Interventional Cardiology

Short-Term Safety and Efficacy of Femoral Vascular Closure after Percutaneous Coronary Intervention with Combination of the Boomerang™ Device and Intravenous Protamine Sulfate

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Background: The Cardiva Boomerang™ is a device used to perform femoral vascular closure. It facilitates passive hemostasis at the arteriotomy site, leaving no residual foreign body.

Methods: We performed a controlled, randomized study of 60 patients undergoing percutaneous coronary intervention. Patients were randomized into two groups (30 per group) to undergo vascular closure with the Boomerang™ or the Perclose™ suture-based device after the intravenous administration of protamine sulfate. We compared overall success rates, patient-reported pain, length of time to achieve hemostasis and mobilization of the patient, and the frequency of complications in the two groups.

Results: Overall success rates using the Boomerang™ and Perclose™ devices were similarly high, at 93% and 97%, respectively. The Boomerang™ was significantly quicker to deploy than the PercloseTM, device deployment time, median (Q1-Q3), [2.00 (1.33-2.75) vs. 3.84 (2.75-4.38) mins, $p < 0.001$)]. The pain score was significantly lower in the Boomerang™ group (1.1 ± 1.7 vs. 6.4 ± 2.9, $p < 0.001$). The time the device remained in the artery and manual compression time were significantly longer with the Boomerang™ ($p < 0.001$), as well as the time taken to achieve hemostasis and time to ambulation. There were no major complications in either group and no significant differences between the groups in the frequency of minor complications.

Conclusions: We conclude that when used in combination with intravenous protamine sulfate, the Boomerang™ device is as safe and effective as the Perclose™ device for femoral vascular closure, but quicker to deploy and less painful to patients.

Key Words: Boomerang • Percutaneous intervention • Vascular closure device

INTRODUCTION

Manual compression is the classic method for achieving hemostasis at the puncture point of the femoral artery after cardiac catheterization. However, complications and long periods of patient bed rest are major drawbacks of manual compression.[1,2] Vascular closure devices incorporating sutures, collagen plugs, or nitinol clip mechanisms have been developed to improve the efficacy, safety, and efficiency of hemostasis procedures after cardiac catheterization.[3-8] Suture-based closure devices, such as the Perclose™, facilitate percutaneous coronary intervention (PCI) and early post-procedural mobilization.[9] Vascular closure devices must be reliable and easy to use, with an overall safety profile equal to or better than that of manual compres-

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sion.[10-13] However, there is currently no device that fulfills all of these criteria.[14,15] The Perclose™ closure device is effective in achieving post-intervention hemostasis, but severe pain can occur when the knot is pushed down onto the artery. The Cardiva Boomerang™, a vascular closure device, facilitates physiologic closure of the femoral arteriotomy site. Temporary hemostasis is achieved using intravascular tamponade, and no residual foreign body remains at the arteriotomy site. However, the manufacturer recommends that the device remains within the artery for 2 hours after PCI, or until the effects of heparin have completely subsided. Time to ambulation is thus prolonged to approximately 5-6 hours. We designed a new protocol for use of the Boomerang™ in patients undergoing PCI, in which we administered protamine sulfate to reverse the effects of heparin. The aim of our study was to determine the safety and efficacy of the Boomerang™ device when used in combination with protamine sulfate, in comparison to the Perclose™ device.

METHODS

We conducted a single-center, controlled, randomized study at the Department of Cardiology, Changhua Christian Hospital. We studied 60 patients undergoing PCI between December 2009 and March 2010. The patients were randomized at a ratio of 1:1 to undergo femoral vascular closure with the Boomerang™ device (group A) or the Perclose™ device (group B). Angiography and vascular closure were performed immediately after PCI. The study protocol had been approved by the ethics committee of the institution. Informed consent was obtained from all patients prior to the study initiation.

We followed the standard pre-procedural protocol before performing PCI; this involved the administration of loading doses of 300 mg plavix and 300 mg aspirin. Heparin was administered intravenously at a dose of 7500-10000 units to maintain the activated clotting time (ACT) at ≧ 300 s. The PCI was performed via the right femoral artery with a 7-Fr sheath. After PCI, angiography was performed at the puncture site, and was followed by deployment of the vascular closure instrument using either the Boomerang™ or Perclose™ device. The manufacturer's guidelines for the Boomerang™ device recommend that the device remains within the artery for 2 hours after PCI, when the ACT usually exceeds 180 s. We administered protamine sulfate intravenously to accelerate reversal of the heparin effect. Patients with ACT > 400 s or an interventional procedure time ≦ 1 h received 20 mg protamine sulfate, whereas those with ACT ≦ 400 s or a procedural time > 1 h received 15 mg protamine sulfate. The ACT was checked 10 min after the initial administration of protamine sulfate, and an additional 5 mg dose was given if it remained at ≧ 180 s (Figure 1). Both closure devices were deployed as soon as the ACT fell to < 180 s.

We excluded patients with "double wall" arterial punctures, intraluminal thrombi, pseudoaneurysms, hematomas, arteriovenous (AV) fistulas or infection in the target artery lesion, history of protamine allergy, or those who had previously received injections of neutral protamine hagedorn (NPH). We also excluded patients who required a long sheath (≧ 23 cm).

Deployment of the Boomerang™ device

The Boomerang™ closure device (Cardiva Medical

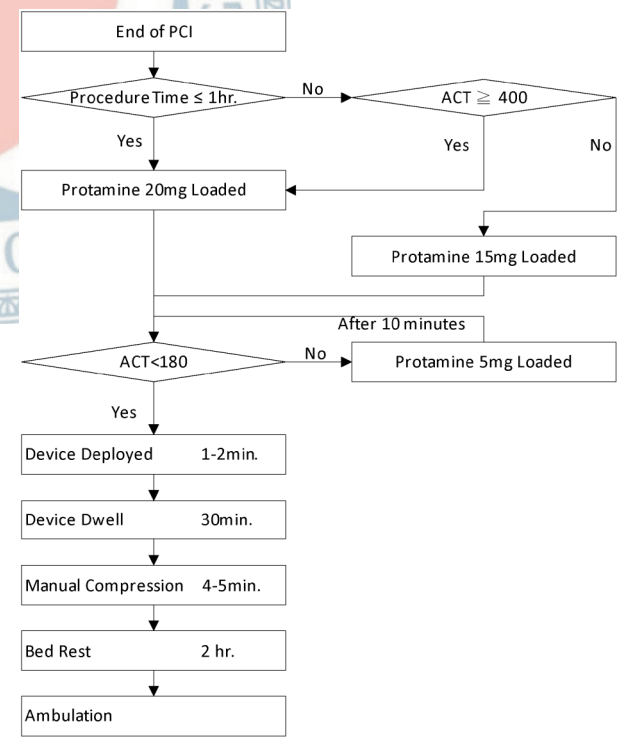

Figure 1. *Deployment of the Boomerang™ device. ACT, activated clotting time; PCI, percutaneous coronary intervention.*

Inc., Sunnyvale, CA, USA) comprises a sterile disposable wire and clip. After the completion of PCI and once the ACT was < 180 s, the Boomerang™ wire was inserted through the existing introducer sheath. We deployed the distal tip of the wire to open the flat, low profile disc within the lumen of the femoral artery. After removing the introducer sheath, the disc was then pulled back and positioned against the inside of the intima to seal the arteriotomy. The wire was positioned gently upwards, and tension was maintained by the clip placed on the surface of the skin. The wire was designed to remain in place in the artery for 30 mins. After removing the wire, we applied manual compression to close the remaining needle puncture site. Patients were confined to bed for 120 min after hemostasis was achieved (Figure 1).

Deployment of the Perclose™ device

The Perclose™ (Abbott Laboratories, Abbott Park, IL, USA) is a suture-based device. Needles loaded with non-absorbable surgical suture materials were passed through the vessel wall via a guide wire to form a suture knot on the surface of the artery. After hemostasis was achieved, only bandage compression was needed. Patients were confined to bed for 120 min after this procedure (Figure 2).

Primary study endpoints

Procedure success

We considered the procedure successful if hemostasis was achieved with 5 min of additional manual compression and the patient became ambulant within 2 h.

Device success

We considered the device effective if we were able to deploy it without failure or cross-over to manual compression, and if hemostasis was achieved without major complications.

Device deployment time

This was the total length of time required to deploy the device.

Device dwell time

This was the total length of time that the device remained in the artery once deployed.

Manual compression time

We defined this as the time taken to achieve hemostasis by manual compression of the femoral artery puncture point after withdrawal of the sheath.

Time to ambulation

This was defined as time taken for the patient to become ambulant after the completion of PCI.

Pain score

We assessed pain by asking patients to score their pain levels on a scale of 0-10, where 0 indicates no pain, 1-3 indicates mild pain, 4-6 indicates moderate pain, and 7-10 indicates severe pain.[16]

Major complications

We defined major complications as the need for vascular repair, bleeding requiring transfusion, or infection requiring hospitalization.

Minor complications

We defined minor complications as hematoma > 6 cm in size, AV fistula, renewed bleeding (requiring > 5

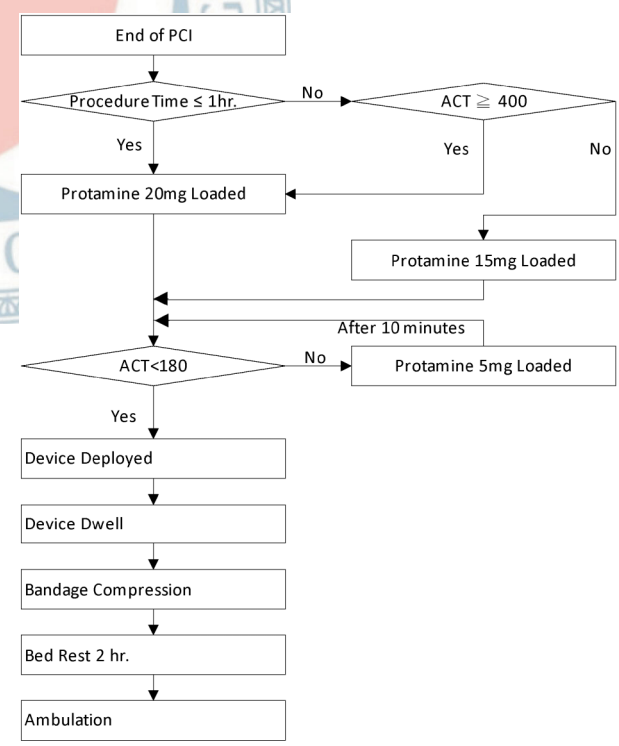

Figure 2. *Deployment of the Perclose™ device. ACT, activated clotting time; PCI, percutaneous coronary intervention.*

min additional manual compression), pseudoaneurysm, or cross-over to manual compression.

Statistical analysis

We compared values in groups A and B using the two-tailed *t*-test to compare continuous data, Fisher's exact test and Mann-Whitney test to compare dichotomous data. Multiple logistic regression was used for multivariate analysis.

RESULTS

Patient demographics

The full study population comprised 60 patients with a mean age of 66.5 ± 10.8 years, of whom 68.3% were male. Group A patients were 70.0% male, with a mean age of 63.1 ± 9.9 years; group B patients were 66.7% male, with a mean age of 69.8 ± 10.6 years (Table 1).

Comparison of endpoints in groups A and B

Patients in group A reported significantly lower pain levels compared with patients in group B (1.10 ± 1.71 vs. 6.40 ± 2.92; p < 0.001) (Table 2). There were no significant differences between the Boomerang™ or the Perclose™ devices in terms of the overall success rate of the device for the femoral closure procedure (93% vs. 97%) (Table 4).

The length of time taken to deploy the device was significantly shorter for the Boomerang™ than with the Perclose™ device (p < 0.001). However, the total dwell, residual and manual compression times were significantly longer with the Boomerang™ (p < 0.001), as were the total time required to achieve hemostasis (p < 0.001) and the time required for the patient to become ambulant (p < 0.001) (Table 3).

There were no major complications in either group. Seven patients in group A and six patients in group B suffered minor complications, but there were no significant differences between the groups (Table 4). Multivariate analysis showed that patients who had CVA and used a high dose of heparin more easily developed hematoma > 6 cm. Patients in the Perclose™ group more easily developed repeat bleeding and required 5 min additional compression (Table 5).

DISCUSSION

We developed a new protocol for the use of the Boomerang™ device that was designed to overcome difficulties associated with the length of time the device is required to be maintained within the artery. Our approach involves the intravenous administration of protamine sulfate to reverse the effects of heparin after interventional catheterization. To our knowledge, this is the first study to use this approach to reduce the procedure time when using the Boomerang™ closure device for femoral closure. In our study population, this approach not only shortened the manufacturer's recommended procedure time (on average we completed the whole hemostasis procedure within 40 min, a decrease of at least 67%), but patients also reported lower levels of pain compared to those who underwent

Table 1. Characteristics of the patients by study group, and p values for between-group comparisons

	Group A (Boomerang™) (n = 30)	Group B (Perclose™) (n = 30)	p value
Male (n, %)	21.0, 70.0	20.00, 66.7	0.78
Age (years)*	63.1 ± 9.9	69.8 ± 10.6	0.01
Height (cm)*	161.8 ± 7.3	158.8 ± 12.4	0.25
Weight (kg)*	67.1 ± 11.1	65.8 ± 9.0	0.64
BMI*	25.5 ± 3.4	26.7 ± 7.2	0.43
DM (n, %)	15.0, 50.0	11.0, 36.6	0.30
HTN (n, %)	23.0, 76.6	22.0, 73.3	0.77
Hyperlipidemia (n, %)	14.0, 46.6	10.0, 33.3	0.30
Smoking (n, %)	7.0, 23.3	8.0, 26.6	0.77
ESRD (n, %)	6.0, 20.0	1.0, 3.3	0.04
CKD (n, %)	2.0, 6.6	3.0, 10.0	0.64
CVA (n, %)	3.0, 10.0	0.0, 0.0	0.08

* Results presented as mean ± SD. BMI, body mass index.

Table 2. Pain scores (number, % patients), average pain score ± SD, and p values for between-group comparisons

Pain score	Group A (Boomerang™) (n = 30)	Group B (Perclose™) (n = 30)	p value
0 (no pain)	16.0, 53.3	0.0, 0.0	
1-3 (mild pain)	11.0, 36.6	6.0, 20.0	
4-6 (moderate pain)	2.0, 6.6	8.0, 26.6	
7-10 (severe pain)	1.0, 3.3	16.0, 53.3	
Average score	1.1 ± 1.7	6.4 ± 2.9	< 0.001

Table 3. Study outcomes and p values for between-group comparisons

	N	Mean	SD	Median	Q_1	Q_3	Min	Max	N	Mean	SD	Median	Q_1	Q_3	Min	Max	p value
Age	30	63.13	9.92	64.00	54.75	71.00	44.00	78.00	30	69.87	10.65	69.00	62.50	76.75	45.00	89.00	0.025
Height (cm)	30	161.86	7.39	163.00	156.00	165.00	147.00	180.00	30	158.82	12.47	159.00	152.00	167.25	108.00	177.00	0.321
Weight (kg)	30	67.10	11.19	66.25	58.60	73.50	43.00	90.00	30	65.89	9.09	63.75	58.75	75.00	52.70	81.50	0.701
BMI	30	25.54	3.40	24.95	24.03	27.55	16.18	34.72	30	26.70	7.29	25.59	24.42	28.09	19.03	61.73	0.515
Systolic pressure (mmHg)	30	154.60	23.10	155.50	135.75	169.50	111.00	200.00	30	152.20	31.06	147.50	128.75	178.00	105.00	219.00	0.535
Diastolic pressure (mmHg)	30	69.90	13.01	70.00	63.00	76.00	37.00	98.00	30	68.93	12.54	68.00	57.00	76.25	50.00	97.00	0.437
Heparin loading dose (units)	30	7926.67	2033.16	7500	5750	10000	5000	10000	30	8266.67	1869.60	7500	7500	10000	5000	15000	0.742
Protamine given 1st (mg)	30	22.00	5.00	23.00	19.50	25.00	10.00	30.00	30	22.03	4.41	23.00	18.00	25.00	10.00	28.00	0.929
Protamine given 2nd (mg)	7	4.43	1.51	5.00	3.00	5.00	3.00	7.00	4	8.25	2.36	9.00	5.75	10.00	5.00	10.00	0.024
Protamine given total (mg)	30	23.03	5.31	24.00	19.75	27.25	10.00	32.00	30	23.13	4.67	23.50	20.00	25.25	15.00	36.00	0.858
ACT at initial (min)	30	3.09	0.70	3.02	2.46	3.68	1.97	4.63	30	3.21	0.79	2.98	2.76	3.44	1.88	5.25	0.762
ACT as protamine given final (min)	30	2.88	0.48	2.98	2.46	3.08	1.97	3.85	30	3.06	0.47	2.98	2.76	3.44	1.88	3.80	0.258
ACT at removal (min)	30	2.87	0.48	2.98	2.46	3.08	1.97	3.85	30	3.06	0.47	2.98	2.76	3.44	1.88	3.80	0.196
Pain score	30	1.10	1.71	0.00	0.00	2.00	0.00	7.00	30	6.40	2.92	7.00	4.75	8.25	1.00	10.00	< 0.001
Device deployment time (min)	30	2.25	1.35	2.00	1.33	2.75	0.55	5.67	30	4.41	2.92	3.84	2.73	4.38	1.45	16.33	< 0.001
Device dwell time (min)	30	30.91	3.33	30.00	30.00	31.25	24.43	45.00	30	0.51	0.92	0.00	0.00	0.85	0.00	2.72	< 0.001
Device residual time (min)	30	33.15	3.60	32.19	31.33	35.17	26.43	46.00	30	4.91	2.76	4.31	3.60	5.21	1.45	16.33	< 0.001
Manual compression time (min)	30	6.92	3.70	5.00	5.00	9.25	0.17	17.68	30	3.10	5.79	1.00	0.33	3.17	0.17	30.00	< 0.001
Time to hemostasis (min)	30	40.07	4.04	38.95	37.16	42.62	32.85	48.23	30	8.02	7.23	5.57	4.31	7.85	2.50	35.50	< 0.001
Time to ambulation (min)	30	167.03	13.49	120.00	120	120	120	1440	30	135.53	12.89	120	120	130	120	450	< 0.001

p-value by Mann-Whitney U Test.

Q_1, Percentile 25; Q_3, Percentile 75; IQR (Interquartile-Range) = Q_1-Q_3.

Table 4. Success rate, minor complications (n, % patients) and p values for between-group comparisons

		Group						
		Boomerang (n = 30)		Perclose (n = 30)		Total (n = 60)		p value
		N	%	N	%	N	%	
Device success	No	2	6.7	1	3.3	3	5.0	1.00
	Yes	28	93.3	29	96.7	57	95.0	
Procedure success	No	2	6.7	1	3.3	3	5.0	1.00
	Yes	28	93.3	29	96.7	57	95.0	
Hematoma > 6 cm	No	26	86.7	30	100.0	56	93.3	0.11
	Yes	4	13.3	0	0.0	4	6.7	
Repeat bleeding requiring 5 min additional compression	No	29	96.7	24	80.0	53	88.3	0.10
	Yes	1	3.3	6	20.0	7	11.7	
Conversion to manual compression	No	28	93.3	30	100.0	58	96.7	0.49
	Yes	2	6.7	0	0.0	2	3.3	

p value by Fisher's Exact Test.

Table 5. Results of multiple logistic regression

Complication	Predictors		β	SE	OR	95% C.I.	p value
Hematoma > 6 cm	Age		0.047	0.076	1.048	0.903-1.217	0.54
	Gender	Male			1.000		
		Female	1.982	1.739	7.261	0.240-219.596	0.25
	Weigh		-0.058	0.088	0.944	0.794-1.122	0.51
	Systolic pressure (mmHg)		-0.051	0.036	0.951	0.886-1.021	0.16
	Heparin loading dose (units)		0.001	0.000	1.001	1.000-1.001	0.046
	CVA	No			1.000		
		Yes	4.112	2.028	61.045	1.146-3251.040	0.043
	Constant		-2.193	9.541	0.112		0.82
Repeat bleeding requiring 5 min additional compression	Age		-0.071	0.056	0.932	0.835-1.039	0.20
	Group	Boomerang			1.000		
		Perclose	3.470	1.581	32.143	1.450-712.721	0.028
	ESRD	No			1.000		
		Yes	1.800	1.654	6.050	0.236-154.836	0.28
	DM	No			1.000		
		Yes	1.859	1.038	6.420	0.839-49.102	0.07
	Constant		-1.049	2.981	0.350		0.73

OR, adjusted odds ratio.

closure using the Perclose™ device. In addition, there was no damage to the immediate or surrounding tissues during deployment of the device, and patients were more at ease during the procedure. Our new protocol was also successful in 93% of our study population.

The total procedure time and time to ambulation were longer with the Boomerang™ than the Perclose™ device, which is probably due to differences in the design of the two devices – the Perclose™ is a suture-based device, while the Boomerang™ is a mechanical device that requires time for physiological response from the human body in order to be effective. Thus, with the Boomerang™, the standard procedure is for the device to remain in the artery for 30 min during arteriotomy site tamponade and hemostasis. However, the Boomerang™ is much easier to manipulate than the Perclose™ and thus is quicker to deploy.

No major complications occurred using either de-

vice. Several patients developed a hematoma > 6 cm with the Boomerang™ device (13.3% vs. 0%), but the incidence of this and other minor complications was not significantly greater than with the Perclose™. These results are probably related to the moderation of the effects of heparin by the protamine sulfate, or to the reduced dwell time for the Boomerang™ device. Besides, multivariate analysis showed that patients who had CVA and used a higher dose of heparin were more likely to develop hematoma > 6 cm. Further modifications to our approach might reduce the incidence of hematomas when using the Boomerang™ device; these might include performing repeat checks of the ACT before removing the wire, increasing the time that the wire remains in situ, or avoiding use of the Boomerang™ device in patients with CVA who used a higher dose of heparin. In our study, we also found that using the Perclose™ device itself seemed to cause repeat bleeding and required 5 mins of additional compression. (Table 5). This might be due to the fact that the Perclose™ device had less device residual time (mean 4.91 vs. 33.15 mins) which causes reduced arteriotomy site and surrounding tissue passive hemostasis. Additionally, oozing from the surrounding tissue or direct arteriotomy site leakage may occur more frequently.

Protamine sulfate is the only agent currently used to reverse the effect of heparin. However, it is known to have potentially adverse effects, including potentially life-threatening complication such as hypotension, cardiac suppression, bradycardia, and desaturation. Thomas et al. have analyzed the safety of protamine sulfate in peripheral vascular intervention and found that protamine sulfate-related adverse effect accounted for 4.0~5.3%, which can be managed promptly. Also, those study results also indicated that there were only a few protamine-related deaths (0.02~0.03%).[17] If used promptly, protamine sulfate is safe in reversal of the heparin effect. In coronary intervention, several studies have documented that reversal of the anticoagulant effect of heparin after coronary stent implantation is an accepted practice.[18,19] Nonetheless, several case reports have announced that protamine sulfate usage immediately after coronary drug eluting stent deployment may cause acute stent thrombosist.[20,21] Recently, a retrospect study has showed that it may be safe to use protamine sulfate to reverse the heparin effect after coronary drug eluting stent deployment.[22] In our study, no acute stent thrombosis developed after protamine sulfate administration.

Our study does have limitations. One limitation of our study was that it was performed as a single center study in a relatively small study population, and thus our results may be subject to bias. The study only presented preliminary data of a modified protocol for usage of the Boomerang™ device. However, the actual results call for larger-scale clinical trials to clarify, and the long-term safety/ efficacy needs to be determined by clinical follow up.

CONCLUSIONS

For femoral vascular closure using the Boomerang™ device after percutaneous coronary intervention, the administration of intravenous protamine sulfate can reduce the time taken to complete hemostasis. This approach is equally effective and safe as compared with the Perclose™ device, and the Boomerang™ is easier to deploy, and causes less patient discomfort. Intravenous administration of protamine sulfate after percutaneous coronary intervention does not appear to be associated with any adverse effects in our study.

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