Microsurgical versus endovascular interventions for blood-blister aneurysms of the internal carotid artery: systematic review of literature and meta-analysis on safety and efficacy

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OBJECTIVE Blood-blister aneurysms (BBAs) of the internal carotid artery (ICA) have a poor natural history associated with high morbidity and mortality. Currently, both surgical and endovascular techniques are employed to treat BBAs; thus, the authors sought to perform a meta-analysis to compare the efficacy and safety of these approaches.

METHODS A literature search of PubMed, MEDLINE, and Google Scholar online databases was performed to include pertinent English-language studies from 2005 to 2015 that discussed the efficacy and safety of either surgical or endovascular therapies to treat BBAs.

RESULTS Thirty-six papers describing 256 patients with BBAs treated endovascularly (122 procedures) or surgically (139 procedures) were examined for data related to therapeutic efficacy and safety. Pooled analysis of 9 papers demonstrated immediate and late (mean 20.9 months) aneurysm occlusion rates of 88.9% (95% CI 77.6%–94.8%) and 88.4% (95% CI 76.7%–94.6%), respectively, in surgically treated patients. Pooled analysis of 12 papers revealed immediate and late aneurysm obliteration rates of 63.9% (95% CI 52.3%–74.1%) and 75.9% (95% CI 65.9%–83.7%), respectively, in endovascularly treated aneurysms. Procedure-related complications and overall poor neurological outcomes were slightly greater in the surgically treated cases than in the endovascularly treated cases (27.8% [95% CI 19.6%–37.8%] vs 26.2% [95% CI 18.4%–35.8%]), indicating that endovascular therapy may provide better outcomes.

CONCLUSIONS Blood-blister aneurysms are rare, challenging lesions with a poor prognosis. Although surgical management potentially offers superior aneurysm obliteration rates immediately after treatment and at the long-term follow-up, endovascular therapy may have a better safety profile and provide better functional outcomes than surgery. A registry of patients treated for BBAs may be warranted to better document the natural course of the disease as well as treatment outcomes.

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KEY WORDS aneurysm; blood-blister aneurysm; endovascular; internal carotid artery; microsurgical technique; meta-analysis; vascular disorders
optimal therapeutic modality. While open surgical techniques offer excellent durability, BBAs often present with thin walls that are prone to intraoperative tearing. If direct clipping cannot be achieved, then Sundt encircling clips or parent artery sacrifice may be necessary. On the other hand, in the context of a wide aneurysm neck, many BBAs cannot be endovascularly coiled without stent assistance. But during stent placement, for either assisted coiling or flow diversion, dual antiplatelet therapies are necessary, which is not ideal in cases of ruptured aneurysms. The uncertainty regarding the optimal therapy for patients presenting with a ruptured BBA may open dialogue and contemplation at multidisciplinary institutions that offer both endovascular and surgical options. Both surgical and endovascular treatments come with a host of complications and concerns that must be considered before administering therapy.

Therefore, a study of the treatment options for BBA is warranted to determine the optimal course for patients requiring intervention. We sought to perform a systematic review of the literature and a meta-analysis to determine the efficacy and safety of microsurgical versus endovascular approaches to treat BBAs of the ICA.

**Methods**

**Study Selection and Inclusion Criteria**

Using the PubMed, MEDLINE, and Google Scholar systems, we performed a literature search for the years between 2005 and 2015 for all articles that included the terms “blood-blister aneurysm” and/or “blister aneurysm” located on the ICA (for example, “Blister Aneurysm”, “Blood blister aneurysm”, “Blood blister aneurysm”, “blood blister-like aneurysm”, “[“internal carotid artery” AND “blister aneurysm”], and so forth). Articles were limited to the English language with human subjects who had been diagnosed with an ICA BBA and who had undergone primary treatment via endovascular (coiling, stenting, flow-diversion) or microsurgical (clipping, wrapping, trapping with or without bypass) intervention. References in the obtained publications were also reviewed for additional studies. Papers with data regarding other types of aneurysms, aneurysms found at sites other than the ICA, or aneurysms whose primary treatment was neither endovascular nor surgical were excluded. Additionally, article types were limited to case reports, case series, retrospective studies, and clinical trials, whereas editorials, commentaries, and reviews were excluded. Duplicate pa-
pers were removed, and all studies meeting the aforementioned criteria underwent a full-text review.

Articles were included in this meta-analysis if we were able to extract pertinent data, such as study characteristics (first author, year study published, and design), patient demographics, patient clinical presentation, aneurysm data (size and location), treatment modalities used, preoperative hemorrhage grade, intra- and/or postoperative complications, follow-up time, and outcome scores. The selection process can be viewed in Fig. 1. Our inclusion criteria did not require a discussion of both treatment arms in studies of interest.

Outcomes

This systematic review and meta-analysis used 2 measurements of outcome: treatment efficacy and safety. Efficacy was determined by postoperative occlusion, confirmed by angiography, at 2 time points: immediately and at follow-up. Occlusion was either complete or partial, and for purposes of this analysis, complete occlusion was used.
as the marker of successful treatment. Safety outcomes were qualitatively studied using reported postoperative complications and were quantified using functional scores. The 2 most common scales used to assess functional outcome are the Glasgow Outcome Scale (GOS), described by Jennett and Bond in 1975, and the modified Rankin Scale (mRS), first reported by Dr. John Rankin in 1957 but remodeled to its current form by Farrell et al. in 1991. Good and favorable neurological outcomes were defined as an mRS score of 0–2, which corresponds to no symptoms, no significant disability despite symptoms, and slight disability but with the capability to look after one’s own affairs, respectively, or a GOS score of 4–5, which corresponds to moderate disability with no assistance in activities of daily living and good recovery, respectively.

We hypothesized that surgical intervention would yield higher complete occlusion rates immediately after treatment and at follow-up, whereas endovascular therapy would result in more favorable neurological outcomes.

Statistical Analysis

We performed a total of 6 overall statistical analyses: immediate endovascular occlusion, immediate surgical occlusion, endovascular occlusion at follow-up, surgical occlusion at follow-up, endovascular neurological outcomes, and surgical neurological outcomes. Meta-analysis was performed using the Comprehensive Meta-Analysis software (Biostat Inc.), and we elected to use the fixed-effects model summary effect measure as well as I² and/or Q values with the forest plots. The random-effects model was reported when appropriate. Given the constraints in analyzing studies with a sample size of 1 patient, we did not include case reports in the quantitative analysis. Publication bias was assessed using standard funnel plots as well as fixed-effects Duval and Tweedie trim and fill.

Results

Study Selection

The PubMed and MEDLINE search revealed 225 possible articles, while the other online database search led to an additional 130 studies. After duplicates were removed from each search and then across searches, we were left with 76 records to screen. The first selection process included a title and abstract review by 2 authors (S.S.S. and M.N.) with disagreements resolved through discussion. Thirty-seven articles were excluded given their inclusion of aneurysms other than BBAs and their analysis of BBAs located on non-ICA parent arteries, which left 39 studies for full text screening. The final phase of selection involved review by only 1 author (S.S.S.), yielding a total of 36 full-text articles to be included in this systematic review and meta-analysis (Table 1). Figure 1 displays the processes and phases of exclusion and inclusion for papers in this study.

Study Characteristics and Designs

A total of 36 papers with 256 patients undergoing 261 total treatments (either endovascular or surgical) for BBAs of the ICA were included in this review. There were 133 patients treated with stand-alone microsurgery, 119 patients treated primarily with endovascular approaches, and 4 patients who underwent combined therapy. All 36 studies were observational cohort studies evaluating endovascular or surgical intervention for ruptured BBAs. Twenty papers discussed retrospective studies. Eighteen studies evaluated endovascular therapy only, 14 evaluated surgery only, and 4 included both endovascular and surgical interventions. For our analysis, 22 and 18 papers were examined and analyzed for endovascular and surgical approaches, respectively.

Patient Demographics

A total of 256 patients were included in this meta-analysis. All papers included information regarding patient sex, and the ratio of male/female subjects was 1:3.33. Raw pooling of the extracted data revealed a mean age of 48.1 ± 11.1 years. The average aneurysm size was 3.2 ± 1.2 mm in diameter, and a majority of aneurysms were located on the supraclinoid (ophthalmic, C-6) segment of the ICA. Numerical data regarding treatments offered to the patients are included in Table 2. Of the 261 total treatments, 122 (46.7%) were endovascular and 139 (53.2%) were surgical. The most common endovascular procedure was coiling (71.3%), including stent-assisted coiling, and the most common surgical procedure was clipping (45.3%). Finally, the average time to the most recent follow-up for all patients regardless of treatment was 20.9 months. A summary of patient demographics per endovascular and surgical treatment arms can be found in Tables 3 and 4, respectively.

Outcomes

Among the 36 papers, 30 had data regarding total occlusion; however, 10 of them could not be statistically analyzed because of the small sample size. Among the remaining 20 papers, occlusion was assessed in 12 and 9 studies for the endovascular and surgical interventions, respectively. One study included data on both treatments and is thus included twice. Occlusion at follow-up was documented in 29 studies, but only 20 papers were statistically evaluated for the aforementioned reason. Twelve studies reported on endovascular therapy, and 8 reported
## TABLE 3. Summary of characteristics of patients who underwent endovascular treatment for BBA

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Age (yrs)</th>
<th>Location on ICA</th>
<th>Size (mm)</th>
<th>Clinical Presentation</th>
<th>PreOp Grade</th>
<th>FU Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahn et al., 2008</td>
<td>1</td>
<td>64</td>
<td>Supraclinoid (1)</td>
<td>NR</td>
<td>SAH (1)</td>
<td>NR</td>
<td>6 mos Angio NR</td>
</tr>
<tr>
<td>Başkaya et al., 2008*</td>
<td>4</td>
<td>40 ± 19</td>
<td>Supraclinoid (2), communicating (1), ophthalmic (1)</td>
<td>2.6 ± 0.8</td>
<td>SAH (4)</td>
<td>HH IV (4), F 3 (4)</td>
<td>1.75 ± 1.5 mos Angio mRS 1 (3), 6 (1)</td>
</tr>
<tr>
<td>Causin et al., 2011</td>
<td>3</td>
<td>49 ± 7</td>
<td>Supraclinoid (3)</td>
<td>2.6 ± 0.6</td>
<td>SAH (3)</td>
<td>F 3 (2), F 4 (1)</td>
<td>10.4 ± 4.6 mos Angio NR†</td>
</tr>
<tr>
<td>Chalouhi et al., 2014</td>
<td>7</td>
<td>51.4 ± 11.6</td>
<td>Ophthalmic (1), NR (6)</td>
<td>2.6 ± 0.5</td>
<td>SAH (4), IF (2), HA (1)</td>
<td>NR</td>
<td>4 ± 1.7 mos Angio mRS 0–2 (7)</td>
</tr>
<tr>
<td>Cho et al., 2012</td>
<td>1</td>
<td>57</td>
<td>Distal dorsal wall (1)</td>
<td>4.4</td>
<td>SAH (1)</td>
<td>HH III (1), F 4 (1)</td>
<td>6 mos Skull radio NR</td>
</tr>
<tr>
<td>Consoli et al., 2012</td>
<td>2</td>
<td>NR</td>
<td>Supraclinoid</td>
<td>5</td>
<td>SAH (2)</td>
<td>F 1</td>
<td>7 mos DSA NR†</td>
</tr>
<tr>
<td>Doorenbosch et al., 2008</td>
<td>1</td>
<td>44</td>
<td>Supraophthalmic (1)</td>
<td>3</td>
<td>SAH (1)</td>
<td>F 2 (1)</td>
<td>6 wks Angio NR</td>
</tr>
<tr>
<td>Ezaki et al., 2006</td>
<td>1</td>
<td>21</td>
<td>Superomedial (1)</td>
<td>NR</td>
<td>SAH (1)</td>
<td>HH IV (1), F 3 (1)</td>
<td>1 mo Angio NR</td>
</tr>
<tr>
<td>Fang et al., 2014</td>
<td>15</td>
<td>45.2 ± 10.1</td>
<td>Ophthalmic (8), communicating (5), C6–7 junction (3)</td>
<td>Max dia &lt;10</td>
<td>HA (15), vomiting (13), LOC (8)</td>
<td>HH I (2), II (5), III (6), IV (1), V (1)</td>
<td>5 days–6 mos Angio mRS 0–1 (14), 3 (1)</td>
</tr>
<tr>
<td>Fang et al., 2013</td>
<td>8</td>
<td>45.8 ± 11.5</td>
<td>Communicating (3), ophthalmic (3), C6–7 junction (3)</td>
<td>Max dia &lt;10</td>
<td>SAH (8)</td>
<td>HH I (1), II (5), III (1), IV (1)</td>
<td>9.2 mos Angio mRS 0–2 (6)</td>
</tr>
<tr>
<td>Gaughen et al., 2010</td>
<td>6</td>
<td>49.7 ± 12.4</td>
<td>Supraclinoid (6)</td>
<td>2.5 ± 0.5</td>
<td>SAH (6)</td>
<td>HH I (1), II (3), III (2)</td>
<td>6.2 ± 4.3 mos Angio mRS 1 (5), 3 (1)</td>
</tr>
<tr>
<td>Ihn et al., 2012</td>
<td>7</td>
<td>45.6 ± 7.2</td>
<td>Supraclinoid (7)</td>
<td>3.2 ± 1.6</td>
<td>SAH (7)</td>
<td>HH II (4), III (2), IV (1)</td>
<td>15.5 ± 5.0 mos Angio mRS 0–1 (5), 4 (1), 6 (1)</td>
</tr>
<tr>
<td>Kim et al., 2007</td>
<td>1</td>
<td>57</td>
<td>Supraclinoid (1)</td>
<td>NR</td>
<td>SAH (1)</td>
<td>NR</td>
<td>6 mos Angio GOS 5 (1)</td>
</tr>
<tr>
<td>Korja et al., 2008</td>
<td>2</td>
<td>51 ± 3</td>
<td>Supraclinoid (2)</td>
<td>2–3 (2)</td>
<td>SAH (2)</td>
<td>F 3 (2)</td>
<td>20 mos Angio NR†</td>
</tr>
<tr>
<td>Lee et al., 2009*</td>
<td>9</td>
<td>50.3 ± 4.0</td>
<td>Supraclinoid (9)</td>
<td>NR</td>
<td>SAH (9)</td>
<td>HH I (1), II (1), III (7)</td>
<td>11.1 ± 6.9 mos Angio GOS 1 (1), 5 (8)</td>
</tr>
<tr>
<td>Lim et al., 2013</td>
<td>34</td>
<td>47.6 ± 6.7</td>
<td>Ant wall (31), pst wall (3)</td>
<td>2.7 ± 1.0</td>
<td>SAH (34)</td>
<td>HH II (8), III (22), IV (5), V (1)</td>
<td>37 ± 18 mos Angio mRS 0–2 (25), 3 (3), 4 (2), 6 (4)</td>
</tr>
<tr>
<td>Meling et al., 2008*</td>
<td>14</td>
<td>48.3 ± 9.3</td>
<td>Medial (6), lat (2), ant (1), anteromedial (5)</td>
<td>3.9 ± 1.3</td>
<td>SAH (14)</td>
<td>F 2 (3), 3 (3), 4 (8)</td>
<td>NR NR GOS 1 (6), 2 (1), 3 (1), 5 (6)</td>
</tr>
<tr>
<td>Park et al., 2007*</td>
<td>7</td>
<td>35.4 ± 6.5</td>
<td>Dorsal surface (7)</td>
<td>NR</td>
<td>SAH (7)</td>
<td>HH II (6), IV (1)</td>
<td>10.8 ± 2.6 mos Angio VS (3), GR (4)</td>
</tr>
<tr>
<td>Princiotta et al., 2011</td>
<td>1</td>
<td>43</td>
<td>Supraclinoid (1)</td>
<td>NR</td>
<td>SAH (1)</td>
<td>HH I</td>
<td>6 mos Angio NR</td>
</tr>
<tr>
<td>Rasskazoff et al., 2010</td>
<td>1</td>
<td>38</td>
<td>Lat wall (1)</td>
<td>2</td>
<td>SAH (1)</td>
<td>F 3</td>
<td>6 mos Angio NR</td>
</tr>
<tr>
<td>Yu-Tse et al., 2012*</td>
<td>13</td>
<td>51.4 ± 10.7</td>
<td>Anteromedial wall (11), lat wall (2)</td>
<td>NR</td>
<td>SAH (13)</td>
<td>F 1 (1), 3 (8), 4 (4)</td>
<td>6 mos Angio mRS 0–1 (4), 3 (1), 4 (1), 5 (7)</td>
</tr>
<tr>
<td>Çinar et al., 2013</td>
<td>7</td>
<td>44.6 ± 5.9</td>
<td>Ant wall (4), pst wall (2), medial ICA (1)</td>
<td>3.86 ± 0.23</td>
<td>SAH (7)</td>
<td>HH I (3), II (3), III (1)</td>
<td>6.4 ± 2.7 mos Angio mRS 0–2 (5), 3 (1), 4 (1)</td>
</tr>
</tbody>
</table>

Angio = angiogram; ant = anterior; dia = diameter; DSA = digital subtraction angiogram; F = Fisher grade; GR = good recovery; HA = headache; HH = Hunt and Hess grade; IF = incidental finding; LOC = loss of consciousness; pst = posterior; radio = radiograph; SAH = subarachnoid hemorrhage; VS = vegetative state.

Values expressed as mean ± standard deviation, unless indicated otherwise.

* Studies with both endovascular and surgical data.

† Outcome scores could not be extracted, but the papers qualitatively confirmed good outcomes.
results from surgery. In all papers quantitatively examined, occlusion was determined using angiography. Cumulatively, we found 27 papers that discussed postoperative outcome, 25 from which we were able to extract the appropriate data. Fourteen papers discussed endovascular neurological outcomes (9 used mRS, 3 used GOS, and 2 used neither scale but provided sufficient detail to confirm favorable or unfavorable outcome). Thirteen papers discussed neurological outcome postsurgery (8 used mRS, 3 used GOS, and 2 specified qualitatively or through another metric, such as the Karnofsky Performance Scale).

Two papers discussed the 2 treatment arms together and were therefore included twice.5,32

Aneurysm Occlusion After Endovascular Treatment

Analysis of immediate aneurysm occlusion after endovascular intervention revealed a rate of 63.9% (95% CI 52.3–74.1%, p = 0.019) using the fixed-effects model and a rate of 65.6% (95% CI 47.9–79.9%, p = 0.083) with the random-effects model (104 endovascular procedures; Fig. 2A). A Q statistic of 21.83 and an I^2 value of 49.61 were

### TABLE 4. Summary of characteristics of patients who underwent surgical treatment for BBA

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Age (yrs)</th>
<th>Location on ICA (no.)</th>
<th>Preop Presentation (no.)</th>
<th>Clinical Presentation (no.)</th>
<th>FU Data</th>
<th>Imaging</th>
<th>Outcome Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Başkaya et al., 2008*</td>
<td>4</td>
<td>40 ± 19</td>
<td>Supraclinoid (2), communicating (1), ophthalmic (4)</td>
<td>SAH (4)</td>
<td>HH IV (4), F 3 (4)</td>
<td>1.75 ± 1.5</td>
<td>Angio</td>
<td>mRS 1 (3), 6 (1)</td>
</tr>
<tr>
<td>Ishikawa et al., 2009</td>
<td>4</td>
<td>53.3 ± 14.6</td>
<td>Dorsal (4)</td>
<td>SAH (4)</td>
<td>WFNS I (2), II (2)</td>
<td>3</td>
<td>Angio</td>
<td>mRS 0 (4)</td>
</tr>
<tr>
<td>Joo et al., 2006</td>
<td>2</td>
<td>31.5 ± 2.2</td>
<td>Cervical (1), petrous (1)</td>
<td>SAH (2)</td>
<td>F 3 (1), HH III (1)</td>
<td>5</td>
<td>Angio</td>
<td>NR</td>
</tr>
<tr>
<td>Kalani et al., 2013</td>
<td>17</td>
<td>45.2 ± 15.8</td>
<td>Nonbranching–unspecified (17)</td>
<td>SAH (12), IF (5)</td>
<td>HH I (1), II (1), III (5), IV (5)</td>
<td>74.5</td>
<td>Angio</td>
<td>GOS 2 (1), 3 (2), 5 (14)</td>
</tr>
<tr>
<td>Kamijo et al., 2010</td>
<td>7</td>
<td>61.0 ± 10.9</td>
<td>Supraclinoid (7)</td>
<td>SAH (7)</td>
<td>F 3 (7)</td>
<td>14.6</td>
<td>Angio</td>
<td>GOS 5 (5)</td>
</tr>
<tr>
<td>Kawashima et al., 2008</td>
<td>1</td>
<td>32</td>
<td>Cervical (1)</td>
<td>SAH (1)</td>
<td>HH II (1)</td>
<td>1</td>
<td>Angio</td>
<td>NR</td>
</tr>
<tr>
<td>Kazumata et al., 2014</td>
<td>20</td>
<td>51.2 ± 12.6</td>
<td>Anteromedial (15), other (5)</td>
<td>SAH (20)</td>
<td>WFNS I (6), II (10), III (1), IV (3)</td>
<td>3</td>
<td>Angio</td>
<td>mRS 0–2 (18), 4 (1), 5 (1), 6 (1)</td>
</tr>
<tr>
<td>Kim et al., 2014</td>
<td>11</td>
<td>43 ± 12</td>
<td>Supraclinoid ICA (11)</td>
<td>SAH (11)</td>
<td>HH II (6), III (4), IV (1)</td>
<td>40 ± 19</td>
<td>Angio</td>
<td>mRS 0–1 (8), 4 (1), 5 (1), 6 (1)</td>
</tr>
<tr>
<td>Kubo et al., 2006</td>
<td>6</td>
<td>48.8 ± 14.8</td>
<td>Anteromedial (4), ant (1), anterolat (1)</td>
<td>1–2</td>
<td>HK II (5), III (1)</td>
<td>41.8 ± 20</td>
<td>Angio</td>
<td>mRS 0 (6)</td>
</tr>
<tr>
<td>Lee et al., 2009/2011</td>
<td>18</td>
<td>50.4 ± 9.0</td>
<td>Dorsal (6), dorsolat (1), dorsomedial (7), medial (4)</td>
<td>SAH (18)</td>
<td>HH II (4), III (10), IV (4)</td>
<td>17 (6–50)</td>
<td>NR</td>
<td>mRS 1–2 (14), 3 (1), 4 (1)</td>
</tr>
<tr>
<td>McLaughlin et al., 2010</td>
<td>7</td>
<td>44.7 ± 9.9</td>
<td>Unspecified (7)</td>
<td>SAH (7)</td>
<td>HH I (2), II (4), III (1)</td>
<td>18.1 ± 18.7</td>
<td>Angio</td>
<td>mRS 0–1 (7)</td>
</tr>
<tr>
<td>Meling et al., 2008*</td>
<td>14</td>
<td>48.3 ± 9.3</td>
<td>Medial (6), lat (2), ant (1), anterolat (5)</td>
<td>SAH (14)</td>
<td>F 2 (3), 3 (3), 4 (8)</td>
<td>NR</td>
<td>NR</td>
<td>GOS 1 (6), 2 (1), 3 (1), 5 (6)</td>
</tr>
<tr>
<td>Otani et al., 2009</td>
<td>6</td>
<td>55.2 ± 8.9</td>
<td>Supraclinoid (6)</td>
<td>SAH (6)</td>
<td>HK II (2), III (1), IV (3)</td>
<td>NR</td>
<td>NR</td>
<td>NR†</td>
</tr>
<tr>
<td>Park et al., 2007*</td>
<td>7</td>
<td>35.4 ± 6.5</td>
<td>Dorsal surface (7)</td>
<td>SAH (7)</td>
<td>HH II (6), IV (1)</td>
<td>10.8 ± 2.6</td>
<td>Angio</td>
<td>VS (3), GR (4)</td>
</tr>
<tr>
<td>Sekula et al., 2006</td>
<td>1</td>
<td>41</td>
<td>Supraclinoid (1)</td>
<td>SAH (1)</td>
<td>HH 2</td>
<td>6</td>
<td>Angio</td>
<td>NR</td>
</tr>
<tr>
<td>Sim et al., 2006</td>
<td>10</td>
<td>49.3 ± 9.6</td>
<td>Supraclinoid (10), ant wall (7), anterolat (2), anteromedial (1)</td>
<td>2–8</td>
<td>SAH (10)</td>
<td>27.2</td>
<td>Angio</td>
<td>Excellent (8), fair (1), poor (1)</td>
</tr>
<tr>
<td>Tekkök &amp; Bakar, 2008</td>
<td>1</td>
<td>43</td>
<td>Supraclinoid (1)</td>
<td>SAH (1)</td>
<td>F 3</td>
<td>NR</td>
<td>NR</td>
<td>KPS 100/100</td>
</tr>
<tr>
<td>Yu-Tse et al., 2012*</td>
<td>13</td>
<td>51.4 ± 10.7</td>
<td>Anteromedial wall (11), lateral wall (2)</td>
<td>SAH (13)</td>
<td>F 1 (1), 3 (8), 4 (4)</td>
<td>6</td>
<td>Angio</td>
<td>mRS 0–1 (4), 3 (1), 4 (1), 5 (7)</td>
</tr>
</tbody>
</table>

HK = Hunt and Kosnik grade; KPS = Karnofsky Performance Scale; WFNS = World Federation of Neurological Societies grade.

Values expressed as mean ± standard deviation, unless indicated otherwise.

* Studies with both endovascular and surgical data.

† Outcome scores could not be extracted, but the papers qualitatively confirmed good outcomes.
calculated, indicating moderate study heterogeneity. Our computed tau (τ) value of 0.859 exposed variance within and between studies.

Aneurysm occlusion rates at the most recently reported follow-up (mean approximately 20.2 months) after endovascular treatment were 75.9% (95% CI 65.9%–83.7%, p < 0.0001) and 75.5% (95% CI 63.1%–84.8%, p < 0.001) using the fixed- and random-effects models, respectively (Fig. 2B). Assessed Q values (14.0) and I² statistics (21.3) showed low heterogeneity, while our τ-value of 0.469 indicated some variance between and within the studies.

The funnel plot looking at immediate endovascular occlusion was overall symmetric and showed no obvious signs of publication bias (Fig. 3A). Duval and Tweedie’s trim and fill revealed 1 point to the left of our calculated effect rate, and the adjusted estimate was 62.4% (95% CI 50.8%–72.7%, Q = 24.5). The funnel plot addressing publication bias in occlusion rates at follow-up was faintly asymmetrical toward the right (Fig. 3B), suggesting that studies with lower occlusion rates may be missing. Duval and Tweedie’s trim and fill also revealed 1 point to the left of the effect rate, and the adjusted rate was 75.0% (95% CI 65.0%–83.0%).

**Aneurysm Occlusion After Microsurgical Treatment**

Pooled analysis of 9 studies regarding immediate occlusion after microsurgical intervention revealed occlusion rates of 88.9% (95% CI 77.6%–94.8%, p < 0.0001) by the fixed-effects model (70 surgical treatments; Fig. 4A). Pooling was possible due to minimal heterogeneity, as our calculated Q was 4.24 and I² was 0. Low variance between studies and within studies was confirmed through the calculation of low tau values (τ = 0).

Total reported occlusion rate at the most recent follow-up (mean approximately 39.1 months, 8 studies) for patients in the surgical treatment arm was 88.4% (95% CI 76.7%–94.6%, p < 0.0001), which was calculated through the fixed-effects model (Fig. 4B). Tests for heterogeneity resulted in a Q of 3.87 and an I² value of 0, which shows low heterogeneity. Tau values were again 0, which indicates low study variance.

Funnel plots for immediate occlusion after surgery revealed asymmetry toward the lower right (Fig. 5A). This finding suggests there may be some smaller studies reporting lower total occlusion rates that are missing. Duval and Tweedie’s trim and fill exposed 4 points to the left of our effect rate, which adjusted the rate to 82.1% (95% CI 76.7%–94.6%, p < 0.0001), which was calculated through the fixed-effects model (Fig. 4B). Tests for heterogeneity resulted in a Q of 3.87 and an I² value of 0, which shows low heterogeneity. Tau values were again 0, which indicates low study variance.

Funnel plots for occlusion at follow-up revealed a similar asymmetrical trend toward the right (Fig. 5B). Duval and Tweedie’s trim and fill exposed 3 points to the left of our effect rate, which adjusted the rate to 83.1% (95% CI 70.4%–91.0%) with a Q of 7.97.
Neurological Outcomes

Thirteen studies reported outcome based on functional scores (that is, mRS, GOS, and so forth) that we pooled for endovascular intervention. A fixed-effects model revealed unfavorable outcomes in 26.2% (95% CI 18.4%–35.8%, p < 0.0001) of patients (Fig. 6A). A Q of 8.46 and an I² of 0 indicated low levels of study heterogeneity. The τ value was 0, which implies low variance in the studies.

Thirteen papers reported neurological outcomes in patients after surgical intervention. Tests of heterogeneity revealed that Q was 21.8 and I² was 54.1, indicating moderate heterogeneity. A fixed-effects model and random-effects model revealed unfavorable outcomes in 27.8% (95% CI 19.6%–37.8%) and 23.1% (95% CI 12.7%–38.2%) of patients, respectively (Fig. 6B).

Publication bias assessed by funnel plot in neurological outcomes of endovascular procedures showed no asymmetry (Fig. 7A). However, the funnel plot of the studies regarding neurological outcome of surgical procedures was markedly asymmetrical toward the lower left (Fig. 7B). This suggests a publication bias toward smaller studies reporting lower unfavorable neurological outcomes. Duval and Tweedie’s trim and fill included 4 points to the right of the observed effect rate. The adjusted estimate indicates unfavorable neurological outcomes in 34.5% of patients (95% CI 24.8%–45.7%).

Complications

Complications for each of the procedure arms were pooled together as raw data from each of the included studies. The most common intraoperative complication (Fig. 8A) associated with both endovascular and surgical procedures was aneurysm rupture; however, surgical approaches showed an increased incidence of rupture (28.8% vs 3.2%). The postoperative period was associated with...
the most complications for either endovascular or surgical aneurysm management (Fig. 8B). While vasospasm, hydrocephalus, and infarction predominated as the leading observed comorbidities associated with surgical treatment (21.6%, 9.9%, and 6.3% respectively), endovascular management was associated with the highest reported incidence of aneurysm regrowth (8.5%), patient mortality (6.6%), and rebleeding (5.6%).

Discussion

The incidence of BBAs represents a minute portion of all intracranial aneurysms, yet the diagnosis and treatment of these lesions are reported to be difficult because of the peculiar zones in which they arise and their thin walls and obscure base. While advances in both endovascular and surgical approaches have led to increased procedural success and overall safety for the patient, BBAs are still unfortunately characterized by their malignant features. The propensity for these aneurysms to rapidly expand and/or rupture makes treatment difficult, and there is controversy surrounding the optimal plan of action. The complexity and delicacy of BBAs, especially those on the ICA, present therapeutic challenges for patients. No randomized-controlled trial has been performed regarding endovascular versus surgical treatment of BBAs. Here, we present the most recent statistical meta-analysis on the efficacy and safety of endovascular versus surgical treatment arms to manage BBAs.

Surgery for BBAs provides higher total aneurysm occlusion immediately (mean 88.9%, 95% CI 77.6%–94.8%, p < 0.0001) than endovascular treatment (mean 63.9%, 95% CI 52.3%–74.1%, p = 0.019). Surgery also provides better total occlusion at the most recent patient follow-up (88.4%, 95% CI 76.7%–94.6%, p < 0.0001) than endovascular treatment (75.9%, 95% CI 65.9%–83.7%, p < 0.0001). While more efficacious in occlusion rates at both time points analyzed, surgery did not seem as safe as endovascular approaches when neurological outcome scores were compared. Negative outcomes in 26.2% of patients (95% CI 18.4%–35.8%) were reported with endovascular procedures, while negative outcomes in 27.8% of patients (95% CI 19.6%–37.8%) were reported with surgery. More importantly, the adjusted safety rates on negative surgical outcomes indicated that the true negative outcome rate might be closer to 35%, implying some inherent reporting bias and further supporting the findings that endovascular therapy may lead to better neurological outcomes than surgical intervention. Raw pooled data analysis from our paper further suggests that endovascular approaches are safer based on complications. Overall, calculated intraoperative complications for endovascular versus surgical approaches were 2.1% versus 14%. Postoperative complications were similar in that endovascular procedures resulted in some complication 29% of the time, while surgery resulted in morbidity 45% of the time.

Two recent systematic reviews published in 2014 and 2015, respectively, also assessed optimal treatment modalities for BBAs of nonbranching segments of the ICA. Despite some similarities between these 2 reviews and the current study, our study is distinct and maintains novelty from the others for several reasons. Gonzales et al. found that endovascular approaches resulted in less morbidity than surgical intervention, mainly clipping (3.4% vs 18%), and this claim supports our findings regarding the safety profile of endovascular therapy. Within their methodology, Gonzalez et al. specified a search criteria cutoff of only July 1, 2013, while our search ended December 31, 2015. Our more recent cutoff revealed 5 additional papers (Chalouhi et al., 2014; Fang et al., 2014; Kalani et al., 2013; Kazumata et al., 2014; and Kim et al., 2014; 70 patients) that had not been previously analyzed. Furthermore, since the course of BBA management has evolved rapidly within the last decade, our search timeline (2005–2015) reflects what we believe to be an accurate representation of the current treatment paradigm. Additionally, Gonzalez et al. solely focused on safety in terms of perioperative complication, mortality and/or morbidity, and regrowth and/or rebleeding of BBAs posttreatment without venturing to investigate which therapy (surgery vs endovascular treatment) was more efficacious. The analysis presented here, however, was expanded to include efficacy in terms of aneurysm obliteration.

Szmuda et al. came to the ultimate conclusion that neither surgical nor endovascular therapy had an impact on clinical outcome, and the primary end point in their study was...
death. Their search timeframe was also shorter than the one used in our current study (2005–2015 vs 2013–2014). In addition, their paper offers no risk assessment or publication bias assessment such as we have highlighted in our study. Most importantly though, our results contrast with those published by Szmuda et al. in that we suggest surgical management may have better aneurysm occlusion than endovascular therapy, especially immediately postprocedurally.

The strength of the evidence in our review seems to be robust. Through our assessment of publication bias by funnel plotting, there is some noted bias with regard to smaller articles that reported higher occlusion rates and better outcomes. However, that was to be expected, which is why we employed the Duval and Tweedie trim and fill technique to estimate the number of missing studies that might exist in our meta-analysis and the effect that these studies might have had on its results. After correcting for these missing studies, the point estimate of the overall effect size has been shown to be approximately correct, and coverage of the effect size confidence intervals is substantially improved. With this extra technique to assess publication bias and adjust our calculated effect rates, the observed mean and the Duval and Tweedie’s adjusted mean were within only roughly 0.3%–6.8% points of each other (mean 3.5%).

The generalizability of this study is also robust. All patients included in our meta-analysis had BBAs of the ICA that were treated with commonly applied endovascular or surgical approaches. Furthermore, tests of heterogeneity revealed rather low Q and I^2 values in most of the statistical analyses we ran. And even in analyzing study cohorts with higher I^2 values, the studies were only somewhat heterogeneous, like with immediate aneurysm occlusion after endovascular procedures and neurological outcomes after surgery. We believe that these results can also be extrapolated to patients with similar thin-walled, delicate aneurysms. Supplementary study through clinical trial of the efficacy and safety of endovascular versus surgical treatment for BBAs is definitely possible. In fact, a randomized trial in Europe, referred to as the Diversion of Flow in Intracranial Vertebral and Blood Blister-like Ruptured Aneurysms Trial (DIVERT), is ongoing but not recruiting patients. This trial looks to compare flow diversion to other commonly used therapies, such as clipping, coiling, stenting, and parent artery occlusion, in patients with acute BBAs and dissecting intradural aneurysms. While the trial does not directly compare endovascular to surgical treatment, it is hoped that its results can be used to determine overall treatment efficacy and safety for patients with BBAs.

Study Limitations

This systematic review and meta-analysis has a few
limitations. First, none of the studies included in our analysis is a randomized controlled trial. Without the benefit of randomization, there is always a possibility of selection bias based on treatment. However, it is possible that some of this selection bias could have been controlled for at the treatment centers based on hypothesized clinical equipoise surrounding the treatment of BBAs. None of the studies in our analysis directly compared endovascular to surgical procedures in a case-control design either, which means that the comparison between the 2 treatment arms was based on pooled data from different studies. Second, there was marked variability in the ways that the included studies reported data, such as neurological outcome and occlusion. Some papers used the mRS to report neurological outcome while others used the GOS. Some studies did not include any information other than qualitative confirmation of a good recovery. Even though there is some crossover between the different scales used (mRS Score 3 is approximately equal to GOS Score 4, moderate disability) and even though we believe that our proposed cutoff (mRS Score 0–2 or GOS Score 5 or qualitative equivalent) was appropriate, breaking our functional outcome scores into either a positive or a negative outcome may have led to an incredibly generalized data point, which may not have been sensitive enough to emphasize discreet discrepancies between treatment arms. Additionally, it was difficult to discern data regarding unruptured versus ruptured BBAs in the included studies. While the natural history of ruptured BBA is rather well documented, the natural course of unruptured BBA is still unclear. Nonetheless, we included both in our analysis and so this may represent a study limitation.

Third, some centers have different treatment inclinations than others. For example, some treatment centers prefer endovascular approaches to surgical approaches and save the latter as backup in case of endovascular failure. Other institutions prefer a more multidisciplinary approach. These predispositions can lead to selective bias toward or away from specific treatments. Furthermore, the long study period has seen a dramatic evolution in endovascular treatment strategies. There is a current trend toward flow diversion as the mainstay of endovascular therapy; however, the most recent literature suggests that stent-assisted coiling is the most common endovascular therapy offered to patients with BBAs, an observation...
may be warranted to better document the natural course of the patient, the aneurysm, and the likelihood of a poor outcome than surgery but only by a moderate margin. Treatment of ruptured blister-like aneurysms with flow diverter stenting.

There were also limitations at the study level. Only 4 papers included information about both endovascular and surgical management. Ideally, all of the included papers would have contained data about both therapies. Additionally, many papers simply could not be statistically analyzed because of their small sample size (n = 1). Nonetheless, the plethora of case reports shows that BBAs are difficult to treat and that there is still a tremendous lack of information regarding their proper management. There may be a need to create a registry for patients treated for BBAs to further understand the differences in the natural history of ruptured versus unruptured lesions, as documentation of surgical and endovascular treatment effects.

Conclusions

Blood-blister aneurysms are a therapeutic challenge with possibly disastrous outcomes even with state-of-the-art care. According to this systematic review and meta-analysis of BBAs of the ICA, surgical management offers superior aneurysm occlusion immediately after the procedure and sustained occlusion at the follow-up. Endovascular procedures provide better functional outcomes than surgery but only by a moderate margin. Treatment decisions should be made only after careful consideration of the patient, the aneurysm, and the likelihood of a poor clinical outcome. A registry of patients treated for BBAs may be warranted to better document the natural course of the disease as well as treatment outcomes.

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