Fractures needing orthopaedic surgery in haemophilic patients: long-term experience of a dedicated team at a single institution

Christian Carulli 1, Matteo Innocenti 1, Tommaso Porciatti 1, Niccolò Castellani 1, Lisa Pieri 2, Roberto Civinini 1

1 University of Florence, Orthopaedic Clinic CTO, Florence, Italy; 2 University of Florence, Center of Hemorrhagic Diseases and Bleeding Disorders, Florence, Italy.

ABSTRACT

Purpose: Haemophilia is a rare inherited X-linked bleeding disorder associated with various levels of coagulative factor VIII (type A) or IX (type B) deficit. Persons with haemophilia (PWH) can be affected by trauma and fractures just like the general population. Due to their bleeding disorder, PWH usually need specific multidisciplinary management, from the emergency room to the operating theatre, in order to limit severe complications. Worldwide, there are few specialized orthopaedic centres dedicated to the management of PWH. The purpose of this paper is to report our experience on the management of fractures in PWH by a multidisciplinary team at a single institution.

Methods: In the period 2000-2017, 19 PWH were treated in our centre: 15 with haemophilia type A, 4 with type B. Patients were classified according to fracture site (lower extremities: 16 patients; upper extremities: 3) and haematological treatment (secondary prophylaxis: 15 patients; “on demand” regimen: 4). All patients were treated by the same multidisciplinary team of orthopaedic-haemophilia specialists. They received specific haematological protocols during the peri-operative period according to their characteristics. All patients were also evaluated using the Numeric Rating Scale and Short Form-36 preoperatively and at specific times postoperatively.

Results: All patients enrolled in the study had a minimum of 2 years of follow-up (mean 8.5 yrs). No patient showed early postoperative complications; no major bleeds or deep venous thromboembolisms were recorded. Satisfactory fracture healing and functional recovery were reported by all the patients except for three, who presented symptoms or functional impairments at mid-term, needing further surgery.

Conclusion: Fractures in PWH are uncommon and their management requires close cooperation with haemophilia specialists. Through multidisciplinary treatment it is possible to manage these challenging conditions in a safe manner and with a low rate of complications.

KEYWORDS

Haemophilia, fractures, periprosthetic fractures, inhibitors, knee arthroplasty, hip arthroplasty, revision, loosening, osteoporosis

Introduction

Haemophilia is the most common bleeding disorder, associated with a high risk of haemorrhages due to deficiency of coagulative factor VIII (haemophilia A) or IX (haemophilia B) [1]. Until a few decades ago, it was considered a life-threatening disease, particularly in cases with bleeding involving noble organs. The modern haematological prophylaxis, with periodic infusions of deficient factors starting from childhood, has dramatically reduced the most severe complications and consequently improved the quality of life of persons with haemophilia (PWH) [2]. Nowadays, haemophilia is mostly associated with musculoskeletal alterations [3]. The most frequent complication is the so-called haemophilic arthropathy [4], related to frequent bleeding in specific joints. The knee, ankle, elbow and, less frequently, the hip, shoulder and wrist joints are the ones most commonly affected, and they are referred to as “target joints” [5-7]. Intra-articular bleedings induce an irreversible and progressive alteration of the involved joints, leading to secondary arthritis, usually in very young subjects, with significant functional sequelae. Mild to moderate cases may be successfully treated with conservative or minimally invasive approaches [5-7] whereas the most severe ones can only be treated with major orthopaedic surgery, typically joint replacement [8-13].

Like anyone, PWH can be affected by trauma and fractures. Compared with subjects without haemorrhagic diseases, PWH usually need specific management, from the emergency...
room to the operating theatre, in order to limit haemorrhages and more severe complications, particularly in the case of long bone, chest or pelvic fractures. Moreover, over recent decades many PWH have undergone joint arthroplasty at very young ages: in such patients, periarticular fractures (defined as fractures of bones near a joint that has previously undergone replacement) are not just challenging (as they are in non-haemophilic subjects, too), but often constitute real emergencies. Unfortunately, periarticular fractures in PWH are associated with severe loosening and bone loss, and often the treatment is not a simple open reduction and internal fixation, but revision or limb salvage surgery.\(^{14,15}\)

Over recent decades, development and advances have greatly influenced the management of fractures in haemophilia. In the 1950s, the period that saw the introduction of the first factor concentrates, the treatment of fractures in PWH was substantially empirical and associated with limited median survival (about 30 years of age)\(^{16}\). PWH at that time were discouraged from practising sport or high-impact activities, to limit the risk of trauma and sequelae such as contractures, stiffness, arthropathy, muscle ossifications and ankylosis. Following development of this treatment and after the introduction of cryoprecipitates at the end of the 1970s, the quality of life and treatment of PWH dramatically improved and some selected sports and other activities became feasible for these patients\(^{17}\). In recent years, thanks to a growing interest in the dual energy X-ray absorptiometry (DEXA) technique, studies have revealed a coexistence of decreased bone mineral density and osteoporosis in PWH together with muscle hypotrophy, joint stiffness, and malalignment\(^{17}\). It is to date unclear whether this condition represents only a theoretical or an actual fracture risk in this population\(^{17-19}\). On the other hand, haemophilic subjects today, thanks to further improvements in their health status, are more likely to engage in physical activity and sport, and there can therefore be little doubt that they are at increased risk of injury-related fractures\(^{20}\). Finally, the outcome and prognosis of fractures in PWH have positively changed with the introduction of recombinant replacement therapy along with their multidisciplinary management, ensuring safety and success of surgical treatments. However, fractures in haemorrhagic syndromes are still a critical clinical issue\(^{21}\).

The present report describes the long-term experience of fracture management in haemophilic subjects by a multidisciplinary team at a single institution.

### Materials and methods

Between 2000 and 2016, 26 haemophilic subjects were treated for fractures at the authors’ institution. Five patients were excluded from the analysis because they were managed conservatively, and a further two because they were followed up for less than the minimum of one year. The final study population thus comprised 19 PWH. Eighteen were males, and one was a female with acquired haemophilia. Fifteen (14 men, 1 woman) were affected by mild to severe haemophilia A, and 4 by mild to severe haemophilia B. Their mean age was 37.4 years (range: 16-77). Sixteen fractures involved the lower limbs, and three the upper limbs. Fifteen patients were following a secondary prophylaxis regimen with clotting or recombinant factors at the time of trauma, while four of them reported that they received “on-demand” treatment (factor or clotting infusions only in the event of bleeding or trauma). Two patients with severe haemophilia A also had high-title inhibitors (alloantibodies against the infused factor able to neutralize its clotting activity). Three patients presented co-infections (HIV + HCV were found in two patients, and HBV in one). The demographic data and characteristics of the patients are reported in Table I.

In the emergency department, all the patients underwent a standard radiological study for assessment of the fracture; in 9 cases a CT scan was also performed (articular and periarticular fractures). In all cases, the surgery was performed by the same orthopaedic team, who were part of the institution’s multidisciplinary team of orthopaedic-haemophilia specialists. Haematology protocols consisting of boluses of 30 to 60 U/kg of FVIII/IX concentrate, plasma or rDNA-derived products, were administered according to the characteristics of the patients. On the day of the operation, a preoperative load of factor was administered 60 minutes before surgery and at specific intervals after surgery, throughout the rehabilitation period. Tranexamic acid was used in all patients at dosages of 2 to 3 g/day just before surgery and in the postoperative period. Based on the pharmacokinetic properties of the haematologic protocols, no prophylaxis for deep venous thromboembolism (DVT) was proposed. A continuous infusion of saline solution

<table>
<thead>
<tr>
<th>TYPE OF HAEMOPHILIA AND CO-INFECTIONS</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilia A (^a)</td>
<td>15</td>
</tr>
<tr>
<td>Haemophilia B (^b)</td>
<td>4</td>
</tr>
<tr>
<td>HIV (^c)</td>
<td>2</td>
</tr>
<tr>
<td>HBV (^d)</td>
<td>1</td>
</tr>
<tr>
<td>HCV (^e)</td>
<td>2</td>
</tr>
</tbody>
</table>

\(^a\) one female with acquired haemophilia; \(^b\) factor or clotting infusions only in the event of bleeding or after a trauma; \(^c\) clotting or recombinant factors at the time of trauma.
was maintained to keep the central venous catheters open (always used in PWH with inhibitors). On the other hand, DVT prophylaxis was administered in a case of mild deficiency of coagulative factor IX. Postoperative major bleeding was defined as unexpected or prolonged bleeding causing haemodynamic instability (a reduction in haemoglobin level of 20 g/L-1 - 1.24 mmol/L-1): in the event of further reduction of the haemoglobin level, packed red cell transfusions were provided. After surgery, all patients underwent ultrasound examination for the detection of DVTs. All patients were also evaluated by means of specific clinical scores, namely the Numeric Rating Scale (NRS) and Short Form-36 (SF-36)\textsuperscript{[22-23]}. The same scores along with X-rays were recorded postoperatively at planned intervals.

**Results**

The mean follow-up was 5.5 years (range: 2-17). All patients were successfully treated and followed-up until two years after fracture healing. No patient showed early postoperative complications or infections: specifically, no major bleeding and no DVTs were recorded after surgery. All the subjects underwent postoperative rehabilitation as hospital inpatients, during which time they were evaluated daily by the multidisciplinary team. NRS and SF-36 scores improved after the surgical fixation and healing of fractures (Table 2). All the patients except three obtained a satisfactory functional recovery. These three experienced symptoms or functional impairments at mid-term (two to three years after surgery) and needed further surgery (Fig. 1).

One of these three, a patient affected by haemophilia A with inhibitors, came to the emergency department with a severely displaced femoral shaft fracture sustained in a sporting accident (skiing); the patient’s haemoglobin value at the first presentation was 4.2 mg/dl: operated on urgently, he had critical anaemia with cardiac failure during open reduction and fixation, so the team decided in extremis to switch from an intramedullary fixation to an unconventional fixation with screws and temporary cast. The patient was then sent to the intensive care unit, where fortunately he survived. Thereafter, he refused further orthopaedic treatments to achieve a definitive fixation and healed with an asymptomatic malalignment of the femur. Given the haemophilic arthropathy in the ipsilateral hip, knee and ankle, two years later the patient reported the onset of pain and functional limitation, and underwent a total knee arthroplasty (TKA), which was successfully performed leading to clinical improvements.

Another patient, with haemophilia A and inhibitors and a previous ipsilateral TKA, sustained a periprosthetic fracture of the femur. He underwent emergency open reduction and long plate fixation, considering the initial stability of the femoral component. After 5 months, despite the healed fracture, he began to experience symptoms of loosening of the femoral component. Thus, he underwent a new surgical procedure consisting of plate removal and revision of the femoral component with a new cementless long-stem femoral prosthesis. After 5 years, the patient is still satisfied and reports good lower limb functional ability (Fig. 2).

Finally, a very young haemophilic subject had an open displaced distal tibial fracture and underwent an urgent surgery with debridement and external fixation. Even though the fracture healed (the external fixation device was removed after 5

**Table II Surgical procedures.**

<table>
<thead>
<tr>
<th>LOWER LIMB FRACTURES</th>
<th>N. OF PROCEDURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRIF a with intramedullary nail c</td>
<td>6</td>
</tr>
<tr>
<td>ORIF b with plate and screws</td>
<td>5</td>
</tr>
<tr>
<td>External fixation</td>
<td>2</td>
</tr>
<tr>
<td>Joint replacement</td>
<td>3</td>
</tr>
</tbody>
</table>

\textsuperscript{a} closed reduction & internal fixation; \textsuperscript{b} open reduction & internal fixation; \textsuperscript{c} one patient, due to undergo emergency intramedullary fixation, was switched in extremis to an unconventional fixation with screws and cast due to intra-operative cardiac arrest

---

Figure 1 A 42-year-old patient affected by severe haemophilia A and HIV/HCV infection suffered a non-displaced tibial shaft fracture. He was initially treated by a cast in another hospital, with early signs of delayed union (a). Due to the very narrow tibial canal (5 mm) (b), neither standard nor pediatric nails were suitable: an external fixation was performed (c). After 5 months, the fracture was well healed and the fixator was removed (d).
months), his previous ankle arthropathy showed a severe worsening: the patient, at the age of 18 years, already presented an ankle ankylosis, but reported high satisfaction in spite of the ROM limitation. At the latest follow-up, no other complaints have been reported.

**Discussion**

Haemophilia is nowadays a less challenging disease than in the past, and affected subjects can enjoy a better quality of life. However, fractures may be challenging conditions to treat in PWH, particularly cases with severe displacement, exposure and periprosthetic fractures. Such conditions are more complicated to treat in facilities without dedicated teams and in PWH with inhibitors.\(^\text{[1,2]}\). Conservative management of non-displaced fractures does not seem to be any more challenging in haemophilic patients than it is in subjects with normal coagulation parameters. On the other hand, displaced fractures as well as long-bone or periprosthetic fractures can show a high tendency to bleed and be associated with significant rates of complications. In such cases, immediate or urgent management should be performed by dedicated multidisciplinary teams. Perioperative tailored haematologic regimens consisting of intermittent infusions of FVIII or IX concentrates, adequate surgical procedures, and early supervised rehabilitation protocols are mandatory to allow fracture healing and to ensure efficient bleeding control.\(^\text{[24]}\).

However, fractures in PWH are not common clinical events,\(^\text{[1]}\) which is at odds with recent findings highlighting the status of osteopenia/osteoporosis reported for groups of subjects: thus, the impact of the decreased bone mineral density in PWH is still not understood.\(^\text{[17–20,25–27]}\)

Certainly, PWH with haemophilic arthropathy are affected by a chronic condition characterized by muscle hypotrophy, joint stiffness, and malalignment. On the other hand, the quality of life of these patients, in terms of the types of sport they participate in and their level of daily activities, has improved in recent years. Why the combination of factors such as osteoporosis, joint functional impairment, and increased activity does not correspond to an increase in the number of fractures in these patients is still unclear.

Moreover, the presence of target joints next to the fracture site alters the final clinical outcome. Indeed, even though the fracture has healed, several patients still need further joint surgeries to correct the potential new imbalance caused by even minimal malalignment or arising during the functional recovery period itself.\(^\text{[14,28]}\)

A particular emerging problem is that of periprosthetic fractures, which carry further risks in terms of functional limitations, given the high probability of loosening of the prosthetic components. The indications for surgical treatment of these fractures are the same in PWH as in non-haemophilic patients, but several other variables, such as the level of arthropathy, bone quality, and limb alignment should be considered in PWH.\(^\text{[13,15,16]}\)

According to the literature, surgical interventions in PWH are associated with an increased risk of intra- and postoperative major bleeding, wound healing disorders, and postoperative infections.\(^\text{[29–31]}\). Due to these considerations and the fact that, worldwide, dedicated teams are sporadic, very few experiences have been reported in recent years. In a recent study, Strauss and colleagues\(^\text{[32]}\) found no substantial difference in fracture management outcomes between haemophilic and non-haemophilic subjects when patients are followed by a dedicated multidisciplinary team.

Caviglia\(^\text{[28]}\) et al.\ reported the largest series of fractures in PWH published to date. They treated 151 fractures in 141 patients: 121 subjects by a conservative strategy, and the rest by internal fixation. In the follow-up period, they found 40 cases of malalignment in the non-operated group, and 3 cases in the operated group. Moreover, they recorded a shorter fracture consolidation time and better anatomical alignment in patients treated by internal fixation than in those receiving conservative treatment.

Ghosh and colleagues\(^\text{[25]}\) reported a series of 20 cases of fractures in PWH from the Comprehensive Haemophilia Care Center...
Center in Mumbai. None of these patients was on a prophylactic factor replacement regimen. In many of these patients, bleeding was treated by symptomatic measures, such as immobilization, ice application, and analgesics. Bone density assessment by DEXA was performed in six of these patients. Osteoporosis of the lumbar spine was found in all the patients, and osteoporosis of the hips in 2 (four patients had osteopenia). The average fracture healing time was 6.5 months (4–18 months), much higher than in healthy individuals with the same fracture.

Gallagher et al.\textsuperscript{17} found a mean Z-score of -0.92 in children with severe haemophilia, confirming that early weight-bearing exercises are crucial for the development of adequate bone mass in childhood.

The present study has some limitations. The limited number of cases makes it impossible to perform a statistical analysis: however, as mentioned before, haemophilia is a rare disease, thus a small series was to be expected, as was the shortage of published literature on this topic. Another limitation concerns the poor standardization of orthopaedic management of fractures, particularly periprosthetic fractures. However, given the very few haemophilia centres present worldwide, orthopaedic approaches have to be tailored to the specific circumstances, specifically the timing of surgery with respect to the timing of patients’ presentation at the hospital.

Finally, fractures in PWH remain uncommon events, in spite of these individuals’ low mean BMD compared with the general population. In short, these conditions are definitely difficult to address promptly and correctly in non-specialized centres.

Conclusions

Despite the improvements in the management of haemophilia and its related clinical issues, severe or displaced fractures in PWH continue to be demanding. This specific category of orthopaedic patients should receive urgent surgical treatment in dedicated facilities in order to ensure good outcomes and low rates of complications. Given the frequent condition of osteoporosis in PWH, further exploration of their low levels of bone density is required in order to achieve better knowledge of their present low risk of fractures.

References

23. Patel, Alpesh A. MD; Donegan, Derek MD; Albert, Todd MD; The 36-Item Short Form, Journal of the American Academy of Orthopaedic Surgeons. 2007;15(2), 126-134.

Fractures management in haemophilia: experience of a dedicated team


21


Ethics approval and consent to participate: All patients accepted the proposed treatment and follow-up after adequate information and written consent. The study and follow-up, respecting the criteria of the Declaration of Helsinki, have been approved by Institutional Review Board of Azienda Ospedaliera Universitaria Careggi (AOUC) Department of Surgery and Translational Medicine. The Institutional Review Board accepted the proposal of the study, and all selected patients were properly informed before surgery about the treatment and follow-up visits after discharge.

Conflict of interest: The authors declare that they have no conflicts of interest.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

Acknowledgements: No acknowledgements.