Case series

The Zoom RDL radial access system for neurointervention: An early single-center experience

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ABSTRACT

Background: The transradial approach (TRA) for neurointerventional procedures is increasingly being used given its technical feasibility and safety. However, catheter trackability and device deliverability are reported barriers to TRA adoption.

Methods: This is the first report describing the technical feasibility and performance of using the Zoom RDL Radial Access System (Imperative Care, Inc., Campbell, CA) in 29 patients who underwent neurointerventional procedures from October 2022 to January 2023 in a single-center institution.

Results: Mean age of the study population was 61.9±17.2 years, 79.3% were male (23/29), and 62.1% were black (18/29). The most common procedures were stroke thrombectomy (31.0%, 9/29) and aneurysm embolization (27.6%, 8/29). All the stroke thrombectomy procedures were successfully performed; first-pass effect rate (mTICI≥2c in one pass) was achieved in 66.7% (6/9) of cases. We used TRA in 86.2% of cases (25/29), including distal radial/snuffbox access in 31.0% (9/29) of cases. The radial diameter was >2 mm for all cases. An intermediate/assistance catheter was used in 89.7% (26/29) of cases. Access success was achieved in 89.7% of cases (26/29); two cases required conversion from TRA to transfemoral approach (6.9%) and one case required conversion to a different guide catheter (3.4%). There were no access site complications or other Zoom RDL-related complications. One intracerebral hemorrhage and one procedure-related thrombus were observed.

Conclusions: The use of Zoom RDL Radial Access System is technically feasible and effective for complex neurointerventional procedures with low complication rates.

INTRODUCTION

Multiple studies, including numerous neurointerventional and intervention cardiology trials, have demonstrated that transradial approach (TRA) for neurointerventional procedures is associated with lower rates of access site complications and conversion to transfemoral access approach (TFA). However, there is resistance to adopting TRA for neurointerventional procedures due to radial artery access failure, radial artery and subclavian anatomical variability, and catheter damage. Also, neuroendovascular catheters are designed for TFA, which can pose challenges navigating the aortic arch when using TRA. A national survey found that TRA improves patient comfort and reduces complications, but a lack of high-quality equipment designed for TRA is the main barrier to broader adoption.

At our institution, we started performing neurovascular interventions utilizing TRA in 2020. Herein, we present our initial experience, the technical feasibility and safety of the novel Zoom Radial Access System (Zoom RDL; Imperative Care, Inc., Campbell, CA) in a wide range of complex neurointerventional procedures and discuss radial access techniques and challenges.

METHODS

Study design and criteria

In this case series, we retrospectively analyzed consecutive neurointerventional procedures completed using Zoom RDL at a tertiary academic center from October 2022 to January 2023. The study protocol was approved by the Institutional Review Board and informed consent requirements were waived. We included 29 consecutive patients treated by one operator, regardless of anatomy, who met the following criteria: age ≥18 years, any neurovascular disease pathology, and use of Zoom RDL. We reviewed data from electronic medical records, including procedural details, radiographic imaging, and hospitalization events. The primary outcome measure was access success, defined as accessing the target vessel without conversion to a different guide catheter or to TFA. Secondary outcome measures included access site complications, procedure or device-related complications, and in-hospital mortality. For thrombectomy cases, we evaluated modified Thrombolysis in Cerebral Infarction (mTICI), number of passes, and first-pass effect (FPE), defined as achieving mTICI≥2c recanalization within one pass.

Zoom RDL radial access system

The Zoom RDL has been cleared by the Food and Drug Administration for introduction of interventional devices into the neuro, peripheral, and coronary vasculature. This system is designed to provide an alternative option for navigating into the intracranial circulation by facilitating vascular access through the radial artery. The purported benefits of the system are related to its catheter design, which incorporates both flexible and supportive segments,
New devices and techniques

Radial access technique

When using Zoom RDL, we typically select the right radial artery as our main access point. This allows for easier navigation of guide catheters into the common and internal carotid arteries while simultaneously maintaining proximity to the right common femoral access site. It is also easier for the neurointerventionalist to operate from the patient’s right side. The Barbeau or Allen’s tests were not performed for pre-procedural collateral circulation testing as they are not necessary for radial artery patency assessment. We utilized ultrasound for radial artery access in all cases and proceeded after confirming the radial artery diameter to be ≥1.5 mm. Using the Seldinger technique, a 6F/7F Glidesheath Slender (Terumo, Tokyo, Japan) is introduced into the radial artery. A Bentson wire guide (Cook medical LLC, Bloomington, IN) or Amplatz super Stiff Guidewire (Boston Scientific, Marlborough, MA) was then introduced through the 6F/7F sheath and positioned in the subclavian artery distal to the vertebral artery origin; the sheath was then exchanged out over the wire for Zoom RDL and guidewire towards the targeted vessel. Further advancement of Zoom RDL (dark gray) to target vessels, such as the suprACLdIOn ICas, or in special circumstances the M1 branch of the middle cerebral artery, is completed over a microwire and microcatheter within an intermediate/aspiration catheter as a tri-axial system (light gray).

enabling it to navigate the twists and turns of the intracranial vasculature.

Figure 1  Illustration demonstrating the Zoom radial access technique. A: a 6F/7F Glidesheath slender (Terumo, Tokyo, Japan) is introduced into the radial artery. B: a Bentson wire guide (Cook medical LLC, Bloomington, IN) or Amplatz super Stiff Guidewire (Boston Scientific, Marlborough, MA) is introduced through the 6F/7F glidesheath. C: Zoom RDL (gray) is introduced directly through the skin with the beveled tip directed upward using the provided 6F vessel dilator (green). D: the select catheter with a Simmons two curvature (purple/black) is reformed to deflect the guidewire off the aortic valve to help facilitate Zoom RDL positioning in the targeted vessel. E: Zoom RDL (gray) is advanced over the select catheter and guidewire towards the targeted vessel. F: further advancement of Zoom RDL (dark gray) to target vessels, such as the supraclinoid ICAs, or in special circumstances the M1 branch of the middle cerebral artery, is completed over a microwire and microcatheter within an intermediate/aspiration catheter as a tri-axial system (light gray).
artery (ICA), the internal maxillary artery branch of the external carotid artery (ECA), or the V2 segment of the vertebral artery (VA). Subsequently, Zoom RDL was advanced over the Select catheter and Guidewire to reach the target vessel (figure 1E). The Select catheter and Guidewire were then removed. Further advancement of Zoom RDL to target vessels, such as the supraclinoid ICA, or in special circumstances the M1 branch of the middle cerebral artery (M1-MCA), was completed over a microwire and microcatheter within an intermediate/aspiration catheter as a tri-axial system (figure 1F).

With Zoom RDL in position, the neurointerventionalist can exchange the intermediate catheters as necessary to complete the procedure. After completing the procedure, Zoom RDL is removed and a closure device, usually the TR Band (Terumo, Tokyo, Japan), is applied at the puncture site to maintain hemostasis. A video of the TRA MYNX CONTROL Vascular Closure Device (Cordis, Miami Lakes, FL) is used to maintain hemostasis. A video of the TRA technique is available online (Supplemental video 1).

### RESULTS

#### Patient and procedural characteristics

The patient and procedural characteristics of all included cases are presented in table 1. The most common pathologies in our cohort were strokes (31.0%, 9/29), aneurysms (27.6%, 8/29), and subdural hematomas (13.8%, 4/29). The most common procedure was endovascular thrombectomy (31.0%, 9/29), followed by aneurysm flow diverter embolization (17.2%, 5/29), and middle meningeal artery (MMA) embolization (13.8%, 4/29). Most cases were done using TRA (86.2%, 25/29), including 31.0% (9/29) of procedures where the distal radial artery or anatomical snuffbox was used for access. The radial artery diameter was >2 mm for all TRA cases. An intermediate/aspiration catheter was used in 89.7% (26/29) of cases, most commonly the Phenom Plus Support Catheter (Medtronic, Irvine, CA) (27.6%, 8/29) and the Zoom 71 Aspiration Catheter (Imperative Care, Inc., Campbell, CA) (27.6%, 8/29), followed by the Zoom 45 Aspiration Catheter (Imperative Care, Inc., Campbell, CA) (24.1%, 7/29). For stroke pathologies, the combination of stent retriever and aspiration techniques was most used (88.9%, 8/9), followed by aspiration alone (11.1%, 1/9). The left ICA was the most targeted vessel (41.4%, 12/29).

#### Outcomes

Technical outcomes and procedural complications are presented in table 2. Access success was achieved in 89.7% (26/29) of cases. There were two cases where crossover from TRA to TFA was required. One case was an aneurysm treated with a flow diverter; after initially introducing Zoom RDL via the snuffbox approach, there was difficulty advancing, so a TFA approach with Zoom RDL was used instead. The other case involved a subdural hematoma, and access was obtained via the snuffbox approach. However, the Zoom RDL tip was damaged during consecutive insertion attempts. As a result, a different guide catheter, the AXS Infinity LS (Stryker Neurovascular, Fremont, CA), was used via transfemoral access. Access success was achieved in all stroke

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient and procedural characteristics (n=29 cases)</th>
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</thead>
<tbody>
<tr>
<td><strong>Age, years (mean±SD)</strong></td>
<td>61.9±17.2</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23 (79.3%)</td>
</tr>
<tr>
<td>Female</td>
<td>6 (20.7%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>18 (62.1%)</td>
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<tr>
<td>White</td>
<td>6 (20.7%)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (17.2%)</td>
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<tr>
<td><strong>Pathology</strong></td>
<td></td>
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<tr>
<td>Stroke</td>
<td>9 (31.0%)</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>8 (27.6%)</td>
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<tr>
<td>Subdural hematoma</td>
<td>4 (13.8%)</td>
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<tr>
<td>Dural arteriovenous fistula</td>
<td>3 (10.3%)</td>
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<tr>
<td>Acute intracranial atherosclerotic stenosis</td>
<td>2 (6.9%)</td>
</tr>
<tr>
<td>Traumatic vessel injury</td>
<td>1 (3.4%)</td>
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<tr>
<td>Carotid blowout syndrome</td>
<td>1 (3.4%)</td>
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<tr>
<td>Vasospasm</td>
<td>1 (3.4%)</td>
</tr>
<tr>
<td><strong>Type of procedure</strong></td>
<td></td>
</tr>
<tr>
<td>Endovascular thrombectomy</td>
<td>9 (31.0%)</td>
</tr>
<tr>
<td>Aneurysm flow diverter embolization</td>
<td>5 (17.2%)</td>
</tr>
<tr>
<td>MMA embolization</td>
<td>4 (13.8%)</td>
</tr>
<tr>
<td>Dural AV fistula embolization</td>
<td>3 (10.3%)</td>
</tr>
<tr>
<td>Rescue intracranial stenting</td>
<td>2 (6.9%)</td>
</tr>
<tr>
<td>Aneurysm coil embolization</td>
<td>2 (6.9%)</td>
</tr>
<tr>
<td>Aneurysm WEB embolization</td>
<td>1 (3.4%)</td>
</tr>
<tr>
<td>Balloon occlusion test</td>
<td>1 (3.4%)</td>
</tr>
<tr>
<td>Traumatic vessel embolization</td>
<td>1 (3.4%)</td>
</tr>
<tr>
<td>Vasospasm treatment</td>
<td>1 (3.4%)</td>
</tr>
<tr>
<td><strong>Access site</strong></td>
<td></td>
</tr>
<tr>
<td>Right proximal radial</td>
<td>15 (51.7%)</td>
</tr>
<tr>
<td>Right distal radial/snuffbox</td>
<td>9 (31.0%)</td>
</tr>
<tr>
<td>Right femoral</td>
<td>4 (13.8%)</td>
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<tr>
<td>Left proximal radial</td>
<td>1 (3.4%)</td>
</tr>
<tr>
<td>Right internal jugular vein</td>
<td>1 (3.4%)</td>
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<tr>
<td>Left femoral vein</td>
<td>1 (3.4%)</td>
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<tr>
<td>Left distal radial/snuffbox</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Radial diameter&gt;2 mm</td>
<td>25 (100.0%)</td>
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<tr>
<td><strong>Use of intermediate/aspiration catheter</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26 (89.7%)</td>
</tr>
<tr>
<td>No</td>
<td>3 (36.0%)</td>
</tr>
<tr>
<td><strong>Type of intermediate/aspiration catheter used</strong></td>
<td></td>
</tr>
<tr>
<td>Phenom Plus Support Catheter</td>
<td>8 (27.6%)</td>
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<tr>
<td>Zoom 71 Aspiration Catheter</td>
<td>8 (27.6%)</td>
</tr>
<tr>
<td>Zoom 45 Aspiration Catheter</td>
<td>7 (24.1%)</td>
</tr>
<tr>
<td>SOFIA 5F Catheter</td>
<td>3 (10.3%)</td>
</tr>
<tr>
<td>Navien 5F Intracranial Support Catheter</td>
<td>1 (3.4%)</td>
</tr>
<tr>
<td>Zoom 35 Aspiration Catheter</td>
<td>1 (3.4%)</td>
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</tbody>
</table>
cases with most cases demonstrating mTICI ≥2c recanalization within one pass (66.7%, 6/9).

Complications
There were no access site complications. However, one case of thrombus formation was detected in the ICA following balloon-assisted coil embolization for a ruptured anterior communicating artery (AComA) aneurysm. It was confirmed that this complication was not related to the use of the Zoom RDL. The lengthy balloon-assisted coiling procedure in a setting of subarachnoid hemorrhage is known to induce a hypercoagulable state, which is likely a contributing factor in the formation of thrombus.\textsuperscript{13}

To manage the thrombus, a combination of the Trevo NXT ProVue Retriever (Stryker Neurovascular, Fremont, CA) and Zoom 71 Aspiration Catheter was successfully employed. There was also one intracranial hemorrhagic complication following a rescue intracranial stenting procedure, which was unrelated to the Zoom RDL and was managed conservatively without new neurologic deficits.

Case illustration
A woman in her 60s with a previous history of aneurysmal subarachnoid hemorrhage treated with coils presented with an aneurysm recurrence originating proximally from the A2 segment of the right anterior cerebral artery (ACA). We decided to proceed with bilateral ‘H-pipe’ flow diverter embolization in both ACAs, given the concern that this aneurysm may have caused the previous subarachnoid hemorrhage. We obtained distal radial access in the anatomical snuffbox and navigated Zoom RDL to the right ICA. We then acquired a 3D angiogram which revealed a small irregularly shaped aneurysm protruding medially and posteriorly from the A2 segment of the right ACA.

After confirming the location of the aneurysm, we deployed two Pipeline Flex embolization stents (Medtronic, Irvine, CA) across the neck of the aneurysm. After confirming flow stagnation within the aneurysm and normal bilateral ACA flow, Zoom RDL was repositioned into the left ICA and an additional Pipeline Flex was deployed. A follow-up angiogram ensured flow stagnation in the aneurysm and continued normal bilateral ACA flow with no evidence of contrast extravasation, thromboembolic, or hemorrhagic complications.

DISCUSSION
This study highlights the Zoom RDL versatility for neurointerventional procedures via TRA, reporting a high access success rate with a relatively low complication rate. It also acknowledges the known challenges associated with TRA and catheter characteristics requiring discussion and careful patient selection.

Radial access considerations
Catheter characteristics
Designed to address challenges of using TFA catheters for TRA, the Zoom RDL has a 0.088-inch inner diameter and can be used without a radial sheath. Using 0.088-inch guide catheters without a sheath can increase the risk of RAS, as seen when using

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**Table 1**

<table>
<thead>
<tr>
<th>Age, years (mean±SD)</th>
<th>61.9±17.2</th>
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**Thrombectomy device techniques used**

- Combination of stent retriever and aspiration 8 (88.9%)
- Aspiration thrombectomy alone 1 (11.1%)
- Stent retriever thrombectomy alone 0 (0.0%)

**Target vessel for intervention**

- Right intracranial ICA 4 (13.8%)
- Left intracranial ICA 12 (41.4%)
- Bilateral intracranial ICA 2 (6.9%)
- Right M1 branch of MCA 2 (6.9%)
- Left M1 branch of MCA 1 (3.4%)
- Left ECA 1 (3.4%)
- Bilateral ECA 1 (3.4%)
- Right internal maxillary artery 1 (3.4%)
- Left internal maxillary artery 1 (3.4%)
- Bilateral internal maxillary artery 4 (13.8%)
- Right vertebral artery 1 (3.4%)
- Left vertebral artery 1 (3.4%)
- Right ascending cervical artery 1 (3.4%)
- Bilateral ascending cervical artery 2 (6.9%)

**Table 2**

**Technical outcomes and procedural complications**

| Technical access success | Yes 26 (89.7%) |
|--------------------------|-----------------
| No, conversion from radial to femoral | 2 (6.9%) |
| No, conversion to different guide catheter | 1 (3.4%) |

**Thrombectomy outcomes**

- Modified TICI score on final angiogram
  - Grade 3 4 (44.4%)
  - Grade 2c 3 (33.3%)
  - Grade 2b 2 (22.2%)

**Number of passes**

- 1 6 (66.7%)
- 2 2 (22.2%)
- 3 1 (11.1%)

**First-pass effect**

- 6 (66.7%)

**Time from puncture to first angiogram of target vessel, min (median (IQR))**

- 10.0 (15.0)

**Fluoroscopy time, min (median (IQR))**

- 25.6 (22.1)

**Access site complications**

- None 29 (100.0%)
- Minor 0 (0.0%)
- Major 0 (0.0%)

**Other procedure-related complications**

- None 27 (93.1%)
- Intracerebral hemorrhage 1 (3.4%)
- Intraprocedural thrombus 1 (3.4%)
- In-hospital mortality 2 (8.0%)\textsuperscript{4}

**Length of stay, days (median (IQR))**

- 15.6 (25)

**Intraprocedural thrombus**

- c with first pass

**Technical access success**

- No, conversion from radial to femoral 2 (6.9%)
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**Length of stay, days (median (IQR))**

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**Intraprocedural thrombus**

- c with first pass

**Modified TICI score ≥2c with first pass**

<table>
<thead>
<tr>
<th>Modified TICI score ≥2c</th>
<th>5 (17.2%)</th>
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\textsuperscript{4}Missing values

IQR, interquartile range; SD, standard deviation; TICI, thrombolysis in cerebral infarction.
8F guide catheters designed for TFA with TRA. However, the larger inner diameter is necessary to facilitate use of large-bore aspiration catheters, which is a common reason why neurointerventionists opt not to use TRA for stroke. In comparison to the Rist Radial Access System (Medtronic, Irvine, CA), Zoom RDL can accommodate larger intermediate/aspiration catheters and can be used with both TRA and TFA in select patients. Zoom RDL also has a hydrophilic coating that can potentially reduce risks associated with catheter manipulation and entrapment in the radial artery. Lack of hydrophilic coating can be associated with increased risk of RAS, radial artery occlusion (RAO) and decreased patient comfort. Severe RAS can make it difficult to remove catheters and sheaths, contributing to hand ischemia, clot formation and infections. In our cohort, we did not encounter any RAS, symptomatic RAO or catheter entrapment, which might be attributed to the Zoom RDL hydrophilic coating. The proximal portion of Zoom RDL is supported by a stainless-steel braid which improves proximal support and achieves better pushability and torque transmission for distal navigation. Our study findings (table 1) demonstrate that Zoom RDL properties allow it to be advanced to the M1-MCA branch with good stability and to the ECA or VA. However, the operator subjectively observed a relatively lower stability in the ECA or VA compared with the MCA.

Catheter capabilities

The role of TRA in neurointerventional procedures remains under scrutiny due to anatomical configuration of the great vessels. Furthermore, the presence of a proximal radial loop, large diameter aortic arch, double subclavian innominate curve, left proximal CCA loop, acute subclavian vertebral angle, and absence of a bovine aortic arch, make TRA challenging. It is imperative to understand these anatomical variations to improve the access success rate and reduce the risk of complications when using TRA. For instance, when encountering a radial artery loop, microwires can be used to access the brachial artery and straighten the loop before placing a long radial sheath.

Zoom RDL is designed to reach the M1-MCA branch, which requires the distal portion of the catheter to remain soft, making it not as stable when targeting more proximal vessels such as the ECA or the VA. Unlike Zoom RDL, femoral catheters typically have a shorter soft distal portion which provides more stability for treatments in proximal vessels. Furthermore, femoral catheters are not designed to navigate the great vessels coming from TRA as the stiff portion of the catheter can increase the likelihood of catheter prolapse into the arch.

Multiple intermediate/aspiration catheters were compatible with Zoom RDL, including the Phenom Plus Support Catheter, Zoom 35, 45, and 71 Aspiration Catheters, SOFIA 5F Catheter (MicroVention, Inc., Aliso Viejo, CA), and the Navien 5F Intracranial Support Catheter (Medtronic, Irvine, CA). This versatility enables Zoom RDL to be used in a variety of different procedure types and target vessels. Radial-designed guide catheters now provide neurointerventionists the ability to complete a wide range of procedures and deploy most types of devices with TRA. However, catheter support profiles need to be tailored to the disease pathology, the anatomical variability, and the experience of the neurointerventionalist.

Outcomes and complications

Crossover from TRA to TFA is approximately 5–8% when using femoral-designed catheters. In our cohort, the crossover rate was approximately 6.9% (2/29). One crossover occurred due to a radial loop, and the decision was made to forego radial access given the time required to overcome this issue during stroke thrombectomy. The other conversion occurred in an aneurysm repair due to difficulty advancing Zoom RDL through brachioradial tortuosity. Within our study’s stroke procedures, the FPE rate was 66.7% (6/9). In one systematic review, balloon guide catheters supported a 49.1% FPE rate in comparison to 37.3% for non-balloon guide catheters. The positioning of the large bore guide catheter intracranially and closer to the clot may have contributed to the promising FPE rate in our population. A single-center TFA study suggested that intracranial guide catheter placement can lead to excellent reperfusion, better FPE, and faster access to final reperfusion time in patients with emergent large vessel occlusion, which supports our hypothesis. However, we caution that future studies are needed to fully elucidate factors associated with better reperfusion and FPE based on TRA. Access site complications were not observed in our cohort, which may be due to consistent use of access site compression devices and radial artery ‘cocktails’ to reduce the risk of hematoma development and RAS, respectively. There was no incidence of radial arteritis in our population. Other complications, not related to Zoom RDL, were observed, including the development of a thrombus during a long balloon-assisted coiling procedure in a patient with an ACOM aneurysm. This was successfully treated with a combination of stent retriever and aspiration thrombectomy. In addition, there was one patient who suffered from intracranial hemorrhage, which was likely due to reperfusion injury.

Future directions

Based on our initial experience, Zoom RDL provides a repertoire of available endovascular strategies for patients with reduced TICI ≥2b reperfusion rate with the TFA approach, it is possible that the TRA approach may be more effective in this cohort.

The available evidence comparing technical success rates between transradial access (TRA) and transfemoral access (TFA) for mechanical thrombectomy in patients with acute ischemic stroke is insufficient. Although that report demonstrated a higher TICI ≥2b reperfusion rate with the TFA approach, it is noteworthy that the TRA approach (n=93) achieved TICI ≥2b reperfusion in 79.6% of patients. In our study, all nine patients who underwent mechanical thrombectomy via TRA achieved self-adjusted TICI ≥2b reperfusion. While the observed reperfusion success in our patients is based on a small sample size and could be subject to selection bias, the results are promising and will undoubtedly require confirmation through a large, prospective trial.
Limitations
This study has certain limitations. Conclusive remarks cannot be extrapolated into clinical practice given the small sample size and retrospective nature of the study. While we did not observe any cases of symptomatic RAO in our population, it is important to note that our practice does not routinely perform post-procedure ultrasounds or follow-up angiograms in asymptomatic patients. Also, our study did not have a control group and therefore we cannot infer the effectiveness of Zoom RDL relative to other catheters. Our neurointerventionalist was also experienced in TRA, which makes these results less applicable to those not frequently using radial access.

CONCLUSIONS
Our study shows that the Zoom RDL Radial Access System is technically feasible and safe for a range of complex neurointerventional procedures, with high success rates and low complication rates observed in our patient population. These results suggest that the system can be a safe alternative for obtaining neurovascular access in complex neurointerventions.

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Contributors All authors participated in the research, data collection, provision of critical revisions for content, and/or writing of the manuscript, and all authors had responsibility for the final content of this manuscript.

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