Evaluation of the Solitaire System in a Canine Arterial Thromboembolic Occlusion Model: Is It Safe for the Endothelium?

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Summary

The Solitaire system has recently been increasingly used for acute stroke treatment in which the endothelial safety immediately after its use has not been evaluated. This study was performed to evaluate the endothelial status when using a Solitaire system in a canine arterial occlusion model.

Thromboembolic occlusion of both internal maxillary arteries was achieved in five mongrel dogs. In each animal, the Solitaire system (ev3, Irvine, CA, USA) was used for primary thrombectomy on the right side and for temporary stenting on the left side. Efficacy was assessed by comparing the recanalization rates, and safety was assessed using angiographic and microscopic assessments. Endothelial injuries were evaluated with light microscopy (LM) and scanning electron microscopy (SEM).

Successful revascularizations were observed following primary thrombectomy in all five animals (100%) and after temporary stenting in two (40%). There was no incidence of vasospasm or vessel perforation in either group. Distal migration of the clot occurred in two animals that underwent primary thrombectomy. Endothelial injury was seen after primary thrombectomy in two animals (40%) and after temporary stenting in one (20%). The lesions presented as defects of the internal elastic lamina on LM and denudation of the wavy endothelial surface on SEM.

During mechanical thrombectomy, the Soli-

taire system can cause endothelial injury both in primary thrombectomy and temporary stenting. Primary thrombectomy is likely to have a higher recanalization rate with increased endothelial injury.

Introduction

The Solitaire system (ev3, Irvine, CA, USA) is a device intended primarily for direct thrombus retrieval. It has become one of the major recanalization devices used for the endovascular management of acute stroke. Its efficacy in terms of the recanalization rate has been reported to be quite high and ranging from 88.8-100 % in humans¹⁻⁶.

On the other hand, little attention has been given to possible local arterial injury. Considering the mechanism of direct clot retrieval using this device, one cannot help but be concerned about the possibility of arterial injury. In that situation, there may be gross morphologic changes such as perforation, kinking or dissection of the target arteries, seen on angiography. Fortunately, compared with a Merci device (Concentric Medical, Mountain View, CA, USA), there have been fewer reported episodes of such local complications when using the Solitaire system^{1,5,7}. However, we lack information regarding microscopic changes such as endothelial injury or subintimal mural injury in humans. Hypothetically, device-induced endothelial injury has possible clinical conse-

quences such as acute thrombotic re-occlusion or late arterial stenosis. Therefore, it is worthwhile evaluating the exact incidence and pattern of local endothelial injury⁵.

Owing to the design of the device, as it differs from that of other types of stents, a Solitaire system can be used in various ways for the endovascular management of acute stroke. It can be used as a primary stenting device, such as the Neuroform stent (Stryker, Fremont, CA, USA) or the Wingspan stent (Stryker, Fremont, CA, USA), by detaching the device after its placement⁸⁻¹¹, as a temporary-stenting device such as the Enterprise stent (Cordis, Miami Lakes, FL, USA)^{12,13} or as a primary thrombectomy device which is currently the primary mechanism used in most instances.

The primary purpose of this study is a histopathological evaluation of endothelial status after primary thrombectomy or temporary stenting using a Solitaire system in a canine thromboembolic arterial occlusion model. We hypothesized that the primary thrombectomy method would be able to show more of the endothelial injury due to its device clot pulling back mechanism.

Materials and Methods

Animal preparation

All procedures were conducted according to the National Institutes of Health guidelines for humane handling of animals and approved by our Institutional Animal Care and Use Committee. We used five male adult mongrels, each weighing 22 to 24 kg. We induced general anesthesia using propofol (5~7.5 mg/kg, IV), isoflurane (1.5~2.5 %), and 100% oxygen.

Thrombus preparation

20 cc of blood was withdrawn from the femoral artery sheath and transferred into two 10 cc centrifuge tubes containing 1.3 ml of 3.6% sodium citrate solution. We mixed the contents of the tubes, and the samples were centrifuged for 10 minutes at 270g at 4 °C. The centrifuged blood was separated into three layers, with the middle (3.9 cc) and lower (0.1 cc) layers of each tube transferred to a different centrifuge tube. To each tube 100 units (0.1 cc) of thrombin and 0.3 cc of 3% calcium chloride were added. After stirring for one minute, the initial clots were

formed. Each clot was then dehydrated for 10 to 20 minutes.

Clot injection

After a 6-F guiding catheter (Envoy; Cordis Neurovascular, Miami, FL, USA) was placed in the proximal external carotid artery (ECA), an angiogram was performed to identify the internal maxillary artery (IMA) (Figures 1 and 3). The diameter of the IMA was then measured on angiography using a reference, 1cm diameter ball. After inserting a detachable coil (Axium; ev3, Plymouth, MN, USA, 4/12 mm) into the distal IMA to prevent clot migration (Figure 3), the clot was injected into the IMA proximal to the coil. The coil was then carefully withdrawn before a control angiogram was performed to confirm the presence, location, and stability of the clot (Figure 1). This procedure was repeated to insert another thrombus into the left IMA. After the clots were positioned in the target vessels, we waited 20 minutes to allow the thrombi to become embedded.

Revascularization procedure

For anticoagulation, a 70U/kg IV dose of heparin was administered. After the microcatheter was inserted into the occluded vessel, the Solitaire system was advanced. After confirming the correct placement of the Solitaire system, primary thrombectomy was performed one or two minutes later by gently pulling the device and microcatheter back into the right IMA. The guiding catheter flushing system was closed to stop antegrade flow, and suction aspiration was performed during the primary thrombectomy procedure. We repeated the procedure if we could not retrieve the clot. A post-thrombectomy angiogram was obtained to check the recanalization rate, vascular perforation, the possibility of spasm, and possible distal thromboembolic complications (Figure 1).

In the left IMA, we advanced the Solitaire system as we had done on the right side. After checking the initial flow restoration, temporary stenting was sustained for one to four hours with or without tirofiban (Aggrastat®; Merck & Co., Inc., Whitehouse Station, NJ, USA). Temporary stenting duration was sustained up to four hours in anticipation of a greater recanalization rate with a longer temporary stenting duration (Figure 3). Tirofiban was administered at a dose of 0.4 µg/kg/min during the first 30

Figure 1 Angiographic and histologic results of primary thrombectomy in animal 2. A) Initial angiogram of the right external carotid artery shows a patent right internal maxillary artery. B) After selection of the right internal maxillary artery, a detachable coil is inserted over the microcatheter. After clot injection, the detachable coil is withdrawn and the clot occludes the right proximal internal maxillary artery (arrow). C) Angiogram obtained after the second thrombectomy shows complete recovery of the occluded segment (arrow) with TIMI grade 3. D) Specimens from the thrombectomy site show injury to the endothelium (arrow) caused by the Solitaire system (SEM, $\times 75$). E) This lesion is shown as a defect of the endothelial internal elastic lamina (arrow) (Elastic Van Gieson's stain, $\times 100$). F) The same defect of the endothelial elastic lamina (arrow) is seen again (Masson's trichrome stain, $\times 100$).

minutes and subsequently at $0.1 \mu\text{g/kg/min}$. Finally, the Solitaire system was resheathed and removed. The technical success was determined according to the deployment of the device at the target site.

In animals 4 and 5, 6×20 mm devices were used for temporary stenting or primary thrombectomy in order to observe the different probability of endothelial injury caused by the stent (Table 1).

Evaluation of angiographic efficacy

The efficacy of both methods was determined by the Thrombolysis in Myocardial Infarction (TIMI) grading score on the final angiogram. The scores of the immediate post-deployment and final recanalization state were determined. For primary thrombectomy, the number of attempts at recanalization over $\text{TIMI} \geq 2$ were recorded¹⁴. Angiographic safety

was assessed according to the vascular complications, including vasospasm, vessel perforation, and distal thrombus migration.

Histological safety evaluation

After euthanizing the animals with potassium chloride (20 ml, 100g/L , IV), specimens were retrieved through neck dissection. Two specimens from the mid portion of the right primary thrombectomy site, two specimens from the mid portion of the left temporary stenting site, and two specimens from the left reference artery were obtained from each animal. A reference artery was chosen from the temporary stenting side at a site 5 mm distal to the guiding catheter. Then one set of three specimens from the right primary thrombectomy site, the left temporary stenting site, and the reference artery from each dog were fixed in formalin for light microscopy (LM) and the other set of three specimens was

Table 1 Baseline vascular status and procedural techniques

	Animal Number									
	1		2		3		4		5	
	PT	TS	PT	TS	PT	TS	PT	TS	PT	TS
VD (mm)	2.5	2.6	3.0	2.8	2.4	2.6	2.6	2.8	2.7	2.7
Occlusion length (cm)	2.0	2.1	2.2	2	2.1	2	1.8	2.1	1.9	2.1
Device size (mm/mm)	4/20	4/20	4/20	4/20	4/20	4/20	6/20	4/20	4/20	6/20
Tirofiban use	Yes	Yes	No	No	Yes	Yes	No	No	Yes	Yes
PT attempts (times)	4	NA	2	NA	4	NA	5	NA	3	NA
Attempts to TIMI $\geq$ 2	2	NA	1	NA	1	NA	4	NA	2	NA
Procedure time (h)	1	1	0.5	1	1	1.5	1	3	0.5	4
Puncture site	R	R	R	R	R	R	R	L	R	L

VD, vessel diameter; PT, primary thrombectomy; TS, temporary stenting; R, right; L, left; NA, not applicable

fixed in 2.5% glutaraldehyde for scanning electron microscopy (SEM). Elastic Van Gieson's and Masson's trichrome stainings for LM were used. For the normal histological reference, the reference artery was viewed on both LM and SEM. Histological injury was evaluated as the presence of defects of the internal elastic lamina on LM and as denudation of the endothelial layer on SEM.

Results

Vascular occlusion by clot injection

Ten proximal IMAs with a mean diameter of 2.67 ± 0.17 mm (range, 2.4-3.0 mm) were successfully occluded in all five animals, the mean length of the occluded segments being 2.03 ± 0.12 cm (Table 1).

Angiographic efficacy

All occluded segments were passed with the Solitaire system showing technical success in all cases. A total of 18 primary thrombectomy attempts were made (mean 3.6, range: 2-5) on five right-vessel occlusions. Post-deployment TIMI ≥ 2 was seen in three cases of primary thrombectomy and in one case of temporary stenting. A final TIMI ≥ 2 was observed in five cases of primary thrombectomy and in two cases of temporary stenting (Figure 2). At the temporary stent-

ing site in animal number 1, TIMI changed from 1 to 2 with the use of tirofiban, although the final TIMI returned to 1. Post-procedural patency was achieved more frequently with primary thrombectomy than with temporary stenting. The mean number of primary thrombectomy attempts per site to achieve TIMI ≥ 2 , was two (range, 1-4). The mean primary thrombectomy procedure time was 0.8 hours (range, 0.5-1 hour). The mean temporary stenting duration was 2.1 hours (range, 1-4 hours). Resheathing of the temporary stent was possible in all animals except animal 3.

Post-retrieval angiograms after primary thrombectomy showed distal migration of the thrombus in animals 1 and 2. None of the animals showed evidence of vasospasm or vascular perforation during the procedure. There was no procedure-related death or puncture site hemorrhage.

Histopathologic safety

Specimens from a reference artery, a primary thrombectomy site, and a temporary stenting site were collected from each animal and were sent for LM and SEM examinations. Because of the device resheathing failure in the temporary stenting site of animal 3, this specimen was sent just for SEM due to the shortage of specimens. Endothelial defects presenting as defects of the internal elastic lamina on LM and denudation of the wavy endothelial surface on SEM (Figure 1) were noted in two of the primary

Figure 2 Revascularization efficacy of primary thrombectomy and temporary stenting. The X-axis denotes the animal number and the Y-axis denotes TIMI. *PD denotes post-deployment; PT denotes primary thrombectomy; TS denotes temporary stenting.

Figure 3 Angiographic and histologic results of temporary stenting in animal number 4. A) The initial angiogram of the left external carotid artery shows good flow of the left internal maxillary artery. B) A detachable coil (arrow) is inserted into the left internal maxillary artery. After clot injection, the detachable coil is withdrawn through the guiding catheter. C) 90-minute follow-up angiogram showed increased flow to the stented segment with more distal flow (arrow). D) Specimens for the stented segment show normal endothelial structures without endothelial damage (SEM, $\times 400$). E) The specimen has preserved intimal structures (arrow) (Elastic Van Gieson's stain, $\times 100$). F) Preserved intimal structures (arrow) are seen (Masson's trichrome stain, $\times 100$).

thrombectomy sites (40%) and in one temporary stenting site (20%). There was no gross intimal dissection or any abnormality beneath the internal elastic lamina in any of those three cases. No other specimen showed any evidence

of endothelial injury on either LM or SEM examination (Figure 3). In the two sites where a 6 mm device was used, endothelial defects were seen only in the temporary stenting site. These results are summarized in Table 2.

Table 2 **Histologic safety of primary thrombectomy and temporary stenting**

Animal number	Histologic safety	PT	TS
1	EI on LM	Yes	No
	EI on SEM	Yes	No
2	EI on LM	Yes	No
	EI on SEM	Yes	No
3	EI on LM	No	UA*
	EI on SEM	No	No
4	EI on LM	No	No
	EI on SEM	No	No
5	EI on LM	No	Yes
	EI on SEM	No	Yes

PT, primary thrombectomy; TS, temporary stenting; EI on LM, endothelial injury on light microscope; ED on SEM, endothelial injury on scanning electron microscope; UA, unavailable
 *: due to failure of resheathing, specimen only for SEM

Discussion

As previously noted, occasional endothelial injury was seen in our canine arterial thromboembolic occlusion model after both primary thrombectomy and temporary stenting using the Solitaire system. What could be the possible mechanisms of the injury? The positive histopathologic changes seen in the three specimens may prove helpful when speculating on the mechanism responsible. LM showed disruption of the intima and exposure of the internal elastic lamina. On SEM, the defects resembled compressed thin bands on the intimal surface. They looked like deep linear defects or cleavages which ran perpendicular to the normal wavy folds of the intimal surface, and formed by contraction of the circular muscles. We believe that direct compression of the intima by the device struts and/or shearing injury to the wall along the axis of the device pull-back could have been the primary mechanism. In a recent report regarding preclinical experience with a new device (Trevor; Concentric Medical Inc, Mountain View, CA, USA) similar to the Solitaire system, in a swine thrombo-occlusion model¹⁵, severe disruption of the intima was found on LM. We therefore believe that these two stent-like thrombectomy devices

have the same endothelial injury mechanism. As the diameter of the canine IMA was not larger than 3 mm, we used a 4 mm device in most cases. We used a 6 mm device in two arteries, i.e. one in the primary thrombectomy and the other in the temporary stenting to be able to see any possible influence of device oversizing. Interestingly, the primary thrombectomy did not show any microscopic change. However, it may be dangerous to draw any conclusions with such limited experience as it may imply that oversizing does not always have a high chance of vessel injury which could also be caused by a more complex device-thrombus interaction mechanism influencing the intimal surface integrity. If the clot jammed between the device struts and the intimal surface is larger and/or less compressible, the device/thrombus complex may generate a higher shearing force to the endothelial surface. On the other hand, the only positive histopathologic change in our temporary stenting cases was seen when we used a 6 mm device. Leaving an oversized device placed for more than one hour was enough for the struts to cause injury to the wall.

What could be the long-term effects of these endothelial injuries? These defects could be sources of acute platelet adhesion and aggre-

gation resulting in acute arterial re-occlusion and late intimal hyperplasia. Fortunately, a study using a swine renal artery model reported only minimal intimal thickening on a follow-up microscopic study¹⁶ evaluating the arterial endothelial status with hematoxylin and eosin staining at 30 and 90 days after the endovascular manipulation using the Solitaire system. Although that study did not include an acute endothelial evaluation, it showed mild intimal thickening at day 30 and minimal to mild intimal thickening at day 90, and no evidence of medial or adventitial proliferation. This thickening led to an approximately 5% luminal narrowing in three vessels and a 1% luminal narrowing in one vessel, thus concluding that there was little clinical significance of the histopathologic changes¹⁶. However, these observations are still limited to clinical experience with animals and therefore cannot be extrapolated directly to human cerebral arteries. Care should be taken to maintain the safety of the endothelium while manipulating the system in the intracranial arteries. As we usually experience in clinical situations, the Solitaire system was observed to have a higher recanalization rate in primary thrombectomy (5/5, 100%) than in temporary stenting (2/5, 40%). In addition to acute in-stent platelet aggregation, low recanalization rates in the temporary stenting may have been due to the experimental thrombus composition or to the insufficient radial force of the device. The radial force of the Solitaire system is 0.0106 N/mm when deployed in appropriately sized vessels^{17,18}. Our results suggest that this device has a lower radial force when used in temporary stenting¹⁹.

Our study had several limitations. First, we

did not use a proximal balloon-tipped guiding catheter during clot retrieval due to the local unavailability of the catheter and this could have been the reason for thrombus migration in two cases.

Second, due to the quality of the angiograms, small clot fragmentation and migration could not be clearly evaluated. Third, the vessels in our study animals were neither tortuous nor atherosclerotic.

The degree and extent of the endothelial injury could, therefore, have been less in our canine model due to the rather straight course of the IMAs, and which is uncommon in real stroke situations.

Conclusions

We were able to demonstrate acute histopathological changes after various endovascular applications of the Solitaire system. The temporary stenting method showed a lower recanalization rate with less frequent endothelial injury, while the primary thrombectomy method showed a higher recanalization rate with a higher incidence of clot migration and endothelial injury. Histologic abnormality of endothelial denudation did occur in some cases, thus suggesting the need for careful device application.

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