ELSEVIER

Recombinant Factor VIIa in Major Abdominal Surgery and Liver Transplantation

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ABSTRACT

The author reviewed the literature regarding recombinant activated Factor VII (rFVIIa) in major abdominal surgery and liver transplantation and concluded that, on the basis of evidence-based medicine, there is no evidence to support an extensive use of rFVIIa. Nevertheless, various case reports suggest the usefulness of rFVIIa to treat life-threatening bleeding after failure of conventional therapies. It appears that there is a consensus that rFVIIa can be used with good results as a rescue therapy in extremely severe situations. Economic cost and potential thrombosis risk remain arguments against more widespread use of rFVIIa. Doses from 5 to 120 kg/kg in each administration have been reported without clear evidence to support a specific protocol. Efficacy of 15 to 20 kg/kg in surgical settings has been reported, but higher doses are more frequently used. The majority of the reviewed investigators accepted the use of rFVIIa after or simultaneously with the use of aprotinin; no data refute the safety of this association.

ONLY ONE randomized clinical trial (RCT), including 185 patients, has evaluated the use of recombinant activated Factor VII (rFVIIa) in liver surgery. Compared with placebo there was a tendency toward fewer transfusions—the primary end point—, but it did not show statistical significance.[1]

OTHER ABDOMINAL SURGERIES

Extrapolating to other kinds of surgeries, an RCT including 36 patients reported a significant reduction in blood loss associated with the use of rFVIIa in retropubic prostatectomy.[2] A retrospective case-controlled study compared 51 patients with 51 matched controls, observing similar results in cardiac surgery.[3]

If controlled studies are scarce, a relevant number of uncontrolled reports exist about the use of rFVIIa in cirrhotic patients, including those undergoing percutaneous liver biopsy,[4,5] laparoscopic liver biopsy,[6] endoscopic retrograde cholangiopancreatography,[7] and esophageal variceal bleeding.[8,9] With respect to other kinds of patients and other types of surgical interventions, the utility of rFVIIa has been advocated in cardiac surgery,[10] orthopedics, intensive care, trauma,[11] gynecological/obstetrical surgery, and neurosurgery.

EVIDENCE ABOUT FACTOR VIIa IN LIVER TRANSPLANTATION

A preliminary study compared six patients who received rFVIIa with six matched controls. It advocated the usefulness of the drug to reduce intraoperative RBC and FFP needs in liver transplantation.[12] Another preliminary controlled but nonrandomized study reported the opposite results.[13]

Beside these studies, some case reports have been published.[14] In general, no complications have been reported to be related to the use of rFVIIa, except a recent description of two thrombotic events observed with its use during four liver transplants.[15] The possibility of increased thrombotic events, particularly increased vascular complications at the graft anastomosis, is a matter of concern. A study to refute this hypothesis must include a sufficient number of patients, a need that is difficult to reach in liver transplantation. For example, if the drug produces a 50% increase in complications above the usual 5% incidence, it will be necessary to enroll almost 1500 patients to prove this harm as statistically significant.

WHEN TO USE rFVIIa?

The use of rFVIIa in surgical settings has been advocated when other measures fail to stop relevant blood loss, the so-called intractable bleeding. Some variation may be observed about this definition, but, in general, investigators defend

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the use of rFVIIa if bleeding persists after failure of correction with plasma, platelets, and antifibrinolytic drugs. The administration of rFVIIa after aprotinin is frequently reported; there seems to exist no harm from this combination.

In specific situations, rFVIIa may be utilized as an adjuvant to standard therapies (particularly FFP), when rapid correction of hemostasis is necessary and renal insufficiency precludes the administration of a large volume of fluids.

A final group of indications are situations where near-normal coagulation is only transiently required. The paradigm of this situation is the insertion of sensors for intracranial pressure in patients with acute liver failure.

HOW MUCH rFVIIa TO USE?

Reports describe the use of a broad range of doses, from 5 to 120 μg/kg at each administration. Doses of 15 to 20 μg/kg seem to be useful to correct coagulation in surgical settings, although, more frequently, investigators have reported higher doses, from 40 to 90 μg/kg. Some researchers claim advantages with the use of these high doses, but the evidence suggests that compared with 20 μg/kg, 60 to 80 μg/kg increased the duration of action,[6] but only produced modest benefits in efficacy.

Among cirrhotic patients, 5 μg/kg shows an ability to correct the prothrombin time to near-normal values. Its use has been defended for minor procedures such as percutaneous liver biopsy.[4]

OUR GUIDELINES

We conclude that several publications suggest the usefulness of rFVIIa to treat coagulation in surgical settings, but this has not been proven. Despite that, we consider it ethical to use rFVIIa when bleeding is a life-threatening event and when other measures, including FFP, platelet concentrates, and aprotinin, were previously unsuccessful.

We administer 15 to 20 μg/kg (usually 1.2 mg to a normal adult) and repeat the dose 3 to 4 hours later, if necessary. In the choice of this dose, economics had some weight, but it was influenced by other factors: benefits claimed for high doses did not seem relevant enough to justify their use, and a short duration of action may be advantageous when there is an increased risk of thrombosis. Particularly after reperfusion in liver transplantation and in recently transplanted patients, we do not need completely normal coagulation. A certain degree of hypocoagulability, within an acceptable risk to the patient, is advantageous to reduce the incidence of any vascular complication of the graft, a life-threatening problem itself. In these conditions, rFVIIa reaches the status of a rescue therapy limited in time to periods where bleeding is considered to be a risk to the patient's life. We consider the existence of surgical conditions that predispose to thrombosis to be a relative contraindication, to be weighed against the presumed advantages.

FUTURE USE OF rFVIIa

The use of rFVIIa as rescue therapy and/or its inclusion in a first-line protocol for rapid correction of coagulation at the start of liver transplant are two points that need separate further studies. Economics could be an objection to the widespread use of this drug. If the future brings evidence supporting the efficacy of rFVIIa, the doses and frequency of administration necessary to reduce RBC and FFP consumption could make a strong difference concerning wider use.

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