Neurosurgical Forum LETTERS TO THE EDITOR

Complications from the use of flow-diverting devices

TO THE EDITOR: We read with great interest the article by Zhou et al.⁸ (Zhou G, Su M, Yin YL, et al: Complications associated with the use of flow-diverting devices for cerebral aneurysms: a systematic review and meta-analysis. *Neurosurg Focus* 42(6):E17, June 2017), who pooled the results of 60 studies to evaluate the safety and complications related to flow-diverting devices (FDDs) for intracranial aneurysms (IAs). This meta-analysis was helpful in identifying the rate of complications in patients undergoing IA treatment with FDDs. However, there were some issues that should be discussed.

Firstly, some patients were duplicated among the studies included in their analysis. For instance, the study by Briganti et al. (2014)² included the 35 patients treated with FDD for IAs at Federico II University in the period from 2008 to 2012, while the study by Briganti et al. (2016)¹ involved the 15 patients treated with FDD for middle cerebral artery aneurysms at Federico II University in the period from 2010 to 2013. Thus, many duplicate patients were included in those studies. The study by Zhou et al. (2014)⁹ included the patients with large and giant unruptured aneurysms admitted to Changhai Hospital in the period from 2010 to 2014, while the study by Zhang et al. (2016)⁷ also included the patients with large and giant unruptured aneurysms at the same hospital between 2010 and 2012. Therefore, the patients in the study by Zhou et al. (2014)⁹ were some of the same patients included by Zhang et al. (2016).⁷ Moreover, some patients admitted to the Mayo Clinic from 2009 to 2013 were repeatedly collected in several studies. Burrows et al. (2015)⁴ included 93 patients undergoing IA treatment with FDD, while Puffer et al. (2014)⁶ included 44 patients who underwent FDD for the treatment of cavernous internal carotid artery (ICA) aneurysms. Brinjikji et al. (2015)³ included patients treated with the Pipeline embolization device across the ostium of the anterior choroidal artery between 2010 and 2013, and Lanzino et al. (2012)⁵ only included 22 patients who underwent FDD for the treatment of paraclinoid aneurysms. The patients in the studies by Puffer et al., Brinjikji et al., and Lanzino et al. were some of the patients included in the study by Burrows et al. Thus, the studies by Puffer et al. (2014),⁶ Brinjikji et al. (2015),³ Lanzino et al. (2012),⁵ and Zhou et al. (2014)⁹ should be excluded.

Secondly, we pooled the incidence of complications in the included studies and found that the overall complication rate was 13.6% (420/3082), which was consistent with results in their Fig. 2; however, the authors reported that the overall complication rate was 17.0% (95% CI 13.6%–20.5%) in the *Results*. This may need correction.

Then, after excluding the studies by Puffer et al. (2014),⁶ Brinjikji et al. (2015),³ Lanzino et al. (2012),⁵ and Zhou et al. (2014),⁹ we pooled the data for all studies and found the overall complication rate was 12.7% (95% CI 10.5%–14.8%), which was lower than the 17.0% reported in this meta-analysis.

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Disclosures

The authors report no conflict of interest.

Response

Flow-diverting devices are a groundbreaking invention with regard to IA treatment. Since their inception in 2007, FDDs have rapidly become the preferred treatment modality for many complex cerebral aneurysms after promising results in large multicenter clinical trials.^{1–3} As the development of such devices has been actively pursued over the past 10 years, it is necessary to determine the safety profile of various flow-diversion techniques to inform future device modifications. To date, the safety issues and complications related to FDDs have not been fully evaluated.

We thank Ye et al. for their interest in our study and their thoughtful comments. Rather than duplicating or expanding on the details they have stated very well, we will focus more generally on the challenges in studying and applying the results of our study. Although we were able to provide the most current overview, our results were still not conclusive given the rapid growth of the flow-diverting field. And the usual limitations of meta-analyses, such as ecological bias, publication bias, statistical heterogeneity, and selection bias, also apply to our report. Moreover, our review was limited to reports published in English; however, excluding articles published in languages other than English did not result in any significant bias.⁵

In our analysis, duplicate publication bias was limited by careful review of the extracted data. When institutions published duplicate studies on the same patient population or with accumulating numbers of patients or with different follow-up periods for the same sample, only the most complete reports were included for assessment. We screened publications that may have had partially overlapping data; in some instances, some case series were published with the same author names or from one center. However, different patients from different locations or participating centers had been included in the studies throughout a different period of patient selection. Improved flow-diverting technology and increased operator experience with FDD techniques have been considered to influence the complication rates, and complication rates vary widely among aneurysms of different sizes, territories, and presentations. We did not believe it was necessary to exclude all of these studies. We included these reports to extract a maximal number of publications and amount of information, but we ensured that the data were not duplicated in the review. Nevertheless, this portion of data was directly extracted from the published articles without having the raw data on hand, and although the complication rates were carefully calculated using the method previously reported,

the accuracy of this result may be decreased. However, as recommended by the Cochrane Collaborative Group and as shown in many studies, not all data must be perfectly accurate when there is a lack of individual patient data.^{6,7} Other authors have also noted that although there may be a degree of patient duplication, it is important to perform data extraction on all relevant studies to ensure pertinent evidence is not omitted.¹⁰

Despite the concerns regarding study quality and patient duplication, the results of the included studies showed promise. Rates of major adverse events such as stroke, neurovascular death, delayed aneurysm rupture, and parent vessel occlusion were low. We must keep in mind that we remain in the early stages of investigation regarding flow diversion and that all analyses remain exploratory; therefore, clinicians should be extremely cautious about using these data for decision making.

As regards their second concern, we confirmed that the overall complication rate was 17.0% (95% CI 13.6%–20.5%). In our meta-analysis, the forest plot displayed in Fig. 2 shows the estimates of the individual effect size obtained from the studies. Effect size is a measure of how effective an intervention is. The effect size at the bottom (0.13) is the pooled effect size. The effect sizes of the individual studies are combined to calculate this overall effect size by using various formulas, weighting according to the variability of the results and sample size and occasionally other parameters.⁴

Besides the concerns regarding the duplication of patients between studies, there were other limitations in the clinical evidence available for flow diverters, including an absence of control groups in most of the series and a lack of clarity in reporting selection criteria. We face increasing pressure to base our treatment decisions on high-quality evidence, as many decisions must be made in the absence of a well-designed trial. Currently, no large randomized controlled trials comparing FDD with coiling have been published. Several multicenter randomized trials comparing flow diversion and conventional endovascular techniques are underway to address this issue (Efficacy Trial of Intracranial Aneurysm Treatment Using Two Different Endovascular Techniques, clinical trial registration no. NCT01084681, clinicaltrials.gov).^{8,9} Flow-diverting devices have the potential to be the first-line treatment in the management of both ruptured and unruptured aneurysms if current findings can be substantiated by multicenter randomized trials.

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