Successful use of recombinant activated factor VII administered via automated bolus pump following emergency laparoscopic appendectomy in a patient with mild congenital FVII deficiency: Case report

Heather Perkins | Robert J. Klaassen

Department of Pediatrics, Division of Hematology/Oncology, University of Ottawa, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada

Correspondence

Robert J. Klaassen, MD, FRCP(C)
Department of Pediatrics,
Division of Hematology/Oncology,
University of Ottawa,
Children's Hospital of Eastern Ontario
401 Smyth Road,
Ottawa,
Ontario,
Canada K1H8L1
Telephone: (613) 737-2393 #2210
Fax: (613) 738-4828
Email: rklaassen@cheo.on.ca

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ABBREVIATIONS TABLE

FVII	factor VII
FVII:C	Factor VII concentration
ICU	Intensive care unit
rFVIIa	recombinant activated FVII

Abstract (<100 words, currently 100 words)

Surgery in patients with factor VII (FVII) deficiency may be complicated by severe bleeding, requiring regular bolus doses of replacement therapy. Eptacog alfa (activated) is a recombinant activated FVII (rFVIIa) used for the treatment of bleeds and perioperative management in patients with approved bleeding disorders, including FVII deficiency. We report that using the B-Braun Perfusor® Space syringe pump to automatically deliver regular bolus rFVIIa doses provided effective hemostasis and no safety concerns in a patient with mild FVII deficiency undergoing emergency laparoscopic appendectomy. Additional benefits included saving nursing/hospital resources, reducing treatment burden and reassurance for the patient/family, and healthcare providers.

1 | INTRODUCTION

Factor VII (FVII) deficiency is a rare congenital bleeding disorder, with an estimated global prevalence of approximately 1 in 500 000.[1-6] Bleeding manifestations in FVII deficiency are highly variable: some patients remain asymptomatic, while others experience severe, spontaneous, and life-threatening bleeds.[1,2,5]

Surgery is associated with excessive bleeding in patients with FVII deficiency unless replacement therapy is used.[1,3,4,7] Therefore, patients undergoing surgery typically require frequent intravenous bolus doses of replacement therapy to ensure optimal hemostasis.[2,8] However, the need to administer frequent bolus doses requires substantial nursing resources and may lead to missed or delayed doses.[9]

Eptacog alfa (activated) (NiaStase RT®), a recombinant activated FVII (rFVIIa), is used to treat bleeds and manage surgery in patients with bleeding disorders, including FVII deficiency.[10,11] rFVIIa is widely used for surgery in FVII-deficient patients[5]; the literature contains numerous reports of successful perioperative hemostasis in patients treated with manually administered rFVIIa.[3-5,7,8,12-14] However, the recommended dose range of 15-30 μg/kg rFVIIa for perioperative management requires repeat bolus doses every 4-6 hours and until hemostasis is achieved; the dose and frequency of injections should be adapted to each individual.[10,11] The use of an infusion pump represents a convenient method of delivering frequent bolus rFVIIa doses to patients undergoing surgery.[9]

Here we report the use of an automated bolus infusion pump (Figure 1) to deliver timely

and accurate bolus rFVIIa doses for perioperative hemostasis in a patient with congenital FVII deficiency undergoing emergency laparoscopic appendectomy, focusing on hemostatic outcome, safety, and impact on treatment burden both on the patient and healthcare provider.

2 | CASE REPORT

A 15-year-old male (65 kg) with mild congenital FVII deficiency (FVII:C, 0.23‐0.26 U/mL) presented to the emergency room with bilious vomiting and severe pain, tenderness, and rigidity in the lower-right abdomen. The patient's bleeding history consisted of mild, recurrent epistaxis easily controlled by pressure and lasting for <5 minutes. Acute appendicitis was diagnosed, the patient was admitted, and an emergency laparoscopic appendectomy scheduled for the following day.

On admission, the patient received manually administered rFVIIa at 40 μg/kg, followed by 40 μg/kg every 3 hours overnight. The patient and family consented to the infusions. Immediately before surgery, another bolus rFVIIa dose of 40 μg/kg was manually administered. Tranexamic acid was also initiated immediately prior to surgery (10 mg/kg/dose every 8 hours).

Beginning 2 hours after surgery, the B-Braun Perfusor® Space syringe pump was used and programmed to automatically administer bolus rFVIIa doses of 30 μg/kg every 2 hours for 24 hours, then every 4 hours for another 24 hours. Background rFVIIa infusion rate was set to 0.01 mL/h and the total amount infused over the 48-hour period was 51

mg. The background infusion was required to ensure there were no blockages to the tubing or cannula tip between bolus doses. The hemophilia nurse retrieved the rFVIIa from the hospital blood bank and reconstitution performed under validated aseptic conditions at the bedside. Two syringes were used for the 48-hour treatment period (one syringe for each 24-hour period); each syringe was prepared by pooling several 1-mg rFVIIa vials. Pediatric lines were used with the pump.

At 48 hours postsurgery, rFVIIa was discontinued and the patient discharged on oral tranexamic acid (25 mg/kg/dose 3 times/day for 10 days). Hemostasis using rFVIIa delivered by the automated bolus pump was successful; no postoperative bleeding or other complications were observed. No additional rFVIIa doses were required either during the 48-hour postoperative period or after discharge. There were no issues with the functioning and programming of the pump. Laboratory values prior to rFVIIa discontinuation are shown in Table 1. At the time of writing this case report, recovery was uneventful.

3 | DISCUSSION

In this patient with congenital FVII deficiency undergoing emergency laparoscopic appendectomy, the B-Braun Perfusor® Space syringe pump delivered timely, accurate bolus rFVIIa doses. Hemostasis was successful and there were no bleeding or other complications, the pump demonstrated a favorable safety and efficacy profile.

The decision to use the B-Braun Perfusor® Space syringe pump was based on its

established safety record in intensive care, and its capacity to deliver bolus doses that were simple and easy to use.[9] Case studies have reported success in using the pump to deliver rFVIIa for arthroscopy, kidney transplantation, and knee replacement (Figure 1).[9,15,16] The pump has been previously used by UK hemophilia treatment centers for various hemophilia/bleeding disorders, demonstrating convenience, a good safety profile, and stabilization of perioperative hemostasis through accurate and timely bolus doses. The treatment programs previously designed by Pollard *et al*[9] were also implemented in Canada to design three programs for the delivery of bolus rFVIIa doses, including two programs for use in congenital FVII deficiency (15 and 30 μg/kg). In the current study, the pump was easy to use, members of the bleeding disorders group had been trained in its use prior to the patient's admission, and one-to-one training was available to staff nurses if needed.

Other key benefits of using the pump included the time saved for multiple healthcare providers: only two trips to the blood bank were necessary; without the pump, 18 trips would have been required over the 48-hour treatment period. rFVIIa reconstitution every 2-4 hours was not required and rFVIIa transportation by porters to the ward every 2-4 hours was no longer needed. Efficiency was also improved by using the pump: only two syringes were required, rather than 18 manual infusions, and pooling several rFVIIa vials meant product waste was avoided. Finally, the pump reduced treatment burden for the patient as doses were administered automatically overnight, thus providing the reassurance that accurate, timely doses were administered conveniently throughout the whole postoperative recovery period without disturbing the patient.

The pump delivered postoperative bolus rFVIIa doses of 30 μg/kg every 2 hours for 24 hours, then every 4 hours for another 24 hours. The pump did not fail or create errors in dosing or infusion, with no blockages to the tubing or cannula tip. At 24 hours, FVII level was 3.07 U/mL indicating that a lower dose and/or a reduced dosing frequency might have provided adequate hemostatic protection. As stated in the prescribing information, dose and frequency of injections should be adapted to each individual, which gives flexibility to clinicians.[10,11] Although the recommended dose range is 15‐30 μg/kg, some patients may require adjustment of the dosing regimen or interval, based on their FVII levels, which ideally should be monitored throughout the hospital stay.

This report adds to a growing body of evidence supporting the use of a bolus pump to administer rFVIIa in the perioperative setting. rFVIIa has been shown to remain physically and chemically stable for up to 24 hours at 25°C when reconstituted in controlled, validated aseptic conditions and stored in a polypropylene syringe.[17] A sterile hood or sterile conditions are not required for reconstitution, supporting automated bolus infusion pump systems across all licensed indications in the hospital setting.[17] The pump has been previously used to deliver perioperative bolus rFVIIa doses to four patients with hemophilia (Figure 1). This is the first report in which the B-Braun Perfusor® Space syringe pump has been used for the acute surgical management of an adolescent with congenital FVII deficiency.

4 | CONCLUSION

In this study, using the B-Braun Perfusor® Space syringe pump to deliver frequent, intermittent bolus rFVIIa doses provided effective hemostasis, with no safety concerns, in an adolescent with mild congenital FVII deficiency undergoing emergency laparoscopic appendectomy. The pump was easy to use, and additional benefits included savings in nursing time and resource use, with greater peace of mind for the patient, his family, and healthcare providers. Effective hemostasis with accurate dosing, timing, and no missed or delayed doses, may allow better postoperative recovery and even early release from intensive care units or hospitals compared with manual dosing.

CONFLICTS OF INTEREST

H. Perkins received speaker fees from Novo Nordisk Canada Inc. **R. Klaassen** received consultancy fees from Agios Pharmaceuticals Inc., Amgen Inc., Hoffman-Laroche LTD, Shire Pharma Canada ULC, Novo Nordisk Canada Inc., Takeda Canada Inc., Sanofi Genzyme; and speaker fees from Octapharma AG., Takeda Canada Inc. and Pfizer Canada ULC.

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AUTHOR CONTRIBUTIONS

H. Perkins and R. Klaassen treated the patient when he presented to the hospital and during his entire stay and helped plan and edit the manuscript. Both authors approved the final draft of the manuscript before submission.

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FIGURE 1 The B-Braun Perfusor® syringe pump

The B-Braun Perfusor® Space syringe pump is widely used in ICUs and has a well-established reputation for safety and capacity to deliver bolus infusions[9]

The B-Braun Perfusor® Space syringe pump[15] can be used to:

- Customize tailor-made solutions for complex therapies into one system.
- Integrate into data communications networks of advanced hospital operations.
- Alarm in the event of malfunction; it can also be locked to prevent any inadvertent change to the dose.
- Assist in the prevention of accidents related to free-flow of medication by the use of an integrated Free-Flow protection mechanism. The integrated piston break holds the syringe in place to avoid unintended bolus during syringe change or when the pump is not running.

- The B-Braun Perfusor® Space syringe pump has been previously used to deliver perioperative bolus rFVIIa doses to four patients with hemophilia A and inhibitors undergoing two minor and four major surgical procedures[9,16] (unpublished data)* and one patient with hemophilia B undergoing a major surgical procedure (unpublished data).*
- In all four patients, rFVIIa doses were delivered timely and accurately, good hemostasis was maintained, and nursing time reduced.

*Case studies have reported success in using the B-Braun Perfusor® Space syringe to deliver rFVIIa for elbow arthroscopic surgery and kidney transplantation in a 40-year-old patient with hemophilia A and inhibitors, and knee replacement in a 32-year-old patient with hemophilia B.

ICU, intensive care unit.

TABLE 1 Laboratory values

Laboratory parameter	Postoperative day 1 (after 24 hours of rFVIIa Q2h)	Postoperative day 2 (after 24 hours of rFVIIa Q4h)
INR (95% CI)	0.87 (0.86-1.24)	0.83 (0.86-1.24)
PTT, seconds (95% CI)	25.9 (20-34)	27.7 (20-34)
FVII, U/mL (95% CI)	3.07 (0.71-1.47)	—

Abbreviations: CI, confidence interval; FVII, factor VII; INR, international normalized ratio; PTT, partial thromboplastin time; Q2h, every 2 hours; Q4h, every 4 hours.