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Efficacy and safety of prothrombin complex concentrate and Vitamin K in a cohort of 76 patients with anticoagulation-related acute intracranial hemorrhage: clinical features and outcomes at three months

Abstract.
Central nervous bleeding emergencies are the most serious complications of Oral Anticoagulant Therapy (OAT), with an incidence of 1% per patient-year. From January 2004 through January 2010, we observed 79 episodes of anticoagulation-related acute intracranial hemorrhages (AIH) in a cohort of 76 consecutive patients reporting to our emergency department. All patients were treated with a systematic approach: single bolus of 25-30 IU per Kilogram of Prothrombin Complex Concentrate (PCC) and intravenous administration of 10 mg of vitamin K1 within one hour after baseline CT scan of the head. All the patients simultaneously received urgent neurosurgical evaluation. Patients' history, clinical and serological data and ongoing therapy were recorded and analyzed. Functional outcomes at 90 days were assessed with the modified Rankin Scale. Median age of our cohort was 77,6 years (range 38-90) with a male-female ratio of 1,32; indications for OAT were: atrial fibrillation in 65 (82%), heart valve prostheses in 10 (13%), other indications in 4 cases (5%). 18 patients (29%) needed emergency neurosurgical intervention; 35 (44%) patients reported a recent trauma. Acute reversal of OAT (INR<1,5) was obtained in 90% of cases within 30 minutes after therapy administration. 8 subjects had non-fatal thrombotic events, (7 pulmonary embolisms and 1 ischemic stroke). Mortality rate at 90 days was 40%. Although hypertension is a well-known risk factor for intracranial hemorrhage, surprisingly in our cohort a previous history of hypertension was associated with a favorable outcome (p<0,002), possibly due to better control of blood pressure during acute bleeding. Of 48 patients alive after three months, 35 (73%) showed a Rankin score ≥4 at diagnosis, 24 (50%) at discharge and only 13 (27%) at three months. These data reveal the possibility of a remarkable margin of recovery improvement and make rapid treatment mandatory.

Introduction

Central nervous bleeding emergencies are the most serious complications of Oral Anticoagulant Therapy (OAT) with an incidence of 1% per patient-year (1). Anticoagulation-related acute intracranial hemorrhage (AIH) accounts for 20% of all intracranial hemorrhages. Aging of population and increased incidence of atrial fibrillation results in a dramatic increase of the use of antivitamin k antagonists (AVKs) and consequent increase of their more severe complications, particularly in people over 80 years old (2,3). Anticoagulation with AVKs increases 2 to 5 times the risk of intracranial hemorrhage (ICH), with a direct correlation to the intensity of anticoagulation; nevertheless, most AIH occur at anticoagulation intensities within the conventional therapeutic range (i.e., INRs of 2.0-3.5). (4).

AIH recognize the same pathogenesis of spontaneous intracranial hemorrhages (SIH). Magnetic resonance studies demonstrate that cerebral microhemorrhages occur even in healthy individuals. Aging of population, cerebral amyloid angiopathy, hypertension are common causes of both SIH and AIH; in fact, localizations of hematomas are similar in SIH and AIH. So, one may argue that probably OAT simply increases the incidence of intracranial hemorrhage. Nevertheless, AIH are characterized by larger initial hematoma extension when INR>3, (5) and by wider hematoma expansion, as bleeding can persist up to 24 hours after onset (6). These features confer a higher mortality in comparison with SIH and open a temporal window for therapeutic interventions. The degree of INR prolongation at the time of AIH seems to be predictive of progressive hematoma enlargement after admission, functional outcome and mortality, although some authors have reported no correlation. The 1-day mortality of patients with OAT-ICH has been reported to be 33% compared to 16% for SIHs. Large hematoma volume (>50 mL), intraventricular leaking, and shift of midline structures are associated with poorer outcome in SIH. AIH are characterized by larger initial volumes, higher frequency of hematoma enlargement and higher incidence of progressive neurological deterioration in the first 24-48 hours.

Number of patients	76
Number of intracranial hemorrhages	79
Median Age (range)	77.6; (38-90)
Male/female ratio:	1.32
Indication for anticoagulant therapy	
• Atrial fibrillation (%)	65/79 (82%)
• Venous thromboembolism (%)	4/79 (5%)
• Mechanical heart valves	10/79 (13%)
Supratherapeutic INR (>3,5)	16/79 (20%)
Therapeutic INR (2-3,5)	56/79 (71%)
Subtherapeutic INR (<2)	7/79 (9%)
Type of intracranial hemorrage	
• Subdural hematoma (%)	36/79 (46%)
• Lobar hemorrhage	27/79 (34%)
• Deep hematoma	12/79 (15%)
• Subarachnoidal hemorrage	3/79 (4%)
• Cerebellar hemorrage	1/79 (1%)
• Intraventricular inundation	15/79 (19%)
• Spontaneous hemorrage	43/79 (54%)
History of fall or trauma within 15 days before bleeding	35/79 (44%)
Neurosurgical operations	18/79 (23%)
Thromboembolic complications	8/79 (10%)
Hemorrage-related deaths	32/79 (40,5%)

Table 1: Patients characteristics

In spite of the importance of this problem, there are no randomized trials assessing clinical outcomes treatment of AIH (7). The aim of this single center investigator-driven observational retrospective study is to evaluate efficacy and safety of a prothrombin complex concentrate (PCC) on reverting the anticoagulant effect of vitamin K antagonists, and to describe the long-term outcome of AIH at three months' follow up.

Materials and method

From January 2004 through January 2010, we observed 79 consecutive episodes of anticoagulation-related acute intracranial hemorrhage (AIH) in a cohort of 76 consecutive patients reporting to the Emergency Department of the non academic public hospital of Ivrea, Piedmont, Italy (catchment area: 300,000 inhabitants). Data were collected retrospectively from the following sources: patient electronic medical records, emergency department reports, neurology and rehabilitation discharge charts, CT and MRI scans report series, specialized database software for anticoagulation management. Table 1 describes the characteristics of our cohort of patients.

The indications for anticoagulant therapy were: atrial fibrillation in 65 (82%) patients, venous thromboembolism in 4 patients and heart valve prostheses in 10 (13%). All patients were treated with a systematic approach: OAT interruption, single bolus of 25-30 IU per Kilogram of Prothrombin Complex Concentrate (PCC) (Uman Complex, Kedrion, Castelvecchio Pascoli, Italy) and intravenous administration of 10 mg of vitamin K1 (Konakion, Roche, Milano, Italy) diluted in 100 ml of physiological solution within 30 minutes after baseline CT scan of the head.

All patients received urgent neurosurgical evaluation (Table 2). Patients with neurosurgical indication were transferred from Ivrea Hospital to the neurosurgical Dept of a regional Hospital in Turin at a distance of 50 km after receiving treatment with aPCC + vit. K. All but eight patients were followed up at our anticoagulation clinics for at least three months. We analyzed the following variables in order to evaluate fatality rate: age, sex, indication for OAT, INR, PTT, fibrinogen at admission and after PCC bolus, site of intracranial bleeding, prior neurosurgery, prior history of diabetes, hypertension and chronic cerebral vasculopathy, platelets count, hemoglobin and hematocrit, serum cholesterol level. We also traced INR values in the previous three months before intracranial hemorrhage, and investigated for traumatic events and drug interactions (we regarded as significant any association of oral anticoagulants with anti-inflammatory drugs and antiplatelet medications). Furthermore, although there are no definitive conclusions about hemorrhagic risk of selective serotonin reuptake inhibitors (SSRI), (8) we recorded concomitant administration of such antidepressant medications.

Step 1	Oral anticoagulant therapy withdrawal
Step 2	Single bolus of 25-30 IU per Kg of Prothrombin Complex Concentrate
Step 3	Intravenous administration of 10 mg of vitamin K1
Step 4	Urgent neurosurgical evaluation

Table 2. Standardized protocol within one hour after baseline CT scan of the head

Functional outcomes at 90 days were assessed by the modified Rankin Scale (where 0 indicates full recovery and 6 indicates death). Scores from 4 to 6 were considered poor outcomes, Table 3 shows modified Rankin Scale.

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Death

Table 3. Modified Rankin Score

Statistical analysis

Statistical analyses were performed using the SAS System software package (SPSS). For univariate statistics, a conventional statistical test was used. Normally distributed data were expressed as mean±SD and were compared using the unpaired t test. Other data were expressed as median and range and were compared with nonparametric tests. Chi-square test and Fischer exact tests were used to determine associations between variables. A value of $P \leq 0.05$ was considered statistically significant.

End points

The primary end-point of the study was the evaluation of the reversal efficacy on the INR value: reversal was considered satisfactory if INR <1.5 30 mins after PCC administration. We also evaluated the following clinical end-points: long-term outcome with modified Rankin Scale, incidence of thrombotic events, perioperative bleeding of neurosurgical cases and mortality at 90 days.

Results

From January 2004 through January 2010, we observed 79 episodes of anticoagulation-related acute intracranial hemorrhage in a cohort of 76 consecutive patients at our Emergency Department. The median follow-up of each patient was at least three months. We were able to treat all patients with the same pharmacological approach (PCC and vitamin K1). PCC showed to be able to counteract the effect of warfarin in all patients; prompt reversal of OAT (INR<1.5) was obtained in 90% of cases within 30 minutes from administration. Average INR value was 2.99 (±1,05 SD) at presentation and decreased to 1,36 (±0,26 SD) 30 minutes after PCC administration (Figure 1 and table 4). Interestingly, among 8 cases who did not achieve INR <1.5, we observed a higher proportion of supra-therapeutic INR at diagnosis: in this subgroup of patients average INR was 4.49 (±1,23 SD) versus 2.69 (0,7 ± SD) in patients who corrected INR after PCC bolus (table 4). We did not observe any adverse event related to PCC or Vitamin K; particularly, vitamin K did not cause any anaphylactic reaction in our cohort of patients and PCC was not associated with any sort of adverse reaction. As regards thrombotic complications of PCC infusion, we observed eight (10%) non fatal thrombotic events: one ischemic stroke at day 25 of hospitalization, seven pulmonary embolisms respectively at days 14, 10, 3, 5, 5, 30 and 5 of hospitalization.

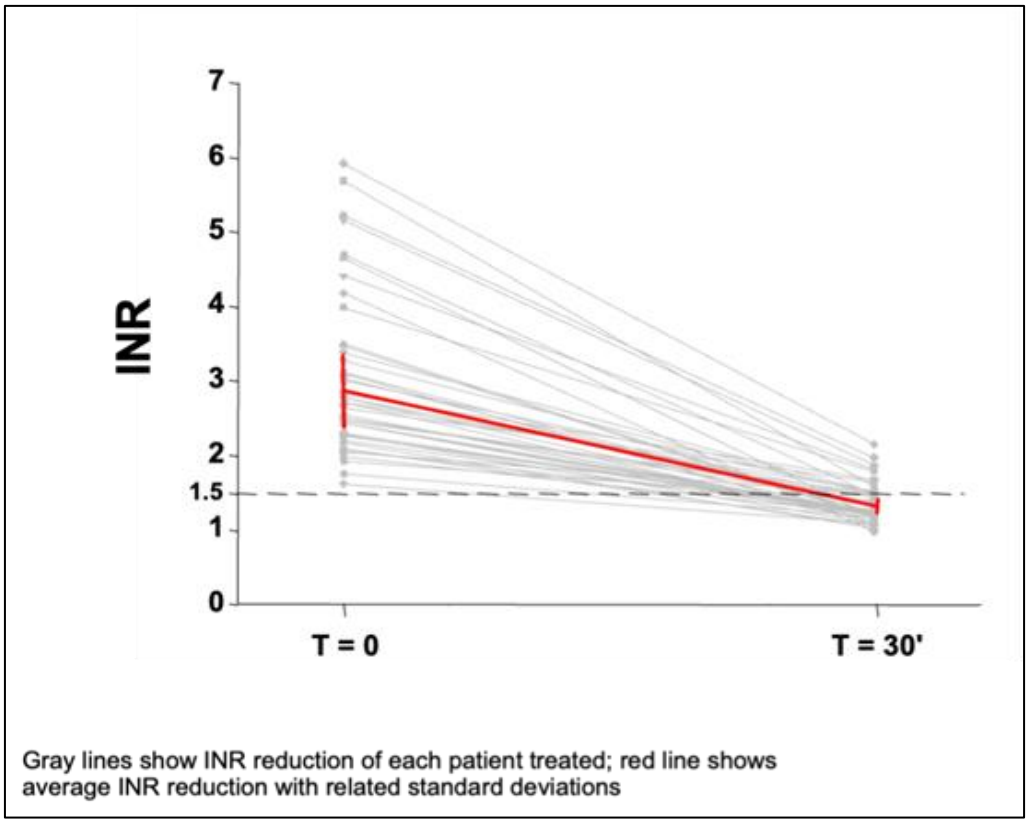

Figure 1: correction of INR in 79 AIH treated with Uman Complex

	Response Rate	Initial average INR (SD)	Average INR 30 min after PCC administration (SD)
Overall cases (79/79)	100%	2.99 (1.05)	1.35 (0.26)
Cases with INR < 1,5 30' after PCC bolus	71/79 (90%)	2.69 (0.7)	1.26 (0.16)
Cases with INR > 1,5 30' after PCC bolus	8 /79 (10%)	4.49 (1.23)	1.80 (0.20)
SD = Standard Deviation			

Table 4: Relevance of initial INR to achieve INR <1.5

Intracranial hemorrhage itself and the clinical state of patients can justify such a high incidence of thrombotic events rather than single PCC administration. We underline that all patients received low molecular weight heparin at prophylactic dosage as soon as possible during their hospitalization. All patients restarted anticoagulation not before 30 days after the previous ICH. Three patients had an intracranial hemorrhagic relapse after resuming oral anticoagulant therapy; an 85 year-old man with parossistic atrial fibrillation, an 83 year-old man with chronic atrial fibrillation and a 73 year-old man with mechanic mitral valve and a history of previous cardioembolic stroke relapses occurring within six months after the first intracranial bleeding. Correlation among recorded patients' variables and mortality rate at 90 days was sought. Although hypertension is a well-known risk factor for intracranial hemorrhage, surprisingly in our cohort a history of prior hypertension was associated with favorable outcome at univariate and multivariate analyses ($p<0.0003$). Similarly, a history of diabetes mellitus ($p<0.023$) and cerebral vasculopathy ($p<0.003$) seemed to be protective in terms of mortality at univariate analysis but not at multivariate analysis. (table 5 and 6).

Characteristics	Died within 3 Months (31 hemorrhages)	Survived for 3 Months (48 hemorrhages)	All intracranial hemorrhages	P value
Age (mean)	78.9	76.8	77.6	0.4 for age > 75 years
Male	19	26	45	0.69
INR (mean)	3.22	2.77	3	0.02 for INR>2
Dangerous drug association	3	9	12	0.4
Recent trauma	10	25	35	0.11
Hypertension	18	44	62	0.000381
Diabetes	4	17	21	0.023216
Cerebral vasculopathy	11	33	44	0.003503
Cholesterol mg/dL	174	171	173	0.55
Follow up at specialized OAT clinic	28	41	69	0.83
INR after PCC administration	1.38	1.33	1.35	0.96
Thrombotic events	2	6	8	0.86

Table 5: Clinical characteristics stratified by outcome in 79 patients with anticoagulant-associated ICH

Variable	Died Within 3 Months (31 hemorrhages)	Survived for 3 Months (48 hemorrhages)	Odds Ratio (95% Confidence Interval)	P-Value
Hypertension	18	44	0.04 (0.005-0.343)	0.000381
Diabetes	4	17	0.2 (0.05-0.343)	0.023216
Cerebral vasculopathy	11	33	0.21 (0.078-0.569)	0.003503

Table 6: Variables affecting case-fatality and mortality rate at three months in a multivariate analysis

All patients received urgent neurosurgical evaluation at diagnosis in the Emergency Department; 18 patients needed emergency neurosurgical evacuation of their subdural hematoma, without perioperative bleeding, except one patient who showed a relapse of bleeding a few days after neurosurgery. The clinical impact of rapid PCC administration in terms of functional physical recovery was quantified by the Rankin Scale. The Rankin score was assessed at diagnosis, at discharge and at three months' follow up visit. Among 48 patients still alive at three months, 35 (73%) showed a Rankin score ≥4 at diagnosis, 24 (50%) at discharge and only 13 (27%) at three months. These data reveal a remarkable margin of improvement and make a rapid treatment mandatory. (Figure 2)

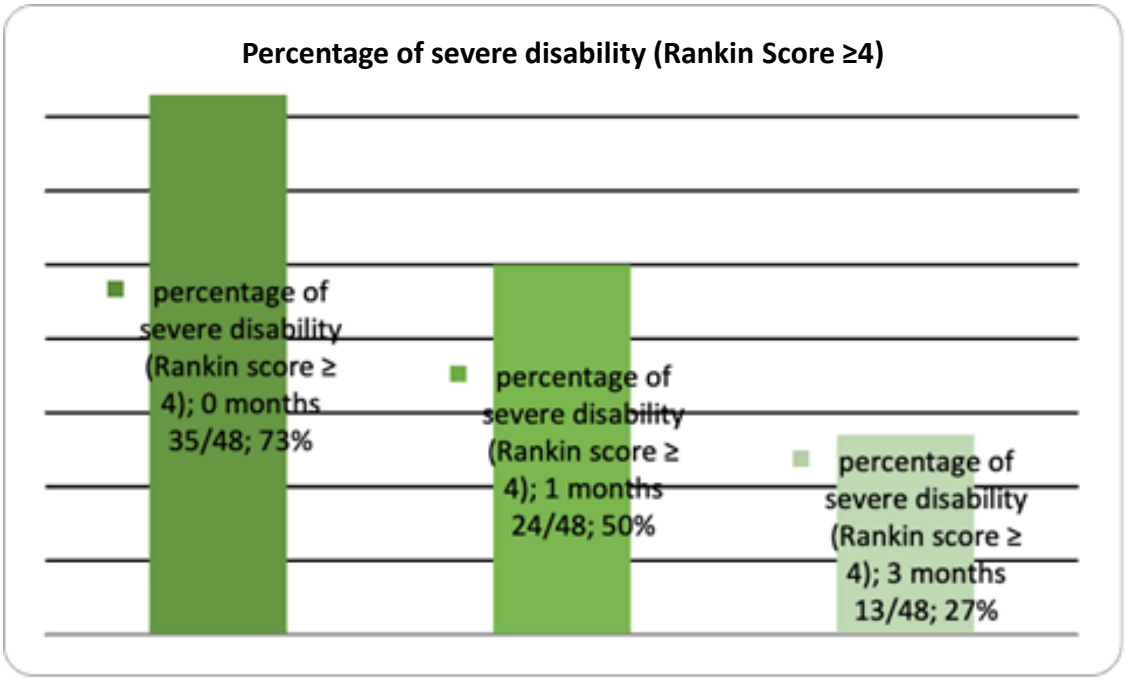

Figure 2: Functional outcome in 48 patients alive at three months.

As regards drug interactions, only two patients had taken acetyl salicylic acid or diclofenac shortly before AIH. We did not find any significant association between SSRI and mortality rate in our cohort. History of trauma within 15 days before AIH was extremely high in our cohort study; 35/79 (44%) patients reported a fall in recent anamnesis. This piece of data highlights that the question of falls in elderly persons is of paramount importance during management of VKAs therapy; however, in our cohort we could not find any significant association between falls and mortality rate.

Discussion

Several neuroradiological studies demonstrated that spontaneous intracranial hemorrhages expand over time owing to bleeding from rupture of small penetrating arteries. The management of acute intracranial hemorrhages is based upon the consciousness that a fast intervention may reduce hemorrhage volume and clinical impact on long-term disability and mortality. Despite wide and consolidated use of antivitamin K agonists and doctors' awareness of potentially life-threatening consequences of oral anticoagulant therapy, no well designed randomized clinical trial has so far been devised in order to assess the best treatment options for anticoagulation reversal. Thus, considerable differences of therapeutic strategies have been observed among intensive care units in different countries. Intravenous administration of vitamin K is a well known therapy for this subset of patients, but it requires almost 4-6 hours to work. Use of fresh frozen plasma (FFP) is an option widely used in USA but with many drawbacks: transfusion of FFP requires at least 30 minutes' thawing before administration and the volume needed to restore deficient coagulation factors may vary between 800 and 3500 ml, and the time lapse to correction of INR is unacceptable. Other pitfalls of FFP are volume overload, allergic reactions, transfusion related acute lung injury (TRALI), citrate toxicity and transmission of viral infections (9). Mayer SA et al. and Mannucci et al. demonstrated that recombinant activated factor VII (rVIIa) in patients with spontaneous acute cerebral hemorrhage reduces significantly hematoma expansion if administered within 6 hours after bleeding onset but mortality and functional outcome were not modified (10,11). There are small case series of patients with warfarin associated intracranial hemorrhage treated with rVIIa; all these studies reported faster correction of INR but only the study of Roitberg et al. reported an improved outcome (12). Furthermore, there are concerns about the efficacy of a single rVIIa dose on reverting warfarin-related coagulopathy and about safety for potential thromboembolic adverse events (13,14). Several case series of rapid reversal of VKAs with PCCs alone reported correction of INR faster than FFP in the setting of warfarin-related intracranial hemorrhage. So far, all studies available have demonstrated that PCCs are faster than FFP in INR normalization, but there is no evidence of outcome improvement.

Our study represents a "real world" picture of AIH management in an Italian community hospital. It shows that a standardized protocol to rapidly reverse INR prolongation and maintain normal values over time is feasible and easy to carry out. It also suggests that the faster the INR correction, the fewer the clinical consequences. Despite literature alerts, in our hands no adverse reactions directly attributable to vitamin K intravenous administration were observed and this study confirmed the rapidity and especially the safety of a specific aPCC in reverting VKAs coagulopathy.

Notwithstanding regular preventive low molecular weight heparin administration, we observed a rather high incidence of non fatal thromboembolic complications (10% of all cases), which was constituted by patients particularly prone to develop thrombosis due to underlying disease and to VKAs suspension. In conclusion our experience confirms the safety and feasibility of concomitant administration of vitamin K and PCC in the emergency setting of AIH. These data maintain a precious value if we consider that there is a notable underuse of PCC by clinicians in the setting of AIH, probably owing to the fear of thrombotic complications, of inadequate knowledge of PCCs and maybe of the multidisciplinary nature of AIH treatment. There is a pressing necessity for well-designed collaborative randomized studies to evaluate the best treatment option of the AIH, one of most common iatrogenic complications of clinical practice.

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