Successful treatment of severe bleeding in hemophilic target joints by selective angiographic embolization

Short title: Embolization for profuse joint bleeds in hemophilia

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Clinical observations, intervention and therapeutic trials

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Abstract

Bleeding into the joints is common in hemophilia. After total knee or elbow replacement, profuse intra-articular bleeding unresponsive to high dose clotting factor replacement sometimes occurs. In some patients who have severely damaged elbow or knee joints the same profuse bleeding pattern can be seen.

To control bleeding in these patients selective catheterization with a microcatheter and therapeutic embolization with microcoils was performed whenever a severe blush or microaneurysm was observed on angiography.

Over 12 years, in 23 cases of massive joint bleeding in 18 patients with hemophilia selective catheterization was performed. In 15 cases the bleeding was post-operative, and in 8 spontaneous. Results of angiographic imaging revealed vascular blush, false aneurysm, true aneurysm and arterio-venous shunt in combination with an aneurysm as cause of bleeding. In two patients the cause of bleeding was not found. In 21 cases an embolization procedure was performed, in which the bleeding was completely controlled by a single procedure in 14 cases. Recurrence of the bleeding occurred in 7 cases requiring a second embolization procedure, in one patient even a third embolization was required to stop the bleeding completely. No difference in the outcome, i.e. clinical end of bleeding and joint range of motion, was observed, when comparing post-operative and spontaneous bleeding.
Introduction

Bleeding into the joints, particularly the elbow, knee and ankle, is common in hemophilia (1). Repeated episodes may result in cartilage damage and synovial changes leading to severe arthropathy (2-4). Some patients have specific target joints, in which they have a higher bleeding frequency. These bleeding episodes are usually successfully treated with replacement of factor VIII or IX by injection of clotting factor concentrates. Long-term prophylaxis can prevent these episodes of joint bleeding and consequent arthropathy (5,6). Older patients with severe hemophilia, as well as hemophilia patients with antibodies developed against factor VIII or IX (inhibitors) often do not receive adequate prophylaxis. In these patients, recurrent hemarthroses have resulted in severe joint damage, for which joint replacement is often necessary. After total knee or elbow replacement, profuse bleeding sometimes occurs into the joint. These episodes of bleeding show a characteristic rapid onset of the bleeding, resulting in a complete loss of function, intense pain, and considerable swelling of the joint, all developing within one hour. Such episodes of bleeding can hardly be prevented by prophylaxis and often are unresponsive to intensive high dose clotting factor replacement therapy. In some patients with end stage hemophilic arthropathy (7) of elbow and knee joints, the same bleeding pattern can occur without previous joint replacement and even despite adequate (secondary) prophylaxis.

Because this kind of bleeding does not respond to the standard therapeutic measures such as clotting factor replacement therapy, immobilization and cold packs, we explored an alternative therapy. Because in this type of hemorrhage, an acute massive amount of bleeding occurs, we thought it might specifically be caused by arterial abnormalities rather than the usual synovial bleeding, and that local interventional therapy might be an option. Therefore, we performed angiography in all patients with this pattern of bleeding into their knee or elbow, when intensive replacement therapy was ineffective. Since 1992, angiography with
embolization has been performed in patients with post-operative massive knee and elbow bleeding (8). In 2000, we started performing angiographic embolization in patients with profuse spontaneous elbow and knee bleedings, whether or not they have just undergone a surgical procedure.

In this paper, we describe the results of our experience with angiographic embolization in these patients.

Methods

Population

Patients with severe hemophilia A or B with or without inhibitors who suffered from profuse persistent bleeding unresponsive to high dose clotting factor substitution, were eligible for embolization. Two groups of patients could be distinguished. Group 1: patients in whom bleeding occurred within the 6 month period after joint replacement. Group 2: patients with end stage hemophilic arthropathy, without previous arthroplasty, with an acute profuse bleeding causing severe pain and total loss of function. Informed consent was provided according to the Declaration of Helsinki.

Angiographic procedure and embolization

After correction of clotting factor levels, a digital subtraction angiogram was performed. When bleeding took place in the knee, an ipsilateral antegrade puncture was done and a 5 FR sheath was introduced. With a cobra-shaped catheter, the popliteal artery and supra- and infragenual arteries were selectively catheterized and an angiograph obtained. Whenever an excessive blush (hyperemic tissue) or a ruptured micro-aneurysm was found, a microcatheter was advanced and embolization was performed with microcoils. Afterwards a repeat angiographic picture of the popliteal artery was obtained to assess the outcome.
When the elbow was the bleeding site, a retrograde puncture was done in the common femoral artery. Next a headhunters shaped catheter was used to catheterise the left or right subclavian artery and to obtain an overview of the arterial pattern in the region of the elbow. Selective catheterization with a microcatheter, and therapeutic embolization with microcoils was performed whenever a severe blush or microaneurysm was observed. Afterwards a repeat angiographic visualization was performed.

**Definition of clinical success**

Clinical success was defined as complete cessation of bleeding following embolization. This was accompanied by a decrease in pain, swelling and an improvement of range of motion within 24 hours after catheterization, which was sustained in subsequent days after the patients circulating level of clotting factor decreased to the low steady-state level.

**Follow-up**

Clinical effects were evaluated after 24 hours and within one week following the procedure. Thereafter, patients were seen for at least every three months during the first year, and every six months during the following years. If recurrent bleeding episodes occurred, patients were seen more often.

**Results**

Since 1992 in 23 cases of acute profuse bleeding in knee or elbow catheterization was performed. Twenty cases suffered from hemophilia A, 3 from hemophilia B (2 inhibitors). The median age at time of angiography was 47 years (range 14-67 years); the median follow-up after angiography 48 months (range 9-134 months). In 15 cases postoperative bleeding initially occurred within six months after knee (n=14) or elbow (n=1) replacement. In eight additional cases, a spontaneous bleeding into elbow (n=7) or knee (n=1) was the indication for angiography. In eight cases a second or third catheterization was performed.
Initial angiograms demonstrated a blush, indicative for hyperemic tissue as cause of bleeding in 15 cases (Fig 1a,b); in two cases a false aneurysm was observed (Fig 2a,b); in one case a true aneurysm was observed; and in three cases an arterio-venous shunt in combination with an aneurysm was observed. In all these cases embolization of the feeding arteries was performed. However in some cases, it was not possible to embolise all the bleeding arteries. In two patients the cause of bleeding could not be localized (one case of post-operative knee bleeding and one case of spontaneous elbow bleeding) and embolization was not performed. Embolization was initially effective in 20 cases. In these patients the bleeding stopped and no profuse bleeding was observed at repeat angiography. In one case repeat angiography demonstrated only a partial occlusion of the bleeding artery following the embolization procedure. However, the clinical result was satisfactory.

Rebleeding occurred in seven cases, six post-operative and one spontaneous bleeding. (table 1). In all these seven cases a second angiography was made, demonstrating the affected artery. In all cases embolization was performed. Repeat embolization resulted in a complete control of bleeding in five cases. In two cases a decrease of bleeding was seen, which could subsequently be controlled effectively with standard conservative therapy with clotting factor concentrates. In one of these cases even a second recurrence of bleeding occurred; this was once again successfully treated with embolization during a third angiography.

**Complications**

In six out of thirty-one angiographic procedures one or more complications were observed. Three patients complained of pain in the affected joint during or shortly after the procedure. One patient had a temporarily spasm of the artery, and one patient had a small thrombus of the anterior tibial artery, for which heparin was locally injected during angiography. This resulted in good resolution of the thrombus and return of arterial pulsation. In a patient with
hemophilia B and an inhibitor treated for repeated excessive right elbow bleeds, a severe psoas bleeding occurred three days after the procedure. The femoral puncture site was the origin of this bleeding complication, the bleeding was probably caused by early mobilization. The patient recovered completely, and for the subsequent eight months he had no bleeding episodes into his right elbow. Later in the same patient, a second catheterization for a repeat episode of bleeding into his left elbow resulted in prolonged bleeding at the puncture site, which could easily be controlled.

**Discussion**

Replacement therapy with clotting factor concentrate is the therapy of choice in the treatment of bleeding episodes in hemophilia. In most cases this therapy is effective. However bleeding episodes in severely damaged joints, or after implantation of prostheses, are occasionally unresponsive to clotting factor replacement therapy.

Until now, embolization used as principal therapy for joint bleedings in patients with hemophilia has hardly been performed. We could only find one report on therapeutic embolization in hemophilia (9). Even more there are only a few reports on therapeutic embolization for postoperative bleeding after total arthroplasty of knee or hip joints in patients without hemophilia (10,11). However embolization for other medical indications is not uncommon. For many years this procedure has been used successfully in treating patients *without hemophilia*, for ruptured intracranial aneurysms, obstetrical hemorrhages, massive hemoptysis or other types of massive bleeding and preoperatively in patients with well-vascularized tumors (12-15).

We found that selective catheterization with placement of embolization coils is also an effective method to stop excessive bleeding in severely damaged hemophilic joints unresponsive to intensive clotting factor therapy. These bleeding episodes spontaneously occurred in patients...
who underwent arthroplastic surgery, and who did not have arterial abnormalities on preoperative angiograms, as well as in patients who had not undergone surgery. No difference in bleeding pattern or effect of embolization was observed between those treated post-operatively and those treated for spontaneous bleeding episodes. Embolization often prevented recurrent bleeding in the same joint post-operatively. However if massive re-bleeding did occur a second embolization procedure was always initially effective in stopping it, although in one patient a second rebleeding occurred. Successful embolization in hemophilia saves costs. Our patients had often been treated with high doses of clotting factor concentrates, more than 700 U/kg body weight for one week or for several months, with little or no success. Once successful control of joint bleeding was obtained with replacement therapy, recurrent bleeding was not uncommon. In our study, bleeding stopped immediately after embolization and further use of high doses of replacement clotting factor concentrates was unnecessary. This procedure improved the quality of life of the patients, as they no longer suffered from painful disabling bleedings into their target joints, responding poorly to clotting factor therapy. Embolization was successful not only in patients in whom a false aneurysm occurred, but also in cases in which a blush of small arteries, probably indicating some minor extravascular leakage was causing the bleeding phenomenon.

In addition to our own experience only Mann et al (9) reported successful embolization of a pseudo-aneurysm in an hemophilia patient with a massive bleeding following total knee replacement. He suggests that selective digital subtraction angiography of the popliteal artery should be considered pre-operatively in patients with hemophilia. However, when we did perform pre-operative angiograms on our patients, who had had massive bleeding following knee replacement, we could find no abnormalities. A false aneurysm of an intra-articular artery might form subsequent to trauma related-surgery, as result of disruption of the vessel wall. In our series a vascular blush without an aneurysm was the major cause of bleeding. In
addition, false aneurysms occurred in patients with spontaneous bleeding episodes without previous surgery, and in one patient with a recurrent bleeding following embolization. In this patient, the angiogram performed for the initial bleeding demonstrated a blush only. Obviously, the false aneurysm had developed spontaneously afterwards. Furthermore, only four cases of aneurysm have been reported in patients without hemophilia following surgical procedures of the knee, so this complication must be very exceptional (16-19).

A limitation of the broader use of embolization procedures is that this method is technically demanding and can only be done by highly skilled radiologists. By bringing this effective treatment modality to the attention of the many specialist groups who care for such patients, its broader application may be possible.

In conclusion, angiographic embolization is an effective, successful, safe and potentially cost-saving therapeutic intervention in hemophilia patients with massive knee and elbow bleedings unresponsive to appropriate and adequate clotting factor replacement.

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Literature


Table 1

**Cause of bleeding and results of embolization**

<table>
<thead>
<tr>
<th></th>
<th>Post operative bleeding</th>
<th>spontaneous bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of initial catherizations (knee/elbow)</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Total number of initial embolizations</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Effective</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Partial effective</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Interval between surgery and embolization (range)</td>
<td>42 (4-180) days</td>
<td>-</td>
</tr>
<tr>
<td>Number of massive recurrent bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 week after embolization</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 1 –26 weeks after embolization</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Second catherization with embolization</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Third embolization</td>
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<td>0</td>
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<tr>
<td>Total number of embolizations</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>Complications</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>
figures 1a and b

Angiogram showing massive blush in a patient with recurrent spontaneous elbow bleeding

Before (1a) and after (1b) embolization
figures 2a and b

Angiogram showing blush in a patient with recurrent massive knee bleeding following joint replacement before (2a) and after (2b) embolization
Successful treatment of severe bleeding in hemophilic target joints by selective angiographic embolization

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