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ORIGINAL ARTICLE
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Efficacy and Safety of Nepcell S™ in Achieving Hemostasis After Removal of a 15-Fr Femoral Venous Sheath in Patients Undergoing Cryoballoon Ablation for Atrial Fibrillation

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Background: Hemostasis at the femoral venous access site after cryoballoon ablation (CA) for atrial fibrillation (AF) is often prolonged because of aggressive anticoagulation and the use of 15-Fr-caliber sheaths. The Nepcell S™ (NC) is a newly developed hemostatic pad made of fibrosed calcium alginate extracted from natural seaweed. The calcium ions from the NC accelerate the clotting cascade. This single-center randomized clinical trial assessed the efficacy and safety of the NC in patients undergoing CA for AF.

Methods and Results: In all, 62 patients undergoing CA for non-valvular paroxysmal AF were randomly assigned to either the NC or control group. The primary endpoints of this study were time to hemostasis, internal hemorrhage, and rebleeding. Secondary endpoints were the length of hospital stay (LOS) and vascular complications at 1 month. The time to hemostasis was significantly shorter in NC than control group (mean [±SD] 377±216 vs. 505±241 s; P=0.031). The frequency of internal hemorrhaging (6% vs. 37%; P=0.003) and rebleeding (0% vs. 13%; P=0.033) was lower in the NC than control group, contributing to a decreased LOS in the NC group (3.56±0.67 vs. 4.23±0.73 days; P<0.001). There were no NC-related vascular complications at the 1-month echographic examination.

Conclusions: The use of NC was associated with a shorter hemostasis time and fewer bleeding complications in patients undergoing CA for AF, leading to a shorter LOS.

Key Words: Atrial fibrillation; Bleeding; Cryoablation; Hemostasis; Nepcell S™

Pulmonary vein (PV) antral isolation (PVAI) with either cryoballoon ablation (Medtronic, Minneapolis, MN, USA) or radiofrequency catheter ablation (RFCA) has proven to be a useful therapeutic strategy for the treatment of atrial fibrillation (AF) worldwide.[1,2] Vascular access site complications are the most common complications of ablation for AF, with an incidence of up to 13%.[3–5] These complications may be associated with increased morbidity, a prolonged hospital stay, and surgical repair.[5,6]

Cryoballoon ablation procedures require a delivery sheath with an outer diameter of 15-Fr under anticoagulation therapy during the procedure, and this may also increase the risk of vascular complications.[5,7] The Nepcell S™ (**Figure A**) is hemostasis pad that is made of fibrosed calcium alginate extracted from natural seaweed.[8] Calcium ions (Ca^{2+}) from the Nepcell S™ work to accelerate the clotting cascade in vessels in patients (**Figure B**). A clinical study on the efficacy of a hemostatic pad reported that the incidence of rebleeding was lower with the hemostatic pad than for conventional manual compression among patients who underwent standard RFCA for AF with an ablation catheter.[9] However, are no data regarding the feasibility, efficacy, and safety of the Nepcell S™ hemostatic pad after cryoballoon ablation for AF. Thus, the aim of the present study was to assess the immediate and short-term (1 month) efficacy and safety profile of the Nepcell S™ pad compared with conventional manual compression in patients undergoing cryoballoon ablation for AF.

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This study has been registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (ID: UMIN000044940).

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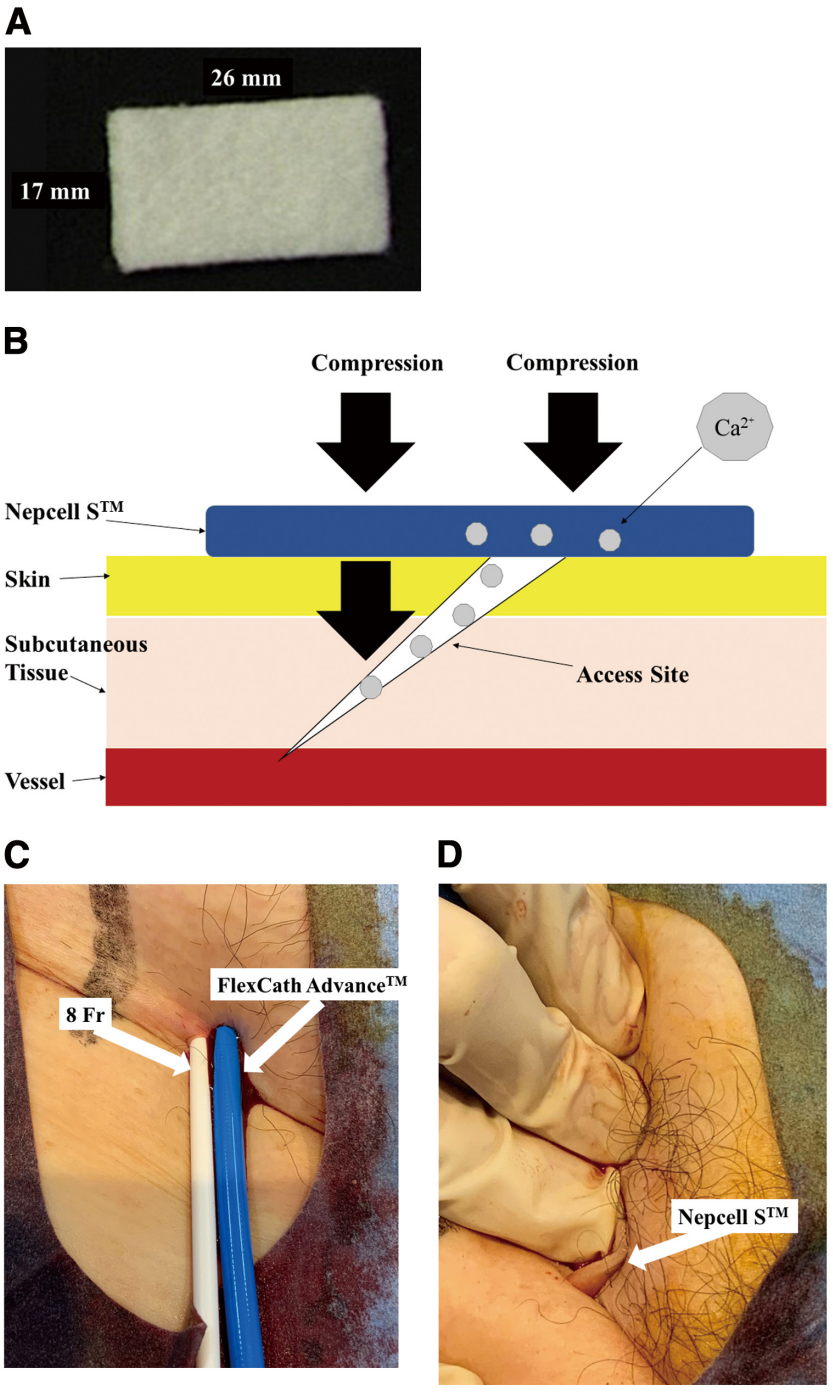

Figure. (**A**) The Nepcell S™ pad is a hemostasis pad made of a fibrosed calcium alginate extracted from natural seaweed. (**B**) Calcium ions from the Nepcell S™ accelerate the clotting cascade in vessels in patients. (**C**) After completion of the ablation and protamine sulfate treatment, both sheaths (8 and 15 Fr of the FlexCath Advance™) from the right femoral vein were removed. Then, 1 mL saline was dropped onto the Nepcell S™ pad and the pad was placed on the access site. (**D**) Compression with the Nepcell S™ pad was applied to the site.

Methods

Study Population and Laboratory Analysis

This single-center prospective randomized clinical trial examined the incidence of vascular access site hemostatic failure after the introduction of the Nepcell S™ technique for hemostasis. This study was approved by the Ethics Review Board of Steel Memorial Yawata Hospital. The procedures were performed in accordance with the Declaration of Helsinki and the ethical standards of the responsible committee on human experimentation. Moreover, this study has been registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (ID: UMIN000044940).

Between 2020 and 2021, 64 patients with non-valvular paroxysmal AF were admitted to Steel Memorial Yawata Hospital to undergo cryoballoon ablation for AF. Excluding 2 patients with end-stage renal dysfunction on hemodialysis, the remaining 62 patients were informed about the study and all agreed to participate. These 62 patients were

randomly assigned to either a Nepcell™ (NC) or control group using the envelope method.

All patients had their history recorded and underwent a physical examination, laboratory analysis, chest radiogram, 12-lead electrocardiogram, and echocardiography within at least 1 month before admission. In addition, before RFCA, the $CHADS_2$ score,[10] chamber size, and left ventricular ejection fraction (LVEF) were evaluated by echocardiography, and the anatomy and size of the PVs and left atrium were evaluated by computed tomography (Aquilion 64; TOSHIBA, Tokyo, Japan). One month after cryoballoon ablation, the right femoral veins were evaluated by vascular Doppler ultrasound.

The primary endpoints of this study were the time to hemostasis, internal hemorrhage, and re-bleeding. The secondary endpoints were the length of hospital stay (LOS) and vascular complications at 1 month.

Anticoagulation Strategies

All patients were effectively anticoagulated with non-vitamin K antagonist oral anticoagulants (NOACs) for at least 1 month before the RFCA procedure. The procedures were performed following transesophageal echocardiography, to rule out any left atrial and left atrial appendage thrombi. All patients provided informed consent.

Patients on NOACs such as dabigatran, rivaroxaban, apixaban, and edoxaban were instructed to stop taking them only on the morning of the RFCA procedure. After RFCA, dabigatran and apixaban were taken in the evening and night, and rivaroxaban and edoxaban were taken in the evening. No patients were receiving antiplatelet agents. During the procedure, an intravenous bolus of unfractionated heparin (3,000 IU) was given immediately after vascular access was achieved. Patients were administered 100 units/kg heparin after transseptal puncture, and heparinized saline was additionally infused to maintain the activated clotting time (ACT) at 300–400 s, which was measured every 15 min during the procedure. At the end of the procedure, the effects of the heparin were empirically reversed in all patients using protamine sulfate, and the activated partial thromboplastin time (APTT) was measured. NOACs were resumed immediately after the procedure. Oral anticoagulation was continued for at least 3 months after the procedure.

Ablation Procedure

All procedures were performed in patients under deep sedation following the administration of intravenous propofol and dexmedetomidine, as described previously.[11] Femoral arterial access was routinely acquired for continuous monitoring of blood pressure and heart rate and the collection of blood samples to measure the ACT. Using the right femoral venous access site, a double transseptal puncture was carefully performed under intracardiac echogram guidance (Ultra ICE catheter; EP Technologies, Boston Scientific, San Jose, CA, USA). Then, 8- and 8.5-Fr sheaths (Biosense Webster, Irvine, CA, USA) were placed in the left atrium. The 8.5-Fr sheath was then exchanged with the steerable transseptal sheath (FlexCath Advance™; Medtronic CryoCath, Minneapolis, MN, USA). The FlexCath Advance™ has an inner diameter of 12 Fr and an outer diameter of 15 Fr (**Figure C**). In all patients, a second-generation 28-mm cryoballoon catheter (Arctic Front Advance™; Medtronic CryoCath, Kirkland, Canada) was used for the PVAI. The cryoballoon was maneuvered to all PV ostia using a steerable 15-Fr sheath and an Achieve™ catheter inserted through the lumen of the balloon catheter. The balloon was inflated in the left atrium and then directed towards the PV ostia.

Balloon occlusion was assessed by injection of 50% diluted contrast through the central lumen of the cryoballoon catheter. The duration of each freezing cycle was 180 s. A minimum of 2 consecutive freezing cycles for each targeted PV was delivered with excellent or good occlusion. The procedure systematically began with the right inferior PV, followed by the right superior and left superior PVs, ending with the left inferior PV. The right phrenic nerve was constantly paced from the superior vena cava during freezing of the right-sided PVs. In addition, direct palpation of the right hemidiaphragmatic excursion was performed during phrenic nerve stimulation.

At the end of the procedure, PV conduction was re-evaluated using a circular mapping catheter (Optima™; St. Jude Medical, St. Paul, MN, USA). Successful PV isolation was defined as the elimination (or dissociation) of all PV potentials recorded from the circular mapping catheter.

Nepcell S™

The Nepcell S™ is a newly developed hemostatic pad (17 mm×26 mm) made of fibrosed calcium alginate extracted from natural seaweed (**Figure A**). The calcium ions from the Nepcell S™ accelerate the clotting cascade[8] in the vessels of patients (**Figure B**).

Post-Procedural Hemostasis

After completion of ablation and treatment with protamine sulfate, both sheaths (8- and 15-Fr sheaths of the FlexCath Advance™) were removed from the right femoral vein (**Figure C**). In the control group, immediate constant manual compression was applied to the site. In the NC group, 1 mL saline was first dropped on the Nepcell S™ pad, after which the pad was placed on the site and compression with the Nepcell S™ pad was applied to the site (**Figure D**). After approximately 3 min, the compression pressure was decreased and hemostasis was checked. If bleeding continued, firm compression was reapplied. The groin puncture site was reassessed for hemostasis in a similar was every 30 s until complete hemostasis was achieved. After immediate hemostasis was achieved in the catheter laboratory, a pressure bandage was applied using a gauze ball, followed by 6 h bed rest. If patients complained of discomfort or pain due to the ablation procedure or bed rest, analgesics such as acetaminophen and/or pentazocine were given at the discretion of the attending physician.

Hematoma was defined as blood retention formed by bleeding in a tissue. Internal hemorrhage was defined as blood retention without hematoma.

Short-Term (1-Month) Follow-up After Hemostasis

One month after discharge, the right femoral veins were evaluated by vascular Doppler ultrasound to determine whether there were any minor or major vascular complications, including a hematoma, rebleeding, fistula formation, pseudo-aneurysm, or deep vein thrombosis, after removal of the 8- and 15-Fr venous sheaths.

Statistical Analysis

Results are presented as the mean±SD. Statistical analyses were performed using Fisher's exact test and Student's t-test for comparisons of 2 groups. Multivariate logistic regression analysis was used to evaluate associations

Table 1. Patient Characteristics and Laboratory Analyses

	NC group (n=32)	Control group (n=30)	P value
Male sex	15 (47)	14 (47)	0.987
Age (years)	72.8±8.7	70.3±7.9	0.239
BMI (kg/m²)	23.7±3.3	24.4±3.4	0.402
BSA (m²)	1.63±0.15	1.65±0.17	0.557
$CHADS_2$ score	2.22±1.39	1.97±0.93	0.391
Type of AF			
Paroxysmal	32 (100)	30 (100)	1.00
Persistent	0 (0)	0 (0)	–
Long lasting	0 (0)	0 (0)	–
Laboratory analysis			
Before RFCA			
Serum creatinine (mg/dL)	0.79±0.16	0.79±0.14	0.955
Platelet count (×10⁴/μL)	220±74	240±72	0.278
PT (s)	13.5±1.6	13.5±1.3	0.990
PT-INR	1.13±0.16	1.13±0.15	0.874
APTT (s)	34.5±4.3	34.9±3.8	0.689
Echocardiogram analysis			
LVEF (%)	68.2±7.3	64.2±13.5	0.157
LA diameter (mm)	36.7±4.2	35.7±6.8	0.496
CT analysis			
LA volume (mL)	81.6±26.9	76.7±18.0	0.404
LA volume index (mL/m²)	50.2±15.6	46.9±13.7	0.394
Medications on admission			
Oral anticoagulation with NOAC	32 (100)	30 (100)	1.000
Apixaban 10 mg/day	18 (56)	18 (60)	0.769
Apixaban 5 mg/day	1 (3)	1 (3)	0.964
Edoxaban 60 mg/day	7 (22)	8 (27)	0.666
Edoxaban 30 mg/day	4 (13)	1 (3)	0.191
Rivaroxaban 15 mg/day	1 (3)	1 (3)	0.964
Rivaroxaban 10 mg/day	0 (0)	0 (0)	1.000
Dabigatran 300 mg/day	1 (3)	1 (3)	0.964
Dabigatran 220 mg/day	0 (0)	0 (0)	1.000
Vitamin K antagonist	0 (0)	0 (0)	1.000
Platelet inhibitor	0 (0)	0 (0)	1.000

Unless indicated otherwise, data are given as the mean±SD or n (%). AF, atrial fibrillation; APTT, activated partial thromboplastin time; BMI, body mass index; BSA, body surface area; CT, computed tomography; INR, International Normalized Ratio; LA, left atrium; LVEF, left ventricular ejection fraction; NC, Nepcell S™; NOAC, non-vitamin K antagonist oral anticoagulant; RFCA, radiofrequency catheter ablation; PT, prothrombin time.

between bleeding and male sex, age, $CHADS_2$ score, prothrombin time (PT), PT-International Normalized Ratio (INR), APTT, and the use of the Nepcell S™. Factors with at least borderline significance ($P<0.15$) according to univariate analysis were included in the multivariate analysis.

All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). Two-sided $P<0.05$ was considered statistically significant.

Results

Patient Characteristics and Laboratory Analysis

Patient characteristics and laboratory findings are summarized in **Table 1**. In the NC group, the Nepcell S™ pad was placed on the right femoral vein where the 2 sheaths had been inserted. In the control group, immediate constant manual compression was applied to this site. Of the 62 patients (29 males, 33 females; mean age 71.6±8.3 years), 32 were allocated to the NC group and 30 were allocated to the control group. All patients received oral anticoagulation with NOACs. There were no significant differences in the type of NOACs used between the 2 groups. No patients were receiving any vitamin K agonists or platelet inhibitors. Before the RFCA, there were no significant differences between the 2 groups in the proportion of males, age, body mass index, body surface area, $CHADS_2$ score, serum creatine, platelet count, PT, PT-INR, APTT, LVEF, the diameter of the left atrium, as determined by echocardiography, and left atrial volume, as determined by cardiac computed tomography (**Table 1**).

Hemostasis Condition and LOS

There were no significant differences between the 2 groups in the total dose of heparin administered and the final ACT

Table 2. Hemostasis Conditions and Length of Hospital Stay

	NC group (n=32)	Control group (n=30)	P value
During/after RFCA			
Total heparin dose (IU)	10,813±1,533	11,133±1,634	0.428
Final ACT during procedure (s)	328±31	334±32	0.475
Protamine before hemostasis (mg)	52.2±12.9	55.3±14.8	0.375
APTT before hemostasis (s)	63.1±43.2	64.9±49.5	0.876
Time of hemostasis (s)	377±216	505±241	0.031
Bleeding complications			
Without bleeding, internal hemorrhage, and hematoma	29 (91)	14 (47)	<0.001
With internal hemorrhage, without hematoma	2 (6)	11 (37)	0.003
With internal hemorrhage and hematoma	1 (3)	1 (3)	0.946
Rebleeding needing re-hemostasis	0 (0)	4 (13)	0.033
Rebleeding after discharge	0 (0)	0 (0)	1.000
LOS (days)	3.56±0.67	4.23±0.73	<0.001

Unless indicated otherwise, data are given as the mean±SD or n (%). ACT, activated clotting time; LOS, length of hospital stay. Other abbreviations as in Table 1.

Table 3. Bleeding Complications at the Short-Term (1-Month) Follow-up After Hemostasis

	NC group (n=32)	Control group (n=30)	P value
Hematoma	0 (0)	1 (3)	0.306
Rebleeding	0 (0)	0 (0)	1.000
Fistula formation	0 (0)	0 (0)	1.000
Pseudo-aneurysm	0 (0)	0 (0)	1.000
Deep vein thrombosis	0 (0)	0 (0)	1.000

Unless indicated otherwise, data are given as n (%). NC, Nepcell S™.

during the RFCA, or in protamine use and the APTT before hemostasis after the RFCA (**Table 2**). However, the time to hemostasis, a primary endpoint of this study, was significantly shorter in the NC than control group (377±216 vs. 505±241 s; P<0.031; **Table 2**). The prevalence of hemostasis without bleeding, internal hemorrhage, or a hematoma was significantly higher in the NC than control group (91% vs. 47%; P<0.001; **Table 2**). Conversely, the prevalence of hemostasis with internal hemorrhaging and without a hematoma (6% vs. 37%; P=0.003) or rebleeding requiring re-hemostasis (0% vs. 13%; P=0.033) was significantly lower in the NC than control group (**Table 2**). There was no significant difference between the NC and control groups in the proportion of patients with internal hemorrhaging and with a hematoma (3% vs. 3%; P=0.964; **Table 2**). Moreover, there were no complications, including fistula formation, pseudo-aneurysm, or deep vein thrombosis (data not shown). The LOS was significantly shorter in the NC than control group (3.56±0.67 vs. 4.23±0.73 days; P<0.001; **Table 2**). Five patients had an adverse reaction (transient hypotension) to protamine.

Short-Term (1-Month) Follow-up After Hemostasis

During the short-term (1-month) follow-up using vascular Doppler ultrasound, there was no evidence of minor or major vascular access site complications, including hematoma, rebleeding, fistula formation, pseudo-aneurysm, or deep vein thrombosis, at the right femoral site after removal of the 8- and 15-Fr femoral venous sheaths in either of the 2 groups (**Table 3**).

Independent Risk Factors for Hemostasis Complications

Independent risk factors for hemostasis complications are summarized in **Table 4**. Univariate and multivariate analyses revealed that not using the Nepcell S™ for hemostasis (odds ratio [OR] 45.6) and prolonged APTT before RFCA (OR 0.003) were independent risk factors for complications of hemostasis in patients with AF who underwent RFCA for AF with a cryoballoon (**Table 4**). In view of these findings, not using a Nepcell S™ for hemostasis may be an important predictor of hemostasis complications in patients who undergo RFCA for AF with a cryoballoon.

Subanalyses of the Effects of Nepcell S™ According to Sex and Age

We analyzed whether the effects on Nepcell S™ differed according to sex and age (**Tables 5**,**6**). The prevalence of hemostasis without bleeding, internal hemorrhage, or a hematoma was significantly higher in the NC than control group regardless of sex and age (<70 vs. ≥70 years). The LOS was significantly shorter in the NC than control group, except among female patients (**Table 5**).

Discussion

Main Findings

This study revealed that the efficacy and safety of the Nepcell S™ pad were better than immediate constant manual com-

Table 4. Results of Univariate and Multivariate Analyses of Independent Risk Factors for Hemostasis Complications

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Male sex	2.42 (0.75–7.79)	0.138		
Age ≤72 years	1.75 (0.56–5.36)	0.330		
BMI ≤20 kg/m²	1.29 (0.19–8.50)	0.788		
BSA ≤1.6 m²	1.97 (0.63–6.08)	0.240		
$CHADS_2$ score ≤2	5.58 (1.51–20.6)	0.010	11.40 (0.70–183.0)	0.086
Laboratory analysis				
Before RFCA				
Serum creatinine ≤0.8 mg/dL	0.9 (0.29–2.74)	0.853		
Platelet count ≤207×10⁴/μL	0.65 (0.21–2.00)	0.453		
PT ≤13 s	2.43 (0.78–7.58)	0.125		
PT-INR ≤1.06	1.75 (0.56–5.36)	0.330		
APTT ≤40 s	0.03 (0.004–0.34)	0.003	0.003 (0.00009–0.142)	0.003
Echocardiogram analysis				
LVEF ≤50%	2.06 (0.37–11.4)	0.406		
LA diameter ≤40 mm	1.78 (0.41–7.55)	0.435		
CT analysis				
LA volume ≤60 mL	0.93 (0.24–3.62)	0.920		
LA volume index ≤50 mL/m²	1.53 (0.49–4.79)	0.462		
During/after RFCA				
Total heparin dose ≤12,000 IU	0.57 (0.17–1.90)	0.360		
Final ACT during the procedure ≤300 s	1.65 (0.38–7.06)	0.497		
Protamine before hemostasis ≤5 mg	1.75 (0.52–5.81)	0.360		
APTT before hemostasis ≤60 s	0.83 (0.24–2.80)	0.768		
Time to hemostasis ≤430 s	1.24 (0.40–3.78)	0.703		
Use of Nepcell S™	7.32 (1.95–27.5)	0.003	45.6 (2.87–726.0)	0.006

CI, confidence interval; OR, odds ratio. Other abbreviations as in Tables 1,2.

Table 5. Bleeding Complications and Length of Hospital Stay According to Sex

	NC group	Control group	P value
Males			
No. patients	15	14	
Without bleeding, internal hemorrhage, and hematoma	15 (100)	5 (36)	<0.001
With internal hemorrhage, without hematoma	0 (0)	6 (43)	0.003
With internal hemorrhage and hematoma	0 (0)	0 (0)	1.000
Rebleeding needing re-hemostasis	0 (0)	3 (21)	0.061
Rebleeding after discharge	0 (0)	0 (0)	1.000
Mean (±SD) LOS (days)	3.27±0.46	4.14±0.66	<0.001
Females			
No. patients	17	16	
Without bleeding, internal hemorrhage, and hematoma	14 (82)	6 (35)	0.007
With internal hemorrhage, without hematoma	3 (18)	5 (29)	0.378
With internal hemorrhage and hematoma	0 (0)	4 (24)	0.028
Rebleeding needing re-hemostasis	0 (0)	1 (6)	0.310
Rebleeding after discharge	0 (0)	0 (0)	1.000
Mean (±SD) LOS (days)	3.82±0.73	4.31±0.79	0.074

Unless indicated otherwise, data are given as n (%). LOS, length of hospital stay; NC, Nepcell S™.

pression in achieving hemostasis after removal of 2 femoral venous sheaths (8 and 15 Fr; **Figure**) in patients who underwent RFCA for AF with a cryoballoon in real-world clinical practice. Manual compression is time consuming and exhausting for qualified medical staff, requires a longer time in the catheter laboratory holding area, and increases bed rest for patients. However, using the Nepcell S™ shortened hemostasis time (**Table 1**) and decreased the incidence of internal hemorrhaging and rebleeding, contributing to a decrease in the LOS (**Table 2**).

Table 6. Bleeding Complications and Hospital Stay in the Patients According to Age (<70 and ≥70 Years)			
	NC group	Control group	P value
Age <70 years			
No. patients	11	14	
Without bleeding, internal hemorrhage, and hematoma	9 (82)	3 (21)	0.002
With internal hemorrhage, without hematoma	2 (18)	5 (36)	0.353
With internal hemorrhage and hematoma	0 (0)	4 (29)	0.056
Rebleeding needing re-hemostasis	0 (0)	2 (14)	0.207
Rebleeding after discharge	0 (0)	0 (0)	1.000
Mean (±SD) LOS (days)	3.36±0.50	4.21±0.80	0.005
Age ≥70 years			
No. patients	21	16	
Without bleeding, internal hemorrhage, and hematoma	20 (95)	8 (50)	0.001
With internal hemorrhage, without hematoma	1 (5)	6 (38)	0.011
With internal hemorrhage and hematoma	0 (0)	0 (0)	1.000
Rebleeding needing re-hemostasis	0 (0)	2 (13)	0.101
Rebleeding after discharge	0 (0)	0 (0)	1.000
Mean (±SD) LOS (days)	3.67±0.73	4.25±0.68	0.018

Unless indicated otherwise, data are given as n (%). LOS, length of hospital stay; NC, Nepcell S™.

Patients Characteristics

Kitakyushu city, where Steel Memorial Yawata Hospital is located, has the oldest population among the ordinance-designated cities of Japan. Thus, the mean age of all the patients in this study (71.5±8.3 years) was comparably older (**Table 1**).

Clinical Merits of Using Two Sheaths From the Right Femoral Vein

To decrease the risk of hematoma and bleeding, only 1 sheath (15 Fr) is used in many institutions across Japan. However, using circular mapping catheters through the 15-Fr steerable transseptal sheath (FlexCath Advance™; Medtronic CryoCath) is prohibited because of the risk of air embolism. However, the Achieve™ mapping catheter (Medtronic CryoCath) is more difficult to pace circumferentially in PVs than circular mapping catheters. This is why using 2 sheaths from the right femoral vein has clinical merit.

Efficacy and Safety of the Nepcell S™ Technique

In most hospitals, standard manual compression is used as an effective technique for hemostasis at vascular access sites in patients who undergo RFCA for AF. However, this method is also associated with risks of rebleeding,[12] thrombosis, and embolisms.[13] Moreover, prolonged manual compression, required to achieve hemostasis after removal of large-caliber venous sheaths, may increase the risk of deep vein thrombosis.[14] In the present study, if rebleeding occurred, immediate constant manual compression was applied to the site again. After approximately 3 min, the compression pressure was decreased and hemostasis was checked. If bleeding continued, firm compression was reapplied. Groin puncture sites were reassessed for hemostasis in a similar manner every 30 s until complete hemostasis was achieved. After immediate hemostasis was achieved, a pressure bandage using a gauze ball was applied, followed by 6 h bed rest.

The rate of bleeding complications in the control group with standard manual compression was comparably high in this study (**Table 3**). The time until hemostasis in the control group (505±241 s) in the present study was shorter than that reported in a previous study (14 min).[5] This shorter time to hemostasis may have affected the high rate of rebleeding complications in the control group.

Previous studies have reported the efficacy and safety of a figure-of-8 suture for hemostasis after removal of a 15-Fr femoral venous sheath in patients after RFCA with a cryoballoon.[3,5] Compared with immediate constant manual compression, the figure-of-8 suture can shorten the time to hemostasis[5] and decrease both the incidence of rebleeding and the post-procedural use of analgesics and/or antiemetic drugs.[3] However, although the figure-of-8 suture is cheaper than the Nepcell S™, it is a more invasive procedure than the Nepcell S™. Moreover, the ability of achieving hemostasis with the Nepcell S™ did not differ according to sex or age (**Tables 5**,**6**).

Finally, in a multivariate analysis, the Nepcell S™ pad was the only independent variable that reduced internal hemorrhaging, rebleeding, and the LOS. Thus, the Nepcell S™ is a simple, effective, and safe technique to achieve hemostasis after removal of the 15-Fr femoral venous sheath in patients undergoing cryoballoon-based RFCA.

Comparison of the Nepcell S™ With Another Pad

A previous study reported that a hemostatic pad containing kaolin decreased the time to hemostasis at a femoral venous access site in patients undergoing conventional, non-cryoballoon-based, RFCA for AF.[9] However, there was no significant difference in the incidence of rebleeding between patients in which the kaolin pad was and was not used.[9] The femoral sheaths used during conventional RFCA for AF are narrower than those used in cryoballoon-based RFCA procedures. In the present study, the Nepcell S™ not only shortened the time to hemostasis, but also decreased the incidence of internal hemorrhaging and rebleeding, contributing to a shortened LOS. Thus, the Nepcell S™ pad may be safer and more effective than the kaolin pad.

Study Limitations

Although this study was a prospective randomized clinical

trial, the interpretation of the results is limited by its single-center study design and the relatively small number of patients. At first, we planned to have more than 50 patients in each group. However, because a significant difference was seen between groups after recruiting approximately 30 patients to each group, we discontinued the study. Whether the results can be safely extrapolated to multicenter trials with a larger number of patients and a longer follow-up period needs to be determined in further studies.

Conclusions

The use of the Nepcell S™ pad for hemostasis in patients who underwent RFCA of AF with a cryoballoon was associated with shorter time to hemostasis and fewer bleeding complications, including internal hemorrhaging and rebleeding. The Nepcell S™ pad is a simple, effective, and safe technique that contributed to a decrease in the LOS.

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Disclosures

The authors declare no conflict of interests for this article.

IRB Information

This study was approved by the Ethics Review Board of Steel Memorial Yawata Hospital (Reference no. 20-54).

Data Availability

The deidentified participant data will not be shared.

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