Endovascular Coiling versus Microsurgical Clipping for Ruptured Intracranial Aneurysms: A Meta-Analysis and Systematic Review.

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Abstract

Objectives: The purpose of this analysis is to evaluate the current evidence with regard to efficiency and safety between coiling and clipping in patients with ruptured intracranial aneurysms (RIAs).

Methods: We performed a meta-analysis that compared clipping with coiling between July 2000 and September 2019. PubMed, EMBASE, and the Cochrane Library were searched for related articles systematically.

Results: We identified three randomized controlled trials and thirteen-six observational studies involving 60217 patients with ruptured cerebral aneurysms. The summary results showed that coiling was related a better quality of life (mRS0-2; OR=1.462; CI=1.237-1.676; P=0.000), a higher risk of mortality (OR=1.116; CI=1.054-1.180; P=0.000), higher rate of rebleeding (RR=1.410; CI=1.092-1.822; P=0.000), lower incidence of vasospasm (OR=0.787; CI=0.649-0.954; P=0.015), lower risk of hydrocephaly (RR=1.143; CI=1.043-1.252; P=0.004), lower risk of cerebral infarction (RR=0.669; CI=0.596-0.751; P=0.000), lower risk of neuro deficits (RR=0.720; CI=0.582-0.892; P=0.003), lower pulmonary complications (RR=0.456; CI=0.232-0.896; P=0.023), and shorter length of stay in hospital and ICU (WMD=-2.290; CI=-3.423--1.157; P=0.000, SMD=-0.346; CI=-0.459--0.234; P=0.000, respectively), a lower rate of complete occlusion (OR=0.495; CI=0.280-0.876; P=0.016). There were no significant difference with regard to the result of GOS (4-5) and the incidence of seizure, intracranial infection.

Conclusion: Coiling was significantly associated with a better life quality (mRS0-2), a lower incidence of postoperative complications (vasospasm, hydrocephaly, cerebral infarction, neuro deficits, pulmonary complications), and a higher rate of mortality, rebleeding than clipping. What's more, coiling was associated with a lower rate of complete occlusion. There was no significant difference about seizure and intracranial infection and the result of GOS (4-5) between the two groups.

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is account for 80% of cases of nontraumatic subarachnoid hemorrhage (SAH)[1], contributing to significant mortality. There are two procedures for treatment of aSAH: microsurgical clipping and endovascular coiling[2]. The first clipping operation was published by Walter Dandy in 1937[3]. In 1991, the Guglielmi detachable coil for coiling was found, putting a platinum coil into a cerebral aneurysm[4]. The treatment methods are aimed to occlude the aneurysm so that reduce the risk of rebleeding. Given this purpose, clipping and coiling are both effective, although there remain controversial with regard to which treatment strategies is better for patients with aSAH.

Until 2002, the International Subarachnoid Aneurysm Trial (ISAT) demonstrated that individuals underwent coiling were associated with a less morbidity and mortality at 1-year follow-up compared with clipping[5]. This finding contributed to endovascular coiling had been widely accepted becoming the preferred strategy of treatment at many centers[6]. However, results of ISAT also caused some criticism, such as 7416 of the 9559 patients with ruptured intracranial aneurysms (RIAs) were excluded, the location and type of intracranial aneurysms (IAs) as well as types of recruiting centers were widely different, the proficiencies of performer of coiling and clipping were varied[5, 7].

In recent years, some randomized controlled trials (RCTs) and retrospective comparative studies and prospective studies have also been published, some results of these publications were different from ISAT[8]. As a result, there remain some debate about the choice of coiling and clipping for patients with aSAH, while it is the aim of this meta-analysis and systematic review to evaluate the two treatments efficiency, complications, length of stay from a great deal of evidence containing RCTs and observational studies to provide a guiding strategy in selecting which treatment methods to perform in patients with aSAH.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses, PRISMA[9], was used for this Meta-analysis guidelines.

Systematic Literature Search

We searched all literatures with regard to the comparison between coiling and clipping for ruptured intracranial aneurysms (RIAs) through PubMed, Medline, EMBASE, and Cochrane Library databases systematically and comprehensively. The date of these studies was ranged from 2000 to 2019. The search strategies were conducted using “ruptured intracranial aneurysms”, “coiling”, “clipping”, as
our search terms and keywords. A manual search for literatures that referenced by other publications but met our inclusion criteria was conducted as a supplement. We would use the most current literature, when a study produced multiple papers.

**Inclusion and Exclusion Criteria**

Literatures were included if they met the PICOS criteria: 1. Population: limited the comparison to the RIAs individuals; 2. Intervention: used coiling and clipping; 3. Comparison: compared the results after coiling and clipping; 4. Outcome measures: the results after treatment and the follow-up; 5. an official published RCTs or non-RCT

The exclusion criteria were as follows: 1. Letters to editor and commentary or conference articles and; 2. Animal trials; 3. Unclear patient outcome data; 4. Case reports and case series; 5. Systematic reviews or meta-analyses; 6. Other types of IAs, such as trauma.

**Selection and Data Extraction**

The data were extracted independently by two observers, C Peng, SF Cai, YH Diao, containing basic data (author, publication time, age), study characteristics (trial type), and outcomes (rebleeding; mortality; complete occlusion, complications of postoperative; length of hospital stay and length of stay in intensive care unit(ICU) ) in a table. The senior investigator (YY Yang) would review the data for completeness and accuracy.

**Statistical Analyses and Quality Assessment**

The results of this study were analyzed by standard software (Stata version 12.0 statistical software). For categorical variable results, risk ration (RR) or odds ratios (ORs) with 95% confidence intervals (CIs) were tested for results assessment. When $I^2 \leq 50\%$, the data was treated as obvious heterogeneity; therefore, a meta-analysis was preformed using random effect model. Otherwise, the fixed effect model was conducted. For continuous variable results, standard mean difference (SMD) or weighted mean difference (WMD) with 95% CIs were calculated for assessment. When $I^2 \leq 50\%$, the data was treated as obvious heterogeneity, and the data analysis was conducted by random effect model. Otherwise, the fixed effect model was conducted. The quality of the RCTs literatures were assessed by Cochrane Collaboration's tool and the Newcastle-Ottawa scale were used to evaluate the quality of the observational studies.

**Result**

**Search results and study characteristics**

Initially, 515 literatures were found by searching electronic database, 17 articles were identified by manual search. And there were 522 articles after duplicates removed. 412 publications were deleted by preliminary screening, Ultimately, 39 articles met the inclusion criteria and were included in this meta analysis. The details were shown in the flow chart (Figure 15). There were 3 RCTs and 36 observational studies[10-36],[7, 37-47]. A total of 60217 patients were included and the size of sample ranged from 32 to 21905, 31462 patients were treated by coiling, 28755 individuals performed by clipping, other information was shown in Table 2.

**Quality of Included Studies**

The article quality assessment was conducted separately by three reviewers, C Peng, YH Diao, SF Cai. 23 observational studies were assessed by the Newcastle-Ottawa scale, the Cochrane Risk of Bias Tool was used to assess the quality of the 4 RCTs. And the results were showed in Table 1.

**Synthesis of Results**

**Efficiency of treatment**

**Modified Rankin Scale (mRS) and Glasgow Outcome Scale (GOS)**

The GOS and mRS were used in this article to assess the quality of life. There were 10 articles, 4106 patients, included the result of mRS. 10 literatures,1867 patients, included GOS result. 73.6% of patients in coiling group and 66.2% patients in clipping group had quality of life defined as mRS0-2. And there was statistical significance in the results of mRS0-2 (coiling1478 of 2007 (73.6%) VS clipping1390 of 2099 (66.2%); OR=1.462; CI=1.2375-1.676; P=0.000; $I^2 = 0.0\%$; Figure1). And 74.4% and 67.8% of patients had good
quality of life (GOS4-5) in coiling and clipping group, respectively. However, there was not significantly difference in the two groups (OR=0.700; CI=0.474-1.035; P=0.074; I²=53.4%; Figure2).

**Rebleeding**

Fourteen articles included a total of 4659 patients with RIAs provided the rate of rebleeding after clipping or coiling. There was higher postoperative rebleeding in coiling group than clipping group. And it was associated with statistical significance (coiling128 of 2232(5.7%) VS clipping103 of 2427(4.2%); RR=1.410; CI=1.092-1.822; P=0.000; I²=10.6%; Figure3).

**Mortality**

Twenty-one literatures encompassing the rate of mortality after coiling or clipping among 44909 patients with RIAs. Coiling had a significant effect on the risk of mortality compared with clipping (coiling3847 of 25268(15.2%) VS clipping2955 of 19641(15.0%); OR=1.116; CI=1.054-1.180; P=0.000; I²=36.9%; Figure4).

**Complete occlusion**

Eight studies included the result of complete occlusion among 2730 patients with RIAs. There was a higher rate of occlusion in clipping group than coiling group with a statistical significance (coiling 992 of 1562 (63.5%) VS clipping 898 of 1168 (76.9%); OR=0.495; CI=0.280-0.876; P=0.016; I²=87.5%; Figure5).

**Postoperative complications**

**Vasospasm**

Thirteen publications included a total of 2857 patients with RIAs provided the result of vasospasm after clipping or coiling. There was a less postoperative vasospasm in coiling group than clipping group with a statistical significance (coiling 241 of 1177 (20.5%) VS clipping 416 of 1680 (24.8%); OR=0.787; CI=0.649-0.954; P=0.015; I²=41.1%; Figure6).

**Hydrocephaly**

Nine literatures contained the result of hydrocephaly after treatment among 3856 patients with RIAs. Coiling had a significant effect on the postoperative hydrocephaly compared with clipping (coiling 611 of 1819 (50.6%) VS clipping 581 of 2037 (39.9%); RR=1.143; CI=1.043-1.252; P=0.004; I²=30.7%; Figure7).

**Seizure**

Eight articles contained the result of seizure after coiling and clipping among 14232 patients with RIAs. Clipping had a significant effect on the postoperative seizure compared with coiling (coiling 502 of 5926 (8.5%) VS clipping 774 of 8306 (9.3%); RR=0.541; CI=0.291-1.006; P=0.052; I²=64.1%; Figure8).

**Cerebral infarction**

There sixteen articles concluded the result of ischemic infarct after coiling or clipping among 5423 patients. Coiling had a lower postoperative ischemic infarct than clipping with statistical significance (coiling 375 of 2598 (14.4%) VS clipping 597 of 2825 (21.1%); RR=0.669; CI=0.596-0.751; P=0.000; I²=18.9%; Figure9).

**Postoperative neuro deficits**

There five articles concluded the result of Neuro complications (defined as any new weakness, decreased level of consciousness, paresthesia or cranial nerve deficit), after coiling or clipping among 3076 patients. Clipping had a higher rate of postoperative neuro deficits than coiling with statistical significance (coiling 119 of 1530 (7.8%) VS clipping 167 of 1546 (10.8%); RR=0.720; CI=0.582-0.892; P=0.003; I²=15.3%; Figure10).

**Intracranial infection**
Five studies included a total of 22608 patients provided the result of intracranial infection after clipping or coiling. Clipping had a higher intracranial infection than coiling. But there was not a statistical significance (coiling 364 of 15674 (2.3%) VS clipping 187 of 6934 (2.7%); RR=0.745; CI=0.422-1.315; P=0.310; I²=73.9%; Figure11).

Pulmonary complications

Four studies included a total of 22614 patients provided the result of respiratory complications after clipping or coiling. Clipping had a higher respiratory complications than coiling. And there was a statistical significance (coiling 77 of 15701 (0.5%) VS clipping 125 of 6913 (1.8%); RR=0.456; CI=0.232-0.896; P=0.023; I²=80.3%; Figure12).

Hospital LOS

Fifteen studies included a total of 36791 patients provided the result of hospital LOS after clipping or coiling. Clipping had a longer length of hospital stay than coiling. And there was a statistical significance (WMD=-2.290; CI=-3.423--1.157; P=0.000; I²=69.4%; Figure13).

ICU LOS

Seven studies included a total of 1573 patients provided the result of LOS in ICU after clipping or coiling. Clipping had a longer LOS in ICU than coiling. And there was a statistical significance (SMD=-0.346; CI=-0.459--0.234; P=0.000; I²=97.6%; Figure14).

Discussion

This meta-analysis summarized the available data with regard to outcomes of patients with RIAs underwent clipping or coiling procedures systematically. Our meta-analysis included 39 articles involving 60217 patients with RIAs. And we compared fourteen outcomes between coiling and clipping including the efficiency of treatment (mRS(0-2); GOS(4-5); postoperative rebleeding; postoperative mortality; the rate of complete occlusion), the postoperative complications (vasospasm; hydrocephaly; seizure; cerebral infarction; postoperative neuro deficits; intracranial infection; pulmonary complications), and length of hospital stay, length of stay in ICU.

This meta-analysis showed that patients who underwent coiling had a significantly better (mRS 0-2; P=0.01) (GOS 4-5; P=0.074; I²=53.4) quality of life than those who underwent clipping at one year after treatment. Liu et al.[36] also reported that coiling patients had more good quality of life outcomes than clipping patients at one year after treatment. And this result was consistent with ISAT data[40, 48]. What's more, there were six articles[19, 23, 28] showed the trend that coiling was related to higher rate of good outcomes (mRS 0-2) than clipping group. Yu et al.[21] reported that the result of GOS (1-3) was lower in endovascular coiling (12/80, 15%) than in microsurgical clipping (30/89, 34%; P=0.005). Zhang et al.[49] had opposite result about the rate of GOS (4-5). Because the admission grade (Hunt-Hess 4 – 5; p < 0.01) [27] was associated with poor outcome, it could explain why there were different results.

250 (23·5%) of 1063 individuals underwent coiling treatment were dependent or dead at one year, compared with 326 (30·9%) of 1055 patients with clipping, an absolute risk reduction of 7·4% (95% CI 3·6–11·2, p=0·0001) reported by Molyneux et al.[40], Spetzler et al.[50] also showed coiling was related with a lower rate of mortality. While Shen et al.[18] had a opposite point, their result showed coiling was associated a higher mortality rate than clipping, this result was similar with our meta-analysis. Our result of mortality was different from published studies, the difference of categorical data may be one of the reasons[18].

Several articles[18, 19, 31, 32] demonstrated that a trend toward postoperative rebleeding in coiling group, while other literatures[30, 33, 35] showed clipping group had a higher rate of rebleeding than coiling group, and there was not significant difference in theirs results. In present article, we find a significantly higher risk of rebleeding in endovascular clipping group(P=0.000). Varelas et al.[33] reported that rebleeding was significantly associated with ventriculoperitoneal shunt(P=0.003), and some published articles suggested that rebleeding also depended on the follow up period and on the rate of occlusion after endovascular clipping or microsurgical clipping[5, 40, 51] and this meta-analysis also found that clipping was significantly associated with higher rate of complete occlusion(P=0.016), this result was consistent with published studies[28, 30, 35]. Murayama et al.[52] also reported that rate of complete occlusion was found in 55% of aneurysms and the lesion neck remnant was identified in 35.4% of aneurysms and the rate of recanalization was up to 20.9%, which was associated with the neck of the aneurysm and size of the dome. And coil compaction and/or loosening and high rate of remnant of neck could also cause recanalization[48, 53]
Our articles showed endovascular coiling was associated with significantly lower risk of vasospasm, cerebral infarction, post neuro deficits and pulmonary complications, but with a significantly higher postoperative hydrocephaly than microsurgical clipping. And there were not a significantly difference in seizure and intracranial infection between coiling and clipping group.

Li et al. [35, 54] also showed the lower incidence of vasospasm and cerebral infarction in coiling group. Some other publications [45, 54] were similar to ours about the infarction. The one of vasospasm reasons is that blood degradation products, accumulating in subarachnoid space and reserve as triggers to cause intramural inflammation and endothelial dysfunction [55]. However, there was a argument about vasospasm, someone thought that remove cisternal blood during clipping would reduce the risk of vasospasm [56]. But this effect could be offset by other effects related with clipping [57], such as surgical operations of vessels and craniotomy with brain retraction would aggravate the preexisting cerebral vasospasm [58-61]. And some previous publications suggested that cerebral vasospasm was associated with the incidence of cerebral infarction [62, 63]. There were some other reasons of cerebral infarction: microsurgical clipping blocked some microvascular during surgery, leading to ischemia event. The compression of small vessels that around the lesion clip may lead to local ischemia [18]. These factors may cause a higher risk of infarction in clipping group. What’s more, vasospasm related cerebral infarction significantly influence the rate of mortality following aSAH, and cause poor clinical outcomes [64].

The result of postoperative neuro complications was consistent with some published studies [20, 57], Dumont et al. also analyzed the risk factor of neuro deficits, such as clipping, ventriculostomy, thick clot size, history of hypertension, and intracerebral hemorrhage [57]. Pulmonary complications were detected to be more prevalent in clipping group, these pulmonary complications were well known in participants with increased LOS in ICU, prolonged artificial ventilation and bed rest. The different incidence of pulmonary between the two methods may be that coiling would provide quicker mobilization in these patients. Therefore, we could avoid prolonging bed rest and discharge from hospital as early as possible [25]. Accordingly we demonstrated that patients underwent clipping were related to a longer LOS in hospital and ICU (P=0.000). Although there were heterogeneous in our article, the trend that clipping was associated with longer LOS in hospital or ICU was similar with previous studies [24, 27, 32]. We speculated that heterogeneous may be caused by small sample of LOS, different characteristics of patient, and the different analysis methods.

So far, some publications had reviewed the morbidity of hydrocephalus after endovascular coiling and microsurgical clipping systematically, while there was no uniform conclusion [8, 65, 66]. While the result of Shen et al. [18] was consistent with this article that coiling was related with higher risk of hydrocephaly, as is known to all, arachnoid granules absorbed cerebrospinal fluid (CSF), and some CSF was absorbed though cerebral capillaries. Blood clots may lead to impairment of CSF absorption by disturbing cerebral capillaries and arachnoid villi, causing cerebral hydrocephaly [65]. While clipping could remove the blood clots, improving circulation of CSF, decreasing the risk of hydrocephaly [18]. And the controversy with regard to the result of hydrocephaly, may be the different diagnosis criteria of cerebral hydrocephalus [19].

Previous studies found the risk of epilepsy was significantly lower in patients with coiling treatment, and it is reasonable for us to believe that aneurysm dissection, the craniotomy, and the use of brain retractors to some extent lead to the incidence of epilepsy [25, 40]. Some articles [18, 23, 25] reported that clipping treatment was associated with a higher development of cerebral infection. Because exposure of brain tissue during the clipping procedure would increase the risk of infection. However, there were not significantly difference in the two results in present study, the small sample sizes of the two indexes may be caused this difference, and there need more studies with regard to seizure and intracranial infection between the two groups.

This study has several potential limitations: 1. The included literatures were only 4 RCTs and this article was limited to the evaluation of short-term results. 2. The sample of some comparative indicators was relatively small.

**Conclusion**

Coiling was significantly associated with a better quality of life (mRS0-2), a lower incidence of postoperative complications (vasospasm, hydrocephaly, cerebral infarction, neuro deficits, pulmonary complications), and a higher rate of mortality, rebleeding than clipping. What's more, coiling was associated with a lower rate of complete occlusion. There was no significant difference about seizure and intracranial infection between the two groups.

**Declarations**

**Acknowledgment**
None.

**Declaration of conflicting interests**

None.

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None.

**Ethical Approval and Consent for publication**

This study protocol was examined and approved by the Ethical Committee of Tianjin Medical University, an academic medical center.

**Author' contribution**

Chao Peng: Writing draft, Editing, data election, quality evaluation of included studies, data analysis

Yu-hang Diao: quality evaluation of included studies, data election, data analysis

Shi-fei Cai: data election, quality evaluation of included studies, data analysis

Xin-yu Yang: Writing - Review & Editing, Supervision, Project administration

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**Tables**

Table 1: the Newcastle-Ottawa scale for quality assessment observational studies.
| Representativeness cohort | Exposure Ascertainment | Comparability | Outcome Assessment | Sufficient follow up of cohorts |
|--------------------------|------------------------|---------------|--------------------|-----------------------------|
| al.                      | Yes                    | database      | No restriction, Matched in 1,2,5,6 | record linkage Yes Yes |
| al.                      | Yes                    | database      | Restricted to MCA, Matched in 1,2,5,6 | record linkage Yes Yes |
| al.                      | Yes                    | database      | No restriction, Matched in 1,2,4,5,6 | record linkage No Yes |
| al.                      | Yes                    | medical record| Restricted to MCA, Matched in 1,2,4 | record linkage No Yes |
| al.                      | Yes                    | database      | No restriction | record linkage Yes Yes |
| et al.                   | Yes                    | database      | No restriction, Matched in 1,2,4,5,6 | record linkage NO Yes |
| al.                      | Yes                    | medical record| Restricted to ACOA, Matched in 1,2,3 | record linkage Yes Yes |
| al.                      | Yes                    | medical record| No restriction, Matched in 1,2,3,6 | record linkage Yes Yes |
| al.                      | Yes                    | medical record| No restriction, Matched in 1,2,6 | record linkage No Yes |
| al.                      | Yes                    | medical record| Restricted to Anterior Circulation, Matched in 1,2,4,5 | record linkage No Yes |
| al.                      | Yes                    | medical record| No restriction, Matched in 1,2,4,5,6 | record linkage Yes Yes |
| et al.                   | Yes                    | database      | No restriction, Matched in 1,2 | record linkage unclear unclear |
| al.                      | Yes                    | medical record| No restriction, Matched in 1,2,5 | record linkage Yes Yes |
| al.                      | Yes                    | database      | No restriction, Matched in 1,2 | record linkage Yes Yes |
| al.                      | Yes                    | medical record| No restriction, Matched in 1,2,3,5,6 | record linkage Yes Yes |
| al.                      | Yes                    | database      | No restriction, Matched in 1,2 | record linkage Yes Yes |
| al.                      | Yes                    | medical record| Restricted to≥65 years, Matched in 1,2,4,5,6 | record linkage Yes NO |
| al.                      | Yes                    | medical record| Restricted to ACOA, Matched in 1,2,4 | record linkage Yes Yes |
| al.                      | Yes                    | database      | Restricted to≥18 years, Matched in 1,2 | record linkage unclear unclear |
| t al.                    | Yes                    | medical record| No restriction, Matched in 1,2,3,6 | record linkage NO Yes |
| song et al.              | Yes                    | medical record| Restricted to ACOA, Matched in 1,2,3,4,5,6 | record linkage Yes Yes |
| wer                      | Yes                    | medical record| No restriction, Matched in 1,2,3,5,6 | record linkage Yes Yes |
| wer                      | Yes                    | medical record| Restricted to Anterior Circulation, Matched in 1,2,3,4 | record linkage Yes Yes |
| wer                      | Yes                    | medical record| Restricted to 60 years, Matched in 1,2,3,6 | record linkage Yes Yes |
| al.                      | Yes                    | medical record| Restricted to basilar tip aneurysm, Matched in 1,2,4,5 | record linkage No Yes |
| al.                      | Yes                    | medical record| No restriction, Matched in 1,2,3,6 | record linkage Yes Yes |
| t al.                    | Yes                    | medical record| Restricted to age older than 18 | record linkage Unclear Unclear |
| al.                      | Yes                    | medical record| No restriction, Matched in 1,2,3,5 | record linkage Yes Yes |
| al.                      | Yes                    | medical record| No restriction, Matched in 1,2,3,5,6 | record linkage Yes Yes |
| t al.                    | Yes                    | medical record| No restriction, Matched in 1,2,4,6 | record linkage Yes Yes |
| al.                      | Yes                    | medical record| Restricted to anterior choroidal artery aneurysms, Matched in 1,2,3,5 | record linkage Yes Yes |

Note: 1=Age; 2=Sex; 3=Hunt and Hess Grade; 4 = World Federation of Neurological Societies Scale; 5=Aneurism size; 6=Aneurism location.

Table 2. Overview of Included Studies.
Note. NA= not available; RCT= randomized controlled trial; RCS= Retrospective comparative study; FM= female.
Table 3. Meta-analysis results

| Author                  | Country     | Years     | Type of Study | Recruitment period | Participants | Gender (FM) | Age (mean ± standard) |
|-------------------------|-------------|-----------|---------------|-------------------|--------------|-------------|-----------------------|
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