Received:
21 December 2015

Revised:
13 June 2016

Accepted:
20 June 2016

<http://dx.doi.org/10.1259/bjr.20151064>

Cite this article as:

Garge S, Keshava SN, Moses V, Mammen S, Ahmed M, Chiramel GK, et al. Role of endovascular embolization in treatment of acute bleeding complications in haemophilia patients. *Br J Radiol* 2016; **89**: 20151064.

FULL PAPER

Role of endovascular embolization in treatment of acute bleeding complications in haemophilia patients

¹SHAILESHKUMAR GARGE, MD, FVIR, ¹SHYAMKUMAR N KESHA, DNB, FRCR,
¹VINU MOSES, MD, DNB, ¹SURAJ MAMMEN, MD, ¹MUNAWWAR AHMED, MD, ¹GEORGE KOSHY CHIRAMEL, DMRD, MD,
²VINOO CHERIAN, MS, DNB, ²NITHYANANTH MANASSEH, DOrtho, MS, ³BIJU GEORGE, MD, DM,
³VIKRAM MATHEWS, MD, DM, ³ABY ABRAHAM, MD, DM, ³AURO VISWABANDYA, MD, DM,
³ALOK SRIVASTAVA, MD, FRACP and ¹SRIDHAR GIBIKOTE, DMRD, DNB

¹Department of Radiology, Christian Medical College, Vellore, India

²Department of Orthopedics, Christian Medical College, Vellore, India

³Department of Hematology, Christian Medical College, Vellore, India

Address correspondence to: Shaileshkumar Garge

E-mail: drshaileshgarge@gmail.com

Objective: Bleeding complications either spontaneously or post-operatively are very common in patients with haemophilia. Sometimes these bleeding complications remain unresponsive despite being on high dose of clotting factor replacement. The aim was to assess the role of endovascular embolization in patients with haemophilia in (a) treating haemorrhagic complications due to local causes refractory to clotting factors substitution and (b) reducing intra-operative blood loss in elective pseudotumour surgery.

Methods: 10 patients seen between January 2000 and April 2015 with severe haemophilia A or B who had unexplained profuse persistent bleeding or required large pseudotumour excision and were taken up for digital subtraction angiography and embolization were included in the study. Data of all these patients were reviewed using the computerized hospital information system and picture archiving and communication system. Details including indications for the procedure, patient preparation for the procedure, imaging findings, details of angiography with intervention, if any, and outcome as well as follow-up data were analyzed.

Results: In 6 of these 10 cases, bleeding was spontaneous, in 2 cases due to trivial fall and in 2 cases due to post-operative bleeding. Angiography in these patients revealed vascular blush, abnormal hypervascularity or active extravasation. In all 10 patients, an embolization

procedure was performed, with bleeding controlled in 8 patients. There were no procedure-related complications during the procedure, post-procedure bleeding or haematoma at the site of arterial access. One patient had recurrence of bleeding for whom surgical exploration was required, and one patient had significant bleeding intraoperatively which was controlled with high-dose clotting factors, blood transfusion and fresh frozen plasma intraoperatively.

Conclusion: Endovascular embolization is a safe, effective and cost-saving procedure in arresting bleeding in selected patients with severe haemophilia who are unresponsive to adequate clotting factor replacement and where local vascular causes could be contributing to the bleeding. Pre-operative embolization is also a good procedure to reduce intraoperative blood loss in patients with large pseudotumours.

Advances in knowledge: Angiography and embolization in patients with haemophilia is technically challenging and should be performed by highly skilled interventional radiologists, which limits its wider use and familiarity among multidisciplinary teams managing haemophilia. By bringing the knowledge of this effective treatment to the specialist groups who care for patients with haemophilia, its wider application may be possible which can save life and/or reduce morbidity.

INTRODUCTION

The bleeding complications in haemophilia vary from simple ecchymosis to profuse bleeding, including haemarthropathy and pseudotumours.¹ To control bleeding in haemophilia patients, a number of alternatives are available including conservative treatment, clotting factor replacement and surgery. But some complications such as

pseudotumour can be difficult to manage conservatively and often are unresponsive to intensive high-dose clotting factor replacement therapy. Surgery in patients with haemophilia is a real challenge, as it can be associated with massive intra-operative bleeding, infection and amputation. We describe our experience in the use of digital subtraction angiography (DSA) and embolization in management of bleeding and

Table 1. Details of haemophilia patients

Case number	Age (years) (all males)	Clinical presentation	Cross-sectional imaging	Angiography access	DSA findings	Embolization material used	Complication	Outcome
1	40	Ac—hist of fall, left iliac fossa haematoma, persistent bleeding post evacuation	CECT abdominal, angiogram	Right femoral, 5-French sheath	Faint parenchymal blush of inferior epigastric artery at the site of haematoma	Gel foam	Nil	Short-term resolution post-embolization, with recurrence of bleeding. Re ope with exploratory laparotomy and debridement of abdominal wall. No further bleeding
2	16	Sub-Ac—right hip disarticulation with post-op bleeding from stump	CECT abdominal, angiogram, MRI of the right thigh	Left femoral, 4-French sheath	Right pelvic mass with hypervascularity along periphery of mass	40–150 u PVA particles	Nil	No further bleeding
3	50	Ac—post-ope right above knee stump bleed	Nil	Left femoral, 4-French sheath	Hypervascularity of distal stump, mild dilation of stump of distal SFA	Pushable 0.035-inch helical metal coils, 500–710 u PVA particles	Nil	No further bleeding. Healing of surgical wound
4	26	Chr—left psoas and L1 vertebral body haematomas	MRI spine	Right femoral, 4-French sheath	Hypervascularity of L1 and L3 vertebral bodies supplied by respective lumbar arteries	500–710 u PVA particles	Nil	No significant bleeding intra-ope
5	27	Chr—right thigh pseudotumour	MRI right thigh	Left femoral, 4-French sheath	Mild hypervascularity from right profunda femoris and SFA branches	150–255 u PVA particles, gel foam	Nil	No significant bleeding intra-ope
6	59	Chr—abdominal swelling with extensive RP right iliopsoas pseudotumour	CECT abdominal, CT pul angio	Left femoral, 4-French sheath	Large iliopsoas pseudotumour	500–710 u PVA particles	Nil	No significant bleeding intra-ope

(Continued)

Table 1. (Continued)

Case number	Age (years) (all males)	Clinical presentation	Cross-sectional imaging	Angiography access	DSA findings	Embolization material used	Complication	Outcome
7	42	Recurrent malena, fistula with blood and pus discharge along posterior wall of the stomach on gastroscopy. Operated for lesser sac pseudotumour. Gradual drop in haematocrit post-op	CECT abdominal	Right femoral, 4-French sheath	A large pseudotumour indenting greater curvature of stomach	Gel foam, 250 u PVA particles	Nil	No further malena
8	24	Chr—right thigh pseudotumour gradually increasing following trivial fall	MRI right thigh	Left femoral, 4-French sheath	Right thigh mass with hypervascularity along periphery from br. of profunda femoris and post. division of internal iliac artery	100 u PVA particles	Nil	3.5 l of blood loss intraoperatively which was controlled with FFP, clotting factors, blood, packed cells transfusion
9	29	Chr—left pelvic pseudotumour gradually increasing	MRI pelvis	Right femoral, 4-French sheath	Left pelvic mass with hypervascularity along periphery from br. of internal iliac and SFA	Gel foam	Nil	No significant bleeding intra-op
10	18	Chr—right pelvic pseudotumour gradually increasing	NECT and MRI pelvis	Left femoral, 4-French sheath	Right pelvic mass with hypervascularity along periphery from br. of B/L internal iliac (right >> left)	Gel foam	Nil	No significant bleeding intra-op

Abd, abdomen; Ac, acute; B/L, bilateral; br., branch; CECT, contrast-enhanced CT; Chr, chronic; DSA, digital subtraction angiography; FFP, fresh frozen plasma; Hist, history; Intra-op, intraoperative; NECT, non-enhanced CT; Post, division, posterior division; post-op, post-operative; Pul, angio, pulmonary angiogram; PVA, poly vinyl alcohol; Re op, repeat operation; RP, retroperitoneum; SFA, superficial femoral artery.

other complications in patients with haemophilia over a period of 15 years. The aim of the study was to assess the role of endovascular embolization in patients with haemophilia in (a) treating haemorrhagic complications refractory to clotting factors substitution and (b) reducing intraoperative blood loss.

METHODS AND MATERIALS

10 patients seen between January 2000 and April 2015 with severe haemophilia A or B who suffered from unexplained profuse persistent bleeding, pre-operative pseudotumour excision and/or post-operative bleeding unresponsive to conservative treatment and high-dose clotting factor substitution were taken up for DSA and embolization and were included in the study. The patients with persistent bleeding were in hypovolemic shock. The data of all these patients were reviewed using the computerized hospital information system and picture archiving and communication system. Details including indications for the procedure, patient

preparation for the procedure, imaging findings, details of angiography with intervention, if any, and outcome as well as follow-up data were collected and analyzed (Table 1). Permission from the institutional review board was obtained.

Angiographic procedure and embolization

DSA was performed (Multistar; Siemens, Berlin, Germany or biplane Artis Zee DSA equipment; Siemens) after appropriate replacement of clotting factor concentrate to achieve haemostatic levels, usually about 80–100% levels. A retrograde right/left common femoral artery puncture under ultrasound was performed using a 4-French micropuncture set using a single-wall puncture technique and a 4-French sheath was introduced, unlike in general populations where a single- or double-wall puncture using a 19-G puncture needle was usually carried out. Using the catheter–wire combination such as a cobra catheter (Cordis, Miami, FL) over a guidewire, the abnormal vessels were

Figure 1. Right thigh pseudotumour embolization in a 24-year-old male patient with haemophilia. (a) Frontal radiograph of the right upper thigh including right hip joint showing large soft-tissue pseudotumour swelling (arrow). (b) Initial digital subtraction angiography (DSA) of the right profunda femoris artery showing displayed vessels (arrow) by pseudotumour with mild hypervascularity. (c) DSA of branch of posterior division of the right internal iliac artery showing hypertrophied abnormal vessels in the periphery of pseudotumour (arrow). (d) Post-embolization using polyvinyl alcohol particles DSA showing complete occlusion of the abnormal vessel (arrow) with no hypervascularity in pseudotumour region.

Figure 2. Right mid-thigh post-amputation bleeding embolization in a 50-year-old male patient with haemophilia. (a) Frontal radiograph of the right thigh showing amputated right femur at mid-thigh level (arrow). (b) Initial DSA of the right common femoral artery showing hypervascularity of distal amputated stump (arrow) with mild dilation of distal superficial femoral artery. (c) DSA (unsubtracted image) showing vertebral glide catheter (curved arrow) with deployment of 0.035-inch coils (arrow) at the distal end of the superficial femoral artery. (d) Post-embolization using polyvinyl alcohol particles (500–710 u) and coils (0.035 inch); DSA showing occlusion of the distal superficial femoral artery with no hypervascularity (arrow) in previously bleeding amputated stump region.

selectively cannulated and angiography obtained. Whenever an abnormal blush and abnormal hypervascularity in patients with pseudotumour or active bleeding in patients with spontaneous bleeding was found, a microcatheter (Progreat®; Terumo, Tokyo, Japan) was advanced and selective embolization was performed with polyvinyl alcohol particles, gel foam and/or microcoils till there was stasis. After angiography, a repeat angiography was obtained to assess for any residual abnormality.

Definition of clinical success

Clinical success was defined as complete cessation of active bleeding for patients with spontaneous bleeding and insignificant

intraoperative blood loss in patients undergoing surgery following embolization.

Follow-up

Clinical effects related to bleeding were evaluated after 24 h and within 1 week following the procedure.

RESULTS

10 patients with severe haemophilic bleeding complications underwent angiography and embolization of the abnormal vessels since January 2000. The mean age at the time of angiography was 33.1 years (range, 16–59 years); and the median follow-up after

Figure 3. Left lower anterior abdominal wall pseudotumour following trivial fall in a 40-year-old male patient with haemophilia. (a) Contrast-enhanced CT scan of the lower abdomen at the level of aortic bifurcation showing large evolving pseudotumour (arrow). (b) Initial DSA of left inferior epigastric artery showing abnormal blush (arrow) in the region of pseudotumour suggestive of hypervascularity. (c) Post-embolization using gel foam DSA showing occlusion (arrow) of the distal left inferior epigastric artery supplying the pseudotumour with no hypervascularity.

angiography was 1 week. In six patients, angiography and embolization were carried out for pre-operative evaluation of expanding pseudotumour before surgical excision of pseudotumours to reduce surgical blood loss (Figure 1) (two in the right thigh and one each in the paravertebral, iliopsoas, left pelvic region and right pelvic region), in two patients with an indication of post-amputation bleeding (Figure 2) (one with above-knee amputation for chronic osteomyelitis and one with right hip disarticulation for immobile limb of infected burst pseudotumour), and in another two patients each with an indication of expanding massive spontaneous anterior abdominal wall haematoma (Figure 3) and pseudotumour adjacent to the gastric wall with chronic upper gastrointestinal bleeding for pre-operative embolization. All patients underwent angiography and embolization through femoral arterial access with adequate clotting factor replacement to cover the procedure and 48 h afterwards. Polyvinyl alcohol, gel foam and microcoils were used for embolization.

Initial angiography showed peripheral hypervascularity in seven patients seen indicative of central haematoma with peripheral hyperaemic tissue which can be a source of bleeding if operated without pre-operative embolization; in one patient, a blush was seen, indicative of hyperaemic tissue as the cause of bleeding,

and in two patients, a hypertrophied vessel with indentation by pseudotumour was seen. Out of 10 patients, 8 patients had complete cessation of bleeding, whereas 1 patient had recurrence of bleeding for whom repeat surgical exploration was required and the other patient had significant (3.5 l) blood loss intraoperatively. This reduced the overall financial burden on the patient including reduction in the cost of surgery, shorter hospital stay, lesser clotting factor replacement and rapid recovery from this minimally invasive interventional procedure. There were no angiography- or embolization-related complications during the procedure nor were there any post-procedure bleeding or haematoma at the site of arterial access.

DISCUSSION

The clinical presentation in patients with haemophilia vary with age and severity of the disease and range from simple bruising to bleeding in muscles, soft tissues, joints or in the central nervous system.²

Treatment of haemophilia is comprehensive.³ Prompt treatment of acute bleeding episodes is essential to minimize long-term complications. Nonpharmacological and pharmacological strategies are used in the treatment of haemophilia. Nonpharmacological

strategies consist of supportive care such as rest, ice, compression and elevation. Pharmacological treatment includes desmopressin, antifibrinolytics such as tranexamic acid, factor concentrates, bypassing agents for treatment of patients with inhibitors and immune tolerance therapy.¹ Replacement therapy with clotting factor concentrate is the therapy of choice in the treatment of most bleeding episodes in haemophilia. In most cases, the therapy is effective. However, occasionally they are unresponsive to replacement therapy, especially unexplained spontaneous gastrointestinal bleeding.⁴ Angiography and embolization of bleeding episodes or pre-operative embolization have rarely been performed as principal therapy. We could only find few case reports on therapeutic embolization in patients with haemophilia⁵ and few case series on embolization of severe bleeding in haemophilic target joint^{4,6} and gastrointestinal bleeding.⁷ However, embolization for other medical indications is not uncommon such as pre-operative tumour embolization.⁸

We found that DSA and selective embolization is an effective treatment option to stop spontaneous/post-operative bleeding or to ease surgical excision. Embolization often prevented recurrent bleeding in patients with haemophilia; however, if massive rebleeding did occur, a second embolization or a surgical re-exploration can be considered as was performed in one patient in our series where surgical re-exploration was required after embolization. Successful embolization in patients with haemophilia saves the cost of surgery and related morbidity, repeated clotting factors transfusion and hospital stay, with improvement in quality of life. Our patients had been treated with high doses of clotting factor concentrates (continuous infusion, targeting a level of 80–100% at a dose of 40 units kg⁻¹ day⁻¹) with little success in clinical improvement. In our study, after embolization, bleeding stopped immediately and significant reduction of blood loss occurred during surgery without any further requirement of high dose of clotting factors replacement.

In addition to our own experience, Mauser-Bunschoten et al⁴ reported a case series on embolization in patients with haemophilia but that was limited to haemophilic target joints. In our series, a vascular blush with peripheral vascularity was the major cause of spontaneous bleeding. However, we could not find any false or true aneurysms as the cause of bleeding in our series, as this complication is uncommon.^{9,10}

Angiography and embolization in patients with haemophilia is technically challenging and should be performed by highly skilled interventional radiologists which limits its wider use and familiarity among multidisciplinary teams managing haemophilia. By bringing the knowledge of this effective treatment to the specialist groups who care for patients with haemophilia, its wider application may be possible which can save life and or reduce morbidity.

This study highlights the safety and benefits of angioembolization in patients with haemophilia who are unresponsive to clotting factors replacement therapy. A limitation of our study is that it is an observational study, and the sample size is small. This is because such cases are not many in number, as many countries now have replacement therapies which are high dose and from childhood, rather than on demand as in India and other developing countries. In future, large randomized controlled studies need to be carried out to substantiate our results.

CONCLUSION

Endovascular embolization is a safe, effective and cost-saving procedure in arresting bleeding in selected patients with severe haemophilia who are unresponsive to adequate clotting factor replacement. Pre-operative embolization is also a good procedure to reduce intraoperative blood loss in patients with large pseudotumours.

REFERENCES

1. Stachik J. Haemophilia: etiology, complications, and current options in management. *Formul J Clin Pharmacol* 2010; **45**: 218–27.
2. Kulkarni R, Soucie J, Lusher J. Sites of initial bleeding episodes, mode of delivery and age of diagnosis in babies with haemophilia diagnosed before the age of 2 years: a report from the Centers for Disease Control and Prevention (CDC) Universal Data Collection (UDC) project. *Haemophilia* 2009; **15**: 1281–90. doi: <http://dx.doi.org/10.1111/j.1365-2516.2009.02074.x>
3. World Federation of Hemophilia. Guidelines for the management of hemophilia. Accessed November 30, 2014. Available from: <http://www1.wfh.org/publication/files/pdf-1472.pdf>
4. Mauser-Bunschoten EP, Zijl JA, Mali W, van Rinsum AC, van den Berg HM, Roosendaal G. Successful treatment of severe bleeding in haemophilia target joints by selective angiographic embolisation. *Blood* 2005; **105**: 2654–7. doi: <http://dx.doi.org/10.1182/blood-2004-06-2063>
5. Mann HA, Goddard NJ, Lee CA, Brown SA. Periarticular aneurysm following total knee replacement in hemophilic arthropathy. A case report. *J Bone Joint Surg Am* 2003; **85**: 2437–40.
6. Klamroth R, Gottstein S, Essers E, Landgraf H, Wilaschek M, Oldenburg J. Successful angiographic embolization of recurrent elbow and knee joint bleeds in seven patients with severe haemophilia. *Haemophilia* 2009; **15**: 247–52. doi: <http://dx.doi.org/10.1111/j.1365-2516.2008.01842.x>
7. Ziernski JM, Szczepanik AB, Misiak A, Rudowski WJ. Endoscopic injection treatment of gastrointestinal bleeding in haemophiliacs. *World J Surg* 1996; **20**: 1166–70. doi: <http://dx.doi.org/10.1007/s002689900178>
8. Head, neck, and brain tumor embolisation. *Am J Neuroradiol* 2001; **22**(Suppl. 8): S14–15.
9. Manning MP, Marshall JH. Aneurysm after arthroscopy. *J Bone Joint Surg Br* 1987; **69**: 151.
10. Vincent GM, Stanish WD. False aneurysm after arthroscopic meniscectomy. A report of two cases. *J Bone Joint Surg Am* 1990; **72**: 770–2.