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# A 13-year review of elective orthopaedic surgery outcomes in patients with hemophilia A and B

From 2004 to 2017 orthopaedic procedures for hemophilia patients in BC shifted from mainly knee surgeries to mainly ankle surgeries, and reductions were observed in both hospital length of stay and the need for coagulation factor prophylaxis.

## ABSTRACT

**Background:** Patients with hemophilia A and B are at risk for progressive arthropathy and are known to have less satisfactory outcomes when undergoing orthopaedic surgery than patients without hemophilia. During the mid-2000s the approach to adult hemophilia care in Canada changed significantly to include preventive coagulation factor replacement therapy. Starting in 2004 adults with significant arthropathies began using coagulation factor prophylaxis. By 2012 this approach was used by over 80% of BC hemophilia patients, and by 2017 coagulation factor prophylaxis was the established approach. A study of patients in BC was proposed to compare management and surgical outcomes from 2004 to 2017 as the approach to hemophilia care changed.

**Methods:** Data were reviewed from the clinical charts and electronic medical records of patients with hemophilia who underwent elective orthopaedic surgery and had follow-up through the Adult Bleeding Disorders Program of BC at St. Paul's Hospital from January 2004 to February 2017. Study subjects were adult orthopaedic surgery patients with mild to severe factor VIII deficiency (hemophilia A) or factor IX deficiency (hemophilia B). The primary outcomes considered were type of hemo-

philia and severity, type of orthopaedic surgery, joints involved, coagulation factor administered, hospital length of stay, and any surgical complications. Hemophilia cases were classified as mild, moderate, or severe. Data collected for coagulation factor VIII and IX utilization (u/kg) included doses from the preoperative period to postoperative day 14. Surgical complications were defined as unexpected postoperative events such as bleeding and thrombotic events. Outcomes were compared for three eras: the "early prophylaxis" era, 2004 to 2009; the "transition to prophylaxis" era, 2010 to 2012; and the "established prophylaxis" era, 2012 to 2017.

**Results:** The study identified 42 patients with hemophilia who underwent 46 elective orthopaedic procedures from January 2004 to February 2017. Of these patients, 31 (74%) had severe hemophilia, 5 (12%) had moderate hemophilia, and 6 (14%) had mild hemophilia. The proportion of patients with severe hemophilia was the same in the early prophylaxis era and the transition era. However, in the established prophylaxis era there was a decrease of more than 30% in the proportion of patients with severe hemophilia. Knee, elbow, and ankle procedures were common in all three eras, with knee procedures predominating in the early era (48% of surgeries) and ankle procedures

predominating in the established era (60% of surgeries). Coagulation factor utilization changed from the early prophylaxis era to the established era, decreasing by 35% for knee procedures and by 44% for ankle procedures. Comparison of arthroscopic and open procedures over the three eras revealed that 27% less factor VIII on average was required for arthroscopic procedures in both the early and transition eras, and 10% less in the established era. The median hospital length of stay for knee arthroplasty patients with hemophilia ranged from 4 to 7 days over the three eras, while the median stay for hip arthroplasty patients declined over the three eras from 7 to 3 days. Postsurgical complications were associated with 10 out of 46 procedures. No thrombotic complications occurred and no coagulation factor inhibitors developed.

**Conclusions:** Over the study period orthopaedic procedures for hemophilia patients shifted from mainly knee surgeries to mainly ankle surgeries, and since 2012 a larger proportion of patients have had mild to moderate rather than severe hemophilia. Centralization of care has allowed for better communication and monitoring among the surgical and hematology teams in BC and resulted in a reduction in coagulation factor VIII utilization per case without untoward surgical complications.

Reductions in both coagulation factor utilization and hospital length of stay have contributed to the cost-effectiveness of treatment. Study limitations included small sample size, inconsistent data collection, and a lack of patient-reported outcomes. Future studies might focus on expanding the database to incorporate more outcome data from patients and data from other centres and provinces.

## Background

Hemophilia patients, especially those with severe or moderately severe disease, are at risk of developing arthropathy related to recurrent hemarthrosis.<sup>1,2</sup> The most commonly affected joints are the knees, ankles, and elbows.<sup>1</sup> Arthropathy can result in major morbidity, including chronic joint pain, loss of joint function, and long-term disability.<sup>2</sup> Orthopaedic surgical intervention can include joint debridement, joint replacement, and arthrodesis.<sup>3</sup>

Patients with hemophilia undergoing orthopaedic surgery have less satisfactory outcomes than patients without hemophilia undergoing similar procedures.<sup>1,3</sup> As well, hemophilia patients can be at high risk for surgical complications when co-infected with HIV and/or hepatitis C.<sup>4</sup> Despite this, there is little information in the literature on the proportion

of hemophilia patients experiencing surgical complications with orthopaedic foot and ankle reconstruction, and a lack of BC experience regarding complications in lower extremity arthroplasty and fusion.

During the mid-2000s the approach to adult hemophilia care in Canada changed significantly to include preventive coagulation factor replacement therapy given in the home—an approach that decreased rates of joint bleeding over the following decade. Starting in 2004 adults with significant arthropathies began using coagulation factor prophylaxis. By 2012 this approach was used by over 80% of BC patients. By 2017 coagulation factor prophylaxis was the established approach.

A study of patients in BC was proposed to compare management and surgical outcomes from 2004 to 2017 as the approach to hemophilia care changed.

## Methods

Data were extracted retrospectively from the clinical charts and electronic medical records of patients with hemophilia who underwent elective orthopaedic surgery and had follow-up through the Adult Bleeding Disorders Program of BC (also known informally as the provincial hemophilia program) from January 2004 to February 2017.

Before 2004 orthopaedic surgery for adults with hemophilia was performed in a variety of BC centres. After the hemophilia program moved to St. Paul's Hospital in 2004 most cases were managed by a team of orthopaedic surgeons and other specialists in accordance with published guidelines.<sup>5</sup>

Study subjects were adult orthopaedic surgery patients with mild to severe factor VIII deficiency (hemophilia A) or factor IX deficiency (hemophilia B).

The primary outcomes considered were type of hemophilia and severity, type of orthopaedic surgery performed (open or arthroscopic

procedure), joints involved (knees, ankles, elbows, or others), coagulation factor utilized (VIII or IX), hospital length of stay (LOS), and any surgical complications.

Hemophilia cases were classified as mild, moderate, or severe according to the level of coagulation factor VIII or IX activity in plasma. Mild hemophilia was defined as 5% to 40% of normal activity, moderate hemophilia as 1% to 5% of normal activity, and severe hemophilia as less than 1% of normal activity.

Knees, ankles, and elbows were considered hemophilia index joints. Hips and shoulder were considered non-index joints.

Data were collected for coagulation factor VIII and IX utilization (u/kg) from the preoperative dose

to the postoperative day 14 dose.

Hospital LOS data were collected for all patients, but only LOS data from the knee and hip arthroplasty cases were compared to data from the Canadian Joint Replacement Registry (CJRR),<sup>6</sup> as other joint groups are not included in the CJRR.

Surgical complications were defined as unexpected postoperative events that may have altered the course of management for the patient. These included bleeding, coagulation factor inhibitor development, infections, thrombotic events, and prolonged hospital stay. Early post-surgical bleeds were defined as those occurring 0 to 14 days after surgery, while delayed bleeds were defined as those occurring 15 days or longer after surgery.

Outcomes were compared for three eras: the “early prophylaxis” era, 2004 to 2009; the “transition to prophylaxis” era, 2010 to 2012 (use of prophylaxis increasing but not yet standard); and the “established prophylaxis” era, 2012 to 2017.

The study received ethics approval from the University of British Columbia and the Providence Health Care Research Institute.

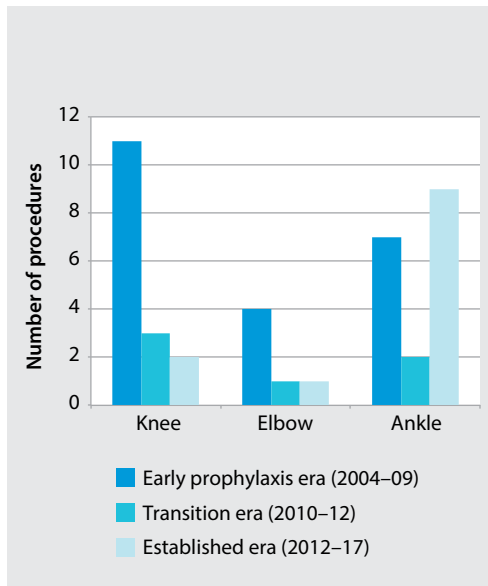
**Hemophilia patients, especially those with severe or moderately severe disease, are at risk of developing arthropathy related to recurrent hemarthrosis.**

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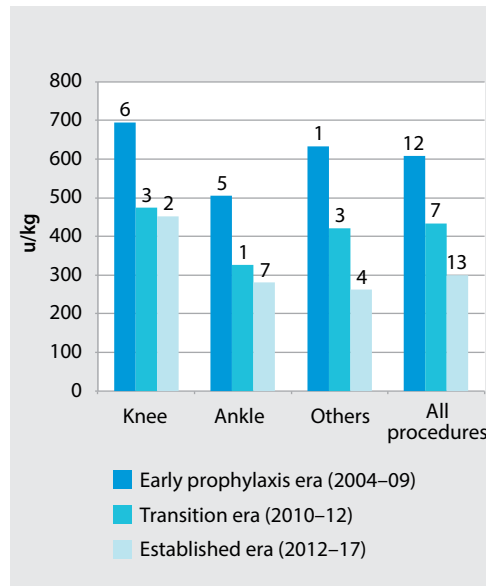
*Mr Hosseini is a medical student at the University of British Columbia, class of 2020. Ms Squire is the practice consultant, interdisciplinary, at Providence Health Care. At the time this article was written she was a physiotherapy specialist with the Adult Bleeding Disorders Program of BC. Dr Younger is an orthopaedic surgeon and director of foot and ankle research at St. Paul's Hospital. He is also a professor in the Department of Orthopaedics at UBC and head of the Division of Distal Extremities. Dr Jackson is medical director of the Adult Bleeding Disorders Program of BC, a hematologist at St. Paul's Hospital, and a clinical associate professor in the Division of Hematology at UBC.*

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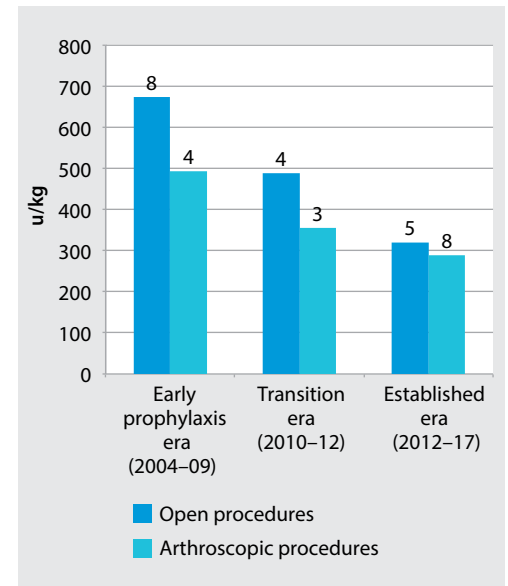
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**FIGURE 1.** Elective orthopaedic procedures performed in three eras of study period by joint type.



**FIGURE 2.** Comparison of factor VIII utilization (preoperative dose to postoperative day 7 dose) per joint procedure in three eras of study period. Number of procedures listed above each column.



**FIGURE 3.** Comparison of average Factor VIII utilization (preoperative dose to postoperative day 7 dose) per joint procedure for open and arthroscopic procedures in three eras of study period. Number of procedures listed above each column.

**Results**

The chart and record review identified 42 patients with hemophilia who underwent 46 elective orthopaedic procedures from January 2004 to February 2017. The mean age of subjects at the time of surgery was 45 years. The number of procedures by era was 23 (2004 to 2009), 8 (2010 to 2012), and 15 (2012 to 2017), and all subjects were male.

**Hemophilia severity**

The review found 31 patients (74%) had severe hemophilia, 5 patients (12%) had moderate hemophilia, and 6 patients (14%) had mild hemophilia. Of the patients with severe disease, 26 had factor VIII deficiency and 5 had factor IX deficiency.

The proportion of patients with severe hemophilia was the same in the early prophylaxis era and the transition era. However, in the established era there was a decrease of more than 30% in the proportion of patients with severe hemophilia, indicating that a larger proportion of patients with mild to moderate hemophilia have been treated since 2012.

**Types of procedures**

Knee, elbow, and ankle procedures were

common in all three eras [Figure 1], with knee procedures predominating in the early era (48% of surgeries) and ankle procedures predominating in the established era (60% of surgeries). A total of six other procedures were performed from 2004 to 2017, including four hip, one shoulder, and one ankle joint soft-tissue surgery.

**Coagulation factor utilization**

While factor VIII and factor IX were both used during the study, factor IX utilization data in each era were not compared because of small sample sizes.

Factor VIII utilization was considered to include doses (u/kg) used for prophylaxis and/or bleeds from the preoperative period to postoperative day 7. Utilization changed from the early prophylaxis era to the established era, decreasing by 35% for knee procedures and by 44% for ankle procedures. Overall, knee procedures required more factor VIII than surgeries for other joints [Figure 2].

Factor VIII utilization was compared for two periods: the preoperative to postoperative day 7 period and the postoperative day 8 to 14 period. However, because postoperative day 8 to 14 data were not consistently available for

the early and transition eras, we were not able to determine how much factor VIII was administered in the two periods for these eras. We did determine that in the established era almost double the amount of factor VIII was used in the preoperative to postoperative day 7 period.

A comparison of arthroscopic and open procedures over the three eras revealed that 27% less factor VIII was used on average in arthroscopic surgeries in both the early prophylaxis and transition eras. Similarly, 10% less factor VIII was required on average for arthroscopic procedures than for open procedures in the established prophylaxis era [Figure 3].

**Hospital length of stay**

The median LOS for knee arthroplasty patients with hemophilia ranged from 4 to 7 days over the three eras. The median LOS for hip arthroplasty patients declined over the three eras from 7 to 3 days. These findings were similar to those in the Canadian Joint Replacement Registry (CJRR),<sup>6</sup> except for the LOS of 7 days for knee arthroplasty in BC in the transition era compared with an LOS of 4 days reported by the CJRR [Table 1].

The median LOS for arthroscopic procedures was lower than for open procedures in all

three eras. The median LOS for open procedures ranged from 3 to 6 days, while the LOS for arthroscopic procedures ranged from 1 to 2 days [Table 2].

**Postsurgical complications**

Postsurgical complications were associated with 10 out of 46 procedures performed in the study period. These included early bleeds (2), delayed bleeds (2), infection (1), wound healing complication (1), and other minor complications such as extreme pain (1), joint non-union (1), and stiff postsurgical joint (2). No thrombotic complications occurred and no coagulation factor inhibitors developed. In addition, no surgical revisions or repeat surgeries were required for any of the 46 procedures.

One of the early bleeds occurred on postoperative day 1 of an open total elbow replacement. This was quickly identified and required additional coagulation factor VIII for management. The second case of postsurgical early bleed occurred on postoperative day 5 of an open total hip replacement and did not require

additional coagulation factor replacement but resolved spontaneously.

The first of the two delayed bleeds occurred 7 to 8 weeks after an open total knee replacement, and the second was a 10-week postoperative spontaneous ankle bleed following an arthroscopic ankle synovectomy and joint debridement procedure.

**Conclusions**

Orthopaedic procedures for adult hemophilia patients in BC have shifted from mainly knee surgeries to mainly ankle surgeries over the past 13 years, and patients with mild to moderate hemophilia now represent a larger proportion of cases than they did before 2012.

Study findings also suggest that centralization of care has allowed for better communication and monitoring among the surgical and hematology teams in BC and resulted in a reduction in coagulation factor VIII utilization per case without untoward surgical complications. Hospital LOS data for BC cases were found to be similar to national LOS data, with

LOS rates in general declining over time. Reductions in both coagulation factor utilization and hospital length of stay contribute to the cost-effectiveness of treatment.

**Increase in ankle procedures**

Although few studies have described recent trends in musculoskeletal procedures in the hemophilia population, the literature does reflect the clinical observation that procedures for the knee, elbow, and ankle (index joints) are most common, while procedures for the hip, shoulder, and wrist are less common.<sup>7,8</sup> Weight bearing is known to make the ankle and knee joints prone to trauma, and it is hypothesized that walking initiates hemarthrosis and leads to subsequent synovitis. The attempt of the synovium to eliminate the excess blood results in synovial inflammation and proliferation and creates a vicious cycle of hemarthrosis-synovitis-hemarthrosis, which eventually leads to chronic inflammation and joint arthropathy.<sup>8</sup> This was confirmed in a study by Gamble and colleagues, which identified the ankle as the first site of bleeding in early childhood. Because of continuous trauma with participation in activities, the ankle is the most common site of hemophilic arthropathy in the second decade of life.<sup>9</sup>

When Jackson and colleagues studied a large cohort of adult Canadian hemophilia patients, they found that the high prevalence of ankle arthropathy was not reduced in younger adults who used coagulation factor prophylaxis compared with older adults, whereas the prevalence of elbow and knee arthropathy was significantly reduced.<sup>10</sup> Thus it can be expected that ankle procedures will continue to predominate in future unless better methods of bleeding prevention are implemented.<sup>11</sup>

**Reduction in severity**

This study found a decrease in the proportion of hemophilia patients with severe disease undergoing orthopaedic procedures in the established era (2012 to 2017) compared with the two earlier eras (2004 to 2009 and 2010 to 2012). This could be largely due to higher rates of prophylaxis in recent years. With sufficient prophylaxis, patients' bleeding phenotype is milder, which would reduce, although not

**TABLE 1.** Median length of stay (LOS) in hospital for BC knee and hip arthroplasty patients with hemophilia compared with national LOS data from Canadian Joint Replacement Registry (CJRR), 2004 to 2017.

	LOS for total knee arthroplasty		LOS for total hip arthroplasty	
	BC	CJRR	BC	CJRR
<b>2004–2009</b> Early prophylaxis era	5 days	4 days	7 days	5 days
<b>2010–2012</b> Transition era	7 days	4 days*	—	4 days*
<b>2012–2017</b> Established era	4 days	3 days†	3 days	4 days†

\*CJRR median value for 2011–2012, †CJRR median value for 2013–2014

**TABLE 2.** Median length of stay (LOS) in hospital for BC patients with hemophilia undergoing open and arthroscopic joint surgery, 2004 to 2017.

	LOS for open surgery	Number of open procedures	LOS for arthroscopic surgery	Number of arthroscopic procedures
<b>2004–2009</b> Early prophylaxis era	5 days	14	2 days	6
<b>2010–2012</b> Transition era	6 days	4	1 day	4
<b>2012–2017</b> Established era	3 days	6	2 days	9



totally prevent, associated musculoskeletal complications of hemophilia.<sup>10,12</sup> This may not have been the case in the first two eras of our study, when on-demand treatment in response to bleeding was more common for our patients. In the established era, eight surgical patients with severe disease were using on-demand treatment and as a result can be expected to develop arthropathy requiring intervention. Two of these patients had undergone orthopaedic procedures in previous eras of the study period.

#### Reduction in factor VIII utilization

The observed reduction in coagulation factor VIII utilization over the study period largely resulted from alignment with international guidelines<sup>5</sup> and an understanding that higher doses provoke coagulation factor inhibitor development and postoperative thrombotic events. The high cost of the coagulation factor concentrates was also a factor in reducing utilization. This study provides reassuring outcome data to support the safety of reducing factor VIII utilization with close monitoring and follow-up from coordinated multidisciplinary teams.

#### Reduction in LOS

The median hospital length of stay for BC hemophilia knee arthroplasty patients ranged from 4 to 7 days over the three eras, while the LOS for hip arthroplasty patients declined over the years from 7 to 3 days. Despite these findings being similar to those reported in the CJRR,<sup>6</sup> no reliable conclusions can be made based on these given the small sample size for certain groups. It is plausible that an extra day or two of admission is necessary to ensure patients receive the intended coagulation factor replacement, particularly for patients with less severe disease who are not accustomed to administering their own replacement therapy. However, the use of prophylaxis in the later eras, as well as less invasive surgical procedures and more advanced rehabilitation programs, are likely

contributing factors in the reduction of postoperative hospital LOS for hemophilia patients. This can be seen in the shorter median LOS for arthroscopic procedures that ranged from 1 to 2 days compared with the longer median LOS of 3 to 6 days for open procedures.

A study by Pakzad and colleagues in 2014 found patients with open ankle fusions had hospital stays 1.36 times longer than patients who had undergone arthroscopic ankle fusions, and identified a similar trend for total ankle replacements compared with arthroscopic ankle fusions.<sup>13</sup> These differences are largely related to reduced postoperative pain after arthroscopic procedures compared with open procedures, which contributes significantly to shorter postoperative hospitalization.<sup>14,15</sup> In addition, arthroscopic procedures are known to contribute to significant cost-savings over open procedures owing to this shorter hospitalization time and significantly less intraoperative blood loss.<sup>14</sup>

#### Thromboembolism risk

In patients without hemophilia, orthopaedic procedures such as knee arthroplasty are associated with an increased risk of venous thromboembolism when thromboprophylaxis is not used. In patients with hemophilia, the risk of bleeding means that most centres do not use thromboprophylaxis in tandem with coagulation factor replacement therapy.<sup>16</sup> The Adult Bleeding Disorders Program of BC does not use thromboprophylaxis for hemophilia cases, and it is reassuring that in our experience over 13 years no cases of clinical thromboembolism were observed.

#### Study limitations

One limitation of this study was small sample size for certain groups, which is largely due to the rarity of hemophilia itself. Another limitation was inconsistent data collection for certain outcomes. The database we relied on did

not consistently and continuously track factor VIII and factor IX utilization for postoperative days 8 to 14 (after hospital discharge). As well, the study did not evaluate patient-reported outcomes.

Future studies might focus on expanding the database to incorporate more outcome data from patients and other centres and provinces. This will create a larger and more robust database that can provide readily accessible results to physicians and surgeons managing hemophilia patients.

#### Summary

This retrospective study demonstrates that over the past 13 years orthopaedic procedures for adult hemophilia patients in BC shifted from mainly knee surgeries to mainly ankle surgeries. Our review provides a long-term profile of these patients and shows the adequacy of previous and current management strategies. We have learned that having a dedicated, specialized hemophilia treatment centre with the surgical team in close proximity has allowed for better communication and support of patients throughout the management process, and better and more cost-effective care of BC hemophilia patients overall. ■

#### Acknowledgments

The authors acknowledge the support of the Bayer-UBC Bleeding Disorders Collaboratory and the Centre for Blood Research Summer Studentship Program. We would also like to thank Dr Julius Elefante and Ms Xiu Qing (Jenny) Wang for their work in the initial stages of the project. The authors are grateful to the late Dr Linda Vickars for her initial vision for this project and we dedicate this article to her memory.

#### Competing interests

Dr Younger is a consultant for Wright Medical Group N.V., Acumed, Zimmer Biomet, ConMed Linvatec, Bioventus, Axolotyl Biologix, and Cartiva. He receives royalties for a book published by Lippincott, and institutional support from Wright Medical Group N.V., Bioventus, Acumed, Zimmer Biomet, Arthrex, DePuy Synthes, and Cartiva. He is a partner in the Cambie Surgery Centre, the Specialist Referral Clinic, and the Footbridge Centre for Integrated Orthopaedic Care. Regarding the

**Having a dedicated, specialized hemophilia treatment centre with the surgical team in close proximity has allowed for better communication and support of patients.**

study described in this article, Dr Younger received no fees or institutional support from any of the companies named. The other authors of this article have no competing interests to declare.

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