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Hematoma Growth and Outcome in Treated Neurocritical Care Patients With Intracerebral Hemorrhage Related to Oral Anticoagulant Therapy

Comparison of Acute Treatment Strategies Using Vitamin K, Fresh Frozen Plasma, and Prothrombin Complex Concentrates

Hagen B. Huttner, MD; Peter D. Schellinger, MD, PhD; Marius Hartmann, MD; Martin Köhrmann, MD; Eric Juettler, MD; Johannes Wikner, MD; Stephan Mueller; Uta Meyding-Lamade, MD; Ralf Strobl; Ulrich Mansmann, MD; Stefan Schwab, MD; Thorsten Steiner, MD

Background and Purpose—Intracerebral hemorrhage (ICH) is the most serious and potentially fatal complication of oral anticoagulant therapy (OAT). Still, there are no universally accepted treatment regimens for patients with OAT-ICH, and randomized controlled trials do not exist. The aim of the present study was to compare the acute treatment strategies of OAT-associated ICH using vitamin K (VAK), fresh frozen plasma (FFP), and prothrombin complex concentrates (PCCs) with regard to hematoma growth and outcome.

Methods—In this retrospective study, a total of 55 treated patients were analyzed. Three groups were compared by reviewing the clinical, laboratory, and neuroradiological parameters: (1) patients who received PCCs alone or in combination with FFP or VAK (n=31), (2) patients treated with FFP alone or in combination with VAK (n=18), and (3) patients who received VAK as a monotherapy (n=6). The end points of early hematoma growth and outcome after 12 months were analyzed including multivariate analysis.

Results—Hematoma growth within 24 hours occurred in 27% of patients. Incidence and extent of hematoma growth were significantly lower in patients receiving PCCs (19%/44%) compared with FFP (33%/54%) and VAK (50%/59%). However, this effect was no longer seen between PCC- and FFP-treated patients if international normalized ratio (INR) was completely reversed within 2 hours after admission. The overall outcome was poor (modified Rankin scale 4 to 6 in 77%). Predictors for hematoma growth were an increased INR after 2 hours, whereas administration of PCCs was significantly protective in multivariate analyses. Predictors for a poor outcome were age, baseline hematoma volume, and occurrence of hematoma growth.

Conclusions—Overall, PCC was associated with a reduced incidence and extent of hematoma growth compared with FFP and VAK. This effect seems to be related to a more rapid INR reversal. Randomized controlled trials are needed to identify the most effective acute treatment regimen for lasting INR reversal because increased levels of INR were predisposing for hematoma enlargement. (*Stroke*. 2006;37:1465-1470.)

Key Words: intracerebral hemorrhage ■ outcome ■ warfarin

Intracerebral hemorrhage (ICH) is the most fatal form of stroke, with mortality ranging from 30% to 55% and severe disability in the majority of survivors.^{1,2} In patients with oral anticoagulant therapy (OAT)-associated ICH, mortality is as high as 67%.^{2,3} The use of warfarin and an increased intensity of anticoagulation are independent predictors of 3-month mortality.²

Initial hematoma volume is the most powerful predictor of neurological deterioration, functional outcome, and mortality both in spontaneous supratentorial ICH and OAT-ICH, whereas level of consciousness is highly predictive in infratentorial ICH.^{4,5} Consistently, early hematoma growth is strongly associated with a poor outcome.¹ A reliable bedside technique for estimating hematoma volume, the so-called ABC/2 technique,

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From the Departments of Neurology (H.B.H., P.D.S., M.K., E.J., J.W., S.M., U.M.-L., T.S.) and Neuroradiology (M.H.), University of Heidelberg, Germany; Institute of Medical Statistics (R.S., U.M.), University of Munich (L.M.U.), Germany; and Department of Neurology (H.B.H., P.D.S., M.K., S.S.), University of Erlangen, Germany.

The first 2 authors contributed equally to this work.

Correspondence to Hagen B. Huttner, Department of Neurology and Neuroradiology, University of Heidelberg, INF 400, 69120 Heidelberg, Germany. E-mail hagen.huttner@neuro.imed.uni-erlangen.de

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has been established and validated repeatedly.^{6,7} In OAT-ICH hematomas, >50% are irregularly shaped, and in these cases, ABC/3 assesses hematoma volume more precisely.⁸ Hematoma expansion occurs in up to 35% of patients with spontaneous ICH within the first 3 hours.^{1,9} In contrast, the incidence, time course, and rate of hematoma expansion in OAT-ICH remain poorly understood, the latter being as high as 28% to 54%.^{10,11}

Pharmacological management is to prevent hematoma growth by prompt reversal of the anticoagulant effect. Treatment options include the use of vitamin K (VAK), fresh frozen plasma (FFP), and prothrombin complex concentrates (PCCs).¹² There is an ongoing controversy with regard to treatment, and although guidelines such as stated by the British Committee for Standards in Hematology exist, the different guidelines are inconsistent on an international level.^{13,14}

The aim of the present study was to compare these acute treatment strategies in OAT-ICH patients with regard to hematoma growth and outcome. We decided to group the patients with OAT-ICH into those who received: (1) PCCs alone or in combination with FFP or VAK, (2) FFP alone or in combination with VAK, and (3) VAK as a monotherapy. Our hypothesis was that administration of PCCs is associated with the least frequent occurrence of hematoma growth because of fastest international normalized ratio (INR) reversal.

Methods

Patient Selection

This retrospective study of our prospectively organized database included all patients treated on our stroke and intensive care units between January 1999 and December 2003 with the diagnosis of an OAT-ICH within 12 hours of symptom onset (n=131). The diagnosis of a parenchymal OAT-ICH was made based on computed tomography (CT; in agreement of the neurologist and neuroradiologist at duty) and an INR ≥ 1.5 . We excluded all patients: (1) with evidence of primary subdural, epidural, or subarachnoid hemorrhage (n=38); and (2) whose hematomas had been surgically evacuated (n=11). These 11 patients were excluded because of preassigned administration of PCCs before surgery, which was performed for volume reduction but not because of hematoma growth. ICH patients with an INR <1.5 were considered to be not sufficiently anticoagulated and were excluded from analysis (n=7). Finally, we excluded all patients with an initial (or made within 24 hours) do-not-resuscitate order (DNR) or do-not-treat order (DNT) as well as patients who received therapy later than 1.5 hours after admission (DNR/DNT; n=20; these were moribund patients who were characterized by >85 years of age, herniation signs on initial CT, being admitted comatose, and experiencing severe comorbidity. None of these patients received a control CT and were therefore excluded. Fifty-five patients remained for analysis.

Clinical Management

Three treatment groups for the reversal of increased INR levels were defined: (1) patients who received PCCs alone or in combination with FFP or VAK (group I; n=31), (2) patients treated with FFP alone or in combination with VAK (group II; n=18), and (3) patients who received VAK as a monotherapy (group III; n=6). All drugs were administered intravenously, PCCs and FFP according to a body weight-adjusted dose, and dosage of VAK was 5 to 20 mg. Treatment decision was made by the physician on duty. Parameters such as coronary diseases or chronic heart failure might have influenced initial treatment decisions but were not assessable in this retrospective study.

Therapy was initiated in all patients within 0.9 ± 0.4 (median 1 [0 to 1.5]) hours after admission. None of the included patients received

drugs later than 1.5 hours. INR was routinely controlled in all patients after 1.5 ± 1.0 (range 0.3 to 2.7) hours after admission. Early reversal was defined as normalization of INR within 2 hours after admission. In patients without complete INR reversal (ie, INR ≤ 1.4), repeated INR analyses and further administration of PCCs and FFP were performed until full INR reversal was achieved. INR was routinely controlled after 12 (12.6 ± 2.8) hours (Table 1).

Imaging

ICH was diagnosed immediately after hospital admission by CT or MRI (Siemens Somatom Volume zoom and Siemens Symphony; 1.5 T). Average time from onset of symptoms to neuroimaging was 4.23 ± 3.04 hours (median 4 [1 to 12] hours). For hematoma growth assessment, all patients received a control CT 24 (25.3 ± 6.2) hours after baseline scan as well as before discharge and in cases of deterioration. Two investigators blinded to treatment and other clinical variables assessed the imaging findings by reviewing the CT and MRI scans.¹⁵ The hematoma site was categorized into deep (ganglionic and thalamic hematomas), lobar (lobar or subcortical nonbasal ganglia hemorrhage), and posterior fossa. If intraventricular hemorrhage was present, the involved ventricles were noted, but the intraventricular blood portion was not considered for hematoma volume measurement. External ventricular drainage was inserted in all patients with evidence of occlusive hydrocephalus. In regularly round-to-ellipsoid-shaped hematomas, ICH volume was calculated using the initial CT or MRI scan according to the formula for ellipsoids $ABC/2$.^{4,7} In cases of irregularly, multinodular, and separated ICH shapes, the hematoma volume was assessed using the modified formula $ABC/3$.⁸

End Points

Hemorrhage Growth

Hemorrhage growth was defined as an increase in the volume of intraparenchymal hemorrhage of >33% as measured by image analysis on the follow-up CT or MRI compared with the baseline scan.¹

Outcome Analysis

Functional outcome was evaluated using the modified Rankin scale (mRS) after 1 year. Therefore, a telephone interview was conducted

TABLE 1. Times of INR and CT

Time Points	Group I (n=31)	Group II (n=18)	Group III (n=6)
Frequency of INR and CT analysis (n)			
INR/CT	INR/CT	INR/CT	
0 h - admission	31/31/31/31	18/18/18/18	6/6/6/6
Start of treatment <1.5 h in all patients			
1.5 \pm 1.0 h	31/31/1/31	18/18/0/18	6/6/1/6
4.1 \pm 1.1 h	5/31/2/31	7/18/1/18	0/6/0/6
8 (5–11) h	1/31/0/31	3/18/1/18	4/6/1/6
12.6 \pm 2.8 h	31/31/2/31	18/18/2/18	6/6/1/6
25.3 \pm 5.1 h	27/31/31/31	14/18/18/18	4/6/6/6
INR (mean \pm SD)			
0 h	4.3 \pm 2.4	3.8 \pm 1.9	4.2 \pm 2.0
1.5 \pm 1.0 h	1.4 \pm 0.4	2.1 \pm 1.1	3.9 \pm 1.8
4.1 \pm 1.1 h	1.3 \pm 0.3	1.8 \pm 0.6	...
12.6 \pm 2.8 h	1.3 \pm 0.1	1.4 \pm 0.3	3.0 \pm 1.7

Time-dependent INR analysis and CT brain scanning for the various subgroups (I to III).

independently by 2 physicians blinded for clinical and imaging information with all surviving patients at the point of investigation and, if already dead, with the closest family members. Good and reasonable outcomes were defined as mRS score of 0 to 3. Poor outcome was defined as mRS score of 4 to 6.

Selection of Variables

The following variables were extracted from the database and medical records: age, gender, Glasgow Coma Scale, mean arterial pressure, glucose, cholesterol, platelets, and treatment regimens.

Statistical Analysis

Statistical analyses were performed using the SPSS software package (SPSS 13.0). Kolmogorov–Smirnov and Shapiro–Wilk tests were used to determine distribution of the data. Normally distributed data are expressed as mean±SD and were compared using the unpaired *t* test and 1-way ANOVA. Other data are expressed as median and range and were compared with nonparametric tests. χ^2 and Fischer exact tests were used to determine associations between variables categorized. A value of $P \leq 0.05$ was considered statistically significant.

We performed 2 logistic regression models to investigate influences of clinical and neuroradiologic parameters on the end points: hematoma growth and long-term outcome after 1 year. Variables with a trend toward significance in univariate analysis ($P \leq 0.1$) were entered into stepwise forward inclusion multivariate logistic regression models for prediction of hematoma growth and outcome. In the multivariate regression analysis, a value of $P \leq 0.05$ was considered statistically significant.

Results

For patient characteristics, clinical and imaging data, INR, and CT analyses, we refer to Tables 1 and 2. Follow-up CT was performed after 25.3±5.1 hours (group I 23.6±4.3; group II 27.3±7.2; group III 28.2±3.4). The frequency of hematoma growth was 6 of 31 (19.3%) in group I, 6 of 18

(33.3%) in group II, and 3 of 6 (50%) in group III ($\chi^2 P < 0.01$ for PCCs). The extent of hematoma growth ranged from 44% (group I), 54% (group II), to 59% (group III), which was not statistically significant (ANOVA $P = 0.36$). Based on these trends of less frequent occurrence and smaller extent of hematoma growth in PCC-treated patients, we subsequently dichotomized the patients into those who received PCCs (group I) versus those treated otherwise (groups II and III). This dichotomization revealed a significantly lower incidence of hematoma growth in PCC-treated patients: 6 of 31 (19.3%) versus 9 of 24 (37.5%; $\chi^2 P < 0.01$).

In a next step, we investigated whether the reduced incidence of hematoma growth in group I was associated with an earlier complete INR reversal; an early INR reversal (within 2 hours) was achieved in 26 of 31 (83.8%) patients of group I, 7 of 18 (38.8%) of group II, and 0 of 6 (0%) of patients of group III ($\chi^2 P < 0.01$). Focusing only on those patients with early INR reversal, there was no longer a significant difference between the patients treated with PCCs or FFP with regard to hematoma growth (5 of 26 [19.2%] group I versus 2 of 7 [28.5%] group II; $P < 0.25$). Further, we analyzed the extent of hematoma growth by comparing all patients with early INR reversal ($n = 33$) versus those without ($n = 22$). We found a trend for increased extent of hematoma growth in insufficiently reversed patients (54% versus 38% in those patients with complete early INR reversal; $P < 0.08$).

Overall outcome was poor, but there were no significant differences between the various groups. An mRS of 4 to 6 was seen in 24 of 31 (78%) in group I, 14 of 18 (78%) in group II, and 5 of 6 (83%) in group III ($P = 0.86$).

In the regression analysis on risk factors for hematoma growth, we found: (1) an increased INR after 2 hours, (2) administration of VAK, (3) administration of PCC, and (4) baseline hematoma volume to be associated with hematoma growth when being tested univariately. In the multivariate analysis, only increased INR levels after 2 hours predicted hematoma growth, whereas administration of PCCs was associated with lack of growth (Table 3).

In the regression analysis on risk factors for long-term outcome, we found: (1) age, (2) Glasgow Coma Scale, (3) glucose, (4) baseline hematoma volume, (5) presence of intraventricular hemorrhage, and (6) occurrence of hematoma growth to be associated with poor outcome (mRS score 4 to 6) in univariate analysis. Because of the parameter “increased INR (after 2 hours)” being a critically important variable, we included it into the multivariate analysis on outcome, although the univariate analysis did not reveal significance. Multivariate regression analysis revealed age, baseline hematoma volume, and occurrence of hematoma growth to be independent predictors for a poor outcome (Table 4).

Discussion

The causes leading to ICH and hematoma growth in patients who are on OAT are not completely understood. Potential mechanisms include the unmasking of pre-existing subclinical intracerebral bleedings by the use of OAT.¹⁶ The under-

TABLE 2. Demographic Data

	Group I (n=31)	Group II (n=18)	Group III (n=6)
Patient characteristics			
Age (y; median)	68 (51–75)	70 (55–76)	71 (64–78)
Gender (male/female)	(18/13)	(11/7)	(4/2)
Clinical parameters			
Glasgow Coma Scale, median	10	9	10
Mean arterial pressure, mean	118	123	119
Glucose, mmol/L	10.1	9.4	9.5
Cholesterol, mmol/L	4.8	4.4	4.0
Platelets, mmol/nL	208	222	212
Imaging findings			
Volume, mean±SD; cm ³ (range)	36±23 (11–65)	40±28 (13–73)	42±28 (12–78)
Location			
Deep	12/31	8/18	3/6
Lobar	11/31	7/18	2/6
Posterior fossa	8/31	3/18	1/6
Intraventricular hemorrhage	12/31	8/18	3/6
EVD	7/31	4/18	1/6

Patient characteristics, clinical and neuroradiologic findings on admission of all treated patients ($n = 55$) and for groups (I to III).

EVD indicates external ventricular drainage.

TABLE 3. Univariate and Multivariate Regression Analysis for Hematoma Growth

	Hematoma Growth	
	Odds ratio (95% CI)	P Value
Univariate		
Age	0.82 (0.72–1.10)	0.52
Glasgow Coma Scale (on admission)	0.75 (0.43–1.36)	0.26
Mean arterial pressure (on admission)	0.92 (0.89–1.07)	0.41
Glucose (on admission)	1.06 (0.92–1.23)	0.75
Cholesterol (on admission)	0.96 (0.91–1.12)	0.40
Thrombocytes (on admission)	0.90 (0.88–1.03)	0.21
INR (on admission)	1.14 (0.82–1.48)	0.69
Increased INR (after 2 h)	2.11 (1.51–2.87)	<i>0.03</i>
Administration of PCC	0.33 (0.15–0.54)	<i>0.02</i>
Administration of FFP	1.52 (0.66–2.01)	0.15
Administration of VAK	2.91 (1.35–3.70)	<i>0.03</i>
Ganglionic hematoma	1.35 (0.47–4.42)	0.61
Lobar hematoma	1.90 (0.43–6.78)	0.82
Infratentorial hematoma	0.51 (0.09–2.06)	0.44
Baseline hematoma volume	1.21 (0.98–1.35)	<i>0.09</i>
Presence of intraventricular hemorrhage	0.63 (0.19–2.10)	0.54
Multivariate		
Increased INR (after 2 h)	1.66 (1.31–2.17)	0.04
Administration of PCC	0.70 (0.35–0.94)	0.03
Administration of VAK	1.85 (0.96–3.97)	0.33
Baseline hematoma volume	1.63 (0.99–4.13)	0.19

Univariate and multivariate regression analysis of risk factors for hematoma growth in patients with OAT-associated ICH. Significant parameters (univariate) are expressed in italics and in the multivariate analysis in bold.

lying causes of spontaneous ICH and OAT-ICH might be the same, with OAT being only a precipitating factor.¹⁷ It is also possible that OAT directly causes ICH by interfering with the synthesis of VAK-dependent clotting factors. Despite the lack of prospective data, rapid reversal of increased INR is the initial treatment of choice to prevent hematoma enlargement.^{2,11,18–20} However, none of the treatment regimens, including VAK, FFP, or PCC, have been proven to be more effective than another.²¹

Two major aspects emerge from our findings. First, our data showed that hematoma growth occurred in 27% but varied considerably with the type of treatment. The association of PCCs with a reduced occurrence of hematoma growth lost significance when comparing only those patients with early complete INR reversal. Because nearly all PCC-treated patients achieved an early INR reversal, the overall positive performance of PCCs compared with FFP and VAK might be because of a faster INR reversal in the acute bleeding phase.¹⁹ This attribute of PCCs might be explained by a higher concentration of coagulation factors in PCCs compared with FFP. Studies based on small numbers of patients found that PCCs were superior to FFP for reversal of an increased INR.^{19,22} FFP contains all coagulation factors in a noncon-

TABLE 4. Univariate and Multivariate Regression Analysis for Long-Term Outcome After 12 Months

	Poor Outcome	
	Odds ratio (95% CI)	P Value
Univariate		
Age	1.77 (1.61–1.93)	<i>0.01</i>
Glasgow Coma Scale (on admission)	0.81 (0.70–0.94)	<i>0.02</i>
Mean arterial pressure (on admission)	1.04 (0.90–1.17)	0.73
Glucose (on admission)	1.22 (1.03–1.39)	<i>0.01</i>
Cholesterol (on admission)	0.99 (0.98–1.01)	0.90
Thrombocytes (on admission)	1.01 (0.99–1.02)	0.62
INR (on admission)	0.75 (0.52–1.16)	0.14
Increased INR (after 2 h)	1.24 (0.97–1.63)	<i>0.72</i>
Administration of PCC	0.87 (0.28–2.39)	0.55
Administration of FFP	1.65 (0.74–3.26)	0.64
Administration of VAK	0.44 (0.05–2.22)	0.80
Ganglionic hematoma	2.28 (0.84–3.12)	0.14
Lobar hematoma	0.46 (0.10–2.04)	0.31
Infratentorial hematoma	1.45 (0.62–4.51)	0.56
Baseline hematoma volume	1.41 (1.05–1.89)	<i>0.04</i>
Presence of intraventricular hemorrhage	2.03 (1.67–2.70)	<i>0.08</i>
Insertion of EVD	1.01 (0.25–4.42)	0.87
Occurrence of hematoma growth	2.46 (1.97–2.90)	<i>0.03</i>
Multivariate		
Age	1.41 (1.27–1.45)	0.05
GCS (on admission)	0.81 (0.42–1.99)	0.27
Glucose (on admission)	1.44 (0.87–3.27)	0.30
Baseline hematoma volume	1.67 (1.48–1.71)	0.03
Presence of intraventricular hemorrhage	1.32 (0.30–4.37)	0.44
Occurrence of hematoma growth	2.21 (1.69–2.30)	0.03
Increased INR (after 2 h)	1.55 (0.83–2.02)	0.26

Univariate and multivariate regression analysis of risk factors for a poor long-term outcome (12 months). Significant parameters (univariate) are expressed in italics and in the multivariate analysis in bold.

EVD indicates external ventricular drainage.

centrated form. A large volume is required for each patient to achieve effective hemostasis,¹⁸ and the actual contents of VAK-dependent coagulation factors in each unit of FFP vary considerably.²² Consequently, the efficacy of FFP in reversing INR is unpredictable and incomplete.^{18,22} However, patients with completely reversed INR levels after 2 hours did not fare worse on FFP compared with PCC. Furthermore, the increased rate of hematoma growth with VAK can be explained by its protracted effect to achieve a sustained reversal of the anticoagulant effect.¹⁴ In our series, patients treated only with VAK showed insufficient INR reversal within 12 hours. Because the majority of hematoma growths occurred within the first 24 hours,¹ VAK may not be effective in such settings.

Consistent with the literature, the regression analyses showed that elevated INR levels were associated with an increased risk for hematoma growth.^{2,11} In addition to the

incidence, the extent of hematoma growth also depended on INR levels. In consequence, no statement in favor of one or the other therapy can be conducted. Time to INR reversal seems to be the most important determinant, and minimizing delays in drug administration should have highest priority.²³ A completely reversed INR rather than the specific treatment seems to prevent hematoma enlargement.

Second, the outcome of OAT-ICH was poor. Age, large hematoma volumes, and occurrence of hematoma growth predicted poor outcome. An overall poor outcome after 3 months in patients with primary ICH and OAT-ICH was found in several studies.^{1,2,4,11,24–26} However, we investigated outcome after 12 months that was comparable to the cited studies, despite the preassigned exclusion of patients with DNR orders. The severity of ICH itself may compromise survival so powerfully that an unfavorable short- as well as long-term outcome results. Between the various treatment groups, no significant differences were found. Although PCCs were associated with less hematoma growth, it had no significant impact on long-term outcome.¹⁹ Sjöblom et al found no significant superiority of either FFP or PCCs in 151 patients.²⁰ For the future, a promising attempt for improving clinical outcome by preventing early hematoma growth for patients with OAT-ICH might be the administration of recombinant factor VIIa²¹ because it has been shown to reduce early hematoma growth and mortality in patients with primary ICH.^{27,28} Park et al used factor VIIa for the rapid correction of coagulopathy in nonhemophilic neurosurgical patients.²⁹ With regard to OAT-ICH, Deveras et al showed that factor VIIa moreover has the ability to reverse increased INR levels sufficiently.³⁰ Hence, a prospective trial comparing FFP, PCC, and factor VIIa in OAT-ICH is justified.²¹

Our study has limitations. Because of the nature of this nonrandomized and uncontrolled design, a variety of combination therapies had been applied, some only for a small number of patients. It is possible that hematoma growth may have occurred before any treatment given, so the data cannot give information on the direction of association between treatment choice and outcome. Confounding factors such as pre-existing physical impairment, history of chronic heart failure, etc, might have influenced treatment decisions, but we were not able to reliably reassess these parameters. Moreover, we focused only on treated patients and excluded moribund patients. These inconsistent treatment regimens and follow-up investigations partially undermine the central conclusion of this study, which, however, has not been performed in a comparable manner. Meanwhile, only limited data exist about hematoma enlargement and how to initially treat OAT-ICH patients,^{10,20} and randomized prospective trials are lacking. Taking this into account, this study reflects the current therapeutic dilemma because still no standardized treatment regimens exist.

In conclusion, our data suggest that administration of PCCs reduces the risk for hematoma growth. However, with respect to frequency of occurrence of hematoma growth, no significant differences between patients treated with PCCs or FFP were found when focusing only on patients who achieved an early complete INR reversal. The extent of hematoma growth was least in the PCC-treated patients, presumably because of

fastest INR reversal. However, neither treatment was associated with an improvement of outcome. Based on these findings, we strongly suggest a randomized prospective trial comparing PCCs and FFP (both in combination with VAK) in OAT-ICH, eventually with factor VIIa as a third study arm. Together, an early and completely reversed INR rather than the specific treatment seems to prevent hematoma enlargement and thus may influence outcome.

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