ORIGINAL ARTICLE

Management of Ruptured Intracranial Aneurysms in the Post-International Subarachnoid Aneurysm Trial Era: A Single-Centre Prospective Series

Alexander D. Wong, Rufus Alubankudi, Judith Jarrett, Thien J. Huynh, Adam A. Dmytriw, Gwynedd E. Pickett

ABSTRACT: ***Background:*** Aneurysmal subarachnoid haemorrhage (aSAH) is associated with significant morbidity and mortality. The International Subarachnoid Aneurysm Trial (ISAT) reported reduced morbidity in patients treated with endovascular coiling versus surgical clipping. However, recent studies suggest that there is no significant difference in clinical outcomes. This study examines the outcomes of either technique for treating aSAH during the 15 years post-ISAT at a Canadian quaternary centre. ***Methods:*** We reviewed prospectively collected data of patients admitted with aSAH from January 2002 to December 2017. Glasgow Outcome Scale (GOS) was compared at discharge, 6 months and 12 months' follow-up using univariate and multivariable ordinal logistic regression. Post-operative complications were assessed using binary logistic regression. ***Results:*** Two-hundred and eighty-seven patients were treated with coiling and 95 patients with clipping. The mean age of clipped patients was significantly younger, and hypertension was significantly commoner in coiled patients. A greater proportion of coiled aneurysms were located in the posterior circulation. No difference in the odds of having a favourable GOS was seen between patients who were clipped versus coiled at any of follow-up time points on univariate or multivariable analysis. In both treatment groups, patient recovery to independence (GOS 4–5) was seen from discharge to 6 months, but not from 6 to 12 months' follow-up, without difference between clipping and coiling. ***Conclusion:*** These real-world findings suggest clipping remains an effective and important treatment option for patients with aSAH who do not meet ISAT inclusion criteria. The results can assist in clinical decision-making processes and understanding of the natural recovery progression of aSAH.

RÉSUMÉ : La prise en charge des ruptures d'anévrisme cérébral à la suite de l'essai ISAT : étude sur le terrain. ***Contexte*** **:** Les hémorragies sous-arachnoïdiennes anévrismales (HSAA) sont associées à une morbidité et à une mortalité importantes. D'après les résultats de l'International Subarachnoid Aneurysm Trial (ISAT), la pose de spires (*coil*) endovasculaires permet une réduction plus importante de la morbidité que la pose d'agrafes (*clip*) chirurgicales. Par contre, selon des études récentes, il n'y aurait pas de différence importante entre les deux techniques quant aux résultats cliniques. L'étude ici présentée visait donc à comparer les résultats de l'une et l'autre des formes de traitement des HSAA, observés au cours des 15 années qui ont suivi l'essai ISAT, dans un centre de soins quaternaires, situé au Canada. ***Méthode*** **:** L'étude consistait en un examen des données recueillies de manière prospective sur des patients hospitalisés pour une HSAA, entre janvier 2002 et décembre 2017. Il y a eu comparaison des résultats au moment du congé de l'hôpital ainsi qu'au bout de 6 mois et 12 mois de suivi, sur l'échelle des résultats de Glasgow (GOS), à l'aide d'une régression logistique ordinale à une ou plusieurs variables. Quant aux complications postopératoires, elles ont été évaluées par régression logistique binaire. ***Résultats*** **:** Dans l'ensemble, 287 patients ont été traités par des spires, et 95, par des agrafes. L'âge moyen des patients soumis à la pose d'agrafes était sensiblement moins élevé que celui des autres patients, et la fréquence de l'hypertension était passablement plus élevée dans le groupe de traitement par les « spires » que dans l'autre. Une proportion plus grande d'anévrismes traités par la pose de spires touchait le segment postérieur de la circulation sanguine. Pour ce qui est de la cote de résultats favorables sur la GOS, aucun écart n'a été relevé entre les patients traités par les agrafes et ceux traités par les spires, et ce, à tout moment du suivi, selon l'analyse à une ou plusieurs variables. Dans les deux groupes de traitement, un rétablissement des patients suivi d'un retour à l'autonomie (GOS : 4-5) a été observé dans l'intervalle écoulé entre le congé de l'hôpital et le 6^{e} mois, mais pas entre le 6^{e} et le 12^{e} mois de suivi, et ce, sans différence de résultats entre les deux techniques. ***Conclusion*** **:** L'étude sur le terrain donne à penser que la pose d'agrafes reste une forme importante et efficace du traitement des HSAA, chez les patients qui ne satisfont pas aux critères de sélection de l'ISAT. De plus, les résultats peuvent faciliter la prise de décision clinique et la compréhension de l'évolution naturelle des HSAA.

Keywords: Interventional neuroradiology, Cerebrovascular stroke, Neurosurgical procedures

doi:10.1017/cjn.2021.45 Can J Neurol Sci. 2022; 49: 62–69

From the Division of Neurosurgery, Department of Surgery, Dalhousie University, Halifax, NS, Canada (RA, JJ, GEP); and Division of Neuroradiology, Department of Diagnostic Radiology, Dalhousie University, Halifax, NS, Canada (ADW, TJH, AAD)

Received January 17, 2021. Final Revisions Submitted February 25, 2021. Date of Acceptance March 6, 2021.

Correspondence to: Gwynedd E. Pickett MD, Division of Neurosurgery, Dalhousie Medical School, 5849 University Ave., Halifax, NS B3H 4R2, Canada. Email: Gwynedd.Pickett@nshealth.ca

Introduction

Eighty-five per cent of cases of SAH are due to aneurysm rupture.[1] The morbidity, mortality and economic burden of aneurysmal subarachnoid haemorrhage (aSAH) continues to be considerable, with an estimated mean cost for hospitalisation of 82,514 USD per patient.[2] Half of the aSAH patients die within 1 month of the haemorrhage, and 40% of those who survive the first month remain dependent.[3] Additionally, early survivors are at elevated risk for a rebleed and secondary complications such as delayed cerebral ischaemia and hydrocephalus.[4] Timely treatment of ruptured intracranial aneurysms reduces the risk of rebleeding and long-term sequelae.

The two primary techniques of aneurysm repair include surgical clipping and endovascular coiling. The International Subarachnoid Aneurysm Trial (ISAT) concluded that for patients with ruptured aneurysms suitable for either treatment modality, endovascular coiling led to improved clinical outcomes at 1-year follow-up, as assessed by the modified Rankin scale (mRS).[5] As a result of ISAT and improvements in both coil technique and technology, coil embolisation has since become the preferred first-line treatment for most ruptured aneurysms in many centres,[5–7] with post-ISAT studies showing greater usage of endovascular coiling regardless of rupture status.[8,9]

However, many critiques have been raised regarding the ISAT study and its narrow choice of participants, study protocol, lack of data on excluded patients and lower durability as well as higher retreatment rates for coiled versus clipped patients in longer term follow-up.[10–12] Although there are studies that echo the results of ISAT,[13] more recent prospective data show no significant difference in clinical outcomes between the two techniques,[11] or an even greater mortality rates in coiled versus clipped poor-grade aSAH patients.[12] Although these smaller studies do not possess the degree of stringency of ISAT, they offer important data that potentially reflect the outcomes achievable in actual clinical practice as compared to the artificial environment of a randomised controlled trial (RCT).

We report the first cohort study in Canada using prospectively collected data to examine the treatment of ruptured intracranial aneurysms using surgical clipping and endovascular coiling techniques and associated patient outcomes over the past 15 years since the publication of ISAT at a quaternary care centre. We hypothesised that patients treated with endovascular coiling would have better clinical outcomes than those treated with craniotomy and clipping.

Methods

Study Population

Research ethics approval was received from the local health authority (REB:1014100). A review of prospectively collected data was performed on the cerebrovascular database consisting of records of all patients with spontaneous aSAH managed at a Canadian quaternary care centre from January 2002 to December 2017.

Exclusion Criteria

Patients with non-aneurysmal SAH, those who died before receiving treatment, or who received surgical clipping and endovascular coiling simultaneously were excluded from this study.

Treatment Decision and Protocols

Decision on the aneurysm treatment modality was made on a case-by-case basis based on clinical status, imaging, aneurysm dome/neck ratio, morphology and location. Cross-sectional imaging (CT angiography) was performed in all cases, with preoperative digital subtraction angiography obtained in cases where it was felt useful or necessary to inform treatment decisions and operative technique. Each case was reviewed with the cerebrovascular team consisting of a neurosurgeon and neurointerventionalist. Pre and post-operative management was performed according to the institutional standard of care for aSAH.

Aneurysm treatment was performed by or under the direct supervision of a specialist with extensive experience. Patients treated with surgical clipping underwent frontal, pterional or skull base approaches depending on the aneurysm location. Patients treated with endovascular coiling received optional balloon or stent assistance as required. Aneurysmal obliteration was confirmed using intra- and post-operative angiography.

All patients were admitted to the intensive care unit or neurosurgical intermediate care unit post-operatively for management of vasospasm, hydrocephalus or other complications under the supervision of a neurosurgeon. Follow-up was performed in an outpatient setting at 6 months and 12 months after the discharge date.

Data Definition and Collection

Baseline patient characteristics included age at admission, gender, current smoking status, hypertension, diabetes mellitus, previous aneurysm repair, prior stroke, time to treatment, number of aneurysms, aneurysm location, maximal diameter of culprit aneurysm (in mm), hospital stay (in days), admission scores (World Federation of Neurological Society [WFNS] score, Fisher scale[14]) and length of hospital stay (in days).

Age at admission was dichotomised into <50 years or ≥50 years. Admission scores were dichotomised into the following groups: WFNS score (grades 1–3 for good, 4–5 for bad) and Fisher score (grades 1–2 for good, 3–4 for bad). Aneurysm location was dichotomised into anterior or posterior circulation (Table 1), and size into <10 mm or ≥10 mm.

The primary outcome was the Glasgow Outcome Scale (GOS) at discharge, 6 and 12 months' follow-up after the discharge date, which was categorised into dead (GOS 1), dependent (GOS 2–3) or independent (GOS 4–5). Secondary outcomes included post-operative complications such as rebleed, vasospasm, infarction, hydrocephalus, seizure, infection and pneumonia.

Statistical Analysis

Baseline patient characteristics were reported as means with standard deviations or as counts with percentages, and then subsequently compared between the two treatment groups using Welch's *t*-tests, Wilcoxon Rank sum, chi-squared and Fisher's exact tests with a significance level of $\alpha = 0.05$.

Univariate analyses of outcome variables were performed using chi-squared and Fisher's exact tests. Crude and adjusted odds ratios with 95% confidence intervals were calculated using an ordinal logistic regression model for GOS at discharge, 6 months and 12 months' follow-up. Models were adjusted for

https://doi.org/10.1017/cjn.2021.45 Published online by Cambridge University Press

Table 1: Baseline patient characteristics

Patient characteristics	Endovascular coiling	Surgical clipping	P-value
	***n* = 287**	***n* = 95**	
Mean age, years (SD)	57.1 (14.0)	53.4 (12.6)	0.02*
Female, *n* (%)	203 (70.7)	63 (66.3)	0.49†
Current smoking, *n* (%)	108 (37.6)	37 (38.9)	0.91†
Hypertension, *n* (%)	99 (34.5)	19 (20.0)	0.01†
Diabetes mellitus, *n* (%)	17 (5.9)	5 (5.3)	1.00†
Prior aneurysm repair, *n* (%)	9 (3.1)	1 (1.1)	0.46‡
Prior stroke, *n* (%)	8 (2.8)	2 (2.1)	1.00‡
Mean time to treatment, days (SD)	0.7 (1.3)	1.2 (2.8)	0.69§
Number of aneurysms, *n* (%)			0.59†
Single	230 (80.1)	73 (76.8)	
Multiple	57 (19.9)	22 (23.2)	
Aneurysm location, *n* (%)			0.01†
Anterior circulation	236 (82.2)	89 (93.7)	
Posterior circulation	51 (17.8)	6 (6.3)	
Mean size of culprit aneurysm, mm (SD)	7.4 (4.0)	7.3 (5.2)	0.13§
WFNS score, *n* (%)			0.29†
1–3	220 (76.7)	67 (70.5)	
4–5	67 (23.3)	28 (29.5)	
Fisher scale, *n* (%)			0.41†
1–2	68 (23.7)	18 (18.9)	
3–4	219 (76.3)	77 (81.1)	
Mean length of hospital stay, days (SD)	23.3 (37.5)	23.5 (23.4)	0.33§

SD = standard deviation; WFNS = World Federation of Neurological Society.
*Welch's *t*-test is used to compare the variables.
†Chi-squared test is used to compare the variables.
‡Fisher's exact test is used to compare the variables.
§Wilcoxon rank-sum test is used to compare the variables.

age at admission, hypertension and aneurysm location using multivariable ordinal logistic regression. Interaction between age at admission and hypertension was also assessed in the models using an interaction term. The proportional odds assumption of the final adjusted model was assessed using the Brant test, model fit was assessed with Hosmer and Lemeshow, Lipsitz goodness of fit and Pulkstenis–Robinson chi-squared and deviance tests and model performance was assessed using the misclassification error. Crude and adjusted odds ratios with 95% confidence intervals were calculated using binary logistic regression models for secondary outcomes. Model fit and predictive ability were assessed with the Hosmer–Lemeshow test and receiver operating characteristic curves, respectively. To evaluate for potential differences in trends in patient demographics, clipping or coiling treatment and treatment outcomes over time, additional subgroup analysis was also performed by grouping patients into three time periods by admission date: 2002–2007, 2008–2012 and 2013–2017. All statistical analyses were performed with R version 3.6.1.

Results

Patient Characteristics

A total of 577 patients were treated with coiling or clipping during this time period, and 382 had 12-month follow-up data available (Figure 1), of whom 287 patients received coiling and 95 patients received clipping (Table 2). The mean age of clipped patients was significantly younger than coiled patients (53.4 ± 12.6 vs. 57.1 ± 14.0 years, $p = 0.02$), and hypertension was significantly more common in those who were coiled versus clipped (99/287 [34.5%] vs. 19/95 [20.0%], $p = 0.01$). A greater proportion of coiled aneurysms were located in the posterior circulation compared to clipped aneurysms (51/287 [17.8%] vs. 6/95 [6.3%], $p = 0.01$). There were no significant differences in gender, current smoking status, diabetes mellitus, prior aneurysm repair, prior stroke, mean time to treatment, number of aneurysms, mean size of culprit aneurysm, WFNS score, Fisher score or mean length of hospital stay between the coiling and clipping groups. No patients experienced a rebleed in the time period between admission and treatment. Subgroup analysis of mean age by time period showed that in 2008–2012, clipped patients were significantly younger than coiled patients (52.1 ± 10.7 vs. 56.7 ± 15.0 years, $p = 0.04$). There was no significant difference in age between the two treatment groups in 2002–2007 and 2013–2017.

Univariate Analysis of GOS and Secondary Outcomes

There were no significant differences in GOS between coiling and clipping patients at discharge, 6 months or 12 months' follow-up (Table 3). There was a moderate improvement in GOS from dependent to independent between discharge and 6 months in both groups, but virtually no change in GOS from 6 months to 12 months. Additionally, no significant differences in post-surgical complications were seen between the two groups in terms of rebleed, vasospasm, infarct, hydrocephalus, seizure, infection and pneumonia.

Multivariable Analyses of GOS and Secondary Outcomes

In the overall multivariable analysis and analysis by time period, patients who were treated with coiling showed no significant difference in odds of having a favourable GOS compared to patients who were clipped at any of the time points: discharge, 6 months or 12 months' follow-up (Table 4). Patient's age >50 years had lower odds of having a favourable GOS at all time points. Patients with hypertension had lower odds of having a favourable GOS at discharge, however, this relationship lost significance after adjusting for treatment type, age at admission and aneurysm location (Adjusted OR 0.66 [95% CI 0.42–1.04], $p = 0.07$). There was no evidence of significant interaction between age and hypertension in the regression model at all time points. Adequate model fitting and performance were demonstrated for GOS at all time points and the proportional odds assumption was satisfied for all three models.

Regarding secondary outcomes, patients who were treated with coiling had lower odds of experiencing infarction at

https://doi.org/10.1017/cjn.2021.45 Published online by Cambridge University Press

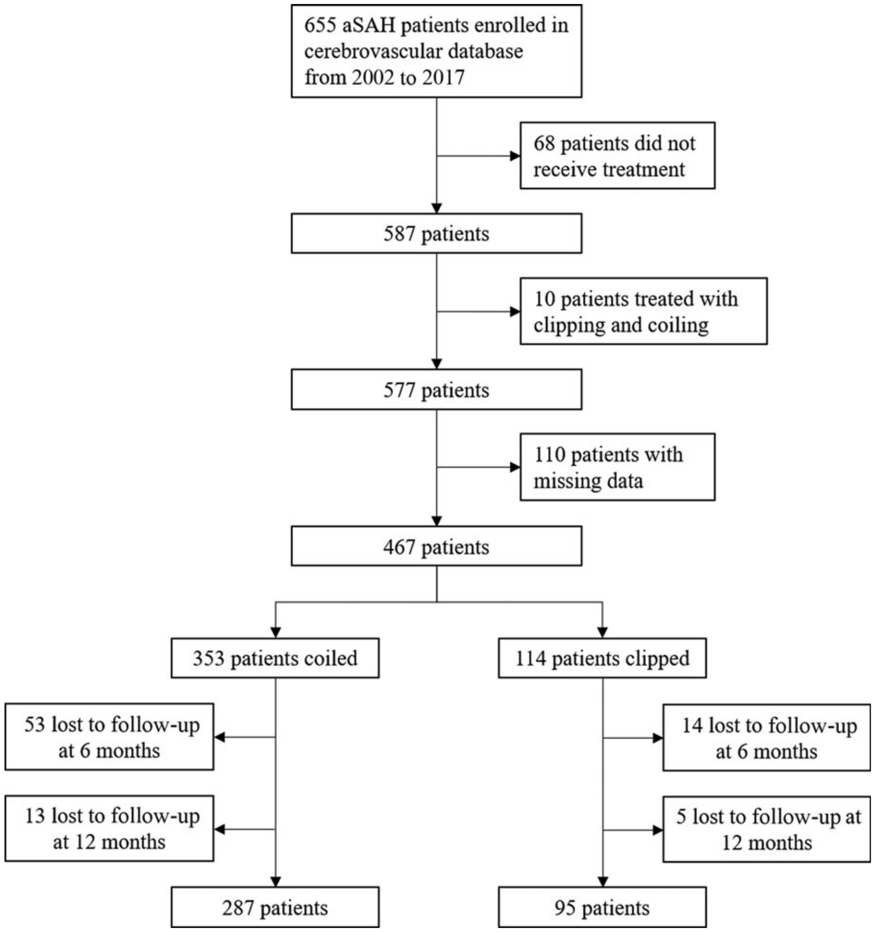

Figure 1: *Patient flow diagram.*

discharge compared to patients who were clipped after adjusting for age, hypertension and aneurysm location (Adjusted OR 0.52 [95% CI 0.29–0.92], $p = 0.02$). Patients who were treated with coiling had greater odds of experiencing hydrocephalus compared to patients who were clipped, but this relationship lost significance after adjustment for age at admission, hypertension and aneurysm location (Adjusted OR 1.62 [95% CI 0.92–2.99], $p = 0.11$) (Table 5). There were no significant differences in the other secondary outcomes (rebleed, vasospasm, seizure, infection, pneumonia) between clipped versus coiled patients.

Discussion

Our study compared surgical clipping versus endovascular coiling and subsequent patient outcomes at discharge, 6 months and 12 months over a 15-year post-ISAT period at a Canadian quaternary centre. There was no significant difference in GOS at any of the follow-up time points between the two treatment methods. This is in contrast with ISAT, which demonstrated a 22.6% (95% CI 8.9–34.2%) relative risk reduction for being dead or dependent in coiled versus clipped patients at 12 months based on the mRS.[5] Although different measures of patient outcome were used between our study and ISAT, comparison can still be made as both studies grouped outcomes to look at the likelihood of being independent versus dead or dependent. The most recent data from the Barrow Ruptured Aneurysm Trial favoured coiling on short-term follow-up, but showed no significant difference in risk of death or poor outcome (defined as mRS > 2) at 10 years follow-up between patients who were coiled or clipped.[11] Although a comparison cannot be made between our results and this recent trial due to a difference in follow-up time points, this trial along with a number of other trials,[15,16] meta-analysis,[17] single-centred[18–25] and multicentred studies[13,26] continue to echo a lack of difference in patient outcomes between the two treatment modalities at various follow-up time points.

Although we cannot definitively conclude that clipping is non-inferior to coiling for patients with aSAH from the results of our study alone, our findings combined with those emerging in literature post-ISAT suggest that surgical clipping remains an important treatment option for patients with aSAH that would not have met the equipoise criteria for ISAT. Further research is required to examine the benefits of clipping versus coiling for patients who do not meet the inclusion criteria for ISAT. The ongoing ISAT-2 study aims to further elucidate this by including the subgroup of aneurysms that were not well represented in the original ISAT study.[27]

Our results suggest that clipping remains a potentially effective and important treatment option compared to coiling with respect to patient outcomes at 6–12 months post-treatment in real-world conditions despite a clear decline in clipping for ruptured intracranial aneurysm repair since the ISAT study was published.[28] This may be attributable to improvements in the clipping

https://doi.org/10.1017/cjn.2021.45 Published online by Cambridge University Press

Table 2: Distribution of culprit aneurysms by location

Location	Endovascular coiling (%)	Surgical clipping (%)	Total (%)
Anterior circulation			
Anterior communicating artery	121 (42.2)	12 (12.6)	133 (34.8)
Anterior cerebral artery	8 (2.8)	2 (2.1)	10 (2.6)
Internal carotid artery	28 (9.8)	6 (6.3)	34 (8.9)
Pericallosal artery	7 (2.4)	0 (0)	7 (1.8)
Middle cerebral artery	14 (4.9)	44 (46.3)	58 (15.2)
Posterior communicating artery*	58 (20.2)	25 (26.3)	83 (21.7)
Posterior circulation			
Posterior cerebral artery	3 (1.0)	0 (0)	3 (0.8)
Superior cerebellar artery	5 (1.7)	0 (0)	5 (1.3)
Basilar artery	26 (9.1)	0 (0)	26 (6.8)
Anterior inferior cerebellar artery	1 (0.3)	0 (0)	1 (0.3)
Vertebrobasilar junction	2 (0.7)	0 (0)	2 (0.5)
Vertebral artery	1 (0.3)	0 (0)	1 (0.3)
Posterior inferior cerebellar artery	13 (4.5)	6 (6.3)	19 (5.0)

*These aneurysms are classified here as anterior circulation due to their anatomical location on the ICA, despite their embryological origin.

procedure, post-surgical care and/or improved patient allocation to treatment modality.[29,30] Furthermore, the prognosis of aSAH may be more importantly determined by patient comorbidities and aneurysm characteristics as opposed to treatment modality.[31] Our results suggest that aSAH patients who receive either treatment experience the greatest chance of improving from dependence to independence during the 6 months post-treatment, with recovery to independence beyond this time frame being unlikely, which may have implications for clinical decision-making and understanding of the natural recovery progression of aSAH.

Additionally, our results showed that patients who were 50 years or older were less likely to have favourable outcomes at discharge, 6 months and 12 months independent of the effects of hypertension, which is consistent with post hoc analyses of ISAT and a number of other studies.[32–34] Patients with advanced age tend to present with poorer status and more comorbidities, contributing to less favourable outcomes.[35] Our study also demonstrated a statistically significant reduction in odds of experiencing an ischaemic infarct for coiled versus clipped patients independent of age at admission, hypertension and aneurysm location. Literature shows mixed conclusions, with some showing no association[36,37] and others echoing our results.[15] Finally, we observed significantly greater odds for coiled patients to develop hydrocephalus, which lost significance after adjustment. This observation was likely confounded, as the coiled group had older mean age and greater proportion of posterior circulation aneurysms. These are both poor prognostic factors for clipping and confer greater risk for developing hydrocephalus, hence the loss of significance after statistical adjustment.

Finally, there was a significant allocation of both anterior and posterior circulation aneurysms to the coiling group in our study,

Table 3: Univariate analysis of Glasgow Outcome Scale and secondary outcomes associated with surgical clipping compared to endovascular coiling

Outcomes	Endovascular coiling	Surgical clipping	P-value
	$n = 287$	$n = 95$	
GOS at discharge, *n* (%)			0.96*
Dead (GOS 1)	54 (18.8)	18 (18.9)	
Dependent (GOS 2–3)	39 (13.6)	14 (14.7)	
Independent (GOS 4–5)	194 (67.6)	63 (66.3)	
GOS 6 months after discharge, *n* (%)			0.60*
Dead (GOS 1)	54 (18.8)	18 (18.9)	
Dependent (GOS 2–3)	16 (5.6)	8 (8.4)	
Independent (GOS 4–5)	217 (75.6)	69 (72.6)	
GOS 12 months after discharge, *n* (%)			0.52*
Dead (GOS 1)	54 (18.8)	18 (18.9)	
Dependent (GOS 2–3)	15 (5.2)	8 (8.4)	
Independent (GOS 4–5)	218 (76.0)	69 (72.6)	
Rebleed, *n* (%)	26 (9.1)	11 (11.6)	0.60*
Vasospasm, *n* (%)	76 (26.5)	22 (23.2)	0.61*
Infarct, *n* (%)	58 (20.2)	26 (27.4)	0.19*
Hydrocephalus, *n* (%)	86 (30.0)	18 (18.9)	0.05*
Seizure, *n* (%)	7 (2.4)	4 (4.2)	0.48†
Infection, *n* (%)	8 (2.8)	3 (3.2)	1.00†
Pneumonia, *n* (%)	13 (4.5)	2 (2.1)	0.38†

GOS = Glasgow Outcome Scale.
*Chi-squared test is used to compare the variables.
†Fisher's exact test is used to compare the variables.

reflective of the post-ISAT era and in contrast to ISAT. We adjusted for the potential effects of aneurysm location in our analysis and found there continued to be no significant difference in patient outcomes between the two treatment modalities, independent of aneurysm location, at any of the follow-up time points.

This study represents the first prospective cohort study to examine the effect of clipping versus coiling on patient outcomes over a 15-year post-ISAT period at a Canadian quaternary centre. It has the advantage of prospective, rigorous data collection and reflects Canadian practice patterns.

However, it was subject to several limitations. In the earlier years of the study period, a significant proportion of patients were referred from other provinces due to the scarcity of interventional resources. This led to a sizeable loss to follow-up from 577 to 382 patients as they were sent back to their home province upon recovery. Our sample size may have limited statistical power and the ability to potentially reach statistical significance for the observed trends.

With 40–50 cases of SAH per year, this represents the experience of a medium–small volume centre. Over the 15-year period, care was delivered by more than one provider in each treatment arm, further reducing the number of cases per provider. This may limit the applicability of our results to current

https://doi.org/10.1017/cjn.2021.45 Published online by Cambridge University Press

Table 4: Ordinal regression analysis of Glasgow Outcome Scale

Glasgow Outcome Scale	Crude analysis		Adjusted analysis*	
At discharge	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Coiling (vs. clipping)	1.05 (0.64–1.69)	0.84	1.42 (0.84–2.36)	0.18
Age ≥ 50 years (vs. < 50 years)	0.38 (0.23–0.61)	<0.001	0.39 (0.23–0.64)	<0.001
Hypertension (vs. no)	0.59 (0.38–0.91)	0.02	0.66 (0.42–1.04)	0.07
Aneurysm location (vs. anterior)	0.65 (0.37–1.16)	0.14	0.60 (0.34–1.08)	0.08
At 6 months				
Coiling (vs. clipping)	1.13 (0.67–1.89)	0.64	1.52 (0.87–2.64)	0.14
Age ≥ 50 years (vs. < 50 years)	0.33 (0.18–0.57)	<0.001	0.33 (0.18–0.58)	<0.001
Hypertension (vs. no)	0.63 (0.39–1.03)	0.06	0.72 (0.43–1.19)	0.19
Aneurysm location (vs. anterior)	0.61 (0.34–1.14)	0.11	0.56 (0.30–1.06)	0.07
At 12 months				
Coiling (vs. clipping)	1.15 (0.68–1.92)	0.46	1.54 (0.88–2.67)	0.13
Age ≥ 50 years (vs. < 50 years)	0.33 (0.18–0.58)	<0.001	0.33 (0.18–0.59)	<0.001
Hypertension (vs. no)	0.65 (0.40–1.06)	0.08	0.74 (0.45–1.23)	0.23
Aneurysm location (vs. anterior)	0.61 (0.34–1.12)	0.10	0.55 (0.30–1.05)	0.06

CI = confidence interval; OR = odds ratio.
*Models were adjusted for all other covariates in the table within their respective follow-up time points.

Table 5: Regression analysis of post-operative secondary outcomes

Secondary outcomes	Crude analysis		Adjusted analysis*	
Coiling (vs. clipping)	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Rebleed	0.76 (0.37–1.67)	0.47	0.76 (0.35–1.70)	0.48
Vasospasm	1.20 (0.70–2.09)	0.52	1.18 (0.68–2.10)	0.56
Infarct	0.67 (0.40–1.16)	0.15	0.52 (0.29–0.92)	0.02
Hydrocephalus	1.83 (1.05–3.32)	0.04	1.62 (0.92–2.99)	0.11
Seizure	0.57 (0.17–2.21)	0.38	0.43 (0.12–1.77)	0.21
Infection	0.88 (0.25–4.08)	0.85	0.68 (0.17–3.35)	0.60
Pneumonia	2.21 (0.60–14.28)	0.30	1.53 (0.38–10.19)	0.59

CI = confidence interval; OR = odds ratio.
*Models were adjusted for age at admission, hypertension and aneurysm location.

procedural experiences at other institutions. However, while a full discussion of case volume and procedural competence is outside the scope of this paper, we believe our results may be relevant to the many centres in the small-to-medium volume range. Treating physicians were fellowship-trained in large centres with significant case volumes, and annual case volumes were within ranges described for maintenance of competence and reduction of complications.[38]

mRs is thought to be a more sensitive measure of patient outcome than GOS,[39] and was not incorporated in the data collection protocol until recent years. The mRS requires a structured interview and completion of training by the assessor in order to ensure inter-rater reliability. It is frequently used in clinical trials, but is rarely assessed for all patients in most practicing clinical groups. Given all this, it precluded us from using the scale in the current 15-year study.

We included both anteriorly and posteriorly located aneurysms to ensure the reported outcomes most accurately represented a real-world clinical setting. Although RCTs offer much more robust control for potential confounders, there is still great value derived from this cohort as it presents real-world results for both treatment modalities that were achievable by a multidisciplinary group working in a post-ISAT period.

Despite efforts to adjust for baseline characteristic differences, variables not collected in our study may have influenced the results. The lack of randomisation and locations of aneurysms present in this cohort naturally promoted mutual exclusivity of patients in the treatment modality decision-making process, which may have limited the comparability of the two treatment groups due to the absence of intervention-equipoise. Generalisability of the results may be limited as this was a single-centred study, and a much greater proportion of our cohort was treated through coiling versus clipping. Finally, it represents real-world clinical practice, in which there was no randomisation, and so there is evidently selection bias. However, it does demonstrate that such selection, when done by subspecialty experts, does not

https://doi.org/10.1017/cjn.2021.45 Published online by Cambridge University Press

lead to inferior patient outcomes in patients treated with surgical clipping.

Conclusion

Our analysis showed no significant difference in clinical outcomes between aSAH patients who were clipped versus coiled at discharge, 6 months and 12 months' follow-up. Overall in both clipping and coiling groups, patient recovery to independence was observed from discharge to 6 months, with no further recovery seen from 6 to 12 months' follow-up. In both groups, patient's age over 50 years decreased the likelihood of recovery to independence. These findings suggest that clipping remains an effective and important treatment option for aSAH compared to coiling when decisions are made by an expert multidisciplinary cerebrovascular team, and can help inform the shared decision-making process between physicians, patients and families. Further research is required to examine the benefits of clipping versus coiling for patients who do not meet the inclusion criteria for ISAT.

Acknowledgements

We acknowledge the imaging technologists and operating room/interventional nurses, without whom this work would not be possible.

Funding

Mr. Alubankudi was supported with a summer research studentship from the Imhotep Legacy Academy (Dalhousie University, Halifax, Canada).

Conflict of Interest

There are no conflicts of interest from any authors of this manuscript, financial or otherwise.

Institutional Review Board Approval

Research ethics approval was granted by the Nova Scotia Health Authority (REB:1014100).

Statement of Authorship

Study design: GEP, JJ, RA, ADW, TJH. Data collection: RA, ADW, JJ, GEP. Data analysis and interpretation: ADW, GEP, AAD, TJH. Drafting the article: ADW, RA, GEP. Critical revision of the article: AAD, GEP, TJH.

References

1. Macdonald RL, Schweizer TA. Spontaneous subarachnoid haemorrhage. Lancet. 2017;389:655–66.
2. Modi S, Shah K, Schultz L, Tahir R, Affan M, Varelas P. Cost of hospitalization for aneurysmal subarachnoid hemorrhage in the United States. Clin Neurol Neurosurg. 2019;182: 167–70.
3. Natarajan SK, Sekhar LN, Ghodke B, Britz GW, Bhagawati D, Temkin N. Outcomes of ruptured intracranial aneurysms treated by microsurgical clipping and endovascular coiling in a high-volume center. AJNR Am J Neuroradiol. 2008;29:753–9.
4. Fraser JF, Riina H, Mitra N, Gobin YP, Simon AS, Stieg PE. Treatment of ruptured intracranial aneurysms: looking to the past to register the future. Neurosurgery. 2006;59: 1157–66; discussion 1166–7.
5. Molyneux A, Kerr R. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomized trial. J Stroke Cerebrovasc Dis. 2002;11:304–14.
6. Lin N, Cahill KS, Frerichs KU, Friedlander RM, Claus EB. Treatment of ruptured and unruptured cerebral aneurysms in the USA: a paradigm shift. J Neurointerv Surg. 2018;10: i69–76.
7. Bederson JB, Connolly ES, Batjer HH, et al. Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage. Stroke. 2009;40:994–1025.
8. Alshekhlee A, Mehta S, Edgell RC, et al. Hospital mortality and complications of electively clipped or coiled unruptured intracranial aneurysm. Stroke. 2010;41:1471–6.
9. Qureshi AI, Vazquez G, Tariq N, Suri MFK, Lakshminarayan K, Lanzino G. Impact of International Subarachnoid Aneurysm Trial results on treatment of ruptured intracranial aneurysms in the United States. J Neurosurg. 2011;114:834–41.
10. Molyneux AJ, Birks J, Clarke A, Sneade M, Kerr RSC. The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT). Lancet. 2015;385:691–7.
11. Spetzler RF, McDougall CG, Zabramski JM, et al. Ten-year analysis of saccular aneurysms in the Barrow Ruptured Aneurysm Trial. J Neurosurg. 2019;1:1–6.
12. Zhao B, Rabinstein A, Murad MH, Lanzino G, Panni P, Brinjikji W. Surgical and endovascular treatment of poor-grade aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. J Neurosurg Sci. 2017;61:403–15.
13. Zhao B, Tan X, Yang H, et al. Endovascular coiling versus surgical clipping for poor-grade ruptured intracranial aneurysms: postoperative complications and clinical outcome in a multicenter poor-grade aneurysm study. Am J Neuroradiol. 2016;37:873–8.
14. Fisher CM, Kistler JP, Davis JM. Relation of Cerebral Vasospasm to Subarachnoid Hemorrhage Visualized by Computerized Tomographic Scanning. Neurosurgery. 1980;6:1–9.
15. Li Z-Q, Wang Q-H, Chen G, Quan Z. Outcomes of endovascular coiling versus surgical clipping in the treatment of ruptured intracranial aneurysms. J Int Med Res. 2012;40: 2145–51.
16. Koivisto T, Vanninen R, Hurskainen H, Saari T, Hernesniemi J, Vapalahti M. Outcomes of early endovascular versus surgical treatment of ruptured cerebral aneurysms. A prospective randomized study. Stroke. 2000;31:2369–77.
17. Xia Z-W, Liu X-M, Wang J-Y, et al. Coiling is not superior to clipping in patients with high-grade aneurysmal subarachnoid hemorrhage: systematic review and meta-analysis. World Neurosurg. 2017;98:411–20.
18. Taha MM, Nakahara I, Higashi T, et al. Endovascular embolization vs surgical clipping in treatment of cerebral aneurysms: morbidity and mortality with short-term outcome. Surg Neurol. 66: 277–84.
19. Tenjin H, Takadou M, Ogawa T, et al. Treatment selection for ruptured aneurysm and outcomes: clipping or coil embolization. Neurol Med Chir (Tokyo). 2011;51:23–9.
20. Shirao S, Yoneda H, Kunitsugu I, et al. Preoperative prediction of outcome in 283 poor-grade patients with subarachnoid hemorrhage: a project of the Chugoku-Shikoku Division of the Japan Neurosurgical Society. Cerebrovasc Dis. 2010; 30:105–13.
21. Kato Y, Sano H, Dong PT, et al. The effect of clipping and coiling in acute severe subarachnoid hemorrhage after international subarachnoid aneurysmal trial (ISAT) results. Minim Invasive Neurosurg. 2005;48:224–7.
22. Hui FK, Schuette AJ, Moskowitz SI, et al. Microsurgical and endovascular management of pericallosal aneurysms. J Neurointerv Surg. 2011;3:319–23.
23. Sandström N, Yan B, Dowling R, Laidlaw J, Mitchell P. Comparison of microsurgery and endovascular treatment on

https://doi.org/10.1017/cjn.2021.45 Published online by Cambridge University Press

clinical outcome following poor-grade subarachnoid hemorrhage. J Clin Neurosci. 2013;20:1213–8.
24. Premananda RM, Ramesh N, Hillol KP. Functional outcome of microsurgical clipping compared to endovascular coiling. Med J Malaysia. 2012;67:585–90.
25. Steklacova A, Bradac O, Charvat F, De Lacy P, Benes V. “Clip first” policy in management of intracranial MCA aneurysms: single-centre experience with a systematic review of literature. Acta Neurochir (Wien). 2016;158:533–46.
26. Wang H-Y, Song J, Gao F, et al. Outcomes of microsurgical clipping vs coil embolization for ruptured aneurysmal subarachnoid hemorrhage: a multicenter real-world analysis of 583 patients in China. Medicine (Baltimore). 2019;98:e16821.
27. Darsaut TE, Roy D, Weill A, et al. A randomized trial of endovascular versus surgical management of ruptured intracranial aneurysms: interim results from ISAT2. Neurochirurgie. 2019; 65:370–6.
28. Grasso G, Alafaci C, Macdonald RL. Management of aneurysmal subarachnoid hemorrhage: State of the art and future perspectives. Surg Neurol Int. 2017;8:11.
29. Brinjikji W, Lanzino G, Rabinstein AA, Kallmes DF, Cloft HJ. Age-related trends in the treatment and outcomes of Ruptured Cerebral Aneurysms: a study of the Nationwide Inpatient Sample 2001–2009. AJNR Am J Neuroradiol. 2013;34: 1022–1027.
30. Hwang US, Shin HS, Lee SH, Koh JS. Decompressive surgery in patients with poor-grade aneurysmal subarachnoid hemorrhage: clipping with simultaneous decompression versus coil embolization followed by decompression. J Cerebrovasc Endovasc Neurosurg. 2014;16:254.
31. Connolly ES, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. Stroke. 2012;43: 1711–37.
32. Mitchell P, Kerr R, Mendelow AD, Molyneux A. Could late rebleeding overturn the superiority of cranial aneurysm coil embolization over clip ligation seen in the International Subarachnoid Aneurysm Trial? J Neurosurg. 2008;108:437–42.
33. Mitchell P, Jakubowski J. Risk analysis of treatment of unruptured aneurysms. J Neurol Neurosurg Psychiatry. 2000;68:577–80.
34. Lanzino G, Kassell NF, Germanson TP, et al. Age and outcome after aneurysmal subarachnoid hemorrhage: why do older patients fare worse? J Neurosurg. 1996;85:410–8.
35. van Donkelaar CE, Bakker NA, Birks J, et al. Prediction of outcome after aneurysmal subarachnoid hemorrhage. Stroke. 2019;50: 837–44.
36. Dumont AS, Crowley RW, Monteith SJ, et al. Endovascular treatment or neurosurgical clipping of ruptured intracranial aneurysms. Stroke. 2010;41:2519–24.
37. Li H, Pan R, Wang H, et al. Clipping versus coiling for ruptured intracranial aneurysms: a systematic review and meta-analysis. Stroke. 2013;44:29–37.
38. Rush B, Romano K, Ashkanani M, McDermid RC, Celi LA. Impact of hospital case-volume on subarachnoid hemorrhage outcomes: a nationwide analysis adjusting for hemorrhage severity. J Crit Care. 2017;37:240–3.
39. Tong JT, Eyngorn I, Mlynash M, Albers GW, Hirsch KG. Functional neurologic outcomes change over the first 6 months after cardiac arrest. Crit Care Med. 2016;44:e1202–7.