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3 **Continuous infusion of simoctocog alfa in haemophilia A patients**  
4  
5 **undergoing surgeries**  
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**Abstract**

## Introduction:

There are two major principles for coagulation factor replacement in the clinical management of surgical procedures in patients with haemophilia, repetitive bolus injections every 6-12 hours or administration of coagulation factor concentrates by continuous infusion.

## Aim:

The aim was to investigate the efficacy of simoctocog alfa (human-cl rhFVIII) delivered by continuous infusion for bleeding prophylaxis during surgery in patients with haemophilia A.

## Methods:

We investigated the use of continuous infusion with simoctocog alfa in haemophilia A patients undergoing major surgical procedures at Oslo University Hospital from Sept 2015 to March 2018. The objectives were haemostatic outcome, in vivo recovery, stability over time at room temperature (three days), and inhibitor development.

## Results:

Simoctocog alfa demonstrated treatment success in terms of haemostatic efficacy in 100% of major surgeries used as CI: 87% (n=21) excellent; 13% (n=3) good. No erythrocyte transfusions were required in any patient, no adverse events occurred and no inhibitors developed. The product was stable

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3 for three days at room temperature without loss of activity. Mean in vivo  
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5 recovery was 1.8 (0.3) (IU/mL/IU/kg).  
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8 Conclusion:  
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10 Continuous infusion with simoctocog alfa was found to achieve good/excellent  
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12 haemostatic efficacy in all procedures. No adverse events occurred and no  
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14 inhibitors developed.  
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For Peer Review

## Introduction

Two major principles for coagulation factor replacement have been adopted in the clinical management of surgical procedures in patients with bleeding disorders such as haemophilia, either repetitive bolus injections (BI) every 6-12 hours or continuous infusion (CI) using a pump delivery system.

CI was first introduced in the 1950s by Brinkhous at the Haemophilia Centre at Chapel Hill [1]. It has been used by some haemophilia treaters for decades. It is favoured by many as it provides a safe and constant level of the deficient clotting factor by balancing input with clearance thereby reducing or eliminating the risk of early or late bleeding and dangerous peaks that may lead to a thrombotic event. CI may also be cost effective as it avoids the troughs and peaks associated with BI [2].

In contrast BI need to be administered every 6-12 hours and there is a certain amount of product wastage as in order to provide adequate haemostasis the trough level needs to be above a certain level. This leads to increased costs compared to CI [3].

Indications for CI are maintenance of an efficient haemostatic coagulation factor level for a prolonged period (> 3 days) in association with major bleeds and major and minor surgical procedures. However, there are some concerns with the use of CI of coagulation factor concentrates. Bacterial growth in the infusion bag with the risk of infection and/or degradation of the coagulation factor concentrate during storage at room temperature are of particular importance. Phlebitis at the infusion site has regularly been reported using continuous infusion, but this can be easily avoided by adding small amounts

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3 of heparin to the infusion bag (5 U/ml). Previously a quite frequently reported  
4 complication was related to loss of battery power or other failures of the  
5 delivery pump system however, this is very seldom reported nowadays due to  
6 new generation of infusion pumps. Finally, suspicion has been raised that CI  
7 may be associated with development of inhibitors, especially in non-severe  
8 haemophilia (although medical evidence in standard terms is lacking).  
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16 In a study comparing bolus injections (18 procedures) with continuous  
17 infusion (25 procedures) in 43 major surgical procedures performed in 40  
18 severe haemophilia A patients Batorova and Martinowitz found improved  
19 safety of CI over BI. Higher trough levels were found in the CI group ( $0.44 \pm$   
20  $0.06$  vs.  $0.31 \pm 0.09$  IU/mL,  $p < 0.01$ ) with a lower incidence of dangerous  
21 drops below 0.3 IU/mL (8% vs. 44% of patients, respectively;  $p < 0.01$ ) and a  
22 lower requirement for blood transfusions (12% vs. 39%,  $p < 0.01$ ). Three of 18  
23 patients in the BI group (17%) developed major bleeding complications  
24 compared to none in the CI group. Factor VIII dosage was lower by 36% in  
25 the CI group ( $467 \pm 104$  vs.  $733 \pm 126$  IU/kg;  $p < 0.01$ ) [4].  
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39 In a cross-sectional study of the current practices in Europe regarding  
40 continuous infusion and the inhibitor incidence following this mode of  
41 treatment, Batorova et al studied 22 comprehensive care centres, where CI  
42 techniques, treatment protocols, efficacy, safety and complications including  
43 inhibitor development was covered [5]. Thirteen centres used CI in 1079  
44 surgical procedures or for major bleeds in 742 patients. Nine centres which  
45 did not use CI reported the following reasons for not adopting this mode of  
46 administration as 1 fear of inhibitor, 2, absence of cost benefit for CI, CI more  
47 complex in comparison to BI. Batorova et al found CI to be very effective with  
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3 a low incidence of complications: median incidence of postoperative bleeding  
4 was 1.8%, six centres reported phlebitis in 2-11% of CI treatments. Only nine  
5 (1.2%) of 742 patients developed inhibitors. The incidence of inhibitors was  
6 higher in children 3/111 (2.7%) than in adults 6/631 (0.95%). Patients with  
7 moderate/mild disease had a higher inhibitor incidence 6/83 -7.2% whereas  
8 patients with severe haemophilia had an incidence of 3/659- 0.45%. The three  
9 patients with severe haemophilia had a major gene defect. In five of the six  
10 patients with mild haemophilia the high risk missense mutation Arg593 Cys  
11 was present. Two of the three severe haemophilia and all mild haemophilia  
12 patients had a low number of previous exposure days to FVIII (< 50 days)  
13 prior to intensive treatment with CI. No local or systemic infection and/or  
14 subcutaneous infusion were reported.  
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29 Simoctocog alfa is a 4<sup>th</sup> generation recombinant FVIII produced in a human  
30 cell line without chemical modification or fusion with any other protein, and  
31 simoctocog alfa is expressing human-specific post-translational modifications  
32 with the aim of reducing immunogenicity [<sup>6</sup>,<sup>7</sup>].  
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39 Clinical studies show that simoctocog alfa is highly effective in the treatment  
40 and prevention of bleeding episodes in previously treated adults and children,  
41 including those undergoing surgery [<sup>8</sup>,<sup>9</sup>,<sup>10</sup>].  
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46 A recent analysis with pooled data from seven clinical studies examined the  
47 safety and efficacy of simoctocog alfa in surgical prophylaxis. The analysis  
48 comprised data from 36 patients (both adults and children) with severe  
49 haemophilia A, who underwent 60 surgical procedures (28 major and 32  
50 minor) and were administered simoctocog alfa as BI for bleeding prophylaxis.  
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3 Efficacy was evaluated in 52 procedures and was rated as excellent or good  
4 in all but one surgery. There was no serious treatment-related adverse events  
5 and none of the patients developed inhibitors to FVIII [11].  
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10 Our aim was to investigate the use of simoctocog alfa delivered by CI for  
11 major surgery in haemophilia A patients.  
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### 18 **Materials and Methods**

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20 We investigated the use of CI of simoctocog alfa in haemophilia A patients  
21 undergoing major surgical procedures at Oslo University Hospital from Sept  
22 2015 to March 2018. The objectives were haemostatic outcome, in vivo  
23 recovery, stability over time at room temperature (3 days) and inhibitor  
24 development. Intraoperative haemostatic outcome was classified in terms of  
25 excellent (intraoperative blood loss  $\leq$  average expected blood loss for the type  
26 of procedure performed in a patient with normal haemostasis and of the same  
27 sex, age, and stature), good (intraoperative blood loss  $>$  average expected  
28 blood loss but  $\leq$  maximal expected blood loss for the type of procedure in a  
29 patient with normal haemostasis) or none (haemostasis was uncontrolled  
30 necessitating a change in clotting factor replacement regimen) and for  
31 postoperative efficacy was classified as excellent (no postoperative bleeding  
32 or oozing that was not due to complications of surgery), good (no  
33 postoperative bleeding or oozing that was not due to complications of surgery)  
34 or none (extensive uncontrolled postoperative bleeding and oozing. Control of  
35 postoperative bleeding required use of an alternate FVIII concentrate).  
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3 Target levels of FVIII for major surgery were at day of surgery and  
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5 postoperatively days 1-3: 0.7 IU/mL, day 4-6: 0.5 IU/mL and days 7-10: 0.3  
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7 IU/mL. The day before surgery a test dose of 1000 IU was administered to  
8  
9 calculate the in vivo recovery and initial bolus dose. The bolus dose was then  
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11 followed by continuous infusion of simoctocog alfa at a concentration of 200  
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13 IU/mL administered by a CAD mini-pump. Unfractionated heparin was added  
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15 to the concentrate (5 U/mL) to avoid phlebitis. Factor VIII measurements were  
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17 performed postoperatively and daily to adjust the infusion rate. The  
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19 maintenance dose of CI was adjusted according to clearance recalculated  
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21 daily according to actual control of FVIII levels using the formula: Clearance  
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23 (mL/kg/h) = infusion rate (IU/kg/h)/measured factor level (IU/mL) [12]. With  
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25 regard to pharmacokinetic data, both a one-stage clotting assay (OSA) (APTT  
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27 reagent Synthasil in combination with calibration plasma and FVIII deficient  
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29 plasma from Instrument Laboratory (IL; Bedford, MA, USA)) and a  
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31 chromogenic FVIII activity assay (Coatest SP) were assessed on a ACL TOP  
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33 instrument to measure factor levels. Testing for inhibitors to FVIII was  
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35 performed using the Nijmegen-Bethesda assay.  
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42 Concomitant treatment with tranexamic acid 25mg/kg was given four times  
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44 daily. No pharmacological thromboprophylaxis was used.  
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## 49 Results

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51 A total of 24 major surgical procedures were performed in 17 patients.  
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53 Twenty-two of these were orthopaedic surgeries, four ankle arthrodeses, six  
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55 knee arthroplasties and three hip arthroplasties. Patients' ages ranged from  
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3 28 to 71 years. There were 11 patients with severe haemophilia A, five with  
4 moderate haemophilia A and one patient with mild haemophilia A. Mean in  
5 vivo recovery was 1.8 (0.3) (IU/mL/IU/kg). The initial loading dose (bolus) was  
6 a mean of 36.3 IU/kg (min 11 – max 50.8 IU/kg). Continuous infusion dose on  
7 days 1-3 was a mean of 54.9 IU/kg/d (min 25- max 91 IU/kg), and on days 4-6  
8 was a mean of 35.7 IU/kg/d (min 9 – max 54 IU/kg). The mean coagulation  
9 factor consumption for major surgery was 29,750 IU during the first nine days.  
10 The amounts of concentrate administered and the type of surgery are shown  
11 in Table 1.  
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26 Simoctocog alfa demonstrated treatment success in terms of haemostatic  
27 efficacy in 100% of major surgeries used as CI: 87% (n=20) excellent; 13%  
28 (n=3) good. No erythrocyte transfusion was required in any patient. Figure 1  
29 shows the effect of continuous infusion in a patient with severe haemophilia A  
30 undergoing ankle arthrodesis. As shown FVIII levels were well maintained  
31 over the course of eight days post-surgery.  
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## 42 **Safety**

43 No adverse events related to simoctocog alfa were observed, and no patients  
44 developed an inhibitor to the factor concentrate.  
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## 50 **Stability**

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3 Simoctocog alfa was dissolved to a concentration of 200 IU/mL and was  
4 found to be stable for 3 days both when measured by a one-stage clotting  
5 assay based method and chromogenic assay (Table 2).  
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## 16 **Discussion**

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18 Our study show that the effects of CI with simoctocog alfa in 17 patients  
19 undergoing 24 surgeries procedures were excellent or good in all cases. The  
20 results reflect the results obtained in the GENA studies in which the efficacy of  
21 BI was rated as excellent or good in all but one procedure [11]. In our study  
22 no patients developed an inhibitor to simoctocog alfa. The use of CI has  
23 raised concerns about the association of CI with an increased risk of  
24 development of inhibitors to FVIII. There have been conflicting results in the  
25 literature. A number of inhibitor cases have been described following CI with  
26 the majority being patients with moderate or mild haemophilia who were  
27 treated intensively for surgery and major bleeds [<sup>13</sup>, <sup>14</sup>, <sup>15</sup>]. Patients with mild or  
28 moderate haemophilia given CI often have low exposure rates to coagulation  
29 factor concentrates. In our study the majority of patients had severe  
30 haemophilia A, and they had a higher number of exposure days than those  
31 with mild or moderate disease. This is borne out in a large retrospective  
32 survey on inhibitor development in European haemophilia centres using CI. A  
33 total of 742 haemophilia A patients who underwent 1079 CI treatments were  
34 included [5]. Nine incidences of inhibitors developed mainly in patients with  
35 mild or moderate disease (incidence of 7.2% (6/83) compared to only 0.45%  
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3 (3/659) in patients with severe haemophilia. Three patients with severe  
4 haemophilia had a major gene defect and in five of six patients with mild  
5 haemophilia the high risk F8 gene missense mutation Arg 593-Cys was  
6 present. None of our patients had this mutation. The study by Batorova et al  
7 indicated that CI does not increase the inhibitor risk in PTPs with severe  
8 haemophilia; an observation borne out by our study. This is in contrast to  
9 previous small case series suggesting that CI may promote inhibitor  
10 development [13,14,15].  
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21 However, CI should be used with caution in patients <20 exposure days as  
22 studies have shown that the risk of inhibitor development is increased in  
23 patients with < 20 exposure days [16] and in mild/moderate haemophilia A  
24 patients with high risk mutations.  
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31 CI may reduce treatment cost compared to bolus injections, since  
32 unnecessary peaks of the coagulation factor level are avoided. Several  
33 studies have shown that coagulation factor concentrate consumption may be  
34 reduced by CI compared to repetitive BI. The area under the curve (AUC) is  
35 two-thirds of the use of BI [25]. We found that the mean coagulation factor  
36 consumption in major surgery was 29,750 IU during the first nine days. CI with  
37 simoctocog alfa in our study showed an estimated 46% lower consumption of  
38 factor concentrate compared to the GENA surgical studies where repetitive  
39 BI were used. (320 IU/kg versus 591 IU/kg) [11] which is also in accordance  
40 to what was reported by Batorova et al (36%) [4]. In our study we adjusted the  
41 infusion rate to reach a FVIII level of 70% during days 0-3, 50% for days 4-6,  
42 and 30% for days 7 and beyond. We believe that this approach is necessary  
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3 to reduce the need for erythrocyte transfusions and avoid the use of  
4 pharmacological thromboprophylaxis following surgical procedures.  
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8 There was no evidence of risk of infection from our study. To avoid any risk of  
9 infection during CI, preparation and filling of the container must be performed  
10 under sterile conditions. Bacterial growth in cultures from minipump reservoirs  
11 and infusion sets appear not to be a problem within 72 hours. Extensive  
12 studies have shown that FVIII and FIX concentrates are poor growth mediums  
13 for the majority of bacterial strains [4,17,18].  
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21 Most concentrates are stable after reconstitution at room temperature. We  
22 found that simoctocog alfa was stable for three days at room temperature.  
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24 Stability studies performed in the early 1990s showed that most concentrates  
25 were stable after reconstitution at room temperature for 3 days or more [17].  
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27 The newer recombinant products have shown extended stability over 24-48  
28 hours [18, 19, 20, 21, 22, 23]. However, for safety reasons it is advisable to test the  
29 stability of each concentrate intended for use with the particular infusion set to  
30 be used.  
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40 None of our surgeries was associated with adverse events. Previously  
41 phlebitis at the infusion site was often reported, most likely due to high  
42 osmolality of undiluted coagulation factor concentrate. In a meta-analysis of  
43 CI publications from 1992 to 2004 Hermans et al observed this complication in  
44 10.5% [24]. Currently phlebitis at the infusion site is very seldom seen after  
45 addition of small amounts of heparin (5 U/mL) in the infusion bag or parallel  
46 infusion of saline [25, 26, 27]. This practice is well documented in a study in  
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3 Europe [5] and in other series [<sup>28, 29</sup>]. We added small amounts of heparin (5  
4 U/mL) to the infusion bag, and no sign of phlebitis was observed.  
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8 Pump failure leading to an unexpected and dangerous drop in coagulation  
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10 factor level are very seldom reported due to increased quality of pumps used  
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12 in current practice [12]. There were no incidences of pump failure in our study.  
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### 16 17 **Conclusion**

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19 Continuous infusion with simoctocog alfa was found to achieve excellent  
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21 haemostatic efficacy in the majority of surgeries. No adverse events occurred  
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23 and no inhibitors developed.  
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39 contributed in designing the research study and in the writing the paper.  
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### 44 45 **Declaration of interests**

46  
47 The department has received grant/research support from Octapharma.  
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Table 1: Major surgical procedures and outcome using continuous infusion of simoctocog alfa in patients with haemophilia A at Oslo University Hospital, Norway.

Procedure nr	Severity	Age (years)	Procedure	Bolus (IU/kg)	CI day 1–3 (IU/kg/d)	CI day 4–6 (IU/kg/d)	Haemostatic outcome	Transfusions	Adverse events
1	Severe	61	Osteosynthesis removal	38.0	48.6	45.0	Excellent	No	None
2	Moderate	63	Ankle arthrodesis	23.6	60.0	44.0	Excellent	No	None
3	Severe	50	Wrist arthrodesis	29.0	57.5	33.0	Excellent	No	None
4	Moderate	65	Ankle arthrodesis	27.5	51.0	43.0	Excellent	No	None
5	Moderate	51	Knee arthroplasty	50.8	55.4	22.0	Excellent	No	None
6	Moderate	71	Ankle arthrodesis	33.0	37.0	21.0	Excellent	No	None
7	Moderate	52	Knee arthroplasty	50.8	34.0	16.0	Good	No	None
8	Severe	28	Fasciotomy due to trauma	42.9	91.0	45.0	Excellent	No	None
9	Mild	64	Ankle arthrodesis	11.0	25.0	9.0	Good	No	None
10	Severe	65	Spinal disc herniation	37.5	56.0	45.0	Excellent	No	None
11	Severe	52	Knee arthroplasty	36.5	51.0	25.0	Excellent	No	None
12	Severe	39	Hip arthroplasty	35.3	56.0	42.0	Excellent	No	None
13	Severe	62	Osteosynthesis removal	37.0	51.0	45.0	Excellent	No	None



14	Severe	62	Osteosynthesis removal	30.0	51.0	39.0	Excellent	No	None
15	Severe	56	Knee arthroplasty	37.6	75.0	37.5	Excellent	No	None
16	Severe	28	Knee arthroplasty	35.0	64.0	47.0	Excellent	No	None
17	Moderate	57	Hip arthroplasty	32.6	64.0	35.0	Excellent	No	None
18	Severe	63	Hip arthroplasty	48.0	60.0	45.0	Good	No	None
19	Moderate	58	Cystoscopy with biopsies	32.6	57.0	47.0	Excellent	No	None
20	Severe	61	Removal of knee arthroplasty	42.8	59.0	34.0	Excellent	No	None
21	Severe	34	Arthrolysis of the elbow	43.4	84.0	54.0	Excellent	No	None
22	Severe	62	Knee arthroplasty	43.9	60.0	40.0	Excellent	No	None
23	Severe	62	Prostate biopsy	43.9	28.0	14.0	Excellent	No	None
24	Severe	53	Wrist arthrodesis	30	36.3	37.7	Excellent	No	None

Figure 1. Continuous infusion of simoctocog alfa in a patient with severe haemophilia A undergoing ankle arthrodesis.

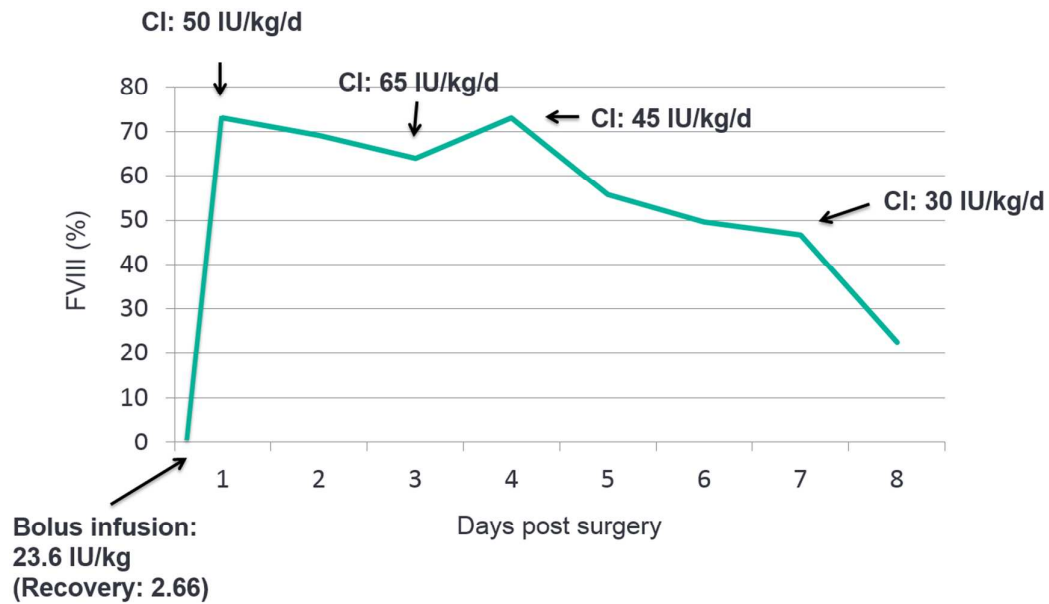


Table 2. Stability of simoctocog alfa over three days measured with a one-stage assay and chromogenic assay.

	One- stage assay	Chromogenic assay
Day 1	328% (3.8)	373% (12)
Day 2	318% (4.12)	366% ( 15.3)
Day 3	343% (2.3)	344% (7.8)

Simoctocog alfa was dissolved to a concentration of 200 IU/mL stored over a 3 days period at room temperature. FVIII activity measured with one-stage assay and chromogenic assay. (Data shown in mean (SD) ).