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Delayed hemorrhagic complications after flow diversion for intracranial aneurysms: a literature overview

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Abstract

Background—Delayed aneurysm rupture and delayed intraparenchymal hemorrhages (DIPH) are poorly understood and often fatal complications of flow diversion (FD) for intracranial aneurysms. The purpose of this study was to identify risk factors for these complications.

Materials and Methods—We performed a systematic review on post-FD delayed aneurysm rupture and DIPH. For each reported case we collected the following information: aneurysm location, size and rupture status, type of flow-diverter used, timing of the hemorrhage, and neurological outcome. We reported descriptive statistics of patients suffering DIPH and delayed aneurysm rupture to determine if there were any characteristics consistently present among patients with these complications.

Results—We identified 81 delayed aneurysms ruptures and 101 DIPH.

76.6% (45/58) of the delayed ruptures occurred within one month. The prognosis of delayed ruptures was poor, with 81.3% (61/75) experiencing death or poor neurological outcome. Giant aneurysms accounted for 46.3% of ruptures (31/67). 80.9% (55/68) of these aneurysms were initially unruptured. 17.8% (13/73) of the delayed ruptured aneurysms had prior or concomitant coiling. DIPHs were ipsilateral to the treated aneurysm in 82.2% (60/73) of cases. 86.0% (43/50) of the DIPH occurred within one month after FDS. Combined morbidity/mortality rate was 68.5% (50/73 following DIPH. 23.0% of DIPHs (14/61) occurred in patients with giant aneurysms.

Conclusions—Our study demonstrates that giant aneurysms represent almost 50% of delayed aneurysm ruptures in the flow-diverter literature. About 20% of delayed ruptures occurred despite associated coiling. A substantial proportion of DIPHs occur early following FDS treatment of giant aneurysms.

INTRODUCTION

Flow diverters are now an established tool for the treatment of intracranial aneurysms with promising clinical and angiographic outcomes[1-3]. However, these devices are not without

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

severe complications, with perioperative morbidity and mortality rates ranging from 8-10%[4,5]. Major complications following flow diversion include ischemic stroke due to device occlusion or thromboembolic complications [6-9] as well as hemorrhagic complications including ipsilateral intraparenchymal hemorrhages and post-operative aneurysm rupture[10-14].

Little is known about the risk factors and mechanisms of these hemorrhagic complications [14,15,3,16,17]. The aim of this study was to systematically review the literature on post-flow diverter intraparenchymal hemorrhage and delayed target aneurysm rupture in order to determine what, if any, patient, procedural and aneurysm characteristics are associated with these complications. Especially, this study focused on aneurysm size to determine if giant aneurysm size is associated with higher risk of complications; also we focused on associated coiling to determine its ability to prevent delayed ruptures as previously suggested.

METHODS

Literature Search and Selection Criteria

We performed a MEDLINE search using the search terms Pipeline, Surpass, Silk, Flow Diverter, p64, FRED, aneurysm, complication, hemorrhage, subarachnoid hemorrhage, intraparenchymal hemorrhage. One author with three years of experience as a neurointerventional radiologist selected potentially relevant articles based on the title and abstract to identify articles reporting on complications related to flow diverter therapy. The author also searched the reference lists of retrieved articles and published review articles for additional studies to supplement the MEDLINE search. Case reports, case series and clinical trials were included in this review. We identified all patients with hemorrhagic complications following flow diverter treatment in the literature. Included hemorrhagic complications were delayed intraparenchymal hemorrhage (DIPH) and delayed aneurysm rupture. Hemorrhagic complications were considered delayed if the study reported the complication as a post-operative complication rather than an intraoperative complication. This definition excluded intra-operative hemorrhagic complications such as wire perforation. Delayed ruptures were defined as rupture of the target aneurysm after the deployment of the flow diverter whereas DIPH are intraparenchymal hemorrhages without aneurysm rupture.

Patient Characteristics and Outcomes

From each case of hemorrhage, we collected the following data: type of flow diverter device used, delay between the treatment and hemorrhage occurrence, initial rupture status of the target aneurysm, giant (>25 mm) size of the target aneurysm, associated coiling with flow diverter, location of the target aneurysms, location of the intraparenchymal hemorrhage in the same or different territory of the target aneurysm, and final clinical outcome. We removed duplicated cases.

Statistical Analysis

This study is a systematic review based primarily accumulation of individual cases of hemorrhagic complications accumulated in the literature. Because information on the total number of patients were not available in many cases, it was not possible to perform a formal

meta-analysis on the incidence and risk factors for these complications. Rather, we reviewed the literature to create a case series of patients suffering DIPH and delayed aneurysm rupture to determine if there were any patient, aneurysm, or procedural characteristics that were consistently present among patients with these complications. We report descriptive statistics only. No formal statistical analyses were performed.

RESULTS

Initial literature search yielded 443 articles. We identified 53 studies reporting 182 delayed hemorrhagic complications after flow diverters. Among those 182 hemorrhages, 81 were delayed aneurysms ruptures and 101 were DIPH without aneurysm rupture.

Delayed rupture of the index aneurysm

Thirty-five studies reported delayed ruptures of 81 index aneurysms after treatment with flow-diverters in 81 patients. Time from treatment to symptoms onset was reported for 58 cases (71.6%). Of these, delay to rupture was less than 1 day in 6 cases (10.3%), 1 to 7 days in 19 (32.8%), 7 days to 1 month in 20 (34.5%), more than one month in 13 (22.4%). Clinical outcome was available for 75 cases (92.6%). Of these, death occurred in 56 cases (74.7%), 5 (6.7%) had poor outcome and 14 (18.7%) had good outcome. Ruptures resulted in 6 direct carotid cavernous fistulas due to rupture of ICA aneurysms in the cavernous sinus.

The location of the index aneurysm was available for 54 cases (66.7%). Of these, the aneurysm was located in the anterior circulation in 41 (75.9%) (40 ICA and 1 MCA) and posterior circulation in 13 cases (24.1%). Aneurysm size was reported for 67 cases (82.7%). Of these, 31 (46.3%) were giant (>25 mm) and 36 (53.7%) were not. Of the 68 (83.9%) delayed ruptured aneurysms with reported initial rupture status, 13 (19.1%) were initially ruptured before the treatment and 55 (80.9%) were unruptured.

Use of coils was mentioned in 73 (90.1%) cases. Of these, coiling was performed in addition to flow-diverter treatment in 13 cases (17.8%) and flow-diverters were the only device used in the remaining 60 cases (82.2%). Flow-diverter devices used was specified for 64 (79.0%) of the 81 cases. Of these 33 (51.6%) were Pipeline, 29 (45.3%) were Silk and 2 (3.1%) were Surpass. Consistent information regarding patient antiplatelet regimens were not available in most studies. These results are detailed in Table 1.

Delayed intraparenchymal hemorrhage anatomically remote from the aneurysm

Thirty-four studies reported 101 DIPH in 101 patients treated with flow-diverters. DIPH location was reported for 73 (72.3%) of the 101 cases. Of these, DIPH was ipsilateral to the treated aneurysm for 60 (82.2%) cases and in another vascular territory in 13 (17.8%) cases. Time from treatment to symptoms onset was reported for 50 cases (49.5%). Of these, time to DIPH was less than 1 day in 12 (24.0%) cases, 1 to 7 days in 21 (42.0%), 7 days to 1 month in 10 (20.0%), more than one month in 7 (14.0%). Clinical outcome was available for 73 cases (72.3%). Of these, death occurred in 31 (42.5%) of the 101 cases, 19 (26.0%) had poor outcome and 23 (31.5%) had good outcome.

The location of the index aneurysm was available for 57 cases (56.4%). Of these, the aneurysm was located in the anterior circulation in 48 cases (84.2%) (45 ICA and 3 MCA) and posterior circulation in 9 (15.8%) cases. Aneurysm size was reported for 61 cases (60.4%). Of these, 14 (23.0%) were giant (>25 mm) and 47 (77.0%) were not. Of the 79 (78.2%) DIPHs with reported initial rupture status of the index aneurysm, 11 (13.9%) were initially ruptured before the treatment, 68 (86.1%) were unruptured.

Use of coils was mentioned for 37 (36.6%) cases. Of these, coil plus flow-diverter treatment was performed in 8 cases (21.6%) and flow-diverters were the only device used in the remaining 29 cases (78.4%). Flow-diverter device used was specified for 85 (84.2%) of the 101 cases. Of these 78 (91.8%) were Pipeline, 2 (2.4%) were Silk and 5 (5.9%) were Surpass. These results are detailed in Table 2.

DISCUSSION

Our study provides a broad overview of the clinical, anatomic and procedural characteristics of patients experiencing delayed aneurysm rupture or DIPH following flow diverter treatment of intracranial aneurysms. We found that approximately 80% of delayed aneurysm ruptures and DIPHs occurred within 30 days of the procedure. In general, patients suffering these complications do poorly with approximately 70-80% of patients with delayed aneurysm rupture or DIPH experiencing poor clinical outcome or death. 45% of patients experiencing delayed rupture had giant aneurysms suggesting that these aneurysms are at a higher risk of delayed rupture than small, medium or large sized aneurysms.

Interestingly, nearly 20% of aneurysms with delayed rupture had either previous or concomitant coiling suggesting that coil occlusion of these aneurysms is not always protective against delayed rupture. Intraparenchymal hemorrhages were ipsilateral to the treated aneurysm in 80% of cases and over 20% of cases involved treatment of giant aneurysms. Complications were not specific to any single device suggesting that flow diversion in and of itself is a potential risk factor for these complications. It is likely that most, if not all, patients were on dual antiplatelet therapy at the time of treatment and in the immediate post-operative period, however data on the exact antiplatelet regimen used and use of platelet testing were not consistently available.

Delayed aneurysm rupture

Post-treatment aneurysm rupture is a serious complication of flow diverter therapy. Despite the fact that numerous case series and case reports have reported on this complication, there continues to be controversy surrounding its origin [12,10]. Prior studies have suggested or demonstrated a higher risk of rupture in giant aneurysms [4,13,12,17]. In this current literature review, nearly 50% of delayed ruptures were from giant aneurysms, similar to the IntrePED study in which 3/5 spontaneous aneurysm ruptures occurred in giant aneurysms with the other 2 occurring in large aneurysms [17]. Indeed, when considering IntrePED as a “real life” setting of aneurysms treated with flow diverters, giant aneurysms made up only 16% of treated aneurysms in that series while they comprised 46% of cases with delayed aneurysm rupture in our literature review [17]. Nearly 20% of delayed ruptures occurred in previously ruptured aneurysms. In the IntrePED study, initially ruptured aneurysms

represented only 8.4% of the treated aneurysms and this higher representation of initially ruptured aneurysms in our study suggests a potential higher risk for delayed rupture[17].

The exact mechanism behind delayed aneurysm rupture is not well established. Some computational fluid dynamic studies have demonstrated that flow modifications after stent placement result in intra-aneurysmal pressure increases which can potentially lead to rupture, especially for giant aneurysms [11]. Other studies suggest a potential role of intra-aneurysmal thrombus in the pathophysiologic mechanism of aneurysm rupture as the intra luminal thrombus is a source of various proteases with high proteolytic activity which could participate in the degradation of the arterial wall and lead to aneurysm rupture[13,18-25]. Since giant aneurysms are generally more likely to have intraluminal thrombus, this mechanism could play a role in the delayed rupture of these aneurysms. Because of the higher risk of delayed rupture in giant aneurysms, some have recommended that giant aneurysms are treated with concomitant coiling and flow diverter treatment in order to protect the dome of the aneurysm in an attempt to prevent delayed ruptures[16,12,10,26]. Indeed, our study found that over 80% of aneurysm that ruptured post flow diverter treatment were not previously coiled. However, it is clear from our results that coiling is no panacea as 20% of aneurysms that experienced delayed rupture were coiled. It was not possible in our review to analyze the impact of the coils packing density since this information was not recorded in most of the included studies. Maybe a high density packing would be more protective against delayed rupture. Ultimately, aneurysm rupture following flow diverter therapy is a complex, multifactorial problem, and preclinical studies would be necessary to evaluate the mechanical and biological protective effects of associated coiling.

Delayed intraparenchymal hemorrhages

DIPH not associated with aneurysm rupture is another dreaded and poorly understood complication of flow-diverter treatment. Overall, occurrence rate of this complication is about 2-3%[4,17]. The mechanism for DIPH is unknown. Over 80% of DIPHs occurred in the vascular territory of the flow-diverter, tending to support a deleterious causal role of the device and/or the procedure itself. However, approximately 20% occurred in other vascular territories. This suggests that antiplatelet therapy (and potentially the variable response of patients to these agents) could play a role in DIPH as non-ipsilateral vascular territories are presumably free of any deleterious hemodynamic or ischemic complications from device placement. However, dual antiplatelet appears to be safer in the setting of secondary stroke prevention with an annual risk of major parenchymal hemorrhage around 1.5 % [27] as well as in the setting of stent-assisted coiling with 2.2% risk of hemorrhage [28]. Some have hypothesized that DIPH results from hemodynamic alterations from flow-diverter placement (i.e. Windkessel effect) [11,29,30]. Other hypotheses are hemorrhagic transformations of ischemic lesions induced by the flow diverter. However, despite post-procedural DWI lesions being quite common after flow diversion[31] previous studies have not definitively demonstrated co-location of ischemic lesions at the sites of hemorrhages[32]. Hu et al. suggested a potential association role of intraprocedural foreign body emboli due to shedding of certain catheter linings[33] however studies included in our analysis did not specify the devices used in each case.

In the studied population, 24% of the DIPH occurred within the first 24 hours of flow-diverter placement and 86% occurred within the first month. We did not note any particular anatomic location with a higher tendency for DIPH. Furthermore, 23.0% of the DIPH occurred in giant aneurysms, which appears to be a higher proportion than the proportion of giant aneurysms treated in “real world” settings (i.e. the IntrePED study) [17]. Based on this observation, we hypothesize that giant aneurysms may be at higher risk for DIPH[4]. There are a few putative explanations for why this may be the case. First, giant aneurysms are more likely require deployment of multiple flow diverters in order to achieve complete angiographic occlusion. Deployment of multiple flow diverters could prolong procedure time, increase platelet activation and potentially result in more substantial hemodynamic alterations than deployment of a single flow diverter[29,34]. In addition, hemodynamic alterations following treatment of a giant aneurysm may be more marked than when treating a small or medium sized aneurysm. Deployment of a flow diverter following treatment of a giant aneurysm could result in the sudden loss of a large capacitance chamber (i.e. the giant aneurysm) potentially resulting in cerebral hyperperfusion distal to the aneurysm as suggested by Chie et al (i.e. Windkessel effect). Similar hemodynamic alterations are seeing following surgical clipping of larger aneurysms[35].

Study limitations

Our study has limitations. This was a retrospective review of all previously published cases of delayed hemorrhages after flow diverter and is subject to both selection and publication bias. Since these complications are rare, most of the included cases were published as case-reports or in small retrospective series. Because of this, our study cannot adhere to the PRISMA guidelines [36]. It was not possible to determine the incidence of aneurysm rupture and DIPH. However, we were able to further characterize these complications. In many cases all the criteria we analyzed were not reported. Furthermore, several criteria with a potential impact on the occurrence of the hemorrhagic complications have not been analyzed because of a lack of these data in the included studies such as patient demographics, number of flow diverters, overlapping of devices, coils packing density, patient risk factors, platelet inhibition and treatment responsiveness.

CONCLUSION

This review of the literature of delayed hemorrhagic complications following flow diverter treatment demonstrated a number of interesting findings. Approximately 80% of patients experiencing these complications have poor clinical outcomes and approximately 80% of these complications occur within 30 days of treatment. Our study confirms a high correlation between delayed aneurysms ruptures and giant aneurysms but suggests that associated coiling doesn't avoid totally the risk for delayed ruptures with 20% of delayed ruptures in aneurysms with associated coiling. DIPH seems to be associated with giant aneurysms in our study, however the exact mechanism behind this is not understood. Further research is needed to determine which clinical and anatomic risk factors place patients at a higher risk of these complications so that appropriate risk modification measures can be put in place.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

FD	Flow-diverter
DIPH	Delayed Intraparenchymal Hemorrhage

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Table 1

Characteristics of delayed aneurysms ruptures.

Outcome		N (Total= 81)	Absolute %	Relative %
Device	Pipeline	33	40.74%	51.56%
	Silk	29	35.80%	45.31%
	Surpass	2	2.47%	3.13%
	Unknown	17	20.99%	
Rupture delay	< 1 day	6	7.41%	10.34%
	1-7 days	19	23.46%	32.76%
	7-30 days	20	24.69%	34.48%
	> 30 days	13	16.05%	22.41%
	Unknown	23	28.40%	
Initial status	Ruptured	13	16.05%	19.12%
	Unruptured	55	67.90%	80.88%
	Unknown	13	16.05%	
Associated coiling	Yes	13	16.05%	17.81%
	No	60	74.07%	82.19%
	Unknown	8	9.88%	
Giant size	Yes	31	38.27%	46.27%
	No	36	44.44%	53.73%
	Unknown	14	17.28%	
Final clinical outcome	Death	56	69.14%	74.67%
	Good	14	17.28%	18.67%
	Bad	5	6.17%	6.67%
	Unknown	6	7.41%	
Aneurysm location	ICA	40	49.38%	74.07%
	MCA	1	1.23%	1.85%
	BA	9	11.11%	16.67%
	Vert	4	4.94%	7.41%
	Unknown	27	33.33%	
CCF	Yes	6	7.41%	

Table 2

Characteristics of delayed intraparenchymal hemorrhages.

Outcome		N (Total=101)	Absolute %	Relative %
Device	Pipeline	78	77.23%	91.76%
	Silk	2	1.98%	2.35%
	Surpass	5	4.95%	5.88%
	Unknown	16	15.84%	
DIPH delay	< 1 day	12	11.88%	24.00%
	1-7 days	21	20.79%	42.00%
	7-30 days	10	9.90%	20.00%
	> 30 days	7	6.93%	14.00%
	Unknown	51	50.50%	
Initial status	Ruptured	11	10.89%	13.92%
	Unruptured	68	67.33%	86.08%
	Unknown	22	21.78%	
Associated coiling	Yes	8	7.92%	21.62%
	No	29	28.71%	78.38%
	Unknown	64	63.37%	
Giant size	Yes	14	13.86%	22.95%
	No	47	46.53%	77.05%
	Unknown	40	39.60%	
Ipsilateral	Yes	60	59.41%	82.19%
	No	13	12.87%	17.81%
	Unknown	28	27.72%	
Final clinical outcome	Death	31	30.69%	42.47%
	Good	23	22.77%	31.51%
	Bad	19	18.81%	26.03%
	Unknown	28	27.72%	
Aneurysm location	ICA	45	44.55%	78.95%
	MCA	3	2.97%	5.26%
	BA	9	8.91%	15.79%
	Vert	0	0.00%	0.00%
	Unknown	44	43.56%	