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Original Investigation

Treatment of Spontaneous Subarachnoid Hemorrhage and Self-Reported Neuropsychological Performance at 6 Months – Results of a Prospective Clinical Pilot Study on Good-Grade Patients

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ABSTRACT

AIM: Limited focus has been placed on neuropsychological patient profiles after spontaneous subarachnoid hemorrhage (sSAH). We conducted a prospective controlled study in good-grade sSAH patients to evaluate the time course of treatment-specific differences in cognitive processing after sSAH.

MATERIAL and METHODS: Twenty-six consecutive sSAH patients were enrolled (drop out n=5). Nine patients received endovascular aneurysm occlusion (EV), 6 patients were treated microsurgically (MS), and 6 patients with perimesencephalic SAH (pSAH) underwent standardized intensive medical care. No patient experienced serious vasospasm-related ischemic or hemorrhagic complications. All patients were subjected to neuropsychological self-report assessment (36-Item Short Form Health Survey and ICD-10-Symptom-Rating questionnaire) subacutely (day 11 – 35) after the onset of bleeding (t_1) and at the 6-month follow-up (FU; t_2).

RESULTS: From t_1 to t_2, MS and EV patients significantly improved in physical functioning (Pfi; p=.001 each) and the physical component summary (p=.010 vs. p=.015). Bodily pain (Pain; MS p=.034) and general health perceptions (EV p=.014) significantly improved, and nutrition disorder (EV p=.008) worsened. At FU, MS patients reported significantly better Pfi (vs. EV p=.046), less Pain (vs. EV p=.040), and more depression (vs. pSAH p=.035). Group-rate analyses of test differences showed a significant alleviation in nutrition disorder in MS (vs. EV p=.009).

CONCLUSION: All sSAH groups reported a significant deterioration in health. Though both MS and EV patients, improved in several physical items over time, our data suggest a better short-term Pfi, less Pain and improved nutrition disorder in surgically treated patients. pSAH patients performed significantly better in various aspects of physical and psychological functioning than patients with aneurysmal SAH.

KEYWORDS: Clip, Cognitive impairment, Coil, Neuropsychological outcome, Subarachnoid hemorrhage

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INTRODUCTION

With a peak age of incidence between 40 and 60 years (6), spontaneous subarachnoid hemorrhage (sSAH) predominantly affects relatively young patients in their most productive years with major responsibilities regarding their social and active family lives and their professional career. Experiencing an aneurysmal SAH (aSAH) or non-aneurysmal sSAH represents a sudden and life-threatening event with immediate and high mortality and significant long-term morbidity (15,63). Both those affected and their relatives suffer from the sequelae of the hemorrhage (15,39). Data on functional outcome in population-based sSAH studies are scarce. Regained independence is estimated at 55%, while 19% remain dependent, and 26% die (75). With increasing advances in neurointensive care and modern management concepts, the survival rates have improved (75), and the patient's long-term outcome is of paramount importance (62). Besides neurological dysfunction, neuropsychological impairment accounts for the primary causes of disability and reduced quality of life (QOL) in the mid- and long-term after SAH (3,23,38,43,48,56,69,85,88,114). Gross neurological outcome measures like the Glasgow Outcome Scale (GOS)(50) or the modified Ranking Scale (mRS)(92), which are commonly applied in clinical SAH trials, are insufficiently sensitive (43) and may falsely certify a favorable outcome, whereas the subtle but serious cognitive and real-world deficits that accompany sSAH often go undetected (3,31,43,61,68,83,97). Since the late 1980s, the focus of clinical SAH research has increasingly shifted to neuropsychological outcome evaluation to identify patients who will benefit from individualized patient management strategies concerning cognitive and vocational rehabilitation programs, social re-integration and modified medical treatment. Up to 50% of SAH survivors suffer from cognitive impairment, disabling for years (3,38,43,56,69), with a negative effect on health-related QOL and the ability to work or live independently (2,10,44,57,72,81,84,107,113,114).

Since the publication of the International Subarachnoid Aneurysm Trial (ISAT)(73,74) on good-grade aSAH patients, there has been a widely accepted paradigm shift toward a "coil-first policy"(60). Given the study biases, there is an ongoing controversy in the literature, whether (7,25,28,34,91,105) or not (7,29,55,91,99,103) coiling is preferable over surgical clipping with regard to a favorable functional and cognitive outcome. To date, only 13 SAH studies (7,24,26,28,29,34,55, 58,59,89,91,99,112) have directly compared the effects of clipping and coiling on cognitive outcome, and, from those, merely two research groups (29,55) provided information on the time course of neurobehavioral impairment after aSAH. Due to the limited number of studies available addressing this issue, no final conclusion can yet be drawn. In the present prospective controlled study, we evaluated the impact of the respective treatment modality after sSAH on self-reported neuropsychological outcome, defined by the 36-Item Short Form Health Survey (SF-36) and the ICD-10-Symptom-Rating questionnaire (ISR). For this purpose, all patients with good-grade sSAH were subjected to the standardized neuropsychological self-assessment in the subacute interval and 6 months after microsurgical clipping and endovascular aneurysm repair. Patients with non-aneurysmal perimesencephalic SAH (pSAH) served as control.

MATERIAL and METHODS

The clinical database and the study protocol were approved by the local institutional Ethics Committee (14-101-0010).

Patient Population

Prospectively, 26 consecutive patients with acute non-traumatic, aneurysmal and non-aneurysmal sSAH in a prognostically favorable neurological condition were enrolled in this single center trial at our University hospital between February 2013 and May 2016.

Study Selection Criteria

We selectively included: 1) German native speakers of both sexes, 2) aged 18 to 75 years after, 3) provision of written informed consent. The recruited patients presented 4) with a nontraumatic sSAH, either with an angiography confirmed etiology of an intracranial aneurysm in the anterior or posterior circulation (aSAH), or with a pSAH, and 5) accordingly underwent microsurgical (MS group) or endovascular (EV group) aneurysm occlusion and standardized intensive care unit (ICU) treatment (pSAH group). 6) Each patient was admitted to hospital within 48 hours of ictus in prognostically favorable, good to moderate neurological condition, i.e. Hunt and Hess (HH) score(41) 1 to 4 and initial Glasgow Coma Scale (GCS) ≥ 9, 8) without any pretreatment cognitive impairment. 7) Within the first 72 hours after the onset of SAH, all patients received an external ventricular drain (EVD) due to acute occlusive hydrocephalus diagnosed by our neuroradiologists. Exclusion criteria were; 1) preceding neurosurgical or neurovascular procedures, 2) previous history of intracranial disorders including repeated or delayed SAH, trauma, or known unruptured intracranial aneurysm (UIA), 3) previous psychiatric history or neurodegenerative diseases, 4) severe autoimmune or systemic diseases, 5) presence of a (giant) aneurysm causing mass effect, or 6) severe post-procedural complications like intracranial bleeding after aneurysm treatment or clinically symptomatic cerebral ischemia.

At hospital admission, the patients were graded according to the GCS (11-15 was considered good, 6-10 moderate), the HH score, the World Federation of Neurosurgical Societies' (WFNS) score (1,109), and the Fisher score (FS)(27). The clinical database comprised all demographic variables, co-morbidities, non-/invasive procedures, complications, outcome grading (GOS(50) and mRS(92)), and a comprehensive pharmacological screening (at discharge and at the 6 month-follow-up (FU)). All patients were examined by cerebral computed tomography (CT) scan and by digital subtraction angiography (DSA) and treated according to our ICU standard operating protocol (51). Each pSAH was confirmed by a magnetic resonance imaging (MRI) of the craniocervical junction to rule out a verifiable bleeding source. Transcranial Doppler ultrasound (TCD) examinations (118) were conducted daily. FU angiography was scheduled after MS during the hospitalization and 6 months after EV. In each pSAH patient, our

neuroradiologists decided on the timing and number of DSA controls individually on a patient-to-patient basis, depending on the initial DSA findings.

Therapeutic Procedures

In the aSAH patients group, the neurosurgeons and neuroradiologists decided on the treatment modality after interdisciplinary consent. Our standardized surgical and endovascular procedure protocols are described elsewhere (17). Considering the general trend toward "coil-first policy", our University Medical Center has an annual volume of 80 patients undergoing clipping for both ruptured and unruptured aneurysms.

Neuropsychological Self-Report Assessment

All patients completed the German version of the SF-36 (20,116), and the ISR (110) in the subacute phase after the onset of bleeding (between day 11 to 35 after SAH; t_1) and in the short-term (chronic phase) at 6 month-FU (t_2). The scores were compared with published normative data, the ISR with a German standard population (n=2512), and the SF-36 with both a reference population from Germany (n=2914) and a population norm from the US health survey (n=2474), to make our results comparable with future data. Outcome evaluation was conducted in a single session in a noise-free setting by having the participants complete both surveys, as an inpatient at t_1 and as an outpatient at t_2, respectively. No effects of fatigue were apparent. FU assessment additionally comprised a neurological examination and a semi-structured interview, including the patient's subjective health status, the current medication, and the employment status. The interview is a non-standardized method and serves as description of the whole sample. A comparison of the interview results between the groups would neither be methodologically correct nor reasonable, taking the small sample sizes into account.

SF-36

The SF-36 is a 36-item generic general health questionnaire that yields scores on eight health subscales relating to physical health (physical functioning (Pfi), role limitations due to physical health problems (Rolph), bodily pain (Pain), general health perceptions (Ghp)) and psychological health (vitality (Vital), social functioning (Social), role limitations because of emotional problems (Rolem), and general mental health (Mhi)). These eight subscales can be summarized in a corresponding physical component summary (PCS) and a mental component summary (MCS). The SF-36 also includes a single item that provides an indication of perceived change in health (health transition item, Rawhtran). Each item is scored on a 0 to 100 range and a high score defines a more favorable health state. Items in the same scale are averaged together to create the 8 scale scores (20,116).

ISR

The ISR aims at a comprehensive evaluation of the severity of psychological disorders. The ISR 2.0 comprises 29 items and six syndrome scales: depression, anxiety, obsessive/compulsive disorders, somatoform disorders, eating disorders, and a supplementary scale, which covers a variety of syndromes (including concentration, suicidality, sleep, appetite, obliviousness, flash backs, problems with activities of daily living, feelings of displacement and alienation, non-organic sexual dysfunction, amongst others), as well as a total score. Each syndrome scale ranges from a minimum of 0 (best performance) to a maximum of 4 points with higher scores indicating a more severe symptom burden. Cut-off values for each syndrome scale grade the degree of severity of symptoms in "suspected", "mild", "moderate", and "severe" (110).

Statistical Analysis

Continuous data and neuropsychological test results are presented as mean±standard deviation (SD) and range (min-max); categorical data as frequency counts. Changes over time within each group were analyzed by using a paired t-test. Differences between groups at post-interventional assessment were analyzed by using an analysis of variance (ANOVA) followed by Fisher's LSD post-hoc pairwise comparisons. A p-value <.05 was considered as statistically significant. Statistical analysis was conducted according to SPSS procedures (version 23.0; SPSS, Inc., Chicago, IL, USA).

RESULTS

Clinical and Radiological Characteristics and Comparability of the Study Groups

Five of the 26 patients were excluded from the analysis, since they did not fulfill the selection criteria (lost during FU: n=3; incomplete answered questionnaires: n=1; postsurgical bihemispheric chronic subdural hematoma requiring revision and epilepsy: n=1). The baseline characteristics of the 21 enrolled patients are presented in Table I. Intergroup comparisons did not reach any statistical significance.

Treatment Modalities and Results

Treatment was given either microsurgically via a pterional craniotomy and clipping (MS n=6) or interventionally (EV n=9: coil n=5, stent-assisted coil n=2; balloon-assisted coil n=1; flow diverter n=1). Periprocedurally, no aneurysm ruptured, and no patient required procedure-related blood transfusion. As blood loss during skin incision and microsurgical preparation did not exceed normal volumes, its contribution to post-treatment cognitive performance is negligible. Aneurysm characteristics and intraprocedural findings are shown in Table II. Intergroup comparisons yielded no significant differences except for more middle cerebral artery (MCA) aneurysms in the MS group (p=.022), an unsurprisingly longer duration of MS vs. EV (p=.004), and a longer time on mechanical ventilatory support in the EV group compared to the pSAH group (EV vs. pSAH p=.0496; EV vs. MS p=.864, MS vs. pSAH p=.065). This is predominantly due to the fact that the pSAH patients, not experiencing major complications, received general anesthesia for diagnostic DSA only.

Postoperative Course and Short-Term Outcome

Descriptive statistics are presented in Table III. Intergroup comparisons revealed no significant differences except for

more intake of antiplatelets at t_1 in favor of the EV group (p=.016). Procedure-related complications recorded were transient thromboembolic events requiring immediate embolectomy and lysis (EV n=2), intraluminal coil dislocation without thromboembolic event (EV n=1), and a dissection of the femoral communicating artery (EV n=2, MS n=1). Postprocedurally, none of these patients presented with a new ND. No patient developed CV-related stroke and no patient required decompressive craniectomy.

At discharge, 20/21 patients had no ND. In all patients, functional outcome was stable or even improved during the 6 month-FU. At t_2, 17/21 patients were asymptomatic or had mild symptoms such as recurrent headache (EV n=4, pSAH n=1), fatigue, poor concentration (EV n=5, pSAH n=2), subjective memory impairment (MS n=1, EV n=4, pSAH n=2), dizziness, and depressed mood (MS n=1, EV n=1). The remainder (4/21) presented with confusion (MS n=1), dysesthesia, dysarthria, and dysdiadochokinesia (EV n=3). Until FU, no late rebleeding and no mortality have occurred.

Neuropsychological Assessment

The time points of testing (Table III) did not differ significantly between the groups (t_1 p=.433; t_2 p=.999).

Intragroup Comparisons: From t_1 to t_2, all groups experienced a significant deterioration in the health transition item (Rawhtran; MS p=.031, EV p=.038, pSAH p=.040). MS patients showed significant improvement in physical functioning (Pfi; p=.001), bodily pain (Pain; p=.034), and in the physical component summary (PCS; p=.010). The EV group significantly improved in Pfi (p=.001), general health perceptions (Ghp; p=.014), and the PCS (p=.015), but deteriorated in nutrition disorder (p=.008).

Intergroup Comparisons: In several subscales of the ISR and the SF-36, our cohort performed significantly worse than the particular population norms, especially at t_1 (Figures 2A, B and Figures 4A, B). At t_2, EV patients still performed significantly worse in Pfi, role limitations due to physical health problems (Rolph), general mental health (Mhi), depression, compulsive-obsessive syndrome, in the ISR total score, and, together with MS patients, in vitality (Vital) compared to healthy controls. Test score comparisons at t_1 revealed significantly poorer scores in nutrition disorder for the MS than for the EV group (p=.035) and worse Vital (p=.006) for the MS than for the pSAH group. Compared to the pSAH group, EV patients performed significantly worse in the ISR supplementary items score (p=.024), in Pfi (p=.045), and in social functioning (Social; p=.046) at t_1. In the test score comparisons at 6 month-FU, MS patients yielded significantly better Pfi (p=.046) and less Pain (p=.040) than the EV group, but reported more depression (p=.035) than the pSAH group. Compared to the pSAH group, EV patients had a significantly worse ISR total score (p=.024), more depression (p=.016), a worse ISR supplementary items score (p=.018), more Pain (p=.044), and worse Social (p=.020) at t_2. Group-rate analyses of test differences $t_2 - t_1$ showed a significant alleviation in nutrition disorder in the MS group compared to the EV group (p=.009). Details can be gleaned from Tables IV, V and Figures 1A-C; 2A, B; 3A-C; 4A, B.

Table I: Demographical and Clinical Patient Characteristics

Clinical features and patient characteristics	Study population		
	MS	**EV**	**pSAH**
Number of patients [n]	6	9	6
Male to female ratio	2 : 4	3 : 6	3 : 3
Age [years], mean ± SD	42.0±13.2	50.1±9.3	59.8±7.4
(range)	(27 - 61)	(30 - 59)	(53 - 72)
Co-morbidities			
Arterial hypertension [n]	3	5	4
Nicotine abuse [n]	3	2	2
Hypothyroidism [n]	2	2	0
Cardiac disorders [n]	1	3	0
Adiposity [n]	1	1	0
Diabetes mellitus [n]	0	0	1
Migraine [n]	0	0	1
Restrictive ventilation disorder [n]	1	0	0
Initial neurological status			
GCS [n]			
15	1	5	4
14	4	2	1
13	1	0	1
11	0	1	0
9	0	1	0
Hunt and Hess score [n]			
0	0	0	0
I	2	5	2
II	2	2	4
III	2	1	0
IV	0	1	0
V	0	0	0
WFNS score [n]			
1	1	5	4
2	4	2	2
3	1	0	0
4	0	2	0
5	0	0	0
Fisher score [n]			
1	0	0	0
2	0	0	0
3	2	2	2
4	4	7	4

EV: *endovascular treatment group;* ***GCS:*** *Glasgow Coma Scale;* ***MS:*** *microsurgical clipping group;* ***pSAH:*** *perimesencephalic subarachnoid hemorrhage group;* ***SD:*** *standard deviation;* ***WFNS:*** *World Federation of Neurosurgical Societies.*

Table II: Aneurysm Characteristics and Procedure Variables

Aneurysm characteristics and procedure variables	MS	EV	pSAH
Aneurysm location			
Single aneurysms [n]			
ACA	1	0	-
ACoA	2	5	-
Pericallosal artery	0	1	-
MCA	**3***	0	1[a]
ICA, PCoA	0	0	-
PCA	0	0	-
BA	0	2	-
VA	0	1	-
Multiple aneurysms [n]			
ACoA + MCA[b] (unruptured)	0	1	-
ACoA + "bleb" ACA (unruptured)	1	0	-
MCA + MCA[c] (unruptured)	1	0	-
Total number of aneurysms [n]			
Anterior circulation	8	7	1[a]
Posterior circulation	0	3	-
	8	10	1[a]
Side of aneurysms [n]			
Left	3	2	1[a]
Right	4	2	-
Side of pterional approach			
Dominant-side	3	-	-
Non-dominant side	3	-	-
Procedure variables			
Latency from onset of the SAH to aneurysm occlusion [d], mean ± SD (range)	0.83±0.75 (0-2)	1.44±1.42 (0-5)	-
Temporary parent artery occlusion [min], mean ± SD (range)	3.42±2.76 (0-7)	-	-
Duration of aneurysm surgery/intervention [min], mean ± SD (range)	**242.33±24.75*** (205-279)	**136.67±46.87*** (55-200)	-
Time with mechanical ventilatory support [hours], mean ± SD (range)	116.03±244.14[d] (2.17-613.63)	**117.99±264.14*** [d] (6.92-808.83)	**5.82 ± 6.34*** (0 - 14.83)
Aneurysm occlusion rate at FU			
Complete [n]	5	6	-
Incomplete [n]	1	3	-

[a, b, c] Unruptured aneurysms were either treated after the study period or were not eligible due to small dome size. ***ACA:*** *anterior cerebral artery;* ***ACoA:*** *anterior communicating artery;* ***BA:*** *basilar artery;* ***[d]*** *1 MS and 1 EV patient required prolonged mechanical ventilatory support (613.63 h vs. 808.83 h) due to compromised pulmonary gas exchange and inadequate waking reaction with intolerance of the intubation tube, consecutive transient peaks of the intracranial pressure and cerebral vasospasm, respectively. Both patients underwent transient tracheotomy for successful weaning from the respirator.* ***d:*** *days;* ***EV:*** *endovascular treatment group;* ***FU:*** *6-month follow-up;* ***ICA:*** *internal carotid artery;* ***MCA:*** *middle cerebral artery;* ***min:*** *minutes;* ***MS:*** *microsurgical clipping group;* ***PCA:*** *posterior cerebral artery;* ***PCoA:*** *posterior communicating artery;* ***pSAH:*** *perimesencephalic subarachnoid hemorrhage group;* ***SAH:*** *subarachnoid hemorrhage;* ***SD:*** *standard deviation;* ***VA:*** *vertebral artery.* $^{*}p < .05$.

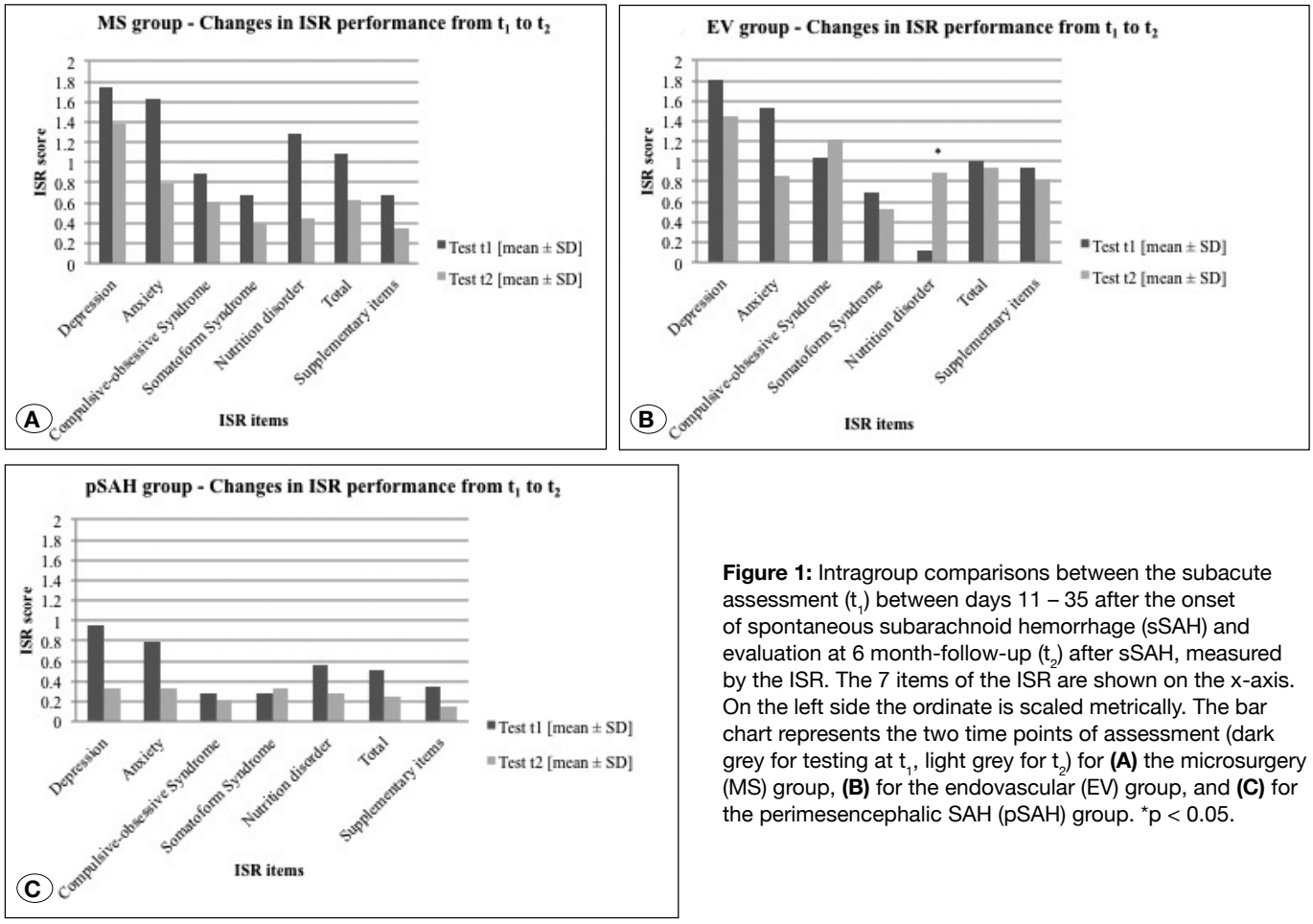

Figure 1: Intragroup comparisons between the subacute assessment (t_1) between days 11 – 35 after the onset of spontaneous subarachnoid hemorrhage (sSAH) and evaluation at 6 month-follow-up (t_2) after sSAH, measured by the ISR. The 7 items of the ISR are shown on the x-axis. On the left side the ordinate is scaled metrically. The bar chart represents the two time points of assessment (dark grey for testing at t_1, light grey for t_2) for **(A)** the microsurgery (MS) group, **(B)** for the endovascular (EV) group, and **(C)** for the perimesencephalic SAH (pSAH) group. *p < 0.05.

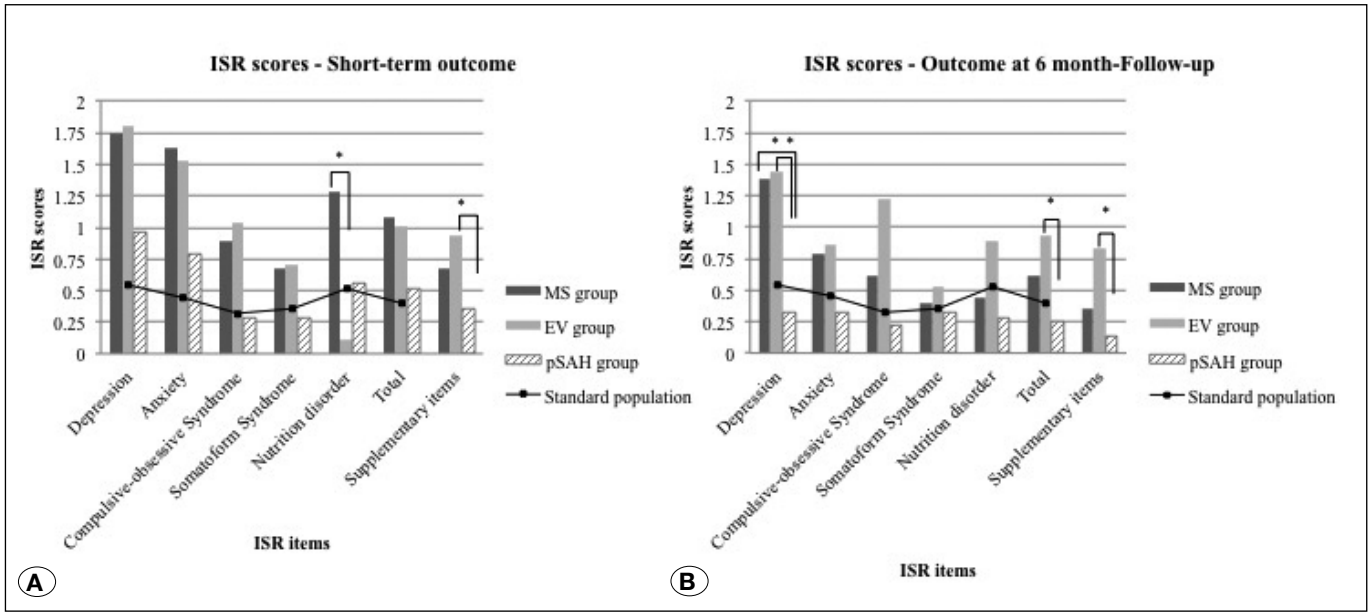

Figure 2: Intergroup comparisons between **(A)** the subacute assessment (t_1) between days 11 – 35 after the onset of spontaneous subarachnoid hemorrhage (sSAH) and **(B)** evaluation at 6 month-follow-up (t_2) after sSAH, measured by the ISR. The 7 items of the ISR are shown on the x-axis. On the left side the ordinate is scaled metrically. The line graph shows the standard population, whereas the bar chart represents the different groups (dark grey for the microsurgery (MS) group, light grey for the endovascular (EV) group, striped bars for the perimesencephalic SAH (pSAH) group). *p < 0.05.

DISCUSSION

Neuropsychological Outcome and QOL after sSAH with a Focus on Good-Grade SAH Patients

Our study substantiates that QOL is considerably impaired in good-grade SAH survivors. As shown in the literature, culture has a considerable effect on neuropsychological tests and, thus, test results cannot be extrapolated from one country to another (4,98). To account for cultural differences, we compared the SF-36 scores not only to the commonly cited normative data from the US health survey but also to a German reference population. For the most part, our SF-36 results were comparable between both population norms. Demands on outcome instruments imply the assessment of essential aspects of daily life with accepted rates of validity and reliability, like the currently used ISR and the SF-36. Multiple previous SAH investigations (39,53,54,101,104,119) have used the SF-36, even in poor-grade SAH (36,104), showing an impact on all tested items of the SF-36 (39,53,101). To the best of our knowledge, this is the first trial measuring neuropsychological impairment after SAH by means of the ISR which is a broadly accepted instrument in psychosomatic disorders and well-established in clinical routine (79). Compared to healthy controls, both the MS and the EV group revealed significantly reduced indices in most SF-36 and ISR subscales, in particular at the early stage of recovery. These differences leveled off at 6 month-FU. Interestingly, however, EV patients still performed significantly worse in Pfi, Rolph, Pain, Vital, Mhi, ISR total score, depression, and compulsive-obsessive syndrome. Given the non-significant intergroup differences between clipped and coiled patients at t_1, these results may indicate that clipped patients recover at a faster rate than their coiled counterparts, at least in terms of QOL aspects. A caveat to this hypothesis is the small sample size in the present study, and the fact that intergroup comparisons of test differences revealed no significant differences between MS and EV. Only a few prospective SAH studies have assessed the QOL either by semistructured interview (43,61,82,100) or by validated instruments (39,40,47) with a broad variance in the timing of examination (2 weeks to 24.5 years), and an even smaller number of authors, like Preiss et al.(90) have considered treatment-specific differences. Analyses of good-

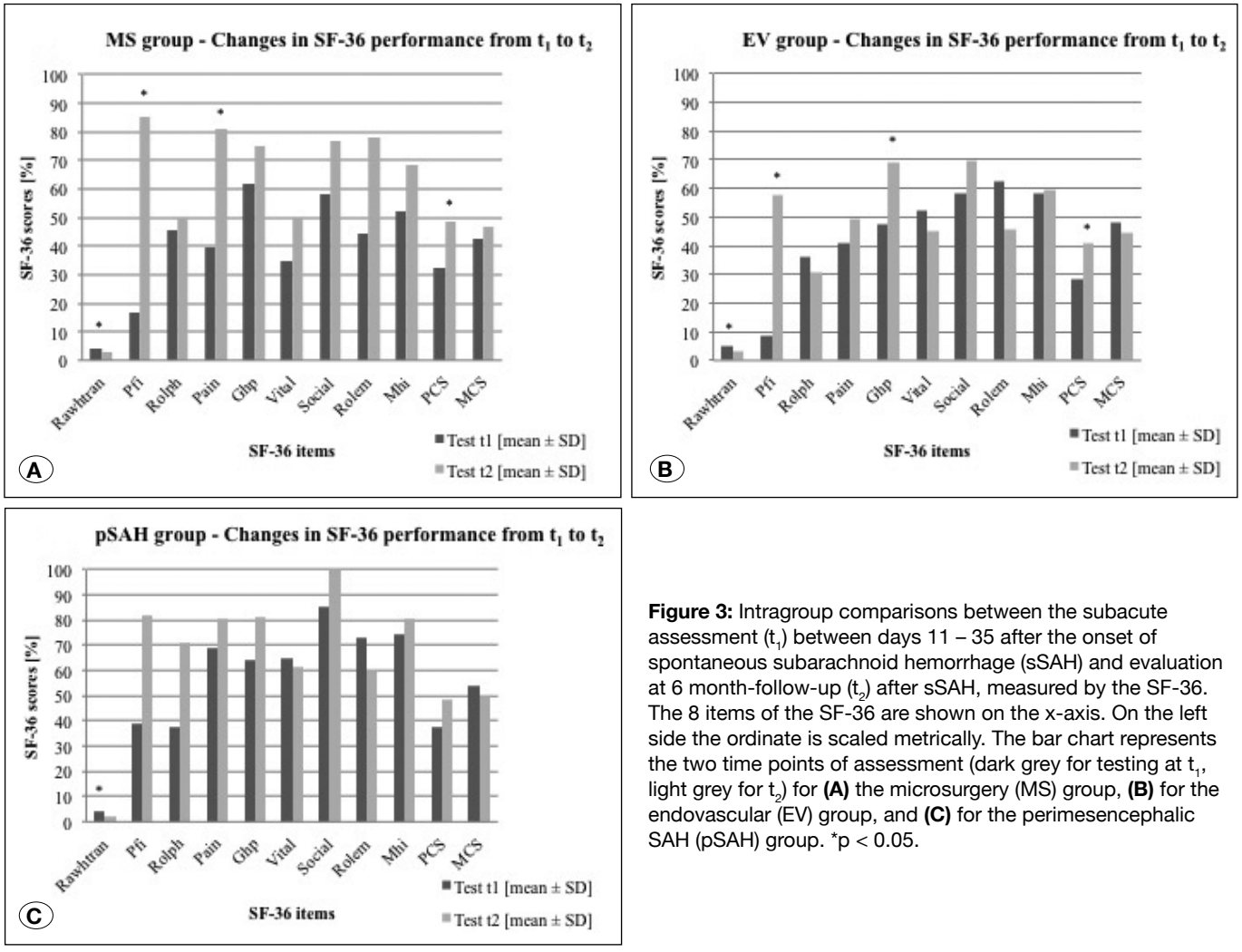

Figure 3: Intragroup comparisons between the subacute assessment (t_1) between days 11 – 35 after the onset of spontaneous subarachnoid hemorrhage (sSAH) and evaluation at 6 month-follow-up (t_2) after sSAH, measured by the SF-36. The 8 items of the SF-36 are shown on the x-axis. On the left side the ordinate is scaled metrically. The bar chart represents the two time points of assessment (dark grey for testing at t_1, light grey for t_2) for **(A)** the microsurgery (MS) group, **(B)** for the endovascular (EV) group, and **(C)** for the perimesencephalic SAH (pSAH) group. *$p < 0.05$.

grade SAH patients by means of the SF-36 revealed divergent data, depending on the time of assessment. At 4 month-FU, a significant reduction in QOL (specifically in Social, Rolem, and Mhi) was observed, followed by a 50 percent improvement of the SF-36 scores at 18 month-FU (39). Only modest deterioration in QOL was reported 4.7 years (101) and 10 years (115) after good-grade SAH. However, even in long-term SAH survivors (107), re-integration difficulties with reduced independence and decreased employment rates have been observed (22,87,107,117).

Impact of the Time of Assessment on Neuropsychological Impairment

Various factors might modulate the severity and nature of neuropsychological deficits measured in the different SAH studies. One of these variables is the time of testing in relation to the initial insult. In our cohort, both MS and EV patients experienced significant improvement in several physical items within 6 months, while psychological SF-36 items seemed to remain stable in all groups. Interpreting our results with caution due to the small sample size, it might be speculated that physical functioning improves at a faster rate than psychological functioning in good-grade SAH patients without major ND. The majority of studies (22,33,39,69,71,86,96) have focused on the early stages of recovery after SAH with limited insight into the neurobehavioral long-term consequences (12,35,44,61,71,82,93,107). Neuropsychological deficits (3), predominantly in cognition (39,69), QOL (40,47,96,115,120), mood (114), and fatigue (114), are most common within the first 3 months (86); however, they can persist as long as 24.5 years after aSAH and perhaps longer (10,94,107).

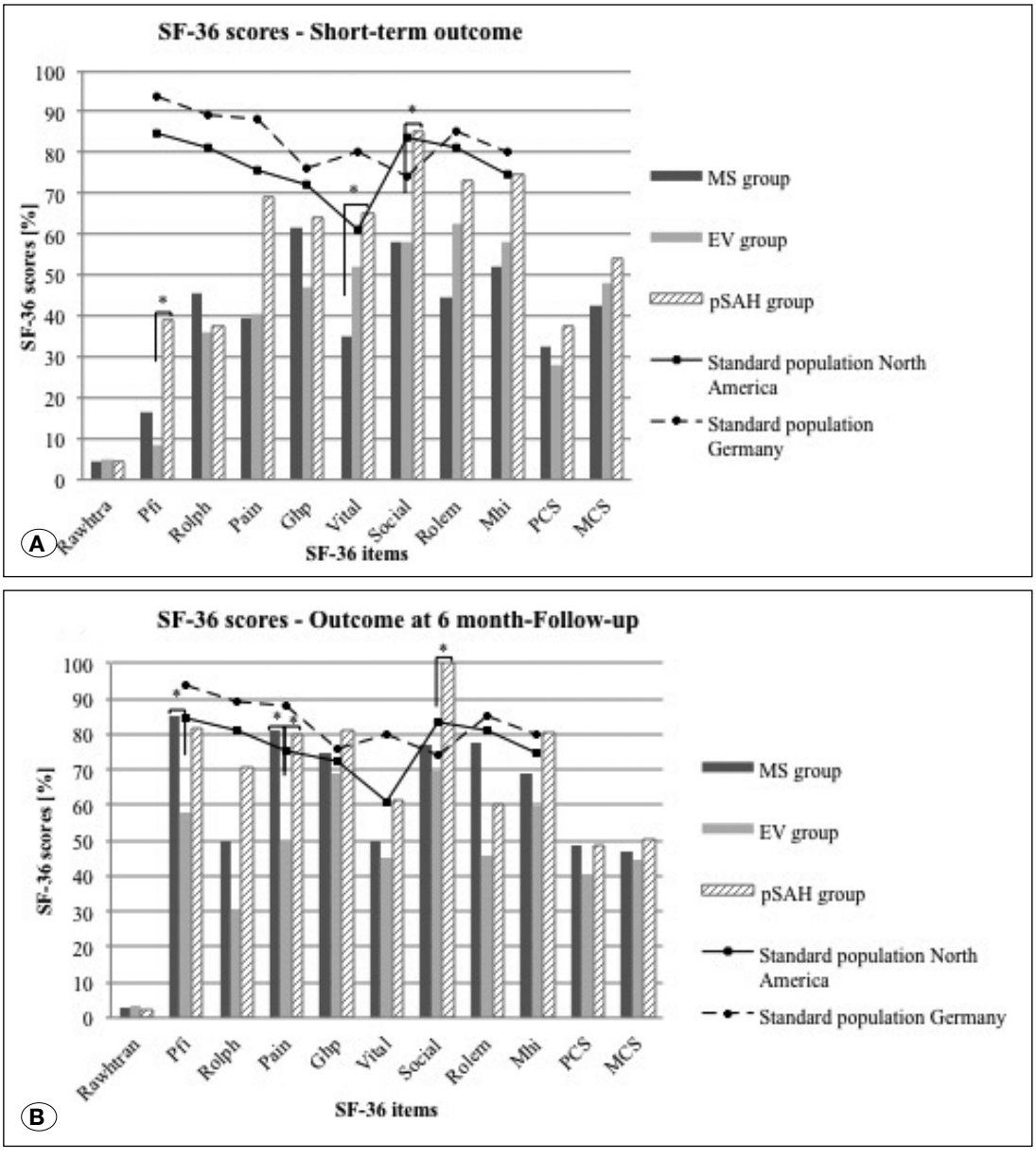

Figure 4: Intergroup comparisons between **(A)** the subacute assessment (t_1) between days 11 – 35 after the onset of spontaneous subarachnoid hemorrhage (sSAH) and **(B)** evaluation at 6 month-follow-up (t_2) after sSAH, measured by the SF-36. The 8 items of the SF-36 are shown on the x-axis. On the left side the ordinate is scaled metrically. The line graph shows the standard population (continuous line for the US norm, dashed line for the German norm), whereas the bar chart represents the different groups (dark grey for the microsurgery (MS) group, light grey for the endovascular (EV) group, striped bars for the perimesencephalic SAH (pSAH) group). *p < 0.05.

Table III: Clinical Course and Outcome Assessment

Clinical Course, Internal Complications and Outcome Assessment	Study population		
	MS	**EV**	**pSAH**
External ventricular drainage			
Implantation after the onset of SAH [d], mean ± SD	0.50±0.55	0.44±0.73	0.50±0.55
(range)	(0 - 1)	(0 - 2)	(0 - 1)
In situ [d], mean ± SD	15.83±4.88	15.13±7.68	12.00±4.95
(range)	(9 - 23)	(9 - 30)	(5 - 18)
Replacement [n]	0	2	1
CSF infection [n]	1	4	2
Permanent ventriculoperitoneal shunt placement [n]	0	2	2
Implantation after the onset of SAH [d], mean ± SD	-	23.50±0.71	29.50 ±6.36
(range)	-	(23 - 24)	(25 - 34)
Cerebral vasospasm [n]			
DIND	1	1	0
TCD	6	7	3
DSA	0	2	1
Multimodal neuromonitoring	1	1	0
Intraarterial cerebral spasmolysis[a]	0	2	0
Treatment-associated lesions on CT scan [n]			
Circumscript ischemia[b]	2	2	0
Brain edema	3	1	0
Bleeding along the EVD entry route	1	0	1
Hygroma	0	0	1[c]
Internal complications [n]			
Pneumonia	2	2	0
Compromized pulmonary gas exchange	1	1	0
Electrolyte imbalance	3	6	5
SIADH	0	0	1
Diabetes insipidus	0	0	1
ECG alterations, arrhythmia	1	2	0
Hypertensive crisis	1	4	2
Seizure	1	1	0
Beginning multiorgan failure (not requiring dialysis)	0	1	0
Acute pancreatitis	0	1	0
Propofol infusion syndrome	0	1	0
Hypothyroidism	0	1	1
Hyperthermia	0	1	1
Hyperglycemia	0	1	1
Delirium	1	1	0
Disorientation/agitation	1	1	0
Average length of hospital stay [d], mean ± SD (range)			
On the ICU	20.17±6.91	20.11±7.85	14.67±7.92
(range)	(12 - 31)	(9 - 35)	(7 - 29)
Total	25.17±4.67	28.44±6.11	26.83±11.05
(range)	(21 - 31)	(22 - 40)	(14 - 42)

Table III: Cont.

Clinical Course, Internal Complications and Outcome Assessment	Study population		
	MS	**EV**	**pSAH**
Medication at discharge / at FU			
Anticonvulsive drugs	1 / 1	0 / 1	0 / 0
Benzodiazepines	0 / 0	1 / 0	0 / 0
Antidepressants	0 / 0	3 / 1	1 / 1
Neuroleptics	0 / 0	0 / 0	0 / 0
Opioid	2 / 0	1 / 1	2 / 0
Nicotine patches	0 / 1	0 / 1	0 / 1
Antihypertensive drugs	4 / 3	4 / 6	3 / 3
Thyroid medication	3 / 3	2 / 2	0 / 0
Antiplatelet agents	0 / 0	**5*** / 3	0 / 0
No medication	0 / 2	0 / 1	0 / 2
Neurological status at discharge / at FU			
GOS [n]			
5	4 / 5	7 / 7	5 / 6
4	0 / 0	1 / 2	1 / 0
3	2 / 1	1 / 0	0 / 0
mRS [n]			
0	4 / 2	7 / 3	4 / 5
1	0 / 3	0 / 3	2 / 1
2	1 / 0	1 / 3	0 / 0
3	0 / 1	0 / 0	0 / 0
4	1 / 0	1 / 0	0 / 0
Patients with new neurological deficit [n]			
At discharge	0	1	0
At FU	1	3	0
Employment status at FU [n]			
Returned to work	1	2	1
Attending vocational integration programs	0	2	0
On sick leave	1	3	0
Unemployed	1	1	0
Unemployed before and after the onset of SAH	0	1	0
Retired at the onset of SAH	0	0	1
No information provided	3	0	4
Neuropsychological assessment after the onset of SAH (SF-36 and ISR)			
Subacute phase (t_1) [d], mean ± SD (range)	15.67±4.89 (12 - 25)	14.78±7.34 (11 - 34)	14.67±3.88 (12 - 22)
Chronic phase (t_2) [d], mean ± SD (range)	186.00±9.94 (176 - 204)	185.67±11.32 (169 - 209)	185.83±16.86 (164 - 208)

[a] Transient placement of transfemoral microcatheters for local intraarterial cerebral spasmolysis (n=1 continuous nimodipine infusion for 3 and 5 days; n=1 single shot infusion of milrinone) to reverse severe cerebral vasospasm. [b] clinically silent ischemia, either in the section of the caudate nucleus, following unintended clipping of the recurrent artery of Heubner, or diffusely in the periventricular white matter; [c] conservatively treated bi-hemispheric hygromas due to CSF overdrainage via the EVD; ***CSF:*** *cerebrospinal fluid;* ***CT scan:*** *computerized axial tomography scan;* ***d:*** *days;* ***DIND:*** *delayed ischemic neurological deficit (transient dysarthria and paresthesias);* ***DSA:*** *digital subtraction angiography;* ***ECG:*** *electrocardiogram;* ***EV:*** *endovascular treatment group;* ***EVD:*** *external ventricular drainage;* ***FU:*** *6-month follow-up;* ***GOS:*** *Glasgow Outcome Scale;* ***ICU:*** *intensive care unit;* ***ISR:*** *ICD-10-Symptom-Rating questionnaire;* ***mRS:*** *modified Rankin Scale;* ***MS:*** *microsurgical clipping group;* ***pSAH:*** *perimesencephalic subarachnoid hemorrhage group;* ***SAH:*** *subarachnoid hemorrhage;* ***SD:*** *standard deviation;* ***SF-36:*** *short form 36-item health survey;* ***SIADH:*** *syndrome of inappropriate antidiuretic hormone secretion;* ***t_1:*** *days 11 - 35 after the onset of SAH (subacute phase);* ***t_2:*** *6 months after the onset of SAH (chronic phase);* ***TCD:*** *transcranial Doppler ultrasound. * $p < .05$.*

Table IV: Changes of Cognitive Performance within Treatment Groups from the Subacute Interval After the Onset of Spontaneous Subarachnoid Hemorrhage (t_1) to 6 Month Follow-up (t_2)

Neuropsychological assessment	MS group				EV group				pSAH group			
	Test t_1 [mean ± SD]	Test t_2 [mean ± SD]	Difference $t_1$vs. t_2 [mean ± SD]	p-value	Test t_1 [mean ± SD]	Test t_2 [mean ± SD]	Difference $t_1$vs. t_2 [mean ± SD]	p-value	Test t_1 [mean ± SD]	Test t_2 [mean ± SD]	Difference $t_1$vs. t_2 [mean ± SD]	p-value
ISR scores												
Depression	1.75±1.23	1.38±.88	.38±1.10	.443	1.81±1.07	1.44±.94	.36±1.30	.429	.96±1.20	.33±.26	.63±1.12	.228
Anxiety	1.63±1.24	.79±.99	.83±1.23	.158	1.53±.83	.86±.93	.67±1.24	.146	.79±1.38	.33±.82	.46±1.79	.558
Compulsive-obsessive	.89±.81	.61±.77	.28±1.04	.542	1.04±1.29	1.22±1.13	-.19±1.97	.785	.28±.68	.22±.54	.06±.95	.892
Somatoform	.67±.63	.39±.65	.28±.85	.462	.70±.75	.52±.47	.19±.99	.589	.28±.68	.33±.82	-.06±1.16	.911
Nutrition disorder	1.28±1.36	.44±.58	.83±1.09	.120	.11±.24	.89±.71	-.78±.67	**.008***	.56±1.20	.28±.53	.28±1.44	.656
Supplementary items	.67±.37	.35±.30	.32±.41	.117	.94±.58	.83±.72	.11±.81	.692	.35±.29	.14±.14	.21±.24	.087
Total	1.08±.61	.62±.41	.46±.61	.121	1.01±.60	.94±.63	.07±.87	.822	.51±.77	.25±.44	.25±.92	.529
SF-36 scores												
Physical items												
Rawhtran	4.33±.82	2.67±1.37	1.67±1.37	**.031***	4.75±.46	3.50±1.41	1.25±1.39	**.038***	4.40±.55	2.20±1.10	2.20±1.64	**.040***
Pfi	16.67±19.41	85.00±8.94	-68.33±21.60	**.001***	8.33±19.69	57.78±29.27	-49.44±27.66	**.001***	39.17±40.67	81.57±25.20	-42.41±54.01	.112
Rolph	45.83±45.87	50.00±38.73	-4.17±57.92	.867	36.11±48.59	30.56±46.40	5.56±67.06	.810	37.50±41.08	70.83±45.87	-33.33±70.12	.297
Pain	39.83±31.10	80.83±18.29	-41.00±34.61	**.034***	40.67±38.29	49.56±33.21	-8.89±34.92	.467	69.00±27.86	80.17±21.99	-11.17±41.96	.543
Ghp	61.83±12.14	75.00±15.68	-13.17±17.10	.118	47.33±15.24	68.89±19.46	-21.56±20.54	**.014***	64.33±18.60	81.17±19.08	-16.83±20.72	.103
Psychological items												
Vital	35.00±15.17	50.00±18.71	-15.00±15.49	.064	52.22±20.48	45.00±16.77	7.22±26.35	.435	65.00±10.00	61.67±25.43	3.33±25.43	.761
Social	58.33±23.27	77.08±25.52	-18.75±29.32	.178	58.33±28.64	69.44±27.32	-11.11±36.68	.390	85.42±14.61	100.00±0.00	-14.58±14.61	.058
Rolem	44.44±45.54	77.78±27.22	-33.34±51.64	.175	62.50±51.75	45.83±50.20	16.67±64.24	.487	73.33±43.46	60.00±54.77	13.33±50.55	.587
Mhi	52.00±15.59	68.67±17.42	-16.67±20.46	.103	58.22±22.81	59.56±24.61	-1.33±36.39	.915	74.67±16.72	80.67±16.86	-6.00±23.97	.567
PCS	32.34±8.01	48.74±4.52	-16.41±10.05	**.010***	28.22±9.36	40.68±11.91	-12.46±11.04	**.015***	37.78±12.95	48.74±9.33	-10.96±19.10	.269
MCS	42.69±9.24	46.69±10.94	-4.01±11.68	.439	48.34±13.61	44.56±12.01	3.78±15.59	.515	54.10±11.42	50.09±8.03	4.02±9.32	.390

(***Statistical significance: p < .05**)

EV: *endovascular aneurysm occlusion group;* ***Ghp:*** *general health perceptions;* ***ISR:*** *ICD-10-Symptom-Rating questionnaire;* ***MCS:*** *Mental component summary;* ***Mhi:*** *general mental health;* ***MS:*** *microsurgical aneurysm occlusion group;* ***Pain:*** *bodily pain;* ***PCS:*** *physical component summary;* ***Pfi:*** *physical functioning;* ***pSAH:*** *perimesencephalic subarachnoid hemorrhage group;* ***Rawhtran:*** *health transition item;* ***Rolem:*** *Role limitations because of emotional problems;* ***Rolph:*** *role limitations because of physical health problems;* ***SD:*** *standard deviation;* ***SF-36:*** *German version of the 36-Item Short Form Health Survey;* ***Social:*** *social functioning;* ***test t_1:*** *test in the subacute phase after the onset of bleeding (between day 11 to 35 after subarachnoid hemorrhage);* ***test t_2:*** *test in the short-term (chronic phase) after treatment at 6-month follow-up;* ***Vital:*** *vitality.*

Table V: Intergroup Comparisons of Cognitive Tests: Differences Between the Treatment Groups

Neuropsychological assessment	ANOVA - Test scores [p-value]		Intergroup comparisons of test scores at test t_1 [p - value]			Intergroup comparisons of test scores at test t_2 [p - value]			Differences test t_2 - t_1 [mean ± SD]			ANOVA - Test differences t_2 - t_1 [p-value]	Intergroup comparisons of test differences t_2 - t_1 [p - value]		
	t_1	t_2	MS vs. EV	MS vs. pSAH	EV vs. pSAH	MS vs. EV	MS vs. pSAH	EV vs. pSAH	MS	EV	pSAH		MS vs. EV	MS vs. pSAH	EV vs. pSAH
ISR scores															
Depression	.355	**.036***	.928	.251	.181	.870	**.035***	**.016***	-.38±1.10	-.36± 1.30	-.63±1.12	.905	.983	.722	.681
Anxiety	.378	.535	.872	.216	.231	.887	.398	.289	-.83±1.23	-.67±1.24	-.46±1.79	.900	.826	.652	.783
Compulsive-obsessive	.372	.127	.786	.314	.176	.216	.465	.050	-.28±1.04	.19±1.97	-.06±.95	.843	.567	.801	.765
Somatoform	.491	.845	.921	.350	.264	.702	.881	.586	-.28±.85	-.19±.99	.06±1.16	.838	.863	.573	.655
Nutrition disorder	.101	.176	**.035***	.213	.396	.197	.652	.082	-.83±1.09	.78±.67	-.28±1.44	**.025***	**.009***	.371	.072
Supplementary Items	.071	**.045***	.265	.243	**.024***	.086	.487	**.018***	-.32±.41	-.11±.81	-.21±.24	.804	.516	.751	.761
Total	.267	.071	.849	.149	.162	.255	.253	**.024***	-.46±.61	-.07±.87	-.25±.92	.665	.374	.666	.672
SF-36 scores															
Physical items															
Rawhtran	.596	.231	.318	.645	.614	.262	.569	.105	-1.67±1.37	-1.25±1.39	-2.20±1.64	.529	.602	.552	.267
Pfi	.122	.080	.567	.168	**.045***	**.046***	.808	.077	68.33±21.60	49.44±27.66	42.41±54.01	.441	.330	.225	.713
Rolph	.917	.249	.692	.757	.955	.415	.425	.101	4.17±57.92	-5.56±67.06	33.33±70.12	.534	.782	.451	.275
Pain	.239	.055	.963	.151	.128	**.040***	.966	**.044***	41.00±34.61	8.89±34.92	11.17±41.96	.242	.116	.179	.908
Ghp	.095	.459	.093	.783	.052	.536	.568	.221	13.17±17.10	21.56±20.54	16.83±20.72	.719	.430	.751	.655
Psychological items															
Vital	**.020***	.308	.066	**.006***	.163	.642	.327	.132	15.00±15.49	-7.22±26.35	-3.33±25.43	.211	.090	.194	.758
Social	.092	.057	1,000	.066	**.046***	.530	.097	**.020***	18.75±29.32	11.11±36.68	14.58±14.61	.890	.634	.812	.828
Rolem	.559	.421	.384	.327	.803	.208	.675	.405	33.34±51.64	-16.67±64.24	-13.33±50.55	.255	.125	.197	.920
Mhi	.137	.185	.550	.058	.125	.417	.331	.070	16.67±20.46	1.33±36.39	6.00±23.97	.618	.335	.538	.767
PCS	.166	.150	.289	.404	.066	.131	.791	.078	16.41±10.05	12.46±11.04	10.96±19.10	.776	.589	.508	.846
MCS	.303	.443	.246	.144	.606	.720	.398	.214	4.01±11.68	-3.78±15.59	-4.02±9.32	.490	.286	.326	.975

(*Statistical significance: p < .05)

EV: *endovascular aneurysm occlusion group;* ***Ghp:*** *general health perceptions;* ***ISR:*** *ICD-10-Symptom-Rating questionnaire;* ***MCS:*** *Mental component summary;* ***Mhi:*** *general mental health;* ***MS:*** *microsurgical aneurysm occlusion group;* ***Pain:*** *bodily pain;* ***PCS:*** *physical component summary;* ***Pfi:*** *physical functioning;* ***pSAH:*** *perimesencephalic subarachnoid hemorrhage group;* ***Rawhtran:*** *health transition item;* ***Rolem:*** *Role limitations because of emotional problems;* ***Rolph:*** *role limitations because of physical health problems;* ***SD:*** *standard deviation;* ***SF-36:*** *German version of the 36-Item Short Form Health Survey;* ***Social:*** *social functioning;* ***test t_1:*** *test in the subacute phase after the onset of bleeding (between day 11 to 35 after subarachnoid hemorrhage);* ***test t_2:*** *test in the short-term (chronic phase) after treatment at 6-month follow-up;* ***Vital:*** *vitality.*

Meta-analyses by Al-Khindi et al. (3), and by Egeto et al.(25) suggest that clipping might be associated with a more favorable cognitive performance in the early stages (i.e. within 6 months after treatment) after SAH and, in the long-term (≥12 months post-treatment), a superior cognitive outcome after coiling. This theory equals our results that, at 6 months, MS patients performed significantly better than the EV group. Interestingly, together with others (30), we yielded contrary results (with impaired short-term executive processing in MS patients) when analyzing treatment-associated effects on cognition in patients with anterior circulation UIA (17). So far, only two other SAH studies (29,55), comparing treatment-specific effects on cognition, conducted FU-testing (10 days (29), 3 months (55), 6 months (29), and 12 months (55) post-treatment) and, thus, provide some information on the time course of cognitive changes. The results are consistent with our findings: In both cohorts, both treatment groups were impaired on a wide range of cognitive tests and experienced minor improvements in a few domains during the months following treatment. At medium-length FU (3(55) and 6 months (29)), clipped patients outperformed the coiled patients in the executive, visuospatial and intelligence domains. No intergroup differences emerged at the 12 month-FU. Several previous SAH studies indicated a recovery of neuropsychological functions at different rates (29,37,55,86,87) over time (13,67,81,86,108). Yet, the data from the recent meta-analysis (25) hypothesizes that SAH survivors do not return to pre-existing levels of cognitive functioning after treatment. To date, only Vieira et al.(112) provided pre-treatment data (1-2 weeks after SAH and 2 weeks post-treatment). In qualification, it should be stated, that the unique results of Frazer et al.(29)(with superior functioning of MS patients) may have been influenced by preexisting group differences as to greater pre-morbid intelligence scores in the surgery group. A comparable limitation of our study, that cannot be disregarded, is the lack of data on pre-morbid intelligence scores and educational status. Due to the variability in educational level, Santiago-Ramajo et al.(99) repeated their study analyses, excluding the participants with less than 7 years of schooling, and obtained the same results.

The inconclusive findings may represent artifacts of incomplete recovery, especially when the neuropsychological outcome is assessed within 1 month after ictus (55,71). The time delay of serial outcome evaluation between the acute stage of recovery and the late stages, approaching maximum recovery, might ensure the stability of cognitive profiles and increase the validity of neuropsychological outcome data.

Impact of the Treatment Procedure on Neuropsychological Impairment

Another factor that can intervene in the cognitive outcome of SAH patients may be the type of treatment applied. Several authors found no treatment-specific differences in cognition at 3 (55) and 4 months (99) after SAH, and similar QOL at 14 months (91), 1 year (90), and 24.5 years (107) after SAH. In our study, summary scores of the two surveys did not differ between the MS and the EV group, either. However, clipped patients reported better short-term Pfi, less Pain, and more alleviation in nutrition disorder than coiled patients. The prolonged cephalgia in the EV group might be related to the longer persistence of blood in the basal cisterns compared to MS patients undergoing craniotomy, clipping, and intraoperative irrigation of subarachnoid blood. Agreeing with Frazer et al.(29), these findings could be interpreted that clipped patients experienced a greater initial decline in cognition from pre-morbid levels and, thus, had further ground to recover than coiled patients. By contrast, others suggested a more deleterious effect of MS compared to EV (49,70,73,105), since they could show more cognitive impairment (depression, executive dysfunction, memory deficits) (7,24,28,34) at least 1 year after surgery. Chan et al. (24) reasoned that, in clipped patients, the deficit might be attributed to an encoding deficit in contrast to a retrieval deficit in coiled patients.

Aneurysm management has been changing (18,102) since the introduction (32) of EV in 1991 (32) and its ongoing technical refinement. Coiled patients scored better in neuropsychological measures in more recent years, which might in part be attributed to advances in endovascular techniques (25). In contrast, MS has been performed since the late 1930s, and the rate of advances in this procedure has slowed. Nowadays, EV has become a common method and oftentimes the initial treatment of choice for repair of intracranial aneurysms given its less invasive nature (7,9,24,34,60,105). In contrast, clipping requires craniotomy, brain tissue retraction, and direct manipulation of arteries, which bears the risk of injury to perforating branches with consecutive reduction of blood flow (21,24). The multicenter ISAT was the first and most comprehensive study, directly comparing the safety and efficacy of MS and EV techniques after aSAH with respect to differences in neurological morbidity and mortality rates (73), and in the N-ISAT, a substudy on the "Neuropsychological Outcomes from the ISAT", in neuropsychological outcome (105). The controversially discussed results deemed EV superior to MS with regard to lower risk of death and dependency at 1 year versus 2 months post-treatment (74). Cognitive impairment was more common in the MS group, and QOL was poorer in neuropsychologically disabled patients across both treatment modalities (23,105). After the publication of this study, a series of studies with conflicting data complicated the discussion. The majority of authors (7,29,55,91,99,103) disproved the hypothesis that the aneurysm-securing procedure poses an influencing factor on cognitive outcome after aSAH. Most recently, a valuable meta-analysis (25) systematically reviewed the literature (7,24,26,28, 34,55,58,59,89,91,99,112) on treatment-specific differences in cognitive outcome after aSAH and dismissed differences between both treatment approaches in most instances.

As highlighted by Egeto et al.(25), with 13 studies available, the comparative literature on treatment modality-dependent effects on cognitive processing after sSAH is sparse. Even fewer authors, like Koivisto et al.(55), have their patients randomly assigned to either MS or EV. Compared to a high volume center treating several aneurysms per day, with MS and EV of 150 patients per year our institution ranges in the middle field. Thus, our institutional neurovascular volume is representative for the majority of neurovascular centers. It has to be emphasized that a randomized study design would be

preferable to our experimental trial to investigate the effects of treatment on cognitive processing. However, bounded by our annual patient volume and ethical considerations, a randomization in a medium-volume clinic on a single-center basis is hardly feasible. Thus, as described in the Material and Methods section, much effort has been made to analyze three homogeneous patient groups including a FU assessment for cognitive short-term and mid-term outcome. The basic characteristics of our cohort were comparable in all treatment groups in terms of gender, age, co-morbidities, severity of subarachnoid bleeding (27), and clinical grade (41). We caveat the statement with the note that our study is not powered to detect differences due to the small number. In a larger series, an additional power analysis of interactions between aneurysm location, treatment, and cognitive outcome is recommended. The presented groups are imbalanced in terms of a higher proportion of MCA aneurysms in favor of the surgical group, more antiplatelet drug intake at t_1 (EV) and a longer mean time spent on mechanical ventilatory support (pSAH). In adults, the time of anesthesia is extremely unlikely to influence cognitive performance, especially 6 months after treatment. Besides, all but one pSAH patient received intubation anesthesia for DSA, which allows the exclusion of general anesthesia as a negative confounding factor for the evaluation of post-treatment neurocognitive outcome. The predominance of MCA aneurysms could have a significant confounding effect on outcomes, given very different potential perforator injuries and extent of dissection required. From a microsurgical perspective, this fact seems to be negligible, as dominant-side and non-dominant-side pterional approaches were used equally (n=3 each). In a larger sample size, these issues should be considered as a covariate in analysis to control for its impact.

MRI studies comparing brain structure damage consequent to MS or EV have rarely been reported. Several authors suggest more frontotemporal lesions after MS (34,91). On the other hand, it is remarkable that silent thromboembolic events are a common finding after coiling despite meticulous technique and systemic anticoagulation. In this context, it is worth noting that (besides the patient's age, overall medical condition or presence of an intraparenchymal hemorrhage) aneurysm location and morphology are crucial in the selection of treatment type, thus introducing a bias. While most anterior communicating artery (ACoA) aneurysm ruptures are eligible for either clipping or coiling, the angioanatomical features of MCA aneurysms (for example, adjacent arterial branches and small dome/neck ratios) usually constitute a contraindication for EV. As a consequence, studies with higher MCA rupture rates were, in some domains, associated with a more similar performance between clipped and coiled patients (25).

We would like to emphasize that MS and EV must not be considered as competing procedures but rather as two complementary methods for optimal aneurysm treatment. Our results underline that a collaborative interdisciplinary discourse between experienced interventional neuroradiologists and vascular neurosurgeons, integrated into a neurovascular team, is crucial for establishing the best and highly individualized therapeutic strategy with respect not only to aneurysm repair but also to the patient's ideal functional and neuropsychological outcome.

Impact of the Bleeding Event Itself on Neuropsychological Impairment

Our cohort comprises a reference group with pSAH patients, characterized by conservative management, to further illuminate the effect of the aneurysm treatment *per se* on cognitive and functional outcome. 10% of spontaneous bleeding events are non-aneurysmal perimesencephalic (63). Both aSAH and pSAH patients suffer from neuropsychological deficits after ictus (14,52). In our series, the pSAH patients performed significantly better in various aspects of physical and psychological functioning at t_1 and t_2 than aSAH patients. In contrast to the treatment groups, our pSAH patients performed similar to healthy controls in most indices. Given our small sample size and the relatively short FU interval of 6 months, it has to be considered that subtle deficits in cognition and QOL after pSAH might not have been detected with the self-report measures applied. Contrary to former assumptions, which attested pSAH patients a favorable prognosis (16,95), more recent findings (64, 65) indicated that pSAH might not be as benign as previously believed. On average 39 months after pSAH, survivors continued to suffer from cephalgia, depression, obliviousness, mild cognitive deficits and inability to resume their previous occupations (64,65). In conclusion, the aneurysm-securing procedure alone does not sufficiently explain impaired neuropsychological outcome. The pathophysiology and origin of cognitive impairment after SAH is not completely understood (94). A growing body of evidence suggests that the severity of the hemorrhage (7,42-44,49,52,81,82) and the consecutive combination of focal (66) and diffuse brain injury (7,8,68,111) primarily cause the neuropsychological alterations after SAH, rather than the aneurysm location or the selected treatment maneuver (43,46,48,56,80,81).

In our trial, all sSAH groups, the pSAH patients alike, experienced a significant deterioration in Rawhtran. This fact might be attributed to the psychological traumatization by the event of bleeding itself (5,11,76-78), especially in the short-term. The risk of developing chronic post-traumatic stress disorder (PTSD) (45) might depend on the traumatic event itself, since, for example, the risk for PTSD seems to be much lower after myocardial infarction than after SAH or mild head injury (106). Interestingly, there are systematic differences in self- and proxy-rated QOL with an under-reporting of symptoms and minimizing of complaints by the burdened patients (19). It is hypothesized that brain injury may weaken the patient's capacity to intentionally suppress intrusive thoughts leading to increased avoidance or to undue unconcern, neglect or unawareness of symptoms (19). We argue that this fact should be considered when evaluating cognition, in particular in self-report assessments. In our study design, however, confounders seem to be minimized by the selection of good-grade SAH patients and by the information given in the semi-structured interview.

Methodological Considerations

Limits: The small sample size is a commonly acknowledged

methodological limitation, which may tremendously affect the results. However, we preferred analyzing homogeneous groups to recruiting a larger but inhomogeneous cohort, which might be susceptible to misinterpretations. The strict and very detailed selection criteria were set up to minimize confounding variables and to maximize the generalizability by generating valid and robust data.

A caveat to our findings is the typically reported selection bias by the overrepresentation of "ideal" SAH patients with good neurological status on admission. This degree of collective homogeneity may limit potential test performance differences. Furthermore, our results, reflecting the best condition attainable, are probably not applicable to poor-grade SAH patients. In almost all SAH trials on treatment-dependent cognitive outcome (7,24,26,28,29,34,55,58,59,89,99,112), the majority of patients enrolled initially presented with a good clinical grade (25). Solely, Proust et al.(91) published a collective with a higher proportion of HH grade III-IV cases. From a methodological point of view, a major reason for the omission of poor-grade SAH individuals is the assumable inability or unwillingness to undergo a demanding neuropsychological test battery. Moreover, only 21/26 recruited patients could be assessed cognitively at FU. One may speculate that the 5 excluded patients were unable to complete the cognitive assessment due to severe neuropsychological impairment, and, hence, the true impairment rate was underestimated.

Instead of a performance-based neuropsychological assessment, this study is based on self-report measures, which might not be sensitive and comprehensive enough to detect all impaired patients, and which do not systematically cover all relevant cognitive domains. However, subjective experience of neuropsychological dysfunction is considerable from a QOL perspective. In addition, the error rate due to potential fatigue in lengthy, comprehensive and demanding cognitive batteries might be minimized. Rapid and sensitive bedside screening tools like the SF-36 and the ISR can be used to identify candidates for detailed neuropsychological assessment.

Early outcome evaluation at acute stages bears the risk of detecting transient and non-final differing negative effects of aneurysm treatment on cognitive performance, leveling off or even worsening over time, or the risk of measuring the impact of the bleeding itself rather than treatment-associated phenomena. FU testing in neuropsychological outcome assessment is scarce (29,55). Thus, our trial contributes valuable data to the time course of neuropsychological performance in the early stages of recovery. Both medium-term and long-term outcome assessments in the setting of (randomized) multicenter trials like the Swiss "Study on Aneurysmal Subarachnoid Hemorrhage" (SOS) study group (121) are required to verify the severity of cognitive impairment and follow the course of neuropsychological changes in individual patients over years.

Strengths: Compared to the limited number of SAH trials dealing with the effects of aneurysm treatment on cognition, the actual strength of this study lies in its prospective and standardized design with an accurate evaluation of functional outcome, QOL, and neurobehavioral dysfunction after sSAH. This is the first study examining SAH patients by means of the ISR. The questionnaire is validated in psychosomatic disorders and can be recommended in the evaluation of neuropsychological sequelae in SAH patients for the future. Eminently, the inclusion of a reference group with pSAH provided further information to what extent aneurysm-securing procedures *per se* affect cognitive outcome.

CONCLUSION

We investigated the treatment-specific differences in the time course of neuropsychological recovery within the first 6 months after sSAH. Our preliminary data on self-reported QOL, and physical and mental well-being after treatment for aSAH indicates that, in the short-term, there are minimal differences between MS and EV for ruptured intracranial aneurysms with a significantly better performance in Pfi, more alleviation in nutrition disorder, and less Pain in surgically treated patients compared to their coiled counterparts. However, the treatment modality does not seem to affect overall neuropsychological outcome, at least at 6 month-FU. Both the MS and EV patients improved in several physical items over time. Yet, the EV patients still performed significantly worse in Pfi, Rolph, Mhi, and, together with the MS patients, in Vital, than healthy controls. Thus, we argue that, from a QOL perspective, MS patients may recover at a faster rate in the short-term after aSAH. pSAH patients performed significantly better in various aspects of physical and psychological functioning than patients with aSAH at t_1 and t_2. The deficiency of studies dealing with this issue prevents any strong conclusions, although a few recent studies yielded similar results. Prospective randomized trials are mandatory to elucidate the treatment-associated neuropsychological morbidity in the long-run and to advise individualized future care management strategies and physical, neurological, cognitive, and occupational rehabilitation approaches.

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