Access Site Management after Peripheral Percutaneous Transluminal Procedures: Neptune Pad Compared with Conventional Manual Compression[1]

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Purpose: To investigate the safety and efficacy of the procoagulant wound dressing Neptune Pad (Biotronik, Berlin, Germany) compared with those of conventional manual compression for access site management after peripheral percutaneous interventions.

Materials and Methods: The study was approved by the institutional ethics committee, and all patients gave written informed consent. Two hundred one consecutive patients were enrolled and were randomly assigned to be treated with the Neptune Pad ($n = 100$) or conventional manual compression ($n = 101$). Patients were followed up clinically until hospital discharge and with duplex ultrasonography at 24 hours after the procedure to evaluate occurrence of access site complications. Time to hemostasis and time to ambulation were recorded, and patient and physician discomfort were measured by using a visual analogue scale.

Results: The risk for access site complications was not significantly different between the Neptune Pad group and the conventional compression group (adjusted odds ratio, 1.15; 95% confidence interval: 0.47, 2.84; $P = .76$). Time to hemostasis was marginally reduced in the Neptune Pad group. Patient and physician discomfort were lessened with use of the device.

Conclusion: The hemostatic device Neptune Pad does not improve the safety of access site management after peripheral percutaneous procedures. Markedly improved comfort was noted among patients in the Neptune Pad group and by the physicians obtaining hemostasis.

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Arterial puncture at the level of the groin is the most frequent means of access to the vascular system for angiographic and interventional procedures. Despite technical advances in catheter systems that have enabled decreasing sheath sizes, access site complications remain the most frequent adverse events after percutaneous transluminal procedures (1,2). Mild or severe vascular complications such as small or large hematomas, bleeding, and pseudoaneurysm at the transfemoral access occur in up to 9% of percutaneous transluminal procedures (2–5). Patients are clearly more prone to vascular complications after percutaneous interventions than are patients who undergo only diagnostic angiographic studies. In particular, with the increasing use of aggressive antithrombotic substances such as thienopyridines and glycoprotein IIb/IIIa antagonists, the frequency of complications at the vascular access site tends to increase (6). Access site complications prolong patient hospitalization and increase the risk for cardiac adverse events (7). Therefore, optimal management of the vascular access site after percutaneous transluminal procedures is a matter of utmost importance.

The most common technique for puncture site management is manual compression. This technique requires extended pressure on the puncture site, and, after hemostasis is achieved, a pressure bandage is applied for several hours during bed rest. The development of specific closure devices has promised a reduction in complications, faster times to ambulation, and a reduction in the patient discomfort associated with the compression maneuver. Several studies (8–18) have addressed the efficacy and practicability of various closure devices compared with those of conventional compression. However, to our knowledge, a consistent benefit of closure devices compared with conventional compression with respect to the rate of access site complications has not yet been demonstrated (9,15,16).

The Neptune Pad (Biotronik, Berlin, Germany) is a soft and hydrophilic wound dressing that has been developed to accelerate local hemostasis and thereby potentially reduce compression times. The Neptune Pad consists of calcium alginate, which is cationically charged and exerts potent procoagulant properties. We investigated the efficacy and safety of this device in the management of arterial access sites after peripheral percutaneous transluminal procedures compared with those of conventional manual compression in a randomized controlled trial. Complication rates, compression times, times to ambulation, and patient and physician discomfort were assessed.

Advance in Knowledge

- The procoagulant wound dressing Neptune Pad is not superior to conventional manual compression after peripheral arterial puncture.

Materials and Methods

All authors have no association with either Biotronik or the Neptune Pad. Furthermore, all authors state no financial relationship or interest to disclose. Our study had no industry support.

Study Design and Inclusion and Exclusion Criteria

The study was designed as a randomized controlled trial. We enrolled 201 consecutive patients with symptomatic peripheral artery disease (PAD) (Fontaine stage II–IV) who underwent peripheral percutaneous transluminal interventions performed by using a transfemoral access in the angiology department of our tertiary care university hospital between January 2006 and September 2007. Sheath sizes of up to 8 F were allowed in study patients. All inguinal punctures (common femoral, superficial femoral, or deep femoral artery; antegrade or retrograde access) were included. No specific limitations on the use of antiplatelet or anticoagulant medication were specified. Patients with extreme obesity (body mass index, >35 kg/m^2) were not included, according to the manufacturer's recommendations regarding the use of the Neptune Pad. Furthermore, patients with known hypersensitivity to components of the device were not eligible. The study was approved by the local ethics committee, and all patients gave their written informed consent.

Study End Points

We defined *(a)* a primary safety end point (the occurrence of puncture-related complications, including major [>20 g/L hemoglobin decrease] and minor bleeding, hematomas, and pseudoaneurysms), *(b)* a secondary safety end point (including potential device-related complications such as wound infections, allergic skin reactions, and tissue necrosis), and *(c)* efficacy end points (including time to hemostasis and patient and physician discomfort as measured with the visual analogue scale [VAS] [18,19]).

All end points were evaluated by two independent observers (S.S. and M.H.), both of whom were angiologists with a minimum of 3 years of experience.

Randomization Process

Randomization was performed with computer-generated random digits and sealed envelopes. Patients were stratified according to *(a)* the femoral access route and whether antegrade or retrograde puncture was performed and *(b)* the size of the introducer sheath used (<6 or ≥6 F).

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Abbreviations:
IQR = interquartile range
PAD = peripheral artery disease
VAS = visual analogue scale

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Study Protocol

At admission, all patients scheduled for elective peripheral percutaneous transfemoral interventions were informed about the study, and written consent was obtained. Patients' medical histories and data from physical examination were recorded, with special attention to antiplatelet therapy and anticoagulant regimen. According to our standard procedure, arterial puncture for elective procedures with the direct influence of oral anticoagulants is prohibited. Warfarin and comparable agents had to be stopped at least 1 week prior to the procedure. Coagulation status was checked on the day prior to the intervention, and a prothrombin time of 29.8 seconds at the longest (at least 50% of the normal range) was generally required for arterial puncture. Sheath sizes of 4–8 F were used for antegrade or retrograde transfemoral procedures during the study period, and 5000 IU of heparin was routinely administered intraarterially at the beginning of the procedure. Immediately after the procedure, patients were transferred from the interventional site to the inpatient ward and were randomly assigned to be treated with either the hemostatic device or conventional manual compression. Before the sheath was removed, patients with a systolic blood pressure greater than 160 mm Hg received antihypertensive drugs with a rapid onset (usually sublingual nitroglycerin) until a sustained systolic pressure of less than 160 mm Hg was achieved. Removal of the sheath with or without the hemostatic device, according to the random assignment, was then performed immediately. All sheath removals were performed by physicians (either staff physicians or physicians in training), including P.D., A.B., M.B., and L.V.

Puncture Site Management with Hemostatic Device

The Neptune Pad was prepared with a small amount of 0.9% saline solution. The artery was then compressed proximal to the puncture site, and the sheath was removed. The Neptune Pad was then placed at the puncture site; moderate pressure was applied on the device, and the proximal pressure was released. Constant pressure at the Neptune Pad was maintained for at least 10 minutes. Pressure was then released, and hemostasis was checked. In cases of persistent bleeding, compression was applied for another 5 minutes. After hemostasis was achieved, compression was applied for another 5 minutes; the puncture site was then covered with a sterile dressing for 20 hours without the use of a compression bandage. The puncture site was checked after 4 hours, and stable patients were allowed to ambulate.

Puncture Site Management with Conventional Manual Compression

After the sheath was removed, compression on the arterial puncture site at the groin was performed for at least 10 minutes and was maintained for 5 minutes after bleeding had completely stopped. After sustained hemostasis was thus achieved, a pressure bandage was applied to the puncture area and was kept in place until the next day. The puncture site was checked after 4 hours, and stable patients were allowed to ambulate.

Laboratory Parameters

Routine laboratory investigations included complete blood cell counts, global coagulation tests, and the evaluation of levels of glycated hemoglobin, low-density lipoprotein and high-density lipoprotein cholesterol, serum triglycerides, liver enzymes, serum creatinine, high sensitivity C-reactive protein, and fibrinogen.

Definitions

The diagnosis of PAD was rendered after clinical evaluation and noninvasive arterial studies that included segmental limb pressure evaluation, ankle-brachial index measurements, and duplex ultrasonography (US). For categorization of PAD, the Fontaine classification was used. Groin hematomas at the access site were defined as ultrasonographically visualized hypodensities in the vascular surroundings. Hematomas that did not require transfusion were considered to be minor complications. Hematomas in which surgical evacuation was believed to be necessary because of their large size were categorized as major complications. Major bleeding was defined as a decrease in hemoglobin of more than 20 g/L with a potential need for transfusion and/or vascular surgical intervention. In all other cases, instances of bleeding were considered minor. A pseudoaneurysm was defined as localized extravascular jets from an iatrogenic fistula. Pseudoaneuryms were considered to be major complications.

Management of Bleeding Complications at Access Site

Any sort of access site bleeding was reported to the treating physician. As per our standard procedure, the wound dressing (simple wound dressing or pressure bandage) at the puncture site underwent careful inspection, and, if necessary, it was replaced after an additional episode of manual compression. If additional episodes of compression were necessary, the patients were not allowed to ambulate 4 hours after the intervention, and the bed rest time was prolonged for an additional 4 hours.

Surveillance Protocol

Patient and physician discomfort were assessed by using a VAS (18,19) immediately after the end of the compression period. Routinely, all patients underwent color-coded duplex US 24 hours after the intervention. Duplex examinations were performed with a US unit (XP128; Acuson, Mountain View, Calif) with a 5-MHz linear array probe. The arterial access was visualized from the external iliac artery down to the superficial femoral artery, including the femoral bifurcation and the deep femoral artery. Scans were performed in transverse and longitudinal views. Clinically, patients were followed up until hospital discharge for the occurrence of any adverse events.

Statistical Analysis and Sample Size Calculation

A sample size calculation was performed during the planning phase of the study, with application of the following assumptions: $\alpha = .05$; $\beta = .80$; fre-

quency of drop out, up to 5% (owing to the short follow-up of only 24 hours and hospital discharge); and frequencies of complications (composite of any vascular or nonvascular complication related to access site management) of 0% in the Neptune Pad group versus 8% in the manual compression group. A sample size of approximately 100 individuals per group was estimated to be necessary to meet these assumptions.

Continuous data are presented as medians and interquartile ranges (IQRs) (from the 25th to the 75th percentile), and discrete data are given as counts and percentages. Univariate comparisons between the study groups were performed by using χ^2 tests, exact tests, and Mann-Whitney *U* tests, as appropriate. A multivariate binary logistic regression model was applied to assess the association between the treatment groups and the study end points and to adjust for possible confounders. Results of the logistic regression model are given as the odds ratio and the 95% confidence interval. $P < .05$ was considered to indicate a statistically significant difference. Calculations were performed with software (Stata, release 8.0, Stata, College Station, Tex; SPSS for Windows, version 15.0, SPSS, Chicago, Ill).

Results

Patients

We enrolled 201 consecutive patients (54% men) with a mean age of 75 years (IQR: 66–81 years). Complete baseline and follow-up data were available for all patients, and all were included in the final analysis. One hundred patients were randomly assigned to the Neptune Pad group, and 101 patients were treated with conventional manual compression. Demographic data and clinical characteristics were comparable between the two groups (Table 1).

Table 1

Demographic Data and Clinical Characteristics for Neptune Pad and Conventional Manual Compression Groups

Characteristic	Neptune Pad ($n = 100$)	Conventional Manual Compression ($n = 101$)	*P* Value
Male sex	50 (50)	58 (57)	.29
Age (y)*	76 (67–83)	72 (64–81)	.14
PAD	67 (67)	54 (54)	.03
Coronary artery disease	46 (46)	59 (59)	.07
Arterial hypertension	82 (82)	85 (85)	.57
Hyperlipidemia	87 (87)	89 (89)	.66
Diabetes mellitus	42 (42)	40 (40)	.89
Smoking	21 (21)	27 (27)	.83
Body mass index (kg/m^2)*	26.4 (23.4–30.2)	27.0 (23.5–31.2)	.38
Sheath size			.75
4 F	11 (11)	12 (12)	
5 F	1 (1)	3 (3)	
6 F	61 (61)	62 (61)	
7 F	2 (2)	4 (4)	
8 F	25 (25)	20 (20)	
Thrombocyte count (g/L)*	246 (201–279)	257 (207–288)	.21
Retrograde puncture†	66 (66)	49 (49)	.01
Antiplatelet therapy‡			.88
None	4 (4)	4 (4)	
One drug	45 (45)	42 (42)	
Two drugs	51 (51)	55 (55)	

Note.—Unless otherwise specified, data are numbers of patients, with percentages in parentheses.

* Data are medians, with IQRs in parentheses.

† All other punctures were antegrade.

‡ One drug: aspirin or clopidogrel; two drugs: aspirin and clopidogrel.

Safety and Complications

Eighteen cases of minor bleeding at the access site during the first 24 hours after sheath removal were recorded (in 15 of 100 patients in the Neptune Pad group vs three of 101 patients in the manual compression group, $P = .003$; Table 2). We recorded no instances of major bleeding. Overall, we observed 27 (13.4%) puncture-related complications in 201 procedures. At US, pseudoaneurysms were noted in 16 patients (8.0%), and hematomas were noted in 11 patients (5.5%). The observed pseudoaneurysms were small (median size, 7 mm; IQR: 6–11 mm). One patient underwent surgical repair of a pseudoaneurysm, 14 pseudoaneurysms were treated with percutaneous injection of thrombin (despite their size, to expedite patient discharge), and one pseudoaneurysm occluded spontaneously after a further 12 hours of bed rest assisted by a pressure bandage. Finally, the frequency of pseudoaneurysm was not significantly different between the Neptune Pad and conventional compression groups (9% vs 7%, $P = .59$) (Table 2).

Consistent with univariate analysis, multivariable logistic regression analysis demonstrated no significant difference for the risk of complications between the Neptune Pad group and the conventional compression group (adjusted odds ratio, 1.15; 95% confidence interval: 0.47, 2.84; $P = .76$). The model was adjusted for age, sex, diabetes, hypertension, body mass index, sheath size, clinical stage of PAD, serum creatinine level, thrombocyte count, access route, and use of antiplatelet medication.

Efficacy

We observed a significantly reduced time to hemostasis in the Neptune Pad group compared with that in the conventional compression group (median, 14.5 minutes [IQR: 11–15 minutes] vs 15.0 minutes [IQR: 12–20 minutes]; $P = .009$). However, time to ambulation was not significantly different in pa-

tients randomly assigned to undergo treatment with the Neptune Pad versus that in patients treated with conventional manual compression (median, 4 hours [IQR: 4–4.2 hours] vs 4 hours [IQR: 4–12 hours]; $P = .32$). Patients, as well as the treating physician, experienced puncture site management with the Neptune Pad to be more comfortable, as indicated by a lower score on the VAS ($P < .001$) compared with the score for standard manual compression.

Table 2

Access Site Management Efficacy and Safety End Points in 201 Patients

End Point	Neptune Pad ($n = 100$)	Conventional Manual Compression ($n = 101$)	*P* Value
Safety end point			
Major bleeding	0 (0)	0 (0)	. . .
Minor bleeding	15 (15)	3 (3)	.003
Pseudoaneurysm	9 (9)	7 (7)	.58
Hematoma	4 (4)	7 (7)	.6
Efficacy end point*			
Time to hemostasis (min)	14.5 (11.25–15)	15 (12–20)	.009
Patient discomfort†	2 (0–3.2)	6.7 (4.8–8)	<.001
Physician discomfort†	3 (2–4)	5 (3–6.6)	<.001

Note.—Unless otherwise specified, data are numbers of patients, with percentages in parentheses.

* Data are medians, with IQRs in parentheses.

† As measured with the VAS (17,18).

Discussion

The concept of the entirely atraumatic closure device Neptune Pad seemed appealing, because no intra- or extravascular foreign material has to be placed, enabling immediate arterial repuncture and avoiding the risk of device-related occlusion of the lumen of the punctured vessel. Most other closure devices are based on a suture, anchor, or clip system that has to be placed at the puncture site. This maneuver includes a certain risk of local complications and device-related occlusion of the punctured vessel (20). In patients with heavily diseased arteries, such as typical patients with PAD, the use of such devices can be particularly problematic. Unfortunately, in this randomized trial, Neptune Pad did not improve the safety of access site management, and—although this difference was not statistically significant—an even higher number of access site complications was observed in the Neptune Pad group compared with the group treated with conventional manual compression. Time to hemostasis was significantly reduced with use of the Neptune Pad. However, looking at the observed effect size, a difference of 14.5 versus 15.0 minutes compression time seems clinically irrelevant. The perception of discomfort of compression was reduced for patients and physicians, but this was mainly protocol driven by the recommendation to apply only moderate pressure with the Neptune Pad. From our recent experience with the Neptune Pad and the previously evaluated Clo-Sur P.A.D. (21), it seems that the technical approach of an external hemostatic wound dressing does not help to reliably achieve local hemostasis. Notably, rates of access site complications in the study arms with manual compression, as well as in the study arms with the hemostatic devices, were closely comparable between the current study and our previous randomized trial of the Clo-Sur P.A.D. device (21).

Nevertheless, our reported complication rate seems rather high. Especially in comparison to results of other interventional studies, this difference is more than obvious. Two potential causes for the overall rather high number of complications at the vascular access site in this trial may be discussed: First, we specifically and thoroughly assessed groin complications with US investigations (24 hours after the intervention) performed by an experienced sonographer, and even minor complications like very small pseudoaneurysms—which clinically may not have been detected—were included in the number of complications. Second, we included patients with advanced PAD, and most of these patients have diseased vascular segments at the arterial access site. This may also account for the higher number of complications.

Of note, the manufacturer's recommendation of a body mass index limit is obviously put forth to optimize the performance of the Neptune Pad. Local hemostasis after percutaneous procedures often becomes a real challenge in obese patients, and ideally such patients should be included in any study assessing the efficacy of an arterial closure device.

We are aware of several limitations of this randomized trial. First, the study was not blinded, which increases the chance of bias. However, unblinded evaluation usually results in better outcomes in favor of the new device, but we observed an even higher rate of complications with the Neptune Pad, despite a positive attitude of the treating physicians toward the device (as reflected by the lower VAS score of physician discomfort). Second, the end points of patient and physician discomfort were indirectly protocol driven (by the recommendation to apply only moderate pressure with the Neptune Pad). A considerably larger sample size with several subgroups for different algorithms of immobilization would have been needed to address the question of an optimal time for bed rest after removal of the sheath. To our knowledge, such a study does not exist even for conventional compression as yet. Furthermore, the assumption for our sample size calculation may be a bit optimistic. In contrast, the device group showed markedly more complications than assumed, and the conventional treatment group performed better than expected. As an additional limitation, we are not able to provide information on the activated clotting time (ACT) lev-

els prior to the sheath removal. However, all anticoagulation was reversed prior to arterial puncture, and all patients received the same amount of heparin. Therefore, a significant difference in ACT levels between the two groups seems unlikely. Finally, the average recorded time to hemostasis of less than the 15 minutes put forth in our protocol implies that there were protocol deviations in both groups that could affect our results. However, the numbers of pseudoaneurysms and hematomas were balanced; therefore, the impact of these deviations is considered to be minor.

In conclusion, patient and physician discomfort were markedly lessened with use of the Neptune Pad. However, this hemostatic closure device did not improve the safety of access site management after peripheral percutaneous procedures in patients with peripheral vascular disease compared with conventional manual compression.

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