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Review Article

Flow diversion with the pipeline embolization device for patients with intracranial aneurysms and antiplatelet therapy: A systematic literature review

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ABSTRACT

Flow diversion with the Pipeline Embolization Device (PED) is reported as a safe and efficient treatment for patients with intracranial aneurysms; however, literature discussing the antiplatelet (APT) regimen used before and after the PED is limited. Our aim was to systematically review and summarize available data regarding the APT regimen and the platelet function test (PFT) that was used. We also sought to provide an overview of the aneurysm morphologies and adverse event rates associated with the PED use. This systematic review was conducted according to the PRISMA statement and eligible studies were identified through search of the PubMed and Cochrane databases. We reviewed 28 studies, involving 1556 patients that underwent aneurysm treatment with the PED. The preprocedural aspirin (ASA) 300- 325 mg (2-14 days) combined with clopidogrel 75 mg (3 to > 10 days) were used as a treatment strategy in 61.7% of patients and ASA 81 mg with clopidogrel 75 mg for 5–10 days for 27%. Patients who received low versus high dose pre-PED ASA, were at less risk for a hemorrhagic event (0.7% versus 3.3%, p = 0.053); however no statistical significance was reached. There was also lack of relationship between patients that received low versus high preprocedural ASA in terms of thromboembolic events. Regarding postprocedural APT, ASA (> 6 months) and clopidogrel (3- 12 months) was the regimen of choice for 93% of patients. Most studies conducted at least one PFT, most common being the VerifyNow. The most frequently reported target P2Y12 Reaction unit (PRU) and Aspirin Reaction Unit (ARU) values were < 230 and < 550 respectively. There was no statistically demonstrable difference in regards to thrombotic events between centers that conducted at least one PFT and centers that did not test their patients with a PFT. The overall rates of symptomatic thrombotic episodes were 6.6% and hemorrhagic were 3%. The pre- and post-PED APT dose and duration varies across different institutions. More prospective studies are needed to compare the efficacy of different APT agents and reach conclusions regarding use of PFT and platelet reaction values in order to decrease hemorrhagic and thromboembolic complications associated with the PED.

1. Introduction

Flow diverters and particularly the Pipeline Embolization Device (PED) (Covidien, Irvine, CA) have gained increasing attention since their approval by the Food and Drug Administration (FDA) in 2011. The PED is a microcatheter-delivered, self-expanding, cylindrical stent composed of a mesh of 48 individual cobalt chromium and platinum strands [1]. PED mechanism of action involves intrasaccular disruption of pulsatile blood flow, reaching the point of stagnation and thrombosis [2]. Patency of side branches and parent vessel is a prerequisite for PED to be effective [3]. The endovascular mesh possibly acts as a scaffolding for endothelial and neointimal overgrowth, which forms a contiguous layer that eventually covers the aneurysm neck entirely [4].

Use of PED was initially restricted only to large and giant wide-necked aneurysms arising from the petrous to the superior hypophyseal segment of the internal carotid artery [5]. A number of retrospective observational studies have been focused on PED efficacy and safety and on extending the indications of PED use [6–10]. The reported incidence

Abbreviations: APT, antiplatelet; ASA, aspirin; PED, Pipeline Embolization Device

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rate of major adverse events, such as central nervous system (CNS) thromboembolism and distal hemorrhages, is inconsistent across the literature. Many research attempts have been devoted to investigate possible contributors to this heterogeneity, concentrating mainly in the P2Y12 reaction unit (PRU), aspirin reaction unit (ARU), pre- and post-procedural antiplatelet (APT) dose and duration and various aneurysmal features [11,12].

In this systematic review, we sought to summarize the APT regimen, dosages and duration, and the frequency of the reported platelet testing, cut-off PRU and ARU values and the APT related adverse events as reported by different studies.

2. Material and methods

2.1. Search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. Eligible articles were identified through searches of the PubMed and Cochrane databases (last search date was May 4, 2017) by two independent reviewers (PT, KB). The following terms were utilized: “pipeline”, “silk flow diverter”, “flow redirection endoluminal device”, “flow diversion”, “flow diverter”, “anticoagulation”, “anticoagulant”, “aspirin”, “acetylsalicylic acid”, “ASA”, “heparin”, “enoxaparin”, “prasugrel”, “ticlopidine”, “plavix”, “clopidogrel”, “p2y12 inhibitors”, “ticagrelor”, “vitamin k antagonists”, “Coumadin”, “warfarin”, “antiplatelet”, “pradaxa”, “dabigatran”, “rivaroxaban”, “apixaban” in combination with Boolean operators AND and OR.

2.2. Study selection

Clinical studies published in English were considered eligible for this systematic review. The following exclusion criteria were followed during the selection process: i) studies including pediatric patients (< 18 years old), ii) experimental studies in animals, iii) papers referring to dissections and dissecting aneurysms treated with PED, iv) papers referring to types of flow diverters (e.g. FRED, SILK) other than PIPELINE, v) studies not specifying the APT regimen used, vi) reviews, *meta*-analyses, editorials and letters to the editor and case reports.,

2.3. Data extraction and statistical analysis

Two reviewers, (PT, KB) independently reviewed the included studies and extracted data. All disagreements were resolved with consensus by the addition of a third reviewer (PJ). Data extraction was based on a predecided excel spreadsheet with the following variables: first author, year of publication, country and institution, study design and study period, sample size, patient baseline demographics, total aneurysm number, size and morphologic characteristics, pharmacologic regimen used before, during and after pipeline placement, platelet testing type, central nervous system related adverse events, and morbidity and mortality rates. The main adverse events that we chose to follow were central nervous system (CNS) hemorrhage, CNS thrombosis or thromboembolism and in-PED stenosis. Morbidity, in this review, was defined as permanent neurologic deficits following an adverse event and mortality as death occurring during PED placement or as a complication of an adverse event. Categorical outcomes were extracted as event rates in cases and controls and continuous values were extracted as mean and standard deviations when available. For studies that presented continuous data with median and range, they were converted to mean and standard deviation according to the method proposed by Hozo et al. [14]

Statistical analyses of categorical variables were performed using chi square (x^2) statistical test. All analyses were conducted using STATA version 13. A value of $p < 0.05$ was considered statistically significant.

2.4. Risk of bias assessment

Risk of bias was assessed by two investigators (PT, KB). Non-randomized trials were evaluated according to the criteria proposed by the Cochrane tool for observational studies (ACROBAT) across the following domains: i) confounding, ii) selection, iii) measurement of interventions, iv) deviations from intended interventions, v) missing data, vi) measurement of outcomes and vii) selection of the reported result. Studies were assessed as low, average or high risk of bias in every domain.

3. Results

3.1. Characteristics of the eligible studies

Literature search yielded 212 potentially relevant records. After screening titles and abstracts, 99 papers were retrieved for full-text evaluation and 28 studies satisfied the predetermined search criteria and were included in the systematic review (Fig. 1). In total 22 studies were assessed as having low overall risk of bias and six as moderate risk of bias.

In terms of study design, 5 prospective [1,15–18] and 23 retrospective studies [3,6,10–12,19–36] were identified. Overall, during the period 2009–2017, 1556 patients aged 11–85 years old underwent treatment with PED (Table 1). The weighted mean age among 1420 patients with available data was 55.3 while 81% were women.

3.2. Aneurysmal features

A total of 1503 aneurysms were described (8% ruptured). Terms used across the studies for aneurysm description included: saccular, blister, fusiform, giant, large, small, anterior and posterior circulation, ruptured and unruptured. More than one description could correspond to one aneurysm (Fig. 2).

3.3. Pre-PED regimen

Details on the pre-PED regimen were provided for 1300 patients among those electively treated. Aspirin (ASA) 300- 325 mg (2-14 days) combined with clopidogrel 75 mg (3 to more than 10 days) were used as a treatment strategy before elective PED placement in 61.7% (803 patients). ASA 81 mg with clopidogrel 75 mg for 5–10 days were used in 27% (351 patients) of the electively treated patients. In 6.3% of them, a combination of 100–150 mg of ASA with clopidogrel 75 mg for 5 days was used.

Details on the pre-PED APT regimen were only reported for 24 patients among the 121 that presented acutely with subarachnoid hemorrhage (18 patients were treated with 650 mg ASA with 600 mg clopidogrel loading doses, two with 325 mg of ASA with 600 mg clopidogrel overnight, two with 325 mg ASA with 75 mg clopidogrel overnight [30], and two with 900 mg ASA with 300 mg clopidogrel for 12 h (Table 1). In 19 out of 28 studies, intraoperative heparin was prescribed, while one study specifically disclosed that heparin was not given at all in the included patients [24]. There was no mention on heparin in the remaining eight studies. The most common activated Partial Thromboplastin Time (aPTT) goal was 2–3 times the baseline or 250 s.

3.4. Post-PED regimen

Data for the postprocedural APT regimen were provided by 17 studies (1180 patients). ASA for more than six months and clopidogrel (3–12 months) was the regimen of choice for 93% (1098 patients) of these patients. During their follow-up, clopidogrel was discontinued in 110 of these 1098 patients after six months if the PED was placed in the anterior circulation and after twelve months if the PED was placed in