Successful use of rFVIIa for major breast surgery prophylaxis in congenital factor VII deficiency
A case report

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INTRODUCTION: Factor VII deficiency is a rare cause of haemorrhagic syndrome. The Authors describe a case of a 46 years old patient with congenital factor VII deficiency that successfully underwent breast surgery after treatment with Novoseven® before the procedure.

MATERIALS AND METHODS: The AA used the schedule reported below to value the levels of PT and aPTT in the patient.

Blood Collection: Venous blood from patient and control was collected in glass tubes for routine serum preparation and into plastic tubes (0.129 M sodium citrate, Becton-Dickinson Vacutainer Systems) in a ratio of blood to anticoagulant of 9:1. Platelet Poor Plasma (PPP) was obtained by centrifugation at 4,000 x g for 15 minutes at room temperature. The plasma was re-centrifuged for another 10 min at 12,000 g to fully eliminate platelet concentration. A normal control plasma pool was prepared by mixing equal volumes of platelet-free plasma obtained from at least 50 normal volunteers. Prothrombin time (PT) was measured with Recombiplastin (IL, Milano Italy). Activated partial thromboplastin times (APTT) was measured with APTT-SP® (IL, Milano Italy). They were performed on the coagulation analyzer ACL 1000 (IL, Milano Italy).

RESULTS: The results were interpreted from the ratio of the patient times to the normal control times (Table I).

CONCLUSION: The infusion of Novoseven solved the clotting problems enabling the surgical procedure, without risks for the patient.

KEY WORDS: Breast cancer, Factor VII deficiency, Major surgery, Recombinant fVIIa
homozygote or compound heterozygote develops a haemorrhagic syndrome. The clinical expression of this disorder is highly variable and no relationship has been found between the severity of the haemorrhagic syndrome and the residual levels of FVII activity. The clinical features can be very severe including intracerebral haemorrhages or haemarthroses or moderate with cutaneous-mucosal haemorrhages (epistaxis, menorrhagia) or haemorrhages during or after a surgical operation. A little amount of patients has no symptoms. The diagnosis is positive with a prolonged PT, confirmed by the dosage of the factor. An FVII activity, below that of pooled normal plasma, characterizes this pathology (normal values usually between 70 and 140%). The deficit is symptomatic only for values below 30%. For the differential diagnosis is important a distinction between congenital and acquired FVII deficits. In the acquired deficiency the consumption or the insufficient production are the most important causes due mainly to hepatocellular insufficiencies and hypo- or avitaminosis K. A rare cause of secondary deficiency is the presence of autoantibodies against FVII. The treatment is based on the replacement of the missing factor. The following products can be used:

1. **Fresh Frozen Plasma**
   One of the major criticisms is the low levels of FVII commonly present and then its short half-life. The risk is to involve too large transfusion volumes.

2. **PPSB**
   It’s a fraction of plasma containing the four vitamin K dependent factors. Its major adverse drug response is the risk of disseminated intravascular coagulation and thromboembolic complications.

3. **FVII concentrates**
   To stop or prevent haemorrhage levels of 20-30% are sufficient to stop or prevent haemorrhage but a level of about 50% is recommended for prophylaxis before surgery.

4. **Activated recombinant FVII (Novoseven®)**
   It has been licensed in the treatment of bleeding episodes

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**TABLE I - Normal PT and aPTT’s values**

<table>
<thead>
<tr>
<th>Test</th>
<th>v.n.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>0.85 – 1.15</td>
</tr>
<tr>
<td>PTT</td>
<td>0.90 – 1.20</td>
</tr>
</tbody>
</table>

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Fig. 1: The MRI shows the area of impregnation and the tumour.
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and in the prevention of bleeding during surgery or invasive procedures for patients with inherited FVII deficiency.

Case Report

The patient, a 46-year-old female, without prior breast cancer history, presented an ulceration on the nipple area complex, compatible with Paget's disease of the nipple, and a palpable mass of about 1.5 cm in diameter, with hard-wooden texture and irregular contours, situated in the upper outer quadrant of the periareolar region, at the clinical examination; the axillary lymph nodes were negative by palpation.

In December 2011, the patient received mammography (MMG), ultrasonography (US), and additional evaluation with FNAC and skin biopsy. MMG evidenced a region with major radio-opacity with little calcification. The US showed two hypogenic, oval formations with lobulated margins, on the upper outer quadrant of the right breast. Each of them measured 13 mm, and had a solid appearance. Cytology and histology confirmed Pagetoid cells presence positive for Paget's disease.

In January 2012, a MRI, an US and a FNAC were performed. The MRI (Fig. 1) indicated a large area of impregnation with nodular components that interested the areola, the lower outer quadrants union, and the lower quadrants union. This pattern was compatible with a multicentric, locally extended lesion. The US confirmed this diagnosis, considering multiple, hypoechogenic, heterogeneous areas of 10-14 mm. In the axillary fossa, two lymph nodes were suspected and a FNAC was indicated. The FNAC hadn't evidenced epithelial cells in the material.

Surgery was mandatory, but the patient presented a prolonged PT (1.38). In order to value the presence of a deficiency or of an inhibitor we realized a PT test on a compound 1:1 of patient's plasma with control plasma. The clotting time improved, so we determined the levels of factor II, V, and VII comparing them with control plasma (Table II).

The assay of clotting factor evidenced low levels of Factor VII (31%), compatible with factor VII deficiency.

Table II - Levels of clotting factors II of the patient compared to control plasma.

<table>
<thead>
<tr>
<th></th>
<th>Patient plasma</th>
<th>Control plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>1.34</td>
<td>11.2 sec</td>
</tr>
<tr>
<td>PTT</td>
<td>1.05</td>
<td>28.3 sec</td>
</tr>
<tr>
<td>PT MIXING TEST</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>Fattore II</td>
<td>99%</td>
<td>97%</td>
</tr>
<tr>
<td>Fattore V</td>
<td>92%</td>
<td>92%</td>
</tr>
<tr>
<td>Fattore VII</td>
<td>31%</td>
<td>99%</td>
</tr>
</tbody>
</table>

The correct dosage allowed the surgical treatment. The patient received Madden's radical modified mastectomy (muscle sparing mastectomy with axillary dissection) with reconstruction by prosthesis and positioning of a port-a-cath. The macroscopic analysis showed an abraded nipple. In the central quadrant there is an area of 1.2 cm of parenchymal thickening, with dilated ducts of starry appearance. In the upper outer quadrant there was another area of 1 cm with similar appearance. The lymph nodes of first and second level and 6 lymph nodes of third level were isolated. The microscopy (Fig. 2) evidenced a nipple Paget's disease with a neoplastic widespread intraductal neoplasia, which had the features of an high grade comedocarcinoma. The remaining breast parenchyma showed a fibrous disease of the breast with areas of intraductal adenosis and epiteliosis associated to papillomatous atypical areas. All the lymph nodes were disease free. The disease was staged as pTisN0.

The IC showed ER- PR- Ki67-Mib1 >60% and Her 2+++ in both components (intraductal and the tumor infiltrating the epidermis). No hemorrhagic dangerous events were detected. There were no thrombotic episodes. Novoseven increases the risk of thrombotic episodes caused by the hypercoagulability. A strong association occurrence between thrombotic events and cancer, but it was not due to the administration of Novoseven, in this case.

The assay of clotting factor evidenced low levels of Factor VII (31%), compatible with factor VII deficiency.

This situation would have exposed the patient to the risk of hemorrhage during the surgical treatment. As first approach we used vitamin K i.m., however with non-encouraging results. The second step was the infusion of fresh frozen plasma, but the quantity of factor VII contained in FFP was not enough to improve the levels of factor VII in the patient. Then we considered the use of Prothromplex® (Factor II, Factor VII, Factor IX, Factor X, Partial Human Prothrombin Complex) but poor effects have been obtained. Our last step was the implementation of therapy with Novoseven® 15 μg/kg to administrate 30 minutes before the operation and 4-5 hours after the first infusion. We saw a marked improvement of factor VII levels (Table III).

Table III - A comparison between factor VII levels before and after the treatment with Novoseven.

<table>
<thead>
<tr>
<th>Test</th>
<th>Before Novoseven</th>
<th>30' after Novoseven</th>
<th>60' after Novoseven</th>
<th>240' after Novoseven</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>1.44</td>
<td>0.52</td>
<td>0.66</td>
<td>0.72</td>
</tr>
<tr>
<td>PTT</td>
<td>1.09</td>
<td>1.01</td>
<td>0.99</td>
<td>1.00</td>
</tr>
<tr>
<td>PT MIXING TEST</td>
<td>0.92</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor II</td>
<td>98%</td>
<td>99%</td>
<td>98</td>
<td>97</td>
</tr>
<tr>
<td>Factor V</td>
<td>94%</td>
<td>95%</td>
<td>94</td>
<td>95</td>
</tr>
<tr>
<td>Factor VII</td>
<td>28%</td>
<td>222%</td>
<td>202%</td>
<td>190%</td>
</tr>
</tbody>
</table>
Discussion

The use FVIIa may have some adverse effects\textsuperscript{13}. Potential thrombotic complications\textsuperscript{14} related to its use have been reported. In our case the risk was increased by the presence of the cancer. Tumor cells produce procoagulant, fibrinolytic and platelet-aggregating activities, proangiogenic cytokines and procoagulant microparticles. In patients with hemophilia, the estimated incidence of serious adverse events due to administration of recombinant factor VIIa, including thrombotic complications, was about 1%\textsuperscript{13}. According to Roberts et al.: In 664 patients with hemophilia A or B participating in clinical trials with recombinant factor VIIa, there were seven thromboembolic events (1%)\textsuperscript{15}. In our case no sign of thrombotic complication was observed. There was also no evidence of the development of inhibitory antibodies\textsuperscript{16}, which is quite rare in patients with FVII deficiency.\textsuperscript{17}

Conclusion

The multidisciplinary collaboration allowed the implementation of a prophylactic therapy with rFVIIa. The success of this treatment put the bases for an appropriate and radical cancer treatment, without any adverse drug effects.

Riassunto

Il deficit del fattore VII è una rara causa di sindromi emorragiche. In questo articolo descriviamo un caso di una paziente di 46 anni con deficit congenito del fattore VII che si è sottoposta a trattamento chirurgico con successo grazie al trattamento con Novoseven prima della procedura. È stato utilizzato il modello riportato sotto per valutare i livelli di PTT e aPTT nel paziente. Per il prelievo ematico il sangue venoso della paziente è stato raccolto in provette di plastica (0,129 M di citrato di sodio, con sistema Vacutainer). Il tempo di protrombina è stato misurato con Recombiplastin (IL, Milano Italy), l’aPTT è stato misurato con l’AFTT-SP (IL, Milano Italy). Come primo approccio profilattico alla paziente è stata utilizzata la vitamina K intramuscolare ma con scarsi risultati, poi si è valutato l’uso del Prothromplex, senza però ottenere un effetto significativo. L’ultimo step è stata la somministrazione di una terapia con Novoseven \(15\mu g/kg\) somministrato 30 minuti prima dell’intervento and 4-5 h dopo la prima infusione. L’infusione del farmaco ha risolto i problemi di coagulazione permettendo il trattamento chirurgico, senza rischio né emorragico né trombotico per la paziente.

References

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