Treatment of Middle Cerebral Artery Aneurysms with Flow-Diverter Stents: A Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND: The safety and efficacy of flow-diversion treatment of MCA aneurysms have not been well-established.

PURPOSE: Our aim was to evaluate angiographic and clinical outcomes after flow diversions for MCA aneurysms.

DATA SOURCES: A systematic search of PubMed, MEDLINE, and Embase was performed for studies published from 2008 to May 2017.

STUDY SELECTION: According to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, we selected studies with >5 patients describing angiographic and clinical outcomes after flow-diversion treatment of MCA aneurysms.

DATA ANALYSIS: Random-effects meta-analysis was used to pool the following outcomes: aneurysm occlusion rate, procedure-related complications, rupture rate of treated aneurysms, and occlusion of the jailed branches.

DATA SYNTHESIS: Twelve studies evaluating 244 MCA aneurysms were included in this meta-analysis. Complete/near-complete occlusion was obtained in 78.7% (95% CI, 67.8%–89.7%) of aneurysms. The rupture rate of treated aneurysms during follow-up was 0.4% per aneurysm-year. The rate of treatment-related complications was 20.7% (95% CI, 14%–27.5%), and approximately 10% of complications were permanent. The mortality rate was close to 2%. Nearly 10% (95% CI, 4.7%–15.5%) of jailed arteries were occluded during follow-up, whereas 26% (95% CI, 14.4%–37.6%) had slow flow. Rates of symptoms related to occlusion and slow flow were close to 5%.

LIMITATIONS: Small and retrospective series could affect the strength of the reported results.

CONCLUSIONS: Given the not negligible rate of treatment-related complications, flow diversion for MCA aneurysms should be considered an alternative treatment when traditional treatment methods are not feasible. However, when performed in this select treatment group, high rates of aneurysm occlusion and protection against re-rupture can be achieved.

ABBREVIATION: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Flow-diverter stents have become a feasible and effective treatment for most intracranial aneurysms, and their indications are constantly extended, including distal aneurysm locations.[1-3] Commonly, middle cerebral artery aneurysms present with a particularly complex anatomy because of the frequency of wide-neck configurations with incorporating MCA branches. Endovascular treatment of MCA aneurysms can be technically more challenging, and in many institutions, surgical treatment is considered the first option because of the high rate of long-term occlusion with low surgical morbidity.[4] However, with the improvement of angiographic images, increased operator experience, and the use of more complex techniques, an increasing number of MCA aneurysms are treated with endovascular techniques.[1] Recently, flow diversion has been used as an alternative technique for complex wide-neck MCA aneurysms, incorporating ≥1 side branch or in cases of previous endovascular or surgical failure.[5-14] However, the role of flow diversion in this location is controversial, and the efficacy and safety of this technique remain unclear. We performed a systematic review and meta-analysis of all published series examining flow diversions for the treatment of MCA aneurysms with the aim of clarifying the following: 1) aneurysm occlusion rate, 2) treatment-related complications and clinical outcome, and 3) the fate of the MCA side branch covered with the device.

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MATERIALS AND METHODS

Literature Search

A comprehensive literature search of PubMed, Ovid MEDLINE, and Ovid Embase was conducted for studies published from 2008 to May 2017. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed.[15] The key words "middle cerebral artery," "flow-diverter," "flow diversion," "anterior circulation," "aneurysms," "pipeline," and "endovascular" were used in both "AND" and "OR" combinations. The detailed search strategy is reported in On-line Table 1. The inclusion criteria were the following: 1) studies reporting series of patients with MCA aneurysms treated with flow diverters. Exclusion criteria were the following: 1) studies with <5 patients, 2) review articles, 3) studies published in languages other than English, 4) in vitro studies, and 5) animal studies. In cases of overlapping patient populations, only the series with the largest number of patients or the most detailed data were included. Two reviewers independently selected the included studies, and a third author solved discrepancies.

Data Collection

From each study, we extracted the following information: 1) characteristics and number of MCA aneurysms, 2) aneurysm occlusion rate and related factors, 3) incidence of aneurysm rupture after treatment, 4) treatment-related complications, and 5) angiographic outcome of covered arteries. The rate of aneurysm occlusion was dichotomized into 2 groups: complete/near-complete occlusion and incomplete occlusion. Accordingly, the influence of 6 parameters (age, mean aneurysm size, type of stent used, first treatment versus retreatment, type of first treatment, and anatomic location of MCA aneurysms) on the occlusion rates was analyzed. MCA aneurysms were divided into 3 categories: saccular, fusiform, and blister. Patients with blister aneurysms ($n = 3$) were considered for only the incidence of arterial occlusion after flow-diverter deployment. On the basis of the location, MCA aneurysms were dichotomized into "prebifurcation" (M1 and early cortical branches) and bifurcation aneurysms (M1–M2 bifurcation and M2 bifurcation branches).[16] Complications related to the treatment were summarized in 4 categories: ischemic/thromboembolic, hemorrhagic, iatrogenic (dissection or perforation), and perianeurysmal inflammation. The rate of occlusion and diminished flow of covered branches was analyzed from only studies that specifically reported the angiographic outcome of covered arteries. Finally, good outcome was defined as a modified Rankin Scale score of 0–2 or a Glasgow Outcome Score of 4–5. In cases in which the mRS and Glasgow Outcome Score were not reported, good neurologic outcome was determined if the study used terms such as "no morbidity," "good recovery," or "no symptoms."

Outcomes

The primary objectives were to define the following: 1) the rate of MCA aneurysm occlusion, 2) the incidence of treatment-related complications, and 3) the rate of MCA branch occlusion covered with flow diverters and the incidence of related symptoms.

Quality Scoring

The Newcastle-Ottawa Scale[17] was used to assess the quality of the included studies (On-line Table 2) evaluating the following: patient selection criteria, comparability of the study groups, and exposure assessment. "High-quality" studies were defined on the basis of the following: 1) the presence of a predefined study protocol, 2) defined inclusion and exclusion criteria, 3) adequate clinical and radiologic follow-up, and 4) detailed information about treatment-related outcomes. Accordingly, a star rating of 0–9 was allocated to each study. The quality assessment was performed by 2 authors independently, and a third author solved discrepancies. Studies receiving ≥6 stars were considered high-quality.

Statistical Analysis

We estimated, from each cohort, the cumulative prevalence and 95% confidence interval for each outcome. Rates of each outcome were pooled in meta-analyses across studies by using the random-effects model.[18] We chose this model a priori because it incorporates both within-study and between-studies variances. This is recommended when data are heterogeneous. Heterogeneity of the treatment effect across studies was evaluated with the I^2 statistic, in which an I^2 value of >50% suggests substantial heterogeneity.[19] We also extracted a 2 × 2 table for each studied outcome for interaction testing and calculated P values for the comparisons between the previously mentioned clinical and anatomic characteristics. Meta-regression was not used in this study. Statistical analysis was performed by using the software program OpenMeta[Analyst] (http://www.cebm.brown.edu/openmeta/).

RESULTS

Literature Review

The search strategy is summarized in On-line Table 1, and studies included in our meta-analysis are summarized in Table. The search flow diagram is shown in On-line Fig 1.

Twelve studies and 244 MCA aneurysms treated with flow-diverter stents were included in our review.

Quality of Studies

Overall, 8 studies were rated high quality. Seven of the high-quality studies specifically analyzed flow-diversion treatment of MCA aneurysms (On-line Table 2). All the high-quality articles reported detailed information about aneurysm occlusion rates, treatment-related complications, flow modifications of covered arteries, and adequate length of follow-up.

Patient Population and Aneurysm Characteristics

The mean age of patients was 54.5 years (range, 3–76 years), and the male/female ratio was 0.6 (On-line Table 3). Overall, 88.1% (95% CI, 83.4%–91.6%) of treated MCA aneurysms were unruptured, whereas 11.9% (95% CI, 8.3%–16.5%) (median, 1%; IQR, 0.4%–2.5%) were previously ruptured and were treated with coils or clipping in the acute phase. The median time of flow-diversion treatment after rupture was 8.5 months (IQR, 3.2–36 months). Saccular and fusiform aneurysms were 81.1% (95% CI, 75.7%–85.5%) and 17.6% (95% CI, 13.3%–22.9%), respectively. Blister aneurysms represented 1.3% (95% CI, 0.2%–3.7%) of the lesions.

Angiographic outcomes and treatment-related complications

Variables	Raw Numbers[a]	No. of Articles	95% CI	I^2	*P* Value
MCA aneurysm occlusion after flow diversion					
Overall rate of complete/near-complete occlusion	137/171 = 78.7%	10	67.8–89.7	76.24	<.001
Factors related to aneurysm occlusion					
Mean age (yr)					.262
Complete/near-complete occlusion	53.6 yr	4	47.3–59.8	75%	
Incomplete occlusion	61.3 yr		48.9–73.5	95%	
Mean size					.614
Complete/near-complete occlusion	7 mm	6	3.6–10.3	83.6%	
Incomplete occlusion	5.5 mm		0.8–10.1	99%	
Complete/near-complete occlusion					.38
Retreatment	64%	5	33.9–93.4	75.2%	
vs	vs				
First treatment	73%		63–83.5	0%	
Complete/near-complete occlusion					.307
Prebifurcation (M1–early cortical branches)	88.1%	11	79.6–96.7	0%	
vs	vs				
Bifurcation aneurysms	77.7%		64.5–89.5	74.92%	
Complications related to treatment and outcome					
Overall rate of treatment-related complications	46/213 = 20.7%	11	14–27.5	34.03%	.126
Transient or asymptomatic	11.3%		7.6–16.2		
vs	vs	11	6.8–15.2		
Permanent	10.3%				
Type of complications					
Ischemic/thromboembolic	16.3%	11	10.1–22.6	36.65%	.106
Hemorrhagic	2%		0.2–3.9	0%	.958
Iatrogenic (dissection/perforation)	1.8%		0%–1.3.5%	0%	.973
Perianeurysmal inflammation	2.6%		0.5–4.7	0%	.997
Complications related to discontinuation of antiplatelet therapy	4/46 = 8.7%	11	2.9–20.8		
Aneurysm rupture after treatment	1/214 = 0.47%	12	0.1–2.8		
Overall rate of good outcome	125/135 = 92.7%	7	86.4–99.1	42.08%	.11
Mortality rate	4/213 = 2%	11	0.2–3.9%	0%	.929

Note:— vs indicates versus.
[a] Results of meta-analysis.

Overall, 76.3% (95% CI, 70.5%–81.1%) of aneurysms were located at the main bifurcation point (M1–M2) or distally (M2), whereas prebifurcation aneurysms (M1–early cortical branches) were 23.7% (95% CI, 18.8%–29.5%). Mean aneurysm size was 8.2 mm (range, 2–20 mm).

Treatment Characteristics

The most common device used was the Pipeline Embolization Device (PED; Covidien, Irvine, California) (71%; 95% CI, 64.1%–75.3%), followed by the Silk flow diverter (Balt Extrusion, Montmorency, France) device (11.4%; 95% CI, 80.3%–15.9%) (On-line Table 3). Most of the aneurysms were treated with 1 device (number of stents/aneurysm = 1.14). The flow-diversion technique was used as a first treatment technique in 75.5% of patients (95% CI, 69.4%–80.6%).

Digital subtraction angiography was the principal diagnostic technique. In about 90% of the reported patients, DSA was performed during the early and long-term radiologic follow-up. In approximately 10% of patients, MRA or CTA was performed during the long-term radiologic follow-up.

Angiographic Outcomes and Treatment-Related Complications

The overall rate of complete/near-complete occlusion during follow-up was 78.7% (95% CI, 67.8%–89.7%) with a 12-month median duration (IQR, 8.1–16 months) of angiographic follow-up (Table and On-line Fig 2*A*). Differences in occlusion rates were not statistically significant among groups of age, mean aneurysm size, first treatment versus retreatment, type of first treatment (endovascular versus surgical), type of device used (PED versus other stents), and MCA aneurysm location ("prebifurcation" versus bifurcation aneurysms) ($P > .05$).

The rate of treatment-related complications was 20.7% (95% CI, 14%–27.5%) (On-line Fig 2*B*), and approximately 10% of complications were permanent. Ischemic/thromboembolic events were the most common type of complications (16.3%), followed by perianeurysmal inflammation (2.6%), hemorrhage (2%), and dissection/perforation (1.8%). The mortality rate after treatment was 2% (95% CI, 0.2%–3.9%). The rate of complications related to premature discontinuation of the antiplatelet therapy was 8.7% (95% CI, 2.9%–20.8%). During follow-up, the incidence of aneurysm rupture after treatment was 0.47% (95% CI, 0.1%–2.8%), with a rupture rate of 0.4% per aneurysm-year. The overall rate of good neurologic outcome after treatment was 92.7% (95% CI, 86.4%–99.1%) with a 12-month median duration (IQR, 7.5–10.5 months) of clinical follow-up. Considering the group of patients with a history of aneurysm rupture, the rate of good neurologic outcome was close to 87% (95% CI, 60.7%–98%).

Outcome of Covered MCA Side Branches

Overall, 174 MCA side branches jailed with flow diverters were available for the analysis (On-line Table 4). The global rate of occlusion of covered arteries was 10.1% (95% CI, 4.7%–15.5%), whereas 26% (95% CI, 14.4%–37.6%) of cases showed diminished flow (On-line Fig 3). The mean number of devices across the ostium of the arteries was similar between arteries with occlusion and those with normal flow (1.07 versus 1). The incidence of symptoms (ischemic stroke in the MCA territory) related to MCA branch occlusion and diminished flow was 2.7% (95% CI, 0.4%–5%) and 2.6% (95% CI, 0.1%–5.1%), respectively (On-line Fig 4).

Study Heterogeneity

Significant heterogeneity was noted in the analysis of aneurysm occlusion rates after treatment. In addition, significant heterogeneity was reported in the analysis of diminished flow of covered branches.

DISCUSSION

Our meta-analysis stressed several important findings related to the flow-diversion treatment of MCA aneurysms. The overall rate of complete/near-complete occlusion was approximately 80%. The rupture rate after treatment was low (0.4% per aneurysm-year), demonstrating that the aneurysms were successfully secured after flow diversion. Most of the lesions were small and located at the main bifurcation point (M1–M2). The overall complication rate of 20% is not negligible, resulting in permanent neurologic deficits in approximately 10% of patients and treatment-related mortality in about 2%. Most interesting, most of the unfavorable outcomes were related to ischemic or thromboembolic complications. Our study also found a remarkable incidence of occlusion (10%) and diminished flow (25%) of covered MCA branches, resulting in neurologic symptoms in about 5% of patients. These findings are important and showed that though flow diversion is an effective treatment, MCA aneurysms amenable to flow diversion should be carefully selected, due to the not negligible rates of treatment-related morbidity.

Angiographic Outcomes of MCA Aneurysms after Flow Diversion

Flow-diverter stents have become a suitable tool for complex, wide-neck, and anatomically challenging intracranial aneurysms. However, while large and prospective studies demonstrated the safety and effectiveness of flow diversion for ICA aneurysms, the literature is contradictory about the treatment of distal locations, such as MCA aneurysms. Although surgery still represents an effective treatment for MCA aneurysms, difficult-to-treat lesions with conventional endovascular or surgical approaches have increased the use of flow diversion in this location. Overall, previous series have reported a rate of complete/near-complete occlusion between 60% and 90% after flow-diversion treatment of MCA aneurysms.[5-9,12-14,20] The paucity of large and prospective studies, the heterogeneity of the reported populations, and the relatively short follow-up periods can explain this variation. Our study, the largest to date, demonstrated that the overall rate of complete/near-complete occlusion is roughly 80% during a mean follow-up of 14 months. This result is comparable with the angiographic occlusion rates of ICA aneurysms after flow diversion. In a recent prospective study of nearly 200 aneurysms, Kallmes et al[3] reported 75% complete occlusion after Pipeline treatment. Similarly, in a large meta-analysis of nearly 1700 aneurysms, the complete occlusion rate was close to 76%.[21]

Aneurysms of the MCA often arose from the main division point (bifurcation aneurysms), whereas in nearly 20% of cases, they originated from an early cortical branch (temporal or frontal).[16] Early cortical branch aneurysms have a close relation with perforators, whereas bifurcation aneurysms are close to or incorporate M2 branches, influencing the outcomes after surgical or endovascular treatment.[12] Very few articles analyzed differences in endovascular treatments for different MCA aneurysm locations, and it is possible that in the literature, most of the early cortical branch aneurysms are referred to as bifurcation aneurysms. Topcuoglu et al,[12] in a series of 29 MCA aneurysms treated with flow diversion, reported better angiographic results among lesions located at the prebifurcation point (M1 or early bifurcations), compared with MCA bifurcation aneurysms (85% versus 60% of complete/near-complete occlusion). In addition, unsatisfactory aneurysm occlusion was significantly related to the patency of the arterial branches originating from it. Our study demonstrated that the prevalence of complete/near-complete occlusion was slightly higher for aneurysms located at the prebifurcation point, compared with bifurcation (M1–M2) or more distal aneurysms (M2), though the result did not reach statistical significance (88% versus 77%, $P = .3$). In addition, there were no differences in occlusion rates between aneurysms treated with the PED and other types of stents. Similarly, we found that occlusion rates among younger patients and the first-treatment group versus the retreatment group appeared slightly higher, but without statistical relevance. However, among retreatment groups, complete/near-complete occlusion after flow diversion was slightly higher for aneurysms previously treated with coiling or stent-assisted coiling (89%), compared with aneurysms previously treated with clipping (63%), though the results were not statistically significant. Finally, the rupture rate after treatment of 0.4% per aneurysm-year showed that flow diversion gives an effective protection against aneurysm rupture.[22]

Treatment-Related Complications

In general, treatment-related morbidity after flow diversion is reported to be between 4% and 10%.[3,23-25] Our meta-analysis provides more representative data on complication rates after flow-diverter treatment of MCA aneurysms. This location should be considered separately in terms of technical complexity and treatment-related outcomes. The overall incidence of complications close to 20% is not negligible. Most important, permanent complications were approximately 10%, whereas the mortality rate after treatment was 2%. However, the literature is still contradictory about flow diversion among MCA aneurysms, and despite some authors concluding that it seems a reasonable treatment,[9,13] others reported that it is not a suitable solution for aneurysms in this location.[8] Our study showed that most of the reported complications were related to ischemic or thromboembolic events (16%). Compared with the general rate of ischemic complications related to flow diversion, MCA location appears associated with a higher risk of ischemic injury. In the IntrePED[24] study, as well as in other large studies,[21,26] the rate of acute ischemic stroke was close to 5%, with most of the reported events occurring in the early postoperative period.

A number of important mechanisms can explain the incidence of postoperative infarction after flow-diversion treatment of MCA aneurysms, such as perioperative catheter-related thromboemboli, acute/subacute in-stent thrombosis, or particle emboli from the devices.[27-29] In our study, nearly 9% of ischemic complications were associated with discontinuation of the antiplatelet therapy, which showed the close relationship between ischemic injury and antiplatelet function.[30] Another important factor is the risk of perforating injury due to coverage of lenticulostriate arteries. Multiple overlapping devices[29] or undersized stents with more condensed pores and higher mesh density[31] can increase the risk of perforator occlusion. In a series of 17 anterior circulation aneurysms, 12 of them arising from the MCA, Gawlitza et al[20] reported 40% ischemic events after coverage of perforator arteries with flow-diverter stents, though most were asymptomatic. Despite the high rate of complications, most of the MCA aneurysms treated with flow diverters were anatomically complex, increasing the risk of procedure-related complications. Accordingly, when more complex endovascular techniques are required, such as X- and Y-stent placement or stent-assisted coiling, a large series and meta-analysis reported permanent complications between 4% and 10%.[32,33]

Angiographic Outcome of Covered Side Branches

Placement of flow-diverter stents at the bifurcation points behind the circle of Willis has a potential risk of arterial occlusion. Due to the mechanical properties of the stent, the pressure gradient across the jailed branch is reduced, and if the "flow competition" from the collateral supply is well-represented, the artery can be occluded.[34] MCA bifurcation presents an anatomic configuration without direct collateral arterial connection, and the anastomotic circulation is only with corticopial branches. Our study found 10% occlusion of covered MCA branches. In addition, remodelling of jailed arteries, such as slow flow or arterial narrowing, was present in about 25% of cases. Among large series of flow diverters covering ICA branches, the rates of side branch occlusion are close to 18% for the posterior communicating artery[35-37] and 5% for the ophthalmic and anterior choroidal arteries, with rates of related symptoms close to 1%.[35,38-42] In our study, approximately 5% of patients with occluded or narrowed MCA branches were symptomatic due to transient ischemic events.

Strengths and Limitations

Our study has several limitations. First, I^2 results were above 50% for many of the estimates, suggesting substantial heterogeneity among the analyzed outcomes. The articles were often small, retrospective, and single-institution series, affecting the strength of the reported results. Factors related to procedural complications were not assessed, due to the scant data available. Details of the management of antiplatelet therapy were variable and infrequently specified. Finally, the small number of cases in some subgroups may not provide sufficient power to demonstrate a statistically significant difference in the rates of occlusion among age groups, different aneurysm sizes, prebifurcation-versus-bifurcation aneurysms, type of stent used, first treatment versus retreatment, and type of first treatment. However, although retrospective data are low in quality, our meta-analysis is the best available evidence to guide neurointerventionalists during flow-diversion treatment of MCA aneurysms.

CONCLUSIONS

Flow diversion for MCA aneurysms should only be considered as salvage therapy when traditional treatment methods are unfeasible, given the 10% rate of permanent neurologic morbidity. However, when performed in this select treatment group, high rates of aneurysm occlusion and protection against re-rupture can be achieved.

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