

# Surgical management of hemophilic pseudotumor complicated by destructive osteoarthropathy

Jiliang Zhai, Xisheng Weng, Baozhong Zhang, Hui-ming Peng, Yan-yan Bian and Lei Zhou

Hemophilic pseudotumor gradually erodes bone and induces fracture or deformity, causing joint dysfunction or destructive osteoarthropathy. Reports about surgery for hemophilic pseudotumor complicated by destructive osteoarthropathy are scarce. The object of this study was to evaluate the results and complications of surgical management for patients of pseudotumor complicated by destructive osteoarthropathy. We retrospectively reviewed records from July 1996 to July 2013, and found eight patients with pseudotumor complicated by destructive osteoarthropathy. We recorded their demographic data, time of surgery, amount of blood loss and transfusion, bone union, and complications. Seven patients were diagnosed with hemophilia A and one with hemophilia B. The mean age at surgery was  $31.9 \pm 8.3$  years. Two of the eight underwent excision of the pseudotumor and metallic fixation, one had amputation, and five underwent autogenous or exogenous bone grafting and fixation with an absorbable screw. The median operating time was 170 min (135–315 min). The median amount of intraoperative blood loss was 1350 ml (100–4000 ml). The amount of red blood cells, plasma, and whole blood transfusion after surgery were 0–24 units, 0–2000 ml, and 0–4600 ml, respectively. After a median

follow-up of 75 months, the numbers of pseudotumor recurrence, fracture nonunion, coagulation factor inhibitor formation, and wound complications were one, one, two, and four, respectively. Surgery is an effective treatment for hemophilic pseudotumor complicated by destructive osteoarthropathy. However, the incidences of wound infection, coagulation factor inhibitor formation, hemophilic pseudotumor recurrence, and fracture nonunion are high. *Blood Coagul Fibrinolysis* 26:373–377 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

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Department of Orthopaedic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, China

Correspondence to Dr Xisheng Weng, Department of Orthopaedic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing 100730, China  
Tel: +86 010 6915 2810; e-mail: xshweng@medmail.com.cn

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## Introduction

Hemophilia is a hereditary hemorrhagic disease caused by a lack of coagulation factors. Hemophilic pseudotumor, also called hemophilic cyst, is a progressively enlarging cyst caused by recurrent bleeding from extra-articular bones or soft tissues. Untreated hemophilic pseudotumor may cause ossification and marginal calcification, often accompanied by bone erosion [1,2]. Hemophilic pseudotumors can be divided into proximal and distal patterns according to the anatomical site. Proximal pseudotumors often occur at the femur and pelvis. They commence in the soft tissues and then slowly but progressively erode the bone, presenting as a multilocular, painless, firm, and expanding mass that adheres to the deeper structures. Such masses occur more frequently in adults and do not respond to conservative treatment. They usually remain asymptomatic until pathological fractures occur [3,4]. We defined pathological fractures or lower limb deformities that cause severe loss of function as destructive osteoarthropathy.

Surgery is the most effective, thorough treatment for hemophilic pseudotumor complicated by destructive osteoarthropathy. There are multiple challenges, however,

such as atypical anatomy, abnormal bone structures, osteoporosis, and perioperative bleeding. The complication rates are high. Complications include pseudotumor recurrence, fistula formation, infection, inhibitor formation, internal fixation failure, and bone graft nonunion. Reports about surgery for hemophilic pseudotumor complicated by destructive osteoarthropathy are scarce. The purpose of this retrospective study was to follow up patients who underwent surgery for hemophilic pseudotumor complicated by destructive osteoarthropathy and evaluate the efficacy of surgical management and the complications associated with it.

## Materials and methods

### Patients and methods

Eight patients with hemophilic pseudotumor complicated by destructive osteoarthropathy who underwent surgical management from July 1996 to July 2013 in one hospital were enrolled in this study. All patients were men. Seven were diagnosed with hemophilia A and one with hemophilia B. Six were classified as having moderate hemophilia (<1% factor VIII:C or <5% factor IX:C). Two had mild hemophilia (>5% factor VIII:C). None of the patients tested positive for inhibitors against

coagulation factors. Three patients tested positive for hepatitis C and one for syphilis.

Among these eight patients, two underwent autogenous fibular grafting and fixation with an absorbable screw, two had internal metal fixation, one underwent amputation, and three had allografting and fixation with an absorbable screw. Among them, two were revision surgeries. The average age of these patients was  $31.9 \pm 8.3$  years (18–45 years). The average hospital stay was  $42.8 \pm 13.5$  days (19–64 days). The patients were followed up by telephone, or their outpatient clinic and medical records were reviewed. The median length of follow-up was 75 months (4–208 months) (Table 1).

#### Protocol for substitution of coagulation factors

Plasma coagulation factor VIII and factor IX concentrations were measured preoperatively to determine the perioperative coagulation factor substitution strategy. Patients with hemophilia type A were treated with plasma-derived or recombinant coagulation factor VIII (FVIII), and those with hemophilia B were treated with activated prothrombin complex. The coagulation factor was given 1 h preoperatively as a single bolus infusion. Additional coagulation factor was given if the procedure lasted more than 6 h after the first infusion. Concentrations of plasma coagulation and inhibitors were monitored on postoperative days (PODs) 1, 4, and 7. The coagulation factor dosage was adjusted to maintain peak factor levels of approximately 80% on the day of surgery, 60% on PODs 1–3, 40% on PODs 4–6, and 20–30% thereafter. Factor substitution was maintained until suture removal. Additional coagulation factors, blood transfusion, and/or antifibrotic drugs were administered depending on the swelling of soft tissues in the operative field, amount of postoperative drainage, and the hemoglobin level.

#### Surgical approach

Surgical management included removing the hemophilic pseudotumor, repairing the fracture, and correcting the bone deficit. Arterial enhanced computed tomography

was performed preoperatively to clarify the relation between the pseudotumor and surrounding vessels. Patients were in a supine or lateral position during the surgery. Pseudotumors were separated from surrounding normal tissue and resected as completely as possible. If the pseudotumors adhered to the surrounding tissue, the surface was incised and the occluded blood drained. Part of the cyst wall was preserved. The outer wall was then folded up to close the cyst cavity, secured by overlapping sutures, taking care to avoid damaging major vessels.

There are three principles to follow when dealing with hemophilia-associated fractures: stop the bleeding; maintain normal coagulation; and stabilize the fracture. Internal fixation is usually adopted, although external fixation has also been used when the condition of the soft tissue was poor [5]. Internal fixation can be accomplished with metal, autograft, or allograft fixation. In addition to the fixation, bone graft should be used to promote bone union. Casting may be used depending on the stability of the fracture.

#### Results

The median duration of the surgery was 170 min (135–315 min). The median amount of blood loss during the surgery was 1350 ml (100–4000 ml). The amount of red blood cells, plasma, and whole blood transfusion after surgery were 0–24 units, 0–2000 ml, and 0–4600 ml, respectively (Table 2).

One patient suffered from recurrent pseudotumor 13 years after the primary surgery for pseudotumor resection, autogenous fibula graft, and absorbable screw fixation. Radiography showed that the fracture had healed, but the FVIII inhibitor assay was positive. The recurrent pseudotumor was resected under FVII substitution without further recurrence. Another patient had tibial fracture union 1 year after external fixation and autogenous iliac bone graft and internal fixation. The other six patients had fracture union, without recurrence of the pseudotumor. Three patients had a wound infection after surgery, with two of them recovering after antibiotics. The third

**Table 1** General information of the patients with hemophilia pseudotumor

Case	Age (years)	Diagnosis	Surgery	Hospitalization (days)	Follow-up (months)
1	45	HA	Pseudotumor excision, fibula metallic internal fixation, and tibia external fixation	19	35
2	34	HA	Femur pseudotumor excision, allograft and absorbable screw fixation	64	95
3	33	HB	Femur pseudotumor excision, and metallic internal fixation	40	4
4	24	HA	Amputation in the thigh	48	55
5	18	HA	Femur pseudotumor excision, osteotomy, autogenous fibular graft and fixation with absorbable screw	36	107
6	26	HA	Femur pseudotumor excision, removal of intramedullary nail, allograft and absorbable screw fixation	60	96
7	34	HA	Femur pseudotumor excision, autogenous fibular graft and fixation with absorbable screw	40	208
8	41	HA	Femur pseudotumor excision, curettage at nonunion site, allograft and absorbable screw fixation	35	30

HA, hemophilia A; HB, hemophilia B.

**Table 2** Surgery and blood transfusion information of the patients with hemophilia pseudotumor

Case	Surgery	Time for surgery (min)	Intra-operative blood loss (ml)	Postoperative drainage (ml)	Blood transfusion		
					RBC (U)	Plasma (ml)	Total blood (ml)
1	Pseudotumor excision, fibula metallic internal fixation, and tibia external fixation	135	100	15	0	0	0
2	Femur pseudotumor excision, allograft and absorbable screw fixation	170	1100	1170	14	800	0
3	Femur pseudotumor excision, and metallic internal fixation	170	450	350	4	400	0
4	Amputation in the thigh	150	4000	200	24	2000	0
5	Femur pseudotumor excision, osteotomy, autogenous fibular graft and fixation with absorbable screw	165	1600	/	0	0	2200
6	Femur pseudotumor excision, removal of intramedullary nail, allograft and absorbable screw fixation	315	4000	200	21	2000	4600
7	Femur pseudotumor excision, autogenous fibular graft and fixation with absorbable screw	180	1100	350	4	400	0
8	Femur pseudotumor excision, curettage at nonunion site, allograft and absorbable screw fixation	180	2200	1300	22	800	0

RBC, red blood cell.

patient developed inhibitors against coagulation FVIII, and the wound remained unhealed even though activated prothrombin complex concentrate (APCC), antibiotics, and dressing changes were applied. Amputation was recommended, but the patient refused and is currently still undergoing dressing changes. Another patient had a wound exudate, but recovered after dressing changes.

## Discussion

The incidence of hemophilic pseudotumor is about 1–2% in patients with severe hemophilia [3,6] and up to 10% in those with inhibitors [3]. It may also occur in patients with mild and moderate hemophilia. There is no consensus about the fracture rate in hemophilic patients. On one hand, the rate may be low because hemophilia patients are not physically active, whereas on the other hand, the rate may be high because the patients have osteoporosis, amyotrophy, and/or hemophilic pseudotumor. Fractures occur in all the parts of long bones, especially in periarticular areas or the shaft of the long bone. The femur is particularly vulnerable [5]. Fractures may occur after mild trauma or because a hemophilic pseudotumor eroded the bone. Among our patients, two had fractures after a traffic accident, four after falling, and two for no obvious cause.

Given the rarity of hemophilic pseudotumor – with an incidence of about 1–2% in patients with severe hemophilia – reports on the management of pseudotumors in hemophilic patients are largely confined to case reports or small case series. There is no consensus about the treatment for hemophilic pseudotumor [7] depending on the size, location, and extent. Conservative treatment is suitable for superficial pseudotumors for less than 6 months, but its effectiveness decreases at any longer duration or in the presence of a thick wall and/or deep location [2]. Surgical resection is curative for most pseudotumors, but is fraught with risks of massive

life-threatening hemorrhage, infection, and amputation [3,8]. Given the risks associated with surgical intervention of pseudotumors, a decision to apply it to a hemophilic pseudotumor cannot be undertaken lightly. Studies about surgical management of hemophilic pseudotumors are scarce, and the results are varied. Pseudotumor in long bones should be excised *en bloc* and the bone stabilized. Prosthetic replacement could be considered for a massive bone defect and should solve the problems of bone deficiency, failure to stabilize the prosthesis, and deficient muscle covering.

Pseudotumor excision should start in healthy tissue, in which the anatomy is clearly identified. Pseudotumors should be excised *en bloc* or as completely as possible [9]. The effect of surgery is better when the pseudotumor is small, although there are still risks of vessel and nerve damage, fistula formation, pseudotumor recurrence, abscess, bleeding, and even death [10]. Surgical excision should be carried out only at major hemophilic centers by a multidisciplinary surgical team [11].

The prognosis of hemophilia-associated fracture is related to the conditions of bone and soft tissue, the location and type of fracture, and the compliance of the patient. The choice of stabilization (splint, plaster, brace, and external and internal fixation) and its timing must be individualized. It is best to use intramedullary nails if internal fixation is needed [5]. In this study, two patients had metallic internal fixation. One experienced tibial fracture nonunion after external fixation, which was addressed by internal fixation at the time of the revision surgery. The other patient had been followed up for only 4 months and callus formation appeared. However, the long-term effect has yet to be seen. The two revision surgeries included one in a patient who had undergone intramedullary nail fixation for femoral fracture. The screw broke without trauma 2 years postoperatively. The other patient had undergone metallic internal

fixation, but the fracture showed nonunion 15 months after the surgery.

From a biomechanical perspective, metallic fixation strength is much higher than that of bone, but there was stress concentration or shielding. Thus, there was a trend toward a second fracture or nonunion. Also, the risks of postoperative bleeding, pseudotumor recurrence, and infection were high. We therefore suggest simple and effective principles for reconstructing the bone: excise the pseudotumor as completely as possible, reduce the use of metallic internal fixation, and using autogenous or exogenous bone graft and fixation with an absorbable screw if internal fixation is need. Plasters may be used after the surgery.

Eliminating the dead space after resection of the cyst is difficult. Many methods had been employed, including filling it with fibrin glue, the use of omentum, muscles, Dexon mesh, and bone grafting [1,9,12–14]. Bellinazzo *et al.* [15] first proposed pseudotumor resection and filling with omentum, which was used successfully in four patients in 1978. Heeg *et al.* [1] reported one case of hemophilic pseudotumor of the ilium with chronic fistulation. Bone cement and gluteus medius muscle had been used to fill the dead space at the initial and second surgeries, respectively. The fistula recurred, however, and pedicled rectus abdominis muscle flap was used to obliterate the dead space. Bone cement is not advocated to obliterate dead space. Resection of the iliac rim could decrease dead space to a minimum. Alternatively, transposition of omentum into the dead space or free transfer of the latissimus dorsi muscle might also be effective [1].

Any kind of filling material was foreign matter, which would increase the possibility of postoperative infection: there would be a residual cavity if the filling material was not absorbed. Also, muscle flap surgery would increase the injury and produce a new wound. Thus, a new method was proposed to obliterate the cavity: use absorbable gelatin sponge and hemostatic gauze to fill the dead space and close the pseudotumor wall with the outer layer and overlapping sutures.

Effective clotting factor replacement was a guarantee of success for the surgery we investigated, but there was no consensus on a strategy for clotting factor substitution. Rodriguez-Merchan proposed the target coagulation factor levels for pseudotumor surgery at 80% for PODs 1–3 days, 60% for PODs 4–9, and 50% from POD 10 and thereafter [9] or 30–40% [5] until day 21. Considering the reduced activity and economic burden for the patients in our study, the target levels of clotting factor concentrations were reduced to lower levels than had been reported. The amount of blood loss was low except in one revision surgery and one amputation surgery whose anatomy was unclear. Therefore, the authors suggested that proper reduction of coagulation concentration was

safe if the dead space was fully closed and there was little functional exercise. The authors recommended maintaining the concentration at 80% on the day of surgery, 60% during PODs 1–3, 40% on PODs 4–6, and 20–30% thereafter. Large dose or long-term substitution therapy for patients with a pseudotumor may induce the appearance of coagulation factor inhibitor. In this study, two patients had FVIII inhibitor. APCC infusion or FVII bypass replacement therapy should be recommended for these patients.

The main postoperative complications included pseudotumor recurrence, infection, fistulization, coagulation factor inhibitor formation, and pathological fracture. Recurrence of a pseudotumor was related to incomplete resection or postoperative hematoma [9]. One patient in this study suffered from recurrence of pseudotumor 13 years after the surgery, which was thought to have been caused by hematoma. There is no concise explanation for the high incidence of infection in hemophilic patients. Infection could be caused by self-injection of the coagulation factor associated with skin contamination, or it could be due to bone grafting or postoperative bleeding [16]. Treatment of infection was difficult. Three patients in our study had infections. Two of them recovered after conservative treatment, but one patient's wound never healed.

#### IRB Statement

This is a retrospective observational cohort study, and the patients' privacy and identifying information were not included in this manuscript. Above all, this study obeyed the IRB rules.

#### Acknowledgements

##### Conflicts of interest

There are no conflicts of interest.

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