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Clinical study

Gamma knife surgery with and without embolization for cerebral arteriovenous malformations: A systematic review and meta-analysis

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ABSTRACT

The benefit and risk of gamma knife surgery (GKS) in the treatment of residual cerebral arteriovenous malformations (AVMs) after endovascular embolization remain controversial. The aim of this meta-analysis was to assess current evidence regarding the efficiency and safety of GKS for AVMs with and without prior embolization. To compare GKS in patients with and without embolization, the authors conducted a meta-analysis of studies by searching the literature via PubMed and EMBASE databases for the period between January 2006 and December 2017. Six retrospective studies were finally identified. Outcomes were the rate of AVM obliteration on a 3-year follow-up angiogram, hemorrhage at 3 years after GKS and permanent neurological deficits. Six studies eligible for analysis included 2069 patients: 637 had undergone embolization followed by GKS, and 1432 had undergone GKS alone. The obliteration rate was significantly lower in patients who had undergone embolization followed by GKS than in those who had undergone GKS alone (49.5% vs 70.4%, OR 2.29, 95% CI 1.55–3.38, $p < 0.00001$). Subgroup analysis also indicated high obliteration rates in 'similar mean nidus volume', 'high quality' and 'sample size over 100 patients' subgroups. However, the rates of rehemorrhage (8.9% vs 4.2%, OR 0.59, 95% CI 0.23–1.57, $p = 0.29$) and permanent neurological deficits rate (3.6% vs 4.6%, OR 0.51, 95% CI 0.57–3.12, $p = 0.51$) were not significantly different between the two groups and subgroups. Embolization prior to GKS significantly decreases the AVM obliteration rate and didn't reduce the risk of hemorrhage and permanent neurological deficits. Further evaluation by well-designed prospective or randomized cohort studies is highly needed.

Cerebral arteriovenous malformations (AVMs) are congenital abnormal connections between arteries and veins leading to arteriovenous shunting with an intervening network of vessels [1], which carried an annual hemorrhage rate for AVMs is between 2% and 4% per year [2]. Although AVMs are uncommon, they are usually detected in young patients, leading to significant overall morbidity and even mortality [3].

Gamma knife surgery (GKS) was used to treat inoperable AVM patients with high hemorrhage risk or as a supplementary treatment for residual AVM after endovascular embolization [4–6]. Endovascular embolization may reduce the volume of nidus and eliminate the radiobiological resistance caused by intranidus aneurysms, hemodynamic aneurysms and AVM-related high flow fistula [7,8]. However, whether pre-GKS embolization reduces the hemorrhage risk of AVM and increases the efficacy of GKS remains controversial compared to GKS alone. Nevertheless, several reports haven shown that pre-GKS embolization may lead to reduced obliteration rates or increased morbidity [9–11]. The purpose of this study was to perform a comprehensive literature search on this topic as well as a systematic review and meta-analysis to demonstrate whether these is statistic differences in the rate of obliteration, hemorrhage, permanent neurological deficits between embolization followed by GKS and GKS alone for AVMs.

1. Methods

1.1. Search strategy

Three reviewers (Deyuan Zhu, Zhe Li and Yongxin Zhang) performed a comprehensive review of articles in the literature published between January 2006 and December 2017. An electronic search of PubMed and EMBASE databases was conducted. This

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search was supplemented by hand searching the six journals in which most studies were published (Neurosurgery, Journal of Neurosurgery, American Journal of Neuroradiology, Surgical Neurology, Journal of NeuroInterventional Surgery and Stroke) and the reference lists of identified articles. Free text searches, used in combination with the Boolean operators "OR" and "AND" were as follows: ('Intracranial' OR 'brain' OR 'cerebral') AND ('arteriovenous malformations' OR 'arteriovenous malformation') AND 'Gamma Knife' AND ('embolization' OR 'Onyx'). When multiple publications described the same cohort, we included the study with the largest cohort.

1.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: 1) studies published in the English language, 2) all available randomized controlled trials and comparative studies (cohort studies) that compared GKS with and without embolization for intracranial AVMs, 3) reporting on at least 10 consecutive patients of any age undergoing the two treatment modalities, 4) reported duration of follow-up, and 5) explicitly reported obliteration rate or hemorrhage risk or permanent neurological deficits.

The exclusion criteria were as follows: 1) studies describing other intracranial vascular malformations (dural arteriovenous fistulas, cavernous malformations, developmental venous anomalies, vein of Galen malformations, and angiographically occult vascular malformations), 2) studies with insufficient data, 3) studies with substantial imbalance of clinical characteristics or absence of baseline information, 4) studies with less than 3-year angiographic follow-up and 5) editorials, letters, review articles, case reports, and animal experimental studies.

1.3. Study quality assessment

The quality of observational studies was assessed using the Newcastle-Ottawa Scale. We evaluated the studies with regard to three items: patient selection, comparability, and outcome. A study can be awarded a maximum of one point for each numbered item within the selection and outcome categories. A maximum of two points is given for comparability. Studies with more than six points are considered high quality.

1.4. Outcomes

The primary outcome was the rate of AVM obliteration on a 3-year follow-up angiogram. The secondary outcome was the rate of hemorrhage at 3 years after SRS. The tertiary outcome was permanent neurological deficits. Because most included studies did not report mortality rates, we did not evaluate the mortality outcomes.

1.5. Statistical analysis

Using the software package RevMan 5.3 (Cochrane Collaboration), we performed a meta-analysis on studies that provided data on the outcomes of GKS in patients with and without embolization. Dichotomous variables were presented as odds ratios (embolization followed by GKS vs GKS alone) with a 95% confidence interval. Heterogeneity between studies was assessed by the calculation of I^2, which describes the proportion of total variation that is attributable to differences among trials rather than sampling error (chance). Values of I^2 <25%, 25%–50%, and >50% are defined as low, moderate, and high heterogeneity, respectively. The random-effects model was used if heterogeneity between studies was >50%. Otherwise, the fixed-effects model was used. The odds ratio was estimated (significance set at $p < 0.10$) if the 95% CI did not include the value 1. Funnel plots were used to screen for potential publication bias. Since some factors like different nidus sizes or AVM volumes might affect the selection of treatment and clinical outcomes, subgroup analyses were performed to seek any difference in 'similar mean nidus volume' (the difference of mean nidus volume between GKS and embolization prior to GKS groups was less than 1 ml), 'higher quality' (Newcastle-Ottawa Scale >6) and 'sample size over 100 patients' subgroups.

2. Results

2.1. Study selection

Fig. 1 shows a flow diagram according to the Quality of Reporting of Meta-analyses statement. Of all the included studies, none was a randomized controlled trial, 6 (100%) were retrospective studies. The studies had been performed in the United States (5) and Japan (1). A total of 729 articles were retrieved from the PubMed and EMBASE databases. After removing duplicated articles, we screened 622 titles and abstracts. No new studies were found in the six journals or the reference lists. As a result, 6 studies were included in this analysis. Overall, these studies included 2069 patients; 637 had undergone embolization followed by GKS, and 1432 had undergone GKS alone. One studies [12] was excluded mainly because the mean imaging follow-up is 2.4 and 2.5 years for two groups which indicates that many of the patients from this studies, at least, did not have 3 years follow-up by definition. Study and patient characteristics and clinical outcomes are summarized in Table 1.

2.2. Study outcomes and sensitivity analysis

Six studies [8,13–17] including 2069 patients reported the rate of AVM obliteration on a 3-year follow-up angiogram. The obliteration rate was significantly lower in patients who had undergone embolization followed by GKS than in those who had undergone GKS alone (49.5% vs 70.4%, OR 2.29, 95% CI 1.55–3.38, $p < 0.00001$; Fig. 2). The heterogeneity was high ($p = 0.03$, $I^2 = 60\%$). Five studies including 1989 patients reported the rate of rehemorrhage at 3 years after GKS. There was no difference between patients who had undergone embolization followed by GKS and those who had undergone GKS alone (8.9% vs 4.2%, OR 0.59, 95% CI 0.23–1.57, $p = 0.29$; Fig. 3). The rate of rehemorrhage demonstrated high heterogeneity ($p = 0.006$, $I^2 = 72\%$). Four studies including 1760 patients reported permanent neurological deficits. There was no difference between patients who had undergone embolization followed by GKS and those who had undergone GKS alone (3.6% vs 4.6%, OR 0.51, 95% CI 0.57–3.12, $p = 0.51$; Fig. 4). The heterogeneity was high ($p = 0.07$, $I^2 = 58\%$) (Table 2.).

2.3. Study quality evaluation and brief subgroup analysis

Subgroups with 'similar mean nidus volume' saw a high obliteration rate in GKS group (51.4% vs 70.2%, OR 2.24, 95% CI 1.65–3.05, $p < 0.00001$; Fig. 2). Similar outcomes were also achieved in 'high quality' subgroup (48.8% vs 73.4%, OR 2.73, 95% CI 2.00–3.71, $p < 0.00001$; Fig. 2) and 'sample size over 100 patients' subgroup 49.7% vs 70.5%, OR 2.21, 95% CI 1.34–3.64, $p = 0.002$; Fig. 2). No subgroup difference was found respectively. Identically, subgroup analysis for rehemorrhage rate and permanent neurological deficits rate were performed. No subgroup difference was found. (Figs. 3 and 4).

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