Low-dose continuous infusion of factor VIII in patients with haemophilia A

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Background. Patients with haemophilia A (HA) or B (HB) can be given prophylactic or on-demand treatment administered by continuous infusion or bolus injections of factor VIII (FVIII) or IX (FIX). In this study we evaluated the efficacy and safety of low-dose continuous infusion of FVIII or FIX.

Material and methods. We studied all eligible patients with HA or HB treated with continuous infusion of factor concentrates over an 18-year period in a single Slovenian Haemophilia Comprehensive Care Centre. Treatment started with a bolus injection of FVIII or FIX, followed by continuous infusion at the initial rate of 2 IU/kg/h of FVIII in HA patients and 4.5 IU/kg/h of FIX in HB patients. The infusion rate was subsequently adjusted according to the indication for therapy.

Results. A total of 66 continuous infusions (40 in major surgery, 10 in minor surgery and 16 with bleeding episode) in 46 HA patients and 16 (15 in severe and 1 in mild HA) in eight HB patients were included in the study. During the first week of treatment, the median continuous infusion rates in HA patients undergoing major surgery, minor surgery and a bleeding event were 2.18 (0.75-3.68), 1.48 (1.0-2.54) and 2.24 (1.33-3.93) IU/kg/h, respectively. The median FVIII activities were 0.69 (0.37-1.19), 0.47 (0.39-0.84) and 0.52 (0.36-1.06) IU/mL. After the first week of treatment, even lower doses of FVIII were needed. Red blood cell transfusions had to be administered to three patients (2 with severe and 1 with moderate HA) during the continuous infusion and inhibitors developed in five patients. In HB patients, the median continuous infusion rate was 1.85 (1.07-2.94) IU/kg/h and the median FIX activity was 0.62 (0.30-1.04) IU/mL. Red blood cell transfusions were not required, and thrombophlebitis and inhibitors did not appear.

Discussion. Overall, low-dose continuous infusion was shown to be an effective and safe way of treating patients with HA. The protocol used also proved efficient and safe in all HB patients.

Keywords: low-dose continuous infusion, factor VIII, haemophilia A, inhibitors, surgery.
The hospital records of eligible patients were reviewed and the following data were collected: the age and weight of the patient, indication for the CI, the number of days of exposure (ED) to factor concentrate before the CI, the type of concentrate given, personal and family history of inhibitor development, amount of FVIII/FIX injected in a bolus in the 24 hours preceding the CI, the FVIII:C/FIX:C before the CI, the CI rate, the FVIII:C/FIX:C during and after the first week of treatment, and the need for additional boluses of factor or red blood cell (RBC) transfusions.

Not all the patients gave written consent to the use of their data for the purpose of this study because they could not be reached. The National Ethics Committee was informed of the fact and approved the study.

Treatment protocol

Patients received CI of a reconstituted clotting factor concentrate, without additional dilution, by a peripheral vein. Heparin was added to the concentrate at a dose of 1 IU/mL and 4 IU/mL, before and after the year 1997, respectively. The Alaris® Products’ IVAC® 50/60 mL syringe pump was used (San Diego, USA). The intervals between pump reservoir exchanges were up to 96 hours. No mechanical failure was noted during treatment. In the event of thrombophlebitis, the infusion site was changed immediately.

If the replacement treatment was indicated for surgery, it was started 30 minutes before the operation with a bolus injection of FVIII/FIX in order to reach a plasma FVIII:C/FIX:C of at least 0.80 IU/mL for major surgery and 0.50 IU/mL for minor surgery. The amount of factor given in a bolus depended on the severity of the haemophilia, the indication for treatment and the time since the last administration of bolus. Thirty minutes after the first bolus injection, the FVIII:C/FIX:C was measured. CI of FVIII at a rate of 2 IU/kg/h or FIX at a rate of 4.5 IU/kg/h was initiated within 2 hours after beginning surgery. The target FVIII:C/FIX:C for major surgery was at least 0.50 IU/mL during the first post-operative week and at least 0.30 IU/mL during the second. For minor surgery, the target FVIII:C/FIX:C was at least 0.30 IU/mL as long as the replacement therapy was required. For intracranial and gastrointestinal bleeding, the target FVIII:C/FIX:C was 0.80 to 1.00 IU/mL during the first 7 to 10 days, and was then slowly reduced. For other patients the target level of FVIII:C/FIX:C was set according to the type of bleeding.

On the day of surgery, FVIII:C/IX:C was determined on two or three occasions. Later, during the first week of CI, the FVIII:C/IX:C was checked on a daily basis, and afterwards every other day if the patient still needed the infusion.

After starting with a fixed CI rate of 2 IU/kg/h, the treatment was adjusted daily according to regularly measured FVIII:C. Once the FVIII:C was stable with an unchanged CI rate for a number of consecutive days, the CI rate was adjusted every other day according to the measured FVIII:C.

Inhibitor development was evaluated on a weekly basis and at an inadequate increase of FVIII:C/FIX:C or in the event of bleeding.

In patients considered to be at risk of thrombosis only mechanical prophylactic antithrombotic measures were applied. Antifibrinolytics were used in addition to CI of FVIII/FIX in all patients undergoing orthopaedic surgery and according to the individual decision of the attending haematologist in other patients.

Statistical analysis

Comparisons between the groups were made with the Mann-Whitney and Kruskall-Wallis tests. Differences with p<0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics, ver. 13.0 (New York, USA).

Results

During the study period, 95 CI of FVIII/IX were given to 59 patients. A total of 78 CI were administered in 51 HA patients and 17 CI in 8 HB patients. Twelve CI were excluded from the analysis; in 8 cases the CI lasted fewer than 4 days, in 2 cases patients were already positive for inhibitors before the start of the infusion and two patients were treated with an unchanged CI rate without regular measurements of the FVIII:C. Another HB patient was treated with CI for fewer than 4 days (3 days). Sixty-six CI in 46 HA patients and 16 CI in 8 HB patients were eligible for efficacy and protocol safety evaluation.

HA patients were divided into 3 groups according to the indication for treatment: major surgery (orthopaedic [21 cases], major abdominal [10 cases], intracranial [1 case], thoracic [2 cases], tonsillectomy [5 cases] and total dental extraction using sutures [1 case]); minor surgery (minor orthopaedic procedures [3 cases], minor dental procedure [1 case], all operations with a low risk of losing a large volume of blood such as removal of an infected haematoma, pilonidal sinus or melanoma [6 cases]); and other bleeding events (patients with post-traumatic or spontaneous bleeding, including bleeding from a gastric ulcer and a Mallory-Weiss tear [16 cases]).

The median age of HA patients was 26.9 years (range: 10 days to 68 years) and that of HB patients was 18.0 years (range: 11 to 67 years). The median weight of HA and HB patients was 72 kg (range: 3.4-110 kg) and 65 kg (range: 44-98 kg), respectively. The median
duration of the CI was 10 days (range: 4-93 days) and 9.5 days (range: 4-28 days) after surgery or the bleeding event in HA and HB patients, respectively.

When comparing the HA patients grouped according to the indication for replacement therapy, there were no statistically significant differences in the patients’ weights and ages, yet patients undergoing major surgery had statistically significantly longer treatment with CI than patients with minor surgery or trauma. Other results comparing patients according to the indication for treatment are shown in Tables I and II. Further analyses were conducted according to the severity of HA. There were no difference between the groups with regards to weights and ages. The only significant difference was seen in the duration of the treatment, such that patients with moderate HA were treated for the shortest period of time. The results of other comparisons of patients with different severity of HA are shown in Table III. The Kruskal-Wallis test was used for comparisons between the groups (Tables II and III).

The daily measured median FVIII:C during and after the first week of CI is shown in Figure 1.

One patient with severe HA and two with severe HB were HIV positive. Their pre-CI CD4 counts were 357, 493 and 276 cells/mm³, respectively.

Among patients with HA, 10 CI were carried out using recombinant FVIII concentrate (Recombinate [Baxter, Deerfield, IL, USA], Advate [Baxter], and Kogenate [Bayer, Leverkusen, Germany]) and 56 with plasma-derived concentrate (Octavi [Octapharma, Lachen, Switzerland], Octanate [Octapharma], and Hemofil M [Baxter]). In HB patients, only plasma-derived FIX concentrates Octanyne and Octanine F (both Octapharma products) were used.

The majority of patients were treated concomitantly with an antifibrinolytic (tranexamic acid).

Additional boluses of FVIII during CI were needed in nine (15%) cases of CI in patients who were negative for inhibitors, and in all five patients in whom inhibitors were detected during (2 patients) or in the first month of CI.

### Table I - Characteristics of 66 CI in 46 HA patients (34 severe, 4 moderate and 8 mild) patients divided according to the indication for the infusion.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Major surgery (n=40)</th>
<th>Minor surgery (n=10)</th>
<th>Other (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HA (type)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N. of CI</td>
<td>32*</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>&gt;50 ED before CI</td>
<td>31</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>&lt;28 ED before CI</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N. of CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50 ED before CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;28 ED before CI</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*10 patients had total knee replacement.
CI: continuous infusion; HA: haemophilia A; Other: trauma and spontaneous bleeding; ED: exposure days before CI.

### Table II - Results of 66 CI in 46 HA patients (34 severe, 4 moderate and 8 mild) patients divided according to the indication for the infusion.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Major surgery (n = 40)</th>
<th>Minor surgery (n = 10)</th>
<th>Other (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median BI before CI (IU/kg)</td>
<td>52.91 (22.0-109.8)</td>
<td>47.62 (22.7-73.7)</td>
<td>44.37 (17.6-100.9)*</td>
</tr>
<tr>
<td>Median FVIII:C before start of CI (IU/mL)</td>
<td>0.84 (0.46-1.37)</td>
<td>0.65 (0.49-0.95)</td>
<td>0.77 (0.39-1.01)</td>
</tr>
<tr>
<td>Median CI rate during 1st week (IU/kg/h)</td>
<td>2.18 (0.75-3.68)*</td>
<td>1.48 (1.0-2.5)</td>
<td>2.24 (1.33-3.9)*</td>
</tr>
<tr>
<td>Median CI rate after 1st week (IU/kg/h)</td>
<td>1.64 (0.45-3.40)</td>
<td>1.49 (0.76-1.60)</td>
<td>1.75 (1.2-4.24)*</td>
</tr>
<tr>
<td>Median FVIII:C during 1st week (IU/mL)</td>
<td>0.69 (0.37-1.19)</td>
<td>0.47 (0.39-0.84)</td>
<td>0.52 (0.36-1.06)</td>
</tr>
<tr>
<td>Median FVIII:C after 1st week (IU/mL)</td>
<td>0.56 (0.21-1.11)</td>
<td>0.38 (0.32-0.57)</td>
<td>0.47 (0.24-1.09)</td>
</tr>
</tbody>
</table>

Numbers in parentheses are ranges.
CI: continuous infusion; HA: haemophilia A; Other: trauma and spontaneous bleeding; BI: bolus injection; FVIII:C: activity of factor VIII.

*10 patients received BI the day before surgery, making lower pre-operative doses sufficient.
* Neonate with massive intracranial bleeding.
* The difference in the median CI rate and FVIII:C during the 1st week of treatment was statistically significant (p=0.047 and p=0.024 respectively).
* Patient was treated for total hip replacement.
*41 patients (26 major surgery, 4 minor surgery and 11 other events) were treated with CI for more than 1 week.

There was no significant difference in other observed parameters between the three groups. Comparisons between groups were made with the Kruskal-Wallis test.
Low-dose continuous infusion of factor VIII

Figure 1 - Median FVIII:C and 95% confidence interval during first 2 weeks of CI.

After the first week of treatment, FVIII:C was not measured every day and since some patients had higher FVIII:C than others, some oscillation in median FVIII:C can be seen. * Only one patient with minor surgery had a CI for more than 9 days.

CI: continuous infusion; FVIII:C: activity of factor VIII.

Table III - Results of 66 CI in 46 HA patients divided according to the severity of HA.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Severe HA (n=52)</th>
<th>Moderate HA (n=6)</th>
<th>Mild HA (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median BI before CI (IU/kg)</td>
<td>50.0 (17.5-109.8)</td>
<td>46.5 (27.6-52.5)</td>
<td>59.6 (30.8-68.5)</td>
</tr>
<tr>
<td>Median FVIII:C before start of CI (IU/mL)</td>
<td>0.73 (0.39-1.37)</td>
<td>0.74 (0.56-0.98)</td>
<td>0.68 (0.46-0.92)</td>
</tr>
<tr>
<td>Median CI rate during 1st week (IU/kg/h)*</td>
<td>2.09 (0.88-3.93)</td>
<td>1.25 (0.75-1.6)</td>
<td>2.26 (1.21-3.2)</td>
</tr>
<tr>
<td>Median CI rate after 1st week (IU/kg/h)</td>
<td>1.64 (0.45-4.241)</td>
<td>NA</td>
<td>2.03 (1.39-2.69)</td>
</tr>
<tr>
<td>Median FVIII:C during 1st week (IU/mL)</td>
<td>0.62 (0.36-1.19)</td>
<td>0.48 (0.38-0.59)</td>
<td>0.55 (0.42-1.07)</td>
</tr>
<tr>
<td>Median FVIII:C after 1st week (IU/mL)</td>
<td>0.55 (0.21-1.08)</td>
<td>NA</td>
<td>0.68 (0.25-1.11)</td>
</tr>
</tbody>
</table>

Numbers in parentheses are ranges. CI: continuous infusion; HA: haemophilia A; BI: bolus injection; FVIII:C: activity of factor VIII; NA: not applicable.

Table IV - Characteristics of 5 patients who developed inhibitors during or soon after CI of FVIII.

<table>
<thead>
<tr>
<th>HA patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of the patient</td>
</tr>
<tr>
<td>N. of patients with mild/severe HA</td>
</tr>
<tr>
<td>N. of patients with major surgery/minor surgery/other event*</td>
</tr>
<tr>
<td>N. of patients who received plasma-derived/recombinant FVIII</td>
</tr>
<tr>
<td>N. of patients with more than 50 ED</td>
</tr>
<tr>
<td>N. of patients with 0 ED</td>
</tr>
<tr>
<td>Median CI rate during first week per single patient (IU/kg/h)</td>
</tr>
<tr>
<td>Median CI rate after first week per single patient (IU/kg/h)</td>
</tr>
<tr>
<td>Median FVIII:C during first week per single patient (IU/mL)</td>
</tr>
<tr>
<td>Median FVIII:C after first week per single patient (IU/mL)</td>
</tr>
</tbody>
</table>

Numbers in parentheses are ranges. CI: continuous infusion; FVIII: factor VIII; HA: haemophilia A; ED: exposure days before continuous infusion; FVIII:C: activity of factor VIII. * Two cases of intracranial bleeding.

Discussion

There is no doubt that CI provides safe, steady-state haemostatic factor levels and is able to reduce the use of...
factor concentrates due to the avoidance of unnecessary peak levels when administered at either a fixed rate and/or in a pharmacokinetically adjusted manner. An often overlooked aspect of CI is the possibility of home treatment, which is safe, efficacious and convenient for the patients and others involved in the treatment.

In 1992, Martinowitz suggested basing the FVIII CI rate on the clearance of 4.5 mL/kg/h for children and 3 mL/kg/h for adults, making the mean CI rate around 2 IU/kg/h, sufficient to maintain the FVIII:C around 0.50 IU/mL. The same protocol, with the addition of tranexamic acid, was introduced in Slovenia in 1994.

Given the lack of common guidelines concerning the use of FVIII CI in patients with HA, different authors have used various infusion rates and different FVIII target levels. A recent study evaluating current practices in Europe has shown that most centres used an "adjusted dose" CI aimed at a median target FVIII:C of 0.8 IU/mL. In our study, the CI rate of 2 IU/kg/h and the target FVIII:C of at least 0.50 IU/mL during the first week and at least 0.30 IU/mL during the second week following major surgery were considerably lower than in other studies. Despite the slower FVIII infusion rate, a stable FVIII:C, even above the target level, with no drops in the median FVIII:C (Figure 1) was achieved in all subgroups. The highest average CI rate was 3.9 IU/kg/h during the first week of treatment and 4.2 IU/kg/h the second week in a preterm neonate who had intracranial bleeding and was confirmed to be positive for inhibitors 2 days after finishing the CI. Before starting the CI the boy had not been exposure to factor concentrates. Additional boluses were needed for non-inhibitor patients in 15% of the CI, mostly due to failure to achieve the target level, while RBC transfusions were given during CI in only 5% of cases.

The same infusion rate was used in a smaller study of 25 CI by Hay and co-workers. The Authors commented that additional boluses were often needed, but in their study the target FVIII:C was considerably higher, as a FVIII:C of 1.0 IU/mL was required during the first 2 days and 0.80 IU/mL later. No bleeding events were observed.

Tagariello et al. reported that no additional boluses were given and no major bleeding events occurred during 14 CI of FVIII at a rate of 3 IU/kg/h. At the given infusion rate, the FVIII:C remained in the range of 0.60 to 0.80 IU/mL.

Stieltjes et al. have published a study on 20 CI in 16 patients undergoing surgery. They used FVIII at a rate of 3.6 IU/kg/h. Additional bolus injections were given in 55% of the episodes, most commonly due to a drop of the FVIII:C below the target level. RBC transfusion was given in 40% of the episodes, but only in three cases due to significant bleeding.

Even higher infusion rates of FVIII (4 IU/kg/h) have been used in some other studies. In Mulcahy's study of 18 CI, there were no documented cases of significant bleeding events, although four (22%) patients (one positive for inhibitors) received RBC transfusion. Dingli et al. investigated 45 CI in 28 patients undergoing surgery (10 minor, 35 major). Additional bolus injections were given in 36% of the cases in order to maintain the target level of 1.0 IU/mL, despite the considerably fast rate of the CI. RBC transfusion was needed in five out of 25 orthopaedic procedures.

Although there is no doubt that CI is an effective and cost-efficient method for replacement therapy in patients with haemophilia, some concerns have been raised regarding the association of CI with the development of inhibitors.

In the most recent, largest published study conducted by Batorova et al., information was collected on current practices in Europe regarding CI and the true inhibitor incidence. Thirteen centres reported a total of 1,079 CI treatments in 742 patients, given perioperatively or for major bleeds. Only nine (1.2%) patients developed inhibitors (0.45% of 659 patients with severe haemophilia and 7.2% of 83 with mild haemophilia). Additional analysis of the inhibitor patients revealed several confounding factors in those with mild HA (low number of prior days of exposure to FVIII [<50], high steady-state factor activity during the CI [1.0-1.9 IU/mL], and high-risk genotype [missense mutation Arg593Cys]). In this large group, CI treatment appeared to be a safe and effective treatment that does not increase the risk of inhibitor development in patients with severe haemophilia. Thus, the previous small case series suggesting that CI may increase the inhibitor rate were not confirmed in this large study. The authors concluded that inhibitor risk in mild haemophilia could not be evaluated, since the influence of other, potentially confounding, risk factors could not be excluded.

With increasing age, patients with mild HA suffer from co-morbidities and often require surgical interventions, which expose them to an increased risk of inhibitor development, since intensive exposure to FVIII is a known risk factor for inhibitor development in mild HA. Similarly, in a large, recently published study analysing 1,112 patients with non-severe HA from 14 centres in Europe and Australia, it was found that the inhibitor risk increased with the number of days of exposure and was 6.7% at 50 ED and 13.3% at 100 ED. In some older studies inhibitor appearance ranged between 4 and 6.1%. In our group, high-responding inhibitors developed during or soon after CI in three patients with severe HA (8.8% of patients and 5.8% of CI) and two with mild/moderate HA (16.7% of patients and 14.3% CI). Among
the three patients with severe HA, two with low-risk mutation for inhibitors (small deletion; p.Glu1801Aspfs) were members of the same family with known inhibitors in a deceased relative. One of them was a neonate treated for intracranial haemorrhage, the other was a 49-year-old patient positive for hepatitis C virus and HIV, who developed inhibitors during replacement treatment after surgery of an infected haematoma with more than 1,000 ED of previous on-demand treatment. In the third, a 14-year-old major trauma patient with a low-risk missense mutation (p.Pro550Arg), inhibitors developed during CI after more than 250 ED of previous on-demand therapy. Two of those patients were re-challenged by CI of FVIII after successful immune tolerance induction (on one and two occasions) and inhibitors did not reappear in either of them. All 3 patients with severe haemophilia had a major challenge (head trauma, intracranial bleeding or infected haematoma) to their immune system, which may have increased the risk of inhibitor development and 2 of them had additional risk factors (intensive treatment at first treatment and co-infection).

Two patients with mild HA developed inhibitors: one was a 12-year-old patient with 0 ED and a high-risk missense mutation (p.Arg593Cys) subjected to intensive perioperative replacement therapy while the other was a 68-year-old patient (>50 ED), who developed inhibitors after intensive FVIII exposure due to major surgery. Inhibitors also appeared in his 74-year-old brother, after 9 ED and after intensive bolus injections of FVIII for post-traumatic intracranial bleeding. Both brothers carry a missense mutation (p.Arg2307Gln), which has been described as one of the FVIII point mutations associated with a higher risk of inhibitor formation. The appearance of inhibitors in the two brothers is in accordance with the statement, that unlike in severe haemophilia A, the risk of inhibitors in patients with mild haemophilia receiving intensive treatment persists even at higher ages and with a higher number of ED.

Conclusions
In conclusion, CI is a safe and effective method of treatment and we support the statement that CI should be the treatment of choice for major bleeding and surgery, but only in cases of severe forms of haemophilia. Nevertheless, we must be aware of the potential risk of inhibitor development in patients with mild HA, and the benefits of alternative treatment with desmopressin should be taken in consideration in patients with moderate or mild HA. Based on the known haemostatic effect, FVIII:C levels of 0.50-1.00 IU/mL should serve as an appropriate target range depending on the indication for treatment.

In the present study of patients treated exclusively in a single centre, we have shown that a CI rate of approximately 2 IU/kg/h of FVIII is enough to maintain the FVIII:C above 0.5 IU/mL in the majority of patients. We believe that this low-dose approach, together with the use of tranexamic acid, does not require thromboembolic prophylaxis and is a safe and effective way of preventing peri-operative bleeding, even in major operations and major bleeds.

In order to avoid the appearance of inhibitors in patients with mild or moderate HA, especially in those with risk mutations and a low number of ED, the use of tranexamic acid and DDAVP, whenever possible, combined with low-dose FVIII bolus injections when necessary, seems the most appropriate.

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Authorship contributions
MBD and LK designed the research study. TP analysed the data. TP, MBD and LK wrote the paper.

The Authors declare no conflict of interest.

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