

SHORT COMMUNICATION

rFVII_a – for acute rebleeding of a cerebral cavernous malformation

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Recurrent bleeding episodes of cavernomas especially in the brainstem can cause progressive neurological deficits. Therefore brainstem cavernomas are still a therapeutic dilemma and a treatment challenge for the neuro critical care community. We report a 39-year-old woman with spontaneous ataxia diplopia and vomiting, who has been treated for multiple intracerebral cavernomas during the last 10 years. A cerebral computed tomography (cCT) revealed a re-bleeding cavernoma in the left cerebral peduncle with consecutive obstructive hydrocephalus. As a result of the difficult anatomical location, no surgical approach was possible. As an off-label treatment, recombinant activated factor VII (rFVII_a) was administered to prevent possible further bleeding and especially further sequelae. The patient recovered well and no adverse events and especially no further bleeding of the cavernoma were observed. To our knowledge, this is the first report of the safe and successful use of rFVII_a to treat re-bleeding episodes in cavernomas. Further clinical studies are needed to specify the future potential of rFVII_a.

Introduction

The prevalence of cavernomas in the central nervous system ranges from 0.4% to 0.9% [1]. Up to 35% of all cavernous malformations are located in the brainstem. Although re-bleedings of brainstem cavernomas are not very common, recurrent haemorrhages can cause progressive potentially life-threatening and severe neurological signs and symptoms [2].

Neuro-surgical extirpation is indicated for brainstem cavernomas with a mass effect because of bleeding and location close to the pial surface. However, subtotally removed cavernomas tend to show a worse prognosis than conservatively treated cavernomas. Whether a cavernoma has been totally or subtotally removed, the intra-operative aspect is more reliable than postoperative radiological imaging. Thus, brainstem cavernomas still constitute a treatment challenge for neurologists and neurosurgeons.

Recombinant activated factor VII (rFVII_a, Novo Seven®, Novo Nordisk, Bagsvaerd, Denmark) was originally developed for the management of bleeding in haemophiliac patients with inhibitors to factors VIII or IX [3]. Subsequently, the efficacy and safety of rFVII_a in these patients have been proven in several prospective trials [4]. Recent case reports and small clinical studies indicate that rFVII_a may also be useful as a

haemostatic agent in nonhaemophiliac patients with high risk of bleeding complications [5–8].

The mechanism by which rFVII_a acts is tissue factor-dependent and -independent. rFVII_a binds to exposed tissue factor and initiates coagulation. In addition, rFVII_a exerts most of its effects on the surface of activated platelets, where it directly accelerates the formation of thrombin in the absence of tissue factor. Thus, rFVII_a enhances haemostasis at the site of injury without systemic activation of the coagulation cascade.

Because of these mechanisms, the idea of a so-called ultra-early haemostatic therapy in acute intracerebral haemorrhage was introduced and recent clinical studies showed efficacy in intracerebral haemorrhage [9–13]. If surgical treatment of a vascular malformation because of its anatomical location like brainstem cavernomas is not favourable, a local enhancement of haemostatic factors might reduce the bleeding rate.

Case report

A 39-year-old woman was admitted to our university hospital with a 1-day history of vomiting and ataxia of the right extremities followed by an increasing right-sided hemihypesthesia. Cerebral computed tomography (cCT) revealed an intracerebral haemorrhage caused by a cavernoma in the left cerebral peduncle (Fig. 1). Cerebral imaging showed a total of five vascular malformations identified as cavernomas. Besides the actual bleeding in the mesencephalic cavernoma on the left side, the malformations were located on the left medial cerebellar peduncle, left cerebellar hemisphere, in the

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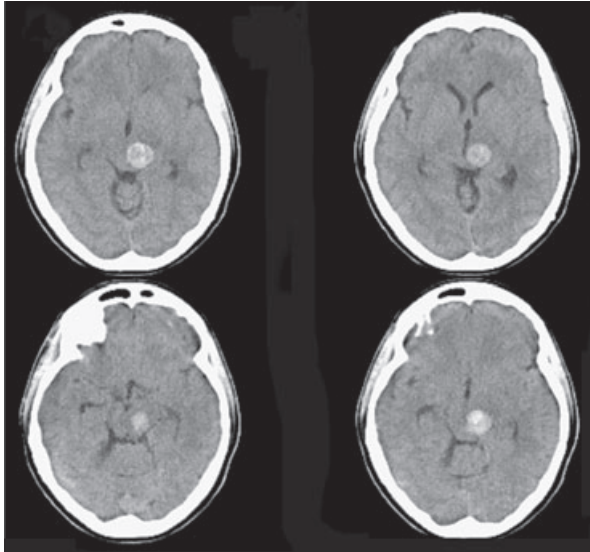


Figure 1 Cerebral computed tomography (cCT) on day 1 illustrating an intracerebral haemorrhage caused by a cavernoma in the left cerebral peduncle.

right frontal lobe and on the left parietal lobe. Up to the recent bleeding, the patient had reported in total three bleeding episodes with consecutive different treatments: 7 years prior to admission a bleeding in the mesencephalic cavernoma as well as in the cerebellar peduncle had been treated with Gamma knife. The patient had suffered initially from drowsiness and gaze deviation but had recovered fully without any neurological deficits; 1 year later the cavernoma on the parietal lobe had been extirpated surgically.

Three months prior to the actual admission, a re-bleeding occurred in the mesencephalic cavernoma, which had been treated by radiosurgery. At this point of time no specific treatment, such as neurosurgical extirpation or radiosurgery had been performed because of the anatomical location and the relative mild neurological sequelae with vomiting, gaze deviation and drowsiness.

During the first 4 days of the actual hospitalization, no signs of re-bleeding were found both clinically and in repeated CT scans. The patient was transferred to a general ward to continue the rehabilitation therapy. On day 5, the patient developed right-sided hemiparesis progressing rapidly to impairment of consciousness. cCT revealed again a re-bleeding of the cavernoma in the left cerebral peduncle with obstructive hydrocephalus (Fig. 2). Although a neurosurgical approach would have been possible, the neurosurgeon recommended a conservative treatment because of the anatomical location of the lesion.

To prevent further bleeding and especially further sequelae, an off-label usage of rFVIIa was considered.

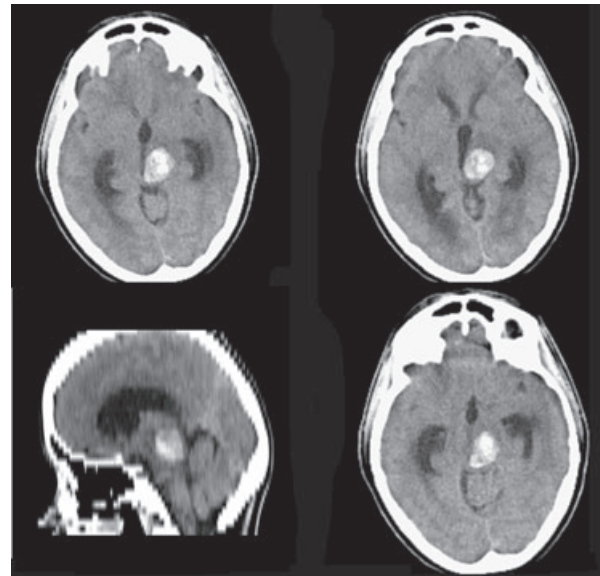


Figure 2 Cerebral computed tomography on day 5 illustrating re-bleeding of the cavernoma in the left cerebral peduncle and beginning obstructive hydrocephalus.

The patient was screened for well-known exclusion criteria recommended in literature for rFVIIa in acute intracerebral haemorrhage. Especially after excluding any history of arterial or venous thromboembolic events, coagulopathy, acute sepsis and pregnancy the patient received 80 $\mu\text{g}/\text{kg}$ body weight Novo Seven® intravenously. rFVIIa was administered 130 min after clinical deterioration.

Laboratory tests 1 and 6 h after administration of Novo Seven® showed no abnormal findings concerning Troponin T. Additionally, electrocardiogram revealed no signs of myocardial infarction and clinical follow-up excluded any thromboembolic events.

An external ventriculostomy was performed 6 h after administration of rFVIIa. In the first cCT after intervention no further bleeding and normal ventricular dimension were found. At day 10, the external ventricular drainage was removed and the patient was transferred to a rehabilitation centre with improved hemiparesis and gaze deviation (Fig. 3). Two months later, the patient was able to walk without assistance mildly hampered by intermittent double visions. The patient was discharged home and neither further bleeding of the mesencephalic cavernoma nor of the other malformations has been detected till date.

Discussion

To our knowledge, this is the first report on an off-label use of rFVIIa in the treatment of recurrent bleedings in the brainstem cavernoma. In our patient, rFVIIa

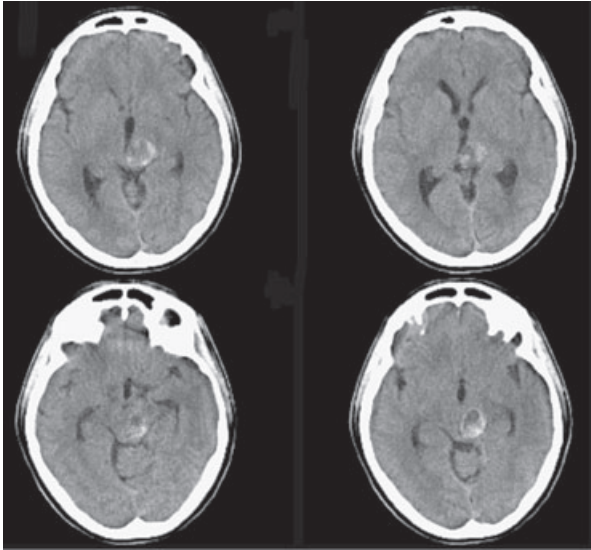


Figure 3 Cerebral computed tomography after off-label usage of rFVII_a at day 10 illustrating resorption of intracerebral haemorrhage and no signs of hydrocephalus.

application was safe and possibly prevented further re-bleedings. The re-bleeding rate of cavernomas rises from 3.8% up to 34.7% per year after the first bleeding complication. Therefore, surgical treatment of symptomatic brainstem cavernomas close to the pial surface is recommended whereas treatment options in cavernomas, which cannot be surgically treated are still limited. rFVII_a may be an option as an ultra-early haemostatic therapy in intracerebral haemorrhage.

The pathophysiological mechanisms of cavernoma growth are discussed as a sudden increase in intracranial pressure, shear forces and disruption of normal cerebral anatomy as well as mechanisms in the penumbra, like reduction of venous outflow, breakdown of blood–brain barrier and possibly a transient local coagulopathy. In contrast to spontaneous hypertensive intracerebral haemorrhage, little is known about the pathophysiology of bleeding cavernomas. The vascular walls in cavernomas demonstrate an abnormal ultrastructure with no basement membranes and astrocytic foot processes and may explain the leakage of blood cells into surrounding brain. The characteristic of cavernoma bleeding is probably more a low pressure bleeding. Although rFVII_a has just a short half-life of approximately 180 min, it may initiate coagulation tissue factor-dependent and -independent on site of ultrastructural abnormalities of cavernous malformations.

The high rebleeding rate with up to 34.7% confirms that these lesions may have a very aggressive course. Some investigators have observed a benign natural history but up to now prospective data to predict the

course of individual patients are still lacking. Even after several bleeding episodes, a long period of silence may follow in many patients without any specific therapy. At least in some patients, local scar formation and the presence of a thick haematoma membrane may prevent further bleeding.

Whether rFVII_a is also a treatment option in vascular malformation such as cavernomas remains open for discussion. Potential adverse events of rFVII_a have to be considered. An open-label dose-escalation and safety study to investigate the re-bleeding rate of aneurysmal subarachnoidal haemorrhages was suspended because of a cerebral ischaemia in one patient. Although it was a small intervention group and dosage was different to our patient it is evident that rFVII_a, especially in high dosage may increase the rate of arterial thromboembolic events especially myocardial infarction and cerebral ischaemia [14,15]. The dosage of our patient is thought to minimize adverse events such as thromboembolic events. Our patient recovered well without any adverse events and no further bleeding episodes were observed. As this is a single case this new and interesting therapeutic option has to be interpreted carefully.

In conclusion, rFVII_a might be an option in recurrent bleedings of inoperable cavernomas; however, further studies are needed to specify the efficacy and safety of rFVII_a in bleeding complications of cavernomas.

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