

Treatment of 817 patients with spontaneous supratentorial intracerebral hemorrhage: characteristics, predictive factors and outcome

Homajoun Maslehaty,
Athanasios K. Petridis, Harald Barth,
Alexandros Doukas,
Hubertus Maximilian Mehdorn

Department of Neurosurgery, University
Hospitals Schleswig-Holstein, Campus
Kiel, Germany

Abstract

The aim of this study was to present the data of a large cohort of patients with spontaneous supratentorial intracerebral hemorrhage (ICH), who were treated in our department or to cerebral ischemic stroke were excluded. The clinical performance at time of admission and discharge were scored using the Glasgow coma scale (GCS) and the Glasgow outcome scale (GOS) respectively. The patients' cohort was divided into surgically and conservatively treated groups. Statistical analysis [Analysis of Variance (ANOVA) and χ^2 -test] was done for various parameters to analyze their impact on morbidity and mortality. In total, we analyzed the data of 817 patients (364 female and 453 male). Two hundred and sixty-nine patients (32%) were treated conservatively and 556 patients (68%) underwent surgical procedures, *i.e.* cerebrospinal fluid drainage in 110 (19.8%), craniotomy in 338 (60.7%) and application of both methods in 108 patients (19.4%). Total mortality rate was estimated with 23.5%. GCS<8, age over 70 years, intraventricular and basal ganglia hemorrhage, coumadin medication, combination of co-morbidities, hypertensive hemorrhage and postoperative re-bleeding were statistically significant risk factors for worse outcome (GOS 1 and 2) in the operated group. Similar to the observations of the operated group, GCS<8, age over 70 years and coumadin medication were statistically significant for worse outcome in the conservative group. In contrast, lobar plus basal ganglia ICH and multi-lobar

hemorrhages were the most significant factors for worse outcome in the conservative group. The results of our study show that ICH remains a multifarious disease and challenges neurosurgeons repeatedly. Selection of the treatment modality and prediction for neurofunctional outcome underlies various parameters. Treatment recommendations of ICH remain an unsolved issue. The consideration of the GCS grade at admission is the most important predictive factor. Old age is not an absolute contraindication for surgery, but cumulative multi-morbidity, especially cerebrovascular and cardiovascular diseases and oral anticoagulant therapy should be regarded critically in view of surgical treatment.

Introduction

Despite ongoing progress in intensive care and multimodal therapy strategies, spontaneous intracerebral hemorrhage (ICH) remains a life-threatening event with associated complex neurofunctional morbidity affecting 10-20 per 100.000 annually. The mortality from ICH is higher compared to cerebral ischemic stroke, whereby the majority of deaths occur within the first days after ICH.¹⁻⁹ Concerning the treatment opportunities, many retro- and prospective studies have been conducted through the years, but a definitive treatment consensus still remains controversial.¹⁰⁻¹⁶ Several studies from different decades have termed different variables and analyzed their prediction for morbidity and mortality.^{2,3,17,18}

The aim of our study was to present the data of a large cohort of patients with supratentorial ICH, which were treated in our department and to share the experiences we gained. We hereby give a current overview considering special clinical characteristics, performed therapy and different predictive factors for morbidity and mortality.

Materials and Methods

Database

We reviewed all patients' data with spontaneous ICH, which were treated in our department in a time span of 11 years through an analysis of our database. The data collection was done descriptively using a computer based data file. A high number of patient data such as neuro-functional status, imaging results, medical history, therapy, complications, clinical course, outcome and follow-up were captured in the database prospectively with continuous updating.

Correspondence: Athanasios K. Petridis, Department of Neurosurgery, University Hospitals Schleswig-Holstein, Campus Kiel, Arnold-Heller-Strasse 3, 24105 Kiel, Germany. Tel. +49.431 597.8550. E-mail: optidisc@aol.com

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Inclusion criteria

In the current study, we excluded patients with hemorrhage located infratentorially from the analysis. Due to an essential impact of the underlying cause of the hemorrhage on performed therapy, patients with immediately diagnosed vascular malformations as the source of the hemorrhage and hemorrhage related to cerebral ischemic stroke were excluded from the study as well. Diagnosis was made by computed tomography (CT) scanning or magnetic resonance imaging. Images were evaluated by neuroradiologists independently to the analysis of the study and ICH was divided into five categories: uni-lobar, bi-lobar, multi-lobar, ventricular hemorrhage and hemorrhage in the basal ganglia.

Patient admittance

Thirty one point nine percent of the patients were transferred to our department from the clinic of internal medicine of our university hospital, where they had been initially admitted. Thirty percent of the patients were admitted from other hospitals of our referral area and were initially seen by general surgeons, neurologists or internal medicine doctors. Seventeen percent of the patients were admitted to our department from home by ambulance and further 15% from the department of neurology of our university hospital due to diagnosed hemorrhage on CT scanning in line with diagnostic evaluation of expected cerebral ischemic stroke. Eighty six percent of the patients were admitted to our department at the same day after occurrence of symptoms and diagnosis, whereas 10.3% were referred

within one week and 3.8% later than one week after onset.

Management and therapy

After admission, the patients were examined in the emergency room to decide between immediate surgical procedure, conservative treatment and the need for further diagnostic evaluations. Patients with ICH and coincidental aneurysmal like bleeding pattern or expected vascular malformation were examined by CT-angiography or digital subtraction angiography. Decision for surgical procedure after diagnosis was done in cases of space occupying hemorrhage, shift of the midline structures and neuro-functional complaints under consideration of co-morbidities, general health condition and age on a case-by-case basis.

Surgical procedure included craniotomy with complete or partial evacuation of the hemorrhage or cerebrospinal fluid (CSF) drainage in cases of ventricular hemorrhage and occlusive hydrocephalus. During surgery tissue samples were routinely collected from the hemorrhage and the surrounding brain tissue to enable histopathological work up.

Conservative treatment strategies aimed to reduce the risk of cerebral edema and enlargement of the hemorrhage. Moreover, supportive drug therapy of present complications, such as hypertension, electrolyte disorders, hyperglycaemia, fever and prevention of other intensive care unit (ICU) related complications like infections and deep vein thrombosis was done for all patients. If necessary, mechanical ventilation was obtained and probes were implanted for monitoring of the intracranial pressure.

All patients were treated in the neurosurgical ICU with continuous measurement of the arterial blood pressure, pulse rate, oxygen saturation and continuous recording of electrocardiogram. The neurological condition in the continuing course was assessed by the physician at the ICU closely. During hospitalization of the patients' control CT scans were done at varying intervals or immediately in cases of new occurrence of neurological deterioration. Patients that underwent surgery were examined by CT scanning within 24 h postoperatively. Re-bleeding or recurrent hemorrhage was defined by gain of hemorrhage on CT scanning.

Classification and follow-up

The clinical performance at time of admission and discharge were scored using the Glasgow coma scale (GCS) and the Glasgow outcome scale (GOS) respectively. To simplify the overview and for further analysis the patients were categorized into three GCS and GOS groups: I: GCS<8, II: GCS 9-12, III: GCS>13; worse outcome: GOS 1 and 2, intermediate outcome: GOS 3, good outcome: GOS 4 and 5. Different parameters were analyzed in

view of their impact on outcome. Subgroups were formed with a cut-off age of 70 years.

The assessment of 30 days follow-up after ICH was done either in our out-patient department or after consultation of further processing institutions by phone calls.

Statistical analysis

Statistical tests were performed by Analysis of Variance (ANOVA) and χ^2 test in this study with an estimated significance of the results with a P-value ≥ 0.05 (< 0.05).

Results

Demographic data

In total, we analyzed the data of 817 patients with spontaneous supratentorial ICH (364 female and 453 male). The female to male ratio was estimated with 1:1.25. The mean age of the patients was 64 years (range 4 months to 94 years). The peak age of the patients was between the 6th and 7th decade of life (58.4%) (Figure 1). ICH was firstly manifest in 770 patients (94.2%), whereby 47 patients (5.7%) had already suffered from ICH in their medical history.

Neurological status at time of admission

Of the total number of 817 patients with ICH, 300 (36.8%) were comatose and 319 (39%) patients had altered consciousness. The remaining patients were alert, but had different neurological impairments. Six hundred and seventy-five patients (82.6%) presented with a contralateral hemiparesis and 454 patients (55.5%) with positive pyramidal signs. One hundred and ninety three patients (23.6%) presented with expressive or sensory aphasia and 159 patients (19.5%) with a dilated and non-responsive pupil. Dysfunction of

other cranial nerves was observed in 39 patients (4.7%). Twenty-four patients (12%) had coincident a dilated and non-responsive pupil and other cranial nerve disorders. Respiratory insufficiency was observed in 108 patients (13.2%) and aspiration in 16 patients (14.8%). Three hundred and thirty-eight patients (41.4%) were in worse clinical condition with a GCS<8, 288 patients (35.2%) were categorized in the intermediate group with a GCS of 9-12 and 191 patients (23.4%) were in good condition with a GCS>13.

Co-morbidities and risk factors

Most common co-morbidities and risk factors were arterial hypertension (78%), coronary heart disease (55.8%), diabetes mellitus (18.6%) and cerebrovascular disease (13.1%). Ongoing anticoagulant therapy and ICH following extracranial thrombolysis was observed in 13.5%. The overall co-morbidities and risk factors and their distribution to the age of the patients are demonstrated in Table 1.

Localization of intracerebral hemorrhage

We defined six categories for further analysis: uni-lobar (n=277, 33.9%), bi-lobar (n=165, 20.2%), multi-lobar (n=32, 3.9%), ventricular hemorrhage (n=20, 2.4%), hemorrhage in the basal ganglia (n=283, 34.6%) and combined lobar and basal ganglia hemorrhage (n=40, 4.9%). ICH was located right hemispheric in 399 (48.8%) and left hemispheric in 392 cases (47.9%). Bi-hemispheric occurrence was observed in 26 cases (3.1%).

Treatment

Two hundred and sixty-one patients (32%) were treated conservatively and 556 patients (68%) underwent surgical procedures, *i.e.* CSF drainage in 110 patients (19.8%), craniotomy in 338 patients (60.7%) and application of both methods in 108 patients (19.4%). Surgical pro-

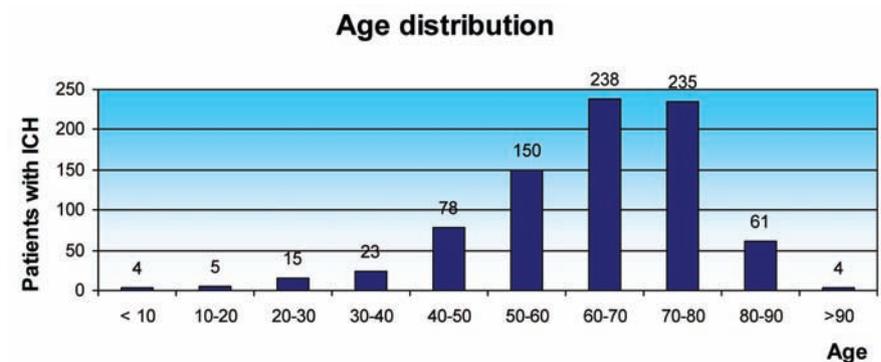


Figure 1. Age distribution of patients with intracerebral hematomas treated. ICH, intracerebral hemorrhage.

cedure was done in 97 of 125 patients (77.6%) younger than 50 years and in 457 of 692 patients (66.18%) older than 50 years. Four hundred nineteen (75.4%) patients were treated surgically during the first 24 h after diagnosis and 137 (24.6%) patients were operated in the continuing course e.g. due to secondary deterioration or delayed transfer to our department.

Complications

Pneumonia was the most common complication during the hospitalization of the patients and occurred in 150 patients (18.4%), followed by cardiac disorders in 89 (10.9%) and re-bleeding in 81 patients (9.9%), diagnosed in line with neurological deterioration. Twenty-eight patients (3.4%) developed cerebral ischemia and 23 patients (2.8%) hydrocephalus with necessity of permanent shunting. Meningitis occurred in 14 (1.7%) and deep vein thrombosis in 6 patients (0.7%). Seventy-four patients (9.1%) were depending on long-term mechanical ventilation longer than 10 days and received tracheotomy.

Etiology of intracerebral hemorrhage

Histological work up of collected tissue samples in 446 patients during surgery revealed cerebral amyloid angiopathy (CAA) in 80 cases (17.9%), preoperatively occult vascular anomalies in 37 cases (8.3%) and tumor bleedings in 49 cases (11%). Hemorrhage related to hypertension was estimated in 208 cases (46.6%), whereby the cause of the bleeding remained unclear in 72 patients (16.1%).

The analysis of re-bleeding (n=81, 9.9%) in relation to the etiology of ICH showed a marked association to CAA in 21 patients (26.2%) and to vascular malformation in 6 patients (16.2%). Re-bleeding was associated to hypertension and tumor in 62 patients (9.7%) and 4 patients (8.1%) respectively.

Overall outcome and predictive factors

In total, 206 of 817 treated patients (25.2%) had a worse outcome (GOS 1 and 2), i.e. 125 patients (22.4%) of the operated and 81 patients (31%) of the conservative group. The overall mortality (GOS 1) was estimated with n=192 (23.5%). Most patients of both groups (428 patients, 52.3%) had an intermediate outcome: 324 (58.2%) of the operated and 104 (39.8%) of the conservative group. Good outcome was observed in 183 patients (22.4%): 107 patients (19.2%) of the operated and 76 patients (29.1%) of the conservative group.

Tables 2 and 3 shows the distribution of various factors and their relation to the outcome grades for both groups. Statistical analysis demonstrated that low GCS grade (<8), age

over 70 years, intraventricular and basal ganglia hemorrhage, as well as the combination of different co-morbidities and coumadin medication had a significant impact for worse outcome in the operated group. Hypertensive ICH was seen most frequently, followed by ICH

associated to CAA. As the most important complication and statistically significant predictive factor re-bleeding occurred in 77 patients (13.8%) with a mortality rate of 45.5%.

Low GCS grade, age over 70 years, combined occurrence of co-morbidities and coumadin

Table 1. Co-morbidities and risk factors.

Age	N (%)	Co-morbidities and risk factor (multiple naming)				
		HTN	CHD	NIDDM	ACG (81/29)	CVD
Total	817 (100%)	636 (77.8%)	416 (50.9%)	152 (18.6%)	110 (13.5%)	107 (13.1%)
< 20	9 (1.1%)	1 (1.1%)	0	0	0	0
21-30	15 (18.4%)	1 (0.7%)	0	0	0	0
31-40	23 (28.2%)	8 (34.7%)	1 (4.3%)	1 (4.3%)	1 (4.3%)	0
41-50	78 (9.5%)	48 (61.5%)	12 (15.4%)	6 (7.7%)	11 (14.1%)	4 (5.1%)
51-60	150 (18.4%)	114 (76%)	44 (29.3%)	23 (15.3%)	11 (7.3%)	14 (9.3%)
61-70	238 (29.1%)	200 (84%)	115 (48.3%)	46 (19.3%)	41 (17.2%)	34 (14.3%)
71-80	239 (29.2%)	209 (87.4%)	188 (89.9%)	56 (23.4%)	39 (16.3%)	37 (15.5%)
> 80	65 (8%)	55 (84.6%)	56 (86.1%)	20 (30.7%)	5 (7.7%)	18 (27.7%)

HTN, arterial hypertension; CHD, coronary heart disease; NIDDM, non insulin dependent diabetes mellitus; ACG, anticoagulants; CVD, cerebrovascular disease.

Table 2. Predictive factors I.

Factors	Total	Predictive factors I (surgical treatment, n= 556)				
		GOS 1	GOS 2	GOS 3	GOS 4	GOS 5
GCS						
< 8	250	83	11	143	13	-
9-12	217	28	3	141	37	8
> 13	89	-	-	40	28	21
Age						
< 70 years	378	60	12	216	63	27
> 70 years	178	49	2	110	15	2
Localization						
Uni-lobar	207	32	2	107	43	23
Bi-lobar	122	18	3	76	21	4
Multi-lobar	14	2	-	10	2	-
Basal Ganglia	174	46	8	109	9	2
Basal + lobar	24	6	1	16	1	-
IVH	15	5	-	8	2	-
Co-morbidities						
H + D	88	24	3	54	7	-
H + Co	277	55	5	185	30	2
H + Ce	57	13	-	37	6	1
H + Co + Ce	49	13	-	31	4	1
H + D + Co + Ce	21	5	-	14	2	-
Coumadin	56	23	1	23	9	-
Etiology						
Hypertensive	414	84	10	261	49	10
CAA	73	13	-	50	9	1
Tumor	43	5	-	21	9	8
CM	8	-	-	7	1	-
AVM	27	3	-	14	7	3
Complications						
Re-bleeding	77	35	2	39	1	-
HCP	22	6	1	14	1	-
Ischemia	28	8	1	18	1	-

GOS, Glasgow outcome scale; GCS, Glasgow coma scale; IVH, intraventricular hemorrhage; H, hypertension; D, diabetes mellitus; Co, coronary heart disease; Ce, cerebrovascular disease; CAA, cerebral amyloid angiopathy; CM, cavernous malformation; AVM, arteriovenous malformation; HCP, hydrocephalus.

Table 3. Predictive factors II.

Factors	Total	Predictive factors II (surgical treatment, n= 556)				
		GOS 1	GOS 2	GOS 3	GOS 4	GOS 5
GCS						
< 8	88	76	-	11	1	-
9-12	71	3	-	53	13	2
> 13	102	2	-	40	41	19
Age						
< 70 years	106	24	-	35	34	13
> 70 years	155	59	-	68	20	8
Localization						
Uni-lobar	71	11	-	27	25	8
Bi-lobar	43	20	-	11	7	5
Muliti-lobar	18	12	-	5	1	-
Basal Ganglia	109	25	-	59	19	6
Basal + lobar	16	12	-	2	2	-
IVH	5	1	-	1	1	2
Co-morbidities						
H + D	59	24	-	22	8	5
H + Co	6	-	-	-	-	6
H + Ce	-	-	-	-	-	-
H + Co + Ce	-	-	-	-	-	-
H + D + Co + Ce	1	-	-	-	-	1
Coumadin	26	14	-	7	4	1
Complications						
Re-bleeding	5	2	-	3	-	-
HCP	1	1	-	-	-	-
Ischemia	-	-	-	-	-	-

GOS, Glasgow outcome scale; GCS, Glasgow coma scale; IVH, intraventricular hemorrhage; H, hypertension; D, diabetes mellitus; Co, coronary heart disease; Ce, cerebrovascular disease; HCP: hydrocephalus.

medication were likewise negative predictors in the conservative group. Considering the localization of the hemorrhage multi-lobar, lobar plus basal ganglia ICH were statistically significant for worse outcome.

Follow-up 30 days after the intracerebral hemorrhage

The overall mortality of the patients with supratentorial ICH was estimated with 23.5% (n=192). During the first 30 days after ICH 52.1% of the patients were still treating in the hospital. Seventeen percent of them still received treatment in rehabilitation hospitals, whereas only 6.4% were already discharged at home. One percent of the patients were transferred in nursing facilities.

Discussion

Arterial hypertension was the primary cause for spontaneous ICH in our study, followed by CAA and less frequently tumor bleedings and hemorrhage from vascular malformations. Our results are congruent to the results of other studies.^{2,3,19-21} The postoperative re-bleeding rate was significantly associated to CAA in

26.2% compared to arterial hypertension in 9.7%. However, the mortality of patients with CAA was lower than patients with hypertension (20% vs. 24.4%). As already described in one of our previous studies, we conclude that re-craniotomy for re-bleeding in CAA does not lead unavoidably to an unfavorable outcome and should be kept in mind for decision making for surgery.²²

The most statistically significant predictive factors for an unfavorable outcome in the operated group were low GCS grade on admission (GCS<8), age over 70 years, basal ganglia and intraventricular hemorrhage, multi-morbidity with a high cerebrovascular risk profile and coumadin medication. Similar results could be established within the conservatively treated group, except those patients with multi-lobar hemorrhage and worse clinical performances, which were not treated operatively. Karnik and co-workers determined age >60 years as an important factor for higher mortality rates.²³ Hill and colleagues found that patient age <45 years reduces the mortality up to 50%.²⁴ Similar observations were done by Kuramatsu, Schwarz and Sorimanchi.²⁵⁻²⁷

Initial level of consciousness as an independent predictive factor was estimated by several authors. Douglas and co-workers observed mortality rates of 43%, Nath *et al.* of

69% and Turhim *et al.* of 78% in patients with a GCS score <8. In contrast to this mortality rate was significantly lower in the patient group of GCS>13.²⁸⁻³⁰ The mortality rate in our study was 33.2% in patients with a GCS score of <8 treated surgically and 66.6% treated conservatively. Within the patient group with GCS>13 the mortality rate was 0% treated surgically and 1.9% treated conservatively. Despite variation in treatment and management strategies of each centre low GCS grade on admission remains one of the major causes for high mortality rates.

Anticoagulant therapy is widely used in varying clinical constellations, whereby the risk of developing severe ICH is elevated. ICH is associated to oral anticoagulants in about 15% and the outcome is inferior to those patients without anticoagulants.^{31,32} As expected, our results show high mortality rates of ICH associated to oral anticoagulants of 41% in the operated and 53.8% in the conservative group. Hence, oral intake of anticoagulants remains a very important and statistically significant predictive factor for worse outcome.

Localization of ICH is another important predictive factor for morbidity and mortality. Several studies have observed that ICH located in the basal ganglia and in the ventricular system have a worse outcome compared to lobar ICH.^{29,33,34} We could confirm this observation in our study, indexing the mortality rate of basal ganglia hemorrhage with 26.4% in the operated and 22.9% in the conservative group. The mortality rate of intraventricular hemorrhage was estimated with 33.3%. Patients with basal ganglia hemorrhage plus lobar ICH, which were treated surgically, had a lethal outcome in 25%. Compared to this, the mortality rate in lobar hemorrhages was significantly lower.

The total mortality rate was estimated with 23.5% and is congruent with the results of other studies.^{5,35} Surgical procedure reduced the mortality and improved the outcome grade in our series, whereby the benefit for the patients with severe disability should be regarded critically.

Patients with small uni-lobar ICH and patients with huge multi-lobar ICH with a GCS grade <8 were not treated operatively. Regarding the outcome results in these two patient groups, conservatively treated uni-lobar ICH showed a higher rate of good outcome (29.1%) compared to the operatively treated group (19.2%). In contrast to this, patients with multi-lobar hemorrhage with an intermediate GCS grade and surgical treatment showed a significantly better outcome score compared to patients with worse clinical performance. Hence, decision making between surgical and conservative treatment should be considered in view of different parameters, whereby a consensus is still controversial.

The largest known study to date is the

International Surgical Trial in Intracerebral Haemorrhage (STICH). The STICH trial randomized 1033 patients from 83 centers in 27 countries and showed no overall benefit from early surgery, compared with initial conservative treatment.¹¹ The initiated STICH II trial has been initiated and will focus on superficial lobar hemorrhages.^{12,36} However, it is to mention that about 25% of all patients of the conservative group included in the STICH trial were treated operatively few days after randomization due to neurological deterioration. Nakano and Ohkuma postulated that neurological deterioration could possibly be preventable, if those patients were initially treated surgically.³⁷ Regarding the number of the surgically treated patients in our study, we pursued an early surgical strategy before deterioration and exhibit consequently more patients in the operative group. Conservative treatment appeared meaningful in patients with good clinical performance and small lobar hemorrhages, as well as in patients with worse clinical performance and large bi- or multi-lobar hemorrhages, since surgery does not improve the condition of these patients. Treatment recommendations for the remaining patients are very difficult to make and should be considered individually. It remains to be seen whether the STICH II trial brings more clarification and gives detailed recommendations, whereby this issue appears questionable.

As Steiner et al. recently published, ICH volume was substantially decreased in patients who underwent hematoma evacuation between 24 and 72 h after hospital admission. This was associated with better clinical outcome.¹⁵ Surgery could also prevent the early hematoma growth, which occurs in about 38% of the patients within the first three hours of occurrence.³⁸

Except from the conventional craniotomy, other surgical methods are also used in different centers. For example, the Stereotactic Treatment of ICH by means of Plasminogen Activator trial (SICHPA) showed a significant reduction of the ICH volume up to 10-20%.⁹ However, a significant difference in overall survival in three months could not be observed.^{39,40} Marquardt and co-workers could improve the levels of consciousness of patients via stereotactic aspiration of ICH.⁴¹

For deep-seated ICH and intraventricular hemorrhage two additional studies were carried out: MISTIE and CLEAR IVH. The first one used borehole aspiration and evacuation of hemorrhage with haemolytic and thrombolytic drugs. In the second trial, r-tPA was injected to the ventricular system to induce lysis of blood clots in hemorrhages less than 30 mL. Both studies delivered positive results with possible accelerated clot lysis compared to conservative treatment.^{42,43}

As a non-invasive supportive treatment

approach, Mayer and co-workers used recombinant activated factor VII (rFVIIa) to prevent enlargement of hemorrhage. In this randomized, double-blinded, placebo-controlled study of 399 patients, application of rFVIIa within 4 h after occurrence of ICH showed limited growth of hemorrhage of about 50%. Furthermore the mortality rate could be reduced up to 38%.⁴⁴ The risk of thromboembolic events in patients who received recombinant Factor VIIa for anticoagulation-associated ICH was not higher, compared to those patients, which were treated for spontaneous ICH in the Factor Seven for Acute Hemorrhagic Stroke (FAST) trial.⁴⁵ The use of vitamin-K dependant coagulation factors in patients with ICH under coumadin medication should be started already upon admission.⁴⁶

Conclusions

The results of our study show that ICH remains a multifarious disease and challenges neurosurgeons repeatedly. Selection of the treatment modality and prediction for neuro-functional outcome underlies various parameters. Treatment recommendations of ICH remain an unsolved issue. The consideration of the GCS grade at admission is the most important predictive factor. Old age is not an absolute contraindication for surgery, but cumulative multi-morbidity, especially cerebrovascular and cardiovascular diseases and oral anticoagulant therapy should be regarded critically in view of surgical treatment.

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