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Flow diversion versus parent artery occlusion with bypass in the treatment of complex intracranial aneurysms: Immediate and short-term outcomes of the randomized trial

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ABSTRACT

Objective: We performed prospective randomized comparison of clinical and surgical outcomes of flow diversion versus PVO and bypass in patients with complex anterior circulation aneurysms.
Patients and methods: Open, prospective, randomized, parallel group, multicenter study of complex intracranial aneurysms treatment was conducted. Patients with complex intracranial aneurysms of anterior circulation with neck is more than 4 mm wide, dome/neck ratio is equal or less than 2:1, which is suitable for flow diversion and occlusion with bypass were included in the study. A total of 111 potential participants were enrolled since March 2015. Additional propensity score matching was performed with 40 patients in each group selected for analysis.
Results: 39 out of 40 patients (97.5%) from matched FD group reached good clinical outcome.

In the matched bypass group acceptable outcome was achieved in 32 (80%) out of 40 patients (difference between groups $p = 0.029$). The morbidity and mortality rates were 15% and 5%, respectively. Difference in the rates of favorable outcomes, compared by $\chi 2$ met statistical significance ($p = 0.014$). The rate of complete aneurysm occlusion at 6 months was 42.5% in the FD group and 95% in surgical group ($p < 0.0001$). The rate of complete occlusion at 12 months was 65% in the FD group and 97.5% in surgical group. The difference between groups was still significant ($p = 0.001$). There were no significant differences between groups by occurrence of ischemic ($p = 0.108$) and hemorrhagic ($p = 0.615$) complications.
Conclusion: The study demonstrated superior clinical outcomes for endovascular flow diversion in comparison with bypass surgery in treatment of complex aneurysms. Though, both techniques grant similar percentage of major neurologic complications and comparable cure rate for cranial neuropathy. Nevertheless, flow diversion is associated with significantly lower early obliteration rate, thus possesses patient for risks of prolonged dual antiplatelet regimen and delayed rupture. Hence, it’s important to stratify patient by the natural risk of aneurysm rupture prior to treatment selection.

Abbreviations: ACA, anterior cerebral artery; AcomA, anterior communicating artery; BTO, balloon occlusion test; CTA, computed tomography angiography; DAT, double antiplatelet therapy; DSA, digital subtraction angiography; DWI, diffusion weighted image; ECA-M2, external carotid artery-to-M2 segment of middle cerebral artery (bypass); FD, flow-diverter; FIAT, flow diversion for intracranial aneurysms (trial); FRED, Flow-Redirection Endoluminal Device; ICA, internal carotid artery; ICG-VA, indocyanine green videoangiography; LTA, light transmission aggregometry; MCA, middle cerebral artery; MRI, magneto resonance imaging; mRS, modified Rankin Scale; PAO, parent artery occlusion; PED, Pipeline Embolization Device; PSM, Propensity Score Matching; PVO, parent vessel occlusion; SAC, stent-assisted coiling; SCAT, study of complex intracranial aneurysm treatment; SSEP, somatosensory-evoked potential

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1. Introduction

Complex intracranial aneurysms include giant aneurysms (maximum dome size exceeds 25 mm), fusiform or blister morphology, wide-necked aneurysms (dome/neck ratio more than 1.5:1), lesions with side branch originating from the neck or sac, those with a significant thrombus in the lumen and considerable atherosclerotic changes in the neck [1]. It is known that the mortality-morbidity rate for giant intracranial aneurysms is oscillating around 15–25% [2–5]. Despite improvements in endovascular and microsurgical techniques, treatment of complex intracranial aneurysms remains challenging. Such aneurysms cannot be occluded by direct clipping, and endovascular coiling requires complex assisting techniques.

Hunterian proximal occlusion is a relatively simple technique that has been used in an attempt to divert flow away from the aneurysm and to induce thrombosis [6]. Despite that Hunterian ligation is very effective, though it is not possible to sacrifice artery in all patients. Different bypass techniques are required to prevent ischemic complications in patients with insufficient flow through communicating arteries after ligation. The risk of ischemic complications exists even in patients with negative balloon test occlusion test (BTO) [7–10]. A plenty of series have been published, which proves the efficacy and safety of parent artery occlusion (PAO) with bypass in treatment of complex aneurysms [9,11–22].

Flow diverters have been approved for the treatment of large and giant aneurysms of cavernous carotid [23,24]. Indications to diverters is expanding to blister, bifurcation [25], distal [26] and posterior circulation [27] aneurysms. However, the results of FIAT trial have showed that flow diversion is not as safe and effective as hypothesized with 5.3% rate of morbidity and 10.7% rate of mortality [28].

We performed prospective randomized comparison of clinical and surgical outcomes of flow diversion versus PVO and bypass in patients with complex anterior circulation aneurysms. In the current study we tested the hypothesis that implantation of flow-diverter provided better clinical outcome in comparison with PAO and bypass.

2. Materials and methods

Study of complex intracranial aneurysms treatment (SCAT) was open, prospective, randomized, parallel group, 1:1 trial with superiority design, conducted in 2 neurosurgical centers in Novosibirsk (Russia). Patients with anterior circulation complex aneurysms with neck wider than 4 mm, where dome/neck ratio $\leq$2:1, that were suitable for flow diversion and occlusion with bypass were included and not eligible for coiling or direct clipping.

Potential participants were identified on the basis of digital subtraction angiography (DSA) or CT-angiography (CTA). There were few exclusion criteria: subarachnoid hemorrhage less than 30 days before admission; any contraindications to endovascular or open surgery; atypical aneurysms (mycotic, flow-related in patients with arterio-venous malformations, traumatic and false aneurysms); informed consent refusal; unavailability of follow up.

We performed sample size calculation before initiation of the study. The difference in favorable clinical outcomes was considered as 20% on the basis of previously published large case series. Thus, assuming 10% follow up loss, 110 patients (55 in each group) were required to achieve the Power = 90%. Unfortunately, we have found differences between groups by major demographic and angiographic baseline characteristics. Our results on 110 patients demonstrated 24% difference between groups, therefore we decided to perform PSM (propensity score matching) to minimize accidental bias. The power of study after PSM was near 85%.

Research team (RK, KO, AD) was responsible for enrollment of patients and randomization process. A total of 111 potential participants were enrolled since March 2015. The protocol of study was approved by Local Ethics Committee and published on clinicaltrials.gov (Identifier NCT03269942). Flow chart of study is presented in Fig. 1.

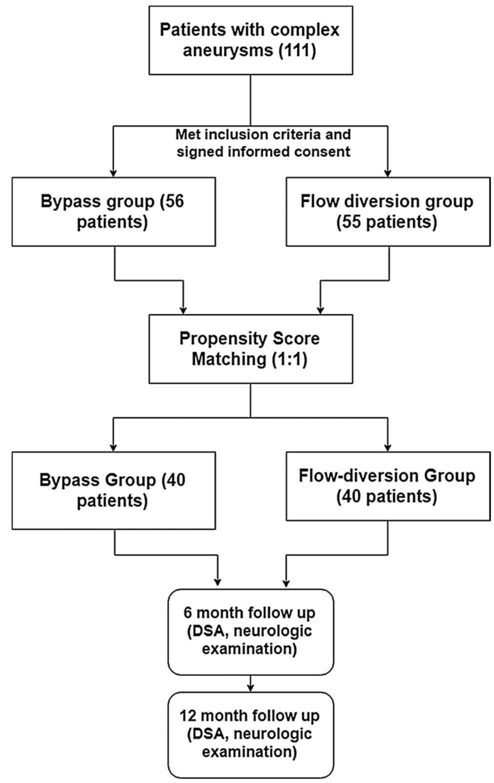

Fig. 1. Flow diagram of study.

Centralized randomization process was provided by sealed envelopes method. 55 patients were randomized into flow diversion group and 56 patients – into PAO with bypass group. After enrollment of patient and comparing baseline characteristics the statistical significant difference between groups was found by age (p = 0.03) and neck size (p = 0.05). The propensity score with 1-to-1 nearest neighbor caliper matching without replacement was used to minimize accidental bias for all major clinical and angiographic characteristics (Fig. 2). Equal groups with 40 patients in each were selected after propensity score matching. The baseline characteristics of patients presented in Table 1.

Written informed consent was provided by each patient. Patients undergoing FD treatment received double antiplatelet therapy (DAT), with baby aspirin and loading dose of clopidogrel 600 mg once followed by 75 mg daily. We assessed platelet response using light transmission aggregometry (LTA) and VerifyNow System (Accriva Diagnostics, San Diego, California). The clopidogrel non-responders received ticagrelor 90 mg twice a day. We did not perform adjunctive coiling in FD cases.

Bypass patients received baby aspirin for 3 days preoperatively. We did not use anticoagulation drugs after procedure. We did not routinely perform BTO due to high rate of false-negative results [7–10]. Operations were accompanied with neurophysiologic somatosensory-evoked potentials (SSEP). High-flow shunts were performed using radial artery graft. We routinely evaluated the graft patency using indocyanine green videoangiography (ICG-VA) and ultrasound flowmeter as described by authors [29–31].

After 6 and 12 months post-operatively we assessed patient mRS score, cross-sectional and angiographic data. The primary end point was the rate of neurological deterioration. We recorded neurological morbidity when the mRS score increased by more than 1 or mRS $\geq$ 4 was achieved. Secondary endpoints included the rates of aneurysm total occlusion, major stroke or neurological death related to the index aneurysm.

The descriptive data are represented as a median (first quantile-third quantile) for non-normal distribution. The categorical and rank

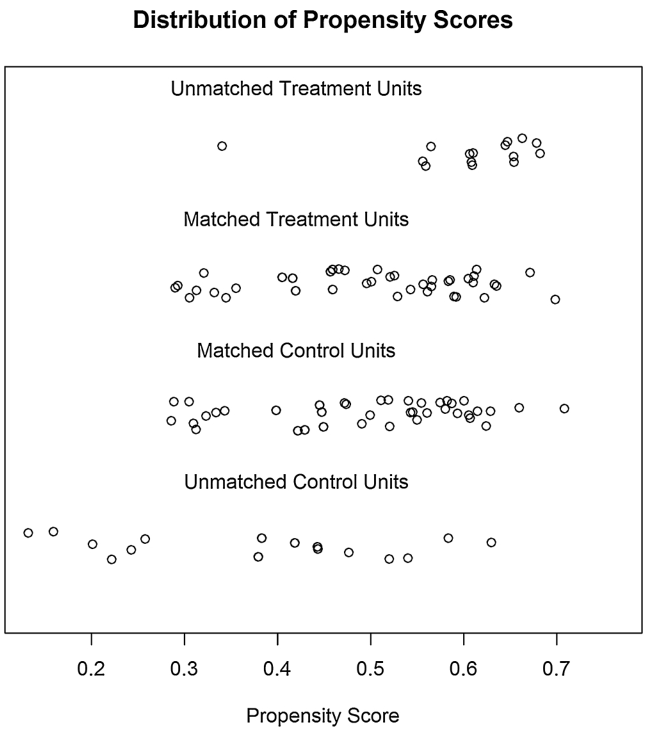

Fig. 2. Visual presentation of patients distribution before and after PSM.

Table 1
Baseline characteristic of patients after propensity score matching.

Characteristic	Bypass	Flow diversion	P value
Age	53.5 (47.5–59.25)	54.5 (47–58.5)	0.732
Gender (female/male)	29 (72.5%)/11 (27.5%)	31 (77.5%)/9 (22.5%)	0.796
Aneurysm location			0.410
- ACA	3 (7.5%)	1 (2.5%)	
- ICA	22 (55%)	27 (67.5%)	
- MCA	15 (37.5%)	12 (30%)	
Aneurysm side (left/right)	21 (52.5%) / 19 (47.5%)	21 (52.5 %)/ 19 (47.5%)	1.000
Aneurysm morphology			
- fusiform	8 (20%)	8 (20%)	1.000
- saccular	32 (80%)	32 (80%)	
Aneurysm maximum size (by MRI)	12 (9–16.75)	15 (9–19.25)	0.415
- small (less than 10 mm)	1 (2.5%)	2 (5%)	0.500
- big (less than 25 mm)	28 (70%)	23 (57.5%)	
- giant (25 mm and more)	11 (27.5%)	15 (37.5%)	
Aneurysm maximum size (by DSA/CTA)	15 (12–19.75)	18 (12–23.5)	0.424
Aneurysm's neck size	6 (3–7)	6 (3.75–7)	0.609
Partial thrombosis of aneurysm	28 (70%)	15 (37.5%)	0.007
Previous rupture	2 (5 %)	7 (17.5%)	0.154
Cranial neuropathy	21 (52.5%)	9 (22.5%)	0.095
mRS on admission			
- mRS 0	12 (30%)	10 (25%)	0.280
- mRS 1	23 (57.5%)	25 (62.5%)	
- mRS 2	5 (12.5%)	2 (5%)	
- mRS 3	0 (0%)	3 (7.5%)	

data are represented as a number (percentage of total). The Mann–Whitney U-test; χ2 test or Fisher's exact test were used for comparison. The Kaplan–Meier model, log-rank and Gehan-Wilcoxon test was employed to analyze the achievement of target indicators. Kendall rank correlation coefficient has been used to define correlation between parameters and univariate logistic regression analyses were used to find predictors. Propensity score with 1-to-1 nearest neighbor caliper matching without replacement was used to minimize accidental bias for all major clinical and aneurism characteristics.

All the reported P values were based on two-tailed significance tests; P values < 0.05 were considered statistically significant. We used the RStudio software version 1.0.136 (Free Software Foundation, Inc., Boston, USA) with R packages version 3.3.1 (The R Foundation for Statistical Computing, Vienna, Austria) for the analyses.

3. Results

3.1. Patients and aneurysms

Between March 2015 and December 2017, 111 patients who met the inclusion criteria, were enrolled into the study. After propensity score matching, 40 patients in each group were included into analysis. The median age of patients was 53.5 (IQR, 47.5–59.25) in bypass group and 54.5 (IQR, 47–58) in flow diversion group. Twelve months follow-up was available for all patients. The patients had following presentations of preoperative symptoms: cranial neuropathy (16 patients in bypass group and 9 patients in flow diversion group), hemiparesis (2 patients in bypass group and 3 patients in flow diversion group), epilepsy (3 patients in bypass group and 1 patient in flow diversion group) and aphasia (1 patient in flow diversion group). Nine patients had a history of rupture (7 in flow diversion group and 2 in group of bypasses). The distribution of aneurysms by segments were as follows: A2 segment of ACA (anterior cerebral artery) (1 patient), AcomA (anterior communicating artery) (3 patients), cavernous carotid (29 patients), ophthalmic segment of ICA (9 patients) communicating segment of ICA (internal carotid artery) (11 patients), M1 segment (20 patients) and M2 segment of MCA (middle cerebral artery) (7 patients). The median size of aneurysm by MRI was 12 (IQR, 9–16.75) in bypass group and 15 (IQR, 9–20.5) in group of flow diversion. The distribution of aneurysms is presented on Fig. 3.

3.2. Interventions

In the matched FD group 35 patients were treated with single device and 5 patients with two devices. Total 45 devices were used: FRED (Flow-Redirection Endoluminal Device; MicroVention, Inc., Tustin, CA; n = 10), p64 Flow Modulation Device (Phenox, Bochum, Germany; n = 3), Pipeline Flex Embolization Devices (PED; Medtronic, MN, USA; n = 4) and Pipeline Embolization Devices (Medtronic, MN, USA; n = 28). Six patients failed previous coiling. Intraoperative technical adverse events occurred in 6 cases (15% of primary procedures): two parent vessel dissections treated with balloon inflation, one distal MCA embolism treated with thrombolysis and one case of suboptimal stent

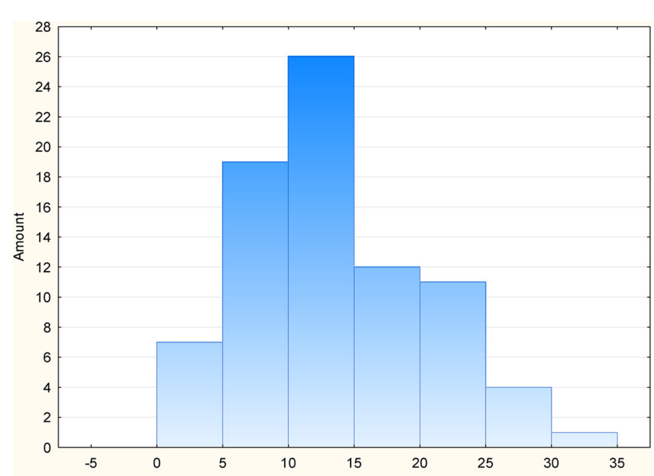

Fig. 3. Distribution of aneurysms by size on MRI.

opening treated with balloon inflation as well. None of the above events caused any clinical consequences. Carotid-cavernous fistula occurred in one case due to intraoperative rupture of giant cavernous aneurysm which was coiled successfully.

There were 40 bypass procedures in the matched cohort: high-flow bypass (n = 20; 50%), double-barrel bypass (n = 7; 17.5%), low flow bypass (n = 4; 10%), and in situ bypass (n = 9; 22.5%). High flow bypass was performed using radial artery graft in all cases. Trapping was performed in 15 cases (37.5%), proximal ligation – 9 cases (22.5%), distal ligation in 1 patient with fusiform M1 aneurysm (2.5%) and in-situ bypass in 14 patients (35%). One bypass procedure has failed. Median time of temporary occlusion during bypass reached 33.5 min (IQR, 28.5–41). Adjunctive low flow bypass was created in 17 cases of high-flow revascularization (85%).

3.3. Primary outcomes

39 out of 40 patients (97.5%) from matched FD group reached good clinical outcome. Out of 14 symptomatic patients, allocated to this group 5 (35.8%) became completely asymptomatic, 2 (14.2%) improved, 6 (42.8%) remained symptomatic and one patient (7.2%) developed early postoperative perforator infarct, that rendered him dependent. In the matched bypass group acceptable outcome was achieved in 32 (80%) out of 40 patients (difference between groups p = 0.029). The morbidity and mortality rates were 15% and 5%, respectively. Out of 21 symptomatic patients from bypass group 9 (42.8%) became completely asymptomatic, 4 (19%) remained stable and 8 (38.1%) deteriorated. Difference in the rates of favorable outcomes, compared by χ^2 met statistical significance (p = 0.014).

3.4. Secondary outcomes

The rate of complete aneurysm occlusion at 6 months was 42.5% in the FD group and 95% in surgical group ($p < 0,0001$). In one patient with fusiform M1 aneurysm we performed high-flow ECA-M2 bypass with distal ligation. Near-total occlusion was achieved in 1 patient at 6 months, however he met total occlusion at 12 months after discontinuing antiplatelets.

The rate of complete occlusion at 12 months was 65% in the FD group and 97.5% in surgical group. The difference between groups was still significant (p = 0.001). In the FD group 8 patients were retreated at follow up due to non-occlusion or intrastent stenosis. Retreatment rate was significantly higher in the FD group (p = 0.02).

The rate of total major complications was 22.5% in surgical group (6 ischemic and 3 hemorrhagic events out of 40 patients) and 5% in FD group (1 ischemic and 1 hemorrhagic events out of 40 patients) during follow up period (p = 0.048). Early bypass thrombosis occurred in 6 patients (15%). All hemorrhagic complications in surgical group occurred before postoperative day 3.

Despite lower occlusion rates in the FD group, there were no cases of late hemorrhage in this group. The only ischemic complication in this group was perforator infarction.

3.5. Predictors of outcomes

The primary analysis was intention-to-treat and involved patients who were included in study after PSM. Univariate analysis has demonstrated that partial thrombosis of the index aneurysm is an independent predictor of aneurysm obliteration (OR = 0.3, p = 0.019) (Table 2), while in situ bypass (OR = 8.375, p = 0.015), prolonged temporary vessel occlusion (OR = 1.07, p = 0.015) and situations demanding protective bypass (OR = 4.911, p = 0.003) are the predictors of ischemic complications (Table 4). There were no predictors of hemorrhagic complications (Table 3). The predictors of unfavorable neurological outcome at 12 months follow-up were: in situ bypass (OR = 10.5, p = 0.004), protective bypassing (OR = 4.354, p = 0.003), prolonged temporary vessel occlusion (OR = 1.08, p = 0.007) (Table 5).

Table 2
Predictors of complete aneurysm occlusion in 12 months.

predictor	Odds Ratio	CI 97.5%	P value
age	0.97	0.926–1.015	0.178
gender	0.678	0.142–2.443	0.58
localization	1.364	0.488–3.873	0.553
ICA	1.026	0.336–3.349	0.965
MCA	1.2	0.366–3.695	0.754
side	0.581	0.179–1.759	0.345
fusiform morphology	0.465	0.137–1.714	0.227
size by MRI	1.166	0.405–3.324	0.772
Small	2.033	0.091–22.633	0.573
Big	0.643	0.21–2.023	0.439
Giant	1.389	0.421–4.312	0.574
neck size	1.004	0.861–1.171	0.954
partial thrombosis	0.3	0.105–0.801	0.019
ruptured aneurysms	2.192	0.42–9.537	0.309
cranial neuropathy	0.248	0.037–0.995	0.082
mRS before operation	1.484	0.689–3.187	0.303
mRS 0	Ref		
mRS 1	0.791	0.26–2.476	0.679
mRS 2	0.633	0.032–4.114	0.683
mRS 3	8.857	0.796–198.677	0.083
2 or more flow diverters	2.857	0.352–18.868	0.274
type of bypass			
High-flow bypass	0.154	0.008–0.849	0.08
Double-barrel bypass	0.633	0.0320–4.114	0.683

Table 3
Predictors of hemorrhagic complications.

predictor	Odds Ratio	CI 97.5%	P value
age	1.014	0.934–1.137	0.768
localization	0.878	0.135–5.687	0.889
ICA	1.957	0.238–40.563	0.569
MCA	0.641	0.031–5.291	0.706
side	1.111	0.128–9.651	0.918
size by MRI	6.663	0.87–137.135	0.104
big	0.173	0.008–1.429	0.137
giant	6.913	0.836–143.853	0.102
neck size	1.206	0.907–1.662	0.215
partial thrombosis	2.7	0.329–55.922	0.399
cranial neuropathy	7.364	0.889–153.353	0.091
type of bypass	1.444	0.669–3.145	0.329
High-flow	3.222	0.366–28.458	0.259
Intra-intracranial	2.833	0.132–25.393	0.391
protective bypass	2.763	0.669–9.972	0.117
time of temporary clipping occlusion	1.034	0.978–1.104	0.261
trapping	4.846	0.542–43.52	0.131
remodelling	1.615	0.077–13.797	0.688
technical adverse events	3.889	0.177–36.418	0.27

4. Discussion

We analyzed prospective data comparing outcomes of flow diversion procedure and PAO with bypass for treatment of complex anterior circulation aneurysms. Flow diversion demonstrated better clinical outcomes at the follow-up. However, follow-up imaging at both 6 and 12 months demonstrated significantly higher aneurysm total occlusion rate in surgical group.

This trial was the first one to compare flow diversion versus microsurgery, to our knowledge. It is known anterior and posterior circulation aneurysms had different natural history, clinical, surgical outcomes and prognosis [32]. Because of this fact we decided to include only aneurysms of anterior part of Willis circle. To prevent selection bias and insures against the accidental bias propensity score matching was performed.

Table 4
Predictors of ischemic complications.

predictor	Odds Ratio	CI 97.5%	P value
Age	1.029	0.96–1.128	0.471
Gender	4.75	0.956–26.264	0.056
Localization	0.591	0.133–2.431	0.47
ICA	0.83	0.171–4.471	0.816
MCA	0.768	0.105–3.848	0.762
ACA	3.889	0.177–36.418	0.27
Side	0.814	0.152–3.943	0.797
Fusiform morphology	1.552	0.239–30.48	0.694
Size by MRI	0.993	0.217–4.333	0.993
small	Ref		
big	0.391	0.072–1.902	0.242
giant	1.63	0.301–7.984	0.543
Neck size	0.942	0.749–1.17	0.589
Partial thrombosis	1.162	0.24–6.248	0.851
Cranial neuropathy	0.87	0.118–4.372	0.873
mRS before operation	0.658	0.175–1.994	0.498
mRS 0	Ref		
mRS 1	0.467	0.087–2.266	0.341
mRS 2	1.861	0.091–13.753	0.593
Type of bypass			
High-flow bypass	2.471	0.45–12.303	0.266
Intra-intracranial bypass	8.375	1.394–47.973	0.015
Protective bypass	4.911	1.734–15.601	0.003
Time of temporary clipping	1.08	1.024–1.165	0.015
Occlusion			
full	0.702	0.036–4.587	0.752
proximal	3.771	0.48–21.591	0.152

Table 5
Predictors of unfavorable clinical outcomes.

predictor	Odds Ratio	CI 97.5%	p value
Age	1.039	0.973–1.131	0.31
Gender	2.75	0.619–11.628	0.165
Localization	0.785	0.214–2.781	0.707
ICA	0.767	0.187–3.333	0.71
MCA	0.979	0.193–4.061	0.978
ACA	2.833	0.132–25.393	0.391
Side	0.514	0.102–2.11	0.373
Fusiform morphology	2.143	0.352–41.349	0.488
Size by MRI	1.202	0.317–4.51	0.783
small	4.312	0.188–50.282	0.254
big	0.409	0.093–1.678	0.211
giant	1.782	0.407–7.373	0.421
Neck size	0.976	0.8–1.185	0.808
Partial thrombosis	1.838	0.448–9.246	0.415
Cranial neuropathy	1.114	0.219–4.639	0.886
mRS before operation	0.769	0.249–2.031	0.622
mRS 0	Ref		
mRS 1	0.814	0.199–3.534	0.773
mRS 2	1.354	0.067–9.467	0.791
Type of bypass	2.048	1.2–3.813	0.013
High flow bypass	2.75	0.619–11.628	0.165
Intra-intracranial bypass	10.56	2.085–54.916	0.004
Protective bypass	4.354	1.659–12.903	0.003
Time of temporary clipping	1.08	1.029–1.155	0.007
Occlusion			
full	1.275	0.176–6.042	0.777
proximal	2.612	0.345–13.668	0.283

Comparing the results of flow diversion and surgical revascularization, better clinical outcomes after 12 months the FD group were obvious (97.5% compared to 80% mRS favorable outcomes, $p = 0.014$). Despite better clinical results, flow diversion provided total occlusion rate of only 65% at 12 months. We suggest that this is due to short follow-up in our study and high percentage of the aneurysms with positive non-occlusion predictors in FD group (side branch originating from sac, bifurcation and distal aneurysms). This factor is unavoidable consequence of the inclusion criteria built for aneurysms with complex morphology approachable by both methods. We can suggest that this is due to relatively short follow-up in our study and relatively high percentage of the aneurysms with positive non-occlusion risk factors (side branch originating from sac, bifurcation and distal aneurysms). It is known that delayed rupture of aneurysms after FD implantation is estimated as less than 1% [33].

Intraoperative or early postoperative hemorrhagic complications occurred in 2.5% and 7.5% in FD and bypass groups respectively. Postoperative ischemic complications occurred in 2.5% and 15% in FD and bypass groups respectively. We evaluated postoperative diffusion weighted images (DWI) to detect clinically silent ischemia. Brasiliense et al [34] reported 62.7% rate of silent ischemic events after PED. Recent meta-analysis [35] demonstrated that FD implantation lead to DWI positive events in 67% of procedures. DSA at 6 months allowed to find clinically silent intrastent stenosis in 7.5%. None of intrastent stenosis led to ischemia. High rate of bypass thrombosis (15%) at 12 months follow up is predominantly related to supraclinoid ICA aneurysms (3 out of 6 aneurysms). Both lethal cases occurred due to early bypass thrombosis, but there was no significant difference between groups in the rate of ischemic events otherwise.

According to our results, in situ bypass and protective bypass were associated with unfavorable clinical outcomes. Due to technical complexity, in situ bypass is associated with an increased risk of complications. On the other hand, protective bypass was used in knowingly more challenging cases which also could contribute to higher complication rate among these patients. Additional cause of ischemic complications was prolonged anastomosing time.

Partial thrombosis of giant intracranial aneurysms occurs in up to 60% of such lesions [36]. Despite this finding complicates microsurgical treatment, our study demonstrated that partial thrombosis is an independent factor of complete aneurysm obliteration. Partial thrombosis of index aneurysm is a predictor of non-occlusion in coiled and clipped aneurysms. However, it is not known to be a risk factor of non-occlusion in flow diversion cases. The majority of partially thrombosed aneurysm at baseline were in the bypass group, which may explain the positive predictive role of partial thrombosis in aneurysm occlusion, according to our series.

According to one recent meta-analysis, PVO with extra- to intracranial bypass in cavernous aneurysms resulted in total occlusion of 93% of lesions with morbidity and mortality 11% and 7% respectively [37] while in our FD cohort 8 of 13 patients reached total occlusion at 12 months with only 1 intraoperative complication which was managed instantly and resulted in no clinical consequences. This corroborates with previously published experience [24,33,38,39,23]. In contrast, PAO resulted in 2 ischemic strokes and 1 hemorrhagic complication in 16 cases. Obviously, implantation of flow-diverters is advantage over PAO with bypass for complex cavernous aneurysms.

Large and giant paraclinoid aneurysms is often associated with cranial neuropathy. According to the literature, the rate of cranial neuropathy regression after flow diversion is comparable to that after microsurgery [40–42]. Our results are in accordance with previously published experience as 5 of 9 patients (55%) in FD group demonstrated complete resolution of symptoms. In our microsurgery cohort there was complete resolution of neuropathy in 9 of 16 (56.2%) of patients. We found no significant difference in terms of cranial neuropathy resolution between the groups and thus do not consider this symptom as an absolute indication for microsurgery. Moreover, all of 5 ophthalmic aneurysms treated by implantation of flow diverter results in 100% obliteration of aneurysm in 12 months without side branch occlusion or any visual disturbances.

The recent studies prove the efficacy and safety of flow diversion in supraclinoid ICA with 82.7% rate of complete aneurysm occlusion and 96.5% patency of anterior choroidal artery [43]. In the microsurgical group, both cases of communicating segment aneurysms were associated with postoperative ischemic strokes due to early graft thrombosis. We consider it as the most unfavorable location for PVO and bypass. In the FD group the aneurysm total occlusion rate was low (4 out of 9 patients, 44.4%), but there were no ischemic or hemorrhagic complications.

For MCA aneurysms, under certain conditions, results of microsurgery remain superior to those of endovascular therapy due to the fact that those aneurysms are amenable for direct clipping with or without bypass [44]. While for FD recent meta-analysis reported the low rate of occlusion (78.7%) with 20.7% treatment-related complication rate and 2% mortality [45]. In our study, treatment of 12 MCA aneurysms by FD resulted in complete occlusion of aneurysm in 5 patients (41.6%) at 6 month and in 8 patients (66,6%) at 12 month follow up. Moreover, the only complication that led to severe disability in FD group happened during MCA aneurysm treatment. In comparison, in our study, bypass for MCA aneurysm provided 86.6% occlusion rate in 6 months and 93.3% occlusion in 12 months with only one minor adverse event.

There are many recent reports about safe and efficient off-label use of flow-diverting stents in treatment of ACA aneurysms [26,46–49]. Unfortunately our study included only 4 patients with complex ACA aneurysms only one of which was treated with flow diverter. Despite a low number of patients there were 1 case of mortality after PAO with revascularization due to thrombosis of bypass and fatal ischemic stroke. The only case of flow diversion for giant anterior communicating artery aneurysms ended with complete aneurysm occlusion at 6 months without neurological deterioration. Literature review and our previous experience off-label usage of flow-diverters for ACA aneurysms proves the efficacy and safety of this procedure [50,26]. The low amount of patients in each groups didn't allow to draw any statistically based conclusions.

During the recent years, with appearance of low profile and neck-bridging devices, stent or device assisted coiling (SAC) for complex aneurysms became the reasonable option of treatment [51]. However, the evidence for superiority of SAC over FD is absent. Nevertheless, a literature data supports the assumption that both methods are at least even in terms of safety and efficacy for small aneurysm treatment [52]. Comparison of SAC vs FD or bypass is an interesting scientific possibility, that requires another study and thus cannot be covered in our paper.

5. Limitations

The main limitation of our study is the short follow-up period, when evaluation of the aneurysm course requires longer observation. The highest total occlusion rates after flow diversion are observed at 1.5-3 years postoperatively, while the radicalism of open surgery may only decrease over the time. We intend to continue our study to report occlusion rate in long-term observation, which we expected is going to be much higher. Other limitations of our study were heterogeneity of included aneurysms (size, location, morphology, rupture status) and diversity of applied surgical techniques (different types of bypasses and aneurysm exclusion techniques in microsurgical group and different flow-diversion devices in endovascular group). The patients were enrolled only in two centers and treated by two leading surgeons (KO, AD).

6. Conclusion

The study demonstrated superior clinical outcomes for endovascular flow diversion in comparison with bypass surgery in treatment of complex aneurysms. Though, both techniques grant similar percentage of major neurologic complications and comparable cure rate for cranial neuropathy. Nevertheless, flow diversion is associated with significantly lower early obliteration rate, thus possesses patient for risks of prolonged dual antiplatelet regimen and delayed rupture. Hence, it's important to stratify patient by the natural risk of aneurysm rupture prior to treatment selection.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs,
materials, or devices described in this article.

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