Review Article

Endovascular coiling versus surgical clipping for aneurysmal subarachnoid hemorrhage: A meta-analysis of randomized controlled trials

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Background: Aneurysmal subarachnoid hemorrhage is a relatively rare cause of stroke, carrying a bad prognosis of mortality and disability. The current standard procedure, neurosurgical clipping, has failed to achieve satisfactory outcomes. Therefore, endovascular detachable coils have been tested as an alternative. This meta-analysis was aimed to compare the outcomes of surgical clipping and endovascular coiling in aneurysmal subarachnoid hemorrhage. **Materials and Methods:** Relevant randomized trials up to June 2018 were identified from Medline, Central, and Web of Science. Data for poor outcomes (Modified Rankin Scale [mRS] scores 3 to 6) at 2–3 months, 1 year, and 3–5 years were extracted and analyzed as odds ratios (ORs) with 95% confidence intervals (CIs), using RevMan software. **Results:** Five studies (2780: 1393 and 1387 patients in the coiling and clipping arms, respectively) were included in the current analysis. The overall effect estimate favored endovascular coiling over surgical clipping in terms of reducing poor outcomes (death or dependency, mRS > 2) at 1 year (OR = 0.67, 95% CI: 0.57–0.79) and 3–5 years (OR = 0.8, 95% CI: 0.67–0.96). Moreover, coiling was associated with a significantly lower rate of cerebral ischemia (OR = 0.37, 95% CI: 0.16–0.86). Postprocedural mortality (OR = 0.79, 95% CI: 0.6–1.05) and rebleeding (OR = 1.15, 95% CI: 0.75–1.78) rates were comparable between the two groups. However, technical failure was significantly more common with coiling interventions than with clipping surgeries (OR = 2.84, 95% CI: 1.86–4.34). **Conclusion:** Our analysis suggests that coiling can be a better alternative to clipping in terms of surgical outcomes. Further improvements in the coiling technique and training may improve the outcomes of this procedure.

Keywords: Intracranial aneurysm, subarachnoid hemorrhage, surgical clipping, surgical coiling

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INTRODUCTION

Subarachnoid hemorrhage (SAH) is a life-threatening condition, caused by space-occupying bleeding in the subarachnoid space.[1] Mortality occurs in almost 50% of patients, while the survivors may be highly dependent. Ruptured intracranial aneurysms account for 85% of the SAH cases.[2] Next to rescuing the patient, poststroke surgery aims at minimizing the dependence in survivors. Neurosurgical clipping is the gold standard intervention for SAH.[3] This classical surgery is conducted through a large craniotomy, which needs a prolonged recovery phase with risks of complications.[4] Therefore, other alternatives have been developed to increase survival and reduce dependence.

With the advances in interventional neuroradiology,[5,6] endovascular coiling has become a common alternative to clipping in aneurysmal SAH.[6,7] The International Subarachnoid Aneurysm Trial (ISAT) showed that in patients with ruptured intracranial aneurysms who were suitable for both interventions, coiling could achieve higher independence rates at the 7-year follow-up period. However, the risk of late rebleeding was found to be relatively higher in the coiling group.[8] This

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contradicts the results of the study by Koivisto *et al*. which showed no late rebleeding with both lines of management.[6]

We aimed to comprehensively evaluate the evidence on the comparative efficacy and safety of endovascular coiling and surgical clipping in SAH by conducting a meta-analysis of the published randomized controlled trials (RCTs) in this regard.

MATERIALS AND METHODS

This study was conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [Supplementary File 1].[9]

Criteria for considering studies for this review

We considered RCTs that enrolled patients with SAH due to spontaneously ruptured cerebral aneurysm within 1 month before presentation. Consequently, traumatic SAH or infected aneurysms were excluded. To be included, a trial must have two arms: endovascular coiling and surgical clipping. SAH can be confirmed either by computed tomography, magnetic resonance imaging, or lumbar puncture. Only RCTs available in full texts were considered for this review, whereas observational studies and conference abstracts were excluded. The trials were eligible if one or more of the following outcomes were reported: poor outcome at short (2–3 months)-, intermediate (1 year)-, and long-term (3–5 years) follow-up; mortality; cerebral ischemia; and rebleeding.

Literature search strategy

Two authors (ML and GD) searched three medical literature databases, namely Medline via PubMed (up to October 2017; updated June 2018), Cochrane Central Register of Controlled Trials (CENTRAL; searched on October 20, 2017; updated June 2018), and Web of Science (searched on October 27, 2017; updated June 2018). No search restrictions were employed by the language or date of publication. We also searched the Clinical Trials Registry (clinicaltrials.gov) for ongoing studies. Hand searching of the reference lists of relevant studies was also conducted. No language restrictions were applied.

A two-stage article selection procedure was followed. In the first step, article titles and abstracts were screened to eliminate duplicates and irrelevant studies. In the second step, full texts of relevant articles were retrieved and screened for eligibility. The selection was conducted independently by two authors (SY and GD), with discrepancies resolved through discussion.

Data extraction

The extracted data included design, sample size, patients' diagnoses, inclusion and exclusion criteria, experimental arms, and assessed outcomes in the included studies. The latter were extracted in the form of the number of events and total sample size in respective arms. The extraction process was performed by two independent reviewers (ML and SY), and disagreements were resolved by discussion. The extracted outcomes included:

- Primary outcome measures: poor outcome, defined as the proportion of patients with a Modified Rankin Scale (mRS) score of 3–6 (dependency or death), at intermediate and long-term follow-up (1 and 3–5 years, respectively). Independence was evaluated using the mRS which measures the degree of disability. It is a 6-point scale ranging from 0 (asymptomatic) to 6 (death). Grades 1 and 2 are assigned for patients with no disability or slight disability not interfering with their daily lives, respectively. Grades 3, 4, and 5 are assigned for moderate, moderately severe, and severe disabilities, respectively[10]
- Secondary outcome measures: included poor outcome at short-term follow-up (2–3 months), mortality, cerebral ischemia (clinical events as stroke or radiological evidence), and rebleeding at 1 year.

Data synthesis

Dichotomous outcomes were analyzed as odds ratios (ORs) with 95% confidence interval (CI), under the fixed-effect meta-analysis model.[11,12] Trials with multiple reports were analyzed for outcomes at different timelines. Review Manager 5.3 was used to collate the data and perform the meta-analysis. Heterogeneity was assessed using the Chi-square test, where $P < 0.1$ indicated statistically significant heterogeneity and $P \geq 0.1$ excluding the possibility of heterogeneity. In case of significant heterogeneity ($P < 0.1$), the analysis was planned under the random-effects model.[11] Heterogeneity was further quantified using the I^2 test as I^2 values above 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively.[5]

We performed sensitivity analyses, using the leave-one-out method, to ensure the reliability of our findings that no single study shifted the effect estimate in its direction. Briefly, we checked all outcomes with ≥ 3 studies, removed one study at a time, and examined the change in the overall direction of the effect estimate.

We examined the risk of publication bias and used the Egger funnel plot-based testing. This test was performed by RevMan software, generating funnel plots. Simply, it is a scatterplot of the effect estimate from each study in the meta-analysis against the measure of its precision (1/standard error) or sample size and is interpreted as symmetrical (no publication bias) or asymmetrical (suggestive of publication bias).[11]

Assessment of risk of bias in included studies

Using the Cochrane's tool for assessing risk of bias, each trial was assessed in the six domains: random sequence generation (selection bias); allocation concealment (performance bias); blinding (of participants and outcome assessors, detection bias); attrition bias (incomplete outcome data due to patient withdrawal, especially in the primary outcome); selective outcome reporting (reporting bias); and other sources of bias. Each trial was labeled as of high, low, or unclear in each domain.[13] The full assessment protocol is presented in Table 8.5.d in the Cochrane handbook for systematic reviews of intervention (version 5.1). A summary of the results of risk of bias assessment was illustrated in ROB summary graph, created using RevMan software.

RESULTS

Literature search results

Our initial database search retrieved 906 papers. We were left with eight eligible articles after completing the two-step selection process. One more trial was retrieved through handsearching (unpublished data).[6,8,14-16] Finally, nine reports, based on 5 RCTs, were included in the analysis. Figure 1 (PRISMA flow diagram) illustrates the flow of article selection process.

Description of the studies

The studies included 2780 patients with SAH: 1393 randomized to the endovascular coiling arm and 1387 randomized to the surgical clipping arm. All studies reported data at a maximum of 1-year follow-up except the ISAT and the Barrow Ruptured Aneurysm Trial (BRAT), which reported follow-up data at 5 and 3 years, respectively. Baseline characteristics of the enrolled patients were reported to be similar between both arms in all included studies. Table 1 provides an outline of the selected trials.

Risk of bias

In the selection bias domain, all the studies were judged to be at low risk of bias, except the study by Wadd *et al.*,[14] which reported neither the method of sequence generation nor allocation concealment. All trials were not blinded owing to the nature of intervention. All studies had a low risk of attrition, reporting or other sources of bias, except

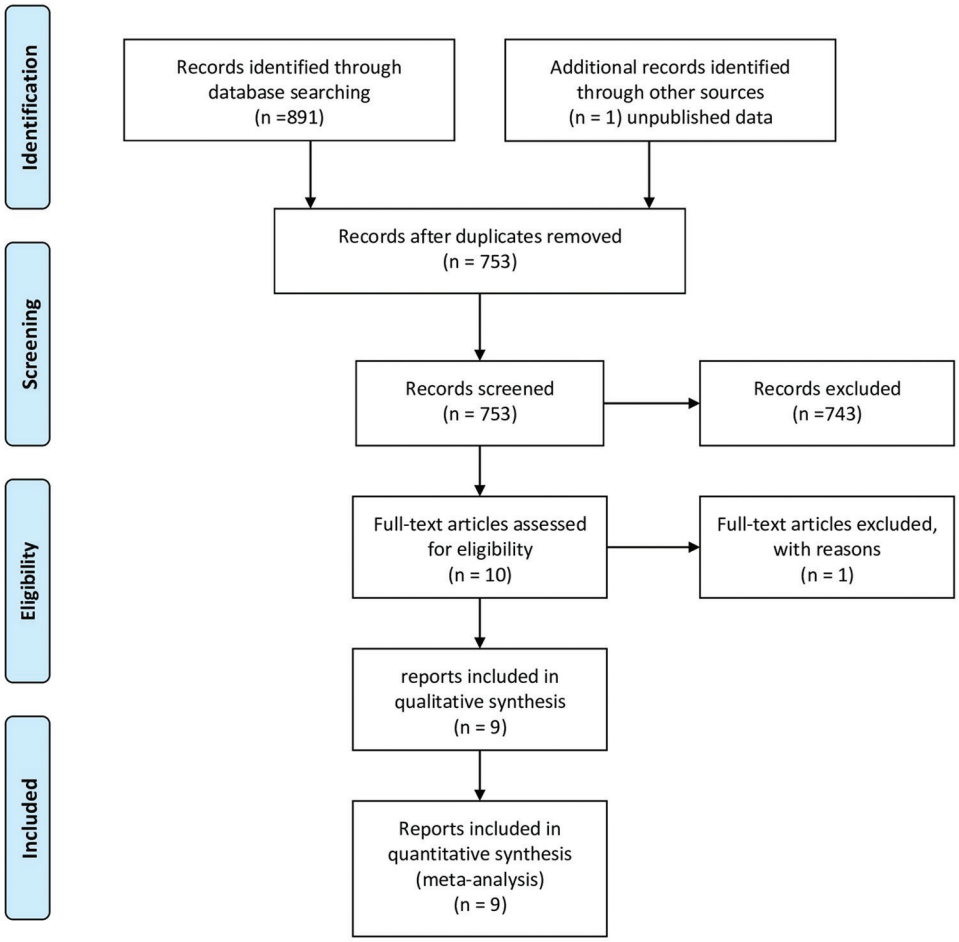

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the search and screening results

Table 1: Main characteristics of the included studies

Study	Country	*n*	Patients	Inclusion criteria	Exclusion criteria	Arms	Outcomes
Wadd 2015	Pakistan	140	Aneurysmal SAH of the anterior circulation	Age: 14-60 years and WFNS grades of 1, 2, and 3	>60 years of age, posterior circulation or giant (>2.5 cm) aneurysms, broad-neck (>5 mm) aneurysm and aneurysm of the cavernous segment of internal carotid artery, who had deteriorated to WFNS grade 4, 5 during a hospital stay	Experimental (*n*=70): Endovascular coiling on the same day of angiography Control (*n*=70): Surgical clipping after 11 days of the aneurysmal rupture	Primary: Poor outcome at 1 year Secondary: Death, complications related to the procedure at 1 year
BRAT	USA (conducted between 2003 and 2007)	408	Patients admitted to the ICU with acute nontraumatic SAH (confirmed by CT scan or lumbar puncture)	Patients between the ages of 18 and 80 years	Traumatic SAH, and <14 days after hemorrhage	Experimental (*n*=233): Endovascular coiling within 24 hours of admission Control (*n*=238): Surgical clipping within 24 h of admission	Primary: The proportion of patients with an mRS score of 3-6 at 1 year Secondary: Patients crossing over from their assigned group to the alternative treatment group
ISAT	Europe (43 centers, most of them in the UK) conducted between 1994 and 2002	2143	Patients with SAH due to ruptured intracranial aneurysms	All the following: definite SAH (proven by CT or lumbar puncture) within the preceding 28 days+intracranial aneurysm, demonstrated by intra-arterial or by CT angiography + clinical state that justified treatment by either neurosurgical or endovascular means+suitable for either technique based on its angiographic anatomy	Any of the following criteria: SAH more than 28 days before randomization, unsuitable for one or both treatments, the patient was participating in another trial of SAH treatment	Experimental (*n*=1073): Endovascular coiling within 1.1 days (IQR 0-1, range 0-30) Control (*n*=1070): Surgical clipping within 1.7 days (0-2, 0-41)	Primary: The proportion of patients with a modified Rankin scale score of 3-6 (dependency or death) at 1 year Secondary: Rebleeding, Cost-effectiveness, epilepsy, QOL at 1 year
Brilstra 2000	The Netherlands	20	Patients with aneurysmal SAH	Documented aneurysmal SAH by either CT or DSA within the preceding 4 days, aneurysm suitable for both treatment modalities	Unsuitable logistic conditions	Experimental (*n*=10): Endovascular coiling Control (*n*=10): Surgical clipping	Primary: Dependency and death at 1 year Secondary: rebleeding, epilepsy, and neuropsychological outcomes
Koivisto 2000	Finland (conducted between 1995 and 1997)	109	SAH from a ruptured aneurysm	SAH from a ruptured aneurysm in the preceding 3 days, suitable for both modalities (based on diagnostic angiographic determinants)	>75 years, large hematoma necessitating surgery, mass effect causing neurological deficit, previous surgery for the ruptured aneurysm	Experimental (*n*=52): Endovascular coiling with the maximum delay between SAH and treatment was 3 days Control (*n*=57): Surgical clipping with the maximum delay between SAH and treatment was 3 days	Primary: Rebleeding or death at 12 months Secondary: Refilling of the aneurysm at 3 and 12 months

SAH=Subarachnoid hemorrhage; ICU=Intensive care unit; CT=Computed tomography; WFNS=World Federation of Neurosurgical Societies; IQR=Interquartile range

the study by Brilstra *et al*.[15] which had an unclear risk of reporting and other bias forms. Figure 2 shows the summary of risk of bias in all domains.

Primary outcomes

At 1 year, 324 (out of 1393) and 435 (1387) patients in the coiling and clipping arms, respectively, experienced

poor outcomes (OR = 0.67, 95% CI: 0.57–0.79). This difference was highly significant ($P < 0.00001$) in favor of endovascular coiling [Figure 3a]. Pooled studies were homogeneous ($P = 0.93$, $I^2 = 0\%$). Sensitivity analysis showed no change of the OR direction of poor outcome at 1 year after removing any of the five included studies [Table 2]. The related funnel plot was symmetrical, showing no evidence of publication bias [Figure 4a].

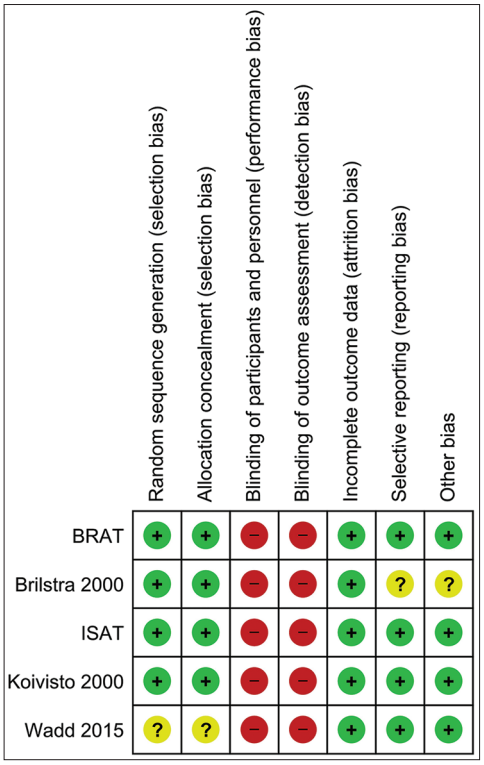

Figure 2: Risk of bias summary in included studies

At 3–5 years, based on ISAT and BRAT, "poor outcome" was reported in 292 (of 1264) and 337 (of 1238) participants in the endovascular and surgical clipping arms, respectively. The long-term "poor outcome" odds were significantly in favor of endovascular arm (OR = 0.8, 95% CI: 0.67–0.96, $P = 0.02$) [Figure 3b]. Pooled studies were homogeneous ($P = 0.55$, $I^2 = 0\%$).

Secondary outcomes

The short-term poor outcome was reported in ISAT at 2 months: 278/1065 (26.1%) in the coiling group versus 392/1063 (36.9%) in the clipping group. Koivisto *et al.* (2000) reported improved neuropsychological outcomes at 3-month follow-up with no significant difference between the two groups. However, the poor outcome data, as previously defined, were not reported; therefore, a meta-analysis was not applicable.

Mortality at 1 year was reported in 97/1193 in the coiling group versus 120/1190 in the clipping group, with no statistically significant difference (OR = 0.79, 95% CI: 0.6–1.05, $P = 0.10$). Pooled studies were homogeneous ($P = 0.85$, $I^2 = 0\%$) [Figure 3c]. Sensitivity analysis showed no change of the OR direction of morality at 1 year after removing any of the four included studies [Table 2]. The mortality funnel plot was symmetrical, i.e., the existence of publication bias is unlikely [Figure 4b].

Another important outcome was cerebral ischemic events after the procedure. At 1 year, a significantly higher

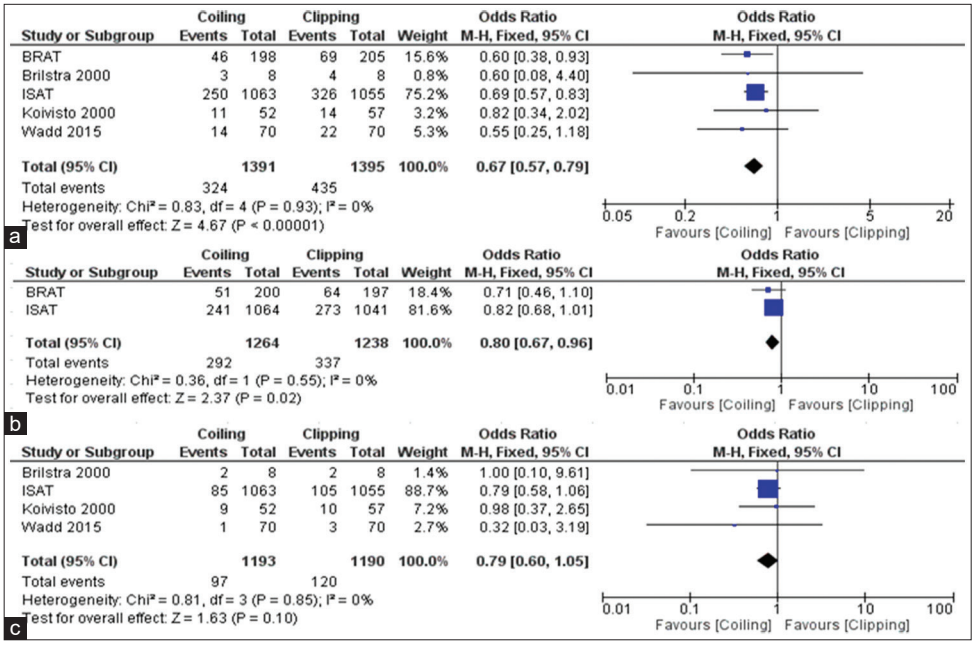

Figure 3: Forest plots of odds ratios of (a) primary outcome at 1 year, (b) primary outcome at 3–5 years, and (c) mortality

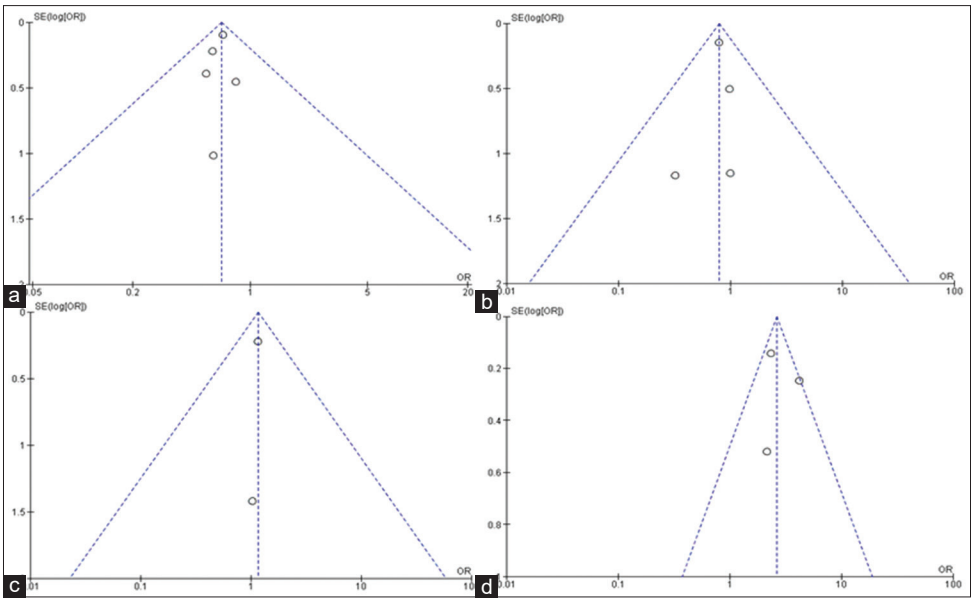

Figure 4: Funnel plots of publication bias of (a) poor outcome at 1 year, (b) mortality at 1 year, (c) rebleeding at 1 year, and (d) technical failure

Table 2: Sensitivity analysis (leave-one-out method) for the assessed outcomes

	Poor outcome at 1 year	Mortality at 1 year	Rebleeding at 1 year	Technical failure
BRAT	0.68 (0.57-0.82), *P*=0.92 and I^2=0%		1.16 (0.75-1.79), *P*=NA and I^2=NA	2.34 (1.79-3.06), *P*=0.86 and I^2=0%
Brilstra 2000	0.67 (0.57-0.79), *P*=0.85 and I^2=0%	0.79 (0.59-1.05), *P*=0.68 and I^2=0%	1.15 (0.75-1.78), *P*=0.94 and I^2=0%	
ISAT	0.61 (0.44-0.87), *P*=0.91 and I^2=0%	0.83 (0.36-1.90), *P*=0.67 and I^2=0%	1.04 (0.06-16.67), *P*=NA and I^2=NA	3.64 (2.34-5.65), *P*=0.25 and I^2=24%
Koivisto 2000	0.66 (0.56-0.79), *P*=0.89 and I^2=0%	0.78 (0.58-1.04), *P*=0.37 and I^2=0%	1.15 (0.75-1.78), *P*=0.94 and I^2=0%	2.67 (2.09-3.40), *P*=0.05 and I^2=75%
Wadd 2015	0.68 (0.57-0.80), *P*=0.91 and I^2=0%	0.80 (0.60-1.07), *P*=0.90 and I^2=0%		

Data are reported as OR (95% CI) for the effect estimate, Cochrane *P* and I^2 (for heterogeneity evaluation). *Indicates shift of the effect estimate (from significant to nonsignificant or *vice versa* on exclusion of the assigned study); not used for the lack of even occurrence. NA= Not available, OR=Odds ratios, CI=Confidence interval

number of cerebral ischemic events (stroke) or radiological evidence of ischemia was recorded in the surgical clipping arm (OR = 0.37, 95% CI: 0.16–0.86, *P* = 0.02), compared to the endovascular coiling arm [Figure 5a]. Pooled studies were homogeneous (*P* = 0.46, I^2 = 0%). However, the incidence of postprocedural rebleeding at 1 year was comparable between the two arms (OR = 1.15, 95% CI: 0.75–1.78, *P* = 0.52) [Figure 5b]. Pooled studies were homogeneous (*P* = 0.94, I^2 = 0%). When any of the four included studies was removed, we detected no change in the OR direction of rebleeding at 1 year [Table 2]. The related funnel plot was symmetrical, showing no evidence of publication bias [Figure 4c].

Technical failure, defined as <100% occlusion at 1 year, was another endpoint to assess. Technical failure was higher in the endovascular coiling arm than the surgical clipping arm (16% vs. 34%; OR = 2.84, 95% CI: 1.86–4.34, *P* < 0.00001) [Figure 5c]. Pooled studies were homogeneous (*P* = 0.13, I^2 = 52%). Removing any of the three included studies, using the leave-one-out method, did not result in a significant change of the overall OR direction [Table 2]. No asymmetry was detected in the funnel plot, showing low risk of publication bias [Figure 4d].

DISCUSSION

We aimed to systematically compare the outcomes of endovascular clipping and surgical coiling in patients with aneurysmal SAH. We included data only from RCTs to ensure that high-quality evidence is generated. Our analysis showed that coiling was superior to surgical clipping in terms of reducing the poor outcome rate at 1 year and 3–5 years, as well as decreasing the rate of secondary cerebral ischemia. In contrast, technical failure was significantly higher in the coiling arm than the clipping arm. Both groups had similar rates of mortality and postprocedural rebleeding.

Data from our analysis, as well from the included studies, showed that coiling was superior to clipping in lowering poor outcomes at 1 and 3–5 years, which confirms the

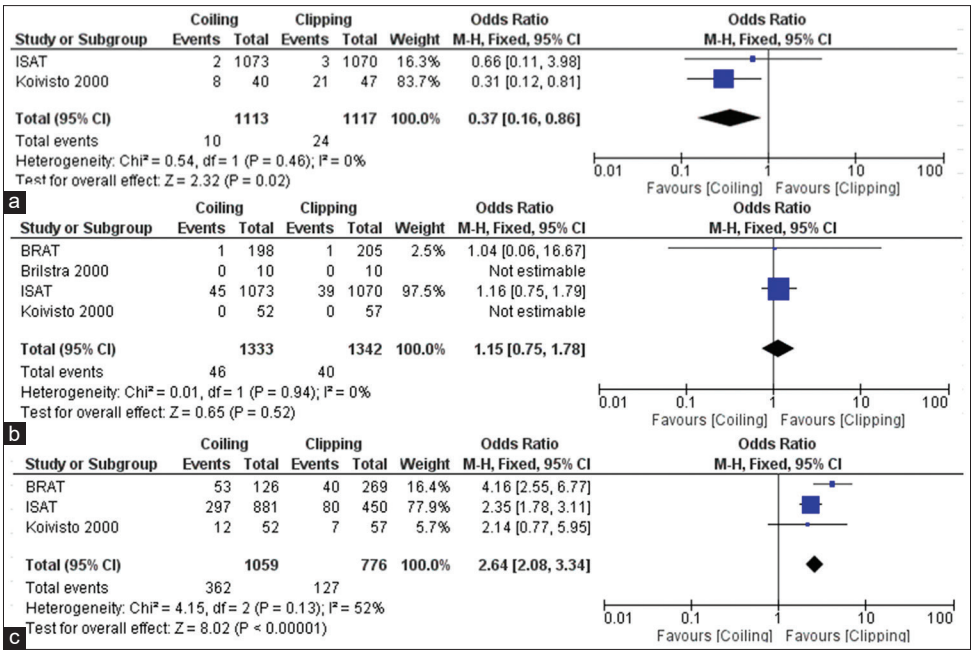

Figure 5: Forest plots of odds ratios of (a) cerebral ischemia, (b) rebleeding, and (c) technical failure

findings of former reviews that were less powered or included nonrandomized studies.[17,18] Because ISAT was the main component in our analysis and former reviews, it is important to note that ISAT included patients who were suitable for both clipping and coiling. Subsequent papers have criticized this inclusion criteria of ISAT as SAH patients excluded from ISAT are now being offered coiling.[19] Therefore, adding data from new randomized trials to our analysis updates and further supports the evidence. Interestingly, the rebleeding rates were statistically similar in both arms, which contradict the findings of Li *et al*., in 2013, who showed that rebleeding rates were higher in coiling arm, likely due to lower aneurysm obliteration potential.[18] Probably, the addition of newer trials increased the power for rebleeding data, leading to different results.

The higher rate of technical failure in the endovascular group compared to surgery deserves attention. First, the access to endovascular treatment is still limited in several countries due to the lack of trained operators, high cost of the procedure, and logistical factors. However, several technical improvements have been introduced in the interventional practice generally and coiling specifically since the publication of the ISAT[20,21] such as more flexible coil shapes and introduction of balloon remodeling. These advances went in parallel with improvements in the angiographic radiography devices and techniques.[22] Our results call for further improvements and trials on the currently available equipment.

Our findings are in line with those of the systematic review by Lindgren *et al*. who showed reduced poor outcome rates at 1 year in the coiling group; however, they showed marginally comparable outcome at 5 years' follow-up between the coiling and clipping arms.[23] This analysis showed comparable rates of mortality and rebleeding at 1 year. On the other hand, our analysis is in discordance with that by Ahmed *et al*. who included 22 randomized and observational studies and showed that clipping was associated with favorable outcomes in these outcomes.[24] This study included more randomized trials than the analysis by Lindgren *et al*. and was planned to exclude observational studies to avoid their potential confounders.

Subgroup analysis for patients with poor preoperative conditions or the World Federation of Neurosurgical Societies grade at randomization and those with basilar artery aneurysm (high risk for surgery) and middle cranial artery aneurysms (difficult coiling) was planned but was not conducted for lack of clear data. Data on other outcomes are poorly reported in the published trials, such as seizures and cognitive and neuropsychological outcomes. The latter are thought to be more affected in patients with anterior circulation aneurysms as surgery for these aneurysms may require retraction or resection of frontal lobe structures.

Limitations

Our meta-analysis has some limitations. First, pooling data only from RCTs as per our inclusion criteria produced a relatively small sample size in our analysis. Despite the funnel plot results, we cannot confidently exclude the possibility of publication bias because this method is reportedly not very accurate for <10 included studies.[25] We are aware of another two ongoing studies (International subarachnoid aneurysm

trial II (ISAT II) and hydrogel endovascular aneurysm treatment trial (HEAT) trials), and their results are eagerly awaited. The majority of our sample size was provided from the ISAT trial; therefore, we performed sensitivity analysis to verify that it did not swing the analysis in its direction. Further, only two studies reported data on long-term follow-up. Further larger RCTs with longer follow-up periods are needed. The increased technical failure risk in the endovascular coiling arm raises the need for further improvements in the technique and its interventional training.

CONCLUSION

Our analysis showed that coiling is significantly superior to clipping in achieving better outcomes. At 1 year, the mortality and rebleeding rates were similar between the two arms, whereas the short- and long-term poor outcome rates were lower in the coiling arm and the technical failure rates were lower in the clipping arm. Further improvements in the coiling surgical technique and training may improve the outcomes of this procedure. Larger trials with longer follow-up periods are needed to provide additional data, especially in high-risk patient subgroups.

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Conflicts for interest

There are no conflicts for interest.

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25. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.

Supplementary File 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (applied to last submitted manuscript version)

Section/topic	#	Checklist item[1]	Reported on page#
		LE	
Title	1	Identify the report as a systematic review, meta-analysis or both	1
		Abstract	
Structured summary	2	Provide a structured summary, including, as applicable: background, objectives, data sources, study eligibility criteria, participants and interventions, study appraisal and synthesis methods, results, limitations, conclusions, and implications of key findings; systematic review registration number	2
		Introduction	
Rationale	3	Describe the rationale for the review in the context of what is already known	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to PICOS	3
		Methods	
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., web address), and if available, provide registration information, including the registration number	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, and publication status) used as criteria for eligibility, giving the rationale	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage and contact with study authors to identify additional studies) in the search and date last searched	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and if applicable, included in the meta-analysis)	4
Data collection process	10	Describe the method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	4 and 5
Data Items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	4 and 5
Risk of bias in individual studies	12	Describe the methods used for assessing the risk of bias of individual studies (including specification of whether this was done at the study or outcome level) and how this information is to be used in any data synthesis	5
Summary measures	13	State the principal summary measures (e.g., risk ratio and difference in means)	5
Synthesis of results	14	Describe the methods of handling data and combining the results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis	5
Risk of bias across studies	15	Specify any assessment of the risk of bias that may affect the cumulative evidence (e.g., publication bias and selective reporting within studies)	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses and meta-regression), if done, indicating which were prespecified	NA
		Results	
Study selection	17	Give numbers of studies screened, assessed for eligibility and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, and follow-up period) and provide the citations	6 and Table 1
Risk of bias within studies	19	Present data on the risk of bias of each study, and, if available, any outcome level assessment (see Item 12)	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1. simple summary data for each intervention group; 2. effect estimates and confidence intervals, ideally with a forest plot	Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	6-7
Risk of bias across studies	22	Present results of any assessment of the risk of bias across studies (see Item 15)	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses and meta-regression (see Item 16))	NA
		Discussion	
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policymakers)	8

Contd...

Supplementary File 1: Contd...

Section/topic	#	Checklist item [1]	Reported on page#
Limitations	25	Discuss limitations at the study and outcome level (e.g., the risk of bias) and at the review level (e.g., incomplete retrieval of identified research and reporting bias)	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence and implications for future research	9
		Funding	
Funding	27	Describe sources of funding for the systematic review and other supports (e.g., the supply of data) and the role of funders in the systematic review	10

PICOS: Participants, interventions, comparisons, outcomes and study design, NA=Not applicable