Occlusion Rate and Visual Complications With Flow-Diverter Stent Placed Across the Ophthalmic Artery's Origin for Carotid-Ophthalmic Aneurysms: A Meta-Analysis.

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Romain Touzé [1] [2], Bastien Gravellier [3], Claudia Rolla-Bigliani [1], Valérie Touitou [2] [4], Eimad Shotar [1] [4], Stéphanie Lenck [1], Anne-Laure Boch [5], Vincent Degos [6] [7], Nader-Antoine Sourour [1], Frédéric Clarençon [1] [4]

Affiliations

1 Interventional Neuroradiology Unit, Department of Neuroradiology, Pitié-Salpêtrière Hospital, Paris, France.
2 Department of Ophthalmology, Pitié-Salpêtrière Hospital, Paris, France.
3 Advanced Scientific Statistics Unit, University of Paris-Saclay, Paris, France.
4 Sorbonne University of Paris 6, Paris, France.
5 Department of Neurosurgery, Pitié-Salpêtrière Hospital, Paris, France.
6 Department of Anesthesiology, Pitié-Salpêtrère Hospital, Paris, France.
7 Neuro-Intensive Care Unit, Pitié-Salpêtrière Hospital, Paris, France.

Abstract:

Background

Flow-diverter stents (FDSs) have recently gained acceptance for the treatment of intracranial aneurysms, especially for carotid-ophthalmic aneurysms (COAs). However, complications have been reported after coverage of side branches, especially the ophthalmic artery (OA).

Objective

The purpose of our study was to evaluate, through a meta-analysis, the occlusion rate and the ophthalmic complications after treatment of COA by FDS.

Methods

We reviewed on MEDLINE via PubMed, Embase via Ovid and Cochrane central database via CENTRAL. We included all case series with at least 15 patients and clinical trials about flow diversion of aneurysms close to the OA's origin. Among these studies, we only included articles with aneurysm occlusion rate and rate of new ophthalmic symptoms.

Results

We included 16 studies with 913 COA treated by FDSs and covering the OA with a mean follow-up of 16.4 months. The random-effect modelling analysis concerning the overall rate of new ophthalmic complications, after FDS deployment covering the OA, was 3.0 % (CI95% 1.0 – 6.0). There was medium-high heterogeneity in the study reports $P<.01$, $I^2 = 70.2\%$ [50.4%; 82.1%]. We were not able to statistically explain this heterogeneity with the performed analysis, which could be related to the design of the included studies. We found an overall aneurysm occlusion rate of 85.0 % (95% CI 80.0 – 89.0).

Conclusion

Our meta-analysis found a high aneurysm occlusion rate (85%) and low rate of iatrogenic visual complications, with only 3.0 % of new visual symptoms, after treatment of COA by FDS.

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INTRODUCTION

During the past decade, flow-diverter stents (FDSs) have gain acceptance as a new tool in the endovascular treatment of complex intra-cranial aneurysms, especially large-necked ones. Despite a slightly higher complication rate than with other regular endovascular techniques, its effectiveness in terms of long-term intracranial aneurysm occlusion seems higher compared to conventional endovascular treatment.[1] Flow-diverters are supposed to promote aneurysm occlusion while preserving collateral branches' patency. Indeed, FDSs redirect the blood flow in the parent artery and their mesh acts as a scaffold on which endothelial cells will proliferate, leading to parent artery reconstruction and eventually neck sealing.[2] In carotid-ophthalmic aneurysms (COAs) treated by FDS, the effect of flow diversion on the ophthalmic artery (OA) is unpredictable. Indeed, some recent studies have reported ophthalmic complications, with various rates, after FDS deployment covering the OA's origin. Occurrence of ophthalmic complications varies in the literature from 0% to 39.1%.[3–19] The main reported ophthalmic complications include retinal emboli, visual field defects and *amaurosis fugax*.

There has been an increasing interest in FDS treatment for COAs, with numerous groups reporting their experience in terms of safety and effectiveness. However, neither review nor meta-analysis about the incidence and the mechanisms of these complications has been published so far. Thus, these visual complications remain poorly known and probably underdiagnosed. We performed here in a systematic review and meta-analysis of the literature on the safety, especially visual complications and their risk factors, and effectiveness, in terms of exclusion rate, of flow-diversion in carotid-ophthalmic aneurysms. We also sought to identify a potential association between ophthalmic complications and: 1) OA's patency, 2) number of FDS used for the same aneurysm and 3) the type of FDS.

METHODS

Our meta-analysis follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[20] No IRB approval was necessary for our study. The authors declare that all data concerning this study are available within supplementary files. (**See Table 1. of data in Supplemental Digital Content 1**).

Data collection

The different studies were analysed using combinations of terms in title, abstract, keywords and free text, until 1st October 2017. We focused our selection of articles dealing with flow-diversion in COAs. We searched on MEDLINE via PubMed, Embase via Ovid and Cochrane central database via CENTRAL with advanced search builder **(See builder search in Supplemental Digital Content 2)**. We used the following terms and synonyms: Aneurysm, ophthalmic, flow diversion and flow diverters. The complete search building is available in supplementary files. Additionally, references from the publications obtained were checked to add relevant studies. This systematic review of the literature was performed by two investigators (RT and CRB).

Inclusion and Exclusion Criteria

The data selection and collection were performed by two investigators, whose results were gathered and merged. All records were selected after reading title and abstract data. When studies were relevant, full texts were screened. We included all case series, reviews and clinical trials in English language about flow diversion of COAs defined as aneurysms arising from the supraclinoid segment of the internal carotid artery (ICA), close to the OA's origin (Fischer's C2 segment[21]; Bouthillier's C6 segment[22]). These aneurysms had to be treated by flow-diverter stents by any of the following FDS: Pipeline Embolization Devices (PED, Medtronic, Irvine, CA), Pipeline flex (Covidien, Paris, France), Silk (Balt, Montmorency, France), Surpass (Stryker Neurovascular, Fremont, California, US), P64 (Phenox, Bochum, Germany), Flow Redirection Endoluminal Device (FRED, Microvention, Tustin, CA), Tubridge (MicroPort, NeuroTech, Shanghai, China). All studies had to mention data on exclusion rate or/and complications rate and on visual outcome. We excluded case reports,

conference abstract, case series with less than fifteen patients, and other aneurysm locations. We excluded all studies designed to assess the visual outcome concerning FDS use in compressive aneurysms to avoid bias and obtain only the rate of "iatrogenic" visual complications after flow diversion. Among these studies, we only included articles reporting rate of new ophthalmic complications.

Data Extraction and Outcome Measures

After dual reviewing, we extracted the following data from all studies included for statistical analyses: title, publishing year, journal, design, population parameters, number of patients, number of ophthalmic aneurysms with OA coverage, type of flow-diverters, additional coils treatment, exclusion rate, morbidity and mortality rates, patency of OA after stenting, visual symptoms before treatment, visual complications after treatment, visual outcome, follow-up, risk factors for ophthalmic complications identified.

Primary outcome assessed with this meta-analysis was the rate of new ophthalmic symptoms (i.e.: ophthalmic complications) after treatment of COAs by FDSs. All studies were included for this analysis.

Secondary outcome assessed proved to be multiple. When data was available, we collected the rate of OA's patency on last angiographic follow-up and the aneurysm occlusion rate on last angiographic follow-up. Since there was variability among the different studies, by convention we defined "patent OA" as no change in flow or calibre of the OA arising from internal carotid artery (ICA). Slow flow was used to describe a reduction of flow and/or calibre of the OA compared to DSA before FDS placement. Finally, OA occlusion was defined as an OA occluded at its origin and thus not arising anymore from the carotid siphon. We performed analyses to identify the impact of the number of devices placed, the type of stents and OA's patency on the occurrence of a new ophthalmic complication. We also evaluated the correlation between the number of devices placed and type of stents on the OA's patency.

We assessed quality of reporting for each study using STROBE Statement (Strengthening of Reporting of Observational studies in Epidemiology). We assessed the 22 items of the

checklist to give a score for each study (**See Table 2 in Supplemental Digital Content 3**). Six or more were required as inclusion criteria.

Statistical Analysis

The meta-analysis was performed using the R (Version 3.3.3 software) packages: metafor (Wolfgang Viechtbauer) and meta (Guido Schwarzer). Random-effect analyses were used in order to weight, pool and explain the data regarding to explanatory variables. Results are presented as rate and 95% confidence interval (CI). The I^2 statistic and the Q test were used to assess the heterogeneity. For each study, we assigned a weight according to the number of patients in the study. Heterogeneity between studies was reported by using the Cochran X^2 (Cochran Q) statistic and the calculation of $I^2 = [(Q– df)/ Q] x100$, where I^2 is the percentage of the variability in effect estimates. I^2 reflects the heterogeneity rather than the sampling error (chance).[23] According to the Cochrane handbook,[24] heterogeneity is classified as moderate ($I^2 \geq 30\%$), substantial or medium ($I^2 \geq 50\%$), or considerable or high ($I^2 \geq 75\%$). We assessed publication bias by using scatter plots according to study size or precision (i.e., the funnel plot).[25] We chose standard error for the vertical axis and the log event rate, defined as log (p) = log (p) - log (1 - p), where p is the event rate, for the horizontal axis.[26] We assessed publication biases by means of a simple visual analysis of funnel plots, as there is no validated statistical test to detect asymmetry and by using funnel plots and the test of Egger et al [25] in the subgroup comparisons. In the absence of bias and when researchers in the studies estimated the same underlying effect, the plot will resemble a symmetric inverted funnel. If there is bias, then the funnel plot will appear asymmetric with a gap in the bottom right-hand side of the graph. The more pronounced the asymmetry, the more likely it is that the amount of bias will be substantial.

Our meta-analysis review protocol has not been published or registered.

RESULTS

The initial searches on Pubmed (Medline), Embase and Cochrane central database yielded 367 results. We excluded 328 non-relevant articles after studied title and abstract; a total of 39 articles were thus kept for first review. We analyzed these 39 full text articles to evaluate data provided; only 16 studies met the inclusion criteria. Eighteen studies had no data about visual outcome, 5 were case series with less than fifteen patients. (**See the Flow Diagram in Supplemental Digital Content 4**). In these 16 studies, we collected 913 COAs treated by flow-diverter covering the ophthalmic artery. All included studies had a high risk of bias because studies were retrospective and non-randomized. These studies were all published after 2010. The mean follow-up was 16.4 ± 11.0 months. All studies' characteristics are summarized in **Table 1.**

Among the 16 studies included in the meta-analysis, we identified 7 studies without objective visual outcome (only reported by patient), 8 studies with visual objective outcome only in patients with complains and 1 study with systematic visual objective data.

The random-effect modelling analysis concerning the overall rate of new ophthalmic complications, after FDS deployment covering the OA, was 3.0 % (95% CI 1.0 – 6.0) (**Fig. 1**). There was medium-high heterogeneity of the variable "New ophthalmic complications" in the study reports (Test Q, $P < .01$) with $I^2 = 70.2\%$ [50.4%; 82.1%]. The overall patency of OA after stent implantation was 90.0 % (95% CI 86.0 – 93.0) (**Fig. 2**). There was medium heterogeneity of the variable "OA's patency" in the study reports (Test Q, $P = .01$) with $I^2 = 50.7\%$ [8.9%; 73.3%]. The total rate of aneurysm exclusion (i.e.: complete occlusion or near complete occlusion) was 85.0 % (95% CI 80.0 – 89.0) (**Fig. 3**). There was no heterogeneity of the variable "aneurysm exclusion" in the study reports (test Q, $P = .20$).

Analyses were performed aiming to explain heterogeneity concerning the rate of new ophthalmic complication and the OA's patency after stent deployment. Concerning the rate of new ophthalmic complications, no statistically significant association (P-value > .05) was observed with the type of stents (PED, Silk, Surpass), the number of FDSs (one FDS, two or more FDSs) or OA's patency.

Concerning the OA's patency, the same analyses were performed. We were not able to explain again this heterogeneity by the type of stents or the number of FDS. All analyses had a P-value > .05.

The funnel plots for each studied variable did not demonstrate any asymmetry. This result was in accordance with the Egger tests, which were all non-significant (funnel a: P = .51, funnel b: P = .39 and funnel c: P = .45, respectively [**Fig. 4A**, **4B** and **4C**]). The absence of asymmetry supports the absence of bias in our analysis. However, the robustness of the analysis was weakened by the small number of aneurysms included in our study.

DISCUSSION

FDSs are recent devices for the treatment of intra-cranial aneurysms which provide a high occlusion rate, especially in paraclinoid aneurysms, with an acceptable complication rate. [1,27,28] Visual complications related to endovascular treatment of COAs by FDS remain poorly known and probably underdiagnosed since the pathomechanism of these complications is unclear. Our meta-analysis gathered all studies reporting the visual complications after treatment of COAs by FDS.

Despite a few studies reporting a high visual complication rate, we found an overall ophthalmic complication rate of 3.0 % (95% CI 1.0 – 6.0) through the 16 studies and 913 COAs screened. However, this result showed medium-high heterogeneity. We evaluated if this heterogeneity could be explained by the type of device, the number of FDSs deployed, or the patency of OA visualized on angiographic control. We could not observe any significant explanation by taking into account these parameters. In the literature, the increasing number of FDS placed across the OA's origin has been suggested as a potential risk factor for the occurrence of ophthalmic complication or OA occlusion.[18] However, Puffer et al[15] did not find any significant correlation between the number of FDSs placed across OA and the occurrence of ophthalmic complications. In our meta-analysis, we also found no influence of an increasing number of FDSs covering the OA and the occurrence of ophthalmic complications.

The heterogeneity observed in our meta-analysis may be explained by the different rates of new visual complications between studies, ranging from 0.0% to 38.0 %. This heterogeneity could be explained by the studies' design. Indeed, when a systematic ophthalmic examination was performed, the reported visual complication rate increased.[17,29]

Zhou et al. performed a meta-analysis focused on complications associated with the use of flow-diverter stents for intra-cranial aneurysms. They found an overall complication rate around 17%, including 10% of procedural technical complications. The permanent morbidity rate and mortality rate were 3.7% and 2.8%, respectively. Compared to these data, the visual complication rate reported in our meta-analysis (3%), with neither severe nor permanent deficit, can be considered as an acceptable minor complication rate. Indeed, our meta-analysis

suggests that symptomatic ophthalmic complications are rare and that most of the ophthalmic symptoms are mild and do not lead to permanent visual impairment.[29]

In our meta-analysis, we chose to include only the studies dealing with patients without pretreatment visual deficit, in order to ensure homogeneity and to reduce the risk of bias in the evaluation of iatrogenic visual complications' rate. Interestingly, Silva et al,[28] in their recent meta-analysis, compared the visual outcome of clipping, coiling or flow diversion for paraclinoid aneurysms with pretreatment visual impairment. They found a rate of visual improvement in 58% of the patients treated by clipping, 49% with coiling and 71% of patients treated with flow diversion. Concerning the rate of iatrogenic visual impairment, new deficits occurred in 1% (95% CI 0 – 3.0%) after clipping, 0% (95% CI 0 – 2.0%) after coiling and 0% (95% CI 0 – 2.0%) after flow diversion.

Two mains subtypes of visual complications after flow diversion in COAs have been described.[17,29] First, there are the *fugax amorauses*; secondly, the small retinal emboli resulting in visual field deficits. The pathomechanisms of these complications is still unclear. They may be related to small emboli outgoing from stent or to a modified blood flow in the OA after FDS placement. Another hypothesis is an insufficient blood flow from the external carotid artery (ECA) collaterals to supply the OA after FDS deployment. Indeed, in cases of poorly developed collaterals from the ECA and high coverage of the OA's origin by the FDS' mesh, patients may have some visual symptoms or minor ophthalmic abnormalities during the period of hemodynamic balance between ECA and ICA systems (i.e.: before the ECA collaterals could be sufficiently developed to supply the OA). However, we were not able to perform an analysis concerning the subtype of visual complications due to a lack of data. Among the 16 studies included in the meta-analysis, we identify 7 studies without objective visual outcome (only reported by patient), 8 studies with visual objective outcome only in patients with complains and 1 study with systematic visual objective data. Indeed, only few studies reported details about the ophthalmic complications. In the two studies cited with independent and objective visual function assessment, the authors found a high rate of visual complications, but most of complications were asymptomatic and not clinically relevant. These two studies have the strongest methods since they performed a systematic examination by an ophthalmologist. They bring new insights in the understanding of the FDS's behaviour

and mechanism of action. However, the remaining studies should not be disqualified since they report visual symptoms described by the patients, which are the most clinically relevant.
We tried to demonstrate a relationship between OA occlusion after flow diversion covering the OA and the occurrence of visual complications. Based on the clinical practice, proximal OA occlusion rarely leads to visual symptoms owing to the rich anastomotic network between ECA's branches and the OA and its branches.[29–31] We found, in our meta-analysis, an overall rate of OA patency of 90% (95% CI 86.0 – 93.0) on last angiographic follow-up. For comparison, the patency of the anterior choroidal artery after treatment by FDS covering its ostium has been reported in about 95% of the cases[32,33] and in 75% of the cases for the posterior communicating artery.[34] However, our meta-analysis failed to demonstrate a statistical relationship between occlusion of the OA and visual symptoms after FDS treatment. A recent animal model study evaluating the diversion effect promoted by FDS demonstrated that the presence of distal collateral supply reduced the flow rate in the covered artery, which may eventually lead to its occlusion. In contrast, a terminal circulation contributed to preserve patency of the covered artery.[35]

The complete/near complete occlusion rate of COAs treated by FDS in our meta-analysis was 85.0 % (95% CI 80.0 – 89.0), confirming the effectiveness of flow diversion for the treatment of COAs. This rate is in accordance with the ones found in the literature (83.3 %) for anterior circulation aneurysms treated by FDS.[27]

Since almost all visual abnormalities depicted after flow diversion for the treatment of COAs had no clinical impact and did not lead to any sequel, we do not recommend a systematic ophthalmic examination for patients treated by FDS for COA. Nevertheless, the operators have to be aware of any ophthalmic symptoms in their patients treated with flow-diverter across the ophthalmic artery and refer these patients to a neuro-ophthalmologist in case of new visual symptoms.
However, for a clinical research purpose, in order to better understand the timing of occurrence of the visual abnormalities, systematic pre and post-treatment, as well as late ophthalmic evaluations may be interesting.

Limitations

Our meta-analysis has some limitations. The main limitation is the design of included studies. All included studies had a low level of evidence since they were non-randomized, retrospective and, for most of them, monocentric.

Another limitation was the quality of the ophthalmic outcome assessment. This evaluation was often a subjective assessment (i.e.: performed by the operator or a member of his team) and was not performed by an independent ophthalmologist with a systematic post-operative full ophthalmic examination. To the best of our knowledge, only two studies with a systematic visual examination performed by an ophthalmologist exist and found a higher rate of postoperative visual disturbances.[17,29]

These limitations concerning design and quality of the ophthalmic outcome assessment could explain the heterogeneity found in our meta-analysis, which should incite a cautious interpretation of our results.

The small number of studies included could be a bias. This small number may be explained by the fact that FDSs are recent devices for which safety and effectiveness have only been reported recently (the oldest included studies were published in 2010). However, the small number of included studies probably failed in explaining solely this heterogeneity. Indeed, we found heterogeneity concerning the studied variables (i.e.: new ophthalmic complications and OA's patency) except for the occlusion rate.

CONCLUSION

We present herein the first meta-analysis evaluating the rate of ophthalmic complications after treatment of COAs by FDSs. We found an acceptable rate of iatrogenic visual complications with only 3.0 % of new visual symptoms after the treatment of paraclinoid aneurysms by FDS. Visual complications after flow diversion of COA remain often benign and/or temporary. However, there was a medium-high heterogeneity between the different studies, which may be explained by the studies' design, the quality of the post-operative ophthalmic assessment and the small number of studies included. Despite its effectiveness in terms of aneurysm occlusion, Neurosurgeons, Neurologists as well as Interventional Neuroradiologists, involved in the management of intracranial aneurysms should be aware of the significant risk of visual complication in patients treated by flow diversion for COA.

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LEGENDS

Figure 1. Forest plot comparing the occurrence of new visual complication in the 16 studies included. CI indicates confidence interval.

Figure 2. Forest plot comparing the patency of the ophthalmic artery in the 14studies included with this data. CI indicates confidence interval.

Figure 3. Forest plot comparing the exclusion rate in the 11studies included with this data. CI indicates confidence interval.

Figure 4. Funnel plot of the studies included for the outcome “new visual complication” (a), “OA’s patency” (b), and “exclusion rate” (c).

LEGENDS OF SUPPLEMENTAL DIGITAL CONTENT

Supplemental Digital Content 1. Methods Table 1. Data. Table summarising all data extracted from all included study.

NR: Not Reported

Supplemental Digital Content 2. Methods. Builder search. Builder search used in Pubmed search field.

Supplemental Digital Content 3. Methods Table 2. STROBE Scale. STROBE scale assessment of all included studies.

Supplemental Digital Content 4. Figure 1. Flow diagram. PRISMA Flow chart