

RESEARCH PAPER

Safety and occlusion rates of surgical treatment of unruptured intracranial aneurysms: a systematic review and meta-analysis of the literature from 1990 to 2011

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ABSTRACT

Background and purpose Surgical clipping of unruptured intracranial aneurysms (UIAs) has recently been challenged by the emergence of endovascular treatment. We performed an updated systematic review and meta-analysis on the surgical treatment of UIAs, in an attempt to determine the aneurysm occlusion rates and safety of surgery in the modern era.

Methods A detailed protocol was developed prior to conducting the review according to the Cochrane Collaboration guidelines. Electronic databases spanning January 1990–April 2011 were searched, complemented by hand searching. Heterogeneity was assessed using I^2 , and publication bias with funnel plots. Surgical mortality and morbidity were analysed with weighted random effect models.

Results 60 studies with 9845 patients harbouring 10 845 aneurysms were included. Mortality occurred in 157 patients (1.7%; 99% CI 0.9% to 3.0%; $I^2=82%$). Unfavourable outcomes, including death, occurred in 692 patients (6.7%; 99% CI 4.9% to 9.0%; $I^2=85%$). Morbidity rates were significantly greater in higher quality studies, and with large or posterior circulation aneurysms. Reported morbidity rates decreased over time. Studies were generally of poor quality; funnel plots showed heterogeneous results and publication bias, and data on aneurysm occlusion rates were scant.

Conclusions In studies published between 1990 and 2011, clipping of UIAs was associated with 1.7% mortality and 6.7% overall morbidity. The reputed durability of clipping has not been rigorously documented. Due to the quality of the included studies, the available literature cannot properly guide clinical decisions.

INTRODUCTION

Unruptured intracranial aneurysms (UIAs) are increasingly detected and treated^{1 2} but the best management remains uncertain.³ Surgical clipping, for years considered the gold standard, has been challenged by the emergence of endovascular treatment (EVT), a minimally invasive alternative.^{1 4 5} Successful clipping is reputed to result in definitive aneurysm exclusion, with retreatment rates as low as 1.5%.⁶ Proponents of EVT claim lower treatment related risks,^{7–10} perhaps at the cost of lower long term occlusion rates,¹¹ but a valid, randomised comparison has never been performed.¹²

A prevailing view is that clinical decision making 'requires knowledge of the natural history

of UIAs and of the risks of repairing them'¹³ and 'adequately balancing benefits and risks requires reliable data on surgical outcome',¹⁴ although this management philosophy has been questioned.¹⁵ Better knowledge of the risks involved in the surgical repair of UIAs may nonetheless help with counselling patients as well as provide hypotheses for clinical trials.¹² The last meta-analysis of surgical outcomes following clipping of UIAs reviewed the published literature up to June 1996.¹⁴ After the publication of the ISUIA registry in 1998, those patients selected for surgery may have changed, with different clinical outcomes following clipping in the more modern era.^{13 16} We conducted an updated review, aiming to: (a) assess morbidity and case fatality rates following surgical clipping of UIAs; (b) identify patient or aneurysm characteristics associated with greater surgical risks; and (c) determine occlusion rates following surgical clipping, according to published clinical or angiographic results.

MATERIAL AND METHODS

A detailed protocol was developed prior to conducting this review according to guidelines published by the Cochrane Collaboration,¹⁷ the Meta-Analysis of Observational Studies in Epidemiology criteria¹⁸ and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement,¹⁹ including methods for literature search, publication eligibility, assessment of quality of reporting, data extraction and analysis.

Search strategy

The literature in French and English on surgical treatment of UIAs was reviewed from 1990 to 2011, using PubMed (Medline), Embase, ISI Web of Knowledge and the Cochrane Library, complemented by hand searching and extensive cross referencing. Only those studies containing outcome data were included for full text review (see supplementary data available online only). In the event of multiple reports with data on the same patients, only the most recent was included. In studies where only a subset of patients met the inclusion criteria, these were selectively included. Multiple aneurysm patients treated for an UIA with a remote history of SAH from a different lesion were included.

Selection criteria

The prespecified inclusion criteria were: (1) explicitly reported mortality or permanent morbidity rate using a validated outcome scale^{20–22} or individual data allowing recalculation into crude numbers. Population based studies based on ICD-10 discharge databases were thus excluded²³; (2) saccular, non-dissecting, non-infectious, previously untreated UIAs not associated with arteriovenous malformations; (3) report contained a minimum of 10 patients with UIAs; (4) peer reviewed original study; and (5) score >6 on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) scale.^{24 25}

Data extraction

Data were extracted by one author (MK) using a standardised critical appraisal and digitised data extraction form. Two authors (TED and EK) reviewed a random sample of 40% of the studies and extracted data. Disagreements were resolved by consensus after reviewing studies.

Study characteristics

Data included type of study, single or multicentre, retro- or prospective data collection, consecutive or non-consecutive patient accrual, year, journal, language, country of origin of publication and study interval. Quality of reporting was assessed for all included publications using the STROBE 22 point checklist. We added 1 point for each of the following criteria: (a) randomised controlled trial (RCT), (b) independent clinical outcome assessment, (c) prospective study design, (d) consecutive patient inclusion and (e) multicentre study. Study scores were classified as poor (6–12), average (13–18) or good (19–27).

Patient and aneurysm characteristics

Data recorded included the number of patients, mean age, sex, clinical presentation and number of patients with multiple aneurysms. Data on aneurysms characteristics included number, location and size of aneurysms. Additional information on treatment modalities (eg, clipping, wrapping, trapping or bypass procedures) was extracted where possible.

Outcomes

The safety endpoints extracted were: (a) death and (b) disability, defined as either a modified Rankin Scale²¹ score of >2, a Glasgow Outcome Scale²⁰ score of <4 or a EGFP (Excellent, Good, Fair, Poor) Scale²² score of 'fair' and 'poor'. In patients with a prior deficit, a loss of 1 point on any outcome scale was considered an unfavourable outcome. When poor outcomes from the treatment of unruptured aneurysms were not distinguished from poor outcomes antedating surgery in populations that could have included patients with a previous history of subarachnoid haemorrhage from another aneurysm, we attributed such outcomes to surgery. Patient populations with only mean outcome or mean difference pre- and post-intervention outcome scores reported were excluded. When the author described a deficit without specifying the outcome, we attributed a modified Rankin Scale or EGFP score from the description.

The time of follow-up clinical assessment was classified as (1) short term (in-hospital morbidity or within 1 month after intervention), (2) mid term (1 month to 1 year after intervention) or (3) long term (>1 year after intervention). When time

of assessment was unspecified, outcome data were considered short term.

Occlusion rate

Data on aneurysm occlusion included number of patients with postoperative imaging, and type and timing of imaging, with results categorised as complete or incomplete occlusion. Incomplete occlusion was defined as attempted yet unsuccessful complete obliteration of the aneurysm dome, including cases where a residual neck remained. Efficacy regarding the prevention of SAH at long term follow-up was also sought in terms of bleeding rates, as well as retreatment rates.

Subgroups

Clinical outcome data were examined using predefined subgroups: (1) age dichotomised as \leq or >55 years; (2) anterior versus posterior circulation location; and (3) aneurysm size, categorised as small (<10 mm), large (10–24 mm) or giant (\geq 25 mm). Other predefined subgroups included the publication quality score, dichotomised as high (19–26) or low (<19), origin of the study, categorised as North American, European or Australasian, and era of publication year, dichotomised to 1990–2000 or 2001–2011.

Manuscripts used for subgroup analyses are detailed in the supplementary file 2 (available online only).

Analyses

The degree of heterogeneity between studies was reported using $I^2 = ((Q - df) / Q) \times 100\%$, where Q is the χ^2 statistic and df is the number of degrees of freedom.^{26 27} I^2 describes the per cent variability in effect estimates due to heterogeneity rather than sampling error. Heterogeneity was classified as moderate ($I^2 \geq 30\%$), substantial ($I^2 \geq 50\%$) or considerable ($I^2 \geq 75\%$). Due to the degree of heterogeneity found, we used a DerSimonian-Laird random effect weight (REW) model for all analyses. Corresponding 99% CI for single proportions were determined using the binomial method. We assessed publication bias with scatterplots according to study size or precision.^{28 29} SE was chosen for the vertical axis and the logit event rate for the horizontal axis, defined as $\text{logit}(p) = \log(p) - \log(1-p)$, where p is the event rate.³⁰ All analyses were performed using Comprehensive MetaAnalysis 2.0 (Biostat Inc, Englewood, New Jersey, USA) and Graphpad QuickCalcs (GraphPad Inc, La Jolla, California, USA).

RESULTS

Studies

Study selection is summarised in figure 1. The initial search yielded 6529 articles. Full text review of 595 articles was performed after selection criteria were met, or when uncertainty remained after review of the title and abstract. Studies were excluded ($n=535$) most commonly when clinical outcomes were not differentiated for ruptured compared with unruptured aneurysms (eliminating 105 studies reporting 10 759 patients).

Table 1 summarises the study characteristics; the 60 included studies reported outcomes for 9845 patients with 10 845 unruptured aneurysms. The median quality score of included publications was 8 ± 2.9 (range 6–19). Reporting was graded 'good' for one (1.6%), 'average' for eight (13.3%) and 'poor' for 51 (85%) studies. One RCT was identified³¹; 59 (98.3%) studies were observational, 11 (18.3%) prospective, nine (15%) consecutive and 11 (18.3%) multicentre studies. Three (5%) studies had independent outcome assessment. Twenty-four (40%)

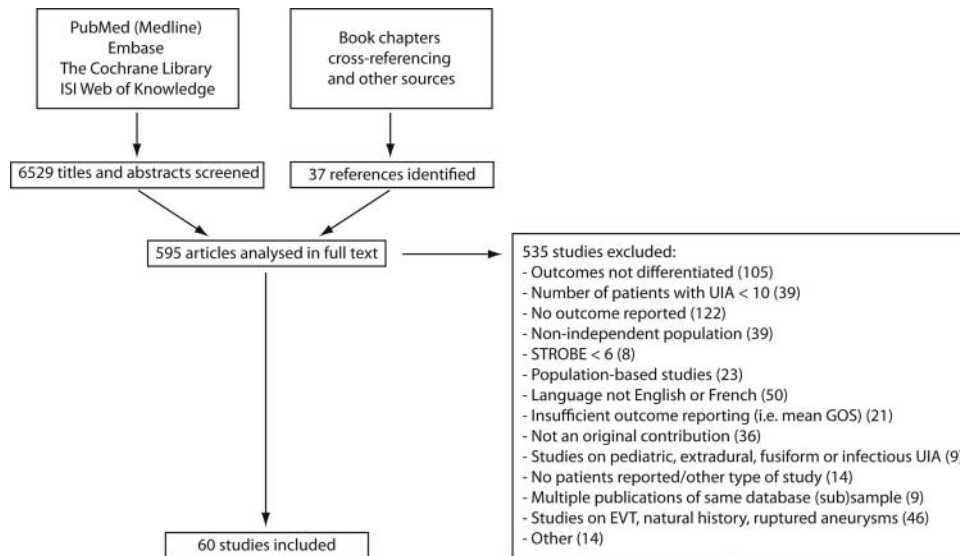


Figure 1 Flowchart of the literature search method. EVT, endovascular treatment; GOS, Glasgow Outcome Scale; UIA, unruptured intracranial aneurysm.

studies comprising 4901 (49.8%) patients were of North American origin, 17 (28.3%) studies comprising 1351 (13.7%) were conducted in Europe and 18 (30%) studies with 3583 (36.4%) patients were from Australasia, including Japan. One additional study reported on 10 (0.1%) South American patients.

Patients

Patient characteristics are summarised in table 2. Reported clinical outcomes were short term for 5984 (60.8%), mid term for 3013 (30.6%) and long term for 152 (1.5%) patients. In 696 (7.1%) cases, outcome was reported using the patient years method.

Details on type of surgical treatment were specified in 26 (43.3%) publications for 3437 (34.9%) patients. Details on periprocedural complications were provided in 18 (30%) publications.

Table 1 Publication characteristics

	Studies	%
Quality score		
6–12 (poor)	51	85
13–18 (average)	8	13
19–26 (good)	1	2
Median (±SD)	8 (±2.9)	
Range	6–22	
Patient enrolment		
Prospective	11	18
Retrospective	49	82
Consecutive	9	15
Non-consecutive	51	85
Study design		
Multicentre	11	18
Single centre	49	82
Type of study		
Randomised controlled trial	1	1.7
Observational studies	59	98
Outcome assessment		
Independent clinical outcome assessment	3	5
Modified Rankin Scale	9	15
Glasgow Outcome Scale	33	55
EGFP	20	33
Loss of follow-up reported	11	18
Time of outcome assessment		
Short term ('discharge' to 1 month)	11	18
Mid term (>1 month to 1 year postop)	23	38
Long term (>1 year postop)	3	5
Patient years' follow-up	11	18
No information on time of outcome measurement	12	20

EGFP, Excellent, Good, Fair, Poor.

Table 2 Patient characteristics

	Patients	%
Total No of patients	9845	100
Female	5427	55.1
Male	2390	24.3
Sex not reported	2028	20.6
M/F ratio	0.44	
Age range (years)	1–86	
Patients with multiple aneurysms	1263	12.8
Presentation		
Symptomatic	1028	10.4
Asymptomatic	2342	23.8
Cranial nerve palsy	312	3.2
Previous episode of SAH from another lesion	628	6.4
Not reported	5535	56.2
Treatment		
Clipping	3122	31.7
Clipping+bypass	28	0.3
Wrapping	118	1.2
Wrapping+bypass	3	0.0
Clipping+wrapping	13	0.1
Proximal occlusion+bypass	53	0.5
Trapping	54	0.5
Bipolar coagulation and gauze reinforcement	39	0.4
Proximal occlusion	120	1.2
Not reported	6295	63.9

SAH, subarachnoid haemorrhage.

Table 3 Aneurysm characteristics

	No of aneurysms	%
Total No of aneurysms	10 845	100
Location of aneurysms		
Anterior circulation aneurysms	6766	62.4
ICA	2732	25.2
MCA	2552	23.5
ACA	1205	11.1
Posterior circulation aneurysms	1014	9.3
Basilar tip	318	2.9
All others	243	2.2
Location not reported	3065	28.3
Size (mm)*		
<10	3771	34.8
10–24	1704	15.7
≥25	476	4.4
Not reported	4894	45.1
Other aneurysm characteristics		
Thrombosed	76	0.7
Calcified	30	0.3

*Regrouped size: aneurysms 7–12 mm were classified as small, 6–16 mm as large. ACA, anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery.

Aneurysms

Location was specified in 44 (73.3%) studies for 7780 (71.7%) aneurysms: 6766 (87%) were located in the anterior and 1014 (13%) in the posterior circulation. Aneurysm characteristics are summarised in table 3.

Clinical outcomes

In total, 157 of 9845 patients died after surgery (REW average: 1.7%; 99% CI 0.9% to 3.0%; $I^2=82.2%$; $p_{\text{het}}<0.001$). Unfavourable outcome, including death, up to 1 year after surgery, was found in 692 patients (REW average: 6.7%; 99% CI 4.9% to 9.0%; $I^2=85.1%$; $p_{\text{het}}<0.001$).

Funnel plot analysis (figure 2) showed substantial bias, with data points concentrated in the lower left hand corner of the plot, which was more pronounced for the estimate of morbidity than mortality. Among studies with a small SE, three

reported higher event rates than others: two studies^{32 33} reported results concerning treatment of posterior circulation aneurysms, and the other large and giant anterior circulation aneurysms.³⁴ Two studies^{35 36} reported death rates that were not within the lower limit of the CI; one was a national survey and the other was a stratification of outcome in terms of hospital caseload and operations of individual surgeons.

Subgroup meta-analysis of surgical risk factors

Table 4 summarises the results for the predefined subgroups. Comparative outcomes with respect to patient age were reported for 500 (5.1%) patients, with respect to aneurysm location for 3010 (30.6%) patients and for aneurysm size for 591 (6%) patients.

Aneurysm location and size reached statistical significance in terms of surgical risk factors ($p<0.0001$). The relative risk for unfavourable outcome of patients with posterior circulation aneurysms was 4.1 (99% CI 2.3 to 7.6) and the relative risk for patients with large and giant aneurysms was 3.5 (99% CI 1.4 to 8.9). Analysis of age as a risk factor did not reach significance (figure 3).

Subgroup meta-analysis of the literature

High quality studies (19–27 points) reported a significantly higher rate of unfavourable outcomes, including mortality, compared with poor and average quality studies ($p<0.0001$). Most high quality studies (67%) were conducted in North America. More recent studies (2001–2011) tended to report fewer unfavourable outcomes compared with studies from 1990 to 2000 ($p<0.0001$). Funnel plots demonstrated persistent bias in both eras. Reported clinical outcomes were significantly different depending on origin of publication, with North American studies publishing higher rates of unfavourable outcomes ($p<0.0001$).

Occlusion rates

The majority of publications did not report aneurysm occlusion rates. Data were missing for 82.2% of all clipped aneurysms. Information on occlusion rates was available for 24 (40%) of the included publications. Of those, five stated that all aneurysms were completely occluded without detailing how results were verified. Only nine (15%) studies defined complete versus

Figure 2 Funnel plot. (A) Death rate and (B) morbidity and death rates. Individual points correspond to published rates from individual studies. The wide distribution and asymmetry suggest bias. Studies with a larger SE tended to report lower morbidity and death rates.

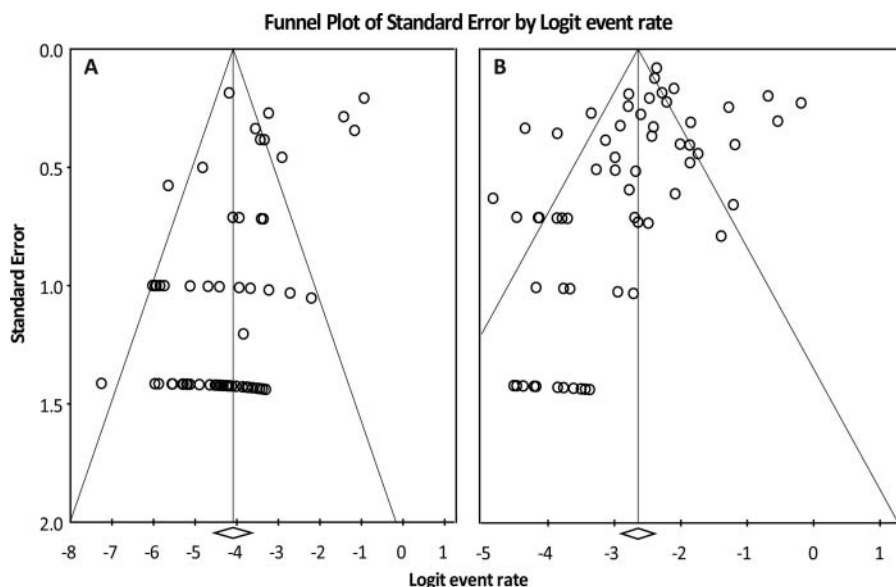


Table 4 Subgroup meta-analysis

	Unfavourable outcome† (%) (99% CI)	Heterogeneity Q value/I ²	p Value (het)*	p Value (sig)
Quality of study				
High quality studies (n=9‡, 2704 patients, 3027 aneurysms)	9.9 (4.9% to 19.0%)	68.1/88.3%	<0.0001	<0.0001
Low quality studies (n=51, 7141 patients, 8012 aneurysms)	6.1 (4.2% to 8.7%)	323.2/84.5%	<0.0001	
Origin of study				
North America (n=24, 4901 patients, 5343 aneurysms)	9.4 (5.9% to 14.6%)	223.8/89.7%	<0.0001	<0.0001
Europe (n=17, 1351 patients, 1764 aneurysms)	4.5 (2.4% to 8.4%)	38.7/58.7%	0.001	
Asia (n=18, 3583 patients, 3920 aneurysms)	5.2 (3.1% to 8.6%)	94.2/90.0%	<0.0001	
Midyear of treatment				
1990–2000 (n=22, 1711 patients, 1853 aneurysms)	8.0 (4.7% to 13.4%)	99.1/78.8%	<0.0001	<0.0001
2001–2011 (n=38, 8134 patients, 9186 aneurysms)	6.0 (4.1% to 8.7%)	282.3/86.9%	<0.0001	
Age (years)				
Mean age >55 (n=9, 433 patients)	11.8 (6.8% to 19.8%)	19.8/64.7%	0.006	0.18
Mean age ≤55 (n=5, 93 patients)	8.2 (3.1% to 20.0%)	1.7/0%	0.79	
Location				
Anterior (n=17, 2461 patients)	5.7 (2.3% to 13.3%)	151.9/90.1%	<0.001	<0.0001
Posterior (n=13, 549 patients)	15.6 (7.4% to 30.1%)	52.3/80.9%	<0.001	
Fundus size (mm)				
<10 (n=6, 240 patients)	4.0 (1.7% to 8.8%)	0.2/0%	1	<0.0001
10–25 (n=7, 195 patients)	12.1 (7.0% to 19.9%)	4.9/0%	0.6	
>25 (n=7, 156 patients)	26.5 (8.5% to 58.3%)	19.9/74.9%	0.001	

*p Value associated with the χ^2 test for heterogeneity.

†Unfavourable outcome: morbidity, including mortality.

‡Number of studies.

incomplete occlusion. Four (6.6%) publications provided the timing of postoperative imaging. Recalculation from proportions into crude numbers was necessary with 10 studies. No publication provided details of adjudication of results, or discussed interobserver agreement. There were no data on long term imaging follow-up. The remaining 19 (32%) publications (1793 patients; 2180 aneurysms) reported imaging data for 1969 postoperative examinations; 91.8% (99% CI 90% to 93.2%) of aneurysms were reported as completely occluded. Neck remnants were present in 3.9% (99% CI 2.9% to 5.2%), with incomplete occlusions in 4.3% (99% CI 3.3% to 5.7%).

Data on bleeding rates after surgical treatment were provided in nine (15%) publications with 773 (7.9%) patients. Three events (0.38%) were reported during an average follow-up of 1.2 years per patient. Due to insufficient power, reliable analysis was not possible for bleeding or retreatment rates.

DISCUSSION

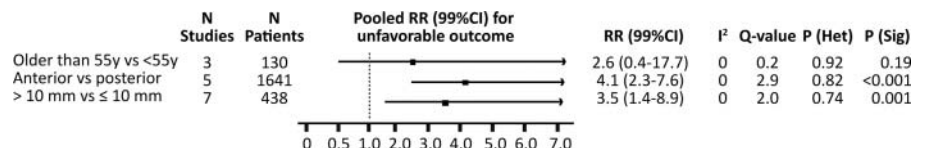
This review found that surgical clipping of UIAs is associated with a risk of unfavourable outcome of 6.7% (99% CI 4.9% to 9.0%), and a risk of death of 1.7% (99% CI 0.9% to 3.0%). However, we also found that the literature on surgical treatment of UIAs is heterogeneous, not of high quality and contains evidence of bias. Published studies often had shortcomings in design, conduct and reporting. Clinical outcomes were most commonly self-assessed, and duration of follow-up short and often incomplete. Finally, there were no reliable data on occlusion rates following clipping. We do not recommend

using the results of surgical clipping obtained from this literature to formulate treatment plans.

Two previous meta-analyses have been published on morbidity and mortality of surgery for UIA. In 1994, King *et al*³⁷ found a morbidity rate of 4.1% and a death rate of 1.0%, whereas Raaymakers *et al*¹⁴ in 1998 found nearly double rates of 10.9% and 2.0%, respectively. Both meta-analyses examined literature published from 1966 to 1992; different study designs and definitions were the most likely explanations for the divergent results. Raaymakers *et al*¹⁴ defined surgical morbidity as “all permanent morbidity not present before operation and ...any outcome except the most favourable...”. They also reported that “half of the patients with surgical morbidity became dependent in daily life”. By requiring dependence to define morbidity, approximately half of the morbidity rate of Raaymakers *et al* can be expected, which would give a result similar to our findings.

Clipping has been challenged by the less invasive, presumably less morbid, endovascular alternative, and recent epidemiological studies have claimed that patients with UIAs are more often discharged to long term facilities when treated with clipping than with coiling.²³ While these results support the fact that patient recover more quickly from less invasive treatments, they do not prove that the risks of significant neurological morbidity are less. Epidemiological results cannot be used to judge the relative merits of each intervention as patients cannot be compared: patients with more difficult aneurysms in any location may have been referred to surgery while those with posterior circulation aneurysms may have been referred to EVT. It

Figure 3 Meta-analysis of risk factors for an unfavourable outcome. Meta-analysis of studies with dichotomised subgroups.



remains nevertheless tempting to compare the results of this study with a recent meta-analysis carried out by our group on the treatment related risks of EVT for UIAs.¹⁰ Analysing the literature from 2003 to 2008, we found a procedural unfavourable outcome, including mortality, of 4.8% (REW average: 99% CI 3.4% to 5.6%) and a mortality of 1.9% (REW average: 99% CI 1.3% to 2.6%) with EVT of UIAs, which is comparable with the results of surgical clipping found here. However, in the absence of randomisation, any attempts to directly compare treatment outcomes remain invalid, as differences in morbidity and mortality will certainly reflect selection bias.

Surgical clipping is reputed to yield more durable aneurysm occlusion than coiling, a notion supported by a randomised study that found higher rebleeding rates after coiling than clipping of ruptured aneurysms.³⁸ Rigorously speaking, this notion should not be extrapolated to UIAs. Occlusion rates following EVT are routinely available, and even though long term angiographic follow-up studies are infrequently done, recurrences have been documented in 24% of cases, with retreatment in at least 9%.¹⁰ Unfortunately, the articles included in our review cannot support the superiority of clipping in terms of long term occlusion rates. Clipping is not always successful or complete, and new aneurysms may develop after surgery.³⁹

Our results suggest that treatment risks have decreased in recent years, but it is unclear if this reflects improved surgical techniques. Changing treatment trends, shifting clinical indications and the progressive use of EVT over time are likely to have had a major influence on clinical outcomes.⁴⁰

Meta-analyses usually focus on RCT results. They can be considered helpful in non-randomised studies when the literature is sufficiently homogeneous in terms of participants, interventions and outcomes to provide a meaningful summary. They may also help identify hypotheses for clinical trials. Given the heterogeneity and poor quality of the studies that were included, we want to ensure that we do not give credibility to potentially misleading results. All potential sources of biases affecting our results cannot be quantified.

There are additional limitations to our study. First, some reports may have been missed, as we included only studies in English and French, potentially introducing language bias.^{41 42} Second, our policy was to extract maximum information. One could argue that we should have restricted inclusion to high quality articles but this would have led to exclusion of 51 (85%) studies. Third, we chose to restrict this review to articles published since 1990. Our justification in excluding older articles was incomparable clinical settings, technological advances, changing range of indications for surgical treatment of UIA and a literature that becomes historically less comparable with current practice. Including more patients would have increased the power of the study but perhaps at the cost of decreased generalisability of results. Finally, lack of individual patient data precluded multivariate analyses; hence we could not correct for potential confounders. Our results should be considered strictly exploratory, and caution is advised regarding use of these data for clinical decision making. We are aware that results may be used in cost effectiveness analyses, but in our view these numbers are too uncertain to use in any decisional treatment algorithm for patients with UIA.

Two dilemmas continue to plague the clinical management of patients with UIAs: whether patients eligible for both treatment options should be treated with clipping or with coiling, and whether risky preventive treatments are justified at all.⁴³ Unfortunately, this review cannot provide answers to these fundamental questions.

CONCLUSIONS

A systematic review of the literature on surgical treatment of UIA showed substantial heterogeneity and suboptimal reporting. Surgical risks were in the range of 6–7%. Reliable data on occlusion rates of surgical treatment were absent. The best management of patients with UIA remains unknown. Randomised evidence should be a priority issue in clinical neurovascular research.

Contributors MK, TED and EK reviewed the literature. MK and ON analysed the data. MK, ON, TD and JR drafted the article. SN and GG designed the extraction database. All authors reviewed the manuscript.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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ONLINE SUPPLEMENT TO:**Safety and Occlusion Rates of Surgical Treatment of Unruptured Intracranial Aneurysms - A Systematic Review and Meta-Analysis of the Literature from 1990 to 2011****Reference list of included publications and search strategy**

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Search strategy: Medline: "Intracranial Aneurysm"[All Fields] AND ("surgery"[Subheading] OR "Clip*"[All Fields] OR "Microsurgery"[Mesh] OR "Ligation "[Mesh]) AND (("1990/01"[PDat] : "2011/04"[PDat]) AND (Humans[Mesh])). Embase: "Intracranial aneurysm" AND "Mortality" OR "Morbidity" AND "Humans" AND "1990-Current". For ISI Web of Knowledge: "UIA" AND "Clip" OR "Surgery" OR "Outcome" AND "1990-2011"

Additional online supplement for submission:
Jnnp-2011-302068.R1

Reference lists of subgroup meta-analyses

Quality Scores of study

Score 19-26 studies (n⁺=9, 2704 patients, 3027 aneurysms)^{6, 16, 24, 38, 39, 48, 52, 54, 55}

Score 6-18 studies (n=51, 7141 patients, 8012 aneurysms)^{1-5, 7-15, 17-23, 25-37, 40-47, 49-51, 53, 56-60}

Origin of Study

North America (n=24, 4901 patients, 5343 aneurysms)^{2-6, 9, 10, 12-14, 16, 22, 25, 26, 30, 33, 35, 36, 40, 43, 47, 48, 54, 55}

Europe (n=17, 1351 patients, 1764 aneurysms)^{1, 8, 11, 15, 19, 24, 27-29, 34, 38, 39, 41, 42, 44, 46, 52}

Asia (n=18, 3583 patients, 3920 aneurysms)^{17, 18, 20, 21, 23, 31, 32, 37, 45, 49-51, 53, 56-60}

Midyear of Treatment

1990-2000 (n=22, 1711 patients, 1853 aneurysms)^{4, 5, 8-10, 16, 17, 20, 22, 26, 27, 29, 31, 37, 39, 40, 44, 47, 48, 51, 52, 59}

2001-2011 (n= 38, 8134 patients, 9186 aneurysms)^{1-3, 6, 7, 11-15, 18, 19, 21, 23-25, 28, 30, 32-36, 38, 41-43, 45, 46, 49, 50, 53-58, 60}

Age

Mean age >55 y (n= 9, 433 patients)^{5, 7, 17, 20, 22, 37, 49, 56, 60}

Mean age ≤55 y (n=5, 93 patients)^{7, 14, 22, 56, 60}

Location

Anterior (n= 17, 2461 patients)^{4, 7, 13-15, 20, 22, 28, 32, 35-37, 41, 42, 44, 45, 56}

Posterior (n= 13, 549 patients)^{2, 13, 20, 22, 30, 32, 35-37, 44, 48, 56, 60}

Fundus Size

<10 mm (n= 6, 240 patients)^{7, 22, 33, 37, 47, 56}

10-25mm (n=7, 195 patients)^{7, 22, 33, 37, 43, 47, 56}

>25mm (n= 7, 156 patients)^{7, 22, 26, 30, 33, 37, 47}

† n = number of studies