Case report: Management of life-threatening oropharyngeal bleeding with recombinant factor VIIa

[Une présentation de cas : le traitement de graves saignements oropharyngiens avec le facteur VIIa recombinant]

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Purpose: To report the use of recombinant factor VIIa (rFVIIa) for management of profuse oropharyngeal bleeding in a cirrhotic patient that nearly resulted in a 'cannot intubate, cannot ventilate' scenario.

Clinical features: A 42-yr-old woman with end-stage liver disease presented for orthotopic liver transplantation. She was dialysis dependent and had marked coagulopathy [international normalized ratio (INR) = 3.1], without evidence of active bleeding. Following uneventful induction of anesthesia, routine airway manipulation for tracheal intubation caused profuse upper airway bleeding making visualization of her airway by direct laryngoscopy impossible. Moreover, several further attempts at tracheal intubation along with the bleeding made manual ventilation progressively more difficult, nearly resulting in a 'cannot intubate, cannot ventilate' scenario. In an attempt to control the bleeding, rFVIIa 4.8 mg iv was administered. Within five minutes, her INR had decreased to 1.1, bleeding was markedly reduced, the vocal cords were successfully visualized using an anterior commissure laryngoscope, and intubation of the trachea was achieved with the use of a gum-elastic bougie. Post-intubation examination of the airway showed several abrasions along the right oropharyngeal wall with minimal bleeding. The remainder of surgery and postoperative airway management were uneventful.

Conclusions: This report demonstrates that in the relatively uncommon setting of upper airway hemorrhage in a patient with pre-existing coagulopathy, rFVIIa can be effective in gaining rapid control of bleeding to facilitate visualization of the vocal cords and securing of the airway.

Objectif : Présenter l'usage du facteur VIIa recombinant (rFVIIa) comme traitement d'importantes hémorragies oropharyngiennes qui ont presque provoqué une situation d'intubation et de ventilation impossibles chez une patiente cirrhotique.

Éléments cliniques : Une femme de 42 ans atteinte d'une maladie terminale du foie a subi une transplantation orthotopique du foie. Dépendante de la dialyse, elle présentait une coagulopathie marquée [international normalized ratio (INR) = 3,1] sans saignement actif apparent. Après l'induction normale de l'anesthésie, la manipulation habituelle de la trachée pour l'intubation a causé un saignement abondant des voies aériennes supérieures rendant la visualisation impossible par laryngoscopie directe. Puis, d'autres tentatives d'intubation en présence des saignements ont compliqué progressivement la ventilation manuelle et ont presque entraîné l'impossibilité d'intuber et de ventiler. Pour contrôler l'hémorragie, nous avons administré 4,8 mg de rFVIIa iv. En moins de cinq minutes, l'INR a baissé à 1,1, le saignement a fortement diminué, les cordes vocales étaient facilement visualisées avec un laryngoscope d'oto-rhino-laryngologie et l'intubation endotrachéale réalisée avec une bougie élastique. Après l'intubation, l'examen des voies aériennes a montré des éraflures sur la paroi oropharyngienne droite et un saignement minime. Aucun autre incident n'est survenu par la suite.

Conclusion : Dans le cadre relativement particulier d'une hémorragie des voies aériennes supérieures chez une patiente qui présentait une coagulopathie préexistante, le rFVIIa a été efficace en permettant un contrôle rapide des saignements, ce qui a facilité la visualisation des cordes vocales et protégé les voies aériennes.

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Funding and conflicts of interest: Dr. K. Karkouti is supported in part by the Canadian Institutes of Health Research and the Canadian Blood Services. K. Karkouti has received an unrestricted research grant and consultant's fees from Novo Nordisk.

Accepted for publication April 7, 2006.

Revision accepted May 4, 2006.

PATIENTS with cirrhosis have varying degrees of coagulopathy that may elevate their risk of bleeding events. Bleeding in such patients may occur spontaneously, or in association with minor trauma as well as major surgery. This case report describes a cirrhotic coagulopathic patient in whom routine airway manipulation following induction of general anesthesia for liver transplantation caused profuse upper airway bleeding that nearly led to a 'cannot intubate, cannot ventilate' scenario. The uncontrolled bleeding was managed successfully with recombinant factor VIIa (rFVIIa). The patient gave informed consent for review of her medical records and publication of this case.

Clinical report

A 42-yr-old woman (51 kg) with end-stage liver disease secondary to autoimmune hepatitis presented for total recipient hepatectomy and orthotopic liver transplantation. She had a history of deteriorating liver function for one year, and one episode of esophageal variceal bleeding four months previously, which was band-ligated. One month prior to surgery, she underwent upper gastrointestinal endoscopy as part of the transplant protocol, which showed grade II esophageal varices, with no active bleeding. Her only previous surgery was for a duodenal ulcer, which was performed uneventfully three years previously. Her renal function deteriorated during the month prior to surgery, to the stage where she required hemodialysis. By the time of surgery, the patient was encephalopathic and drowsy. Her preoperative airway examination was unremarkable – mouth opening, oropharyngeal view, thyromental distance, and neck movement were all normal. She did not have any active bleeding prior to surgery, despite her marked coagulopathy. The results of the preoperative blood tests are presented in Table I. During the three hours prior to surgery, the patient received two units of fresh frozen plasma (FFP), but coagulation tests were not repeated.

For anesthetic induction, after three minutes of pre-oxygenation with 100% O₂ and initiation of cricoid pressure, the patient received midazolam 2 mg *iv*, fentanyl 300 µg *iv*, propofol 60 mg *iv*, and succinylcholine 80 mg *iv*. Tracheal intubation was attempted using a #3 Macintosh laryngoscope blade. Upon insertion of the blade into the oropharynx, before the vocal cords could be visualized, the patient began to bleed profusely from her oropharynx. As a result of the bleeding, two further attempts to secure the airway using both curved and straight laryngoscope blades, with and without cricoid pressure and concomitant suctioning of the oropharynx, failed.

During this time the patient's lungs were ventilated manually by bag and mask, maintaining her oxygen saturation > 94%. As a result of the severity of bleeding, the patient was kept anesthetized with supplemental *iv* boluses of propofol and succinylcholine *prn* to maintain paralysis. Rather than attempting fibreoptic bronchoscopy at this stage, further assistance was requested. An otorhinolaryngologist attempted to intubate the patient's trachea using an anterior commissure laryngoscope, but failed as a result of ongoing severe bleeding. Meanwhile, manual ventilation was becoming progressively more difficult, despite use of an oropharyngeal airway, and oxygen saturation decreased to 88%. Intravenous anesthesia was maintained since the source of bleeding was unknown, and the ability of the patient to protect her airway upon emergence was uncertain. To minimize the likelihood of possible further trauma to the airway, the use of an extraglottic device such as the laryngeal mask airway was not attempted.

Two more units of FFP were rapidly transfused with no noticeable effect on bleeding. Given the critical and progressive nature of the situation, priority was given to obtaining rapid control of the bleeding by rFVIIa. Approval was obtained via consultation with a hematologist, and 4.8 mg of rFVIIa (Novoseven®, Novo Nordisk, Mississauga, ON, Canada) was administered intravenously over one minute. Within five minutes there was a marked reduction in the bleeding, and the otorhinolaryngologist was able to visualize the vocal cords with the anterior commissure laryngoscope. A bougie was advanced through the cords, and an endotracheal tube was railroaded over the bougie to secure the airway.

Approximately 30 to 45 min elapsed from anesthetic induction to securing of the airway. Post-intubation examination of the airway showed several abrasions along the right oropharyngeal wall with minimal bleeding. Fibreoptic bronchoscopy revealed that considerable blood had been aspirated, but there were no clots and the airways were patent. Post-rFVIIa hematological variables are presented in Table I, and pre- and post-intubation arterial blood gas values are presented in Table II.

The remainder of the case was uneventful. The patient received seven units of red blood cell concentrate, 12 units of FFP, and five units of platelets during surgery. The estimated surgical blood loss was 6 L. Postoperatively, the patient was managed in the intensive care unit. On the fourth postoperative day, her trachea was extubated in the operating room (as a precaution) with no difficulty. She was discharged home on postoperative day 12.

TABLE I Coagulation tests before and after rFVIIa administration

Laboratory tests	Preoperative	Post rFVIIa
Hemoglobin (g·L ⁻¹)	72	65
Platelet count (× 10 ⁹ ·L ⁻¹)	71	98
International normalized ratio	3.05	1.13
Prothrombin time (sec)	30	15
Activated partial thromboplastin time (sec)	80	62
Fibrinogen (g·L ⁻¹)	1.4	1.8

rFVIIa = recombinant factor VIIa.

TABLE II Arterial blood gases pre-induction and after tracheal intubation

Arterial blood gases	Pre-induction (F _i O ₂ = 0.21)	Post-intubation (F _i O ₂ = 1.0)
pH	7.5	7.1
pCO ₂ (mmHg)	34	81
pO ₂ (mmHg)	59	218
Bicarbonate (mmol·L ⁻¹)	26	25
Base excess (mmol·L ⁻¹)	3.3	-3.5

Discussion

In coagulopathic patients, upper airway bleeding precluding visualization of the vocal cords for tracheal intubation is a critical event, particularly if it compromises the anesthesiologists' ability to maintain adequate ventilation. This case demonstrates that rFVIIa can rapidly restore hemostasis in this setting, allowing for adequate visualization of the airway for tracheal intubation.

Coagulopathy is one of the main characteristics of cirrhosis, and is caused by low blood concentrations of coagulation proteins normally synthesized in the liver, as well as thrombocytopenia from hypersplenism, enhanced fibrinolysis due to decreased hepatic clearance of its inhibitors, and platelet dysfunction if there is accompanying renal dysfunction.¹ Consequently, even minor injuries can result in major bleeding events in cirrhotic patients.² In this case, routine airway manipulation resulted in profuse upper airway bleeding that precluded vocal cord visualization and tracheal intubation by direct laryngoscopy, and eventually compromised the ability of the anesthesiologist to maintain adequate ventilation.

Current standard of care for restoring hemostasis in cirrhotic patients with elevated international normalized ratio is by FFP transfusions.¹ Fresh frozen plasma transfusions, however, cannot restore hemostasis rapidly, and in fact are often ineffective in cirrhotic patients.¹ Owing to the grave condition of the

patient and the impending 'cannot intubate, cannot ventilate' scenario, this case required rapid restoration of hemostasis.

Faced with an impending 'cannot intubate, cannot ventilate' scenario, practice guidelines recommend use of extraglottic devices such as the laryngeal mask airway as a temporizing measure to aid ventilation, or failing that, obtaining emergency invasive airway access by surgical or percutaneous tracheostomy or cricothyrotomy.³ In this case, however, rapid restoration of hemostasis with rFVIIa made tracheal intubation possible, thereby avoiding the need for temporizing or invasive measures for securing the airway.

Activated recombinant factor VII is a synthetic analogue of human plasma factor VII with similar structure and activity. The mechanism of action of rFVIIa involves enhanced thrombin generation on thrombin-activated platelet surfaces, leading to increased platelet activation and clot formation at the site of injury.⁴ While the product was developed originally as an alternate therapy for hemophilic patients with inhibitors against factor VIII and IX, there have been an increasing number of reports describing its successful application in a diverse range of clinical situations in non-hemophilic patients.⁵ The ability of rFVIIa to increase thrombin generation has initiated numerous 'off-label' uses for rFVIIa either as a prophylactic agent against hemorrhage, or as rescue therapy for patients who have failed conventional hemostatic therapy, and there are successful reports of its use in various patient populations including cirrhotic, trauma, and cardiac surgical patients.^{1,5-7}

Use of rFVIIa for intractable oropharyngeal bleeding has been limited to hemophilic patients undergoing tooth extraction.^{8,9} This is the first reported case where rFVIIa was used to rapidly control profuse oropharyngeal bleeding in a non-hemophilic coagulopathic patient, thereby helping to prevent an impending 'cannot intubate, cannot ventilate' scenario. Although rFVIIa is not part of the difficult airway algorithm, anesthesiologists should consider its use when faced with coagulopathic patients with intractable upper airway hemorrhage.

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