The efficacy and safety of flow-diverting device and coil embolization for intracranial aneurysms: a meta-analysis

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Abstract. – OBJECTIVE: To compare the clinical efficacy and safety of flow-diverting device (FDD) and coil embolization therapy (CET) in the treatment of intracranial aneurysms through a meta-analysis.

MATERIALS AND METHODS: We comprehensively searched in PubMed, Embase, Cochrane Library, CNKI, Wan Fang, VIP databases, and China Biology Medicine disc (CBM) for eligible literature. Odds ratio (SMD) and 95% confidence intervals (CIs) were considered as effect measures. Statistical heterogeneity was tested by Cochran's Q statistic and I^2 tests, and sensitivity analysis was used to evaluate the stability of research results. Publication bias was detected by funnel diagrams.

RESULTS: A total of 888 patients from 9 studies were finally enrolled in our analysis. Through meta-analysis, the results showed that the aneurysm occlusion rate in the FDD group was significantly higher than that in the CET group (OR, 95% CI=1.68, 1.20 to 2.36, p=0.002), and the retreatment rate after aneurysm operation in the FDD group was significantly lower than that in the FDD group (OR, 95% CI=0.40, 0.22 to 0.74, p=0.003). There was no significant difference in the proportion of mRS score (0-2) between the two groups during postoperative follow-up (OR, 95% CI=0.63, 0.20 to 1.94, p=0.43). In terms of safety, there was no significant difference in the incidence of postoperative complications (OR, 95% CI=1.11, 0.68 to 1.81, p=0.67) and mortality (OR, 95% CI=1.35, 0.53 to 3.42) between the two groups.

CONCLUSIONS: Compared with CET, FDD has achieved satisfactory results in increasing the rate of aneurysm occlusion and reducing the rate of retreatment of intracranial aneurysms. There is no significant difference in security between FDD and CET, though. These findings are reported in this paper, but because of the limitations of the included study, they need to be further verified by well-designed multicenter randomized controlled trials (RCT).

Key Words:
Intracranial aneurysm, Flow-diverting device, Coil embolization therapy, Efficacy, Safety, Meta-analysis.

Introduction

Intracranial aneurysm is a common cerebrovascular disease, which is due to the tissue structure damage caused by congenital or acquired factors in the arterial wall, which causes the release of a large number of inflammatory factors and acts on the vascular wall, resulting in the degradation of the elastic layer and the decrease of the elasticity of the vascular wall. aneurysms occur under the impact of blood flow[1]. The incidence of intracranial aneurysms is 0.5%-6.0%[2]. There are usually no evident symptoms of intracranial aneurysms, but the clinical manifestations of subarachnoid hemorrhage (SAH) caused by ruptured aneurysms are severe headache, nausea, and vomiting, cranial nerve paralysis, or nerve dysfunction. Once a ruptured aneurysm causes subarachnoid hemorrhage, it has a high rate of death and disability.

At present, the methods for the treatment of intracranial aneurysms include microsurgical clipping, endovascular interventional therapy, and follow-up conservative treatment. In recent years, with the development of interventional technology and interventional materials, the technology of endovascular interventional treatment of intracranial aneurysms has gradually matured, and it has been gradually accepted by the majority of patients because of its advantages such as small trauma, high embolization rate, short postoperative recovery time and so on. Coil embolization therapy (CET) is a breakthrough in the development of interventional therapy.

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Balloon-assisted embolization[3] and stent-assisted embolization[4] are the most exciting parts of CET. CET is becoming more and more mature, and its clinical efficacy has been recognized, but it is not effective in the treatment of intracranial large/huge, fusiform, wide-necked, and other complex aneurysms, showing a higher retreatment rate and a lower aneurysm occlusion rate. In this case, a new interventional material: flow diversion device (FDD) arises at the historic moment, and the concept of parent artery reconstruction is another milestone in the endovascular treatment of intracranial aneurysms. So far, there is no consistent conclusion on the safety and efficacy of FDD and CET in the treatment of intracranial aneurysms. Here, we performed a meta-analysis to evaluate the aneurysm occlusion, aneurysm retreatment rate, complication rate, mortality and the proportion of patients with postoperative follow-up mRS score of 0-2 among different endovascular treatment techniques, to study whether there is a difference in the efficacy and safety of FDD and CET in the treatment of intracranial aneurysms, and to provide more basis for the choice of treatment of intracranial aneurysms.

Materials and Methods

Search Strategy

Under the PRISMA statement[5], this study searched the published literature in Chinese and English until December 2020. The English search words “aneurysm”, “flow diversion” or “flow divert” and “coil” or “intervention” are searched in PubMed, Embase, and Cochrane library databases. Take “intracranial aneurysm”, “coil” or “interventional therapy” and “flow device” as the Chinese subject words to search China Nation knowledge Infrastructure (CNKI), Wanfang Database, VIP Database, and China Biology Medicine disc (CBM), and search the literature of ongoing and completed clinical trials and important conferences, and there is no language restriction. The literature comparing the efficacy and safety of FDD and CET in the treatment of intracranial aneurysms was screened.

Eligibility Criteria

The inclusion criteria of this study were as follows: (1) to compare the study of the flow-diverting device and coil embolization in the treatment of intracranial aneurysms; (2) the study reported at least two of the following outcome indicators: “aneurysm occlusion”, “aneurysm retreatment rate”, “complication rate”, mortality and the proportion of patients with postoperative follow-up mRS score of 0-2; (3) a total sample number of more than 10 cases; (4) the type of study was observational clinical study or cohort study.

Exclusion criteria included: patients with any of the following conditions were excluded: (1) trauma, dissection, “infectious aneurysm”, “arteriovenous fistula” or “arteriovenous malformation with aneurysm”; (2) the study with significant differences in endpoints or lack of baseline data between the two groups before intervention; (3) serious loss of follow-up; (4) repeated publications or multiple articles using the same data, only the one with the most complete research information was included, and the rest were excluded.

Study Selection and Data Extraction

Two investigators (Wang, K and Aisha, M) independently completed the literature screening work according to inclusion and exclusion criteria. The extracted information included: (1) basic information of included studies, including author name, type of study design, publication year and region; (2) basic characteristics of the subjects, including sample size, age, gender, and aneurysm size, etc.; (3) At the same time, the occurrence of the above clinical endpoints was recorded. At each step, the differences were resolved through discussions with the third author (Kadeer, K).

Assessment of Methodology Quality

In the observational study, the Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the literature. The scale included three indicators: the study population selection, the comparison between groups, and the outcome. A total of 8 items with a full score of 9 and the score of 7-9 was classified as high-quality.

Statistical Analysis

Review Manager 5.3 software was used for statistical analysis. Because all clinical endpoints were binary variables, the odds ratio (OR) and its 95% confidence interval (95% CI) was used as the effective index. The heterogeneity of meta-analysis results was tested by Cochran’s Q and I^2. If there was a Q statistic $p<0.1$, or $I^2>50\%$, it showed significant heterogeneity among the studies, which needed to be merged by a random-effect model. If not, a fixed-effect model was adopted. Sensitivity analysis was carried out by excluding the included studies one by one. Publication bias was evaluated directly by a funnel chart. $p< 0.05$ showed that there was a statistical difference.

Results

Study Retrieval

1241 articles were obtained by preliminary examination. After excluding repeated detection, 601 articles were excluded after reading the title and abstract of the remaining literature. after reading the full text, 9 articles[6-14] were included in the study (Figure 1).

Study Characteristics

As shown in Table I, all the 9 articles included in this study were retrospective studies, with a total sample size of 888 cases, including the FDD group (n = 480) and the CET group (n = 408).

Quality Assessments

Among the 9 articles included in this study, the NOS quality evaluation indicates that one of them has a score of 6, and the rest of them have a score of ≥ 7, so the overall quality of the literature included in this study is high (Table II).

Aneurysm Occlusion Rate

A total of 9 articles[6-14] reported the clinical differences between the FDD group and the CET group in the aneurysm occlusion rate. The heterogeneity of the meta-result was non-significant (P=0.52, I^{2}=0%), so a fixed-effect model was used to combine outcomes. The aggregated data showed that the aneurysm occlusion rate of the FDD group was significantly higher than that of the CET group (OR, 95% CI=1.68, 1.20 to 2.36, p=0.002, Figure 2). The aneurysm occlusion rate in FDD group is 76.7% (368/480), CET group is 65.2% (266/ 408).

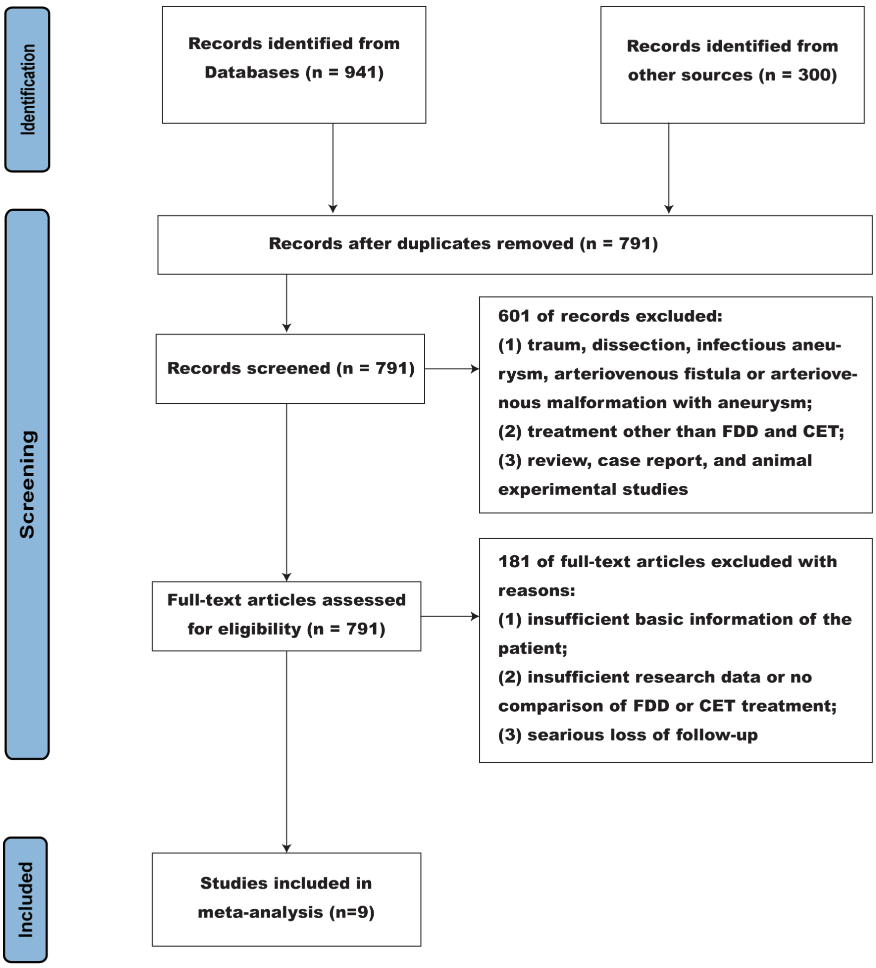

Figure 1. Literature Search Flowchart.

Table I. Characteristics of individual studies of patients treated with FDD and CET included in our analysis.

Author	Year	Study design	Region	FDD/CET No. of Subject	FDD/CET Men Age (year)	FDD/CET Mean Aneurysm Size(mm)	Follow-up time (months)
Mohamed M. Salem et al	2020	Retrospective	USA	170/32	58/60	5.1/5.3	16.3
Nohra Chalouhi et al	2014	Retrospective matched	USA	40/160	51/56	6.2/6.0	17
Nohra Chalouhi et al	2017	Retrospective matched	USA	40/40	55/55	6.3/6.3	16
Alejandro Enriquez-Marulandad et al	2019	Retrospective	USA	21/17	59/59	4.9/8.6	8.3
Shigeru Miyachi et al	2017	Retrospective	JAPAN	9/18	73/62	16.6/14.6	6
Nimer Adeeb et al	2017	Retrospective	USA	106/62	57/57	6.4/7.1	8.7
Peng Yan et al	2019	Retrospective	CHINA	61/41	53/53	21.1/21.1	6
G.lanzino et al	2012	Retrospective	USA	21/22	51/58	6.3/6.7	6
Ning Lin et al	2015	Retrospective	USA	12/16	61/61	8.1/8.6	26.1

Retreatment Rate

A total of 8 articles[6-9, 11-14] reported the clinical differences between the FDD group and the CET group in the retreatment rate. The heterogeneity of the meta-result was non-significant ($p<0.26$, $I^{2=}22\%$), so a fixed-effect model was used to combines outcome. The aggregated data showed that the retreatment rate of the FDD group was significantly lower than that of the CET group (OR, 95% CI=0.40, 0.22 to 0.74, $p=0.003$, Figure 3). Compared with the retreatment rate of aneurysms in the CET group (11.1%), the retreatment rate of aneurysms in the FDD group was 4.4% (20/459).

Postoperative Complication

All of the 9 articles[6-14] reported the clinical differences between the FDD group and the CET group in the postoperative complication, including hemorrhagic and ischemic complications. The heterogeneity of the meta-result was non-significant ($p=0.21$, $I^{2=}26\%$), so a fixed-effect model was used to combine outcomes. The aggregated data showed that there was no significant difference in the incidence of postoperative complications between the FDD group and the CET group (OR, 95% CI=1.11, 0.68 to 1.81, $p=0.67$, Figure 4). The incidence of complications in the CET group was 8.8% (36/408), FDD group was 10.6% (51/480).

Death Rate

A total of 8 articles[6-9,11-14] reported the clinical differences between the FDD group and the CET group in the death rate. The heterogeneity of the meta-result was non-significant ($P=0.85$, $I^{2=}0\%$), so a fixed-effect model was used to combine outcomes. The aggregated data showed

Table II. Literature quality assessment.

Author	Year	NOS Selection	NOS Comparability	NOS Outcome	Total points
Mohamed M. Salem et al	2020	★★★★	★★	★★★	9
Nohra Chalouhi et al	2014	★★★★	★★	★★	8
Nohra Chalouhi et al	2017	★★★	★★	★★	7
Alejandro Enriquez-Marulandad et al	2019	★★★★	★★	★★	8
Shigeru Miyachi et al	2017	★★★★	★★	★★	8
Nimer Adeeb et al	2017	★★★★	★★	★★	8
Peng Yan et al	2019	★★★★	★★	★	7
G.lanzino et al	2012	★★★	★	★★	6
Ning Lin et al	2015	★★★★	★	★★	7

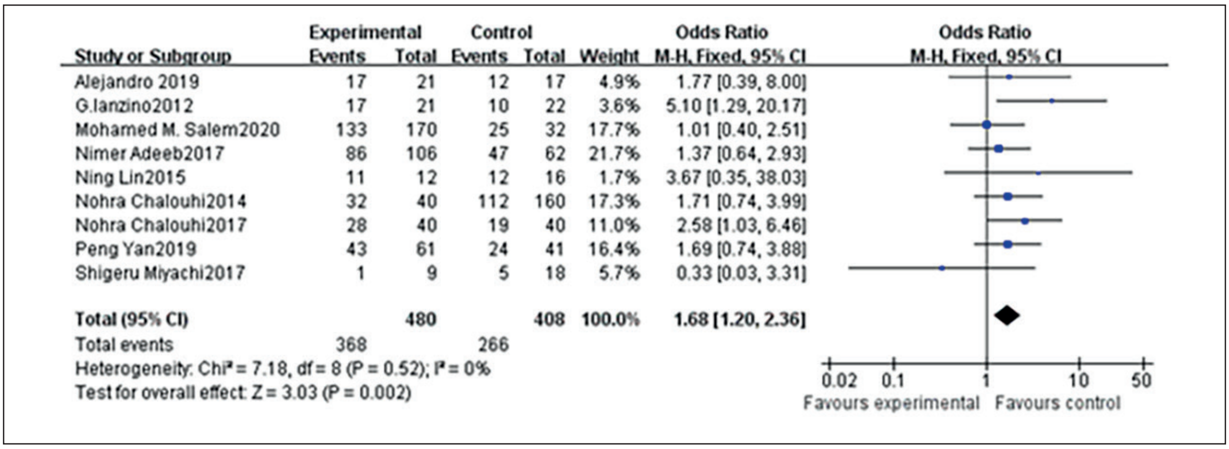

Figure 2. Forest plot of aneurysm occlusion rate.

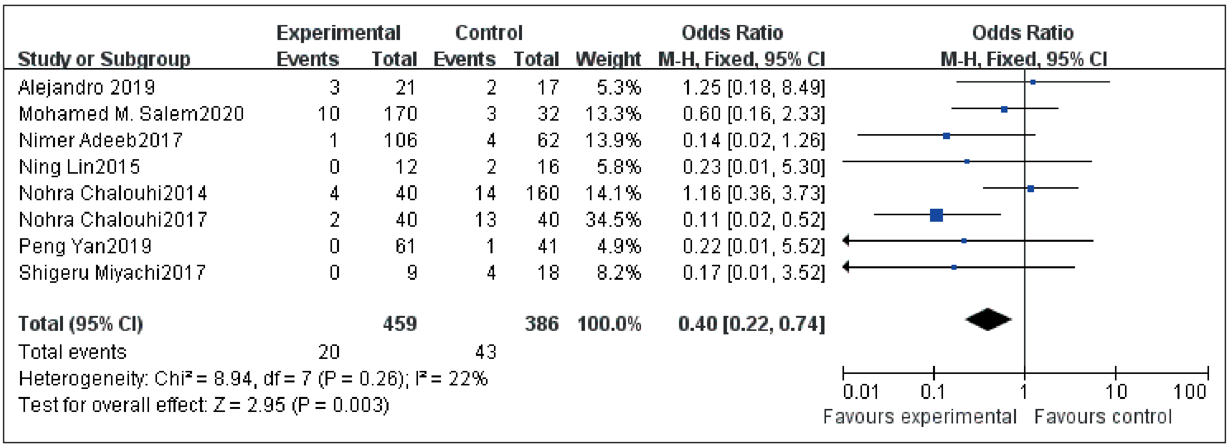

Figure 3. Forest chart for aneurysm retreatment.

that there was no significant difference in post-operative mortality between the FDD group and the CET group (OR, 95% CI=1.35, 0.53 to 3.42, p=0.52, Figure 5). The mortality rate was 2.2 % (10/459) in the FDD group, CET group was 1.8% (7/ 386).

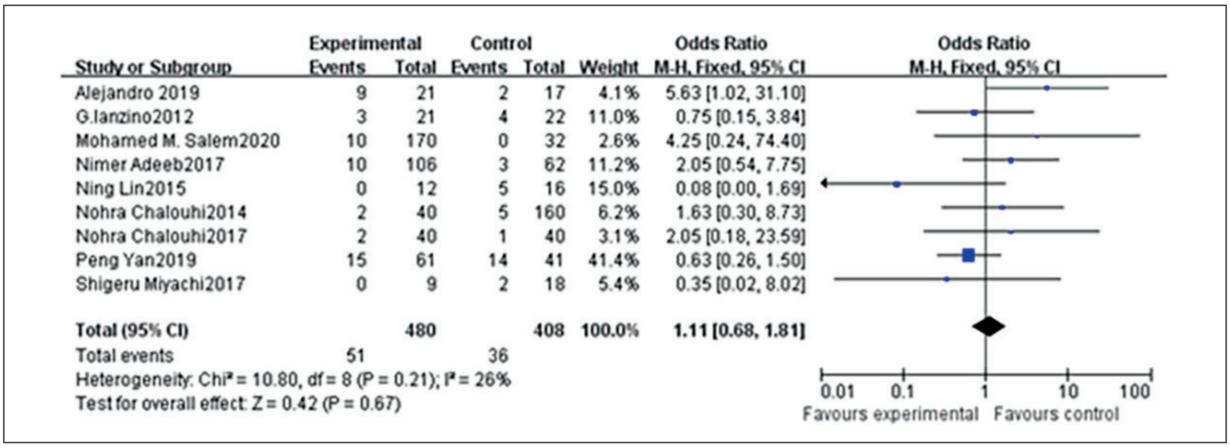

Figure 4. Forest plot of the incidence of complications.

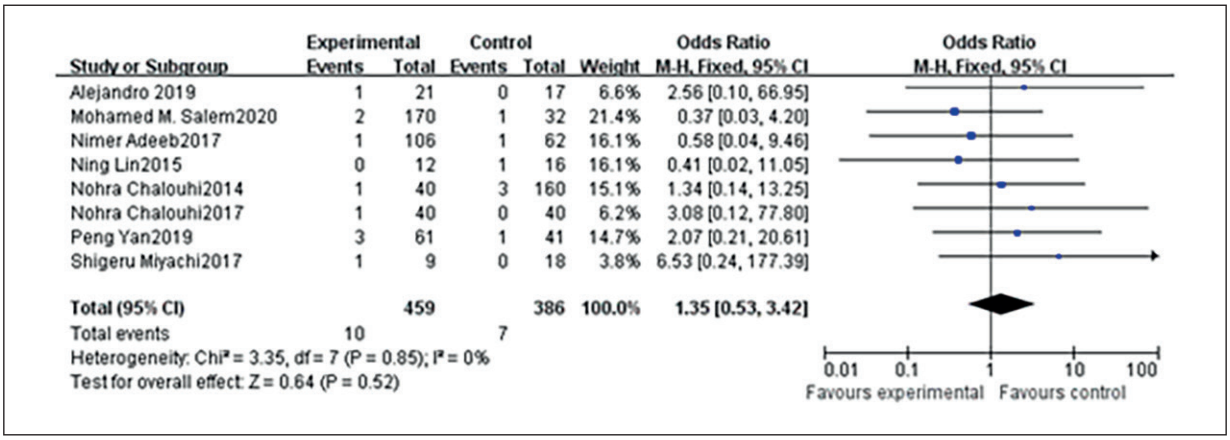

Figure 5. Forest plot of mortality rates.

Favorable Clinical Outcome

The mRS, at last, follow- up was extracted to evaluate clinical outcome; mRS <3 was defined as favorable. A total of 5 studies[6-8,11,13] were included for analysis. The heterogeneity test showed that there was no obvious heterogeneity in the study (p=0.31, I^{2}=14%), so a fixed-effect model was used to combine outcomes. The result of the meta-analysis showed that there was no significant difference in the recovery of neurological function between the FDD group and the CET group (OR, 95% CI=0.63, 0.20 to 1.97, p=0.43, Figure 6).

Sensitivity and Publication Offset Analysis

Using the method of single exclusion of one study for sensitivity analysis, it was found that there was no significant effect on the combined results of the above five clinical endpoints, indicating that the stability of the results of the study analysis was good. The funnel diagrams of the five clinical endpoints studied are intuitively symmetrical, so there is no publication offset in this study.

Discussion

With the gradual deepening of the study of intracranial aneurysms, hemodynamic factors gradually appear in our field of vision. Many studies have shown that hemodynamic disorder is one of the main reasons for the occurrence, growth, and rupture of intracranial aneurysms. Therefore, reconstruction of vascular walls and correction of hemodynamic abnormalities have become a hot method for the treatment of intracranial aneurysms. Therefore, based on the concept of parent artery reconstruction, a flow diversion device (FDD) came into operation. As a new embolic material, FDD has been

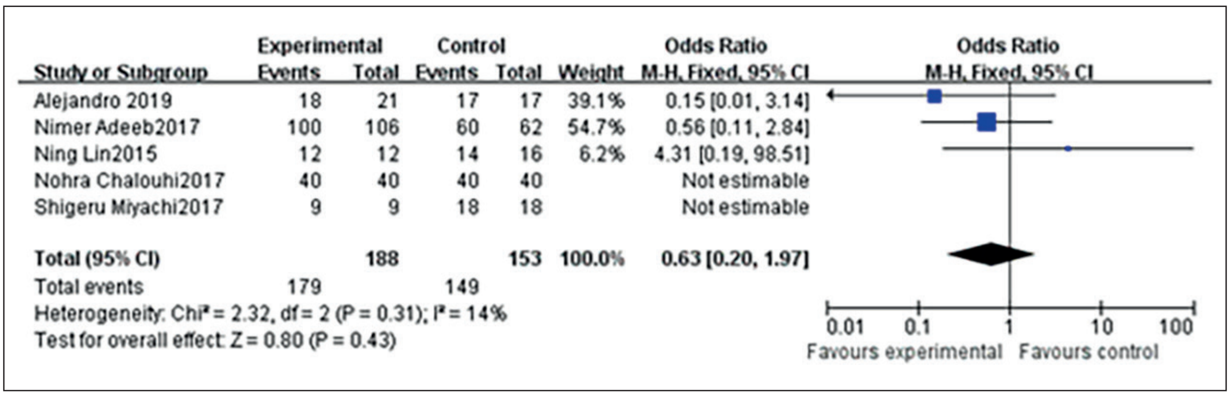

Figure 6. Forest plot of clinical prognosis.

gradually used in the treatment of various types of aneurysms, and its safety and efficacy have been confirmed in PUFS[15] and PITA[16] experiments. However, there is no clear conclusion as to whether FDD is superior to CET, in the treatment of intracranial aneurysms. In this study, 9 clinical studies were included for meta-analysis. The results showed that compared with CET, FDD could significantly increase the rate of complete aneurysm occlusion and reduce the rate of aneurysm retreatment and did not increase the incidence of complications.

Incomplete aneurysm occlusion and high retreatment rate have always been inevitable problems in CET, especially in the treatment of large or large aneurysms, its disadvantages will be exposed. As a product of the new concept, FDD is a kind of stent designed for wire weaving. The mesh size of the stent is 0.02 to 0.05 mm^2. After the stent is fully opened, the metal coverage of the stent parent artery can reach 30%. The blood flow guidance of FDD can interfere with the amount of blood into the tumor, increase the retention time of blood in the tumor, and promote the formation of thrombus in the tumor. In recent years, studies on the hemodynamics of aneurysms have found that WSS plays an important role in the growth and rupture of aneurysms. High WSS can lead to arterial wall endothelial cell degeneration and apoptosis, vascular smooth muscle cell degeneration, the gradual disappearance of the internal elastic layer under the action of matrix metalloproteinases, and finally, lead to the formation of the aneurysm[17]. Studies have shown that after the implantation of FDD, the average wall shear stress (WSS) decreased significantly (by 40.7%), the intratumoral blood inflow decreased significantly (by 52.2%), and the retention time of blood in the tumor increased significantly (increased by 224.1%). There was no significant change in intratumoral pressure[18]. A hemodynamic study of FDD in the treatment of intracranial aneurysms shows that FDD implantation can reduce the mean intratumoral flow velocity, maximum intratumoral inflow rate, and mean WSS, which indicates the occlusion of the aneurysm. FDD can be used for vascular endothelial cells to climb and grow. After FDD is completely covered by vascular endothelial cells, the aneurysm is isolated from the blood circulation, which greatly reduces the risk of aneurysm rupture and bleeding. After endothelialization, it forms a permanent biological seal in the neck of the aneurysm, which has reached an anatomical cure[19]. In previous studies, it has been reported that the complete occlusion rate of intracranial aneurysms treated with FDD is between 55% and 95%. In this study, the complete occlusion rate and retreatment rate of the FDD group were 76.7% and 4.4% respectively, which were significantly better than 65.2% and 11.1% of the CET group, which further supported the efficacy of FDD in the treatment of intracranial aneurysms.

In the application of FDD in the treatment of intracranial aneurysms, the complications cannot be ignored. Ischemic and hemorrhagic complications caused by FDD will not only increase the mortality and disability rate of patients but also bring a huge economic burden to patients' families. The hemorrhagic complications caused by FDD mainly include intraoperative and postoperative aneurysm rupture and delayed ipsilateral cerebral parenchyma hemorrhage (delayed ipsilateral intraparenchymal hemorrhage, DIPH)[20]. Studies have shown that the occurrence of complications may be related to the use of dual antiplatelet drugs, changes of intravascular pressure, blood pressure, and microemboli shedding caused by distal small vessel occlusion and reperfusion bleeding after recanalization[21]. The thrombus in the aneurysm contains many proteases, most of which have high proteolytic activity and can participate in the degradation of the aneurysm wall, which may also be one of the causes of bleeding. Most of the ischemic complications caused by FDD are related to inadequate use of antiplatelet drugs, occlusion of the perforating artery, and so on. For the preoperative detection of the function of antiplatelet drugs, it is extremely important to standardize the use of antiplatelet drugs before and after the operation. Some studies have shown that[22] low-dose tirofiban is pumped continuously for at least 24 hours during and after the operation, which can reduce the occurrence of ischemic complications after FDD without increasing the risk of bleeding. The efficacy of new antiplatelet drugs (such as prasugrel) in the prevention of ischemic complications was reflected in a Meta[23]. This study reported that 682 and 672 patients with intracranial aneurysms who received endovascular treatment were treated with antiplatelet therapy and clopidogrel, respectively. The results showed that the incidence of ischemic complications in the prasugrel group was significantly lower (2% *vs* 6% $p = 0.03$). In a multicenter study[24], the incidence and mortality of postoperative neurological complications in the treatment of intracranial aneurysms with blood flow guiding devices were 1.9% and 0.5%, respectively. In this study, the mortality and the incidence of complications in the FDD group were 2.2% and 10.6%, respectively, similar to those in the CET group (1.8%, 8.8%), suggesting that FDD is relatively safe in the treatment of intracranial aneurysms.

Using the mRS obtained at the last follow-up as an index to evaluate the clinical effect and the recovery of neurological function of the patients, the postoperative mRS:0-2 score was defined as advantageous. In this study, there was no significant difference in the degree of neurological functional recovery between the two groups. In summary, it shows that the application of FDD in the treatment of intracranial aneurysms not only maintains good safety but also improves the safety of treatment.

The research compared the clinical efficacy and safety of FDD and CET in hospitalization and long-term follow-up in the treatment of intracranial aneurysms by meta-analysis, and to provide more basis for the choice of treatment of intracranial aneurysms. However, this study also has some limitations. Meta-analysis itself has some limitations, and the reliability of its results depends excessively on the quality of the included literature. although all the articles included in this study are of high quality evaluated by NOS, the literature are retrospective studies lack of randomized controlled studies (RCT), future clinical studies should take more prospective studies, perfect randomized controlled trial design and implementation. And analyze it to get more accurate and persuasive results.

Conclusions

In this meta-analysis, we analyzed the safety and efficacy of FDD in the treatment of intracranial aneurysms. The complete occlusion rate of intracranial aneurysms was higher than that of the CET group, and the retreatment rate of intracranial aneurysms was lower than that of the CET group. There is no significant difference in security between FDD and CET.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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