Does orthopaedic surgery reduce bleeding rate in patients with haemophilia A?

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objective

To investigate whether orthopaedic surgery can reduce bleeding frequency in patients with haemophilia A who are receiving standard prophylaxis with turoctocog alfa, a B-domain-truncated recombinant factor VIII (rFVIII) product from Novo Nordisk, as part of the long-term guardian™2 trial.

introduction

- Repeated joint bleeding in patients with haemophilia A can result in progressive arthropathy.[1]
- Bleeding frequency, which may be measured by annualised bleeding rate (ABR), acts as a short-term surrogate marker for joint damage.[1,2]
- The guardian™ clinical trial programme investigated the PK, safety and effectiveness of turoctocog alfa a B-domain-truncated rFVIII product (NovoEight®, Novo Nordisk A/S, Bagsvaerd, Denmark).
- Previous data from guardian™1, 3 and 2 have shown a reduction in ABR over time.[3]
- The guardian™2 extension trial provided an opportunity to investigate whether orthopaedic surgery can further reduce ABR in patients receiving prophylaxis with turoctocog alfa, beyond that seen over time in the trial to date.

methods

- Data from previously treated patients (ages 1–61 years) were collected in the guardian™2 clinical trial, an ongoing extension of the guardian™1 and guardian™3 trials.
  - Data were gathered between October 27, 2009 and the interim cut-off date of March 25, 2015.
- Inclusion criteria: male patients with severe haemophilia A (FVIII ≤1%).
- Participants in the guardian™2 trial received turoctocog alfa prophylactically (20–50 IU/kg every second day or 20–60 IU/kg three times weekly).
- Participants in the guardian™2 trial who received surgery, including orthopaedic surgery, were included in the sub-trial.

DATA ANALYSIS

- Two separate analyses were carried out:
- The data presented in the abstract were for ABR associated with all causes of bleeding (spontaneous and traumatic).
- In order to determine whether any drop in ABR following orthopaedic surgery was due to the intervention or was in line with previously observed falls in ABR,[3] an additional 'paired cases' analysis was carried out as described below.
- For each orthopaedic surgery case, a control was selected among patients without orthopaedic surgery with the same age (± 1 year).
  - If more than one candidate was available, the one with the closest body mass index (BMI) was selected.
  - Each case and control made a pair in the analysis.
  - The study day of surgery for the pair-case was used to split the study period for the pair-control into 'before' and 'after'.
- In order to exclude chance traumatic bleeds from the analysis, the ABR for spontaneous bleeding only (sABR) was measured before (from study start to first surgery) and after (from first surgery to study end, excluding surgery periods) orthopaedic surgery.
- Poisson estimates of mean population sABR were calculated prior to and after the date of surgery for the surgery patient.
- Haemostatic effect during surgery was assessed according to a predefined four point scale: none, moderate, good or excellent, as described previously.[4]

Table 1 ♦ Baseline patient demographics in the guardian™2 trial

	Total in trial	*Orthopaedic surgery cases*	*Control population*
Number of patients, n	213	9 (11 major surgeries*)	9
Age, years Mean (SD)	23.6 (14.6)	38.8 (11.9)	38.8 (11.6)
Historical dosing regimen†, n (%)			
Prophylaxis	81 (40.5)	4 (57.14)	2 (22.22)
Non-prophylaxis	76 (38.0)	1 (14.29)	5 (55.56)
Both	43 (21.5)	2 (28.57)	2 (22.22)
Exposure, years Median (range)	3.36 (0–5.35)	Pre-surgery: 0.66 (0.40–2.36) Post-surgery: 1.28 (0.16–2.84)	Pre-surgery: 0.65 (0.40–2.36) Post-surgery: 2.28 (1.33–4.60)

No surgical patients were excluded due to short follow up in this analysis.
*Only the first surgery of three performed in one patient was used in the analysis.
†Regimen that patients were using prior to entry to the guardian™ clinical trial programme

results

- At the interim cut-off date, data were available from 213 patients (aged 1–61 years), recruited from 19 countries:
  - In the total trial population, bleeds were mainly joint (75.3%) versus non-joint (24.7%); over half of bleeds were spontaneous (59.0%) versus traumatic (40.9%), spontaneous/traumatic (0.1%) or of unknown cause (0.1%).
  - 17 patients underwent surgery of which 9 orthopaedic surgeries were assessed (Table 2); all received prophylactic treatment during the trial.
  - Turoctocog alfa provided successful ('excellent' or 'good' haemostatic outcome) coverage in all procedures (data not shown).
  - No inhibitors or safety concerns were identified.

ALL-BLEED ANALYSIS

- A reduction in mean ABR of 1.98 bleeds/person/year was observed for patients undergoing orthopaedic surgery.
  - Prior to orthopaedic surgery, observed ABR was mean 6.16 (range: 4.18–9.09); afterwards, this fell to 4.18 (range: 2.03–8.64) bleeds/person/year.
- Median ABR fell from 5.65 bleeds/person/year (interquartile range [IQR]=5.58) to 1.46 bleeds/person/year (IQR=6.33).

EVALUATION OF PAIRED CASES

Orthopaedic surgery patients

- A reduction in mean sABR of 1.61 bleeds/person/year was observed (Figure 1).
  - Before orthopaedic surgery, Poisson estimates of mean sABR was 5.15 (range: 3.27–8.12); after surgery, this fell to 3.54 (range: 1.49–8.40) bleeds/person/year.
- Median sABR fell from 3.55 bleeds/person/year (IQR=5.58) to 0.00 bleeds/person/year (IQR=4.57) after surgery.

Control patients

- A reduction in mean sABR of 0.27 bleeds/person/year was observed (Figure 1).
  - Before the split day, Poisson estimates of mean sABR: 1.01 (range: 0.49–2.10) bleeds/person/year; after split day, this fell to 0.74 (range: 0.30–1.83) bleeds/person/year.
- Median sABR fell from 0.71 bleeds/person/year (IQR=2.26) to 0.50 bleeds/person/year (IQR=0.88) after surgery.

Table 2 ♦ First major orthopaedic surgical intervention of participants

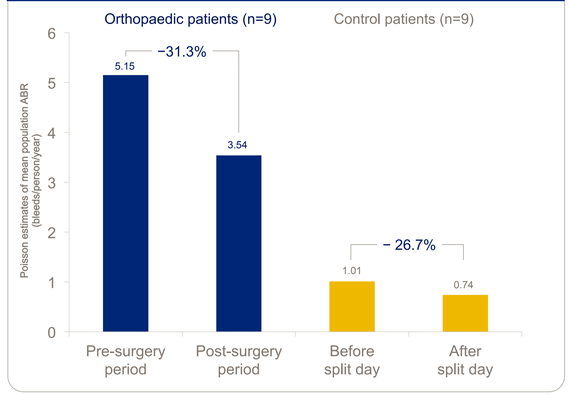
Age (years)	*Description of surgery*	*Surgery indication*
24	Arthroscopy left ankle	Pain in left ankle
37	TKR and THR	Chronic arthropathy left knee and right hip
55	Left hip arthroprosthesis, reduction finger fracture	Polytrauma
28	Right knee arthroprosthesis	Haemophilic arthropathy
47	Evacuation of damaged tissue with metallosis; evacuation of broken fragment of right elbow implant and replacement	Right elbow implant loosening
39	Revision replacement of acetabular part and head of right hip endoprosthesis	Loosening of right hip endoprosthesis
56	Resection of radial head, preparation of n. ulnaris	Severe arthropathy with sensible paresis of ulnaris
25	Implantation endoprosthesis totalis genus I sin synovioectomia subtotalis	Arthropathia haemophilica genus I sin, synovitis chr, gonarthrosis
41	Knee replacement and elbow radial head excision	Arthropathy

THR=total knee replacement; TKR=total knee replacement.

DISCUSSION

- In the guardian™ clinical trial programme, both ABR and sABR fall following orthopaedic surgery.
- Evaluation of a 'paired cases' analysis showed that similar relative reductions in sABR were also observed in control patients receiving prophylaxis with turoctocog alfa who did not undergo surgery.
- However, there are a number of limitations of this *post-hoc* analysis that future studies should address, including:
  - Small study population.
  - Use of age and BMI for case matching: the most meaningful parameter for matching cases and controls might be the pre-surgery ABR/joint ABR, but as this was the outcome variable and therefore not suitable, age and BMI were used instead.
- It is important to consider that the primary aims of orthopaedic surgery in people with haemophilia were to relieve pain, restore function and achieve stability.[5]

Figure 1 ♦ Change in sABR with surgery compared with control patients



conclusions

- The safety and efficacy of turoctocog alfa has been previously demonstrated. In this analysis, patients undergoing orthopaedic surgery have an observed reduction in post-operative spontaneous ABR, similar to patients who did not undergo surgery.
- This analysis suggests that ABR is not the optimal outcome predictor of elective orthopaedic surgery.
- Further studies should consider use of more relevant outcomes, such as the impact of surgery on pain, function and stability.

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CONFLICT OF INTEREST DISCLOSURE

- IM and LK are employees of Novo Nordisk.
- ES has received speaker fees for meetings organised by Bayer, Baxter, Pfizer, CSL Behring, Novo Nordisk, Kedrion and Grifols; ES acted as paid consultant for Bayer, Pfizer, CSL Behring, Novo Nordisk, Sobi/Biogen, Roche, Octapharma and Grifols and has received unrestricted research grants from Pfizer.
- LS has received fees for speaking from Novo Nordisk, Baxter, Pfizer and Bayer.

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