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Over Two Decades of Orthopaedic Surgery in Patients with Inhibitors – Quantifying the Complication of Bleeding

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Abstract

Patients with haemophilia who have developed inhibitors against factor VIII (FVIII) or factor IX present a significant concern to those surgeons who operate on them.

The evidence base for bypassing agents such as recombinant factor VIIa and activated prothrombin complex concentrate has amassed over several decades. The literature is open to positive interpretation on the successful use of these agents in the treatment of inhibitor-positive patients. However, there are equally persistent concerns amongst surgeons, in particular orthopaedic surgeons, regarding the high complication rate of bleeding.

To explore and quantify this concern, we present a literature review spanning two decades of publications on haemophilia patients with inhibitors undergoing orthopaedic surgery.

Irrespective of the progress made with haemostatic protocols, trepidation on embarking on surgery is valid. The high risk of bleeding is a function of the inherent complexity of the disease and rightfully translates into difficulties in its management. Combined with the prospect of orthopaedic surgery, those involved in the care of such patients are justified in their continued anxiety and diligence when considering the benefits in quality of life against the prevalent complications.

Introduction

Between ten to thirty per cent of patients with Haemophilia A will develop antibodies to exogenous factor VIII, while only two to five per cent of those with Haemophilia B will develop antibodies to exogenous factor IX therapy ¹⁻³. The development of an inhibitor remains one of the most severe complications of replacement therapy in haemophilia patients.

The perspective with regards to surgical intervention in patients with haemophilia who have acquired antibody-mediated resistance to factor VIII and IX therapy has changed considerably over the last two decades. In orthopaedic surgery, with evidence suggesting not only an effective cost-benefit ⁴ but also significant quality of life improvements ⁵⁻⁸, there has been a shift from only considering emergency procedures to advising patients on elective surgery ⁹. This paradigm shift is of special clinical significance to the inhibitor population.

One of the treatment goals in patients with haemophilia is to prevent haematoma formation in the synovium and cartilage, thereby avoiding a proclivity for haemophilic arthropathy. However, in those patients that develop antibodies to exogenous factor replacement, in the absence of newer agents that bypass the antibody inhibitors, haematoma formation is of greater risk. Unfortunately, treatments available for the control of acute bleeds are not as predictable as replacement therapy and therefore active bleeding is harder to control in the inhibitor population than non-inhibitor ¹⁰. As such, this cohort often demonstrate more severe joint morbidity and hence significant orthopaedic disability ^{11,12}.

In 1956, De Palma and Cotler ¹³ considered it inadvisable to operate on patients with severe haemophilia. A decade later, a series by Ahlberg ¹⁴ positioned him as forefather of orthopaedic surgery in patients with inhibitors. However, antibody inhibitors to exogenous factor replacement were as recently as 1994 still widely regarded as an absolute contraindication to elective surgery by authors such as Robert Duthie ¹⁵. Certainly, in elective orthopaedics, peri- and post-operative risks were significant ^{16,17}. The advent of bypassing agents such as factor eight inhibitor bypassing agent (FEIBA; Baxter Bioscience, Vienna, Austria) and recombinant

factor VIIa (rFVIIa; NovoSeven, Novo Nordisk A/S, Bagsvaerd, Denmark) prevent bleeding in this treatment resistant group. These agents have now enabled surgery to be considered with increasing confidence and this is reflected in the literature ^{16,18-26}.

FEIBA is plasma-derived and primarily composed of four coagulation factors: factor II (prothrombin), factor IX and factor X, which are chiefly in zymogen form, and factor VII, predominantly in the activated form ²⁷. The zymogenic FEIBA proteins support the haemostatic process by increasing the level of substrates available for activation by the appropriate enzymes, which are present in trace amounts within FEIBA. The enzymes in FEIBA contribute to clot formation in the absence of FVIII or FIX through direct action and via the various feedback mechanisms ²⁷.

NovoSeven is a vitamin K-dependent glycoprotein and is structurally similar to human plasma-derived FVIIa. It acts by forming an extrinsic tenase complex with tissue factor expressed on cell surfaces at the site of injury. This then activates Factor X, leading to thrombin generation and subsequent haemostasis ^{28,29}. The first surgical procedure performed with NovoSeven was reported in 1988 by Hedner et al ³⁰. The authors described the successful synovectomy of the knee in a patient with inhibitors. Shortly thereafter, a seminal publication by Shapiro et al ²¹ described a randomised trial to assess the clinical safety and efficacy of NovoSeven. Consequently, following this early validation study, NovoSeven has been progressively utilised in the surgical management of inhibitor patients.

The general increased use and understanding of haematological factors has, over time, provided a concomitant growing body of evidence. The aforementioned humble pioneering beginnings in the form of case reports were followed by departmental and national reviews. The literature has culminated in the formation of international consensus groups. Parallel to these gains, orthopaedic surgeons have steadily developed guidance through multidisciplinary forums looking to optimise the outcome for their afflicted patients. As such, considering invasive procedures in haemophilia A or haemophilia B patients with factor VIII or IX antibodies

respectively has moved on from the admonitory historic maxims of our prior opinion leaders. However, caution persists, as those patients who have developed an inhibitor to factor VIII or IX remain rare and their medical and surgical management continues to challenge those clinicians tasked.

Perhaps based on the literature's perceived inclination to field positive outcomes when faced with such a difficult cohort, there seems to be a mismatch between the face-value interpretation of published data and clinician experience. To the authors of this review, the personal experiences albeit anecdotal, are more cautionary and in keeping with historic opinion. Certainly, the catastrophic consequences of infection are well known to any orthopaedic surgeon. The correlation between intra- and peri-operative bleeding and an increased risk of infection, of particularly grave consequence in arthroplasty³¹⁻³⁴, continues to be a focal point for improvement³⁵.

We have performed a scoping review of the literature describing major orthopaedic surgery in patients with inhibitors to summarise the key publications over the last two decades and provide perspective on numbers of patients, surgical procedures and bleeding complications. We believe haemophilia patients with inhibitors remain very challenging, and from an orthopaedic perspective continue to pose a high bleeding complication rate due to the inherent nature of the condition.

Materials and Methods

Medline via PubMed was the primary source of all articles. Google Scholar was utilised as a second line source especially in the location of book chapters. A cross-database literature search was employed as a tertiary filter (BIOSIS, Current Contents, and EMBASE). The search was through 'Clinical queries' therapy section using the broad, sensitive filter and search terms: 'inhibitor AND/OR orthopaedic AND/OR surgery AND/OR haemophilia'. No limits were placed on the manuscript type. The language was set to English. Dates included January 1996 to December 2017.

A total of 79 publications were found on the index search. Cross-referencing within these publications yielded a further 14 papers, totalling 93 articles. This was reduced to 49 original papers after filtering to remove review articles; papers on non-orthopaedic surgery; and using the classification of Ozelo et al ³⁶ in which synoviorthesis and arthrocentesis are classified as minor and all other procedures are classified as major. Where possible the details of each orthopaedic surgical procedure and the corresponding bleeding complication were noted.

There was non-uniformity in the description of bleeding complications across the data set. The heterogeneity seen was not only for definitions in general terms, but those definitions and descriptors changed when considering the intra- and postoperative periods. To ensure both a mutually exclusive and collectively exhaustive capture for all possible bleeding complications, all manuscripts were meticulously interrogated and a lexicon for haemostatic concerns and/or bleeding complications derived. With respect to haemostasis, inclusive adjectives and/or outcome descriptors were as follows: not effective, ineffective, unexpected, prolonged bleeding, inefficient, poor or inadequate control, continued oozing, requirement of prolonged bypassing agent, bleeding complications, re-bleed, haemostatic difficulty, substantial bleeding, substantial blood loss, moderate bleeding complications, wound haematoma, haemarthrosis, postoperative bleeding, significant bleeding, uncontrolled bleeding, blood loss of more than expected and requiring transfusion, unable to maintain haemostasis.

Therefore, “bleeding complications” were all episodes as per the above descriptors that were highlighted either in the results table and figures, or in the body of the text in both the intra-operative and/or post-operative periods for the duration of each study concerned.

An in-depth analysis of the original manuscripts led to further deductions being made. A case study, involving a patient who had previously tested positive for inhibitors but was inhibitor negative pre-operatively was excluded ²⁸.

Multiple articles from groups with multiple publications over the search time period have published their experiences on the same and/or expanding cohort. If appropriate, only the

most recent and comprehensive study belonging to that group was considered for inclusion. This resulted in 5 further outright omissions and the exclusion of part of a data set that was represented in a more recent publication by the same author.

The cases covered by Tagariello in 2000 ³⁷ were considered in Goudemand et al ³⁸. Work published in 1996 by Ingerslev et al ³⁹ has been followed up and expanded in 2002 ⁴⁰. Rodriguez-Merchan et al have sequentially expanded upon their experience with publications in 2003 ²⁴, 2007 ²⁵ and 2010 ⁴¹.

Takedani et al publish in 2010 ⁴² and subsequently in 2014 ⁴³ describing their 10-year experience. Caviglia et al published in 2011 ⁴⁴ and 2015 ⁴⁵. The former encompasses a number of major orthopaedic procedures including psuedotumour surgery between 1997 and 2008. The latter involves only pseudotumour surgery between 2000 and 2013. The inherent issues associated with potential data slicing were overcome by considering the 2011 publication without the pseudotumour data as this was presumed to be covered in 2015.

Secondary searches were performed on the Cochrane database, Clinical Evidence and SUMsearch. No additional articles were found.

Details of the final 43 relevant studies are outlined in Table 1.

Results

The analysis of the pooled published data reveals that there were 317 cases of major orthopaedic surgery performed in 235 patients over the review inclusion period with a total of 129 individual bleeding complications, Table 1.

The percentage rate of bleeding complications in major orthopaedic surgery is 40.7% (129 complication in 317 procedures).

In the assessment of bleeding complications as they relate to operative sub-groups, the percentage of major orthopaedic procedures that experienced a bleeding complication was

30.6% (97 procedures experienced 1 or more complications in a total of 317 operations performed, Table 2).

In decreasing volume, knee arthroplasty (130 procedures, 41.0%), followed by knee arthroscopy (43 procedures, 13.6%) and hip arthroplasty (27 procedures, 8.5%) made up 63.1% (200 of the 317) of total procedures performed. They accounted for 73.6% (95 of the 129) complication episodes.

Of the 130 knee arthroplasty procedures, 33.8% (44) suffered a bleeding complication. In hip arthroplasty and knee arthroscopy the complication rates were 51.9% (14 in 27) and 25.6% (11 in 43) respectively.

The remaining top 10 procedures performed on inhibitor-positive patients were in decreasing order of volume: pseudotumours (5.0% of all operations); open synovectomies (4.4%); open reduction and internal fixation of fractures (4.4%); incision and drainage and/or wound debridement (4.1%); amputation (2.5%); ankle arthrodesis (2.2%); and fasciotomy (1.9%). They accounted for 24.6% of all procedures performed (78 of 317); 15.5% (20 of 129) of the complications, with 23.1% of those procedures experiencing one or more bleeding complications (18 of the 78 procedures).

Other than arthroplasty and arthroscopy, the procedures noted to have the highest rate of bleeding complication were 83.3% during osteotomy (5 in 6 procedures), 66.7% during fasciotomy (4 of 6); 50.0% of synovectomies (7 in 14); 30.8% during incision and drainage (4 in 13); 14.3% of ORIF (2 in 14); 120% in fractured neck of femurs (6 complications in 5 procedures); and 100% of shoulder arthroplasty, radial head excision and knee chondroplasty (each of these operations feature only once in the dataset and each had a single bleeding complication reported).

Table 3 demonstrates the data divided into each of the two decades reviewed. The proportion of procedures with a complication seen in each decade is roughly the same: 31.3% in the current decade, versus 28.4% in the previous decade.

Literature Review

In 1996 Ingerslev et al³⁹ published the first series of 12 patients with inhibitors undergoing major surgery. NovoSeven treatment was considered to be excellent in 11 patients. Following this series where bypassing agents were described as a “tempting alternative”, agents such as NovoSeven and FEIBA have been subsequently deployed in a multitude of procedures.

In Ludlam et al's⁴⁶ prospective study observing NovoSeven continuous infusion during elective orthopaedic surgery, 6 of 9 patients experienced in total 16 significant bleeding complications. Four severe adverse events (3 operative site haemarthrosis, 1 anaemia requiring transfusion), 7 moderate adverse events (haemarthrosis), and 5 mild adverse events in one patient (incision site bleeding over an extended period of inpatient stay). The study concludes that major orthopaedic surgery can safely be carried out with continuous infusion of NovoSeven with bolus supplementation to reliably restore haemostasis.

In 2005 Goddard⁴⁷ presented our hospital's haemophilia centre experience, culminating in 78 joint replacements in 51 non-inhibitor patients, and two inhibitor patients undergoing a revision TKR in one, and a radial head excision followed by a primary knee replacement in the other. The primary TKR experienced a significant bleeding episode on day 3 post-operatively following dose reduction with a further less severe bleeding episode on day 12. This patient was hospitalised for a period of 3 weeks.

The haemostatic efficacy and safety of bolus versus continuous infusion NovoSeven has been tested in a randomised study⁴⁸ and found to be comparable. Twenty-six patients were recruited into the treatment arms, and ten patients into the control arm. Seven therapeutic failures were recorded; 3 in the bolus arm, 3 in the continuous infusion arm, 1 in the control group. Although the authors describe major weaknesses in the study design, the 6 bleeding complications in 16 patients (37.5%) undergoing major orthopaedic procedures seems representative.

Lauroua et al ⁴⁹ reported a series of successful major and minor surgery using relatively low-dose FEIBA (70 units per kilogram) in 12 procedures; seven were orthopaedic, with one patient enduring five separate interventions. The complications all required multiple transfusions often for prolonged bleeding, and also included a deep prosthetic infection and a prosthetic debridement. Despite the deleterious orthopaedic outcomes, the authors conclude that “haemostasis has generally been judged to be good or excellent” and that inhibitors were not a contraindication to surgery.

Rangarajan et al ⁵⁰ presented the experience of major and minor surgery across four centres in the United Kingdom with FEIBA as a first-line bypassing agent. Involving 18 major procedures, the peri-operative haemostatic outcome with FEIBA was considered to be excellent or good in 14 episodes (78%). A total of 9 (69.2%) documented bleeding complications were listed, predominantly within the arthroplasty (6, 46%) subgroup. Rangarajan et al discuss how fair or poor haemostatic outcomes reflect the challenges presented by significant initial blood loss, and that the need for prolonged haemostatic cover to promote postoperative wound healing is of special importance in orthopaedic surgery. We agree with the authors' conclusions that the series is not only representative and unbiased, but remains reflective of more contemporaneous experiences with FEIBA.

In 2011 Boadas and colleagues ⁵¹ reported the experience of the Venezuelan National Haemophilia Centre. In a mixed surgical series involving 7 inhibitor-positive patients undergoing orthopaedic surgery, 3 patients had bleeding complications. Taking support from comparable rates in prior publications, the authors consider haemostasis to be effective in 85% of major surgery stating that there were no safety concerns. The complications include moderate bleeds, profuse bleeding, and wound haematoma requiring revision surgery. Highlighting the disparity in inter-speciality thinking and given the increased morbidity and mortality risk of such complications, orthopaedic surgeons would hold an opinion in diametric opposition to this paper.

The Scottish experience was described by Jenkins et al ⁵², who measured patient reported, functional, and radiological outcomes. Over an 8-year period, 13 TKRs were performed on 8 male patients, all of whom had severe haemophilia with levels of factor less than 0.01 IU/ml. There were three patients who had inhibitors to factor VIII. As one patient had a staged bilateral procedure in the presence of inhibitors, four knees were operated on in the presence of inhibitor antibodies. Irrespective of the presence of inhibitors, all knee replacements developed haemarthroses. These were diagnosed clinically or with the rapid filling of surgical drains. Two of the inhibitor patients developed delayed “severe haemarthroses” causing readmission in one patient and prolonged wound care secondary to fracture blisters in the other. Notwithstanding the specific complications, the authors conclude that the inhibitor cohort retained both a significant fixed flexion deformity and a reduced arc of movement.

Négrier et al ⁵³ examined FEIBA use in a 3-year world-wide open-label, prospective study of surgery. Patients were recruited between 2006 and 2009 into an international registry. FEIBA was dosed at the discretion of the attending physician in accordance with guidelines in the published literature (50–100 U/kg administered at intervals of 6–12 hours during or after surgery, taking care not to exceed the maximum daily dose of 200 U/kg). The study included 11 orthopaedic operations on a total of 7 patients. The intraoperative and overall haemostatic efficacy of FEIBA was considered “excellent” or “good” in 92.3% (12) of those patients undergoing operations considered to be “severe”. However, the results indicate that blood loss was higher than expected in 40% of those patients; 42.9% (3 of 7 orthopaedic procedures) demonstrated clinically significant decreases in haemoglobin; 30.8% required extra measures (use of fibrinolytic inhibitors, ice and a compression/bandage; local wound revision; additional sutures; and full surgical revision) to control bleeding. Two arthroplasty procedures required FEIBA dosing over 20 days.

The authors describe 4 procedures when post-operative efficacy was “fair” and “poor”. One can interpret these results as showing at least 6 procedures that had suboptimal haemostatic efficacy.

In 2014, Saeki et al ⁵⁴ reported sequential joint arthroplasty surgery on a single patient. The authors stressed the importance of efforts to minimise blood loss, especially as the cost-burden of NovoSeven-based management resultant bleeding complications was \$150,000 over rFVIII treatment. However, in keeping with other authors who have specifically assessed the cost versus quality of life outcomes for inhibitor patients ¹², Saeki et al also respectfully acknowledge the importance of such treatment in ‘uncontrollable and fatal bleeding’.

The use of a hybrid regimen in major surgery was first described by van Veen et al ⁵⁵ who concluded that although the overall outcome was good, their complication profile was higher than previously represented in the literature: 4 patients who underwent 6 TKRs, experiencing 4 bleeding complications all in the postoperative phase.

Ju et al ⁵⁶ present one of the larger series involving 15 patients and 25 orthopaedic procedures. Only one patient was noted to have complications, they underwent two total knee replacements and required sequential bypassing therapy in one knee with a switch in therapy from NovoSeven to FEIBA in the other. These 2 complications represent 8% of the orthopaedic cohort. However, on detailed review of the results, 6 procedures in 4 patients required significant multiple red blood cell transfusions and/or a change in bypassing treatment. This increases the reportable and orthopaedically relevant bleeding complication rate from 8% to 24%.

Mancuso et al ⁵⁷ present their observations around major orthopaedic surgery with the aim of advancing the monitoring of clinical efficacy of bypassing agents. Following on from some evidence in *in vitro* ⁵⁸⁻⁶⁰ with inconsistent *ex vivo* ^{61,62} studies, Mancuso et al conclude that thrombin generation assay (TGA) fails as a reliable laboratory tool to monitor haemostatic efficacy and as a predictor of the risk of bleeding in inhibitor patients undergoing orthopaedic surgery. With regards to surgical haemostasis, they report 7 bleeding complications in 6 patients, defining haemostasis as excellent to good in 4 procedures; and fair to poor in 7. The complications are reported as lasting for 1-2 days and “promptly” rescued. As first-line

treatments, five patients received NovoSeven, and one exclusively FEIBA. Six cases of sequential bypassing therapy are highlighted. Two relate to uncomplicated postoperative courses, and 4 to rescue bleeding not controlled by a single agent. In one case, sequential therapy was a second line strategy associated with failure of NovoSeven intensification after day 13. Mancuso et al report a 63.6% chance of a bleeding complication across their cohort of patients. Of note is the complexity of the case mix involving two revision arthroplasty procedures. Furthermore, by dosing every 2 – 3 hours in the first 72 postoperative hours, potential for quantitative error may also rest in the delayed administration of bypassing agent. In our opinion, unless given every 2 hours, NovoSeven does not provide adequate cover.

Two publications involving orthopaedic surgery in inhibitor patients were reported in 2017. The first to be printed involves a general outcome descriptor of patients with haemophilia and von Willebrand disease undergoing invasive or surgical procedures⁶³. The latter highlights the destructive nature of haemophilia, the authors documenting the experience of their surgical colleagues tasked in replacing the hip of an inhibitor-positive adolescent⁶⁴.

Cumulatively, these papers contribute additional retrospective data involving 3 inhibitor-positive patients who have had joint arthroplasty, with 2 of the 3 joint replacements suffering bleeding complications. It is pertinent to note that Chapin et al⁶³ conclude that physicians should not underestimate the risks of bleeding, even in cases where the procedure may be minor. The authors argue that the knock-on effect being a relaxation to both vigilance and the aggressiveness of treatment. We would wholeheartedly agree with the summation, but add, as per the driver to this literature review, that more than an underestimation, there is an underrepresentation of complications compounding the issue across the literature. A case in point being the latter paper. Despite a bleeding complication requiring 4 units of red cell transfusion, compression dressings, sequential tranexamic acid, a therapy change to FEIBA, and continued bleeding for more than 36 hours post-surgery, Kaya et al⁶⁴ title their case presentation as “successful”. By concentrating on the application of sequential bypassing

agent therapy, much like the multitude of authors before them, Kaya et al exemplify the variation in sensitivity, or tolerance, when reporting patient-focused outcomes.

Kaya et al use a small literature review to illustrate the issues of prior investigators by highlighting 12 of 16 patients as having experienced a clinically significant bleeding episode. To differentiate their own case, the authors label the bleeding they observed as refractory and therefore “successful” rather than a complication. However, we would argue that Kaya et al’s response time of 4 weeks to control refractory bleeding would not be considered “successful” from an orthopaedic perspective.

Discussion

The advent of the bypassing agents has made previously impossible surgery possible. Due partly to validated dosing regimens, the global experience of the use of such agents is increasing and surgeons are more willing to undertake surgery in patients with inhibitors. However, despite repeated calls, there is little in the way of a robust evidence-base for such regimens. Furthermore, although the research continues, regimens are limited by the lack of simple assays to monitor their haemostatic efficacy during and after surgery. Recent advances however such as thrombin generation assays can prove useful in assessing the balance between thrombin generation and decay in the presence of these inhibitors ⁶⁵.

Currently, there are no widely agreed efficacy parameters that can be used to evaluate haemostatic response to bypassing agents during surgery. Agreement on such parameters would enable robust comparisons to be made between studies, rather than authors having to rely on qualitative assessments for bleeding ⁴⁴.

In our review of the literature it was not uncommon to find face-value outcomes being described as effective or efficient haemostasis whilst a deeper analysis revealed continued or prolonged bleeding with or without the need for transfusion and the requirement of continued bypassing therapy. In part, the disparity between our collected data and conclusions drawn by original articles is a function of our definition criteria. There is no doubt however that many

studies exist where significant blood loss requiring transfusion, increased dosing or a change in bypassing agent and/or surgery have not ultimately registered as an issue of global haemostatic efficacy.

Although thrombotic complications remain rare, bleeding complications in orthopaedic cases in particular are more frequent than had been previously thought.

This review has revealed multiple publications with duplications of prior series within their dataset potentially confounding interpretation. In addition, given the inherent bias to report positive findings, it is likely that there has been a reluctance to publish treatment failures. In a number of studies, the post-operative follow-up has been relatively short and frequently measured by the ability to achieve haemostasis, rather than the formal assessment of any orthopaedic outcome measures.

Conversely one must consider the high number of challenging cases reported, such as revision or pseudotumour surgery, which would influence bleeding complication rate independently of whether a patient was inhibitor positive or not. Interestingly, the data does not support such higher risk surgery being associated with a higher proportion of bleeding complications.

It is unfortunate, but understandable why, the type of thromboprophylaxis regimen used, or tourniquet use, is rarely mentioned. In a normal population, chemical prophylaxis would be withheld if post-operative bleeding should ensue. Given that authors reported immediate post-operative bleeding often lasting for days after surgery, information on regimen loses its relevance and it is understandable why the inclusion of such data is sparse. With regards tourniquet use, we would strongly argue that internationally there would be no difference in approach amongst surgeons for the top three operative procedures in this cohort: tourniquets being universally applied in arthroscopy and knee arthroplasty, but obviously not in hip arthroplasty.

There is a heterogeneity both to the type of procedures performed, with 25 different orthopaedic procedures recorded, and the haemostatic regimen. Notwithstanding the importance of these limitations when analysing the pooled data in Tables 1-3, we believe they do not influence or detract from our main message: that bleeding complications in orthopaedic procedures are underreported and not emphasised appropriately in the inhibitor population.

There have been a number of different dosing strategies, although there is now general consensus towards more standard regimens. The optimal dose for NovoSeven has now been defined as 120-180 micrograms per kilogram preoperatively, decreasing to 90 micrograms per kilogram as a two-hourly bolus postoperatively. For FEIBA 100 units per kilogram are recommended preoperatively followed by 75-100 units per kilogram postoperatively with a maximum dose of 200 units per kilogram ⁶⁶.

Unfortunately, cost still remains a concern for both agents, and secondary to their invariable application, it is essential that the rescue treatments are accurately defined and included within protocols and therefore costing estimates. Furthermore, in keeping with considerations surrounding health economics and cost-effectiveness, certainly within orthopaedics, surgeons are increasingly mandated to report their outcomes. Rather than merely judging success by achieving haemostasis, such outcomes are often functional and frequently involve patient reported outcome measures (PROMs).

With direct relevance to outcome, registries play an invaluable role in the management of many conditions and surgical interventions, their importance is heightened in rare disorders. Key registries for haemophilia patients with inhibitors experiencing acute bleeds are running, collecting substantial post-approval data and have already changed practice ⁶⁷⁻⁶⁹. The ONE registry revealed that fewer injections were required for bleeds treated with initial high doses, but that single and standard dose treatments were associated with similar overall effectiveness ⁶⁹. HemoRec, a prospective observational registry reported that higher initial doses and early treatment initiation of NovoSeven achieved a significantly faster bleed resolution ⁶⁸. The

Hemostasis and Thrombosis Research Society (HTRS) registry supports the efficacy profile of NovoSeven established by the prospective clinical trials and represents the most comprehensive collection of data on NovoSeven use ⁶⁵.

A recent Cochrane review has emphasised the lack of post-operative data on bleeding complications in the bleeding disorder patient population ⁷⁰. Notwithstanding this generic call for data, we also propose that a registry should be established in order to collate the broad and specific essential multivariate outcomes in inhibitor positive patients. Ultimately one should be in a position to compare the outcome variables of haemophilia patients with inhibitors versus those without. In unison with other authors, we believe that attention and transparency of the high bleeding complication rates should drive added vigilance and aggression of treatment. As has been the case for orthopaedic national joint registries, the open publication of multiple outcome measures has refined and optimised patient care. Given the findings of this literature review, multidisciplinary teams tasked with inhibitor patients should not stagnate or indeed regress under a false sense of security provided by only considering eventual haemostasis.

Conclusion

Ultimately, it is our collective professional and legal duty to patients with inhibitors, to ensure that the narrative surrounding major surgery is transparent and reflective of the realities. In so doing, we both engage with the autonomy of patients, whilst driving advances in the management of this challenging cohort of patients.

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GE and NJG performed the research, analysed the data, wrote the paper, BG and AA wrote the paper.

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

Table 1: The pooled published data from 43 studies

	Year of Publication	Years analysed in study	First Author	Patients	Total Orthopaedic Operations	Hip Arthroplasty	Knee Arthroplasty	Arthroscopy	Other Surgery	Total Bleeding Complications	FEBIA use	rFVIIa use
1	2017	2015	Kaya ⁶⁴	1	1	1	0	0	0	1		x [*]
2	2017	2006-2012	Chapin ⁶³	2	2	0	2	0	0	1		x [†]
3	2016	2006-2013	Mancuso ⁵⁷	10	11	1	7 [‡]	2	1	7		x
4	2015	2004-2014	Ju ⁵⁶	15	25	1	9	9	6	6		x
5	2015	2000-2013	Caviglia ⁴⁵	6	9	0	0	0	9 [§]	0	x	x ^{**}
6	2014	2006-2012	van Veen ⁵⁵	4	6	0	6	0	0	4	x	x ^{††}
7	2014	2013	Dolatkhan ⁷¹	1	1	0	1	0	0	0		x
8	2014	2000-2010	Takedani ⁴³	13	26	2	2	14	8	5		x
9	2014	2010-2013	Saeki ⁵⁴	1	2	1	1	0	0	2		x
10	2013	2006-2009	Negrier ⁵³	7	11	3	4	1	3	4	x	
11	2013	1999-2007	Jenkins ⁵²	3	4	0	4 ^{††}	0	0	6		x
12	2012	2000-2007	Zülfikar ⁷²	4	6 ^{§§}	0	2	2	2	2	x	
13	2012	2008	Shimada ⁷³	1	2	0	0	2	0	0		x
14	2012		Polyanskaya ⁷⁴	17	17	0	6	0	11	0		x
15	2011	2006-2009	Boadas ⁵¹	7	8	0	0	1	7 ^{***}	5		x
16	2011	1998-2008	Rangarajan ⁵⁰	8	13	2 ^{†††}	3	0	8	9	x	
17	2011	1997-2008	Caviglia ⁴⁴	6	9	0	0	3	6	4		x
18	2010		Frauchiger ⁷⁵	1	2	0	2	0	0	0		x
19	2010	2001-2009	Balkan ⁷⁶	1	2	0	0	0	2	0	x	
20	2010		Rodriguez ⁴¹	6	8	1	3	0	4	1	x	x ^{†††}
21	2009	1989-2004	Lauroua ⁴⁹	7	7	1	1	1	4	6	x	
22	2009	2007-2009	Giangrande ⁷⁷	8	13	2	7	0	4 ^{§§§}	2	x	

* rFVIIa given pre- and post-operatively for first 24 hours; after 24 hours of no response to rFIIa, treatment switched to APCC 200 IU/kg.

† Either FEBIA or rFVIIa used for inhibitor positive patients, not further specified in methodology.

‡ 2 Revision procedures.

§ Pseudotumour surgery.

** Four of the 6 patients received rFVIIa and the remaining received 2 FEIBA.

†† Hybrid regimen of rFVIIa in the immediate postoperative period and FEIBA subsequently.

	Year of Publication	Years analysed in study	First Author	Patients	Total Orthopaedic Operations	Hip Arthroplasty	Knee Arthroplasty	Arthroscopy	Other Surgery	Total Bleeding Complications	FEIBA use	rFVIIa use
23	2007	1998-2005	Pruthi ⁴⁸	16	16	3	4	8	1	6		x
24	2007	2006-2007	Stumpf ⁷⁸	1	3	0	1	0	2	0	x	x ****
25	2007	1996-2006	Bossard ⁷⁹ ††††	25	27	0	27	0	0	9		x
26	2007		Kraut ⁸⁰	4	8	0	0	0	8	4	x	x ††††
27	2007	2000-2004	Stine ⁸¹	1	4	0	0	0	4 §§§§	1	x	
28	2006	1995-2001	Dimichele ⁸²	3	3	0	1	0	2	2	x	
29	2006		Solimeno ⁸³	6	6	0	6	0	0	6	x	x
30	2005		Goddard ⁴⁷	2	3	0	2 *****	0	1	2		x
31	2005	2001	Dargaud ⁸⁴	1	2	0	2	0	0	0	x	
32	2004	1996-2004	Tjønnfjord ⁸⁵	3	3	0	3	0	0	2	x	
33	2004	1999-2002	Habermann ⁸⁶	4	6	0	4	0	2	0		x
34	2004		Mehta ⁸⁷	2	3	0	3	0	0	0		x
35	2004		Goudemand ³⁸	6	7	4	2	0	1	5	x	x ††††
36	2004	1983-2003	Molina ²⁶	5	5	1	1	0	3	1	x	x ††††
37	2003		Ludlam ⁴⁶	9	9	0	8	0	1	16		x
38	2002		Hvid ⁴⁰	4	13	1	5	0	7	2		x
39	2002	2002	Nakamura ⁸⁸	1	1	0	0	0	1	0		x
40	2002	2002	Perez ⁸⁹	1	1	1	0	0	0	0		x
41	2001	1998-2001	Faradji ⁹⁰	1	1	0	1	0	0	1		x
42	1998	1995-1996	Shapiro ²¹	10	10	2	0	0	8	6 §§§§§		x
43	1996	1970-1989	Löfqvist ¹⁷	1	1 *****	-	-	-	1	1		†††††
Total				235	317	27	130	43	117	129		

**** A combination of rFVIIa and FEIBA was used during each procedure.

†††† The preliminary results of European Register on Knee Arthroplasty (EUREKA) study by Laurian et al are referred to in Bossard et al, the abstract for the presentation is unavailable through a broad literature search.

†††† Two patients received FEIBA and two combination bypassing therapy.

§§§§ Three procedures for compartment syndrome and a wound debridement and closure.

***** One primary and one revision TKR.

††††† Publication representing personal series by the three authors Goudemand, Tagariello and Lopaciuk. Only Goudemand and Tagariello present orthopaedic cases. The former author used FEIBA for his single fractured neck of femur case, whereas the later employed rFVIIa for 6 arthroplasty procedures on 5 patients.

††††† One hip and one knee arthroplasty with rFVIIa, one knee arthrodesis with FEIBA, one arthrodesis and a femoral fracture with FVIII concentrate.

§§§§§ Authors describe separately 4 orthopaedic patients regarded as “haemostatic treatment failures” requiring escape dosing or alternative therapy. In addition, a further 2 orthopaedic patients are reported as requiring blood transfusion for volume expansion secondary to blood loss.

***** Original paper mentions 8 procedures in 3 patients, but only describes one patient in detail as having had “abnormal bleeding” following open synovectomy.

††††† Patients were high dose FVIII (haemophilia A) or FIX (haemophilia B) in combination with intravenous IgG and cyclophosphamide, as per the Malmö protocol ¹⁶.

Table 2: Bleeding complications as they relate to the operative sub-groups

Operative Subgroups	Number of procedures performed	Total number of bleeding complications in each procedure	Number of procedures experiencing a bleeding complication	Operative Subgroups	Proportion of bleeding complications seen in each operative subgroup (%)	Proportion of the 97 procedures with a bleeding complication (%)	Proportion of operative subgroup that have had a bleeding complication (%)	Proportion of procedures with a complication seen in each operative subgroup (%)
	A	B	C		B/A	C/ΣC	C/A	C/ΣA
Knee Arthroplasty	130	68	44	Knee Arthroplasty	52.3	45.4	33.8	13.9
Arthroscopy	43	11	11	Arthroscopy	25.6	11.3	25.6	3.5
Hip Arthroplasty	27	15	14	Hip Arthroplasty	55.6	14.4	51.9	4.4
Pseudotumour	16	1	1	Pseudotumour	6.3	1.0	6.3	0.3
Synovectomy	14	7	7	Synovectomy	50.0	7.2	50.0	2.2
ORIF *	14	2	2	ORIF	14.3	2.1	14.3	0.6
I&D Wound †	13	4	4	I&D Wound	30.8	4.1	30.8	1.3
Amputation	8	2	1	Amputation	25.0	1.0	12.5	0.3
Ankle Arthrodesis	7	0	0	Ankle Arthrodesis	0.0	0.0	0.0	0.0
Fasciotomy	6	4	3	Fasciotomy	66.7	3.1	50.0	0.9
Osteotomy	6	5	3	Osteotomy	83.3	3.1	50.0	0.9
NOF surgery ‡	5	6	3	NOF surgery	120.0	3.1	60.0	0.9
Tenotomy	5	1	1	Tenotomy	20.0	1.0	20.0	0.3
Knee Arthrodesis	4	0	0	Knee Arthrodesis	0.0	0.0	0.0	0.0
MUA §	4	0	0	MUA	0.0	0.0	0.0	0.0
ROM **	4	0	0	ROM	0.0	0.0	0.0	0.0
Ilizarov Frame	2	0	0	Ilizarov Frame	0.0	0.0	0.0	0.0
Ankle Arthroplasty	1	0	0	Ankle Arthroplasty	0.0	0.0	0.0	0.0
Knee Chondroplasty	1	1	1	Knee Chondroplasty	100.0	1.0	100.0	0.3
Femoral Tumour	1	0	0	Femoral Tumour	0.0	0.0	0.0	0.0
Spinal Stenosis	1	0	0	Spinal Stenosis	0.0	0.0	0.0	0.0
Radial Head Excision	1	1	1	Radial Head Excision	100.0	1.0	100.0	0.3
Elbow Arthroplasty	1	0	0	Elbow Arthroplasty	0.0	0.0	0.0	0.0
Shoulder Arthroplasty	1	1	1	Shoulder Arthroplasty	100.0	1.0	100.0	0.3
Femoral bone graft	1	0	0	Femoral bone graft	0.0	0.0	0.0	0.0
Joint drainage	1	0	0	Joint Drainage	0.0	0.0	0.0	0.0
TOTALS	317	129	97					30.6%

* ORIF: Open Reduction and Internal Fixation of a fracture

† I&D Wound: Incision and drainage and/or wound debridement

‡ NOF Surgery: Surgery for a fractured neck of femur: 2 cannulated screws, 1 blade plate and 1 dynamic hip screw

§ MUA: Manipulation under anaesthetic

** ROM: Removal of metalwork

Table 3: Results of literature review by decade

Period	Number of patients	Total number of procedures performed	Total number of bleeding complications	Number of procedures experiencing a bleeding complication	Proportion of bleeding complications per procedure (%)	Proportion of procedures with a complication seen in each decade (%)
2017 – 2007	176	243	85	76	35.0	31.3
2006 – 1996	59	74	44	21	59.5	28.4
Totals	235	317	129	97	40.7	30.6

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