Successful Hemostasis after Dental Extraction with the Use of Recombinant Activated Factor II in a Factor II Deficient Patient

Koji Satoh, Masataka Okamoto*, Aya Torimura, Rina Taguchi, Yasuhisa Mineno and Hideki Mizutani

Department of Oral and Maxillofacial Surgery, School of Medicine, Fujita Health University
(Chief: Professor Hideki Mizutani)
*Department of Hematology, School of Medicine, Fujita Health University
(Chief: Professor Kohji Ezaki)

Abstract: We report our experience of successful hemostasis after dental extraction with the use of rFIXa in a FIX deficient patient. Preoperative PT% was 25%, and FIX was less than 3%. Thirty minutes before tooth extraction, 1.2 mg of rFIXa was injected. At the beginning of the operation, PT% was more than 200%, FIX was 336%, and the hemostasis after dental extraction was excellent. rFIXa was used effectively and safely for dental extraction in this case of FIX deficiency.

Key words: factor II deficiency, recombinant activated factor II, hemostasis, dental extraction

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Requests for reprints: Koji Satoh, Department of Oral and Maxillofacial Surgery, School of Medicine, Fujita Health University, 1-98 Dengakukakubo, Kutsukake-cho, Toyoake, Aichi, 470-1192, Japan, Phone: + 81-562-93-2209, Fax: + 81-562-93-6038, E-mail: kjsato@fujita-hu.ac.jp
On May 2003, she visited complaining of gingival bleeding again. The periodontal pockets of her molar teeth were 3–5 mm, and she bled when brushing. She underwent root scaling of all teeth and gingival curettage on her molar teeth. After dental procedures, bleeding could be controlled by local application of thrombin (5000 U) and compression with a dental appliance. On September 2004, pericoronitis of the lower right wisdom tooth could not be controlled, and continuous pain and pus discharge were observed. As the tooth was the backmost molar, it was thought that compression with a dental appliance after tooth extraction might not be a reliable approach, so the preoperative replacement with rF[VII]a (Novoseven<sup>®</sup>, Novo Nordisk) was planned. It was arranged to administer rF[VII]a by intravenous bolus injection of the dose 20 μg/ kg, 30 min before tooth extraction followed by a half dose every 6 hours until hemostasis was achieved. Preoperative PT% was 25%, and FVII was less than 3%. Thirty minutes before tooth extraction, 1.2 mg of rF[VII]a was injected. At the beginning of the operation, PT% was more than 200%, FVII was 336% (Table 1), and the hemostasis after dental extraction was excellent (Fig. 1). FVII was 61% even 6 hours after operation and no postoperative bleeding was observed, so additional administration was not necessary.

**Table 1** PT% and FVII activity in response to rFVIIa infusion

<table>
<thead>
<tr>
<th>Time after infusion (hrs)</th>
<th>0</th>
<th>0.5</th>
<th>6</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT% (%)</td>
<td>25</td>
<td>&gt; 200</td>
<td>112</td>
<td>27</td>
</tr>
<tr>
<td>FVII activity (%)</td>
<td>&lt; 3</td>
<td>336</td>
<td>61</td>
<td>&lt; 3</td>
</tr>
</tbody>
</table>

Discussion

In patients with FVII deficiency, the symptoms most frequently reported are recurrent epistaxis and moderate delayed bleeding after dental extraction. Epistaxis is the most common hemorrhagic manifestation.<sup>2</sup>

The diagnosis of FVII deficiency is suggested by a prolonged PT with a normal APTT. No other congenital coagulation disorders have a similar pattern. If hepatic dysfunction and vitamin K deficiency are not present, definitive diagnosis can be made by the specific assay of FVII. Replacement therapy is required for the management of severe to moderate bleeding. Prothrombin complex concentrates or activated prothrombin complex concentrates have been used. However, these concentrates have serious disadvantages. First, the risk of thrombotic complications causes an unnecessary rise in the vitamin K dependent factors. Second, using blood donor products carries the risk of human viral transmission.

Recently, the rFVIIa preparation (Novoseven<sup>®</sup>, Novo Nordisk) was developed as a second-generation bypassing material intended mainly for use in hemophilia patients with inhibitors<sup>3</sup>. The process is independent of the presence of factors VIII or IX and is not affected by inhibitors<sup>4</sup>. As human plasma contains only a low level of FVII, this drug was produced using a genetically modified technique. Compared with the concentrates from human plasma, when the rFVIIa is applied to patients suffering from FVII deficiency, it reduces the risk of thrombotic complaints because it is inactive in the blood circulation, is activated only after arrival at the injured lesion, and it does not activate the other vitamin K dependent factors<sup>3</sup><sup>4</sup>. Though several articles have been published regarding the use of rFVIIa for the treatment of FVII deficiency, there are no reports about disadvantages except for one case. In that case, antibodies to FVII appeared 4–5 weeks after the administration of a dose, by mistake, which was 40 times higher than the average effective dose<sup>3</sup>. The half life of FVII has been determined as 3.5 hours<sup>5</sup>, but in vivo it is reported to range from 5.3 hours<sup>6</sup> to 6 hours<sup>7</sup>. According to the report about FVII after intravenous bolus injection of rFVIIa, the activity was at its maximum during the first 30 min, and was completed...
within 6 hours\textsuperscript{1,7}. In our case, only a single use of 20μg/kg, 30 min before surgery raised the FⅦⅡ level to 336% at dental extraction and it stayed at 61% even 6 hours after. Mariani et al.\textsuperscript{3} summarized the median dose of rFⅦⅡa to normalize the mean PT ratio as 25.66μg/kg in their 17 FⅦⅡⅡ deficient patients. It is generally agreed that surgical intervention will cause bleeding in patients with FⅦⅡⅡ levels below 10–15%\textsuperscript{8} of normal, and levels of 15–25% are thought to be sufficient for normal hemostasis\textsuperscript{9}. The recommended dose range for the treatment of bleeding episodes in patients undergoing surgery or invasive procedures is 15–30μg/kg, every 4–6 hours until hemostasis is achieved. The dose and frequency of injections should be adapted to each individual. In our computer database search, we found only two documented cases of the use of rFⅦⅡa for dental extractions in FⅦⅡⅡ deficient patients. In the first case, for five teeth extractions, the dosage was 24μg/kg before surgery, repeated after 7 hours, thereafter two doses of 12μg/kg were administered at 6 hours\textsuperscript{10}. Based on the preliminary experience, it was suggested that further reduction of the dosage of rFⅦⅡa could be exploited in the setting of minor oral surgery prophylaxis\textsuperscript{10}. In the second case of dental extraction, the dosage was 25μg/kg, and despite only single use the result was excellent\textsuperscript{3}. Our case was treated with 20μg/kg (1.2 mg/body) single use 30 min before surgery. The local hemostasis was excellent.

It is thought that 20μg/kg single use 30 min before surgery is enough for the extraction of a few teeth. Replacement therapy by rFⅦⅡⅡa is the first line therapy to control bleeding in a situation of spontaneous bleeding and in surgical interventions for FⅦⅡⅡ deficiency, because it corrects the clotting default at a low dosage.

References