	Odds Ratio	P Value
	n=146	n=142	(95% CI¶)	
Patient related				
Age (in years)	75.1 ± 8	76.1 ± 6.6	NA§	0.265
Male sex (%)	65 (48.1)	70 (51.9)	1.21 (0.76-1.92)	0.417
Major CVD£ risk				
Hypertension	109 (45.8)	129 (54.2)	3.36 (1.7-6.65)	<0.001
Obesity	19 (44.2)	24 (55.8)	1.36 (0.71-2.61)	0.355
Tobacco smoking	20 (40)	30 (60)	1.68 (0.91-3.13)	0.096
Atrial Fibrillation	12 (28.6)	30 (71.4)	2.99 (1.46-6.11)	0.002
Glycemic indices				
Admission Plasma Glucose (mg/dl)	128.4 ± 29.8	179.2 ± 36.6	NA§	<0.001
Glycosylated Hemoglobin (%)	8 ± 1.52	9.18 ± 1.64	NA§	<0.001
Stroke subtype				
Large-artery atherosclerosis n (%)	6 (16.2)	31 (83.3)	6.51 (2.62-16.17)	<0.001
Cardioembolism n (%)	15 (46.9)	17 (53.1)	1.18 (0.56-2.48)	0.647
Small-artery occlusion (lacunar) n (%)	108 (56.3)	84 (43.8)	0.51 (0.31-0.83)	0.008
Stroke of other determined etiology n (%)	8 (80)	2 (20)	0.24 (0.05-1.18)	0.059
Stroke of undetermined etiology n (%)	9 (52.9)	8 (47.1)	0.91 (0.34-2.42)	0.849
Impairment Scales (Mean±SD)				
Baseline NIHSS£	8 ± 4.7	22.7 ± 8.6	NA§	<0.001
Baseline SSS†	42.9 ± 7.1	20.8 ± 10.5	NA§	<0.001
Baseline OPS‡	2.8 ± 0.7	5.1 ± 1.1	NA§	<0.001
Severity of Ischemic Stroke n (%)				
Major (according to NIHSS£)	9 (7.6)	110 (92.4)	52.32 (23.96-114.25)	<0.001
Major (according to SSS†)	8 (8.3)	88 (91.7)	28.11 (12.76-61.88)	<0.001
Major (according to OPS‡)	2 (2.5)	79 (97.5)	90.28 (21.51-378.87)	<0.001

¥Cardiovascular Disease, £National Institutes of Health Stroke Scale, †Scandinavian Stroke Scale, ‡Orpington Prognostic Scale, §Non-Applicable, ¶Confidence interval.

Values were expressed as mean ± the standard deviation (continuous variables) or as n (%) of the variable from which they derived (categorical variables). Continuous variables were compared by the Student t test. Categorical variables were evaluated by using the Pearson Chi-Square test or Fisher's exact test as required.

cardioembolic strokes (Table 1). However, patients with large-artery atherosclerosis stroke had significantly higher odds (OR=6.51, 95% CI: 2.62-16.17, $p<0.001$) for RS or death than patients with lacunar stroke (OR=0.51, 95% CI: 0.31-0.83, $p=0.008$) (Table 2). As expected, higher scores on all stroke scales and major strokes were significantly associated with worse outcome. Interestingly, patients with major stroke according to OPS had higher odds ratio of RS or death (OR=90.28, CI:21.51-378.87) compared to the other stroke scale severity indices (Table 2). Analysis by Spearman's rank correlation coefficient indicated a statistically significant linear relationship between all three stroke scales which were strongly correlated and

agreed in the baseline neurological information (Fig. 2). There was significant correlation between NIHSS and OPS (NIHSS:15.2±10.1, OPS:3.9±1.4, $r=0.89$, $p<0.001$), between NIHSS and SSS (NIHSS:15.2±10.1, SSS:32.1±14.2, $r=-0.92$, $p<0.001$), and between OPS and SSS (OPS:3.9±1.4, SSS:32.1±14.2, $r=-0.9$, $p<0.001$), while NIHSS and SSS (NIHSS:15.2±10.1, SSS:32.1±14.2, $r=-0.92$, $p<0.001$) revealed the stronger correlation. Association of SSS with the other scales had a negative indicator, specifying an inverse correlation between them. Lower scores on the SSS scale were indicative of severe neurological deficits, whereas lower scores of NIHSS and OPS were indicative of less physical and mental impairments.

Table 3. Logistic regression analysis regarding the predictive ability of impairment scales and their severity indices after major CVD risk factor adjustment.

Variables	Odds Ratio	P Value	Variables	Odds Ratio	P Value
	(95% CI¶)			(95% CI¶)	
Impairment Scales			Severity of Ischemic Stroke n (%)		
Baseline NIHSS£	1.14 (1.01-1.28)	0.032	Major (according to NIHSS£)	28.18 (10.49-75.68)	<0.001
Baseline SSS†	0.88 (0.81-0.97)	0.009	Major (according to SSS†)	1.67 (0.51-5.47)	0.397
Baseline OPS‡	2.46 (1.21-4.99)	0.012	Major (according to OPS‡)	31.61 (6.44-155.04)	<0.001
Major CVD risk			Major CVD risk		
Hypertension	3.35 (0.71-15.67)	0.124	Hypertension	3 (0.9-9.95)	0.072
Obesity	2.59 (0.9-7.47)	0.078	Obesity	2.48 (0.93-6.61)	0.069
Tobacco smoking	1.55 (0.46-5.15)	0.475	Tobacco smoking	2.15 (0.78-5.95)	0.138
Atrial Fibrillation	2.12 (0.41-11.08)	0.373	Atrial Fibrillation	1.89 (0.39-8.98)	0.422

¥Cardiovascular Disease, £National Institutes of Health Stroke Scale, †Scandinavian Stroke Scale, ‡Orpington Prognostic Scale, ¶Confidence interval.

Binary logistic models were used in order to identify the significant predictors of RS or death within the 12 months following the initial stroke episode after major cardiovascular disease (CVD) risk adjustment, such as tobacco smoking, obesity, history of hypertension and atrial fibrillation. Baseline NIHSS (OR=1.14 95% CI:1.01-1.28, $p=0.032$), SSS (OR=0.88 95% CI:0.81-0.97, $p=0.009$) and OPS (OR=2.46 95% CI:1.21-4.94, $p=0.012$) could significantly predict RS or death. However, severity stroke index as defined by OPS (OR=31.61 95% CI:6.44-155.04, $p<0.001$) had a higher prognostic capacity followed by NIHSS (OR=28.18 95% CI:10.49-75.68, $p<0.001$), while SSS (OR=1.67 95% CI:0.51-5.47, $p=0.397$) severity index could not predict RS or death within the 12 months (Table 3).

Discussion

As diabetic patients constitute a high risk group for major cardiovascular events, early diagnosis of IS, accurate assessment of neurological symptoms, and timely therapeutic intervention may result in better prognosis (17). Although many issues have been raised over time regarding their adequacy (16-18), stroke impairment scales have been developed to support physician's diagnosis, prediction of recovery and early establishment of therapeutic goals. However, the ability of these scales to predict RS or death is challenging and difficult because diabetes influences negatively the time of post-stroke recovery.

NIHSS is recognized as one of the most consistent and valid tool of neurological impairment measurement in stroke (8), while various data support SSS to be a very reliable and consistent stroke scale (10,19-21), able to predict mortality in patients with mild ischaemic stroke (18). OPS is a simpler stroke neuro-

logical scale which has been documented as a potent instrument for stroke presentation (22), stroke severity categorization, and poor functional outcome (9,22). These scales were developed to evaluate neurological status, but their predictive value is focused primarily to short functional post-stroke outcome. A study by Muir et al. showed that baseline NIH Stroke Scale predicts 3-month outcomes in non-diabetic patients (15), while Kalra and Crome reported that OPS two weeks post-stroke is an indicator for the 14-week post-stroke activities of everyday living scores in elderly patients (23). In another study, Edwards et al. reported that SSS has great sensitivity and specificity in predicting 3 month term mortality, regardless the stroke mechanism (24).

In our study, we evaluated and compared NIHSS, SSS, and OPS regarding long term outcome of IS diabetic patients and found that all three impairment scales have significant prognostic value within the 12 months following the initial episode after major CVD risk factor adjustment. Despite that SSS revealed the stronger correlation with NIHSS, its severity index could not predict RS or death within 12 months in IS diabetic patients. One possible explanation is that NIHSS and SSS exhibit different cutoff values for determining severe stroke. On the other hand, OPS establishes closer focus and certainty on major strokes and, thus, it has a powerful hard-end point predictive ability. However, OPS includes less information in its standardized examined components in comparison with NIHSS and SSS, while it adds points to the final score in an ordinal but symmetric manner. It is focused equally at motor strength, proprioception, balance and cognition, neglecting extraocular movements, facial palsy and dysarthria. In addition, differences are observed

in the method of calculation as lower scores on SSS represent more severe deficits whereas lower scores on NIHSS and OPS are associated with less severe deficits. Nevertheless, despite their different calculation nature, all three stroke impairment scales show a common derivation and interception of structure because they are mainly structured for the evaluation of neurological condition and severity of the stroke during admission. It seems that the resemblance of a lot of standardized assessments between NIHSS and SSS had as consequence their equivalent predictive ability. Their detailed and solid tasks in relation to OPS seem to play an important role in the prognosis of our diabetic patients.

The severity indices of impairment scales dichotomize stroke into two categories, major and minor, while each stroke scale categorizes differently the severity of IS (10,11). Therefore, patients considered to have major stroke according to NIHSS presented with minor stroke according to SSS or moderate stroke according to OPS. NIHSS and SSS divide strokes in major and minor, but OPS stratify them into three categories: minor, moderate and major; that explains the increased accuracy of OPS in our study. Generally, all three impairment scales showed that major stroke occurred more frequently in diabetic patients who suffered RS or died within 12 months. However, major stroke as defined by baseline NIHSS and OPS predicted significantly our study's hard end points, with the latter having higher prediction value than the first.

It is known that stroke in diabetic patients has a specific clinical pattern which is correlated to poor prognosis (25). In our study, lacunar strokes were more frequent compared to other subtypes, followed by atherothrombotic and cardioembolic strokes. However, lacunar strokes were significantly related with less probability of RS or death, while atherothrombotic strokes were related significantly to higher odds of the same end points within the first year. Our results are in agreement with other studies which found lower RS risk and better survival rates for lacunar strokes than for other stroke subtypes (26-29).

Epidemiological studies demonstrate greater decline in stroke death rates in men than in women who have greater stroke mortality rates in ages over 85 years (1). Interestingly, our results revealed insignificant gender incidence differences of RS or death, even though 90% of study's population was younger than 85 years old. This can be explained by the fact that more women than men die of stroke each year due to their larger number (3). Also, diabetes seems to be responsible for higher rates of death between stroke women. Tuomi-

lehto et al. calculated that 16% of all stroke mortality in men and 33% in women could be directly attributed to diabetes (30). Our data indicated that acute hyperglycemia or glycemic deregulation prior to IS is linked to worse outcome. Stress hyperglycemia contributes negatively to stroke prognosis and, compared to diabetic patients, non-diabetic patients are more vulnerable during the acute phase of stroke (31). However, overall definition of stress hyperglycemia is not well identified in diabetic patients because their pre-stress baseline glucose levels remain unknown.

Our study has several limitations. First, the study was conducted in a merely Caucasian population, while its population is restricted by means of originating from a single hospital with similar demographic characteristics. However, the study population consisted of consecutive patients who were prospectively followed-up. Secondly, patients were not categorised by duration or complications of diabetes, despite the fact that advanced microvascular and macrovascular alterations may elongate time of stroke recovery and influence prognosis. Nevertheless, all scales were found to be significant predictors of RS or death within the year following initial stroke after major CVD risk adjustment.

Conclusions

Neurological stroke scales can be used in order to predict long-term outcome in type 2 diabetic patients of Caucasian origin after IS. NIHSS, OPS and SSS are strongly correlated and predict accurately RS or death after major CVD risk factor adjustment. OPS severity index might represent the most accurate tool in identifying long-term prognosis.

Conflicts of interest: None.

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