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ORIGINAL ARTICLE

Muskuloskeletal

Pre-operative synovial hyperaemia in haemophilia patients undergoing total knee replacement and the effects of genicular artery embolization: A retrospective cohort study

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Abstract

Aim: Haemophilia is characterized by recurrent joint bleeding caused by a lack of clotting factor VIII or IX. Due to repeated joint bleeding, end-stage arthropathy occurs in relatively young patients. A total knee replacement (TKR) can be a solution. However, TKR may be complicated by perioperative and postoperative bleeds despite clotting factor therapy. The aim of this study was to evaluate the prevalence of pre-operative synovial hyperaemia and the effects of Genicular Artery Embolization on synovial hyperaemia and 3-month postoperative joint bleeding.

Methods: In this retrospective cohort study, all patients with haemophilia who underwent periarticular catheter angiography between 2009 and 2020 were evaluated after written informed consent. Synovial hyperaemia on angiography was scored by an interventional radiologist.

Results: Thirty-three angiography procedures in 24 patients were evaluated. Median age was 54.4 years (IQR 48.4–65.9). Preoperative synovial hyperaemia was observed in 21/33 joints (64%). Moderate and severe synovial hyperaemia was observed in 10/33 joints (30%). Synovial hyperaemia decreased in 13/15 (87%) joints after embolization. Three-month postoperative joint bleeding occurred in 5/32 joints: in 2/18 joints (11%) without synovial hyperaemia and in 3/14 joints (21%) with mild synovial hypertrophy. Non-embolized and embolized joints did not differ regarding 3-month postoperative bleeding ($P = .425$). No complications were observed after embolization.

Conclusion: One-third of patients with haemophilia requiring a TKR had moderate or severe synovial hyperaemia which can be reduced safely by Genicular Artery Embolization prior to TKR. Three-month postoperative bleeding appears to occur independently of the presence of residual mild synovial hyperaemia.

KEYWORDS
arthroplasty, embolization, haemophilia, hemarthrosis

1 | INTRODUCTION

Persons with haemophilia might suffer from recurrent spontaneous joint bleeding due to a lack of clotting factor VIII or IX, in haemophilia A and B respectively. A vicious circle is induced by an initial synovial bleed resulting in synovial hypertrophy, swelling, inflammation and neovascularization with subsequent vulnerability to recurrent bleeding.[1] Repeated joint bleeding leads to osteochondral damage, and ultimately, end-stage arthropathy.[2–4] Prophylactic treatment by intravenous administration of clotting factors concentrates (prophylaxis) is effective in preventing joint bleeding and subsequent joint damage, and may prevent life-threatening bleeds.[5] Prophylaxis is the preferred treatment for severe haemophilia, but prophylaxis is associated with high costs (approximately US$170,000/year for intermediate-dose prophylaxis).[6,7] Despite continued prophylaxis in adulthood, persons with haemophilia still experience hemarthroses, and blood-induced arthropathy is frequently observed already at the age of 30—40 years.[8]

Total knee replacement (TKR) may be considered for patients with severe haemophilic knee arthropathy. Joint replacement can be performed safely with good functional outcomes, when performed by a multidisciplinary experienced team.[2,3,9] The most frequent complication after TKR in haemophilia patients is bleeding in 9% of TKR procedures, despite recommended high levels of costly clotting factor perioperatively.[6,10] Postoperative joint bleeding impacts the rehabilitation process and is associated with higher clotting factor consumption. Therefore, reducing synovial hyperaemia preoperatively might lower the risk of postoperative joint bleeding.

Genicular Artery Embolization may be performed in patients with a severe joint bleeding and is nowadays also a treatment option for symptomatic knee osteoarthritis.[11] Case series of angiographic embolization for joint bleeding in persons with haemophilia have been published.[12–15] A recent systematic review by Shanmugasundaram et al. evaluated literature regarding safety and efficacy of embolization for treating severe joint bleeding in patients with bleeding disorders like haemophilia.[16] Their review included 15 articles with a total of a total of 93 embolization procedures in 78 patients and reported CIRSE grade 3—4 complications (additional postprocedural therapy, prolonged hospital stay, or permanent mild sequelae) in 5%.[16,17] The authors concluded that angiographic evaluation and embolization can be performed safely to effectively treat joint bleeds unresponsive to conservative treatment.[16] Embolization of the synovial tissue may also be performed to treat chronic synovitis as well in order to prevent repetitive bleeding as described by Galli et al., who observed a significant reduction of bleeding episodes in treated joints after 3, 6 and 12 months.[18] Saris et al. evaluated knees by angiography prior to TKR and observed and embolized vascular abnormalities in the synovium in 4 out of 7 knees. Based on these observations, they suggested that pre-operative angiography and embolization is a simple and effective procedure prior to TKR in persons with haemophilia avoiding high-cost post-operative haemorrhage treatment (factor VIII and IX).[19]

Pre-operative angiography with Genicular Artery Embolization is therefore part of the standard pre-operative work-up before TKR in persons with haemophilia in our centre. Angiography may reveal synovial hyperaemia and pseudoaneurysms, which can be treated pre-operatively in order to reduce bleeding complications which have a great impact on rehabilitation and requires intensified clotting factor replacement.[12–16] Although case series of embolization for the treatment of joint bleeding and chronic haemophilic synovitis has been described with reduced bleeding rates postembolization, the role of angiography and embolization in the preoperative workup in persons with haemophilia is not clearly defined or reported yet.

The aims of this study were (1) to describe the prevalence of synovial hyperaemia before TKR in persons with haemophilia and (2) to evaluate the effect of pre-operative genicular artery embolization on synovial hyperaemia and 3-months postoperative joint bleeding. We hypothesized that Genicular Artery Embolization would reduce synovial hyperaemia and that post-operative bleeding episode is more often observed in joint with residual synovial hyperaemia after embolization.

2 | MATERIALS AND METHODS

In this retrospective cohort study, all persons with haemophilia treated at the Van Creveldkliniek that underwent preoperative Genicular Artery Embolization between January 2009 and December 2020 at the department of radiology of the University Medical Center Utrecht, The Netherlands, were selected. Both knees of a patient were included if both knees underwent preoperative Genicular Artery Embolization. An information folder with informed consent form was sent to these patients by mail. Patients with a preoperative angiography of the knee were included when written informed consent was obtained. The study (protocol ID 19-775/C) was approved by the institutional review board.

2.1 | Periprocedural care

The indication for TKR was decided in consensus with the patient by a haemophilia specialized multidisciplinary team including a haematologist, orthopaedic surgeon, rehabilitation physician, and physical therapist. Pre-operative angiography with Genicular Artery Embolization is part of the standard pre-operative work-up before TKR in persons with haemophilia in our centre. Prior to surgery, patients underwent catheter angiography to evaluate the presence and extent of synovial hyperaemia. If indicated, Genicular Artery Embolization was performed in order to reduce synovial hyperaemia and aiming to limit the chance of postoperative joint bleeding. Peri-procedural clotting factor replacement was based on national guidelines for the treatment of haemophilia.[20] An initial bolus FVIII/FIX was given prior to the angiography to achieve a clotting factor activity level of 100%, followed by half the dose after 12 and 24 h. Geniculate Artery Embolization procedures were performed in line with the procedure that has been described into detail by Heller and colleagues.[11] During a sterile procedure under local anaesthesia, arterial access was obtained in the groin, either antegrade ipsilateral or cross-over, up to the interventional radiologists' discretion. If Genicular Artery Embolization was indicated at the discretion of the interventional radiologist, super selective

embolization of the hyperaemic synovium was performed after angiography, using a 2.7 F or 2.4 F microcatheter (PROGREAT®, Terumo Interventional Systems, USA) and PVA particles (150-250 μm or 250−350 μm, Contour™, Boston Scientific, USA). A postembolization angiogram was obtained to evaluate the results of treatment.

Perioperative clotting factor administration during surgery consisted of an initial bolus FVIII/FIX to achieve levels of 80%−100%. Thereafter either bolus therapy aiming at FVIII/FIX through levels > 50% or continuous infusion aiming at FVIII/FIX levels of 50%−80% was continued for 7 days post-surgery followed by bolus therapy aiming at through levels > 30% for 3 more days.[20] TKR was performed under sterile circumstances, under general anaesthesia in the supine position, after placement of a pneumatic tourniquet to suffice a bloodless surgery field. Postoperative protocols included mobilization guided by a physiotherapist during hospitalization, and patients were instructed to use two crutches for >6 weeks after surgery. Controls visits were planned two weeks after surgery in general and treatment was personalized based on the clinical course and needs of the patient.

2.2 | Data collection

Age at the time of angiography, haemophilia type (A or B) and severity (severe [FVIII/IX < 1%], moderate [FVIII/IX 1%−5%], mild [FVIII/IX > 5%]) were collected from electronic patient records. The number of embolized vessels (defined as selective catheter positions in branches of the geniculate artery), used embolization materials, and peri-procedural complications were retrieved from the patient records. All cases were reviewed to evaluate the range of synovial hyperaemia in our cohort. Angiograms were retrospectively scored by one experienced interventional radiologist (>11 years' experience) to prevent inter-observer variances in interpretation of hyperaemia. Synovial hyperaemia was scored semi-quantitatively as absent, mild, moderate, or severe. Mild hyperaemia was scored when the synovial blush was mild and focal or discrete diffuse, when more prominent as moderate, and when the synovial blush was intense and diffuse as severe. Blinding for pre-embolization and postembolization was not possible as postembolization angiography images were annotated accordingly. A decrease ≥1 category of synovial hyperaemia after Genicular Artery Embolization was interpreted as decreased synovial hyperaemia. CIRSE defined grade 3−4 complications,[17] three-month post-operative joint bleeding requiring clotting factor replacement, duration of hospitalization after surgery, and pre-operative and post-operative haemoglobin levels were extracted from patient records.

2.3 | Statistical methods

All eligible patients who provided informed consent were evaluated. Descriptive statistics were reported as frequencies (with percentages) or medians (with interquartile ranges (IQR)). The Mann-Whitney U test was used to compare skewed data between non-embolized joints and embolized joints. The Chi-Square Test was used to evaluate the association of synovial hyperaemia and embolization with the presence/absence of 3-months postoperative joint bleeding. P-values < .05 were considered statistically significant.

Analyses were performed by using SPSS version 23.1.10 (IBM SPSS Statistics, IBM Corporation, Armonk, NY).

3 | RESULTS

The retrospective study design with selection of patients, performed angiographies with/without Genicular Artery Embolization and number of surgeries is summarized in Figure 1. Out of 32 eligible persons with haemophilia, we did not receive a written reply from four patients, and one patient was unwilling to participate. Eight procedures were excluded because these were performed to treat severe joint bleeding and were not performed preoperatively. Two repeated procedures because of delayed surgery were excluded, only the most recent procedure before TKR was included. One procedure was excluded because of an arthrodesis instead of TKR. A total of 33 preoperative angiography procedures in 24 persons with haemophilia (both knees of 9 persons) were included in this study. Sixteen out of 34 joints (47%) underwent genicular artery embolization because of synovial hyperaemia. Three-month clinical postoperative follow-up data was available for all operated joints. Median age was 54.4 years (IQR 48.4–65.9, range 37.4–78.4). Most angiography procedures were performed in persons with severe haemophilia A (67%). Baseline patient and joint characteristics are shown in Table 1.

3.1 | Angiography and embolization

Angiography findings and results of Genicular Artery Embolization are summarized in Table 2. Angiography showed synovial hyperaemia in a total of 21/33 joints (64%). Synovial hyperaemia was moderate or severe in 10/33 joints (30%). Synovial hyperaemia pre-embolization was more severe in joints that underwent subsequent Genicular Artery Embolization compared to non-embolized joints ($P < .001$). Genicular artery embolization was performed in 15/33 joints (45%). A total of 6/11 joints (55%) with mild hyperaemia were not embolized and the other 5/11 joints (45%) with mild hyperaemia were embolized. All patients with moderate and severe hyperaemia were embolized (10/33 joints). The median number of embolized vessels was 2 (IQR 1−2). PVA particles were used in all embolized joints.

Genicular Artery Embolization resulted in a decrease of synovial hyperaemia in 13/15 (87%) joints. No peri-procedural complications occurred.

At the end of the trans-arterial angiography procedure, normal synovial vascularization was observed in 17/33 joints (52%). Mild residual synovial hyperaemia was observed in 14/33 joint (42%), and moderate residual synovial hyperaemia in 2/33 joints (6%). Figure 2 shows

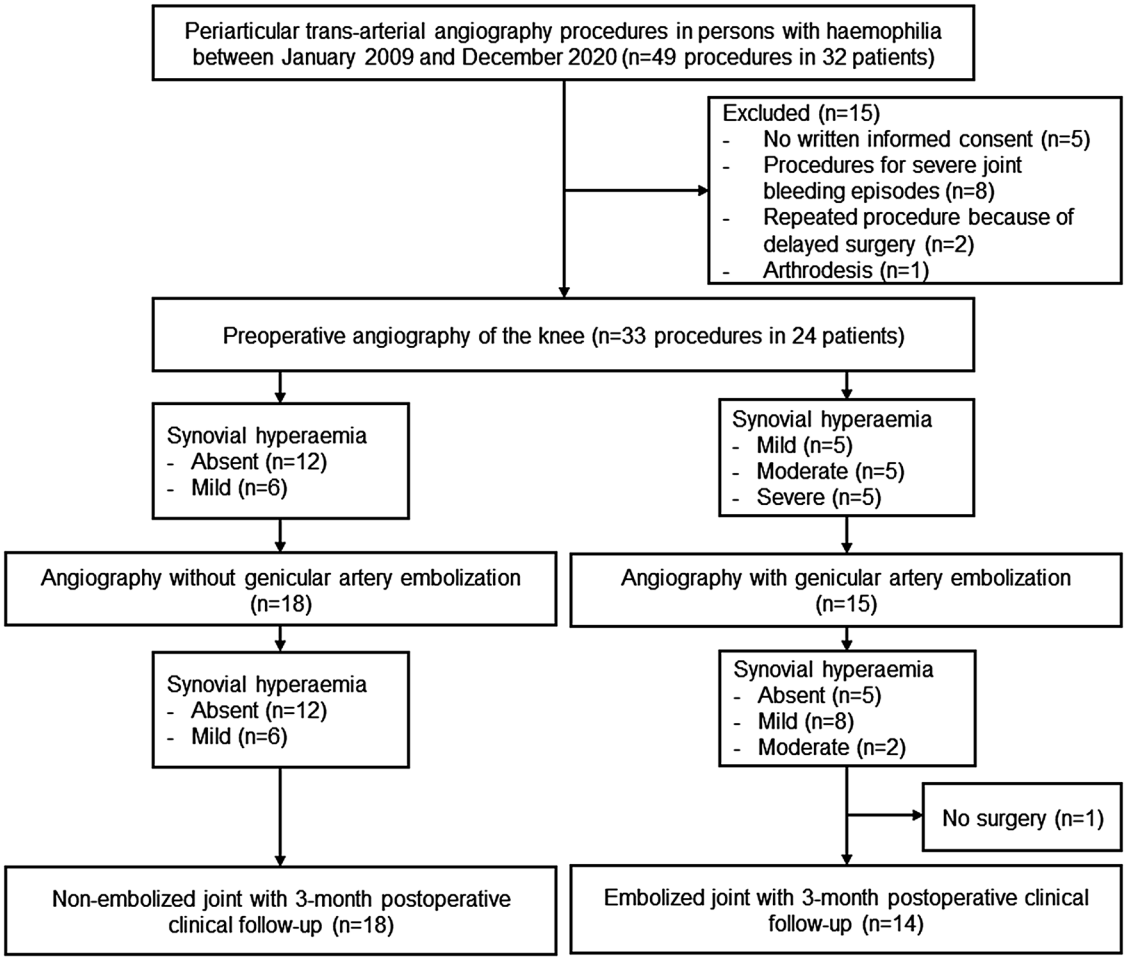

FIGURE 1 Flowchart.

TABLE 1 Baseline patient and joint characteristics.

Characteristics	Non-embolized	Embolized	Overall	*P*
N	18	15	33*	
Age, y	55.9 (46.7–66.6)	49.8 (48.6–65.9)	54.4 (48.5–65.9)	.215
Haemophilia				
Severe A	12 (67%)	10 (67%)	22 (67%)	
Severe B	1 (6%)	1 (7%)	2 (6%)	
Moderate A	0	3 (20%)	3 (9%)	
Moderate B	0	0	0	
Mild A	4 (22%)	1 (7%)	5 (15%)	
Mild B	1 (6%)	0	1 (3%)	
Knee				
Right	11 (61%)	10 (67%)	21 (64%)	
Left	7 (39%)	5 (33%)	12 (36%)	
Days between angiography and TKR	1 (0–1)	1 (0–2)	1 (0–2)	.955

Values are medians (IQR) or numbers (%). Percentages may not add up to exactly 100% because of rounding.
*Both knees of 9 patients were included.

TABLE 2 Pre-operative angiography findings, effects of embolization and postoperative bleeding.

Joint characteristics	Non-embolized joints	Embolized joints	Overall	P†
N	18	15	33	
Synovial hyperaemia pre-embolization				
Absent	12 (67%)	0	12 (35%)	<.001
Mild	6 (33%)	5 (33%)	11 (33%)	
Moderate	0	5 (33%)	5 (15%)	
Severe	0	5 (33%)	5 (15%)	
Embolization				
Embolized vessels	0	2 (1-2)		
PVA particles	0	16 (100%)		
Synovial hyperaemia end of procedure				
Absent	12 (67%)*	5 (33%)	17 (52%)	.067
Mild	6 (33%)*	8 (53%)	14 (42%)	
Moderate	0	2 (13%)	2 (6%)	
Severe	0	0	0	
Surgery (N)	18	15	33	
Peri-procedural complications	0	0	0	
3-month postoperative bleeding	0 (0–1)	0 (0–1)	0 (0–0)	.642

Values are medians (inter quartile range) or numbers (percentages). Percentages may not add up to exactly 100% because of rounding.
*Unchanged; no embolization performed.
†*P* value for comparison of non-embolized joints with embolized joints.

an example of decreased synovial hyperaemia on angiography as a result of Genicular Artery Embolization. Although residual synovial hyperaemia at the end of the procedure was to some extend more severe for embolized joint compared to non-embolized joints, this was not statistically significant ($P = .067$).

3.2 | Surgery and postoperative bleeding

In total, 32 TKRs were performed. Median length of hospitalization after surgery was 9 days (IQR 8—14, range 7—35). Haemoglobin levels were determined 1 day (IQR 0—14) before surgery and postoperatively at day 1 (IQR 0—1), and dropped from 9.1 mmol/L (IQR 8.6–9.6) to 7.4 mmol/L (IQR 7.0–7.9). A joint bleed within 24 h after surgery occurred in 1/32 joints (3%). Three-months post-operative joint bleeding occurred in 5/32 joints (16%) and was treated by clotting factor replacement. In 1/5 joints (20%) with postoperative bleeding, incision and drainage was performed in the operating room.

Three-months post-operative joint bleeding occurred in 2/18 joints (11%) without synovial hyperaemia and in 3/14 joints (21%) with residual -predominantly mild- synovial hypertrophy, which was not significantly different ($P = .425$). Likewise, no differences in 3-month post-operative joint bleeding were observed by comparing non-embolized joints with embolized joints (11% vs. 21% with bleeds respectively, $P = .425$).

4 | DISCUSSION

Synovial hyperaemia was observed by angiography in the majority of knees (64% in total, 30% with moderate/severe hyperaemia) in persons with haemophilia prior to TKR. Without any observed complications, a successful decrease in synovial hyperaemia postembolization was observed in 87% of joints after Genicular Artery Embolization.

Previous studies evaluated postoperative complications after TKR in persons with haemophilia. A meta-analysis in 2016 included 10 studies and reported joint bleeding as the most observed complication after TKR in persons with haemophilia.[10] Percentages of postoperative bleeds varied from 3%—32%, with a total of 31/361 (9%) joints with postoperative bleeds after TKR.[21–29] In the present study, a post-operative joint bleed within 24 h occurred in 1/34 joints (3%) which is comparable to the lowest published incidence in literature.[24] However, previous studies did not report on the time window of postoperative joint bleeding and clotting factor replacement protocols varied among studies making comparison difficult. The observed 18% of joints with joint bleeding during 3-months of follow-up in the present study cannot be compared reliably with previous literature on TKR in persons with haemophilia.

Angiography and embolization-related complications were reported in a meta-analysis evaluating angiographic treatment of severe joint bleeding in persons with haemophilia.[16] CIRSE defined grade 3—4 complications occurred in 5% of procedures and included

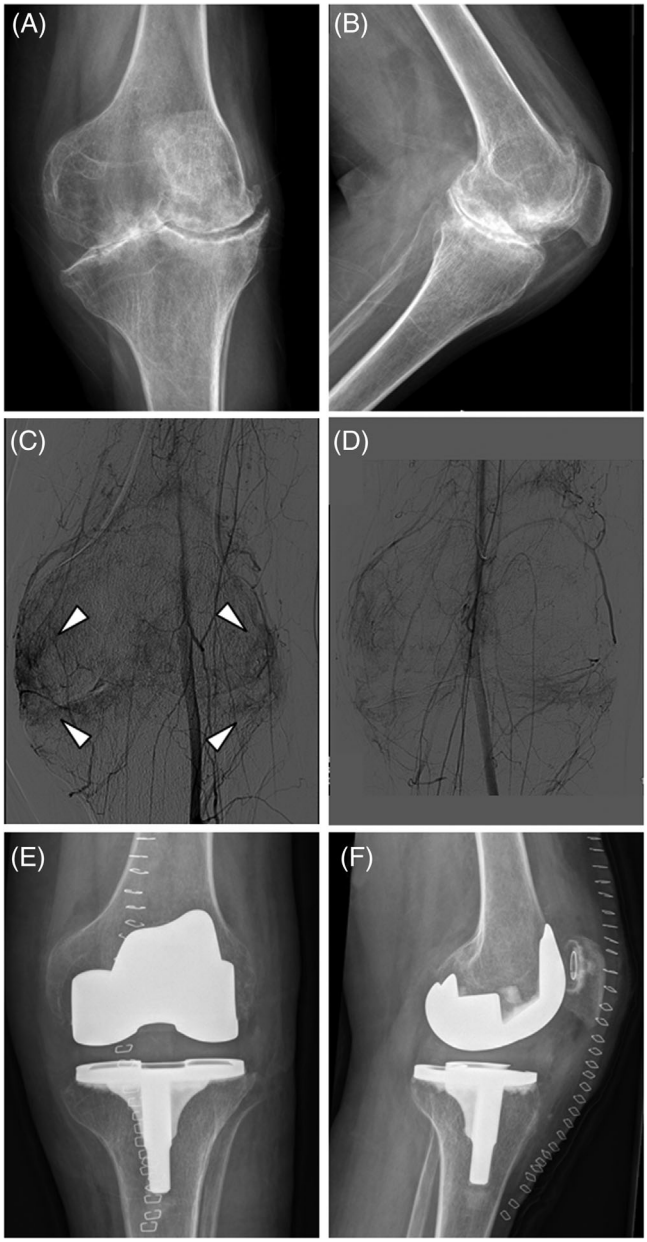

FIGURE 2 Pre-operative genicular artery embolization in the left knee with synovial hyperaemia. (A,B) Pre-operative radiographs of the left knee with severe haemophilic arthropathy. (C) Angiography pre-embolization with synovial hyperaemia (arrowheads). (D) Angiography post-embolization with particles showing a decrease of synovial hyperaemia. (E,F) Postoperative radiographs of the left knee.

paresis of a nerve near the site of arterial access, pseudoaneurysm at the puncture site, retroperitoneal bleeding, and a muscle bleed.[16,17] These complications were not observed in the present study.

4.1 | Strengths and limitations

Although this study is the first evaluating the prevalence synovial hyperaemia in severe haemophilic arthropathy and the effects of Genicular Artery Embolization preoperatively, limitations should be taken into account. Firstly, the absolute number of angiographic procedures ($N = 33$) in this retrospective study was limited due to low prevalence of haemophilia. However, our results provide new information about the high prevalence of synovial hyperaemia in knees prior to TKR in persons with haemophilia (65″% in total, 30% with moderate/severe hyperaemia). Our sample was relatively large compared to the total of 78 cases from 15 publications evaluating the results of angiography and embolization of haemophilia related joint bleeding and comparable with a previous publication with 30 cases on embolization of chronic haemophilic synovitis.[16,18] As a result of the limited absolute number of procedures, our analyses may lack power to observe statistically significant differences in 3-month post-operative joint bleeding in the comparison of no synovial hyperaemia versus residual hyperaemia, and in the comparison of non-embolized versus embolized joints.

Secondly, inter-observer variances may result in different interpretations on the severity of synovial hyperaemia. In the present study, angiographic studies were retrospectively scored by an experienced interventional radiologist but blinding to pre- and postembolization images was not possible. Although this may result in an overestimation of the effect of Genicular Artery Embolization on synovial hyperaemia, real changes in synovial hyperaemia could be interpreted more accurately by one-to-one comparison of pre- and postembolization images. Joints with synovial hyperaemia were embolized based on the decision of the interventional radiologist performing the procedure. However, not all joint with mild synovial hyperaemia were embolized. The distribution of hyperaemia (focal mild hyperaemia from one branch versus diffuse mild hyperaemia from multiple branches), or inter-observer differences may play a role in these discrepancies regarding embolization-choices of mild hyperaemia.

Thirdly, this study did not evaluate a control group of persons with haemophilia who received a TKR without preoperative embolization of hyperaemic synovial, as the angiographic procedure is standard of care before TKR in our centre. Such a control group would enable evaluation whether preoperative embolization results in a decrease in postoperative bleeds in the rehabilitation period after TKR compared to non-embolized knees.

4.2 | Clinical relevance and future research

Postoperative joint bleeding may have a serious impact on the rehabilitation and clotting factor consumption in persons with haemophilia. Preoperative Genicular Artery Embolization reduced synovial hyperaemia and is expected to limit postoperative bleeds in the vulnerable joint during rehabilitation. We observed a significant reduction of synovial hyperaemia after embolization. However, no significant difference was observed in 3-months postoperative joint bleeding between joints with and without residual synovial hypertrophy. This may be explained by the low number of joints with predominantly mild residual synovial hyperaemia after Genicular Artery Embolization. Whether

postoperative bleeding is more prevalent in joints with moderate of severe synovial hyperaemia remains to be established.

5 | CONCLUSION

One third of patients with haemophilia requiring a TKR have moderate or severe synovial hyperaemia which can be reduced safely by selective arterial Genicular Artery Embolization prior to TKR. Three-month postoperative bleeding appears to occur independently of the presence of residual mild synovial hyperaemia.

AUTHOR CONTRIBUTIONS

W. Foppen—Conceptualization, Data acquisition, Data analysis, Interpretation of data, Writing—Original Draft. I.C. van der Schaaf—Data acquisition, Interpretation of data, Writing—Review & Editing, Supervision. F.H.P. van Leeuwen—Interpretation of data, Writing—Review & Editing. D.H. Verlind—Data acquisition, Data analysis, Interpretation of data, Writing—Review & Editing. L.F.D. van Vulpen—Interpretation of data, Writing—Review & Editing. H.C. Vogely—Interpretation of data, Writing—Review & Editing. M.W. Barentsz—Conceptualization, Data acquisition, Writing—Review & Editing, Supervision. The manuscript has been read and approved for publication by all authors. All authors agree to be accountable for all aspects of the work.

CONFLICT OF INTEREST STATEMENT

W.F. has received research grants from NovoNordisk and Pfizer which were paid to the institution, and consultancy fees from Pfizer. L.V. received research grants from CSL Behring and Griffols which were paid to the institution and reports to be in the advisory boards of Swedish Orphan Biovitrum BV (sobi), Tremeau Pharmaceuticals and CSL Behring. I.S., F.L., D.H., H.V., and M.B. declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data is available from the corresponding author upon request.

ETHICS STATEMENT

The study was approved by the Medical Research Ethics Committee of the University Medical Center Utrecht, The Netherlands (protocol ID 19—775/C).

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