Endovascular treatment of ruptured blood blister-like aneurysms with multiple (≥3) overlapping Enterprise stents and coiling

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Abstract
Background Blood blister-like aneurysms (BBAs) are difficult to treat both surgically and endovascularly, and the optimal treatment remains controversial. The aim of this study was to evaluate the clinical and angiographic feasibility of multiple overlapping stents (≥3) with coiling for treating BBA.
Methods A retrospective review from four institutions identified ten patients with ruptured BBAs who were treated with multiple overlapping stents (≥3). We included both the patients who were initially treated with more than three stents and those who eventually had more than three stents as a consequence of retreatment. Angiographic results (Raymond scale), clinical outcomes (mRS) and treatment courses were evaluated.
Results Initially, seven patients were treated with triple stents and three with double stents. Immediate angiographic results revealed that six aneurysms were Raymond grade 1, three were grade 2, and one was grade 3. Complementary treatment was required in four patients. All three patients who were initially treated with double stents required complementary treatment (100 %). One patient required complementary treatment among the seven patients who were initially treated with three stents (14.3 %). The last follow-up angiography (mean, 12.2 ± 14.7 months; range, 1–44 months) revealed grade 1 in all ten patients. Clinical data (mean follow-up period, 18.2 ± 20.1 months; range, 1–62 months) revealed eight patients with a mRS score of 0–2 and two with mRS 3–5.
Conclusions Even in the era of flow diverter stents, multiple overlapping stents (≥3) with coiling could be a feasible alternative for treating ruptured BBAs. Additional experience and follow-up are needed in a larger series to state the long-term efficacy of this treatment.

Keywords Blood blister-like aneurysm · Endovascular treatment · Stent

Abbreviations
BBA blood blister-like aneurysm
EVT endovascular treatment
EVD external ventricular drain
SAH subarachnoid hemorrhage
HH Hunt and Hess scale
mRS modified Rankin Scale
PAO parent artery occlusion
SAC stent-assisted coil embolization
SOT stent-only therapy
FD flow-diverting device
Introduction

Endovascular treatment is used increasingly for ruptured and unruptured intracranial aneurysms. Despite advances in endovascular and microsurgical techniques, blood blister-like aneurysms (BBAs) frequently present a tremendous therapeutic challenge due to their unfavorable morphology and histology. BBAs are a subtype of dissecting aneurysm, classically described as small, bleb-like and ill-defined neck lesions at non-branching sites of the dorsal wall of the intracranial carotid and basilar arteries [3, 12, 13]. Histologically, these lesions have been shown to represent focal wall defects covered with thin, fibrous tissue and adventitia, lacking the usual collagen layer [4]. Given these characteristics, they are associated with high surgical morbidity and mortality because of intraoperative rupture, postoperative hemorrhage and regrowth, and they are not amenable to conventional coil embolization. Although numerous treatment techniques have been suggested, the optimal management of these lesions remains controversial.

Recently, endovascular treatment with stent-assisted coil embolization (SAC) or the stent-within-stent technique was attempted for ruptured BBA. However, the results still showed high recurrence rates [12, 13]. In this series, we evaluate the clinical and angiographic feasibility of multiple overlapping stents (≥3) with coiling to treat ruptured BBAs.

Materials and methods

Patient population

This study was approved by the institutional review board at each center. The requirement to obtain written informed consent to participate in this study was waived.

We retrospectively collected all patients who were treated with multiple (≥3) overlapping stents with or without coiling for BBAs in four referral hospitals (Seoul St. Mary’s Hospital, Gachon University Gil Medical Center, Ajou University Hospital and Inha University Hospital). These institutions have a tertiary neurointerventional center. We included both the patients who were initially treated with more than three stents and those who eventually had more than three stents as a consequence of retreatment. BBA was diagnosed based on the following characteristics: (1) typical appearance as a small hemispherical bulge or an irregular bleb-like protrusion at non-branching sites of the parent artery and/or (2) a newly developing or rapidly growing lesion at a non-branching portion of the parent artery trunk on very short-term follow-up angiography, typically obtained within 1 week. We excluded patients who were not available for angiographic follow-up. Between February 2011 and July 2014, ten patients (18 procedures) were treated with multiple overlapping stents (≥3) and coiling. All aneurysms were ruptured and had blood blister-like morphology. One of these patients has been reported previously [12].

Antiplatelet and anticoagulation protocols

Immediately after the procedure, a loading dose of antiplatelet medication (200 mg aspirin and 300 mg clopidogrel) was given orally via a Levin tube in both the acute and subacute settings. Dual antiplatelet medication (100 mg/day aspirin and 75 mg/day clopidogrel) was maintained for 3–6 months at the physician’s discretion and then was changed to aspirin monotherapy for an additional 6–12 months. In the acute phase of subarachnoid hemorrhage (SAH), systemic heparinization with 3000 units of heparin was injected intravenously after the first coil detachment, and 1000 units of heparin was administered every hour. Every coaxial catheter-flushing fluid was mixed with heparin at a concentration of 1000 units heparin per 1000 ml saline. For the retreatment or delayed treatment cases, a 3000-unit heparin bolus was injected intravenously before placing the guide catheter, and a 1000-unit bolus was administered every hour to maintain an activated coagulation time of 250–300 s. Heparin was stopped but not reversed after the procedure was completed. Three cases were treated in the subacute rupture setting, and we applied the same antiplatelet medication protocols.

Procedure

After the guiding catheter (5 F, 6 F or 7 F Envoy, Cordis Neurovascular, Miami, FL, USA) or sheath (6-F Shuttle Select, Cook, Bloomington, IN, USA) was introduced into the parent artery, the Prowler Select Plus microcatheter (Cordis) for the Enterprise Stent was navigated across the aneurysm neck portion to a distal branch of the parent artery. A second microcatheter (Excelsior; Boston Scientific, Natick, MA, USA) for coil deployment was inserted into the aneurysm sac, and the initial Enterprise stent was deployed, bridging the aneurysm neck. After the first stent deployment, the Prowler Select Plus microcatheter was readvanced to the initial position over the stent loading wire, which was left in situ within the deployed stent. Next, coil embolization was performed as compactly as possible, including the aneurysm neck portion, if needed. A second Enterprise stent was introduced and deployed in an overlapping manner. The stent was positioned across the lesion with enough overlap on each side of the target to anchor the stent securely. This procedure was repeated to insert more overlapping stents.

Clinical and radiologic follow-up and outcome evaluation

We retrospectively reviewed the patients’ data from the medical records and neurosurgical database. The neurosurgical
database was prospectively recorded by neurosurgical fellows with regard to the following characteristics: sex, age, presence of hypertension, diabetes, dyslipidemia, statin medication, smoking status, family history of aneurysm, multiplicity of aneurysms, aneurysm location, size of the aneurysm, treatment methods, devices used in the procedure, treatment result according to the modified Raymond Scale (complete, residual neck and residual aneurysm), procedure-related complications, mRS score at discharge, and remarks concerning morbidity and mortality cases. All clinical and radiographic data were prospectively registered into the neurosurgical databases in each hospital at the time and then analyzed retrospectively by the authors. Collected data were thoroughly reviewed by one interventional neuroradiologist (B.S. Kim) and two neurosurgeons (Y.S. Shin and J. Song). Patients were assessed with the Hunt and Hess (HH) grading system on admission and before endovascular treatment. Treatment-related complications were evaluated and recorded during and after treatment. Clinical outcomes were evaluated according to the modified Rankin Scale (mRS) at discharge, and at the last clinical follow-up, defined as the final clinical outcome.

Angiographic follow-up was available at least once in all patients. The follow-up was typically performed at 1–2 weeks, 2–4 months and 6–24 months postoperatively. Retreatment was usually performed for recurrent BBA at the same session. If retreatment was not feasible, the next follow-up angiography was obtained 1–4 weeks later. Initial and follow-up angiographic results were classified using the Raymond classification: grade 1, complete; grade 2, residual neck; grade 3, residual aneurysm. On follow-up angiography, aneurysms were considered as stable (no change on the Raymond scale), improved (aneurysm moving from a higher to a lower point on the Raymond scale, suggesting improved occlusion) and regrowth (aneurysm moving from a lower to a higher point on the Raymond scale, suggesting worsening occlusion). In-stent stenosis or in-stent occlusion and the patency of the branch vessel or the perforators covered by stents were also evaluated on follow-up angiography.

**Results**

**Patients**

Seven patients were treated in the acute rupture setting (within 3 days), and three were treated in the subacute rupture setting (1–3 weeks post-hemorrhage). In the latter three cases, diagnosis was delayed because of misinterpretation as a vascular irregularity on the initial DSA. Case 5 experienced rebleeding at 3 weeks post-hemorrhage.

**Periprocedural complications**

Ten patients were treated with 18 procedures. One patient (case 2, Fig 1) experienced transient diffuse in-stent fibrin formation, which was resolved with intra-arterial Tirofiban (1 mg) injection without neurologic events. Additional treatment was delayed for 1 month. The 43-day angiography shows an enlarged BBA (compared to e), and it was treated almost completely (f, grade 1). The 3-month follow-up angiography shows aneurysm filling (grade 3), and it was treated with one more stent and coil embolization (h, grade 1).
complications. One patient required an external ventricular drain for hydrocephalus and experienced intracranial hemorrhage along the catheter insertion tract.

**Angiographic results and durability**

The angiographic and clinical outcomes are summarized in Table 1. Initially, seven BBAs were treated with triple stents, and three BBAs were treated with double stents. Nine aneurysms were treated with SAC, and one aneurysm was treated with the stent-only technique (SOT) because the aneurysm morphology was too shallow to insert a coil. Initial angiographic results revealed that six aneurysms were Raymond grade 1, three were grade 2, and one was grade 3 (which was treated with SOT). Angiographic follow-up was available in all patients (mean, 12.2 ± 14.7 months; range, 1–44 months). Early complementary treatment was required in four patients, three of whom were initially treated with double stents. One hundred percent of the patients showed recurrence in the double stent treated group. Seven patients who were initially treated with three overlapping stents showed only one recurrence (14.3% recurrence). The last angiographic results revealed grade 1 in all patients. Case 1, who was treated with SOT, showed grade 3, but the aneurysm size had decreased on follow-up angiography. Seven cases were available for midterm follow-up (>6 months) with DSA, and no patients showed in-stent stenosis, occlusion of perforating vessels or delayed ischemic events.

**Clinical outcomes**

Clinical follow-up was performed (mean, 18.2 ± 20.1 months; range, 1–62 months). Five patients had an mRS score of 0, two had an mRS score of 1 because of residual headache, one had an mRS score of 2 because of mild right-side weakness, and two had an mRS score of 3–5, initially presenting HH grade 4. No delayed infarcts or hemorrhages were documented.

**Discussion**

**Previous surgical or endovascular treatment of BBA**

BBA usually presents as SAH and is one of the most challenging lesions to treat. For surgery, several approaches, such as clipping or wrapping material techniques, are used. Parallel clipping under hypotension, and direct staple clip reconstruction of the artery, have been tested with variable success [13]. However, these approaches were often associated with high surgical mortality and morbidity due to the friable walls. Therefore, these cases are often associated with high surgical mortality and morbidity because intraoperative rupture, regrowth and rebleeding are common, even after adequate aneurysm clip application [5]. Parent artery occlusion (PAO) or endovascular trapping after a balloon occlusion test (BOT) has been suggested as an effective approach [2, 10, 16]. However, this approach exposes patients to increased ischemic risks or an elevated hemodynamic burden of the contralateral ICA [2, 10]. Bypass has been proven to be helpful in reducing the stroke risk; nevertheless, the technique is quite complicated and is related to a high risk of surgical complications [18]. Additionally, PAO is not suitable for cases in which anterior choroidal/posterior communicating arteries arise close to the BBA or if there is an insufficient collateral blood supply. Furthermore, PAO may also interfere with the endovascular access required for later vasospasm treatment [8]. Meling et al. [14] reported a particularly poor outcome in patients after surgical ICA sacrifice because of the development of early as well as delayed cerebral infarcts. The latter occurred even though spontaneous cross-flow was evident on preoperative angiography, presumably as a consequence of vasospasm-induced compromise of cerebral collateral flow. For endovascular management, the shallow and wide neck morphology of BBAs makes it difficult to deploy coils, and these aneurysms react unfavorably to coil embolization because of their incomplete wall. Therefore, it increases the risk of further aneurysm rupture or coil migration. The lack of a true aneurysm wall allows for frequent aneurysm regrowth [4]. Reconstructive treatment such as SAC or SOT can be an alternative option. In this study, we treated nine cases (9/10) with SAC, expecting a better preventive effect on immediate rupture by coil insertion. We also used the jailing technique to overcome morphological difficulties.

**Feasibility of multiple overlapping stents, even in the era of flow diverters**

To treat ruptured BBAs in the acute stage, it is critical to block the blood flow from the affected wall to prevent rebleeding and regrowth. Stent porosity is strongly correlated with hemodynamic changes, and an animal study confirmed that higher metal coverage rate was positively related to the angiographic and clinical results [13]. The overlapping stents may divert more blood flow from the affected segment than a single stent by decreasing the stent porosity, further straightening the parent vessel and increasing the stent thickness. The greater the strut density and thickness, the more easily neo-intima formation is promoted [8]. Therefore, multiple stents provide not
Table 1  Characteristics of the patients, aneurysms, and clinical and angiographic outcomes

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex/age</th>
<th>Clinical setting</th>
<th>Location/size (depth × neck, mm)</th>
<th>Used stents (no.)</th>
<th>Treatment course (f/u intervals, no. of used stents)</th>
<th>Initial Raymond grade</th>
<th>Last Raymond grade (months)</th>
<th>Comments</th>
<th>Last mRS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/53</td>
<td>Acute</td>
<td>3H 3H 3 F</td>
<td>1.3 × 3.3</td>
<td>SOT (2 stents) → regrowth (day 7), coiling → rebleeding (day 6), SAC (2 stents)</td>
<td>3</td>
<td>1 (7)</td>
<td>Rebleeding after second treatment</td>
<td>1 (10)</td>
</tr>
<tr>
<td>2</td>
<td>M/55</td>
<td>Acute</td>
<td>3H 3H 3 F</td>
<td>2.5 × 4.8</td>
<td>SAC (2 stents) → regrowth (day 14), delayed SAC (day 45, 1 stent) → regrowth (month 3), SAC (1 stent)</td>
<td>1</td>
<td>1 (10)</td>
<td>Diffuse in-stent thrombosis at second treatment</td>
<td>0 (10)</td>
</tr>
<tr>
<td>3</td>
<td>F/59</td>
<td>Subacute (2 weeks)</td>
<td>4H 5H 4 F</td>
<td>1.9 × 6.0</td>
<td>SAC (2 stents) → regrowth (day 34), coiling → regrowth (day 45), SAC (1 stent)</td>
<td>1</td>
<td>1 (6)</td>
<td>Diffuse in-stent thrombosis at second treatment</td>
<td>4 (44)</td>
</tr>
<tr>
<td>4</td>
<td>F/42</td>
<td>Acute</td>
<td>2H 2H 2 F</td>
<td>3.7 × 4.8</td>
<td>SAC (3 stents) → regrowth (day 7), coiling → regrowth, SAC (month 3, 2 stents)</td>
<td>2</td>
<td>1 (44)</td>
<td>Diffuse in-stent thrombosis at second treatment</td>
<td>0 (41)</td>
</tr>
<tr>
<td>5</td>
<td>F/59</td>
<td>Subacute (3 weeks)</td>
<td>2H 4H 3 F</td>
<td>1.9 × 6.0</td>
<td>SAC (3 stents), stable</td>
<td>1</td>
<td>1 (9)</td>
<td>Rebleeding due to delayed diagnosis, EVD, EVD tract hemorrhage, VPS Delayed diagnosis</td>
<td>1 (24)</td>
</tr>
<tr>
<td>6</td>
<td>F/70</td>
<td>Subacute (1 week)</td>
<td>4H 2H 3 F</td>
<td>1.7 × 2.7</td>
<td>SAC (3 stents), improved</td>
<td>2</td>
<td>1 (3)</td>
<td>Delayed diagnosis</td>
<td>0 (3)</td>
</tr>
<tr>
<td>7</td>
<td>M/78</td>
<td>Acute</td>
<td>4H 4H 3 F</td>
<td>1.7 × 2.4</td>
<td>SAC (3 stents), improved</td>
<td>2</td>
<td>1 (1)</td>
<td>Delayed diagnosis</td>
<td>5 (1)</td>
</tr>
<tr>
<td>8</td>
<td>F/50</td>
<td>Acute</td>
<td>2H 2H 3 F</td>
<td>2.3 × 2.5</td>
<td>SAC (3 stents), stable</td>
<td>1</td>
<td>1 (12)</td>
<td>Delayed diagnosis</td>
<td>2 (62)</td>
</tr>
<tr>
<td>9</td>
<td>M/39</td>
<td>Acute</td>
<td>2H 2H 3 F</td>
<td>2.1 × 2.8</td>
<td>SAC (3 stents), stable</td>
<td>1</td>
<td>1 (6)</td>
<td>Delayed diagnosis</td>
<td>0 (25)</td>
</tr>
<tr>
<td>10</td>
<td>F/54</td>
<td>Acute</td>
<td>2H 2H 3 F</td>
<td>2.1 × 3.3</td>
<td>SAC (3 stents), stable</td>
<td>1</td>
<td>1 (1)</td>
<td>Delayed diagnosis</td>
<td>0 (2)</td>
</tr>
</tbody>
</table>

only immediate protection from hemorrhage by flow redirection with the disruption of intra-aneurysmal flow and dispersion of the inflow jet, but also angiographic improvement and long-term durability of the coils by promoting further stent endothelialization by subsequent intravascular remodeling [3].

Table 2 summarizes the results of BBAs that were primarily treated with stent-assisted techniques described in the literature [2, 4, 6, 8, 11–13, 17]. Fang et al. [2] reported that the BBA recurrence rate was reduced to 20% (3/15), and no recurrence was detected in cases treated with triple stents. The present study showed similar results: seven patients who were initially treated with three overlapping stents showed only one recurrence (14.3%). From the previous reports (Table 2), we found nine cases treated with ≥3 stents, eight of which were initially treated with triple stents, and only one showed recurrence. Including our seven cases and one recurrence, the recurrence rate of those who were initially treated with triple stents was 13.3% (2/15).

Flow-diverting devices (FD), which have high metal coverage ratios and low porosity, seem to be more effective in assisting flow diversion to treat BBAs. Aydin K et al. reported successful application of FD in treating BBAs [15] with 9% mortality and 91% good clinical outcomes [1]. With the multiple overlapping stent technique, we could deploy coils with the jailing technique or through a strut stent within the shallow aneurysm wall. Therefore, we could expect to prevent immediate rupture. Also deployment of the Enterprise stent is technically easier than for FDs. Therefore, we could deploy stents more precisely when BBAs were close to the ICA bifurcation.

In South Korea, FD has recently been introduced and is currently allowed for limited indications. FD is not allowed for treating ruptured aneurysms. When ideally deployed without overlapping the stent struts, overlapping three stents seems to have similar effectiveness as a single FD [9]. Therefore, until the safety of FDs in ruptured BBAs has been proved, multiple overlapping stents could be a good option for these patients.

**Concerns about multiple overlapping stents in ruptured BBAs, antiplatelet medication and delayed complications**

For acute SAH, the use of antiplatelet medications inherent to stent use is a major concern. In a systematic review of the literature on stent use for SAH treatment, clinically significant intracranial hemorrhagic complications occurred in 27 of 339 patients (8%) [12]. Some authors proposed reduced perioperative antiplatelet protocols to prevent regrowth or rebleeding of the BBAs, which can cause fatal consequences [2, 12, 13]. They assumed that the risk of early fibrin formation or clotting was presumably not so important in the presence of a high-flow state within the stented lumen of large-sized basal arteries.

The other concern with this technique is the long-term patency of the stented parent artery as in the cases treated with flow diverters. Jeon et al. [9] reported cases of multiple overlapping stents; all ten patients showed complete occlusion of the aneurysm sac, which had been initially incompletely occluded, although one patient developed a severe degree of in-stent stenosis. The space between the parent artery and deployed stent may serve as thromboembolic source [7]. This

**Table 2 Summary of previous reports treating primarily with stent-assisted techniques in ruptured blood blister-like aneurysms**

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Case no.</th>
<th>No. of stents used at initial treatment</th>
<th>Stent type</th>
<th>Techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of retreated cases/no. of cases (Timing of recurrence or retreatment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Single</td>
<td>Double</td>
<td>≥Triple</td>
</tr>
<tr>
<td>Lim et al. 2013</td>
<td>29</td>
<td>4/6 (≤5 weeks)</td>
<td>4/23 (≤5 weeks)</td>
<td>0/2</td>
</tr>
<tr>
<td>Fang et al. 2014</td>
<td>15</td>
<td>0</td>
<td>3/9</td>
<td>0/6</td>
</tr>
<tr>
<td>Walsh et al. 2014</td>
<td>8</td>
<td>0</td>
<td>1/7 (2 weeks, 6 months, 6 months)</td>
<td>1/1 (1.5 months)</td>
</tr>
<tr>
<td>Lee et al. 2009</td>
<td>9</td>
<td>3/5 (1 week, 2 months, 2 months)</td>
<td>0/3</td>
<td>0</td>
</tr>
<tr>
<td>Meckel et al. 2011</td>
<td>12</td>
<td>2/11 (6 months, 24 months)</td>
<td>1/1 (4 months)</td>
<td>0</td>
</tr>
<tr>
<td>Ihn et al. 2014</td>
<td>7</td>
<td>0/2</td>
<td>2/5 (2 weeks, 2 weeks)</td>
<td>0</td>
</tr>
<tr>
<td>Gaughen et al. 2010</td>
<td>6</td>
<td>0</td>
<td>3/6 (1 week, 2 weeks, 1 month)</td>
<td>0</td>
</tr>
<tr>
<td>Gonzalez et al. 2014</td>
<td>6</td>
<td>3/4 (NA)</td>
<td>2/2 (NA)</td>
<td>0</td>
</tr>
</tbody>
</table>

Ent Enterprise stent, NF Neuroform stent, NA not available, SOT stent-only technique, SAC stent-assisted coil embolization, FD flow-diverting device
raises concern about the long-term patency of the stented parent artery and delayed ischemic events. The use of antiplatelet medication reduces the rate of symptomatic thromboembolic complications. However, there are no unifying guidelines about antiplatelet medication for intracranial stents. In this study, seven patients were available for more than 6 months of angiographic and clinical follow-up, and none of them showed delayed complications. Lack of follow-up data for the other three patients is a weakness of this study.

Conclusions

In this small series, multiple overlapping stents (≥3) with coiling were found to be a feasible alternative for treating ruptured BBAs, even in the era of FDs. Further experience and follow-up are needed in a larger series to determine the long-term efficacy of this treatment.

Compliance with ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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Conflict of interests All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers’ bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Informed consent Informed consent was obtained from all individual participants included in the study.

References
