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Exoseal for puncture site closure after antegrade procedures in peripheral arterial disease patients

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PURPOSE
Exoseal is a vascular closure device consisting of a plug applier and a bio-absorbent polyglycolic acid plug available in sizes 5 F, 6 F, and 7 F. In this study, we aimed to evaluate the effectiveness and safety of the Exoseal vascular closure device (Cordis Corporation, Bridgewater, New Jersey, USA) for puncture site closure after antegrade endovascular procedures in peripheral arterial occlusive disease (PAOD) patients.

MATERIALS AND METHODS
In this retrospective study, a total of 168 consecutive patients who underwent an interventional procedure due to PAOD, were included. In each case, an antegrade peripheral endovascular procedure was performed via the common femoral artery using the Seldinger technique, and Exoseal 5 F, 6 F, or 7 F was used for access site closure. The primary endpoint was a technically successful application of Exoseal. All complications at the access site within 24 hours were registered as a secondary endpoint.

RESULTS
In a group of 168 patients (64.9% men, average age 71.9±11.9 years), the technical application of Exoseal was successful in 166 patients (98.8%). Within the first 24 hours after the procedure, 12 complications (7.2%) were recorded including, three pseudoaneurysms (1.8%) and nine hematomas (5.4%). None of the complications required surgical intervention.

CONCLUSION
Exoseal is a safe and effective device with high technical success and acceptable complication rates for access site closure after antegrade peripheral endovascular procedures.

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Femoral access sites are important sources of complications in endovascular procedures. In addition to conventional manual compression, arterial closure devices have been successfully used for the purpose of hemostasis at the femoral arterial access site in interventional radiology, cardiology, and angiology for several years. The effectiveness and safety of these devices have already been proven in numerous studies (1). Vascular closure devices were developed to address the increasing time constraints in everyday clinical routine, as well as to increase patient comfort after interventional procedures. Most of these devices have been evaluated for retrograde access.

Exoseal (Cordis Corporation, Bridgewater, New Jersey, USA) is a vascular closure device consisting of a plug applier and a bio-absorbent polyglycolic acid plug available in sizes 5 F, 6 F, and 7 F. Exoseal is inserted into the branch canal directly outside the arterial vessel wall and underneath the fascia of the neurovascular bundle. The polyglycolic acid plug increases platelet aggregation, as well as promoting erythrocyte accumulation within the network of the plug. This results in closure of both vessel wall and branch canal. Exoseal gets hydrolyzed into carbon dioxide and water via the Kreb's cycle and it is completely reabsorbed within 60–90 days (2).

The available data studying the role of Exoseal in peripheral vascular interventions is limited, and to this date, there are only two studies published that address the use of this device in antegrade femoral access (3, 4).

The aim of this study was to evaluate the effectiveness and safety of Exoseal use for access site closure following antegrade vascular procedures on peripheral arterial occlusive disease (PAOD) patients. According to our literature research, this is the largest patient cohort that has been investigated in that respect so far.

Materials and methods

Patients

In this retrospective study, all antegrade interventions, such as digital subtraction angiographies, percutaneous transluminal angioplasties with or without stenting, as well as aspiration embolectomies with access via the common femoral artery (CFA), using Exoseal 5 F, 6 F, or 7 F for access site closure were included. In total, 168 consecutive patients suffering from symptomatic PAOD were included. In accordance with the TransAtlantic Inter-Society Consensus II (TASC II) criteria, these patients underwent endovascular therapy (5). Patients with intra-arterial local thrombolysis were excluded, because the procedure carries a high-

er bleeding risk. Patients were included independently of their body mass index. The study was approved by the Institutional Review Board (IRB number: 24-271 ex 11/12). Patient characteristics are depicted in Table 1.

Procedures

All procedures were performed according to a standard operating procedure. On the day prior to the intervention, patients underwent a color-coded duplex ultrasonography of the prospective access site in order to determine the antegrade direction as technically possible (<50% stenosis of the CFA, evaluation of abdominal girth/anatomical proportions which allow antegrade puncture).

Antegrade CFA puncture was achieved through palpation via Seldinger technique, and after the application of the guidewire an antegrade sheath (Cook Medical Inc., Bloomington, Indiana, USA) was placed. All patients received 3000 international units (IU) of unfractionated heparin intra-arterially immediately after sheath insertion. The endovascular procedures were performed according to the European Society of Cardiology (ESC) guidelines 2011 regarding the aspect of the underlying morphology of the arterial lesions (6). At the end of the intervention, a 5 F, 6 F or 7 F Exoseal closure device was applied, followed by a short manual compression of two minutes, for the purpose of hemostasis. All catheter-directing physicians who applied the closure devices were trained in the handling of Exoseal by the manufacturer's instructor and had many years of experience with endovascular procedures.

In accordance with our standards, we opted for access via the crossover technique in case of more than 50% stenosis in the area of the CFA. Consequently, the antegrade application of Exoseal was omitted in case of more than 50% stenosis in the CFA area within the present patient cohort. Furthermore, Exoseal was not used if preceding interventions required more than two punctures or if a stent was present in the CFA area. Each patient was given a pressure bandage for 24 hours and prescribed bed rest for 12 hours after the intervention, as is our standard procedure for access site closure. If hemostasis could not be achieved using Exoseal, a conversion to manual compression for the duration of at least 20 minutes was carried out. Postprocedural anticoagulation was achieved by subcutaneous application of low molecular weight heparin (Enoxaparin 40 mg) twice daily for two days. The activated partial thromboplastin time guided application of unfractionated heparin for 24 hours was performed only in dialysis patients, patients with severe chronic renal failure, and patients with peripheral embolizations. After stent insertion patients received a loading dose of clopidogrel 300 mg and received dual antiplatelet therapy (acetylsalicylic acid 100 mg and clopidogrel 75 mg daily) for three months. On the day after the procedure, all patients were subjected to color-coded duplex ultrasonography at the access site as well as in the area of the treated vascular bed, without exception. In the context of the follow-up care, the ankle-brachial index in the area of the treated extremity was recorded. All complications from intervention to discharge were documented in a standardized protocol.

Device

Within the framework of the study, Exoseal was used in sizes 5 F, 6 F, and 7 F. Exoseal was inserted into the sheath of the branch canal and subsequently retracted far enough to stop the bleeding of the marker lumen. Then the polyglycolic acid plug was positioned directly outside the vessel wall, yet still underneath the vessel fascia so that fascia and the surrounding adventitial connective tissue covered the plug. Consequently the plug extended and closed the branch canal.

End points

Primary endpoint was the successful application of Exoseal. The application was deemed successful if the device was applied easily and no hints of bleeding or other complications could be identified after the removal of the sheath. Primary complication was defined as the necessity of other interventions such as prolonged compressions (for at least 15 minutes) for the purpose of hemostasis.

The secondary endpoint was defined as the incidence of complications at the access site after the intervention until the time of discharge. In accordance with the Ensure's vascular closure device speeds hemostasis trial (ECLIPSE trial), complications were retrospectively classified into minor adverse events (local bleeding, hematoma, pseudoaneurysm, arteriovenous fistula, retroperitoneal bleeding, ipsilateral embolization, access site-related nerve injury) and major adverse events (need for vascular repair by surgical or nonsurgical techniques, bleeding requiring a blood transfusion, infection requiring antibiotics, new-onset ischemia of the ipsilateral lower extremity, access site-related nerve injury which is permanent or requiring surgical repair) (7).

Statistical analysis

We performed an intention-to-treat analysis. All cases with antegrade application of Exoseal were included. In case of continuous variables, patient characteristics, as well as data regarding the interventions were summarized as mean±standard deviation and median. Categorical variables were represented by frequency and percentages. The normal curve of distribution was examined via Kolmogorov-Smirnov and Shapiro-Wilk test. In case of parametrical distribution, patients with and without complications were compared by means of a two-sided t-test for independent samples. In case of nonparametrical data, Mann Whitney U Test was utilized for the comparison of the groups. The comparison of categorical variables between groups was performed using the chi-square and Fisher's exact tests. Statistical significance was assumed when P value was <0.05. Statistical analyses were executed via SPSS version 20.0 (SPSS Inc, Chicago, Illinois, USA).

Results

In total, 168 antegrade interventions were performed using Exoseal for closure of the inguinal access site (average age 71.9±11.9 years, 109 males [64.9%]). The most frequently accessed vessel was the superficial femoral artery (in 59.5% of interventions). Most patients were suffering from PAOD in Fontaine stage II b (n=80, 47.6%). The mean duration of procedure was 34±17.2 minutes. Percutaneous transluminal angioplasties were conducted in 66.7% of patients (n=112), stenting procedures in 25.6% (n=43), and digital subtraction angiographies in 7.1% (n=12). One patient underwent aspiration embolectomy (0.6%). Exoseal 5 F was used in 8.3% (n=14), 6 F in 91.1% (n=153), and 7 F in 0.6% (n=1). For intervention characteristics, see Table 1.

Primary hemostasis in the area of the groin puncture site could not be achieved using Exoseal in two cases (1.2%). In these cases, prolonged manual compression was utilized in order to achieve hemostasis. Therefore, the primary endpoint of a successful Exoseal application was reached in 166 (98.8%) interventions.

A total of 12 complications (7.2%) were observed, including three pseudoaneurysms (1.8%) and nine hematomas (5.4%). Postinterventional bleeding did not occur in any of the cases. All pseudoaneurysms were successfully treated by the local injection of thrombin and the subsequent application of a pressure bandage followed by 24 hours of bed rest. In two cases, a pseudoaneurysm as well as the respective hematoma was detected. In one case, the hematoma could be observed together with a primary error in device application. In accordance with the ECLIPSE trial, not a single major adverse event was witnessed. For further results see Table 2.

Postinterventional low molecular weight heparin application was performed in 161 patients. Seven patients were treated with unfractionated heparin for 24 hours postinterventionally: five patients were suffering from renal insufficiency, while two patients were treated with unfractionated heparin due to peripheral embolization detected during the intervention (preceding the application of Exoseal). The use of low molecular weight heparin was not significantly associated with the occurrence of adverse events ($P = 0.38$).

A comparison of potential covariates between patients with and without complications is shown in Table 3.

Table 1. Patient characteristics and procedural details

	n=168
Men, *n (%)*	109 (64.9%)
Age (years), *median (25^{th}–75^{th} percentile)*	72.2 (63.6–81.4)
Fontaine classification, *n (%)*	
Complicated stage	13 (7.7)
Stage II b	80 (47.6)
Stage III	6 (3.6)
Stage IV	69 (41.1)
Arterial hypertension, *n (%)*	138 (82.1)
BMI (kg/m^2), *median (25^{th}–75^{th} percentile)*	26 (24–29)
Diabetes, *n (%)*	86 (51.2)
Smoking status, *n (%)*	
Current smoker	28 (16.7)
Ex-smoker	67 (39.9)
Nonsmoker	73 (43.4)
Type of procedure, *n (%)*	
DSA	12 (7.1)
PTA	112 (66.7)
Stent	43 (25.6)
AE	1 (0.6)
Procedure duration (min), *mean±SD*	34±17.2
Vascular closure device, *n (%)*	
Exoseal 5 F	14 (8.3)
Exoseal 6 F	153 (91.1)
Exoseal 7 F	1 (0.6)
Sheath size (F), *median (range)*	6 (5–7)
Treated vessels, n	
Superficial femoral artery	100
Popliteal artery	67
Below the knee	78
Antiplatelet therapy before procedure, *n (%)*	
None	20 (11.9)
Single (aspirin or clopidogrel)	124 (73.8)
Dual (aspirin and clopidogrel)	24 (14.3)
Postprocedural anticoagulation, *n (%)*	
Enoxaparin	161 (95.8)
Unfractionated heparin	7 (4.2)

BMI, body mass index; DSA, digital subtraction angiography; PTA, percutaneous transluminal angioplasty; AE, aspiration embolectomy.

Table 2. Effectiveness and safety of Exoseal in antegrade procedures

	n (%)
Procedural success	166 (98.8)
Access site complications	12 (7.2)
Major adverse events	0 (0.0)
Minor adverse events	12 (7.2)
Hematoma	9 (5.4)
Pseudoaneurysm	3 (1.8)

Table 3. Comparison of potential covariates in patients with and without complications

Covariates	Complication	No complication	*P*
Age (years)	73.6±9.3	71.8±12.1	0.64
BMI (kg/m^2)	25.1±2.6	26.5±3.9	0.23
Sheath size (F)	5.8±0.4	5.9±0.3	0.22
Prothrombin time (%)	81.8±28.1	88.1±23.4	0.54
Platelet count (10^9/L)	333±187	249±94.5	0.05
PTT (s)	34.2±5.0	33.5±7.5	0.27

Data are presented as mean±standard deviation.
BMI, body mass index; PTT, partial thromboplastin time.

None of the covariates analyzed (age, body mass index, sheath size, prothrombin time, platelet count, partial thromboplastin time) showed significant differences between patients with and without complications.

Discussion

In order to achieve hemostasis at the femoral puncture site, various closure devices with different modes of action have been developed in the last couple of years. To date, the data is ambiguous, particularly in comparison to conventional manual compression. The use of closure devices in antegrade interventions has so far been insufficiently discussed in the relevant literature. Exoseal is a vascular closure device deploying a completely absorbable plug. As opposed to other closure devices, Exoseal does not leave behind foreign bodies, such as an anchor (e.g., Angioseal, St. Jude Medical, St. Paul, Minnesota, USA), nitinol clip (e.g., StarClose, Abbott Vascular, Redwood City, California, USA), or sutures (e.g., Perclose Proglide, Abbott Vascular). Severe and partially limb-threatening complications associated with the use of anchor-mediated closure device Angioseal have already been published (8–11). However, Angioseal is the most frequently used vascular closure device and has the most extensive data collection, which might account for the number of reported serious adverse events. Even in antegrade interventions, Angioseal has already been investigated extensively. Existing literature describes a successful antegrade device application of Angioseal between 80.8% and 100%, and "major complications" between 0% and 1.1% (12–19).

With regards to the antegrade application of Exoseal, to our knowledge only two studies have been published so far. Both studies included relatively small numbers of patients (n=93 and n=59), but were conducted prospectively (3, 4). Unfortunately, these studies differed in classification of major and minor adverse events. Schmelter et al. (3) used the ECLIPSE classification as published by Wong et al. (7). Successful device application was accomplished in 96% of their patients, and no major adverse event was observed. Maxien et al. (4) reported successful device application in 98.3% of patients, and one major adverse event, a pseudoaneurysm within a hematoma, which was successfully treated by 20 minutes of manual compression. According to the ECLIPSE trial, this complication would have been classified as a minor adverse event.

In order to establish a larger comparability in potential later reviews, we adhered to the ECLIPSE classification in our study. With a successful device application rate of 98.8% and minor complications in 7.2% of the cases, the safety and effectiveness of Exoseal was determined to be similar to the two studies mentioned above. Three pseudoaneurysms and nine local hematomas were identified in our study. No complication necessitated surgical repair or blood transfusion. The pseudoaneurysms observed in our study were treated successfully with single, local thrombin injections and subsequent application of pressure bandages for 24 hours. Local thrombosis of pseudoaneurysms via thrombin injection could be accomplished independently of Exoseal use. Local ultrasound-guided thrombin injection is a safe and effective method for treatment of pseudoaneurysms developing as postinterventional complications (20–23). Thus, pseudoaneurysms rarely require further surgical measures.

The hematomas identified in our study were minor adverse events. No hematoma required surgical removal, peri-interventional administration of antibiotics or prolonged hospitalization. As long as hematomas do not cause a great amount of pain, induce a superinfection or require surgical removal, they are considered relatively harmless. The exact definition of hematoma is still difficult. According to the ECLIPSE trial, only hematomas ≤6 cm are seen as minor adverse events. In the literature, however, different definitions of hematomas in the area of the inguinal access sites can be found. The size of a hematoma is hard to specify because its edges are frequently undefined and the hematoma itself often slides into the groin crease or scrotum. A circular, clearly delineated hematoma is the exception in clinical practice.

In addition, the size of a hematoma should be observed relative to the body surface and mass, as these could cause differences. Moreover, interobserver variability is conceivable. Therefore, we defined hematomas as minor adverse events independently of their size, unless further therapeutic measures were required as detailed above. In our study, Exoseal was used in antegrade procedures in all sizes available on the market (5 F through 7 F). However, the 7 F system was only used once; therefore we cannot make further conclusions on it. In general we could not identify a significant difference in complications with regards to sheath size.

The first study published on Exoseal 7 F included 60 patients and concluded Exoseal to be safe in size 7 F. Furthermore, a short time to hemostasis, short time to ambulation and low complication rates were observed (24). In another, recently published retrospective study on Exoseal 5 F, 6 F and 7 F, the device was assessed as safe and effective independently of its size or whether an intervention had previously taken place at the puncture site; however, the study was conducted exclusively on retrograde vascular interventions (25).

The use of Enoxaparin instead of unfractionated heparin is standard procedure in our department and seems to be safe with regards to complications of peripheral vascular interventions (26, 27). Due to its superior handling in clinical routine as well as the avoidance of heparin induced thrombocytopenia type II, this procedure is generally accepted and did not influence our results.

Our study was limited in particular because of its retrospective design. Potential late complications could not be recorded as there was no follow up within the first 30 days after the intervention. Furthermore, randomization could not be performed due to the retrospective nature of the study. Randomization would have been important to minimize the "selection bias" for the use of Exoseal.

In conclusion, similar to other published studies, we found the Exoseal vascular closure device to be safe and effective with high technical success rates and acceptable complication rates in antegrade procedures. Further prospective studies using larger patient cohorts comparing Exoseal with manual compression or other vascular closure devices would be desirable.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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