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ecombinant factor VIIa has been introduced in clinical medicine in the 1980's and has been shown to be a highly effective prohaemostatic agent (1-3). It is thought to act locally at the site of tissue injury and vascular wall disruption, by binding to exposed tissue factor and generating small amounts of thrombin, sufficient to activate platelets. The activated platelet surface can then form a template on which rFVIIa can directly or indirectly mediate further activation of coagulation, resulting in the generation of much more thrombin that ultimately leads to the conversion of fibrinogen to fibrin (4, 5). Clot formation is stabilized by inhibition of fibrinolysis, due to factor VIIa-mediated activation of thrombin-activatable fibrinolysis inhibitor (6).

Primarily, rFVIIa was used in patients with congenital or acquired haemophilia and inhibiting antibodies towards factor VIII or IX, for which it has been licensed in Europe, the US and many other parts of the world (7, 8). In recent years, the potential of recombinant factor VIIa to act as a prohaemostatic agent in other categories of patients with severe coagulation defects or in patients with excessive bleeding has been explored (9). Although this application of recombinant factor VIIa is still in its initial phase and most of the experience is based on uncontrolled series of observations, it seems that this agent can indeed be used to treat serious bleeding in many types of patients.

There are an abundant number of case reports and case series on the haemostatic efficacy of rFVIIa in patients undergoing surgery. However, virtually all these reports did not include adequate controls, which makes it very hard to draw any clinical conclusion. More helpful is the increasing number of randomized clinical trials in patients undergoing surgery that is associated with major blood loss. In this article we will briefly review the efficacy and safety of recombinant factor VIIa in this setting.

Surgery and rFVIIa

The first controlled clinical trial showing that the administration of this agent minimizes perioperative blood loss and transfusion requirements was performed in patients undergoing transabdominal prostatectomy, an operation that is associated with major blood loss (10). In this trial 36 patients undergoing abdominal prostatectomy, that is associated with major blood loss, were randomized to a single injection of rFVIIa (20 or 40 mg/kg) or placebo during the operation. Administration of rFVIIa (40 mg/kg) at the beginning of the operation resulted in a 50% reduction of blood loss as compared with placebo and eliminated the need for blood transfusion, which was required in about 60% of placebo-treated patients. Patients that received 20 mg/kg rFVIIa showed a smaller (35%) but still significant reduction in blood loss and of these patients 38% needed a blood transfusion.

Another small study was the first to show that administration of rFVIIa in patients with a pre-existent normal coagulation system could reduce blood loss and transfusion requirements in major surgery.

Another study compared the administration of rFVIIa with placebo in 48 patients undergoing major pelvic-acetabular surgery (11). In this study there was no significant difference in the total volume of perioperative blood loss, the primary outcome variable, between the rFVIIa and placebo groups. In addition, there were no differences between the two groups in the total volume of blood components, and the number of patients requiring allogeneic blood components.

In addition, rFVIIa has been evaluated in a small randomized controlled study in 20 patients undergoing non-coronary cardiac surgery requiring cardiopulmonary bypass (12). Administration of this agent (90 mg/kg after discontinuation of bypass and reversal of heparin) significantly reduced the need for blood transfusion (relative risk of any transfusion 0.26, 95 per cent confidence interval 0.07-0.90).

Liver transplantation

Another area where the administration of rFVIIa might be effective is liver transplantation. An initial open-label pilot study in six patients undergoing orthotopic liver transplantation showed a strong reduction in trans-
fusion requirements in patients that received a single dose of rFVIIa (80 mg/kg) as compared with historic matched controls (13). However, a randomized placebo-controlled dose finding trial in liver transplantation did not show a reduction in transfusion requirements by administration of rFVIIa in doses up to 80 mg/kg (14). A subsequent trial in 183 patients undergoing orthotopic liver transplantation found no significant effect of repeated administration of 60 or 120 mg/kg recombinant factor VIIa on intraoperative blood loss or the number of red blood cell units transfused (15). However, a significantly higher number of patients who had received rFVIIa did not need any transfusion. Lastly, the efficacy of rFVIIa to prevent blood loss and transfusion requirements was studied in a randomized placebo-controlled trial in 204 patients undergoing partial hepatectomy. Administration of rFVIIa at a dose of 80 mg/kg resulted in reduced blood loss as compared with placebo and the proportion of patients receiving postoperative blood transfusion decreased from 37 to 25% (p = 0.05) (16).

**Trauma**

Bleeding is one of the leading causes of death in patients with severe trauma. Several case reports and case series indicate that rFVIIa may potentially be effective in reducing excessive blood loss and transfusion requirements in these patients (17, 18). Experiments in hypothermic coagulopathic swine (but not in non-coagulopathic swine) with severe liver injury showed a reduction in blood loss by rFVIIa (19, 20). A large placebo-controlled trial of rFVIIa (400 µg/kg in three doses) in 301 patients with severe blunt and/or penetrating trauma, aiming to achieve a reduction in transfusion requirements, has recently been completed. This study showed a significant reduction of red cell transfusion in patients with blunt trauma and a trend towards a reduced incidence of multiple organ failure and ARDS in patients receiving recombinant factor VIIa. Mortality in blunt trauma patients receiving recombinant factor VIIa was 25% in comparison to 30% in the placebo group (NS) (21). There were no significant effects in 134 patients with penetrating trauma. Currently, two large placebo-controlled trauma trials with high dose recombinant factor VIIa are ongoing.

**Meta-analyses of rFVIIa in surgery**

There are two recent meta-analyses on the use of rFVIIa in surgery (22, 23). In the first analysis seven controlled studies investigating the efficacy and safety of recombinant factor VIIa in patients undergoing major surgical procedures were included (22). Efficacy was determined as the rate of patients receiving allogeneic packed red blood cells. Treatment with rFVIIa was associated with a reduced risk of receiving allogeneic red blood cells (odds ratio, 0.29; 95% confidence interval, 0.10–0.80). In a subgroup analysis, only patients receiving at least 50 µg/kg of rFVIIa had a significant benefit (odds ratio, 0.43; 95% confidence interval, 0.23–0.78).

In the second paper the authors performed a meta-analysis of both case series and placebo-controlled studies (23). The analysis found a reduction or cessation of bleeding in 39 out of 50 patients after administration of rFVIIa (estimated mean effect 73.2%, 95% confidence interval 51.0% to 95.4%) and a mean probability of survival of 53.0% (95% CI 26.4% to 79.7%). Among the rFVIIa responders, 19 out of 29 patients (66%) survived versus 1 out of 10 non-responders (P = 0.003).

**Perioperative use of rFVIIa**

Any intervention in the coagulation system aimed at either thrombosis or bleeding may simultaneously affect the other condition. Hence, the pro-haemostatic properties of rFVIIa may theoretically have a downside in the form of potential thrombotic complications associated with its use (24). In particular, clinical conditions that are mediated by tissue factor exposure to the circulation may theoretically carry the risk of adverse thrombotic reactions upon the administration of rFVIIa. An example of such a condition may be the patient with a (semi)ruptured atherosclerotic plaque, that is known to contain abundant tissue factor. In this situation rFVIIa may hypothetically precipitate an acute thrombotic event, such as a myocardial infarction. Another condition that is associated with systemic tissue factor exposure to the circulation is disseminated intravascular coagulation (DIC), due to exposure of tissue factor on circulating mononuclear cells (25), whereby administration of rFVIIa could theoretically lead to a more severe coagulopathy and aggravate systemic microvascular thrombosis.

In patients with haemophilia the estimated incidence of serious adverse events due to administration of rFVIIa, including thrombotic complications, was about 1%. In 664 patients with haemophilia A or B participating in clinical trials with rFVIIa there were 7 thromboembolic events (1%) (26). In addition, there are case reports of myocardial infarction in 6 patients with haemophilia (three congenital and three acquired), of which five patients were known with coronary artery disease (27, 28). A recent article estimates that the incidence of thrombotic events associated with the use of rFVIIa is 24.6 per 105 infusions as compared with a rate of 8.2 per 105 infusions of activated prothrombin complex concentrate (FEIBA) (29). DIC appears to be a very infrequent complication during treatment with rFVIIa (only 5 patients reported) and was mostly considered not to be attributable to this agent. In fact, all reports on DIC in association with rFVIIa are related to patients that already had DIC or were at high risk to develop DIC (e.g. septic patients). In our literature search there were 15 patients in which rFVIIa was used for severe bleeding, despite the concomitant presence of DIC (30). These cases concern patients with acquired haemophilia or severe liver failure, most of which with infectious problems complicated by DIC. Remarkably, rFVIIa was reported to be effective in 14 of these 15 patients and in none of these patients there were signs of escalation of the DIC. Together, the available evidence tentatively indicates that the risk of thromboembolic complications due to factor VIIa is low, although safety data from placebo-controlled studies with rFVIIa are scarce. However, most of these studies were carried in patients with impaired coagulation or at low risk for thrombosis. In the trial carried out in patients with a much higher risk, such as those with intracerebral haem-
orrhage, serious thromboembolic events, mainly myocardial or cerebral infarction, occurred in 7 percent of patients treated with rFVIIa, as compared with 2 percent of placebo-treated patients (31).

A review of thromboembolic complications reported to the FDA MEDWATCH database showed that thromboembolic events do occur in both the arterial and venous systems, particularly in cases of unlabeled use of rFVIIa in patients other than those with haemophilia (32). It is not clear to which extent the clinical setting that required the use of this agent may have contributed to the thrombotic risk. A more precise safety profile of rFVIIa is required to more accurately assess its place in prevention and treatment of excessive bleeding. The ongoing placebo-controlled trials will be helpful in that respect.

Conclusion

Recombinant factor VIIa is a potent pro-haemostatic agent that can be used for treatment and prevention of severe bleeding in patients with complex coagulation disorders, but probably also in a number of other clinical conditions that are dominated by severe blood loss. Its use in surgery to prevent major perioperative blood loss is attractive, although various controlled studies show contradictory results regarding the efficacy of this intervention. The efficacy of recombinant factor VIIa will probably depend on the clinical setting and its exact place warrants further clinical trials. Appropriately controlled clinical trials will definitively assess the place of recombinant factor VIIa in surgery.

References


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