CONTROVERSIES IN THE INVESTIGATION AND MANAGEMENT OF SUBARACHNOID HAEMORRHAGE AND ITS COMPLICATIONS:

IS A MORE PRAGMATIC APPROACH AND COMPREHENSIVE ENDOVASCULAR TREATMENT JUSTIFIED?

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TABLE OF CONTENTS

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DECLARATION

I declare that this thesis is an accurate record of results obtained by myself following work at North Bristol NHS Trust, United Kingdom and Royal North Shore and Westmead Hospitals, Sydney, Australia. The work has previously been published in peer reviewed journals and the original papers are presented in the appendices. All sources of support and assistance have been stated in the text of the acknowledgments. None of the work has been previously submitted for a higher degree. All sources have been specifically acknowledged by means of reference.

ABSTRACT

There are multiple factors that may impact on the outcome of a patient with subarachnoid haemorrhage (SAH). As well as the acute injury, these include the mode of treatment: surgical clipping (SC) or endovascular coiling (EVC); the complications and durability of investigations and treatment and the delayed ischaemic processes/cerebral vasospasm. The International Subarachnoid Aneurysm Trial (ISAT) demonstrated a significant reduction in the rate of death or dependency for patients treated with EVC rather than SC but ISAT did not address certain issues that remain controversial. This research focuses on some of the reasons for the ISAT findings and investigates areas that were not specifically investigated in the trial including the role of EVC of middle cerebral artery (MCA) aneurysms; cognition and the brain injury incurred through SC and EVC of anterior communicating artery (ACOM) aneurysms; the interaction between SC and EVC and the physiological derangement of the patient; the potential use of non-invasive imaging only in the investigation of more benign perimesencephalic subarachnoid haemorrhage (PMSAH); endovascular treatment of severe vasospasm and finally, the follow-up necessary for adequately coiled aneurysms.

The findings of this thesis suggest that EVC is a suitable first line treatment for MCA aneurysms; that the injury sustained by brain regions heavily involved with cognition is significantly greater in patients with ACOM aneurysms treated with SC; that clinical outcomes in patients with more severe physiological derangement are superior for coiled patients; that invasive imaging may be unnecessary in patients with PMSAH; that endovascular treatment of vasospasm results in low rates of cerebral infarction and may negate its clinical impact; and finally that long term follow-up of adequately occluded coiled aneurysms is probably not necessary.

GLOSSARY OF TERMS

ACA, anterior cerebral artery

ACOM artery, anterior communicating artery

APACHE II, Acute Physiology and Chronic Health Evaluation II score

ATENA, Analysis of Treatment by Endovascular Approach of Nonruptured Aneurysms (study)

aVSP, angiographic vasospasm

BA, basilar artery

BRAT, Berrow Ruptured Aneurysm Trial

CARAT, Cerebral Aneurysm Rerupture After Treatment

CBF, cerebral blood flow

CI, confidence interval

CLARITY, Clinical and Anatomical Results in the Treatment of Ruptured Intracranial Aneurysms

CT, computed tomography

CTA, CT angiography

DSA, digital subtraction angiography

EVC, endovascular coiling

FLAIR, Fluid-attenuated inversion recovery

GCS, Glasgow Coma Scale

GOS, Glasgow Outcome Score

HELPS, HydroCoil Endovascular Aneurysm Occlusion and Packing Study

IA, intra-arterial

ICA, internal carotid artery

ISAT, International Subarachnoid Aneurysm Trial

ISUIA, International Study of Unruptured Intracranial Aneurysms

MCA, middle cerebral artery

MRA, magnetic resonance angiography

MRI, magnetic resonance imaging

mRS, modified Rankin Scale

NCCT, non-contrast CT

NPV, negative predictive value

OR, odds ratio

PCA, posterior cerebral artery

PCOM artery, posterior communicating artery

PMSAH, perimesencephalic subarachnoid haemorrhage

RAH, recurrent artery of Heubner

TBA, transluminal balloon angioplasty

TCD, transcranial Doppler

SAH, subarachnoid haemorrhage

SC, surgical clipping

VA, vertebral artery

WFNS, World Federation of Neurosurgical Societies

CHAPTER 1

INTRODUCTION AND SUMMARY OF RESEARCH

1.1 Subarachnoid haemorrhage

1.1.1 Definition

Subarachnoid haemorrhage (SAH) describes extravasation of blood into the subarachnoid space (the cerebro-spinal fluid-filled area lying between pia mater deeply and arachnoid membrane more superficially). This can be as a result of head trauma or can be spontaneous and in the latter case an underlying neurovascular abnormality is commonly identified. Spontaneous SAH was first described in detail in the British medical literature in the late 19th century (Bramwell, 1886) and, by the 1920's there was considerable understanding of the clinical and pathological features of the condition (Symonds, 1924).

1.1.2 Aetiology

When spontaneous, SAH usually lies within the cisterns at the base of the brain and most commonly results from the rupture of a cerebral aneurysm, a focal abnormal dilatation in the wall of a cerebral artery. Indeed, aneurysmal SAH accounts for approximately 85% of all SAH, whilst perimesencephalic haemorrhage (which may have a venous origin and represents a distinct clinic-radiological entity) accounts for approximately 5% (van Gijn *et al,* 2001, Flaherty *et al,* 2005). There are a number of other pathological processes that can result in spontaneous SAH including dural arteriovenous fistula, arteriovenous malformations, cavernous angiomata, reversible cerebral vasoconstriction syndrome, vasculitis, venous sinus/cortical vein thrombosis and amyloid angiopathy. In these cases, there may be a distinct clinical course and the SAH is usually of a more peripheral distribution and often present in combination with intra-parenchymal haemorrhage (reviewed by Mortimer *et al*, 2013).

Although a minority of aneurysms may be the result of an arterial dissection (and in that instance are usually fusiform), the vast majority are saccular in morphology. A systematic review of 68 studies, which reported on 83 study populations and 1450 unruptured aneurysms in 94, 912 patients from 21 countries, estimated that the overall prevalence of saccular aneurysms was 3.2% (95% CI 1.9–5.2) in the general population (Vlak *et al*, 2011).

1.1 Cerebral Aneurysms

1.2.1 Pathophysiology of cerebral aneurysm formation

It is likely that aneurysm formation is a result of a complex interaction between inherent and environmental factors. Family history, connective tissue disease and smoking predispose to aneurysm formation (Ronkainen *et al*, 1997; Raaymakers, 1999; Wardlaw *et al*, 2000; Juvela *et al*, 2001; Kissela *et al*, 2002). Arteriosclerosis and hypertension may be associated (Hokari *et al*, 2014) and developmental deficiency of the media and internal elastic lamina has also been cited as an aetiological factor (Crawford *et al*, 1959).

Aneurysm formation most commonly occurs at outer curvatures, bifurcations, or branching points of cerebral arteries; points that have been shown to suffer the highest wall shear stress (Kulcsar *et al*, 2011). In turn, this stress may induce pathological vascular remodeling of the vessel transmitted by endothelial cells (Resnick *et al*, 2003) and vessel wall inflammation which appears to be a dominant mechanism in cerebral aneurysm formation and has been the subject of a considerable body of aneurysm research (reviewed by Chalouhi *et al*, 2013a). Indeed, there is evidence that patients with unruptured aneurysms treated with aspirin, a cyclooxygenase 1 and 2 inhibitor have a lower risk of hemorrhage than those who have never used aspirin (Hasan *et al*, 2011).

The most common locations for aneurysm formation are the anterior communicating artery, middle cerebral artery bifurcation, posterior communicating artery and ophthalmic artery origins, the terminal basilar artery and origins of the posterior inferior cerebellar arteries (van Gijn *et al*, 2007).

1.2.2 Aneurysm rupture

In the International Study of Unruptured Intracranial Aneurysm Investigators, a multicentre cohort study of unruptured aneurysms, the overall rate of rupture was 0.5% per year (Wiebers *et al*, 2003) but there is a large body of opinion that this may be an under-estimation. There are factors that increase the risk of rupture for an individual aneurysm. Features that have been shown to predispose to aneurysm rupture include female sex, current smoking, hypertension, larger aneurysm size, the

aneurysm location and morphology including the presence of a daughter sac or high aspect ratio (height divided by neck diameter) as well as aneurysm growth (Ujiie *et al,* 2001; Villablanca *et al,* 2013; Korja *et al,* 2014, Murayama *et al,* 2016).

A number of scoring systems have been developed to assess the risk of aneurysm rupture on a per aneurysm basis (Greving *et al*, 2014*;* Etminan *et al,* 2015). Factors that merit firm consideration for treatment include aneurysm size ≥7mm, young patient age, change in the size or configuration of the aneurysm, and the presence of a daughter sac, or associated symptoms. Factors that may support intervention over observation are posterior circulation aneurysm location, anterior/posterior communicating artery aneurysm location, active smoking, hypertension, previous SAH, history of familial SAH, and high aspect ratio.

The overall incidence of aneurysmal SAH is approximately 9 per 100 000 person-years but varies significantly by region, with rates doubled in Japan and Finland and far lower in South and Central America. The incidence is higher in women and increases with age, though the gender distribution varies with age. At young ages, incidence is higher in men, while after the age of 55 years, the incidence is higher in women (de Rooij *et al*, 2007).

1.2.3 Complications of aneurysm rupture and SAH

Aneurysm rupture and SAH is almost always accompanied by sudden onset (‘thunderclap’) headache which may be followed by a focal neurological deficit such as limb weakness and/or a reduction in the level of consciousness, coma or death (Schwedt *et al*, 2006). SAH carries a mortality of 11% prior to seeking medical attention (Hijdra *et al*, 1987a). As well as the impact of the primary haemorrhagic injury, early ischaemic brain injury (Wartenberg *et al*, 2011), hydrocephalus and rebleeding may complicate SAH in the early stages. In addition to the latter two conditions, non-neurological complications and delayed cerebral ischaemia may complicate the subacute phase.

1.2.3.1 Clinical and radiological grading systems

There are more than forty grading scales, either historical or in use that have been applied to patients with aneurysmal SAH. Rosen & Macdonald (2005) have undertaken an extensive review of this subject. In principle, the contemporary approach is to clinically grade patients on the basis of their level of consciousness (adjudged using the Glasgow coma scale, (GCS)) and whether they exhibit a focal neurological deficit. The most commonly used grading system is the World Federation of Neurosurgical Societies (WFNS) scale (table 1.1); another that is often used in research emanating from the United States is the Hunt and Hess grading system though this is less commonly used in the United Kingdom. There is evidence that initial neurological grade impacts on eventual functional outcome (Rosen *et al*, 2004) and as such this is likely an approximate measure of the acute neurological injury.

Grade	GCS	Focal neurological deficit
1	15	Absent
2	13–14	Absent
3	13–14	Present
4	7–12	Present or absent
5	<7	Present or absent

Table 1.1 The World Federation of Neurological Societies Grading scale for aneurysmal SAH.

Non-contrast computed tomography is usually the first line imaging modality employed to assess these patients. The extent of primary haemorrhage can be graded using a number of systems but the most commonly quoted scales are the Fisher grade (Fisher *et al*, 1980) and modified Fisher grade (Frontera *et al*, 2006) which take into account the thickness of the basal SAH on axial images and the presence of intracerebral or intraventricular haemorhage (tables 1.2. and 1.3).

Fisher grade	CT findings
1	No haemorrhage evident.
2	Subarachnoid haemorrhage less than 1mm thick.
3	Subarachnoid haemorrhage more than 1mm thick.
4	Subarachnoid haemorrhage of any thickness with intra-ventricular haemorrhage (IVH) or parenchymal extension.

Table 1.2 The Fisher Grade for CT imaging distribution of SAH.

Modified Fisher grade	CT findings
0	No SAH or IVH
1	Focal or diffuse, thin SAH with no IVH
2	Focal or diffuse, thin SAH with IVH
3	Focal or diffuse, thick SAH with no IVH
4	Focal or diffuse, thick SAH with IVH

Table 1.3 The Modified Fisher Grade (thin SAH is < 1mm thick and thick SAH is >1 mm in depth).

The modified Fisher grade was developed to include patients with thick cisternal blood and concomitant intraventricular or intraparenchymal haemorrhage. Additionally, the risk of developing angiographic vasospasm progressively increases with each level of the modified Fisher grade, whereas the risk was highest for Grade 3 and then decreased for Grade 4 while using the original Fisher scale (Frontera *et al*, 2006).

1.2.3.2 Rehaemorrhage

Risk of acute rehaemorrhage is greatest in the first 24 hours; approximately 4% of aneurysms will rebleed during this time and if an aneurysm is left untreated there is a 40% chance of rebleeding in the following 4 weeks, with about an 80% chance of death or disability (Hijdra *et al*, 1987a; Kassell *et al*, 1990; van Gijn *et al*, 2007). In an assessment of 40 (6.9%) of the 574 patients who had suffered rehaemorrhage during the course of their treatment, rebleeding was associated with a markedly reduced chance of survival with functional independence (modified Rankin Scale score ≤4; OR, 0.08; 95% CI, 0.02-0.34) at 3 months (Naidech *et al*, 2005). Larger aneurysm and poorer neurological grade were risk factors for rehaemorrhage.

1.2.3.3 Early ischaemic brain injury

This is a concept that is receiving increasing attention. In a recent observational study, acute ischaemic injury was seen in 60% of patients undergoing diffusion weighted magnetic resonance imaging at days 0-3 post SAH (Frontera *et al*, 2015). Ischaemic lesions could be the result of a hypoxic ischaemic injury (Wartenberg *et al*, 2011; Frontera *et al*, 2015) or possibly acute vasospasm as a result of aneurysm rupture. Early ischaemic injury is associated with poor acute neurological status after SAH, is more common in patients of poor grade and can predict future ischaemia and worse functional outcomes (Frontera *et al*, 2015).

1.2.3.4 Hydrocephalus

Up to 20% of patients suffer post SAH hydrocephalus (Suarez-Rivera *et al*, 1998), defined as ventricular dilatation that ultimately results in an elevation of intracranial pressure (Woernle *et al*, 2013). This most commonly occurs in patients with greater haemorrhagic loads/Fisher grades and those with intraventricular haemorrhage. This is managed with external ventricular drainage which itself can be complicated by infection or haemorrhage. Approximately 20-30% of patients will go on to require permanent cerebrospinal fluid diversion with shunt placement (Lu *et*

al, 2012; Woernle *et al*, 2013). Controversy exists about whether open microsurgical methods serve to reduce shunt dependent hydrocephalus compared with endovascular techniques but the most recent evidence suggests that there is no difference in shunt dependency among patients treated by either technique (Zaidi *et al*, 2015).

1.2.3.5 Non-neurological complications

SAH can also be complicated by non-neurological abnormalities. Common non-neurological complications of SAH include anaemia, hypertension, cardiac arrhythmia, fever, electrolyte changes, pulmonary oedema, pneumonia, hepatic dysfunction, renal dysfunction, and thrombocytopenia (Solenski *et al*, 1995). Pneumonia, sepsis, fever, anaemia, and hyperglycaemia independently predict poor outcome and death (Wartenberg *et al*, 2006). Medical complications are linked to severity of presenting grade (Solenski *et al*, 1995).

1.2.3.6 Delayed cerebral ischaemia

Post haemorrhage arterial vasospasm and the delayed ischaemic process was recognised in the 1950's (Fletcher *et al*, 1959). Delayed cerebral ischaemia refers to a clinical phenomenon occurring at days 3-10 post onset of SAH, characterised by a new focal neurological deficit or reduction in the level of consciousness. These patients are at risk of cerebral infarction which is strongly associated with poor outcome (Furgusson & Macdonald, 2007; Vergouwen *et al*, 2011b). Angiographic cerebral vasospasm refers to a pathophysiological phenomenon which contributes to the delayed ischaemic process in which the proximal cerebral arterial luminal diameter is reduced secondary to smooth muscle contraction in response to the presence of subarachnoid haemorrhage (figure 1.1).

An additional mechanism of delayed ischaemia, cortical spreading depression has also been demonstrated in a cohort of SAH patients (Woitzik *et al*, 2012). The use of nimodipine as a prophylactic treatment and intravascular volume expansion/hypervolaemia, haemodilution and induced hypertension as rescue

treatments (triple-H) was established in the 1980's (Kassell *et al*, 1982; Allen *et al*, 1983). A systematic review of eight prospective randomised trials including 1514 patients designed to assess the efficacy of prophylactic nimodipine (Liu *et al*, 2011), concluded that nimodipine reduced the rate of delayed cerebral ischaemia by 38% and the rate of cerebral infarction by 48%. Conversely, the evidence for the use of triple-H therapy remains sparse despite relatively widespread acceptance. A systematic review of triple-H therapy components suggested that induced hypertension was the most effective at improving cerebral blood flow (Dankbaar *et al*, 2010).

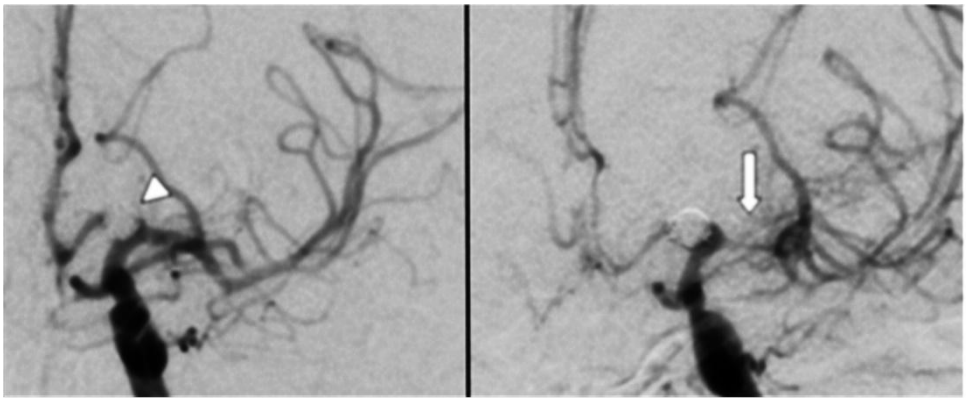

Figure 1.1 Frontal projection left internal carotid artery angiogram at day 2 post ictus immediately post coiling (left) and day 6 post ictus (right) performed to investigate an acute right hemiparesis and aphasia. The coiled aneurysm is labelled with an arrowhead. The immediate post coiling appearances demonstrate a normal left M1 MCA calibre and at day 6 show severe left M1 MCA (arrow) and A1 ACA vasospasm.

Endovascular approaches to treating this condition were fist applied in the 1980's also (Higashida *et al*, 1989). Transluminal balloon angioplasty (TBA) and chemical angioplasty using papaverine were the initial methods employed. The use of the latter agent has now largely been superseded by other vasodilators, most commonly verapamil, with safer side-effect profiles (Bulsara *et al*, 2015).

1.2 Prognosis

1.2.1 Outcome scales

The Glasgow Outcome Scale (GOS) and modified Rankin Scale (mRS) are the most commonly used systems for measuring the degree of disability or dependence in activities of daily living in patients who have suffered SAH. The GOS is a five-point scale (table 1.4) and was originally developed to assess outcome after traumatic brain injury (Jennett *et al*, 1981). This has largely been superseded by the mRS (table 1.5) that was developed to assess outcome, principally following stroke (van Swieten *et al*, 1988) and encompasses a seven-point scale. In many studies, favourable outcomes are dichotomised as GOS scores of 4 and 5 or 5 alone and mRS scores of 0-2 or 0-3.

Score	Definition
1	**Death.**
2	**Persistent vegetative state.** Patient exhibits no obvious cortical function.
3	**Severe disability.** Conscious but disabled. Patient depends upon others for daily support due to mental or physical disability or both.
4	**Moderate disability.** Disabled but independent. Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	**Good recovery.** Resumption of normal activities even though there may be minor neurological or psychological deficits.

Table 1.4 The Glasgow Outcome Score.

Score	Definition
0	**No symptoms.**
1	**No significant disability.** Able to carry out all usual activities, despite some symptoms.
2	**Slight disability.** Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	**Moderate disability.** Requires some help, but able to walk unassisted.
4	**Moderately severe disability**. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	**Severe disability.** Requires constant nursing care and attention, bedridden, incontinent.
6	**Death.**

Table 1.5 The modified Rankin Scale.

1.2.2 Factors impacting on patient outcome

Recent studies of in-hospital mortality for SAH suggest that this lies in the order of 20% and has fallen since the 1980s (Rincon *et al*, 2013; Lantigua *et al*, 2015), likely due to advances aneurysm treatment and in critical care. Nevertheless, up to 30% of the survivors exhibit significant morbidity and will depend on others for activities of daily living and of those patients who survive the acute phase non-disabled, many suffer cognitive impairment (Hijdra *et al*, 1987a). As many as a third in the International Subarachnoid Aneurysm Trial (ISAT) cohort suffered cognitive imparirment (Scott *et al*, 2010).

Established patient risk factors for death or dependency include poor clinical grade at presentation, older age, aneurysm rebleeding, large aneurysm size, early ischaemic brain injury, cerebral oedema and intraventricular haemorrhage (Claassen *et al*, 2002; Naidech *et al*, 2005; Rosen *et al*, 2004; Wartenberg *et al*, 2011; Lantigua *et al*, 2015). Mode of aneurysm treatment and treatment complications, physiological derangement, complications of invasive imaging with digital subtraction angiography, cerebral vasospasm and the delayed ischaemic process and long term imaging follow-up all have implications for early patient outcome and/or longer term well-being (Ruigrok *et al*, 2000; Molyneux *et al*, 2002; Vergouwen *et al*,

2011; Ferns *et al*, 2011a; Lantigua *et al*, 2015). These factors are the subject of this thesis and will be discussed in turn.

1.3 Aneurysm treatment modality

1.4.1 A brief history of aneurysm treatment

In the 1930's, the first neurosurgical procedures to protect aneurysms from rehaemorrhage were performed in Edinburgh, UK and Baltimore, USA with clipping of aneurysms first successfully performed by Dandy in 1937 (Dandy, 1938) and, with microsurgery first employed to aid clipping in the 1970's (Krayenbühl *et al*, 1972). Endovascular occlusion of aneurysms first employed detachable balloons in the 1980s (Scialfa *et al*, 1983) but in the early 1990s, the first use of electrolytically detachable platinum coils, the mainstay of aneurysm treatment today in most institutions, was described by Guglielmi (Guglielmi *et al*, 1991). The first of a number of land-mark publications as a result of the ISAT trial of 2143 patients, comparing endovascular coiling with microsurgical clipping was published in 2002 (Molyneux *et al*, 2002).

Since the development of simple coiling techniques, endovascular treatment options evolved. Balloon-remodelling and stent-assisted coiling are adjunctive treatments that allow endovascular occlusion of more complex aneurysms (Pierot *et al*, 2009). In the last ten years both luminal and intra-aneurysmal flow diverters have been developed and although the evidence for their use is still building, they do aid occlusion of aneurysms with difficult morphology and further add to the neurointerventionalist's armamentarium.

1.4.2 Controversies

The mode of aneurysm treatment and complications of treatment are significant factors which may impact on functional and cognitive outcomes (Molyneux *et al*, 2002, Scott *et al*, 2010, Ayling *et al*, 2015). Broadly, arguments for the continued use of clipping in the context of SAH are that there is a perceived higher chance of complete long-term occlusion, lower risk of rehaemorrhage and

improved ability to fully treat aneurysms of more complex morphology (Johnston *et al*, 2008). Conversely, coiling is less invasive, is associated with fewer peri-operative complications (Ayling *et al*, 2015) and lower levels of biochemical markers of brain injury (Shim *et al*, 2012) but critics of the technique cite incomplete occlusion as a major flaw, suggesting that in the long term there may be an increased risk of rebleeding and complications associated with further treatment.

The results of ISAT have gone some way to satisfying this concern. This trial randomised patients with aneurysms that were deemed suitable for both surgical clipping and endovascular coiling. At 1 year there was an absolute 6.9% reduction in the rate of death or dependency for patients treated with coiling rather than clipping (Molyneux *et al*, 2002). In longer term follow-up of 1003 patients at 10 years (Molyneux *et al*, 2015), 435 (82%) patients treated with endovascular coiling and 370 (78%) patients treated with surgical clipping were independent (mRS 0-2; OR 1.25; 95% CI 0.92-1.71). Patients in the endovascular treatment group were more likely to be alive and independent at 10 years than were patients in the neurosurgery group (OR 1.34, 95% CI 1.07-1.67). Although there was a small increased risk of rebleeding in the coiling group, this did not translate to a significantly worse clinical outcome when compared with that of the surgically treated group. Patients were 40-times more likely to die from another cause than from the treated aneurysm.

After the initial ISAT results there was a shift in the treatment of aneurysms in the UK and coiling became the dominant modality. In 2006, an audit of subarachnoid haemorrhage treatment in the UK demonstrated that 85% of patients treated for ruptured aneurysms had coiling (Royal College of Surgeons, 2006).

There was much criticism of the trial, particularly from neurosurgeons in the United States. The study was designed to randomise aneurysms for which the treating clinicians had equipoise. A principle criticism is that only 20% of eligible patients with SAH were enrolled into the study and as a result there is considerable bias in terms of the population included and that there is a significant proportion of aneurysmal SAH patients to whom the ISAT results do not apply.

As a result, a more recent study from the Berrow institute (the Berrow Ruptured Aneurysm Trial, BRAT) aimed to answer whether the results of clipping and coiling differed if randomisation occurred at an early stage, soon after diagnosis

of SAH (McDougall *et al*, 2012). This study was initially constructed as a pilot and as a result was always underpowered. A total of 725 patients were screened, with 472 assigned to coiling or clipping either by alternating fashion or by lottery for the last 100 patients. 'Right of first refusal' and crossover were allowed but results were presented in an intent-to-treat analysis. There was a 38% cross-over rate from clipping to coiling and a large proportion (12%) of patients without an aneurysm who did not undergo either treatment were also included, making the results somewhat difficult to interpret. Indeed, whether this can still be interpreted as a randomised trial is questionable. Initial results at 1 year showed a 10% reduction in death or disability (mRS >2) in the coiling group. In a post hoc analysis of the 3-year outcome data (Spetzler *et al*, 2013) in which those patients without an aneurysm were excluded, the authors concluded that for anterior circulation aneurysms there was no difference in outcomes for clipping and coiling and that clipping should be considered a more appropriate treatment due to the risks associated with retreatment, completeness of obliteration, and subsequent SAH risk.

A subsequent 6-year outcome analysis was interpreted in a similar way (Spetzler *et al*, 2015), though independent analysis of the results (Macdonald *et al*, 2015) highlighted that poor outcomes were observed in 41% of patients (72 of 174) who underwent clipping versus 35% of patients (57 of 162) who underwent coiling, with an absolute risk reduction for coiling of 6% and a relative risk reduction of 17%. This is very similar to the results of ISAT. Nevertheless, the authors stand by their interpretation of the results, and also suggest that scientific data from well-designed trials is less important than an individual operator's talent (McDougall & Spetzler, 2015).

In some quarters, the optimal treatment option for anterior circulation aneurysms therefore remains a subject of debate and two topics are of particular importance. Firstly, middle cerebral artery aneurysms lie in an anatomical location traditionally felt most suitable for surgical clipping and routine use of coiling here remains contentious. The results of a study assessing a coil-first policy would be intriguing. Secondly, although functional outcomes (measured using the mRS or GOS) may not be dissimilar, it has been reported that coiling is associated with better cognitive outcomes than clipping among patients whose level of dependence lies within the traditional ratings of independence (mRS 0-2 or GOS 5) (Hutter &

Gilsbach, 1993; Mavaddat *et al*, 1999; Hadjivassiliou *et al*, 2001; Scott *et al*, 2010). Despite lying within this range, patients may suffer cognitive deficits that prevent them from working and participating in other activities (Al-Khindi *et al*, 2010).

Therefore, it is possible that there might be a much larger difference in outcomes between clipping and coiling but that functional outcome scales are insensitive to it. A study assessing the anatomical reasons for a difference in cognition at a defined location would be of value.

1.5 Endovascular treatment of middle cerebral artery aneurysms

Ruptured middle cerebral artery (MCA) aneurysms represented only 303 (14.1%) of the 2143 enrolled patients in ISAT (Molyneux *et al*, 2002) and of all aneurysm locations assessed in ISAT there was least difference in functional outcome between clipping and coiling at the MCA location (Molyneux *et al*, 2005). Many specialists consider this anatomical location an indication for surgical clipping: the location aids surgical access, and in some cases, surgery facilitates haematoma evacuation. There is also a perceived increased risk for coiling in terms of thrombo-embolism and infarction at this site because these aneurysms are often wide-neck and have branches arising from the neck (Ausman *et al*, 1997, Regli *et al*, 1999). Recently, several surgical series have been published that demonstrate excellent clinical results with low rates of morbidity and mortality (Morgan *et al*, 2010, van Dijk *et al*, 2011; Choi *et al*, 2012; Rodrıguez-Hernandez *et al*, 2013) and this practice has extended to treatment of unruptured aneurysms.

As practice in the United Kingdom has shifted in many institutions to a coil-first policy, there is a need for assessment of clinical outcomes using this approach to analyse how this compares to the results in ISAT and also those of recent surgical series. A retrospective analysis was therefore undertaken of a prospectively acquired data base including 295 patients with 300 saccular MCA aneurysms treated using endovascular coiling at a regional neuroscience centre between November 1996 and June 2010 (Mortimer *et al*, 2014). This is described in detail in Chapter 2. Of the total, 244 (80.7%) ruptured aneurysms were treated. The technical failure rate was 4.3% (13 patients). Complete occlusion or neck remnant was achieved in 264

(91.4%). Complications included rupture in 15 patients (5%), thromboembolism in 17 patients (5.7%), and early rebleeding in 3 patients (1%). Overall permanent procedural-related morbidity and mortality were seen in 12 patients (7.8%). Of the ruptured aneurysms, 189 (79.4%) had a favourable clinical outcome (GOS 4–5). A total of 33 patients (13.6%) died. On initial angiographic follow-up, aneurysm remnant was seen in 18 aneurysms (8.1%). A total of 13 patients (4.3%) were retreated.

These results compare very favourably with that of the best published surgical series (Morgan *et al,* 2010, van Dijk *et al*, 2011; Choi *et al*, 2012; Rodrıguez-Hernandez *et al,* 2013). They are also in line with the results published in other smaller endovascular series and ISAT which suggests that they are reproducible (Molyneux *et al,* 2002; Iijima *et al,* 2005; Quadros *et al,* 2007; Oishi *et al,* 2009; Suzuki *et al,* 2009; Bracard *et al,* 2010) and that although the approach was different to ISAT (treating all-comers as opposed to just those aneurysms with more favourable morphology for coiling), clinical outcomes, complications, anatomical results and retreatment rates were in line with published benchmarks for aneurysms at all locations (Molyneux *et al,* 2002; Cognard *et al*, 2011). Therefore, although the conservative view is that surgery should remain the treatment of choice of ruptured MCA aneurysms, except when there are extenuating comorbidities or overriding patient preferences, the results suggest that for the range of ruptured MCA aneurysms, at least equivalent clinical outcomes to the best surgical series can be obtained by use of conventional endovascular techniques.

The use of adjunctive devices such as stent placement or balloon remodelling was very infrequent in this series, and intra-aneurysmal flow diverters were not used. Adjunctive devices have been used in 20.4% of other published MCA series (Brinjikji *et al*, 2011a), with the aim of obtaining complete occlusion to minimize the risk for subsequent haemorrhage (Johnston *et al*, 2008). A critical appraisal of the available literature has suggested that balloon assistance, which increases the range of lesions that can be treated has a very similar safety profile to coiling without remodelling (Pierot *et al,* 2012b). Stent assistance has also been used successfully in large series of MCA aneurysms (Johnson *et al*, 2013a). Stents allow more complete treatment of more complex lesions and may lower recurrence. However, there are reservations regarding procedural safety in patients with ruptured aneurysms.

Intra-aneurysmal flow diverters now represent an additional treatment option for wide-neck bifurcation aneurysms. Pierot et al (2013) treated 34 ruptured and unruptured MCA aneurysms with the Woven Endobridge (WEB) device, a first generation intra-aneurysmal flow diverter. Adequate occlusion (total occlusion or neck remnant) was observed in 83.3% of aneurysms with an acceptable safety profile; mortality rate of the treatment was 0.0% and morbidity rate was 3.1% (intraoperative rupture with an mRS of 3 at 1-month follow-up). It is likely therefore, that new devices will further increase the range of endovascular options for aneurysms at this location and are potential avenues for future research into the optimal strategy for these lesions.

1.6 Brain injury following treatment of anterior communicating artery aneurysms

Approximately 50% of the patients treated in ISAT suffered SAH as a result of ruptured anterior cerebral artery (ACA) or anterior communicating artery (ACOM) aneurysms. Minimal differences in the rate of poor functional outcome or death assessed using the modified Rankin Scale were demonstrated between clipping and coiling for aneurysms at this location (27.5% v 24.6%) (Molyneux et al, 2005). Nevertheless, patients may suffer significant cognitive impairment despite favourable functional outcome scores (Hutter & Gilsbach, 1993; Mavaddat *et al*, 1999; Hadjivassiliou *et al*, 2001, Scott *et al*, 2010) and it has been recognised for some time that surgical clipping may be associated with greater rates of cognitive impairment than coiling for aneurysms treated at this location (Chan *et al*, 2002; Fontanella *et al*, 2003; Proust *et al*, 2009). Various patterns of neuropsychological impairment can occur (Böttger *et al*, 1998).

Injuries to the basal forebrain and the fornix specifically have been implicated in resulting in memory impairment (Damasio *et al*, 1985; Phillips *et al*, 1987; Abe *et al*, 1998; Wright *et al*, 1999; Hashimoto *et al*, 2000; Mugikura *et al*, 2014; Meila *et al*, 2015).

The basal forebrain contains a number of important structures including the nucleus accumbens, substantia innominata, nucleus basalis of Meynert, and medial septal-diagonal band of the Brocca complex (Fujii, 2008). Basal forebrain lesions have been linked to the occurrence of amnesia and/or confabulation in a number of

case reports and series (Damasio *et al*, 1985; Phillips *et al*, 1987; Böttger *et al*, 1998; Abe *et al*, 1998; Goldberg *et al*, 1999; Wright *et al*, 1999; Hashimoto *et al*, 2000) and a functional imaging study has also suggested that the basal forebrain is likely to play a role in episodic memory recall (Fujii *et al*, 2002). The medial septal-diagonal band of the Brocca complex region is likely to be an important interface within the so-called septohippocampal system (Böttger *et al*, 1998). Bilateral basal forebrain lesions do produce more severe memory deficits (Böttger *et al*, 1998). The fornix is a compact fiber bundle connecting the hippocampus with the hypothalamus and a number of other structures including the septal area of the basal forebrain. It is an important constituent of the Papez circuit and is involved in the formation and consolidation of declarative memories (Meila *et al*, 2015). Diffusion-weighted MRI-proven infarction limited to the fornices has been reported in conjunction with acute onset of amnesia, suggesting that an isolated injury to this structure may be critical (Mugikura *et al*, 2014). Injuries to other vulnerable structures including the corpus callosum and caudate nucleus have also been implicated in resulting in neuro-behavioural sequelae (Mendez *et al*, 1989; Kasow *et al*, 2000). Caudate nucleus lesions may result in depression, agitation, abulia, neglect (right-sided lesions), memory disturbance (particularly if bilateral), dysarthria, aphasia (left-sided lesions), movement disorders (ballistic, choreatiform), or motor weakness. (Kumral *et al*, 1999).

Structures within the basal forebrain, basal ganglia, and limbic system are vulnerable to injury during neurovascular procedures, probably through occlusion of ACA or ACOM artery complex perforating branch vessels, notably the recurrent artery of Heubner (RAH) or subcallosal artery (Mugikura *et al*, 2014; Meila *et al*, 2015). Following treatment of ACOM artery aneurysms, a detailed radiological investigation into the rates and distribution of injury to the above structures is required to assess whether surgical treatment is associated with greater rates of injury; a potential cause of inferior cognitive outcomes in the surgical group.

A retrospective dual-centre radiological investigation was undertaken of a consecutive series of patients with ruptured and unruptured ACOM aneurysms treated between January 2011 and October 2014 (Mortimer *et al*, 2016a). This is described in detail in Chapter 3. Sixty-six patients treated with clipping were compared with 93 patients treated with coiling. Post-treatment CT or MRI showed 32/66 (48.5%) patients in the clipping group suffered treatment-related injury (31

ischemic, 1 haemorrhagic) compared with 4/93 (4.4%) patients in the coiling group (3 ischemic, 1 haemorrhagic) ($p<0.0001$). For patients with subarachnoid haemorrhage, the multivariate OR for infarction for clipping over coiling was 24.42 (95% CI 5.84 to 102.14), $p<0.0001$. The most common site of infarction was the basal forebrain (28/66 patients, 42.4%), with bilateral infarction in four patients. There was injury of the septal/subcallosal region in 12/66 patients (18%).

Clipping of ACOM aneurysms was clearly associated with significantly higher rates of structural injury than coiling, and this may be a reason for superior cognitive outcomes in patients treated with coiling in previously published studies. Chan *et al* (2002) studied 18 patients who had undergone treatment for ruptured ACOM aneurysms, half with clipping and half with coiling; 33% of the clipped patients showed severe impairment of memory and executive function whereas no coiled patient demonstrated this impairment.

Fontanella et al (2003) assessed 37 consecutive WFNS grade I or II patients who underwent treatment of ACOM aneurysms within 48 h of rupture; 20 of 37 were treated with clipping and 17 were treated with coiling. Both groups were compared with 16 angiogram-negative patients with SAH and 18 normal controls. All patients were neurologically intact at discharge and were independent at 6-month follow-up after SAH. Surgically treated patients showed a significant worse performance on the logical memory and on the frontal lobe executive functions compared with controls, while the endovascular group and the angiogram-negative group showed a significant decrease only in the literal fluency score. Furthermore, the surgical group showed a significant impairment in using grammatical and syntactical rules to produce sentences. Proust et al (2009) studied 36 clipped and 14 coiled patients at 14-month follow-up. They found no difference in executive dysfunction although there was a significant impairment of verbal memory in the clipped group.

This raises the question of how to optimally treat these patients and this is one factor which may sway a decision towards endovascular approaches, and possibly the use of adjunctive techniques such as stent-assisted coiling for more complex lesions. A systematic review of stent coiling at all locations in patients with SAH who were managed with dual antiplatelet therapy demonstrated clinically significant intracranial haemorrhagic complications in 27 (8%) of 339 patients, including 9 (10%) of 90 patients known to have had ventricular drain-related

haemorrhages. Clinically significant thromboembolic events occurred in 16 (6%) of 288 patients (Bodily *et al*, 2011). Perhaps a trial comparing more aggressive endovascular approaches (e.g. using stents or even flow diversion) with clipping for less favourable aneurysms, particularly for locations such as this, would be worthwhile. Such a study should include neuropsychological testing as part of the outcome measures.

1.7 Physiological derangement and choice of treatment modality

Although there was little reference to physiological derangement or medical comorbidity or complications in either ISAT or BRAT studies, there is increasing recognition that these factors are significant contributors to poor outcome after SAH (Wartenberg *et al*, 2006; van der Bilt *et al*, 2009, Lantigua *et al*, 2015). Physiological derangement and medical complications are more common in poorer grade patients (Enblad & Persson, 1997). Only 4.4% of patients recruited into ISAT were of poor clinical grade (WFNS 4 or 5). The results of ISAT may therefore not directly apply to poor-grade patients. A recent multicentre prospective observational study demonstrated that after adjustment for baseline characteristics there was no significant difference in outcomes for coiling or clipping in this patient group (Zhao *et al*, 2015).

Severity of illness scoring systems have shown better correlation with poor outcomes in SAH patients than acute neurological grading (Gruber *et al*, 1999) and there is little evidence regarding the interaction of treatment modality and presenting physiological derangement rather than neurological grade in isolation. In comprehensive centres, the decision on whether to clip or coil an aneurysm is often based on the morphology and location of the aneurysm. An alternative approach is to subject an acutely unwell patient to the least stressful procedure (namely an endovascular coiling), if even just to protect the aneurysm dome in the short term in order that they may recover to undergo a further protective procedure if required (Waldau *et al*, 2012).

The Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system is widely used in many intensive care units and allows approximate prognostication based on a score from 0 to 71 for clinical and biochemical markers

of physiological function (Knaus *et al*, 1985). This has been validated in the SAH population (Lantigua *et al*, 2015). An assessment of how physiological derangement interacts with treatment approach is required to answer whether the physiological condition of the patient should influence mode of treatment in the sickest patients.

An exploratory analysis of prospectively collected trial data was therefore undertaken, comparing the outcomes of sixty-nine patients treated with clipping to sixty-six treated with coiling (Mortimer *et al*, 2016b). This is described in detail in Chapter 4. More profound physiological derangement (APACHE II score >15) was the strongest predictor of poor outcome in the overall cohort (OR 17.80, 95% CI 4.78 to 66.21, $p<0.0001$). For those with more deranged physiology (APACHE II score>15; 59 patients), WFNS grade ≥4 (OR 6.74, 1.43 to 31.75) and surgical clipping (OR 6.33, 1.27 to 31.38) were significant predictors of poor outcome ($p<0.05$). Favourable outcome (mRS 0-2) was seen in 11% of surgical patients compared with 38% of coiled patients in this subgroup. The results indicated an advantage for coiling in the more profoundly physiologically deranged subgroup. On multivariate analysis both poor grade and clipping were predictors of poor outcome. Furthermore, functional outcome differences by treatment modality for the WFNS grades 1–2 patients with high APACHE II scores tended to significance (favourable outcomes for clipping were seen in 30% and in 56% for coiling in this subgroup). Perhaps this did not reach significance as the study was underpowered.

A number of authors have attempted to explain superior outcomes for coiling based on lower rates of cerebral vasospasm. We did not see a significantly increased rate of angiographic vasospasm in the clipped patients yet clipped patients did have significantly increased total norepinephrine dose, ventilated days, and hospital stay ($p<0.05$). A large Canadian multicentre study demonstrated that clipped patients more commonly suffered medical complications, such as urinary tract infection, pneumonia, cardiorespiratory arrest, and seizures, and that these complications were linked to poor outcome (Vergouwen *et al*, 2011c).

It is therefore plausible that patients undergoing a more invasive procedure may require more inotropic support, more time ventilated, and more time in hospital. They could therefore take much longer to recover and are therefore more at risk of nosocomial infection and other medical complications. The results also raise the

question of whether more profoundly sick patients should undergo a coiling as opposed to a clipping procedure.

1.8 Invasive imaging in patients with perimesencephalic subarachnoid haemorrhage

Perimesencephalic subarachnoid haemorrhage (PMSAH) accounts for approximately 5% of SAH and represents a distinct clinic-radiological entity characterised by haemorrhage centred on the perimesencephalic cisterns, aneurysm negative angiographic investigation and a more benign clinical course (van Gijn *et al,* 1985; Rinkel *et al,* 1991a; Rinkel *et al,* 1991b; Brilstra *et al,* 1997; Flaherty *et al,* 2005; Greebe *et al,* 2007). An aneurysm is likely responsible for this pattern of haemorrhage in less than 1% of cases and CT angiography (CTA) with modern systems are highly sensitive for aneurysm detection (Westerlaan *et al,* 2011; Kalra *et al,* 2015).

CTA is now commonly performed prior to digital subtraction angiography (DSA) to aid treatment planning through aneurysm identification and characterisation. The traditional approach to investigating patients with SAH also includes mandatory use of DSA, the gold standard angiographic modality. A review of the literature has demonstrated that the average risk of permanent neurological complications from DSA in patients with perimesencephalic haemorrhage was 0.74% (95% CI, 0.09% to 2.7%) (Ruigrok *et al,* 2000). This is a higher rate than seen in two subequent very large series of all consecutive DSA procedures performed in 19,826 (Kaufmann *et al,* 2007) and 2,899 patients (Willinsky *et al,* 2003). The permenant neurological complication rate was 0.14% and 0.5% respectively. The relative increased risk in PMSAH patients could relate to age. Nevertheless, current European and American guidelines are ambiguous as to the need for invasive imaging with DSA in this setting and the majority of previous studies are of a relatively low number of patients (Connolly *et al,* 2012; Steiner *et al,* 2013). There is a need for an assessment of the diagnostic yield of DSA in the face of a negative CTA in a large cohort of patients with strictly defined PMSAH to elucidate the negative predictive value of CTA in this population and to guide whether DSA is a necessary investigation in the majority of cases.

The negative predictive value (NPV) of CTA was assessed in a series of 72 patients with PMSAH treated at a regional neuroscience centre over a 9-year period (Mortimer *et al*, 2016c). This is described in detail in chapter 5. A PMSAH pattern defined as blood centred anterior to the midbrain and/or pons within the pre-pontine or interpeduncular cistern with possible quadrigeminal or ambient cistern extension; possible extension into the basal parts of the Sylvain fissures but not the lateral sylvian fissures; possible extension to the cisterna magna but not centred on the cisterna magna; and possible extension into the fourth ventricle and occipital horns of the lateral ventricles.

Of 72 patients, one patient showed a potentially significant finding on DSA that was not demonstrated on initial CTA (NPV 98.61% (95% CI 92.47% to 99.77%)). However, when cisterna magna extension was excluded from the definition of PMSAH, no false negative CTAs in 56 patients were encountered (NPV 100% (95% CI 93.56% to 100.00%)). The NPV of normal CTA for an arterial abnormality in patients with PMSAH is high and our results therefore question the role of invasive imaging and certainly imply that if a prospective study is required to fully evaluate this then this would be safe and feasible.

1.9 Delayed cerebral ischaemia, cerebral vasospasm and endovascular approaches to prevent delayed infarction

Cerebral infarction is strongly associated with poor outcome following SAH (Furgusson & Macdonald, 2007; Vergouwen *et al*, 2011b). In the context of SAH, infarction could be the result of the acute injury, complications of the aneurysm securing procedure or the delayed ischaemic process. For decades it has been assumed that the latter results from the development of cerebral vasospasm (Graham *et al*, 1983), detected angiographically as luminal narrowing of the proximal cerebral arteries. The dominant factor determining the development of vasospasm is the presence of thick subarachnoid clot adjacent to the proximal cerebral arteries (Inagawa, 2015). Angiographic vasospasm is an independent predictor of poor outcome following SAH (Vergouwen *et al*, 2011a). An association between vasospasm in the development of delayed infarction is supported by the results of radiological studies that suggest that the majority of delayed infarcts occur in association with vasospasm, (Crowley *et al*, 2011; Brown *et al*, 2013) and that there

is a correlation between vasospasm severity and the incidence of infarction. The majority of vasospasm-related infarcts are associated with severe vasospasm, (Weidauer *et al*, 2007; Crowley *et al*, 2011; Inagawa *et al*, 2014) which results in the most severe perfusion deficits (Dankbaar *et al*, 2009; Vatter *et al*, 2011; Dhar *et al*, 2012). Of patients with severe vasospasm, 50–100% develop cerebral infarction compared with 3–5% of patients without significant vasospasm (Weidauer *et al*, 2007; Crowley *et al*, 2011; Inagawa *et al*, 2014). Severe vasospasm is associated with poor cognition, worse patient-relevant outcomes, and greater inpatient healthcare resource use (Macdonald *et al*, 2012).

More recently, the role of vasospasm in delayed ischaemia has been brought into question largely secondary to the finding that the trial drug clazosentan has been shown to improve rates of vasospasm but this did not translate into improved functional outcomes whereas nimodipine has been shown to improve clinical outcomes without an impact on vasospasm (Petruk *et al*, 1988; Feigin *et al*, 1998; Macdonald *et al*, 2008; Macdonald *et al*, 2011).

There are many potential reasons for a failure in correlation between reductions in the incidence of vasospasm but not in rates of poor outcome in the clazosentan trials. First, poor grade patients who suffer a more significant acute neurological injury are those who are more likely to suffer the most severe vasospasm and therefore detecting differences with current outcome measures would probably require very large trials or alternative outcome measures. Second, only severe vasospasm may result in significant reductions in cerebral blood flow so as to result in infarction and the inclusion of those with moderate vasospasm may dilute the treatment effect. Third, vasospasm is likely to exert its clinical impact through infarction: factors such as age (Danière *et al*, 2014) govern the impact of infarct size on functional outcome. Furthermore, the eloquence of the infarct area will result in variable functional impact. Fourth, the systemic side effects of the treatment may have resulted in poor outcome through alternative mechanisms (medical complications) in the treatment arm. Lastly and importantly, rescue treatments such as endovascular intervention and systemic hypertension may have been effective in preventing a poor outcome in patients in the placebo arm.

Some authors also question the correlation between vasospasm and the presence of clinical symptoms, the former approximately twice as common as the latter (Vergouwen *et al*, 2011a). It is true that some patients with evidence of vasospasm are clinically asymptomatic or do not show overt clinical deterioration. This may be because moderate degrees of vasospasm that are not necessarily haemodynamically significant are included in analyses. In many studies, non-invasive measures of vasospasm with limited accuracy, sensitivity and specificity have also been used. Furthermore, current measures of vasospasm severity often do not incorporate collateral flow or perfusion information or the eloquence of ischemic parenchyma, perhaps best assessed through combining angiographic and perfusion imaging. Moreover, patients have variable haemodynamic reserve and respond differently to flow limitation; clues to this can be gleaned from the ischemic stroke literature. Hakimelahi et al (2014) have recently reported that patients with ICA or proximal MCA occlusions demonstrated a wide range in diffusion-weighted infarct volumes within 30 hours of occlusive stroke onset; there was no correlation between infarct volume and time from stroke onset. The observations suggest that highly variable cerebral perfusion via the collateral circulation may primarily determine infarct growth dynamics, and this has implications for patients with significant vasospasm.

An intriguing possibility for this lack of correlation is that an alternative mechanism of delayed ischemia exists that may occur alone or in combination with proximal vasospasm. It has been demonstrated that infarction can occur independently of severe cerebral vasospasm (Vergouwen *et al*, 2011a), and spreading depolarization with cortical ischemia may represent one mechanism that could account for this. Woitzik et al (2012) have demonstrated in a series of 13 patients that the number of spreading depolarizations in patients suffering delayed ischemic neurological deficits was significantly higher than in those without, when proximal vasospasm was minimised through treatment with nicardipine beads.

Importantly though, just as vasospasm does not necessarily result in infarction, this process occurred without subsequent infarction in 6 of 10 patients on follow-up CT or MRI and the infarcts that were demonstrated in this series were small. Spreading depolarization with vasoconstriction also occurs in the ischemic penumbra of stroke patients (Strong *et al*, 2012), raising the possibility that this

process could be triggered or compounded by the sustained ischemia of proximal vasospasm with the two mechanisms acting as a 'dual hit' (Strong & Macdonald, 2012). Of note, the incidence of spreading depolarizations is similar in patients with and without proximal vasospasm, (Dreier *et al*, 2006; Woitzik *et al*, 2012) suggesting that the spreading depolarization is not triggered by proximal vasospasm. When spreading ischemia was demonstrated in the absence of severe proximal vasospasm, infarcts were small (Woitzik *et al*, 2012). In contrast, it has been demonstrated that patients can develop large infarcts in the presence of proximal vasospasm (Mortimer *et al*, 2015a). Is it possible that perfusion deficits due to proximal vasospasm could increase the severity of spreading ischemia and expand infarcts? Experimental evidence suggests that spreading ischemia is intensified by a decline in cerebral perfusion pressure, while increasing perfusion pressure can reverse the spreading ischemic process to an almost normal spreading hyperaemic response to depolarizations (Drier *et al*, 2000; Sukhotinsky *et al*, 2010).

If it is assumed that both spreading ischemia and proximal vasospasm act in concert, perhaps with the latter augmenting the former, the rationale for treatments that increase proximal luminal diameter including endovascular treatments may therefore be to improve cerebral perfusion and limit the impact of a microvascular process such as spreading ischemia. This may be most relevant in instances where medical measures employed to improve flow (i.e. therapeutic hypertension) cannot overcome severe proximal stenoses and where collateral flow is limited. The Poiseuille equation states that flow is directly proportional to the pressure gradient and radius to the fourth power and inversely proportional to the fluid viscosity and vessel length. This formula forms the basis for hypertensive treatment in the intensive care unit but also for attempts to improve flow through an increase in vessel diameter. While flow will increase with a change in pressure, it will increase markedly with a change in vessel diameter.

Endovascular methods are most commonly employed as 'rescue' procedures. This has been shown to be effective in case series but neurological improvement is maximal if treatment is performed early and delayed treatment is probably futile. The use of prophylactic TBA undertaken prior to development of vasospasm has also been investigated in a multicentre randomised trial (Zwienenberg-Lee *et al*, 2009). Although there were significant reductions in the rate of patients requiring rescue

therapy in the treatment arm and possible outcome benefits in the good grade patients, overall clinical outcome was not significantly improved. An alternative approach is to screen for vasospasm at or just before the time when the majority of patients develop symptoms. The goal of this practice is to identify those patients with significant vasospasm who may benefit from treatment prior to development of symptoms or who are at risk of silent infarction as they are clinically too difficult to clinically assess. One system employs angiographic surveillance for cerebral vasospasm at days 5–7 post ictus, at or just before the time point that most patients become symptomatic, with subsequent endovascular treatment and multiple procedures where necessary based not only on symptomology but also on radiographic features. An assessment of the safety and efficacy of this approach is required.

Studies encompassing both retrospective (Mortimer *et al,* 2015b) and prospective data (Mortimer *et al,* 2015c) were undertaken. This is described in detail in Chapters 6 and 7 respectively. In the former, the clinical and radiological outcomes of 57 WFNS grade 1-5 patients with severe vasospasm treated using this intensive endovascular regime were investigated (Mortimer *et al,* 2015b). The mean number of procedures/patient was 6, range 2-13. Mean verapamil dose administered to the ICA was 14 mg and VA was 12 mg. Thirty-one patients underwent TBA (52.6%). The rate of proximal vessel infarction was 3/45 (6.7%) for patients presenting < 72 hours. Rates of favourable outcome (mRS 0-2) were 16/19 (84.2%) for WFNS grades 1-2, 12/19 (63.2%) for grades 3—4 and 5/19 (26.3%) for grade 5 patients. Delayed presentation >72 hours was the only factor on multivariate analysis to significantly predict vasospasm related infarction (OR 19.3 (3.2-116.6) P = 0.0012). Large vasospasm related infarct (OR 19.0 (1.7-216.4) 0.0179) and poor WFNS grade (OR 6.6 (1.3-33.9) P = 0.0233) were significant predictors of poor outcome on multivariate analysis.

In a second study (Mortimer *et al,* 2015c) which involved an exploratory analysis of prospectively acquired data, the clinical outcomes of 63 WFNS grade 1–2 patients with minimal vasospasm were compared to those of 17 WFNS grade 1–2 patients with severe vasospasm treated with induced hypertension and endovascular therapy. For those with severe vasospasm, 8/17 patients (47%) underwent TBA with a total of 15 procedures. Seventeen patients underwent verapamil chemical

angioplasty with a total of 67 procedures. The mean total dose of verapamil that any one patient received at each procedure was 20.3±2.3 mg (range 5-40 mg). Functional outcomes were available in 62 and 16 patients, respectively. Rates of favourable outcome did not differ significantly between the two groups. For patients with treated severe vasospasm, 90 day mRS 0-2 was seen in 15/17 (88.2%) and GOS 4–5 was achieved in 16/17 (94.1%).

The results of both studies suggest that the rates of infarction for patients with severe vasospasm treated using this protocol are relatively low compared to literature benchmarks; rates of infarction in other studies documenting severe vasospasm range from 46-81% (Weidauer *et al*, 2007; Cowley *et al*, 2011; Inagawa *et al*, 2014). Additionally, functional outcomes are encouraging and were not dissimilar to those patients who did not suffer vasospasm with good initial presenting grade. Complication rates were low but this regime is labour intensive. Furthermore, there is a danger that employing this approach could result in invasive imaging and unnecessary treatments in the group of patients who can withstand relatively severe vasospasm without detriment. Other centres employ non-invasive methods of vasospasm detection including transcranial Doppler (TCD) and/or a combination of CT angiography and CT perfusion. This may be the optimal approach, particularly in those patients who are sedated and difficult to assess clinically but TCD is operator dependant and CT techniques incur use of radiation, though with modern systems perfusion imaging can be acquired using a more acceptable radiation dose.

The results of these studies are encouraging but the realm of vasospasm intervention remains relatively evidence-light and the literature contains many studies with variable indications for treatment and variable treatments and, the disease itself is heterogeneous and there are many other factors which could potentially impact on outcome. There is an on-going randomised controlled trial assessing the use of intra-arterial verapamil versus a cocktail of intra-arterial vasodilators, including verapamil, nicardipine and nitrates (Chen, 2015). The doses of drugs used in this trial are relatively low compared to that published in other series including the present studies. There is much work to be done on identifying the optimal dosage and duration of action which could employ the use of animal models. An additional area of research is the study of the effect of intra-arterial

agents on other mechanisms of delayed ischaemia such as cortical spreading depression, a topic that has thus far received little attention due to the difficulty of measuring the latter process non-invasively.

1.10 The need for long term follow-up of coiled aneurysms

Aneurysm recurrence following coil occlusion is well recognised (Ferns *et al,* 2009). Intuitively this is investigated to allow retreatment of recurrent aneurysms that may pose a risk of rehaemorrhage. A number of studies have demonstrated an inverse relationship between the degree of occlusion and the risk of rerupture (Johnston *et al,* 2008; Sherif *et al,* 2012). This risk is dominant in the acute phase and it is unlikely that a high risk persists after a treated aneurysm has stabilised.

There is little consensus regarding which aneurysms should be retreated and there is little consensus regarding how long aneurysms should be followed with imaging to assess for recurrence. This is now commonly performed with magnetic resonance angiography (MRA) rather than DSA but long-term follow-up may be linked to anxiety/depression so could be detrimental (Ferns *et al,* 2011a). Furthermore, the results of analyses by other groups suggest that the majority of recurrences are identified on early follow-up at 6 months (Sluzewski *et al,* 2003, Ferns *et al,* 2011b). There is therefore a need for analysis of the rate of late recurrence in aneurysms that appear adequately occluded at initial 6-month follow-up. An additional question that requires investigation is whether with improving coil and angiographic technology rates of later recurrence are falling.

A retrospective analysis of aneurysms treated at a neuroscience centre between 1995 and 2010 was undertaken (Mortimer *et al,* 2015d). This is described in detail in Chapter 8. Four hundred and thirty-seven patients with 458 adequately occluded aneurysms at 6 months had mean long-term follow-up of 31 months; 57 (12.4%) were large (≥10 mm) and 104 (22.7%) were wide-necked (>4 mm). Nine aneurysms (2%) showed significant late anatomical deterioration whereby retreatment was considered or undertaken. The risk was greater for large aneurysms (≥10 mm) (OR 15.61, 95% CI 3.79 to 64.33, p=0.0001) or wide-necked aneurysms (>4 mm) (OR 12.70, 95% CI 2.60 to 62.13, p=0.0017). Of those aneurysms that were completely occluded at 6 months, 16 (5.5%) showed deterioration to small neck

remnant on late follow-up, but none of these aneurysms required retreatment. All remain adequately occluded.

The 1996–2005 cohort, (197 patients with 198 aneurysms) and 2006–2010 cohort, (241 patients with 260 aneurysms) were compared. The rate of significant recurrence was 3.5% in cohort 1 and 0.8% in cohort 2 (p=0.0345). The rate of retreatment was also significantly lower in cohort 2 (p=0.0221). It was speculated that this coincided with the introduction of a biplane unit and 3D rotational angiography that could have improved assessment of the aneurysm neck and local anatomy and also the introduction of next generation coil technology including 360 (Boston, now Stryker) and Axium 3D (eV3/Covidien) coils. Although we did not formally assess packing density, complex-shaped platinum coils have been shown to increase packing density (Wakhloo *et al*, 2007).

The results therefore suggest that at 6-month follow-up, adequately occluded, small, narrow-necked aneurysms may not need further imaging evaluation. Furthermore, the results suggest that the rate of late re-opening may be lower in patients treated with more contemporary coil technology. It should be remembered that the degree of occlusion is being used as a surrogate for risk of rebleeding. There is some evidence that the degree of occlusion is related to rebleeding risk (Johnston *et al*, 2008; Sherif *et al*, 2013) but the risk of rehaemorrhage beyond the first year is low and lies between 0.11% and 0.21% per year (Johnston *et al*, 2008; Molyneux *et al*, 2009). Conceivably, if only adequately occluded aneurysms are included in this analysis, the rate of delayed rebleeding would be lower than this. The very low incidence of aneurysm rebleeding therefore questions the validity and cost-effectiveness of performing routine long-term follow-up imaging of small, narrow-necked intracranial aneurysms completely obliterated after 6-12 months.

1.11 Conclusion

The results of this research suggest that a pragmatic imaging approach to subarachnoid haemorrhage may well be justified. In both the initial investigation of perimesencephalic haemorrhage, where non-invasive imaging may well suffice and, in post-coiling follow-up imaging, where a single episode may be all that is required

following adequate coiling, this may well be the case. The results of a large consecutive series of middle cerebral artery aneurysms suggest that the endovascular approach to treating the lesions (often regarded as the most favourable for surgical clipping) is justified. Furthermore, the differences in cognitive outcome following clipping or coiling of aneurysms are now well established and the results of a detailed post procedural imaging analysis suggest that this is likely due to differences in local ischaemic brain damage. The results of this work also suggest that the more physiological derangement there is in a patient with SAH, the less outcomes favour a surgical approach. An additional finding is that an aggressive endovascular approach to delayed cerebral ischaemia may result in low rates of delayed infarction and equivalent rates of favourable outcome when compared to patients of similar grade without vasospasm.

CHAPTER 2

ENDOVASCULAR TREATMENT OF 300 CONSECUTIVE MIDDLE CEREBRAL ARTERY ANEURYSMS: CLINICAL AND RADIOLOGIC OUTCOMES

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2.1 Abstract

2.1.1 Background

There is controversy as to the best mode of treating MCA aneurysms. We report the results of a large endovascular series of patients treated at our centre.

2.1.2 Materials and methods

This study was a retrospective analysis of a prospectively acquired data base. All patients with saccular MCA aneurysms treated between November 1996 and June 2012 were included. World Federation of Neurosurgical Societies grade, aneurysm site, size, and aneurysm neck size were recorded, along with clinical outcome assessed with the Glasgow Outcome Scale and radiographic occlusion assessed with the Raymond classification at 6 months and 2.5 years.

2.1.3 Results

A total of 295 patients with 300 MCA aneurysms were treated including 244 ruptured aneurysms (80.7%). The technical failure rate was 4.3% (13 patients). Complete occlusion or neck remnant was achieved in 264 (91.4%). Complications included rupture in 15 patients (5%), thromboembolism in 17 patients (5.7%), and early rebleeding in 3 patients (1%). Overall permanent procedural-related morbidity and mortality were seen in 12 patients (7.8%). Of the patients with ruptured aneurysms, 189 (79.4%) had a favourable clinical outcome (Glasgow Outcome Scale score, 4–5). A total of 33 patients (13.6%) died. On initial angiographic follow-up, aneurysm remnant was seen in 18 aneurysms (8.1%). A total of 13 patients (4.3%) were retreated.

2.1.4 Conclusion

Our experience demonstrates that endovascular treatment of MCA aneurysms has an acceptable safety profile with low rates of technical failure and retreatment. Therefore, coiling is acceptable as the primary treatment of MCA aneurysms.

2.2 Introduction

The International Subarachnoid Aneurysm Trial (ISAT) demonstrated an absolute 6.9% reduction in the rate of death or dependency at 1 year for patients treated with endovascular coiling (EVC) (Molyneux *et al,* 2002). ISAT did not, however, address the specific issue of patients with MCA aneurysms, who represented only 303 (14.1%) of the 2143 enrolled patients. This has resulted in controversy as to the best mode of treatment of aneurysms at this location. Surgical clipping remains the standard treatment in many institutions. The anatomic location aids surgical access, and in some cases, surgery facilitates haematoma evacuation. There is also a perceived increased risk for EVC at this site because these aneurysms are often wide-neck and have branches arising from the neck (Ausman *et al,* 1997, Regli *et al,* 1999). Recently, several surgical series have been published that demonstrate excellent clinical results with low rates of morbidity and mortality (Morgan *et al,* 2010, van Dijk *et al,* 2011; Choi *et al,* 2012; Rodrıguez-Hernandez *et al,* 2013). Therefore, we analysed the strategy at our institution where EVC is the first-line therapy for aneurysm treatment at any location and focused on the more controversial MCA aneurysms.

2.3 Materials and methods

2.3.1 Patient population

This was an observational, prospectively collated study of 295 consecutive patients referred to our institution for endovascular treatment of ruptured and unruptured MCA aneurysms. All patients underwent primary EVC during a 15.5-year period (between November 1996 and June 2012). All patients with SAH were considered for EVC as the primary treatment technique when a consultant interventional neuroradiologist was available. Elective cases were discussed at our institutional neurovascular multidisciplinary meeting. Patients with fusiform or dissecting aneurysms and those treated with primary parent vessel occlusion were excluded from this study. Patient information, aneurysm characteristics, details of treatment, and clinical course were entered prospectively into a data base and subsequently analysed.

SAH was confirmed by cranial CT or lumbar puncture and CSF analysis. Of those with unruptured aneurysms, 21 patients with 23 aneurysms had previous SAH and delayed treatment of additional MCA aneurysms or SAH that was clearly the result of another aneurysm, with the additional MCA aneurysm treated in the same procedure. Thirty-two patients with 33 MCA aneurysms diagnosed incidentally were also treated.

2.3.2 Endovascular procedure

All procedures were performed by consultant interventional neuroradiologists (S.A.R., M.D.B., and A.J.M. with 5, 3, and 20 years of endovascular experience when they started coiling patients within the study period, respectively). EVC was performed by use of conventional techniques with the patients under general anaesthesia and systemic heparinisation. A bolus of 3000–5000 IU of heparin was followed by continuous infusion via the catheter flushing system at a concentration of 5 IU/mL. The aim was to place coils sequentially into the aneurysmal sac to the point of angiographic occlusion. Most coils deployed were bare platinum (Boston Scientific, now Stryker, Kalamazoo, Michigan; Micrus, now Codman Neurovascular, Raynham, Massachusetts; ev3, now Covidien, Dublin, Ireland). After diagnostic angiography, the aneurysm was selectively catheterised with a microcatheter by use

of standard techniques, through a guide catheter positioned in the internal carotid artery.

Where necessary, balloon remodelling (12 cases primary treatment, 4 cases retreatment) and stent-assisted coil embolization (1 case primary treatment, 1 case retreatment) were used for the treatment of wide-neck aneurysms. Intravenous aspirin (500 mg) was used as a prophylaxis to prevent thromboembolic complications in both ruptured and unruptured aneurysms, administered after initial coil deployment when a degree of protection had been attained. Intravenous aspirin was also administered if a stent was deployed. Technical failure was defined as an attempted embolization procedure during which coils could not be deployed safely. Any procedural or other subsequent complication was recorded in addition to any deterioration in the patient's neurologic status after the procedure. Craniotomy and haematoma evacuation or decompressive hemicraniectomy were performed to manage haematoma/herniation, after coil embolization.

2.3.3 Aneurysms treated

The aneurysm responsible for haemorrhage was identified by blood distribution on CT, aneurysm appearance, and vasospasm distribution. This aneurysm was treated first. Additional aneurysms were treated during the same procedure or after recovery from haemorrhage. If it was not possible to clearly identify the ruptured aneurysm, all possible candidates were treated initially, and aneurysms were classified as ruptured. If contralateral aneurysms were treated at a later date, these were classified as unruptured.

2.3.4 Clinical and radiologic follow-up

Clinical outcome was independently obtained for all at a 3 to 6-month clinic visit with a specialist neurovascular nurse practitioner and was assessed by use of the Glasgow Outcome Scale (GOS). Each patient was scheduled to undergo either cerebral angiography (before 2004: 48 patients) or MRA (since 2004: 174 patients) at 6 months after treatment and then at approximately 30 months after initial treatment. If early recurrence was anticipated, initial follow-up was obtained earlier. If recurrence was demonstrated on MRA, formal conventional angiography was performed.

The degree of aneurysm occlusion was assessed on immediate post embolization angiography and on follow-up angiography. Angiographic and MRA outcomes were determined by the treating physician and were classified according to the Raymond classification. An aneurysm was considered stable on follow-up if there was no increase in contrast filling on angiography or flow on MRA. Retreatment was considered in persistent or evolving aneurysmal remnants.

2.4 Results

2.4.1 Patient population and aneurysm characteristics

Of the 295 patients, 196 (66.7%) were women and 98 (33.3%) were men. A total of 244 ruptured aneurysms in 242 patients and 56 unruptured aneurysms in 53 patients comprised the study cohort. The mean age of the patients in the ruptured cohort was 53.9 years; for the patients in the unruptured cohort, it was 52.7 years (table 2.4.1.1). For the 242 patients with SAH, World Federation of Neurosurgical Societies (WFNS) and Fisher grading is shown in table 2.1.

A total of 264 aneurysms (88%) were located at the main MCA branching point; 23 (7.7%) were positioned proximal to this location, and 13 (4.3%) were positioned more distally. There were 232 aneurysms (77%) that were small (10 mm) and 64 (21%) that were large (11–24mm). Giant aneurysms constituted 1.3% of the cohort (4 cases), and 93 aneurysms (31%) were wide-neck (4 mm). Twenty patients (8.3%) with SAH (other than those subsequently referred for clipping after a failed attempt at coiling) went on to have a craniotomy and haematoma evacuation or hemicraniectomy.

Surgical data were available from 2000–2012; 51 patients with ruptured aneurysms underwent primary surgical clipping. A total of 36 patients were treated with primary clipping because of either lack of availability of an interventional neuroradiologist or if the patient was being treated by a vascular neurosurgeon (most aneurysms were clipped before 2003). Eight aneurysms were clipped because of anatomic considerations after angiography.

CHARACTERISTIC	Unruptured	Ruptured
Number of patients (n=295)	53	242
Number of aneurysms (n=300)	56	244
Mean (SD) age (y)	52.7 (9.6)	53.9 (12.4)
Median (IQR) age (y)	55.0 (13.5)	53.0 (17)
Age range (y)	29-72	21-84
No of females	38 (73.1%)	158 (65.3%)
WFNS Scale		
1	-	136 (56.2%)
2	-	38 (15.6%)
3	-	25 (10%)
4	-	21 (8.6%)
5	-	22 (9.1%)
Fisher Grade		
1	-	11 (4.5%)
2	-	20 (8.3%)
3	-	104 (42.6%)
4	-	108 (44.6%)

Table 2.1 Descriptive data for the study population.

In 13 cases, the patients were treated with clipping after attempted coiling. In the same period, 16 patients with unruptured MCA aneurysms were treated with elective primary clipping. The indications were patient choice or difficult aneurysmal morphologic features.

2.4.2 Procedural success

Initial coiling results are summarised in table 2.2. Technical failure was seen in 13 aneurysms (5 unruptured and 8 ruptured), equating to 4.3% of treated aneurysms. These patients went on to have microsurgical clipping. A total of 215 aneurysms were completely occluded on initial conventional angiography (71.7%), and neck remnant was seen in 59 patients (19.7%), resulting in a rate of satisfactory occlusion of 91.4%. An aneurysmal remnant was seen in 9 patients (3%). In 2 patients, a complication precluded EVC.

Initial angiographic result	Unruptured N=56	Ruptured N=254	Total N=300
Complete occlusion	28	187	215 (71.7%)
Neck remnant	17	42	59 (19.7%)
Aneurysm remnant	3	6	9 (3.0%)
Technical failure	5	8	13 (4.3%)
Complication precluding coiling	1	1	2 (0.7%)
Missing data	1	1	2 (0.7%)

Table 2.2 Initial coiling results.

2.4.3 Complications

Complications and clinical outcome are summarised in table 2.3. The technical complication rate was 12.9%, including aneurysmal perforations and thromboembolic events with either silent or transient symptoms. The overall permanent procedural-related morbidity rate was 3.8% (11 patients) and mortality rate was 4% (12 patients), equating to a permanent morbidity and mortality rate of 7.8% (23 patients). Of those patients who experienced a technical complication, 26 (68.4%) of 38 had a favourable outcome (GOS, 4 or 5).

When unruptured aneurysms were considered separately, 1 patient had transient arm weakness that fully resolved and 1 patient (1.8%) died as a result of aneurysmal perforation, but no other permanent complications were encountered.

Complication	Aneurysm rupture	Thromboembolic	Early rebleed	Other	Total
Total number	15 (5.0%)	18 (6%)	3 (1.2%)	2 (0.7%)	38 (12.9%)
Clinically silent	6	6		2	14 (4.7%)
GOS 5	7	10		2	19
GOS 4	5	2			7
GOS 1	3	6	3		12 (4%)

Table 2.3 Complications and subsequent clinical outcomes.

2.4.3.1 Aneurysmal perforation

Fifteen patients (5% of procedures) had intra-procedural aneurysmal perforations. In 10 patients, the perforation occurred during coil insertion. In 1 patient, the perforation was secondary to remodelling balloon inflation; in another patient, perforation was secondary to contrast injection before intervention. When rupture occurred, heparin was reversed immediately with protamine; coiling continued to limit the extent of haemorrhage and occlude the aneurysm; and measures were used, if necessary, to reduce intracranial pressure via ventricular drainage of CSF. Six ruptures were clinically silent. Three patients died after rupture; 12 had an independent outcome (GOS, 4–5).

2.4.3.2 Thromboembolic events

Eighteen patients (6% of procedures) experienced thromboembolic complications. These were managed by intravenous aspirin and abciximab and induced hypertension. Of these thromboembolic complications, 6 were clinically silent and 3 were transient. Twelve patients were independent (GOS, 4–5), and 6 patients died.

2.4.3.3 Rebleeds

Three patients (1.2%) experienced early rebleeds. All occurred within 24 hours of the procedure, and 3 patients died.

2.4.3.4 Other complications

Coil protrusion was noted in 2 patients with no clinical sequelae.

2.4.4 Clinical outcome

Of the patients with ruptured aneurysms, 79.8% had a favourable clinical outcome (GOS, 4–5). A total of 33 patients (13.6%) died (table 2.4). One of 53 patients with an unruptured aneurysm died as a result of procedural rupture and was the only patient who experienced a permanent change in neurologic status as a result of the procedure. Of the patients who underwent a craniotomy or craniectomy for management of haematoma or mass effect, 8 (40%) of 20 achieved a clinical outcome of GOS 4. The mortality rate was 45% in this subgroup.

Clinical outcome	Patients
GOS 5	170 (70.3%)
GOS 4	23 (9.5%)
GOS 3	15 (6.2%)
GOS 2	0
GOS 1	33 (13.6%)
Missing data	1 (0.4%)

Table 2.4 Clinical outcomes for patients with ruptured MCA aneurysms. GOS, Glasgow Outcome Score.

2.4.5 Anatomic outcome

Initial follow-up (mean, 7 months; range, 3–17 months) was available in 219 patients. Allowing for those patients who died, follow-up was available in 84%. Reasons for no follow-up included a dead or severe outcome in 38 patients, advanced age in 12 patients, microsurgical clipping as a definitive treatment in 13 patients, patient choice in 7 patients, and unknown reasons in 6 patients. Medium- to long-term follow-up (mean, 35 months; range, 18–108 months) was available in 158 patients. Twenty-two patients were ineligible because they were due this follow-up beyond the study period. Therefore, medium- to long-term follow-up was available in 80% of patients who had undergone initial follow-up and in 66% of the patients who were eligible for late follow-up and had survived the acute episode. Reasons for halting anatomic follow-up after initial follow-up were advanced age in 17 patients, out-of-region follow-up in 5 patients, patient choice in 12 patients, death from unrelated cause in 3 patients, and unknown reasons in 2 patients. Initial angiographic follow-up is summarised in table 2.5.

Complete occlusion was seen in 148 aneurysms (67.6%), a neck remnant was seen in 53 (23.3%), and an aneurysmal remnant was seen in 18 aneurysms (8.1%). Stable or improved appearances were seen in 178 (81.3%) of 219 aneurysms. Twenty-three (10.5%) showed minor anatomic deterioration to the neck remnant but remained satisfactorily occluded. Of those aneurysms with complete occlusion at post-coiling angiography undergoing initial follow-up (n=164), the probability of complete occlusion was 84.1% (138 aneurysms), of a neck remnant was 12.2% (20 aneurysms), and of aneurysmal remnant was 3.6% (6 aneurysms). Of those aneurysms with a neck remnant at post-coiling angiography undergoing initial follow-up (n=47), the probability of complete occlusion was 19.2% (9 aneurysms),

of a neck remnant was 70.2% (33 aneurysms), and of an aneurysmal remnant was 10.6% (5 patients).

CHARACTERISTIC	Complete occlusion	Neck Remnant	Aneurysm remnant	Retreat
All aneurysms (n=219)	148 (67.6%)	53 (23.3%)	18 (8.1)	13 (5.9%)
Ruptured aneurysms (n=175)	117	42	16	13
Unruptured aneurysms (n=44)	31	11	2	0
-Small ≤10mm	137	26	11	6
-Large 11-24mm	9	26	6	6
-Giant ≥25mm	2	1	1	1
-Wide neck >4mm	29	24	10	7

Table 2.5 Angiographic outcomes at initial follow-up.

A total of 18 aneurysms (8.1%) showed an aneurysmal remnant at initial follow-up, 6 had shown a similar aneurysmal remnant on immediate post-coiling angiography, and 12 aneurysms demonstrated deterioration from complete occlusion or a neck remnant to an aneurysmal remnant. Aneurysmal remnants were more common in patients with large and giant aneurysms compared with small aneurysms at follow-up (15.6% vs 6.3%; $P=0.04$). Wide-neck aneurysms were also significantly more common in patients who showed an aneurysmal remnant at follow-up compared with those with complete occlusion (19.6% vs 55.6%; $P < 0.001$). There were 13 (4.3%) of these patients who were retreated (12 with further coiling and 1 with microsurgery). The remaining 5 patients showed a stable aneurysmal remnant and were treated conservatively.

A total of 158 patients underwent long-term follow-up: 110 patients (69.4%) showed complete occlusion, 43 (27.4%) showed a neck remnant, and 5 (3.1%) showed an aneurysmal remnant. A total of 150 (95%) patients, including the retreated patients, showed stable appearances. A new neck remnant that did not warrant retreatment was seen in 7 patients, and new aneurysmal remnant was seen in only 1 patient.

2.4.6 Retreatment

Twelve of 13 recurrent aneurysms were retreated (4.3% of all aneurysms) with coil embolization and 1 with microsurgical clipping. One of 12 endovascular patients required 4 additional treatments for a recurrent, large, wide-neck aneurysm; she refused surgery. Subsequent angiographic follow-up was available in these patients, and 5 achieved complete occlusion (including 1 patient who underwent microsurgery), 4 showed a neck remnant, and 4 showed a residual aneurysm. Stent or balloon-assisted coiling was used in 5 recurrent aneurysms. No morbidity or mortality was related to EVC.

2.5 Discussion

Controversy has existed as to the best mode of therapy for MCA aneurysms. The anatomy of MCA aneurysms is often considered more favourable for surgical treatment because of the frequency of a wide-neck configuration with incorporation of MCA branches that are technically more challenging to treat by EVC. ISAT demonstrated that 116 (71.6%) of 162 endovascular patients and 100 (71.9%) of 139 surgical patients attained independence (mRS, 0–2) (Molyneux *et al*, 2005); however, MCA aneurysms were relatively underrepresented in ISAT, owing to the absence of clinical equipoise at the time of recruitment. This has led to criticism of the practice of applying ISAT to MCA aneurysms and the generalised adoption of EVC for aneurysms at this location. We therefore review the clinical and radiologic outcomes of this series in the context of the endovascular and surgical literature.

2.5.1 Clinical outcome in patients with ruptured aneurysms

Favourable clinical outcomes (mRS, 0–2) for ruptured aneurysms at all locations in ISAT (Molyneux *et al*, 2002) and CLARITY (Cognard *et al*, 2011) (Clinical and Anatomical Results in the Treatment of Ruptured Intracranial Aneurysms, a multicentre prospective study of consecutively coiled patients) were 76.3% and 72.3%, respectively, with the proportion of favourable presenting clinical grade patients (WFNS, 1–2) being 88% and 65.7%, respectively. Favourable clinical outcomes (mRS, 0–2 and GOS, 5) in other large series of ruptured MCA aneurysms comprising at least 50 patients treated with EVC, are within the 67%–85% range (Iijima *et al*, 2005; Quadros *et al*, 2007; Oishi *et al*, 2009; Suzuki *et al*, 2009; Bracard *et al*, 2010).

In the present study, the largest published single-centre experience to date, patients with consecutive ruptured MCA aneurysms achieved good outcome (GOS, 5) in 70.3% and favourable outcome (GOS, 4 and 5) in nearly 80%, with the proportion of favourable presenting clinical grade patients (WFNS, 1-2) being 72%. We were able to directly compare the results of our present study to a large audit of ruptured aneurysms at all locations treated through EVC at our institution with similar distribution of clinical grade (Renowden *et al*, 2009). In this study, 711 patients with 717 ruptured aneurysms were reviewed. In the 605 patients with aneurysms at all locations other than the MCA, favourable outcome (GOS, 4 and 5) was seen in 490 (80.9%). Mortality occurred in 89 patients (14.7%). Statistical

comparison of clinical outcomes for patients with ruptured MCA aneurysms in the present study showed no significant difference in the favourable outcome (P=0.58) or mortality ($P=0$.69).

Other than the ISAT results (Molyneux *et al*, 2005), prospective data on outcomes for clipping of ruptured MCA aneurysms are lacking. In 1990, The International Cooperative Study on the Timing of Aneurysm Surgery (Kassell *et al*, 1990), a multicentre prospective observational study, included 786 patients with ruptured MCA aneurysms. A total of 480 patients (61%) achieved good outcome (GOS, 5) at 6 months. Following this, Rinne et al (1996) published one of the largest series of 561 patients with 690 MCA aneurysms, 91% presenting with SAH and 80% with Hunt and Hess grades I-III. Overall favourable outcome (GOS, 5) was 60%. Poor outcomes (GOS, 1-3) were seen in 32%, and this rate was higher in large or giant aneurysms. It is surprising to note that there were significantly more poor outcomes among patients with ruptured MCAs than among those with any other anterior circulation aneurysms (32% and 25%, respectively).

After ISAT, several single-centre studies have been published. Guresir et al (2011) treated 168 patients with ruptured MCA aneurysms. Favourable outcome (mRS, 0–2) was 55% at 6 months. At the other end of the scale, among 80 patients treated by Van Dijk et al (2011) including 67% with WFNS grades I–II, 80% achieved an mRS of 0–2 at longer-term clinical follow-up (mean, 4.7 years). In one of the largest and most complete recent series, Rodrıguez-Hernandez et al (2013) treated 282 ruptured MCA aneurysms with 78% of patients presenting with Hunt and Hess grades I–III; favourable outcomes (mRS, 0–2) were achieved in 70.2%.

These results are similar to those achieved in the present study by using EVC. Therefore, although the conservative view is that surgery should remain the treatment of choice of ruptured MCA aneurysms, except when there are extenuating comorbidities or overriding patient preferences, we believe that for the range of ruptured MCA aneurysms, at least equivalent clinical outcomes to the best surgical series can be obtained by use of conventional endovascular techniques.

2.5.2 Coiling in the presence of intracerebral haematoma

One of the traditional advantages of a clipping strategy is that it allows haematoma evacuation. An alternative approach is to protect the aneurysm before evacuation through coiling. It is possible that this approach is more advantageous

because haematoma evacuation in the presence of an unprotected aneurysm may initiate intra-procedural rupture (Houkin *et al,* 1999). Furthermore, clipping may require a more extensive surgical exposure to access the aneurysm, perhaps involving retraction of contused parenchyma, which can result in oedema or ischemia (Yundt *et al,* 1997); this would no longer be required. By use of this approach in the present series, of 20 patients with WFNS grades III or higher (14/20 were grades IV and V), 40% of patients achieved an outcome of GOS 4. Other small series have also achieved more impressive outcomes in poor-grade patients by using this approach (Tawk *et al,* 2010).

2.5.3 Technical success

The coiling procedure was successfully performed in 94.4% of aneurysms with post-treatment imaging, demonstrating that 71.7% were completely occluded and 19.7% exhibited a neck remnant, equating to a satisfactory occlusion rate of 91.4%. The technical failure rate was 4.3%. These results are very similar to the results of a systematic review of 12 series comprising a total of 1030 patients with 1076 MCA aneurysms (500 patients had ruptured aneurysms, and 541 had unruptured aneurysms) (Brinjikji *et al,* 2011a). In that study, the EVC failure rate was 4.8% (95% CI, 3.7%–6.3%). Overall, 82.4% (95% CI, 80.0%–84.6%) of MCA aneurysms were completely or nearly completely occluded at immediate postoperative angiographic follow-up, and 12.7% (95% CI, 10.9%– 14.9%) were incompletely occluded. Prospective data specifically for MCA aneurysms are available from the results of the ATENA (Analysis of Treatment by Endovascular Approach of Nonruptured Aneurysms) study, which included 86 unruptured MCA aneurysms (Pierot *et al,* 2010a). Complete occlusion was achieved in 69.4%, neck remnant in 19.4% (adequate occlusion in 88.8%), and aneurysmal remnant in 11.3%. In the CLARITY study, 105 MCA aneurysms were included. Complete occlusion was achieved in 45.7%, neck remnant in 39% (adequate occlusion in 84.7%), and aneurysmal remnant in 15.2% (Pierot *et al,* 2010b). It is important to note that though occlusion rates were lower in this study, the results did not differ significantly from other anterior circulation locations.

We hope that this case series dispels the contradictory conclusions of previous publications (Ausman *et al,* 1997; Regli *et al,* 1999), suggesting that EVC is

appropriate only in a minority of MCA aneurysms. Our experience, and the experience of others, concludes that EVC is feasible in most aneurysms.

2.5.4 Short-term follow-up

Initial angiographic follow-up demonstrated satisfactory occlusion in 92% of aneurysms, with 8.1% showing residual aneurysm. A total of 81% of MCA aneurysms, most treated as part of a coil first policy, were stable or showed improved appearances at initial angiographic follow-up. A systematic review of 748 MCA aneurysms treated by endovascular means also showed angiographic stability or progression to better obliteration in 81% of patients undergoing follow-up angiography (Brinjikji *et al,* 2011a). In the CLARITY study (Pierot *et al,* 2012a), of 53 patients undergoing midterm follow-up, 57.4% (95% CI, 44.8–69.3) showed stability or improved appearances and 42.6% (95% CI, 30.7–55.2) had shown some degree of anatomic worsening, but presumably, this was not significant in most because 77.9% (95% CI, 66.2–87.1) were classified as having adequate occlusion. Although the rate of anatomic worsening was higher in other studies, the rate was very similar to that at other anatomic locations and was not specific for MCA aneurysms.

2.5.5 Adjunctive therapies

In this series, bare platinum coils were the mainstay of treatment during a long enrolment period, with many aneurysms treated by use of old-generation technology. The use of adjunctive devices such as stent placement or balloon remodelling was very infrequent, and intra-aneurysmal flow diverters were not used. This trend may explain the relatively low thromboembolic complication rate, but also lower rates of complete occlusion compared with some recently published series on use of adjunctive devices (Vendrell *et al,* 2011; Johnson *et al* 2013a). Adjunctive devices have been used in 20.4% of other published MCA series (Brinjikji *et al,* 2011a), with the aim of obtaining complete occlusion to minimize the risk for subsequent haemorrhage (Johnston *et al,* 2008).

A critical appraisal of the available literature has suggested that balloon assistance has a very similar safety profile to coiling without remodelling (Pierot *et al,* 2012b). In the CLARITY (Pierot *et al,* 2011) and ATENA (Pierot *et al,* 2009) studies, the use of a balloon was not associated with significantly increased rates of

thromboembolic events or aneurysmal perforation but was associated with an increased rate of adequate postoperative occlusion. Vendrell et al (2009) treated 63 MCA aneurysms with a balloon remodelling technique. It is interesting to note that they found that though this technique allowed treatment of aneurysms with more complex morphologic features, it was associated with more recurrences in the long term than were treatments without balloon remodelling.

Stent assistance may lower recurrence and allow more complete treatment of more complex lesions. However, there are reservations regarding procedural safety. Procedural morbidity and mortality risks have been shown to be significantly greater in those patients who have undergone stent-assisted coiling compared with those who have not under gone stent-assisted coiling (Piotin *et al,* 2010). Procedural morbidity and mortality risks are significantly increased when treating ruptured aneurysms as opposed to unruptured aneurysms with a stent (Chalouhi *et al,* 2013b). Several series have recently been published that focus specifically on complex MCA aneurysms (Vendrell *et al,* 2011; Johnson *et al,* 2013a; Fields *et al,* 2013). In the largest series, Johnson et al (2013a) treated 100 MCA aneurysms with stent assistance. Follow-up imaging showed complete occlusion in 90.6% of aneurysms, residual neck in 3.5%, and residual filling in 5.9%. Four aneurysms (4.7%) required retreatment. Long-term MRA follow-up revealed stability or progressive thrombosis in 97.9%. Permanent morbidity was seen in 1% and mortality in 1%. These authors suggested that this treatment method represented a safe and acceptable alternative to craniotomy.

Intra-aneurysmal flow diverters now represent an additional treatment option for wide-neck bifurcation aneurysms. Pierot et al (2013) treated 34 ruptured and unruptured MCA aneurysms with the WEB device. Adequate occlusion (total occlusion or neck remnant) was observed in 83.3% of aneurysms with an acceptable safety profile; mortality rate of the treatment was 0.0% and morbidity rate was 3.1% (intraoperative rupture with an mRS of 3 at 1-month follow-up).

2.5.6 Long-term follow-up, retreatment, and surgical occlusion rates: do they confer a long-term advantage?

In the present series, 4.3% were retreated. In other endovascular series of at least 50 patients, retreatment rates varied from 2.4%-13.9% (Iijima *et al,* 2005; Quadros *et al,* 2007; Oishi *et al,* 2009; Suzuki *et al,* 2009; Vendrell *et al,* 2009;

Bracard *et al,* 2010). It is well recognised that the decision to retreat is highly variable (McDonald *et al,* 2013). Our cohort had no additional morbidity or mortality relating to the additional procedures, and in line with previous findings (Campi *et al,* 2007; Renowden *et al,* 2008), the risk for further coil embolization did not negate the advantage of the initial embolization. At late follow-up, including retreated aneurysms, 157 of 158 aneurysms showed complete occlusion, neck remnant, or stable aneurysmal remnant. One case showed significant delayed anatomic deterioration.

Surgical series have shown high rates of complete occlusion. Each of the series published since ISAT have claimed excellent rates of initial complete aneurysm obliteration ranging from 89%–98.3% (van Dijk *et al,* 2011; Guresir *et al,* 2011; Rodrıguez-Hernandez *et al,* 2013). Long-term angiographic follow-up was available in only 22% (Rodrıguez-Hernandez *et al* 2013) and 29% (Guresir *et al,* 2011) in 2 of these series but reported excellent rates of complete occlusion ranging from 96%–98%. This is perhaps one of the principal arguments for clipping aneurysms at any location; many of the reservations in the neurosurgical literature regarding the use of coiling stem from the lower rate of complete occlusion. A major limitation of this study was the lack of long-term morbidity data, and therefore, based on our data, long-term efficacy was unclear. However, the risk for rerupture occurs mostly within the first year (Johnston *et al,* 2008; Molyneux *et al,* 2009). Beyond this, the risk lies between 0.11% (Johnston et al 2008) and 0.21% (Molyneux *et al,* 2009) per year. Both ISAT (Molyneux *et al,* 2009), CARAT (Cerebral Aneurysm Rerupture After Treatment) (Johnston *et al,* 2008), and BRAT (Barrow Ruptured Aneurysm Trial) (McDougall *et al,* 2012) studies have suggested that the benefits of coiling are unlikely to be superseded by the risk of delayed haemorrhage. The predicted risk has been calculated from the CARAT study, in which 57% showed a neck remnant, and ISAT, in which 27% showed a neck remnant. Prospectively acquired, independently assessed anatomic data have suggested that the neck remnant rate is not significantly different for MCA aneurysms vs other locations (Pierot *et al,* 2012), and retreatment rates, both in our own series and on systematic review of the literature (Brinjikji *et al,* 2011a), are not in excess of retreatment rates at all anatomic locations (Ferns *et al,* 2009).

Therefore, the argument that endovascular MCA occlusion rates are low and result in a greater risk of rebleeding is unlikely to be true. The data from both

CARAT and ISAT also raise the question of how aggressively to manage stable neck remnants. Most of these remnants are likely to be benign. We have noted a trend to manage neck remnants conservatively. This trend may be reflected in the proportion of retreated patients in the more recent Cerecyte (Molyneux *et al*, 2012) and HELPS (HydroCoil Endovascular Aneurysm Occlusion and Packing Study) (White *et al*, 2011) trials compared with ISAT (5.5% and 3%, respectively, vs 17%).

2.5.7 Morbidity and mortality outcomes

Aneurysmal perforation was seen in 5% of patients, with permanent morbidity and mortality relating to this at 3%. The perforation rate lies within the range of previously published studies that have demonstrated procedural perforation complicating 1%– 8.5% of MCA aneurysm treatments (Iijima *et al*, 2005; Quadros *et al*, 2007; Oishi *et al*, 2009; Vendrell *et al*, 2009; Suzuki *et al*, 2009; Bracard *et al*, 2010). In 2 large prospective series of unruptured aneurysms (ATENA) (Pierot *et al*, 2008) and ruptured aneurysms (CLARITY) (Pierot et al 2010c) treated by endovascular means, the perforation rate for MCA aneurysms was 4.1% and 8.5%, respectively. We have previously suggested that the rate of aneurysmal perforation may be higher at the MCA location (Renowden *et al*, 2009); we demonstrated that MCA aneurysms accounted for 13% of cases but 24% of all intra-procedural ruptures. In the CLARITY study, the frequency of procedural perforation was significantly higher in the MCA group compared with aneurysms at other locations, though the cumulative morbidity and mortality rates of procedural perforation were not significantly increased (Pierot *et al*, 2010c).

The thromboembolic rate was 6%, with permanent morbidity and mortality rate relating to this at 3%. This rate is lower than in many large endovascular series (Iijima *et al*, 2005; Quadros *et al*, 2007; Oishi *et al*, 2009; Suzuki *et al*, 2009; Bracard *et al*, 2010) and in prospective series (Pierot *et al*, 2008 and 2010c) that demonstrate thromboembolism complicating 7%–19.6%. We attributed this finding, at least in part, to the routine use of intravenous aspirin and low use of adjunctive devices, particularly stents. In other series, aspirin administration was not routine with ruptured aneurysms that comprised most aneurysms in this series. In the CLARITY study (Pierot et al 2010c), although the rate of thromboembolic complications was not significantly higher in MCA aneurysms compared with those at other locations, the cumulative morbidity and mortality rate related to

thromboembolic events was significantly higher in the MCA group than in the non-MCA group (7.5% vs 3.3%, respectively; *P*=0.038). Therefore, it was suggested that the clinical consequences of thromboembolism are important because of the size and function of the MCA territory.

In this study, 3 patients (1.2%) experienced rebleeds and all died. All aneurysms appeared completely occluded on post-procedure angiography, and all occurred within the first 24 hours of the procedure. The CARAT study (Johnston *et al,* 2008) demonstrated a risk of rebleeding at all anatomic locations after complete occlusion by use of coiling to be 1.8% and clipping to be 0.9%. It appears, therefore, that the results for MCA aneurysm coiling are not dissimilar to those for all locations.

2.5.8 Surgical morbidity and mortality

Published single-centre surgical series specifically focusing on ruptured MCA aneurysms have variably reported procedural complication rates. Two recent series have described complication rates. Guresir et al (2011) described infarction complicating 5.5% of cases and peri-procedural haemorrhage complicating 5.5% of cases in their series of 168 cases. Rodrıguez-Hernandez et al (2013) reported the procedural-related combined morbidity and mortality to be 1.1% in a series of 282 ruptured MCA aneurysms. Intra-procedural rupture occurred in 7.5%, but there was no permanent morbidity or mortality relating to this. These results are very impressive and reflect a highly specialised service, but we do question whether they can be generalised to the neurosurgical community as a whole, particularly to centres with modest volume. Indeed, database analysis of a large US population (2454 patients) with ruptured aneurysms from 2006–2011 at multiple centres demonstrated that patients treated with clipping demonstrated an increased likelihood of morbidity, as defined by hospital discharge to long-term care facilities, ischemic complications, and other postoperative complications, compared with patients treated with coiling (McDonald *et al,* 2013).

Prospective data on procedural morbidity and mortality relating to ruptured MCA aneurysm clipping are lacking, but data from the PRESAT (Prospective Registry of Subarachnoid Aneurysms Treatment) trial (Taki *et al,* 2011) (40.5% of surgical cases were MCA aneurysms) show an overall clipping-related complication rate of 17.2%. This rate included intraoperative rupture in 6.7%, ischemic

complications in 6%, and haemorrhagic complications in 5.4% (the latter included parenchymal contusions, extradural and subdural haematomas, and primary haematoma extension).

An additional potential drawback of the use of open neurosurgery is the risk for epilepsy. This finding was not assessed in the present series, but in late follow-up of ISAT (Hart *et al,* 2011), it has been demonstrated that MCA location is associated with an increased epilepsy risk for both coiling and clipping but that this risk is significantly greater in patients who had undergone clipping. In the coiling group, the risk for epilepsy at 1 year was 2.6% for non-MCA locations compared with 6.5% for MCA aneurysms. At 5 years, the cumulative risk was 10.3% for the MCA location. For clipping, the risk at 1 year for non MCA locations was 4.3%, but for MCA aneurysms, this risk was 11.5% and at 5 years, the cumulative risk was 21.7%.

2.5.9 Surgical and endovascular treatment of unruptured MCA aneurysms

A safety profile is key to an effective treatment in the elective setting. In the endovascular cohort of ISUIA (International Study of Unruptured Intracranial Aneurysms) (Wiebers *et al,* 2003), mortality rate was 1.7% and morbidity rate (mRS, 3–5) was 2.2% in 451 patients. In our cohort of patients with unruptured aneurysms, the mortality rate was 1.8%. There was no permanent morbidity. The prospective ATENA study (Pierot *et al,* 2008) was not powered to compare outcomes by anatomic location, but the rate of thromboembolism and aneurysm perforation was 9.6% and 4.1%, respectively, for the MCA location and overall morbidity and mortality rate was 1.7% and 1.4%, respectively. A systematic review (Brinjikji *et al,* 2011a) of 500 patients with 541 unruptured MCA aneurysms treated at 12 centres by EVC demonstrated a permanent procedural morbidity rate of 5.1% and a mortality rate of 0.3%. ATENA also demonstrated no difference in anatomic occlusion between the MCA and other anterior circulation aneurysms.

For unruptured aneurysms, several large surgical series from high-volume centres have demonstrated an excellent procedural safety profile, with morbidity rates ranging from 2%–6% and mortality rates from 0%–2% (Moroi *et al,* 2005; Morgan *et al,* 2010; Choi *et al,* 2012; Rodrıguez-Hernandez *et al,* 2013). In 2 studies, (Moroi *et al,* 2005; Choi *et al,* 2012) approximately half of all aneurysms treated were <5 mm and most were <10 mm in size. This characteristic may well have contributed to the good outcomes, as it is evident that increasing age and

aneurysm size are associated with increasing surgical morbidity rates. In the largest series of 263 patients with 339 aneurysms who underwent surgical clipping in 280 operations, Morgan et al (2010) assessed risk based on age and aneurysm size. Patients <60 years old with an aneurysm <12mm constituted a low-risk group with a procedural-related combined mortality and morbidity rate of 0.6% (95% CI, 0–3.8). Patients >60 years old with an aneurysm >12 mm had a procedural-related combined mortality and morbidity rate of 7.4% (95% CI, 1–24.5). Patients 60 years old with an aneurysm size of 12 mm had a procedural-related combined mortality and morbidity rate of 9.3% (95% CI, 4.3–18.3). Patients >60 years old with an aneurysm size of >12 mm had a procedural-related combined mortality and morbidity rate of 22.2% (95% CI, 8.5–45.8).

These data suggest a good safety profile for small aneurysms but do raise the specific question of whether EVC would be more appropriate for older patients with larger aneurysms. Furthermore, whether the results of these surgical series can be extrapolated to general neurosurgical practice is questionable. Multicentre data are limited, but one source is the ISUIA study. MCA aneurysms comprised 29% of the prospective ISUIA cohort, and surgical-related morbidity and mortality was seen in 13.7% of patients (Wiebers *et al,* 2003). International Classification of Diseases code data base analysis of 2535 patients with unruptured aneurysms treated between 1998 and 2000 demonstrated that EVC was associated with fewer adverse outcomes (6.6% vs 13.2%), decreased mortality rates (0.9% vs 2.5%), and shorter lengths of hospital stay (4.5 vs 7.4 days) (Higashida *et al*, 2007). Using a similar, but larger data base analysis of patients treated between 2001 and 2008, Brinjikji et al (2011b) showed that the percentage of patients discharged from the hospital to long term facilities was 14.0% (4184/29,918) for patients who underwent clipping compared with 4.9% (1655/34,125) of patients who were treated with coiling (P=0.0001). Patients who received clipping also had a higher mortality rate because 344 (1.2%) of these patients died compared with 215 (0.6%) of patients who received coiling (P =0.0001).

2.6 Conclusion

Most MCA aneurysms can be effectively treated with EVC, achieving satisfactory rates of occlusion with acceptable safety profiles and rates of favourable outcome. For ruptured aneurysms, clinical results are similar to those for aneurysms at other locations and also to those achieved in many surgical series. The clinical and anatomic results of this series are also similar to those of a recently published systematic review, suggesting that they are repeatable. Recurrence is, not unexpectedly, more common in giant, large, and wide-neck aneurysms, but results of prospective trials suggest that anatomic results are not dissimilar to other anatomic locations. Therefore, the endovascular approach to MCA aneurysms is justifiable.

CHAPTER 3

RATES OF LOCAL PROCEDURAL-RELATED STRUCTURAL INJURY FOLLOWING CLIPPING OR COILING OF ANTERIOR COMMUNICATING ARTERY ANEURYSMS

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3.1 Abstract

3.1.1 Background

Surgical clipping and endovascular coiling yield similar functional outcomes for the treatment of saccular aneurysms of the anterior communicating (ACOM) artery. However, surgical treatment may be associated with greater rates of cognitive impairment due to injury of adjacent structures. We aimed to quantify the rates of injury (infarction/haemorrhage) for both clipping and coiling of ACOM aneurysms.

3.1.2 Methods

This was a retrospective dual-centre radiological investigation of a consecutive series of patients with ruptured and unruptured ACOM aneurysms treated between January 2011 and October 2014. Post-treatment CT or MRI was assessed for new ischemic or haemorrhagic injury. Injury relating to the primary haemorrhage or vasospasm was differentiated. Univariate analysis using χ^2 tests and multivariate analysis using binary logistic regression was used.

3.1.3 Results

66 patients treated with clipping were compared with 93 patients treated with coiling. 32/66 (48.5%) patients in the clipping group suffered treatment-related injury (31 ischemic, 1 haemorrhagic) compared with 4/93 (4.4%) patients in the coiling group (3 ischemic, 1 haemorrhagic) ($p<0.0001$). For patients with subarachnoid haemorrhage, the multivariate OR for infarction for clipping over coiling was 24.42 (95% CI 5.84 to 102.14), $p<0.0001$. The most common site of infarction was the basal forebrain (28/66 patients, 42.4%), with bilateral infarction in 4. There was injury of the septal/subcallosal region in 12/66 patients (18%).

3.1.4 Conclusion

Clipping of ACOM aneurysms is associated with significantly higher rates of structural injury than coiling, and this may be a reason for superior cognitive outcomes in patients treated with coiling in previously published studies.

3.2 Introduction

The anterior communicating (ACOM) artery represents the most common site for cerebral aneurysm formation and the most common site for ruptured aneurysms (Kassell *et al*, 1990). The International Subarachnoid Aneurysm Trial demonstrated minimal differences in the rate of poor functional outcome or death between surgical clipping (SC) and endovascular coiling (EVC) for treatment of ruptured aneurysms at this location (Molyneux *et al*, 2002). However, patients may suffer significant cognitive impairment despite favourable functional outcome scores (Hutter & Gilsbach, 1993; Mavaddat *et al*, 1999; Hadjivassiliou *et al*, 2001) and it has been recognised for some time that SC may be associated with greater rates of cognitive impairment than EVC for aneurysms treated at this location (Chan *et al*, 2002; Fontanella *et al*, 2003; Proust *et al*, 2009). A post-surgical syndrome of amnesia and confabulation is also recognised (DeLuca & Diamond, 1995), although this may well be an oversimplification since various patterns of neuropsychological impairment can occur (Böttger *et al*, 1998). A number of structures within the basal forebrain, basal ganglia, and limbic system are vulnerable to injury, probably through occlusion of anterior cerebral artery (ACA) or ACOM artery complex perforating branch vessels, notably the recurrent artery of Heubner (RAH) or subcallosal artery (Mugikura *et al*, 2014; Meila *et al*, 2015). Injuries to the basal forebrain and the fornix specifically have been implicated in resulting in memory impairment (Damasio *et al*, 1985; Phillips *et al*, 1987; Abe *et al*, 1998; Goldberg *et al*, 1999; Wright *et al*, 1999; Hashimoto *et al*, 2000; Mugikura *et al*, 2014; Meila *et al*, 2015).

We aimed to quantify the incidence of treatment related injury for patients treated with SC and EVC in a consecutive series. We hypothesize that rates of local infarction are greater for patients who undergo SC than for those undergoing EVC procedures. We undertook a radiological review of consecutive patients undergoing treatment for both ruptured and unruptured ACOM aneurysms at two neurovascular centres to assess the rates of local injury for each treatment modality.

3.3 Methods

Consecutive patients with ACOM aneurysms treated between January 2011 and October 2014 at two neurovascular centres were included in the analysis. The treatment of both ruptured and unruptured aneurysms was assessed. Patients were treated by six neurovascular surgeons and three interventional neuroradiologists. The decision to clip or coil was not necessarily based on aneurysm morphology but was dependent on the philosophy of the admitting neurosurgeon, some advocating aggressive surgical management with others regularly referring for EVC. However, those lesions that were not favourable for EVC based on neck anatomy were referred for clip occlusion on a case-by-case basis.

CT imaging consisted of triplanar reconstructions acquired using 16–128 section machines. MRI consisted of FLAIR and/or T2 axial and coronal images acquired on 1.5 or 3 Tesla machines. Acute MRI included diffusion-weighted imaging. The presenting CT scan, post-treatment imaging (CT) performed 24–72 h after the aneurysm securing procedure, subsequent CT or MRI scan performed during the course of the patient's treatment, and eventual follow-up imaging at 4 weeks to 6 months was reviewed. Angiography at day 5–10 was also reviewed to record the presence of at least moderate ACA vasospasm (defined as >33% arterial narrowing). The presenting CT scan was interpreted for distribution of haemorrhage (Fisher grade, maximal clot thickness, intraventricular haemorrhage, and intra-parenchymal haemorrhage) and presence of hydrocephalus. The surgical approach was assessed from analysis of the post-procedure CT scan. The endovascular technique was recorded from the intra-procedural imaging.

The location and rate of treatment-related infarction or haemorrhage was assessed on CT imaging performed 24–72 h after treatment (this was supplemented by MRI in two patients). Localization of injury was based on a standardised visual proforma (figure 3.1) to assess specific structures, but also included each ACA territory. Basal forebrain lesions were also specifically assessed for involvement of the more medial subcallosal or septal structures (figure 3.2). Treatment-related injury was defined as new hypodensity (ischemic injury) or hyperdensity (haemorrhage) on the post-treatment CT images. Where available, post-treatment MRI was also included in the assessment. If follow-up CT or MRI was available (MRI most commonly performed for post-coiling follow-up), this was cross-

referenced with the post-treatment imaging for eventual gliosis to improve diagnostic certainty. CT hypodensities relating to ventricular drain insertion or hydrocephalus and those lying adjacent to haematomas were differentiated from new focal low density appearing on the post-treatment imaging. Low density in the perisylvian regions secondary to surgical access/retraction was not included in the analysis of treatment-related injury. Gyrus rectus hypodensity was categorised as having parenchymal injury whether secondary to infarction or resection, but was classified as ischemic injury rather than resection when the full length of the gyrus and adjacent gyri were involved whereas focal low density within the gyrus was categorised as resection, especially if a cavity containing gas was demonstrated. Infarcts secondary to the acute injury or vasospasm were also differentiated through co-analysis of the presenting CT scan and subsequent angiographic and CT imaging, respectively.

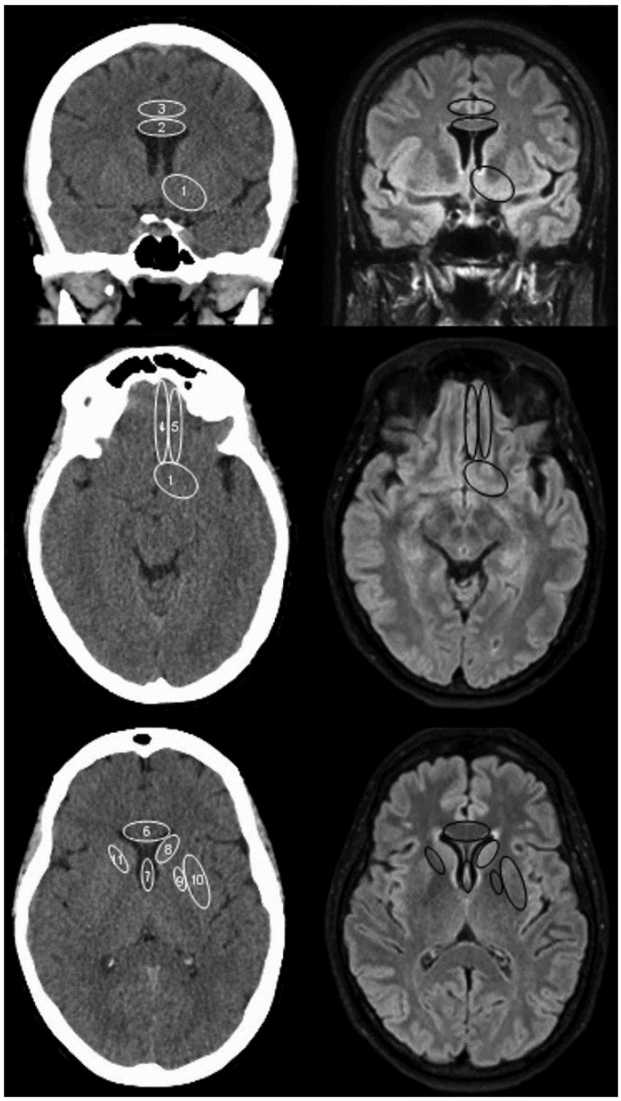

Figure 3.1 Proforma for identification of infarct location (multiplanar CT reconstructions, left and FLAIR axial and coronal images, right): (1) basal forebrain; (2) body of corpus callosum; (3) cingulate gyrus; (4) gyrus rectus; (5) medial olfactory gyrus; (6) genu of corpus callosum; (7) fornix; (8) caudate nucleus; (9) globus pallidus; (10) putamen; (11) anterior limb of internal capsule.

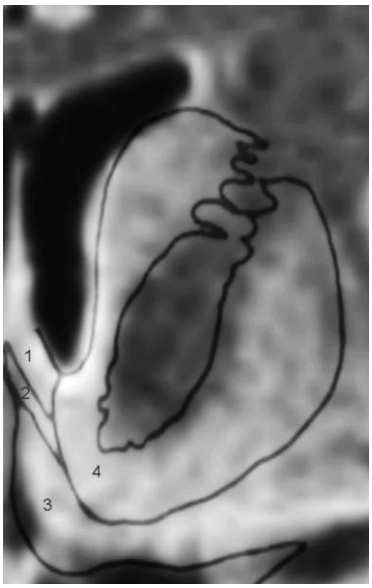

Figure 3.2 Structures within the basal forebrain: (1) septum; (2) diagonal band of Brocca; (3) subcallosal area; (4) nucleus accumbens.

The data were compared using univariate and multivariate analysis. Univariate analysis was undertaken using analysis of variance for continuous variables and χ^2 tests for non-parametric data. Multivariate analysis was also undertaken for variables impacting on treatment-related injury in the group with subarachnoid haemorrhage (SAH) using binary logistic regression. Statistical significance was defined as a p value <0.05.

3.4 Results

Sixty-six patients who underwent SC were compared with 93 patients treated with EVC. Of the SC patients, 45 (71.2%) presented with SAH compared with 75 (80.6%) of the EVC patients. Descriptive statistics for each treatment modality are shown in table 3.1. There was no significant difference in the baseline parameters or in the rate of moderate to severe vasospasm. Nine of the 66 SC patients and 39 of the 93 EVC patients had follow-up MRI available in addition to CT.

The balloon-assisted coiling technique was used in 63 patients (67.7%), simple coiling in 23 (24.7%), and stent-assisted coiling in 7 (7.5%). In the surgical group, a modified orbito-zygomatic approach was used in 41 (62.1%) patients and a frontotemporal approach in 25 patients (37.9%).

Thirty-two of the 66 (48.5%) patients in the SC group demonstrated local post-treatment injury. Eight of 21 (38.1%) patients with unruptured aneurysms and 24 of 45 (53.3%) patients with ruptured aneurysms developed injury following a clipping procedure ($p=0.2485$). Four of the 93 patients in the EVC group developed treatment-related injury (4.4%). All patients had suffered SAH. The distribution of lesions is shown in table 3.2. In one patient in each of the SC and EVC groups, this was due to a peri-procedural haemorrhage rather than infarction.

Variable	Clip (n=66)	Coil (n=93)	P
Age	54.76+/-3.16	54.36+/-2.71	0.7624
≥65	12 (18.2)	24 (25.8)	0.2576
Female	37 (56.0)	57 (61.3)	0.5086
Ruptured	45 (68.2)	75 (80.6)	0.0718
Unruptured **Retreatment after clip** **Retreatment after coil** **De novo treatment**	21 (31.8) 1 4 16	19 (20.4) 3 4 11	
Aneurysm size	5.78+/-0.69 (2.91)	6.45+/-0.56 (2.58)	0.1437
Size ≥10mm	7 (10.6)	14 (15.1)	0.4143
Wide Neck (≥4mm or dome/neck ratio of ≤1.5)	23 (34.8)	31 (33.3)	0.4147
Cistern of the lamina terminalis haematoma width (mm) **<5** **5-9** **10-14** **≥15**	16 (35.6) 13 (28.9) 11 (24.4) 5 (11.1)	22 (29.3) 26 (34.7) 16 (21.3) 11 (14.7)	0.7963
Fisher grade **1** **2** **3** **4**	 1 (2.2) 6 (13.3) 37 (82.2) 1 (2.2)	 2 (2.7) 13 (17.3) 54 (72.0) 6 (8.0)	0.5118
Intraventricular haemorrhage	18 (40.0)	40 (53.3)	0.1055
Intra-parenchymal haemorrhage	16 (35.6)	24 (32.0)	0.6891
Hydrocephalus	27 (60.0)	44 (58.7)	0.8942
Vasospasm	12 (26.7)	16 (21.3)	0.5914

Table 3.1 Baseline characteristics of the study groups.

Region of injury	Clip (n=66) N (%)	Coil (n=93) N (%)
Caudate nucleus	9 (14.9)	2 (2.2)
ALIC	8 (11.9)	0
Putamen	7 (10.6)	0
Globus pallidus	3 (4.5)	0
Basal forebrain	28 (42.4) (bilateral in 4 cases (6.1%))	1 (1.1)
Septal/subcallosal	12 (18.1)	1 (1.1)
Hypothalamus	1 (1.5)	0
Gyrus rectus	9 (13.6)	1 (1.1)
Medial orbital gyrus	6 (9.1)	0
Genu of corpus callosum	7 (10.6)	3 (3.3)
Body of corpus callosum	4 (6.0)	0
Cingulate Gyrus	1 (3.0)	0
Fornix	5 (7.6)	1 (1.1)
Superior frontal gyrus	0	1 (1.1)
Other	1 (1.5)	0

Table 3.2 The distribution of treatment related injury for clipped and coiled patients. ALIC, anterior limb of internal capsule.

The median number of regions involved per patient in the SC group was three. Nineteen of 41 patients (46.3%) with a modified orbito-zygomatic approach and 13/25 (52%) with a frontotemporal approach suffered injury (p=0.6554). For ruptured aneurysms, SC was a stronger predictor of treatment-related infarction than EVC on multivariate analysis (OR 24.42, 95% CI 5.84 to 102.14, p<0.0001), along with large aneurysm size (≥10 mm) (OR 6.73, 95% CI 1.08 to 41.98, p<0.05) when taking into account aneurysm neck width, local haematoma width (≥10 mm), intra-parenchymal extension of haemorrhage, intraventricular extension of haemorrhage, and older patient age (≥65 years) (see table 3.3).

The site of the most common lesion was the basal forebrain (28 patients with 33 lesions, bilateral in four patients). The basal forebrain lesion was present on the side of the approach in 25/28 (88.9%) patients. Basal forebrain lesions were

accompanied by caudate head lesions in 9/28 cases (figure 3.3). This was the next most common site for treatment-related injury. Injury to the basal forebrain occupied or extended into the more medial subcallosal or septal region in 12 patients in the SC group. The fornix and genu of corpus callosum lesions were seen in five (7.5%) and seven (10.6%) of the 66 SC patients and in three (3.3%) of the 93 EVC patients (figure 3.4). Gyrus rectus lesions were classified as ischemic in six of nine patients and after resection in three.

Variable	Infarct	%	OR	95% CI	P
Clipping	24/45	53.3	24.42	5.84-102.14	<0.0001
Aneurysm size ≥10 mm	5/16	31.3	6.73	1.08-41.98	0.0411
Wide neck > 4mm or dome/neck ratio of ≤1.5	8/35	22.9	0.70	0.18-2.79	0.6139
Intra-parenchymal extension of haemorrhage	10/40	25	2.76	0.72-10.60	0.1398
Intraventricular haemorrhage	11/58	18.9	0.66	0.18-2.35	0.5211
Local haematoma width ≥10 mm	10/40	25	1.41	0.43-4.60	0.5729
Age ≥65	5/28	17.9	1.24	0.31-4.95	0.7591

Table 3.3 Multivariate odds ratios for treatment related infarction for patients with treated ruptured anterior communicating artery aneurysms

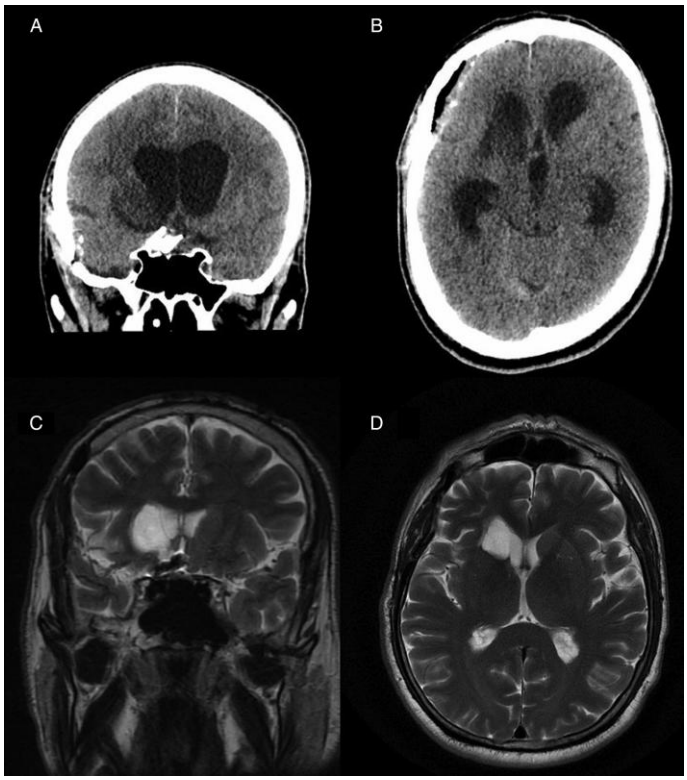

Figure 3.3 Coronal (A) and axial (B) CT demonstrating right caudate nucleus, anterior limb or internal capsule, and putaminal infarct extending into the region of the nucleus accumbens. T2-weighted MR coronal (C) and axial (D) images in a different patient demonstrate a similar pattern.

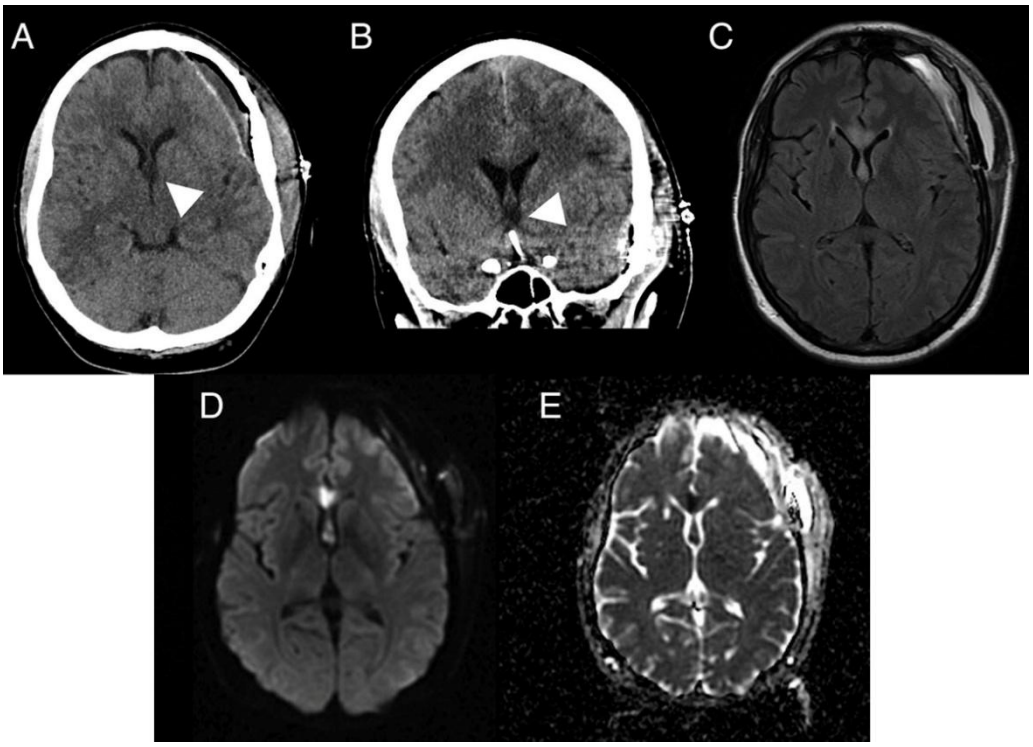

Figure 3.4 Axial (A) and coronal (B) CT demonstrating low density in the genu of the corpus callosum, fornix and subcallosal region indicative of an ischemic injury. Axial FLAIR (C), diffusion-weighted imaging (D), and apparent diffusion coefficient maps (E) demonstrating forniceal and genu of corpus callosum infarction.

Several patterns of infarction were recognised. These included:

1. basal forebrain injury associated with caudate, internal capsule, and lentiform nucleus injury akin to the territory of the RAH (figure 3.3);
2. septal/subcallosal infarction in association with forniceal andgenu of corpus callosum infarction akin to the territory of the subcallosal artery (figure 3.4);
3. unilateral subcallosal infarction (figure 3.5);
4. unilateral basal forebrain injury involving the nucleus accumbens but sparing the subcallosal/septal region (figure 3.6);
5. a combination of any of the above patterns (figure 3.7);
6. body of corpus callosum infarction (figure 3.8).

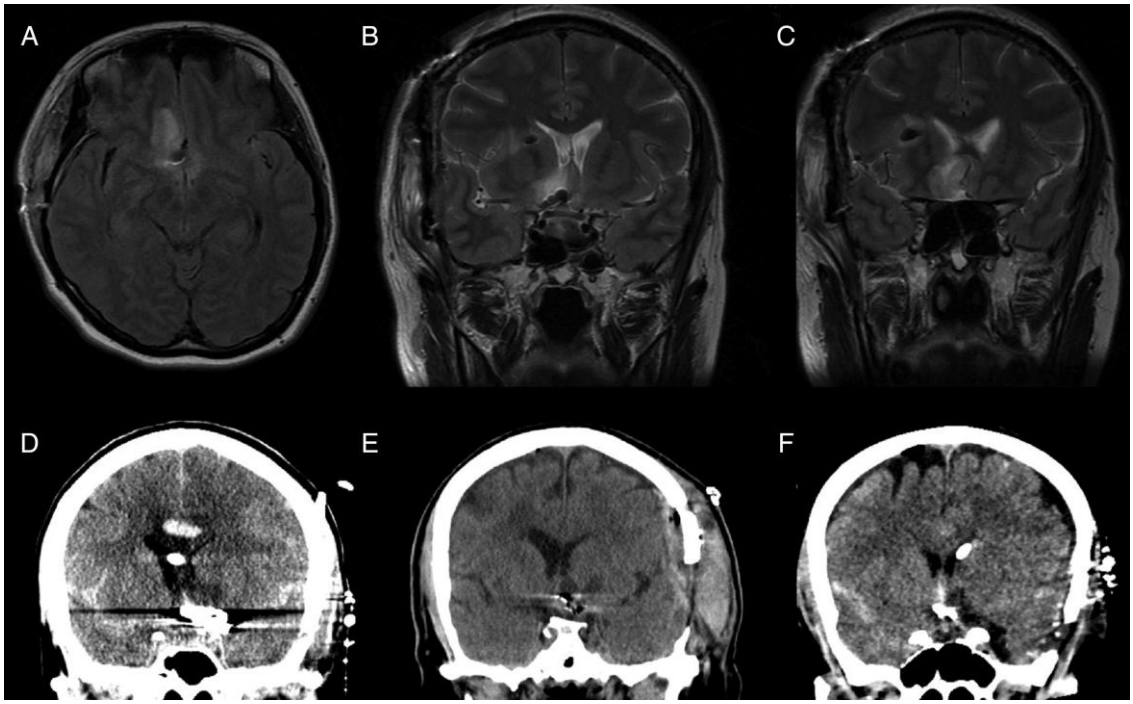

Figure 3.5 Axial FLAIR (A) and T2 coronal (B and C) images demonstrating ischemic injury to the right septal and subcallosal region. Note also the high signal in the contralateral left subcallosal region, although this is less marked. Coronal CT reconstructions (D–F) in three additional patients with a similar pattern of infarction.

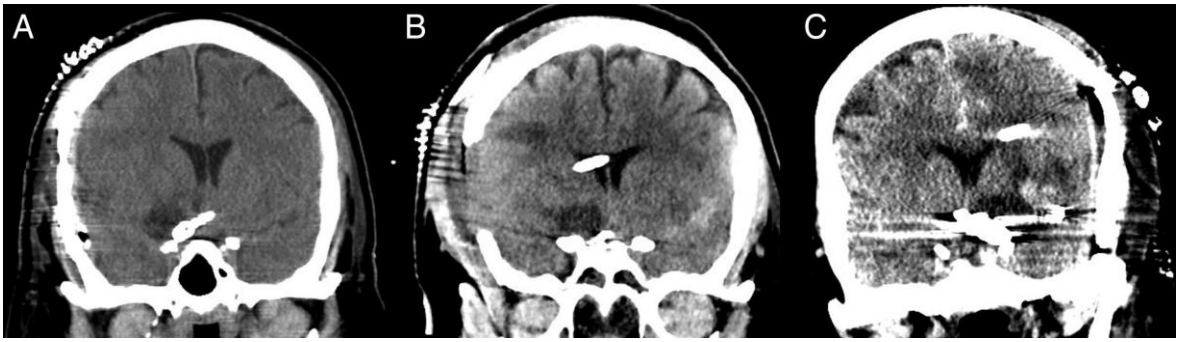

Figure 3.6 Coronal CT reconstructions in three different patients (A–C) demonstrating low density in the basal forebrain involving the region of the nucleus accumbens.

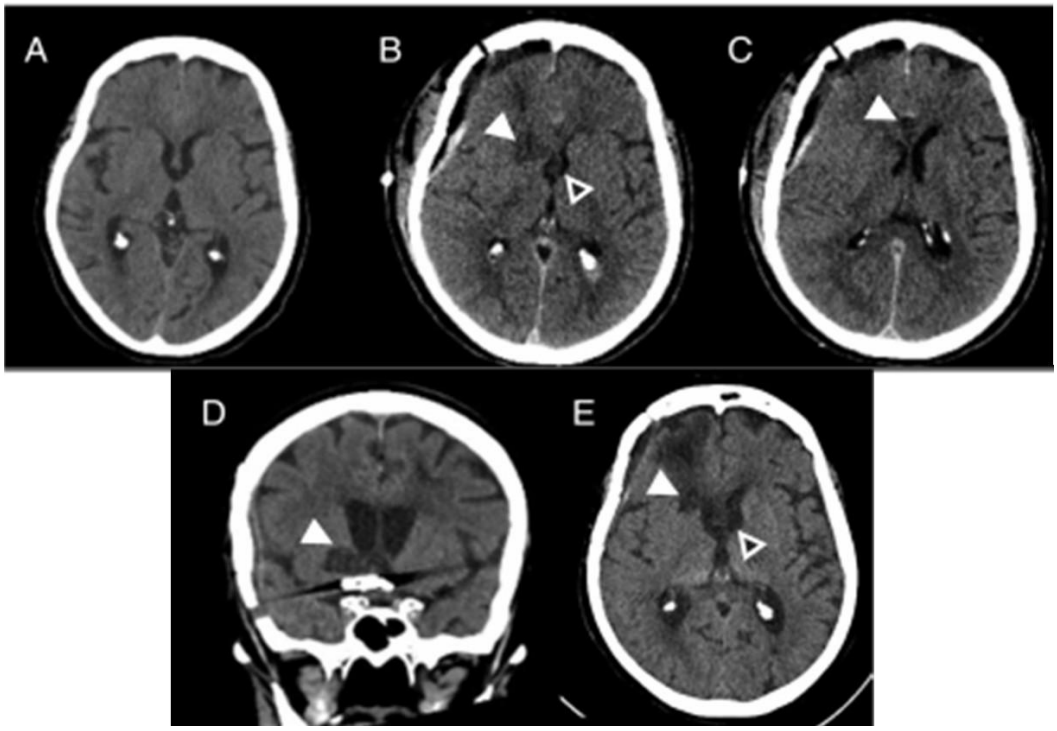

Figure 3.7 Baseline axial CT (A) and immediate post-clipping axial CT scans (B and C) demonstrating right caudate/basal forebrain infarction (white arrowhead) with forniceal (hollow arrowhead) and genu of corpus callosum infarction (white arrowhead). Follow-up coronal (D) and axial CT scans (E) demonstrating right basal forebrain infarct extending into the right septal region (white arrowhead), right caudate and internal capsule infarct (white arrowhead) and forniceal infarct (hollow arrowhead).

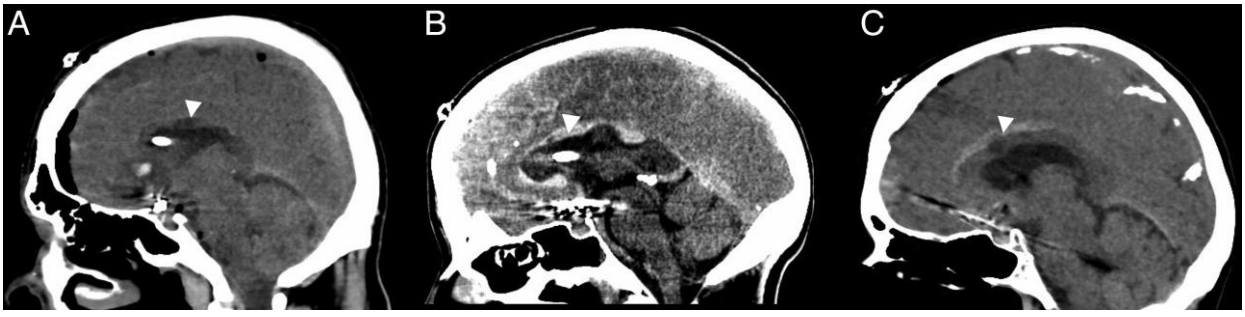

Figure 3.8 Sagittal CT reconstructions in three different patients (A–C) demonstrating body of corpus callosum infarction (white arrowheads).

3.6 Discussion

It has been demonstrated in several studies that SC may result in inferior cognitive outcomes following treatment of ACOM aneurysms (Chan *et al*, 2002; Fontanella *et al*, 2003; Proust *et al*, 2009). Domains of memory, attentional, and executive functions may be affected. A number of case reports and series have suggested that lesions of the basal forebrain and/or fornix are predominantly responsible for memory deficits (Damasio *et al*, 1985; Phillips *et al*, 1987; Böttger *et al*, 1998; Abe *et al*, 1998; Goldberg *et al*, 1999; Wright *et al*, 1999; Hashimoto *et al*, 2000; Mugikura *et al*, 2014; Meila *et al*, 2015). Prefrontal lesions may be associated with attentional, executive, and psychopathological dysfunctions (Böttger *et al*, 1998). We aimed to quantify the difference in the rate of treatment-related structural injury for SC and EVC of both ruptured and unruptured aneurysms. In a consecutive population of patients with treated ACOM aneurysms, the rate of local treatment-related injury was significantly greater in the SC group than in the EVC group. Forty-nine per cent of the SC group versus 4.4% of the EVC group had treatment-related injury. Clipping was a strong predictor of treatment-related injury on multivariate analysis. The infarct rate for coiling was in line with a recent systematic review of the literature (Fang *et al*, 2014). The majority of the surgical lesions were probably ischemic in aetiology; most were on the side of the surgical approach. One possibility is that the clip(s) may result in compromise of adjacent minute perforators, that perforators need to be sacrificed to access the aneurysm, or that the direct exposure and handling of the artery may result in subsequent ischemic lesions.

The most common site of infarction was the basal forebrain with approximately 42% of patients in the SC group suffering injury to this location; 14% of patients in the SC group also suffered infarction of the caudate nucleus. Other authors have demonstrated that clipping represents an independent risk factor on multivariate analysis for postoperative ACA territory infarction (Moussouttas *et al*, 2013). The finding of such a high rate of treatment-related ischemic injury in this series is surprising. A review of all-cause infarction at all locations in clipped patients treated in the tirilizad trials demonstrated that 707 (27%) out of 2741 patients developed cerebral infarction (Furgusson & Macdonald, 2007), but other authors have recognised high rates of postoperative infarction in patients with ACOM artery aneurysms (Proust *et al*, 2009; Umredkar *et al*, 2010). Using CT

imaging, Umredkar et al (2010) demonstrated a postoperative infarct rate of 42.5% in patients with SAH who underwent SC. The current study could be criticised for relying on CT hypodensity for diagnosis in the majority of patients. There is a possibility that postoperative oedema could limit specificity. However, where subsequent follow-up imaging was available, these regions demonstrated residual low density and/or atrophy implying regions of permanent structural injury. Use of triplanar imaging could have resulted in a greater rate of lesion pick-up compared with studies using axial imaging only. Additionally, there were recurring patterns of hypodensity in regions not normally subject to retraction or resection in the majority. Furthermore, our findings are in keeping with those of a cohort of 50 patients (14 EVC, 36 SC) in whom a significantly greater number of SC patients suffered foci of encephalomalacia on follow-up MRI (Proust *et al*, 2009). In that series, 33% of SC patients had basal forebrain lesions, 28% corpus callosum lesions, 11% caudate lesions, and 64% had frontobasal lesions.

An additional finding in this study was that infarction of structures presumed to be supplied by ACOM perforators including the subcallosal artery was greater in the SC group; lesions of the septal or subcallosal area that may harbour structures more vital with regard to memory (Böttger *et al*, 1998; Fujii, 2008) were seen in 12 SC patients (18%) and one EVC patient (1.1%). Infarcts of the fornix (7.5% vs 1.1%) and genu of the corpus callosum (10.5% vs 3.3%) were also more common in the SC patients. We suspect that this may well be an underestimation of the true incidence of subcallosal artery or ACOM perforator disruption since MRI was not used universally or acutely. Interestingly, it also illustrates that these vessels can rarely be vulnerable during EVC procedures, although perhaps less often than in SC procedures.

We noted a number of patterns of infarction (figures 3.4–3.8): (1) more lateral basal forebrain injury sparing the septal and subcallosal structures but involving the nucleus accumbens; (2) basal forebrain injury in addition to caudate, internal capsule and lentiform nucleus injury; (3) isolated basal forebrain injury involving the septal and subcallosal structures unilaterally; (4) fornix, subcallosal region and genu of corpus callosum; and (5) body of corpus callosum infarction. We suggest that the first two patterns are secondary to either A1 or A2 perforators or RAH disruption and the latter three patterns are due to disruption of subcallosal artery, median callosal artery, or other ACOM artery perforators.

Perforators may arise from the A1 and A2 ACA; 2–15 perforating arteries travel superiorly and posteriorly from the A1 into the anterior perforated substance (Harrigan & Deveikis, 2009). Additionally, perforating branches of the A2 segment are located along the first 5 mm of the vessel and penetrate the brain at the gyrus rectus and olfactory sulcus (Harrigan & Deveikis, 2009). The most important perforator is the RAH. This vessel doubles back on its parent ACA and passes above the carotid bifurcation and middle cerebral artery into the medial part of the sylvian fissure before entering the anterior perforated substance. In a more recent autopsy study (Loukas *et al*, 2006) the RAH was found as a single vessel in 77%, as double arteries in 17%, and was absent in 6%. The origin of the RAH was from the junction of the ACA and ACOM artery in 62.3%, from the proximal A2 segment in 23.3%, and from the A1 segment in 14.3%. Both the length and diameter of the vessel can vary widely. During surgery the vessel is liable to injury during elevation of the frontal lobe from the optic nerve and chiasm or during exposure of the A2 segments (Loukas *et al*, 2006). Occlusion of the RAH may result in infarction of the caudate head, anterior limb of the internal capsule, putamen, globus pallidus and basal forebrain.

The ACOM artery perforators are highly variable in number and territory supplied (Sekhar *et al*, 2007). Broadly, they can be categorised as hypothalamic, subcallosal, and median callosal and may vary in number from 0 to 11 (Sekhar *et al*, 2007; Hernesniemi *et al*, 2008). The subcallosal artery and the implications of occlusion have been described in two recent case series (Mugikura *et al*, 2014; Meila *et al*, 2015). This is usually a single vessel and typically the largest of the arteries arising from the ACOM artery. The subcallosal artery supplies the bilateral subcallosal areas, but also the bilateral columns of the fornix and the genu of the corpus callosum. It may extend to the body of the corpus callosum and is therefore recognised as the medial callosal artery (Serizawa *et al*, 1997). The unilateral subcallosal infarction recognised in this study is not consistent with previous descriptions of the subcallosal perforators since a bilateral supply is often stressed in descriptions of these vessels (Serizawa *et al*, 1997; Hernesniemi *et al*, 2008). However, we were using CT to assess many of these patients, and limitations in sensitivity for ischemic changes in relatively small structures (whereby less marked contralateral ischemia was present but not recognised) could account for this finding (see figure 3.5).

The basal forebrain contains a number of structures that are believed to play a role in cognition. These include the nucleus accumbens, substantia innominata, nucleus basalis of Meynert, and medial septal-diagonal band of the Brocca complex (Fujii, 2008). Basal forebrain lesions have been linked to the occurrence of amnesia and/or confabulation in a number of case reports and series (Damasio *et al*, 1985; Phillips *et al*, 1987; Böttger *et al*, 1998; Abe *et al*, 1998; Goldberg *et al*, 1999; Wright *et al*, 1999; Hashimoto *et al*, 2000) and a functional imaging study has also suggested that the basal forebrain is likely to play a role in episodic memory recall (Fujii *et al*, 2002). The medial septal-diagonal band of the Brocca complex region is likely to be an important interface within the so-called septohippocampal system (Böttger *et al*, 1998). Bilateral basal forebrain lesions do produce more severe memory deficits (Böttger *et al*, 1998).

The fornix is a compact fiber bundle connecting the hippocampus with the hypothalamus and a number of other structures including the septal area of the basal forebrain. It is an important constituent of the Papez circuit and is involved in the formation and consolidation of declarative memories (Meila *et al*, 2015). Diffusion-weighted MRI-proven infarction limited to the fornices has been reported in conjunction with acute onset of amnesia, suggesting that an isolated injury to this structure may be critical (Mugikura *et al*, 2014). Injuries to other vulnerable structures including the corpus callosum and caudate nucleus have also been implicated in resulting in neuro-behavioural sequelae (Mendez *et al*, 1989; Kasow *et al*, 2000). Caudate nucleus lesions may result in depression, agitation, abulia, neglect (right-sided lesions), memory disturbance (particularly if bilateral), dysarthria, aphasia (left-sided lesions), movement disorders (ballistic, choreatiform), or motor weakness (Kumral *et al*, 1999). There is controversy as to the role of the gyrus rectus in cognition, particularly as the gyrus rectus is deliberately resected to gain access to the aneurysm on occasions (Sekhar *et al*, 2007). An association between memory quotient and gyrus rectus resection was demonstrated in a neuropsychological analysis of 32 patients with clipped ACOM artery aneurysms (Teissier du Cros & Lhermitte, 1984). Other studies have failed to demonstrate an association (Horikoshi *et al*, 1992; Böttger *et al*, 1998).

A number of studies have found significantly increased rates of cognitive impairment in patients with ACOM artery aneurysms treated with SC as opposed to EVC. Chan et al (2002) studied 18 patients who had undergone treatment for

ruptured ACOM aneurysms, half with SC and half with EVC; 33% of the SC patients showed severe impairment of memory and executive function whereas no EVC patient demonstrated this impairment. Fontanella et al (2003) assessed 37 consecutive WFNS grade I or II patients who underwent treatment of ACOM aneurysms within 48 h of rupture; 20 of 37 were treated with SC and 17 were treated with EVC. Both groups were compared with 16 angiogram-negative patients with SAH and 18 normal controls. All patients were neurologically intact at discharge and were Glasgow Outcome Scale 1 at 6-month follow-up after SAH. Surgically treated patients showed a significant worse performance on the logical memory and on the frontal lobe executive functions compared with controls, while the endovascular group and the angiogram-negative group showed a significant decrease only in the literal fluency score. Furthermore, the surgical group showed a significant impairment in using grammatical and syntactical rules to produce sentences. Proust et al (2009) studied 36 SC and 14 EVC patients at 14-month follow-up. They found no difference in executive dysfunction although there was a significant impairment of verbal memory in the SC group.

These results raise the question of how to optimize patient treatment in future. However, while cognition is a factor that may impact on a patient's life, it needs to be weighed against other factors such as safely securing the aneurysm and durability of treatment. Balloon assistance has increased the number of patients who can be treated using the endovascular techniques without a significant increase in complication rate (Pierot *et al*, 2011). For elective cases, a number of case series have described success in stent coiling at the ACOM location (Huang *et al*, 2009; Johnson *et al*, 2013b). In the largest series comprising 64 patients (Johnson *et al*, 2013b) the morbidity was 1.6% and mortality was 1.6%; 5.5% required retreatment. A systematic review of stent coiling at all locations in patients with SAH who were managed with dual antiplatelet therapy demonstrated clinically significant intracranial haemorrhagic complications in 27 (8%) of 339 patients, including 9 (10%) of 90 patients known to have had ventricular drain-related haemorrhages. Clinically significant thromboembolic events occurred in 16 (6%) of 288 patients (Bodily *et al*, 2011). Perhaps a trial comparing more aggressive endovascular approaches (e.g. using stents or even flow diversion) with SC for less favourable aneurysms, particularly for locations such as this, would be worthwhile. Such a study should include neuropsychological testing as part of the outcome measures.

3.7 Limitations of the study

This was a retrospective study of a relatively small patient sample reflecting practice at two centres only. There was inherent bias as to which patients were selected for EVC or SC. Some aneurysms were referred for SC on the basis of being morphologically challenging for endovascular treatment whereas others were selected for SC on the philosophy of the managing neurosurgeon, some favouring surgical management. It is conceivable that the rate of infarction for EVC patients would have been greater if less favourable aneurysms were treated using an endovascular approach. The imaging assessment was predominantly with CT, which has an inherent lack of sensitivity for identification of lesions in this anatomical region, especially in the presence of clip or coil artefact. Another potential source of error was the limited specificity of CT hypodensity for infarction. In the absence of diffusion-weighted MRI, it could be claimed that a proportion of the focal hypodensities noted could represent postoperative oedema. We were also unable to assess the rate of microinfarction with diffusion imaging that is known to complicate endovascular procedures. However, follow-up MRI was available for many EVC patients and we believe that, if MRI was available for all SC patients, then the differences in the rate of structural injury may have been more marked. At this stage we do not have cognitive test scores available for this cohort with which to assess the neurophyschological significance of the radiological findings, and we can only hypothesize based on other reports in the literature as discussed. It is possible that many patients did not suffer overtly clinically detectable neurocognitive deficits despite the high rate of injury as few SC patients were imaged with MRI during their postoperative course.

3.8 Conclusion

This retrospective analysis suggests that the degree of structural damage in regions known to impact on the cognitive outcome of the patient incurred through treating ACOM aneurysms using SC is significantly greater than that for EVC. Further work is necessary to assess the direct effect on cognitive outcomes.

CHAPTER 4

SHORT TERM OUTCOMES FOLLOWING CLIPPING AND COILING OF RUPTURED INTRACRANIAL ANEURYSMS: DOES SOME OF THE BENEFIT OF COILING STEM FROM LESS PROCEDURAL IMPACT ON DERANGED PHYSIOLOGY AT PRESENTATION?

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4.1 Abstract

4.1.1 Background

Endovascular coiling (EVC) has been shown to yield superior clinical outcomes to surgical clipping (SC) in the treatment of ruptured cerebral aneurysms. The reasons for these differences remain obscure. We aimed to assess outcomes of EVC and SC relative to baseline physiological derangement.

4.1.2 Methods

This was an exploratory analysis of prospectively collected trial data. Physiological derangement was assessed using the Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system. Other contributory variables such as age, World Federation of Neurosurgical Societies (WFNS) grade, and development of complications, including hydrocephalus and vasospasm, were included in the analysis. Clinical outcome was independently assessed at 90 days using the modified Rankin Scale (mRS). Hospital stay, ventilated days, and total norepinephrine dose were also used as secondary outcomes. Multivariate analysis was performed using binary logistic regression.

4.1.3 Results

EVC was performed in 69 patients and SC in 66 patients. More profound physiological derangement (APACHE II score >15) was the strongest predictor of poor outcome in the overall cohort (OR 17.80, 95% CI 4.78 to 66.21, $p<0.0001$). For those with more deranged physiology (APACHE II score>15; 59 patients), WFNS grade ≥4 (OR 6.74, 1.43 to 31.75) and SC (OR 6.33, 1.27 to 31.38) were significant predictors of poor outcome ($p<0.05$). Favourable outcome (mRS 0–2) was seen in 11% of SC patients compared with 38% of EVC patients in this subgroup. SC patients had significantly increased total norepinephrine dose, ventilated days, and hospital stay ($p<0.05$).

4.1.4 Conclusion

More profound physiological derangement at baseline is a strong predictor of eventual poor outcome, and outcomes for patients with more profound baseline physiological derangement may be improved if undergoing a coiling procedure.

4.2 Introduction

The International Subarachnoid Aneurysm Trial (ISAT) demonstrated an absolute 6.9% reduction in the rate of death or dependency at 1 year for patients treated with endovascular coiling (EVC) following aneurysmal subarachnoid haemorrhage (SAH) (Molyneux *et al*, 2002). Subsequent systematic reviews of this and other prospective controlled studies have also concluded that EVC yields better clinical outcomes compared with surgical clipping (SC) (Lanzino *et al*, 2013; Li *et al*, 2013). The reasons for this difference have been debated in the literature and include rates and severity of cerebral vasospasm and delayed ischemia, (Dumont *et al*, 2010; Dorhout Mees *et al*, 2012), degree of procedural brain tissue damage (Shim *et al*, 2012) and the rate of medical complications (Vergouwen *et al*, 2011c). Physiological derangement and medical comorbidities are also recognised as risk factors for poor outcome following aneurysmal SAH (Claasen *et al*, 2004; Schuiling *et al*, 2005; Mocco *et al*, 2006; Rosengart *et al*, 2007). However, assigning patients to either SC or EVC has traditionally been based on anatomical rather than physiological criteria, and there is little evidence regarding the interaction of treatment modality and presenting physiological derangement.

The Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system is widely used in many intensive care units and allows approximate prognostication based on a score from 0 to 71 for clinical and biochemical markers of cardiopulmonary, renal, haematological, and neurological function (Knaus *et al*, 1985). Using this system, we aimed to investigate the difference in outcomes for EVC and SC patients relative to the degree of physiological derangement at baseline.

4.3 Methods

4.3.1 Study design and inclusion/exclusion criteria

This was an exploratory analysis of prospectively acquired clinical trial data obtained primarily for the assessment of clinical outcomes, and vasospasm severity and incidence, in patients treated with magnesium following aneurysmal SAH (Bradford *et al,* 2013). The study was approved by the Northern Sydney and Central Coast Ethics Committee and written informed consent was obtained from each patient or legal surrogate.

Patients admitted between April 1, 2005 and February 1, 2010, presenting within 72 h of SAH confirmed by CT were included. Exclusion criteria included age <18 years, serum creatinine >200 mmol/L, if death was thought imminent within 72 h, if the patient had myasthenia gravis or was pregnant, or if vasospasm was present prior to inclusion in the study. The original study included 166 patients. This explorative analysis included only patients treated in the acute period with EVC or SC. Those patients who were angiographically negative were not included.

4.3.2 Patient management

All patients were managed on the neurointensive care unit with routine insertion of arterial and central lines. After admission, digital subtraction angiography or CT angiography was performed, and the aneurysm responsible for the bleeding was occluded by operative or endovascular means using conventional techniques within 48 h. Decision to clip or coil was not necessarily based on aneurysm morphology but was dependent on the philosophy of the admitting neurosurgeon, some advocating aggressive surgical management with others regularly referring for EVC. At one of the centres participating in the study, there was limited endovascular availability. During the study period, young patients, those with multiple aneurysms accessible via a single surgical approach, or those with a haematoma requiring evacuation were primarily clipped.

Following clipping or coiling of the aneurysm, systolic blood pressure was maintained between 120 and 150 mm Hg. A nimodipine infusion of 20 mg/kg/h was commenced on arrival in the intensive care unit. All patients received nimodipine for 21 days, with at least 10 days of intravenous administration. Body temperature was aimed to be maintained below 37.5°C. Oxygen saturation was monitored

continuously by pulse oximetry and maintained at >95%. Serum electrolytes were maintained within normal limits, and glucose levels were maintained at 6–10 mmol/L. Angiographic screening for vasospasm was performed routinely at days 5–7 or at an earlier time point if vasospasm was suspected. Patients were managed with adequate hydration, systolic blood pressure maintained between 140 and 160 mm Hg, and continued nimodipine infusion. The majority of patients with moderate–severe vasospasm (>25% arterial narrowing) were managed with a pre-emptive endovascular approach previously documented (Mortimer *et al*, 2015b).

4.3.3 Data collected and analysis

Baseline variables were collected, including demographic data, history of smoking, hypertension, use of statins, use of trial magnesium, previous SAH or stroke Glasgow Coma Scale (GCS) score, World Federation of Neurosurgical Societies (WFNS) grade, and APACHE II score. Aneurysm site, size, and presence of hydrocephalus were recorded through assessment of angiographic and CT imaging, respectively. Modified Rankin Scale (mRS) scores were obtained at 90 days by independent assessors. Favourable outcome was defined as mRS 0–2. Secondary outcome measures, including norepinephrine dose (mg), length of stay in the intensive care unit, ventilator time, and length of hospital stay were also assessed.

Statistical analysis was performed using Openstat statistical software. Non-parametric data (sex, WFNS grade, history of smoking, hypertension, SAH, stroke, magnesium or statin use, hydrocephalus, aneurysm location, and aneurysm securing modality) were compared using Fisher's exact test, and parametric data (age, length of stay in the intensive care unit (days), ventilation duration (days), hospital stay (days), norepinephrine dose) were compared using analysis of variance. Ordinal data (APACHE II score and GCS) were compared using the Mann– Whitney U test. Binary logistic regression was used for analysis of multiple variables, including age, gender, smoking history, vasospasm, hydrocephalus, aneurysm securing technique, APACHE II score, and WFNS grade with respect to patient outcome. Statistical significance was defined as $p<0.05$.

4.4 Results

A total of 135 patients (69 EVC and 66 SC) were included in the analysis. Two patients who underwent SC were lost to follow-up and were therefore not included. Descriptive statistics are shown in table 4.1.

There tended to be more patients with a prior history of previous stroke, statin use, and smoking among patients in the EVC group but this was not statistically significant. The magnitude and distribution of APACHE II and GCS scores was very similar between the EVC and SC groups (see figure 4.1). The incidence of moderate–severe and severe vasospasm was similar although there tended to be more endovascular interventions per treated patient in the SC group. Patients in the SC group as a whole received a significantly increased total norepinephrine dose and had a significantly longer hospital stay ($p<0.05$) (see table 4.2).

Variable	Clipped (n=66)	Coiled (n=69)	P
Age (Mean +/- 95% CI (SD))	54.56+/-3.41 (12.34)	56.65+/-3.33 (15.43)	0.3873
Age ≥75	2 (3.03)	13 (18.84)	0.0048
Female Sex	49 (72.24)	44 (63.77)	0.4678
Previous SAH	1 (1.51)	2 (2.90)	1.0000
Hypertension	24 (36.36)	29 (42.03)	0.5973
Smoker	23 (34.85)	30 (43.48)	0.2867
Previous CVA	0	4 (5.80)	0.1198
Statin	9 (13.36)	16 (23.19)	0.1863
Magnesium	36 (54.54)	35 (50.72)	0.7311
WFNS grade 1-3	47 (71.21)	49 (71.01)	1.0000
WFNS grade 4-5	19 (28.78)	20 (28.99)	
APACHE II score, Median (IQR)	13 (10)	14 (10.5)	0.3681
APACHE>15	27 (40.91)	32 (46.37)	0.6033
GCS, Median, (IQR)	14 (3)	14 (6)	0.5962
Aneurysm location **Anterior** **Posterior**	 61 (92.42) 5 (7.58)	 52 (75.36) 17 (24.64)	0.0096
Aneurysm size **≤10 mm** **>10 mm**	 52 (78.79) 8 (12.12)	 57 (82.60) 8 (11.59)	0.7546
Hydrocephalus	35 (53.03)	37 (53.62)	1.0000
Moderate-severe vasospasm	35 (53.85)	30 (46.88)	0.4831
Severe vasospasm	19 (29.23)	15 (23.44)	0.5498
Endovascular treatment of vasospasm **TBA** **Vasodilators**	19 (29.23) 8 18	23 (35.94) 5 22	0.4561
Vasospasm interventions (mean±95% CI)	4.89+/-1.38	3.23+/-1.28	0.0806

Table 4.1 Descriptive analysis of the overall cohort. Values are (n (%)) unless otherwise stated. APACHE II, Acute Physiology and Chronic Health Evaluation II; CVA, cerebrovascular accident; EVC, endovascular coiling; GCS, Glasgow Coma Scale; SAH, subarachnoid haemorrhage; SC, surgical clipping; TBA, transluminal balloon angioplasty; WFNS, World Federation of Neurosurgical Societies.

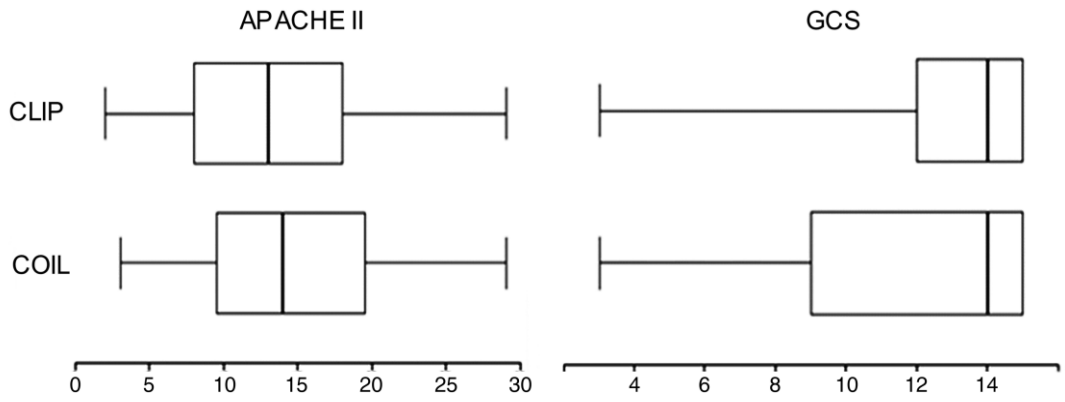

Figure 4.1. Distribution of Acute Physiology and Chronic Health Evaluation II (APACHE II, left) scores and Glasgow Coma Scale (GCS, right) scores in patients undergoing endovascular coiling or surgical clipping.

When APACHE II score was plotted against outcome for all patients (figure 4.2), a threshold of 15 was evident for the majority of outcomes clearly moving from favourable to unfavourable. Fifty-nine of 135 patients (43.7%) had an APACHE II score of >15. This value was close to the median score (13 for SC and 14 for EVC). Multivariate analysis (table 4.3) of the overall study cohort demonstrated that age ≥75 years (OR 9.9, 95% CI 1.62 to 60.60, $p<0.05$), WFNS grade ≥4 (OR 10.81, 95% CI 3.51 to 33.31, $p<0.0001$), and SC (OR 5.27, 95% CI 1.63 to 16.95, $p<0.01$) were significant predictors of poor outcome; 35/66 (53.03%) SC patients versus 44/69 (63.76%) of EVC patients achieved a favourable outcome. However, the greatest predictor of poor outcome was an APACHE II score of >15 (OR 17.80, 95% CI 4.78 to 66.21, $p<0.0001$). When WFNS grade 1–2 patients were individually investigated so as to minimize the neurological influence within the APACHE II score on outcome, on multivariate analysis, an APACHE II score of >15 was the strongest predictor of poor outcome (OR 11.89, 95% CI 3.08 to 45.07, $p<0.001$).

Outcome Mean and 95% CI (SD)	All patients			APACHE II ≤15			APACHE II >15		
	SC (n=66)	EVC (n=69)	P	SC (n=39)	EVC (n=37)	P	SC (n=27)	EVC (n=32)	P
Noradrenaline dose (mg)	175.5+/-39.00 (188.23)	101.44 +/-37.43 (116.58)	0.0069	136.03+/-38.98 (145.46)	80.35+/-40.02 (91.32)	0.0507	232.52+/-71.50 (227.90)	126.61+/-66.7 (138.36)	0.0343
Ventilated days	8.36 +/-2.76 (14.55)	5.13 +/-2.75 (6.94)	0.1040	2.87+/-1.76 (5.79)	2.67+/-1.80 (5.21)	0.8773	16.29+/-5.5 (19.23)	8.17+/-5.25 (7.66)	0.0371
Hospital days	37.07+/-4.91 (23.08)	25.64 +/-4.86 (16.07)	0.0014	29.87+/-4.46 (17.15)	21.89+/-4.6 (9.5)	0.0150	48.56+/-9.12 (26.22)	27.87 +/-8.51 (21.16)	0.0016
ITU days	15.53+/-2.70 (14.36)	14.67+/-2.68 (6.43)	0.6562	13.73+/-2.28 (4.40)	12.10+/-2.22 (8.71)	0.3111	20.48+/-5.54 (19.01)	15.83+/-5.26 (8.23)	0.2280

Table 4.2 Total noradrenaline dose (mg), ventilated days, ITU and hospital length of stay (days) by treatment modality (Values are mean±95% CI (SD)). APACHE II, Acute Physiology and Chronic Health Evaluation II; EVC, endovascular coiling; ITU, intensive therapy unit; SC, surgical clipping.

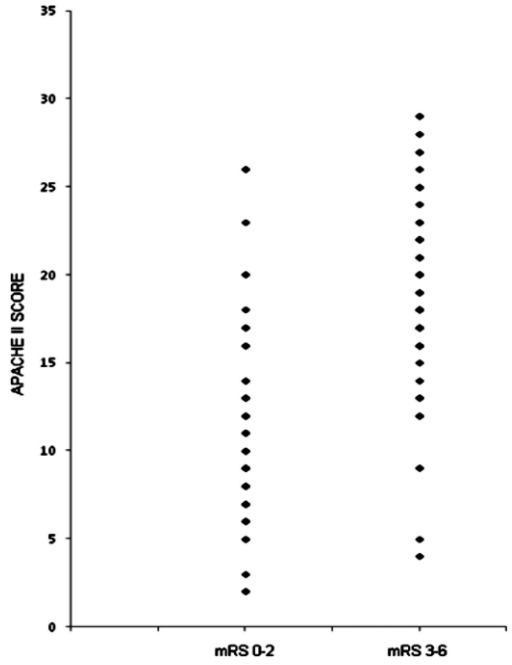

Figure 4.2 Acute Physiology and Chronic Health Evaluation II (APACHE II) score plotted against favourable outcome (modified Rankin Scale (mRS) score of 0–2) and unfavourable outcome (mRS score 3–6) for the population as a whole.

Variable	OR (95% CI)	P
Age ≥75	9.9 (1.62-60.60)	0.0131
Female sex	0.56 (0.17-1.81)	0.3353
Smoker	3.07 (0.97-9.67)	0.0556
WFNS grade ≥4	10.81 (3.51-33.31)	<0.0001
Vasospasm	1.23 (0.43-3.89)	0.6400
Clipping	5.27 (1.63-16.95)	0.0053
Hydrocephalus	0.71 (0.23-2.16)	0.5482
APACHE II score >15	17.80 (4.78-66.21)	<0.0001

Table 4.3 Multivariate analysis of variables potentially impacting on outcome in the study population as a whole. APACHE II, Acute Physiology and Chronic Health Evaluation II; WFNS, World Federation of Neurosurgical Societies.

The study population was then dichotomised by APACHE II score of ≤15 or >15 to explore outcomes by modality relative to the degree of physiological derangement. Descriptive statistics for two groups are shown in table 4.4. In the APACHE II ≤15 group, there was a significant increase in length of hospital stay in the SC group ($p<0.05$). On multivariate analysis, poor WFNS grade was the only significant predictor of poor outcome (OR 13.76, 95% CI 2.25 to 83.93, $p<0.05$). For patients with an APACHE II score of ≤15, there was no significant difference in outcomes between SC and EVC patients across all grades or within the good grade (WFNS 1–2) subgroup. There tended to be more severe vasospasm in the SC group but this was not significant. The distribution of favourable and unfavourable outcomes by baseline APACHE II score subgroupings (≤15 or >15) for each aneurysm securing modality is shown in table 4.4.

	APACHE II Score ≤15			APACHE II Score >15		
Variable	SC (n=39)	EVC (n=37)	P	SC (n=27)	EVC (n=32)	P
APACHE II Median (IQR)	9 (6)	10 (4.5)	0.5619	19 (5)	20 (6)	0.9362
Age Mean, 95% CI (SD)	50.64+/-4.26 (13.10)	51.97+/-4.38 (13.63)	0.6653	60.22+/-5.02 (8.58)	62.06+/-4.61 (15.81)	0.5907
Age ≥75	1 (2.56)	2 (5.4)	0.6100	1 (3.7)	11 (34.38)	0.0037
Female Sex	28 (71.79)	19 (51.35)	0.0980	22 (81.48)	26 (81.25)	1.0000
Previous SAH	1(2.56)	1(2.70)	1.0000	0	1 (3.13)	1.0000
Hypertension	10 (25.64)	10 (27.03)	1.0000	14 (51.85)	19 (59.38)	0.6068
Smoker	13 (33.33)	15 (40.54)	0.4833	10 (37.04)	15 (46.89)	0.5976
Previous stroke	0	0	1.0000	0	4 (12.5)	0.1176
GCS Median (IQR)	15 (1)	15 (2)	0.7279	11 (8)	13 (7)	0.6312
WFNS grade 1-3	36 (92.31)	30 (81.08)	0.1858	11 (40.74)	19 (59.38)	0.1954
WFNS grade 4-5	3 (7.69)	7 (18.92)		16 (59.26)	13 (40.63)	
Hydrocephalus	21 (53.85)	15 (40.54)	0.2616	16 (59.23)	20 (62.5)	1.0000
Vasospasm	16 (41.03)	19 (51.35)	0.4902	19 (70.37)	11 (34.38)	0.0089
Severe Vasospasm	12 (30.77)	7 (18.92)	0.2935	7 (25.93)	8 (25.0)	1.0000

Table 4.4 Descriptive analysis for dichotomised populations with APACHE II scores of ≤15 or >15 Values are (n (%)) unless otherwise stated. APACHE II, Acute Physiology and Chronic Health Evaluation II; EVC, endovascular coiling; GCS, Glasgow Coma Scale; SAH, subarachnoid haemorrhage; SC, surgical clipping; WFNS, World Federation of Neurosurgical Societies.

APACHE II	WFNS	Favourable outcome (mRS 0-2) (%)		OR (95% CI)	P
		SC	EVC		
>15	1-5	3/27 (11.1)	12/32 (37.5)	6.33 (1.27-31.38)	0.0238
	1-2	3/10 (30)	9/16 (56.3)	5.30 (0.74-37.92)	0.0970
≤15	1-5	32/39 (82.05)	32/37 (86.49)	3.02 (0.63-14.39)	0.1658
	1-2	32/35 (91.42)	27/30 (90.00)	0.96 (0.16-5.66)	0.9654

Table 4.5 Favourable outcomes (mRS 0-2) for clipped and coiled patients by dichotomised APACHE II subgroups (≤15 or >15) and multivariate odd ratios (OR) with 95% confidence intervals (CI) for poor outcome in each subgroup for clipped versus coiled patients. APACHE II, Acute Physiology and Chronic Health Evaluation II; EVC, endovascular coiling; mRS, modified Rankin Scale; SC, surgical clipping; WFNS, World Federation of Neurosurgical Societies.

For those patients with an APACHE II score of >15, there tended to be more vasospasm and poorer grade patients in the SC group but this did not reach significance. There were a significantly greater number of older patients (≥75 years of age) in the EVC group ($p<0.05$). On multivariate analysis, WFNS grade ≥4 (OR 6.74, 1.43 to 31.75) and SC (OR 6.33, 1.27 to 31.38) were the only significant predictors of poor outcome ($p<0.05$). In this population, 11% (3/27) of SC patients achieved a favourable outcome compared with 37.5% (12/32) of patients in EVC group. For good grade patients (WFNS 1–2) with an APACHE II score of >15, favourable outcome for SC was 3/10 (30%) and for EVC 9/16 (56.3%). SC patients also demonstrated significantly increased total norepinephrine dose, ventilated days, and hospital stay ($p<0.05$) relative to EVC patients. As grouped APACHE II scores increased, these outcome measures and the percentage favourable outcome (mRS 0-2) diverged for SC relative to EVC patients (figure 4.3, table 4.6).

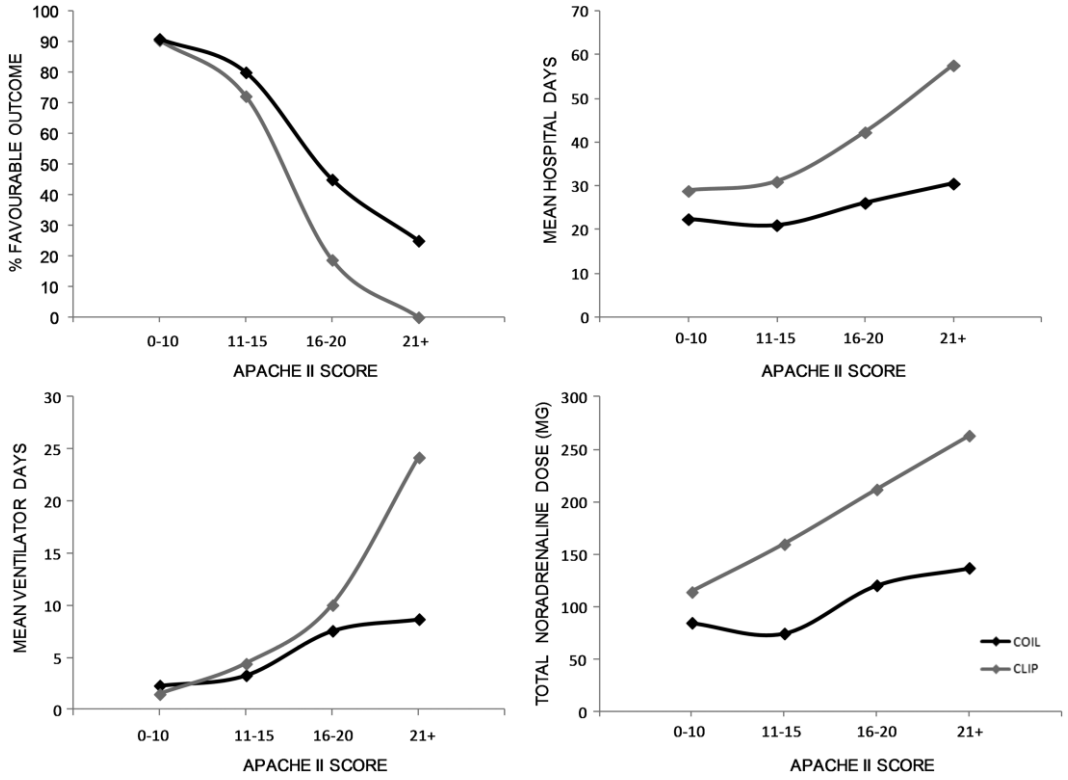

Figure 4.3 Outcome variables by grouped Acute Physiology and Chronic Health Evaluation II (APACHE II) scores for patients undergoing endovascular coiling or surgical clipping.

APACHE II score	Favourable outcome (mRS 0-2) (%)		Hospital days		Ventilator days		Noradrenaline dose (mg)	
	SC	EVC	SC	EVC	SC	EVC	SC	EVC
0-10	19/21 (90.5)	20/22 (90.9)	28.9+/- 9.18	22.45+/- 6.84	1.45+/- 5.53	2.27+/- 2.28	113.8+/- 82.6	84.5+/- 47.58
11-15	13/18 (72.2)	12/15 (80)	31+/- 9.92	21.07+/- 8.29	4.37+/- 5.67	3.26+/- 3.35	159.42+/- 84.76	74.27+/- 64.18
16-20	3/16 (18.8)	9/20 (45.0)	42.31+/- 10.52	26.16+/- 7.37	10.0+/- 6.38	7.35+/- 3.60	211.63+/- 92.36	120.21+/- 57.03
≥21	0/11 (0)	3/12 (25.0)	57.63+/- 12.69	30.58+/- 9.27	24.17+/- 7.13	8.65+/- 3.15	262.91+/- 111.4	136.75+/- 61.9

Table 4.6 Favourable outcome, hospital days, ventilator days, and total norepinephrine dose by increasing grouped APACHE II scores for patients undergoing endovascular coiling or surgical clipping. Values are mean±95% CIs unless otherwise stated. APACHE II, Acute Physiology and Chronic Health Evaluation II; EVC, endovascular coiling; mRS, modified Rankin Scale; SC, surgical clipping.

4.5 Discussion

The APACHE II scoring system is well established in intensive care practice. The system allows approximate prognostication based on a score from 0 to 71 for clinical and biochemical markers of cardiopulmonary, renal, haematological, and neurological function (Knaus *et al,* 1985). A breakdown of the scoring system is displayed in table 4.7. A number of observational studies have related other physiological scores to outcomes in SAH patients (Schuiling *et al,* 2005; Mocco *et al,* 2006). We aimed to identify whether the physiological derangement expressed by the APACHE II score had implications for differences in clinical outcome following either EVC or SC.

To our knowledge, this is the first study that has investigated the impact of a dichotomised APACHE II score in SAH. We have demonstrated that more significant physiological derangement, defined as a dichotomised APACHE II score of >15 at presentation, is a strong independent predictor of poor outcome in the SAH population as a whole. We did not investigate the impact of specific physiological variables within the score but it has previously been shown that hypoxemia, metabolic acidosis, hyperglycaemia, and cardiovascular instability are the dominant factors that influence eventual outcome (Claasen *et al,* 2004).

Physiological Variable	Points range
Age	0-6
Temperature	0-4
Mean Arterial Pressure	0-4
Heart rate	0-4
Respiratory rate	0-4
PaO2	0-4
Arterial pH	0-4
Serum Sodium	0-4
Serum Potassium	0-4
Serum Creatinine	0-8
Haematocrit	0-4
White Blood Cell Count	0-4
Glasgow Coma Scale	0-12
Chronic Health Problems: **1) Cirrhosis of the liver confirmed by biopsy 2) New York Heart Association Class IV** **3) Severe COPD: hypercapnia, home O2 use, or pulmonary hypertension** **4) Regular dialysis** **5) Immunocompromised**	None 0 Emergency procedure 5

Table 4.7 Breakdown of the physiological variables with contribution to the APACHE II score. APACHE II, Acute Physiology and Chronic Health Evaluation II; COPD, chronic obstructive pulmonary disease.

While clinical outcomes did not differ by treatment modality in the less physiologically deranged population (APACHE II ≤15), for those with more profound physiological derangement (APACHE II >15) there was a significant difference in clinical outcome by treatment modality. Within this population there tended to be more poor grade (WFNS ≥4) patients in the SC group, but on multivariate analysis both poor grade and SC were predictors of poor outcome. Furthermore, functional outcome differences by treatment modality for the good grade subgroup (WFNS grades 1–2) tended to significance (perhaps not reaching significance as the study was underpowered), suggesting an effect independent of presenting grade. In keeping with this, outcomes in the EVC group were improved despite having a significantly greater number of older patients. SC was associated with a marked increase in inotropic support (total norepinephrine dose), and hospital and ventilated days, suggesting a more profound physiological impact. This may

have been confounded by a higher incidence of vasospasm in the SC group but the incidence of severe vasospasm was similar, and on multivariate analysis, clipping and poor WFNS grade were significant predictors of poor outcome of similar magnitude in these patients, whereas vasospasm was not.

Functional outcomes for SC and EVC patients appeared to diverge with increasing APACHE II grouped scores along with degree of inotropic support, time ventilated, and hospital stay. The findings do suggest that the impact of the clipping procedure relative to a coiling procedure on deranged physiology may result in worse clinical outcomes.

These findings may give a clue as to why EVC is associated with better outcomes following treatment of aneurysmal SAH. Nevertheless, a clear underlying reason for these differences is uncertain. In one study, surgical and endovascular aneurysm therapies were associated with similar risks of cardiac injury and dysfunction after SAH (Miss *et al*, 2004). Rates of postoperative pulmonary oedema were also similar when the treatment modalities were compared (Horie *et al*, 2014). Craniotomy and SC is associated with longer procedural times but whether it results in a greater systemic inflammatory response (which is known to complicate SAH) (Yoshimoto *et al,* 2001) remains to be demonstrated. Immunodepression is also known to complicate SAH (Sarrafzadeh *et al*, 2011) and predisposes to pneumonia but the impact of aneurysm securing procedure has not been studied. Could a more minimally invasive aneurysm securing procedure limit these processes in some patients?

Common non-neurological complications of SAH include anaemia, hypertension, cardiac arrhythmia, fever, electrolyte changes, pulmonary oedema, pneumonia, hepatic dysfunction, renal dysfunction, and thrombocytopenia (Solenski *et al*, 1995). Pneumonia, sepsis, fever, anaemia, and hyperglycaemia independently predict poor outcome and death (Wartenberg *et al,* 2006). Medical complications are linked to severity of presenting grade (Solenski *et al*, 1995). Additionally, a large Canadian multicentre study demonstrated that SC patients more commonly suffered medical complications, such as urinary tract infection, pneumonia, cardiorespiratory arrest, and seizures, and that these complications were linked to poor outcome (Vergouwen *et al,* 2011c). Our finding that SC patients with more profound physiological derangement (APACHE II >15) were noted to have significantly

increased total norepinephrine dose, days ventilated, and hospital stay is consistent with this finding.

Many authors have attempted to explain the differences in outcome between patients undergoing EVC and SC through assessing the rates of cerebral vasospasm or delayed ischemia. Although there is some controversy regarding this, the general consensus is that that clipping results in more vasospasm and delayed ischemia (Dumont *et al*, 2010; Dorhout Mees *et al*, 2012). Naidech *et al*, (2006) have also demonstrated an association between baseline physiological derangement and rates of infarction on CT. We demonstrated a significantly increased incidence of moderate–severe vasospasm in the SC population with more deranged physiology (APACHE II >15) but not in the SC population with an APACHE II score of ≤15, which suggests that a possible synergistic effect may exist, with both physiological derangement and craniotomy/clipping combining to result in a greater risk of vasospasm. However, the rate of vasospasm in the coiled population with an APACHE II score ≤15 was higher than in the population with an APACHE II score >15, suggesting that physiological derangement did not necessarily contribute to the development of vasospasm. Furthermore, we did not demonstrate a difference in the rate of severe vasospasm between treatment modalities. Interestingly, vasospasm failed to represent an independent predictor of poor outcome but the majority of patients in this study were managed using a paradigm employing angiographic screening and pre-emptive hypertensive and endovascular management on identification of significant angiographic vasospasm (Mortimer *et al*, 2015b), which may limit its clinical impact.

The results of this study have implications for daily practice: the choice of whether to clip or coil an aneurysm has traditionally been made on the basis of morphological criteria, such as aneurysm location, size, and neck anatomy. We suggest, on the basis of these findings, that as well as anatomical criteria it is worth considering the physiological condition of the patient as one of the primary factors in assigning treatment modality. For example, is it preferable to clip a complex aneurysm in a medically unwell patient or would it be preferable to treat with partial coiling of the dome (Waldau *et al*, 2012) in order that the patient can be brought back for retreatment (using stents, flow diversion, or surgery) following recovery rather

than undergo an acute clipping procedure? This approach has not been answered by this study but certainly warrants future investigation.

This was a small explorative analysis, and although the data suggest some interesting findings, it is necessary to explore these concepts in a larger population. The data were not collected specifically to answer the impact of physiological derangement relative to aneurysm securing procedure on outcome. Dichotomising APACHE II score based on the available data introduces bias, and the assignment of treatment modality was not randomised so there is an inherent selection bias with respect to this also. The procedural complication rate was not specifically recorded. There were more posterior circulation aneurysms in the coiling group, and Fisher grade was not taken into account; it is plausible that the results were therefore biased by patients needing surgical haematoma evacuation being selected into the clipping group. However, in a recent prospective study of 381 consecutive SAH patients, haematoma evacuation was a reason for SC in only 3% of patients (Cognard *et al*, 2014). Furthermore, in this study, SC was a significant predictor of poor outcome of similar magnitude to poor WFNS grade (indicative of acute neurological injury) on multivariate analysis, and there also tended to be more favourable outcomes in the good grade (WFNS 1-2) subgroup with more deranged physiology (APACHE II >15) when coiled rather than clipped, suggesting an interaction between treatment modality and physiological derangement independent of the acute neurological injury.

An additional criticism of this study is that the short follow-up period of 90 days is likely to show a poorer outcome when assessing a more invasive intervention, such as a craniotomy. Ideally, if a future study were to be constructed to explore the interaction between deranged physiology, treatment modality, and outcome, a longer follow-up period would be needed. On the other hand, it could be argued that this is precisely the point; patients undergoing a more invasive procedure may require more inotropic support, more time ventilated, and more time in hospital. They could therefore take much longer to recover and are therefore more at risk of nosocomial infection and other medical complications. The results do therefore give an interesting insight into the role that physiological assessment could have in shaping the design of future prospective investigations.

4.6 Conclusion

In summary, we have demonstrated that in this population, more marked physiological derangement at baseline is a strong predictor of eventual poor outcome. These preliminary results also suggest that clinical outcomes for patients with more severe baseline physiological derangement could possibly be improved if undergoing a coiling rather than a clipping procedure but this should be investigated using a prospective approach in the future.

CHAPTER 5

THE NEGATIVE PREDICTIVE VALUE OF CT ANGIOGRAPHY IN THE SETTING OF PERIMESENCEPHALIC SUBARACHNOID HAEMORRHAGE

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5.1 Abstract

5.1.1 Background

Perimesencephalic subarachnoid haemorrhage (PMSAH) is only rarely associated with a ruptured cerebral aneurysm and CT angiography (CTA) has very good sensitivity and specificity for aneurysm detection. The necessity for invasive imaging with digital subtraction angiography (DSA) is therefore debatable. We chose to assess the negative predictive value (NPV) of CTA in a series of patients with PMSAH treated at our institution over a 9-year period.

5.1.2 Methods

We retrospectively assessed the diagnostic yield of DSA after initial negative CTA in patients with a PMSAH pattern defined as blood centred anterior to the midbrain and/or pons within the pre-pontine or interpeduncular cistern with possible quadrigeminal or ambient cistern extension; possible extension into the basal parts of the Sylvain fissures but not the lateral sylvian fissures; possible extension to the cisterna magna but not centred on the cisterna magna; and possible extension into the fourth ventricle and occipital horns of the lateral ventricles.

5.1.3 Results

Using this definition of PMSAH, of 72 patients, one patient showed a potentially significant finding on DSA that was not demonstrated on initial CTA (NPV 98.61% (95% CI 92.47% to 99.77%)). However, when cisterna magna extension was excluded from the definition of PMSAH, no false negative CTAs in 56 patients were encountered (NPV 100% (95% CI 93.56% to 100.00%)).

5.1.4 Conclusion

The NPV of normal CTA for an arterial abnormality in patients with PMSAH is high and our results therefore question the role of invasive imaging. The findings also suggest that a prospective study designed to clarify the necessity of performing DSA in this population would be feasible.

5.2 Introduction

Perimesencephalic subarachnoid haemorrhage (PMSAH) represents a distinct clinic-radiological entity characterised by haemorrhage centred on the perimesencephalic cisterns, aneurysm negative angiographic investigation and a more benign clinical course (van Gijn *et al,* 1985; Rinkel *et al,* 1991a; Rinkel *et al,* 1991b; Brilstra *et al,* 1997; Greebe *et al,* 2007). The PMSAH pattern is demonstrated in approximately 5% of patients with subarachnoid haemorrhage (SAH) and has an incidence of 0.5/100 000 patients (Flaherty *et al,* 2005). The incidence of an underlying aneurysm presenting with a PMSAH pattern has been reported in as many as 12% (Kallmes *et al,* 1996), but a recent meta-analysis of 1031 patients with strict criteria for PMSAH concluded a rate of 0.78% (Kalra *et al,* 2015). Angiographic imaging is mandatory, but the question of how far to investigate these patients has been debated for some time, largely owing to reports of low diagnostic yield for digital subtraction angiography (DSA) in the face of negative CT angiography (CTA) (Velthuis *et al,* 1999; Kalra *et al,* 2015; Kershenovich *et al,* 2006; Westerlaan *et al,* 2007; Agid *et al,* 2010; Cruz *et al,* 2011; Moscovici *et al,* 2013; Delgado Almandoz *et al,* 2013; Zhong *et al,* 2014) and the risk to the patient incurred by the former investigation (Willinsky *et al,* 2003).

Critical to defining which patients could forgo DSA is the definition of PMSAH itself, and various definitions have been used (van Gijn *et al,* 1985; Schievink *et al,* 1994; Delgado Almandoz *et al,* 2012; Wallace *et al,* 2016). The pattern of haemorrhage first described by van Gijn *et al* in 1985 was that of blood centred anterior to the midbrain or pons but not extending to the lateral Sylvain fissures or anterior interhemispheric fissure and only a small volume of intraventricular haemorrhage. More recently, Wallace et al (2016) have described a pattern whereby haemorrhage could extend to the cisterna magna but not into the Sylvain fissures, with intraventricular blood confined to the fourth ventricle or occipital horns of the lateral ventricles only. Using their algorithm, no patients had an underlying aneurysm in their series.

We aimed to investigate the diagnostic yield of DSA in the face of a negative CTA in patients with PMSAH to elucidate the negative predictive value of CTA in this population. We based our investigation on 9 years of practice in a regional neuroscience centre where the established protocol was to investigate all patients with CTA and DSA.

5.3 Methods

This retrospective investigation was approved by the institutional audit committee. All CTAs performed between January 2006 and December 2014 in patients aged 18 years an over were screened and those performed in the context of non- traumatic SAH were reviewed by two consultant neuroradiologists (SR and AA) for the presence or absence of an underlying aneurysm. Patients with CT-confirmed SAH but a negative CTA were initially identified. Each non-contrast CT (NCCT) scan was then reviewed for the pattern of SAH; those with a PMSAH pattern agreed by two consultant neuroradiologists (SR and AM) by consensus were then included in the final study cohort. The presence of hydrocephalus, intraventricular extension, and extension of haemorrhage to the cisterna magna was also recorded. Subsequent DSAs were assessed for the presence of underlying arterial pathology that could account for the SAH, principally aneurysmal disease or arterial dissection. CTA studies from outside institutions were excluded from the study. For patients with defined PMSAH, the medical notes were reviewed to confirm the presentation and performance of initial NCCT imaging within 72 h of ictus. Patients who did not undergo DSA were excluded from the final analysis. Descriptive statistics and negative predictive value for CTA were calculated using Medcalc statistical software.

5.3.1 Definition of perimesencephalic subarachnoid haemorrhage

Patients were categorised radiologically as having PMSAH on the basis of features modified from van Gijn et al (1985) and Wallace et al (2016). See figure A1, appendix 1.

1. Haemorrhage centred anterior to the midbrain and/or pons within the pre-pontine and interpeduncular cisterns with possible extension to the quadrigeminal or ambient cisterns.
2. No deep extension into the anterior interhemispheric fissure.
3. Possible extension into the basal parts of the Sylvain fissures with no extension into the lateral Sylvain fissures.
4. Possible extension to the cisterna magna but not centred on the cisterna magna.
5. Possible extension into the fourth ventricle and occipital horns of the lateral ventricles.

5.3.2 Imaging protocol

All patients underwent CTA using a 64-slice scanner (Siemens Medical Systems, Erlangen, Germany). CTA was acquired using a contrast bolus of 75 mL Iomeron 400 (400 mg iodine/mL; Bracco, UK) followed by a 40 mL saline chaser injected via an 18–20-gauge cannula in the upper limb with a flow rate of 5 mL/s. A bolus tracking technique was used with a marker placed at the ascending aorta, triggering at 120 Hounsfield Units above baseline with a 10 s delay prior to image acquisition. Images were acquired from C2 to vertex. CTA parameters were as follows: 120 kVp; 110 mA; 0.37 s/rotation; 0.6 mm thick sections; and table speed 1.2 mm/rotation. Images were reconstructed and reviewed in three planes using Synapse picture archiving and communications system (Fujifilm, New York, USA). DSA was performed using a dedicated biplane neuroangiography suite (Siemens Medical Systems, Erlangen, Germany and Philips, Massachusetts, USA). Using a 5 F system, injections of both internal carotid arteries and the dominant vertebral artery were performed with standard anteroposterior, lateral, and oblique views. Three-dimensional rotational angiography was used for problem solving.

5.4 Results

CTA-negative SAH was identified in 243 patients. Of these patients, 74 were classified as having PMSAH and presenting within 72 h of ictus. Two did not undergo DSA and were therefore excluded from the final analysis, leaving 72 patients in the primary study cohort. Patient age ranged from 33 to 79 years (mean 52.7 years, SD 10.8 years). The cohort comprised 24 women (33.3%) and 48 men (66.6%) (M:F 2:1). Of the patients defined as having PMSAH, 9 (12.5%) had radiological evidence of hydrocephalus, 3 (4.2%) had intraventricular extension, and 16 (22.2%) had extension of haemorrhage to the cisterna magna.

Two patients demonstrated findings on DSA that were not identified on CTA, but the abnormality in each case was of debatable significance. This included a small A1 anterior cerebral artery bleb in one patient that was felt not to be responsible for the haemorrhage and was successfully managed conservatively. A second patient who had a poor quality CTA owing to movement and non-dominant vertebral artery irregularity was identified on DSA; this was equivocal for underlying atheroma or dissection but was managed with parent vessel occlusion on a risk/benefit basis (see figure A2, appendix 1). CTA therefore had a negative predictive value of 98.61% (95% CI 92.47% to 99.77%) for significant arterial pathology using a definition of PMSAH that allowed extension of haemorrhage to the cisterna magna. However, none of the 56 patients with haemorrhage that did not extend to the cisterna magna had a significant finding on DSA, equating to a negative predictive value of 100% (95% CI 93.56% to 100.00%) in this subgroup. Importantly, one patient (1.4%) suffered a complication of DSA, developing presumed neurotoxicity to the contrast agent resulting in widespread MR detectable cerebral oedema, hemiparesis and coma, but this subsequently resolved (see figure A3, appendix 1).

5.5 Discussion

Approximately 5% of patients with SAH present with a perimesencephalic pattern of bleeding (Flaherty *et al*, 2005), and these patients usually have a more benign clinical course; quality of life and life expectancy are normal in this population (Rinkel *et al*, 1991b; Brilstra *et al*, 1997; Greebe *et al*, 2007). However, aneurysmal rupture may rarely present with a PMSAH pattern of haemorrhage (Kalra *et al*, 2015) and accurate angiographic imaging is therefore necessary. The role of invasive versus non-invasive imaging in this population has been debated for over a decade.

We have demonstrated that the diagnostic yield for DSA in the face of a negative CTA is low and that the negative predictive value of CTA is 98–100%, depending on the definition of PMSAH. Excluding patients with haemorrhage extending to the foramen magnum resulted in a negative predictive value of 100%. These findings are in line with those of other published series in which the rate of abnormality detection on DSA following an initial negative CTA is low (table 5.1) (Velthuis *et al*, 1999; Kershenovich *et al*, 2006; Westerlaan *et al*, 2007; Agid *et al*, 2010; Cruz *et al*, 2011; Moscovici *et al*, 2013; Delgado Almandoz *et al*, 2013; Zhong *et al*, 2014; Kalra *et al*, 2015).

The sensitivity and specificity of CTA for aneurysm detection with modern 16- and 64-section machines have been systematically reviewed and have demonstrated values in the order of 98% and 100%, respectively (Westerlaan *et al*, 2011). Techniques that allow bone subtraction may improve sensitivity, particularly for aneurysms lying adjacent to bone (Chen *et al*, 2013; Cheng *et al*, 2015). It therefore appears that, for the subgroup with PMSAH (particularly if the haemorrhage is not seen to extend to the cisterna magna), who are likely to exhibit a low yield for any angiographic imaging, investigation with CTA only maybe sufficient. Technological improvements may also see aneurysm detection improve further. For example, 320-slice bone subtraction CTA in 282 consecutive patients yielded sensitivity, specificity, and accuracy for depicting aneurysms of 99.2%, 100%, and 99.4%, respectively, on a per aneurysm basis (Chen *et al*, 2013).

Study	Number of patients	False negative CTA
Velthuis et al, (1999)	15	0
Kershenovich et al, (2006)	30	0
Westerlaan et al, (2007)	30	0
Agid et al, (2010)	93	0
Cruz et al, (2011)	49	1 (2.4%)
Moscovici et al, (2013)	25	0
Delgado Almandoz et al, (2013)	11	0
Zhong et al, (2014)	49	0
Kalra et al, (2015)	18	0
Present study	72 56 (no cisterna magna haemorrhage)	1 (1.4%) 0

Table 5.1 Summary of studies assessing the use of CT angiography (CTA) in the investigation of perimesencephalic subarachnoid haemorrhage.

CTA offers a swift, non-invasive investigation, whereas DSA necessitates arterial puncture and a recognised permanent neurological complication rate in the order of 0.5% (Willinsky *et al*, 2003). Ruigrok et al (2000) calculated from the literature combined with their own series that the average risk of permanent neurological complications from DSA in patients with PMSAH was 0.74% (95% CI 0.09% to 2.7%). We noted one transient but potentially serious complication of DSA in our series. However, the risk of forgoing DSA does have to be weighed against the risk to the patient if an aneurysm is missed. Rehaemorrhage is associated with poor outcome; Hijdra et al (1987b) studied patients surviving the first 24 h after initial rupture and only 7/39 patients (18%) who suffered rehaemorrhage had survived at 3 months. The International Cooperative Study on the Timing of Aneurysm Surgery (Kassel *et al*, 1990) reported that aneurysm rerupture was the second most common cause of morbidity and mortality.

Current European Stroke Organisation guidelines suggest that, although it is uncertain as to whether DSA may be avoided in this population, repeat DSA is not necessary (Steiner *et al*, 2103). The American Heart Association/American Stroke Association guidelines suggest that DSA may not be necessary if a classic perimesencephalic pattern of haemorrhage is present and CTA may suffice (Connolly *et al*, 2012). We are currently debating our own institutional guidelines and one protocol that could conceivably be introduced is that of forgoing DSA in the presence of a perimesencephalic pattern of haemorrhage and normal CTA as agreed by two experienced neuroradiologists on separate reads.

Critical to applying a protocol using CTA to investigate PMSAH exclusively are that strict definitions of what constitutes a perimesencephalic haemorrhage are understood and applied and that there is good inter-observer agreement. This is of importance as the likelihood of an underlying vascular abnormality is probably greater with a non-perimesencephalic pattern (Westerlaan *et al*, 2007; Delgado Almandoz *et al*, 2013; Dalyai *et al*, 2013). Dalyai et al (2013) demonstrated that the diagnostic yield of repeat angiography was 0% in patients with a PMSAH pattern and 12.5% in those with a non-PMSAH pattern when they systematically performed follow-up angiographic imaging in patients with a negative initial angiogram. However, the diagnosis of a PMSAH pattern is not straightforward. Inter-observer disagreement rates vary considerably among studies from 2.8% to 22% (Cruz *et al*, 2011; Wallace *et al*, 2016), highlighting a potential problem with institution of such a protocol. Most definitions of PMSAH stress that the focus of haemorrhage is centred on the perimesencephalic cisterns, but definitions vary as to whether it is acceptable to allow basal Sylvain fissure, ventricular, or cisterna magna extension (van Gijn *et al*, 1985; Schievink *et al*, 1994; Delgado Almandoz *et al*, 2012; Wallace *et al*, 2016). We chose to unify the initial description of PMSAH (van Gijn *et al*, 1985), which allows extension into the basal Sylvain fissures, with a more recent definition allowing extension to the cisterna magna also (Wallace *et al*, 2016). However, when cisterna magna extension was included in the definition, one patient was identified as having a possible vertebral artery dissection on follow-up DSA, raising doubt as to whether this should be used as a criterion.

This was a retrospective study of a relatively small sample of patients, although it should be said that the majority of studies investigating this clinico-radiological dilemma are of similar design but of smaller cohort size. Application of

the results of this type of investigation could be criticised but the results do pave the way for a larger prospective study that could be used to comprehensively answer the question of whether invasive imaging is necessary or justified in this subgroup with SAH.

5.6 Conclusion

The results of this retrospective study suggest that perimesencephalic haemorrhage without extension to the cisterna magna may be investigated with CTA with a high negative predictive value for an arterial abnormality in the order of 100%. If a prospective study is required to conclusively answer whether invasive imaging is necessary in patients with PMSAH, the results of this investigation and others suggest that this would be a safe and potentially beneficial study.

CHAPTER 6

INSTITUTION OF SUSTAINED ENDOVASCULAR TREATMENT PRIOR TO CLINICAL DETERIORATION IN PATIENTS WITH SEVERE ANGIOGRAPHIC VASOSPASM: A RETROSPECTIVE OBSERVATIONAL STUDY OF CLINICO-RADIOLOGICAL OUTCOMES

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6.1 Abstract

6.1.1 Background

Severe angiographic vasospasm (aVSP) is a risk factor for infarction following subarachnoid haemorrhage and infarction is strongly associated with poor outcome. We present the clinico-radiological results of cohort with severe aVSP who underwent a program of angiographic surveillance and sustained endovascular treatment using multiple verapamil infusions and/or transluminal balloon angioplasty (TBA).

6.1.2 Methods

This was a dual-centre retrospective observational study. Angiographic screening for vasospasm was undertaken at days 5-7 post-ictus. Treatment was instituted principally on the basis of radiographic findings. The rate of infarction was evaluated on follow-up CT. Clinical outcome was assessed using the modified Rankin Scale (mRS).

6.1.3 Results

Fifty-seven WFNS grades 1-5 patients were studied. The mean number of procedures/patient was 6, range 2-13. Mean verapamil dose administered to the ICA was 14 mg and VA was 12 mg. Thirty-one patients underwent TBA (52.6%). The rate of proximal vessel infarction was 3/45 (6.7%) for patients presenting < 72 hours. Rates of favourable outcome (mRS 0-2) were 16/19 (84.2%) for WFNS grades 1-2, 12/19 (63.2%) for grades 3-4 and 5/19 (26.3%) for grade 5 patients. Delayed presentation > 72 hours was the only factor on multivariate analysis to significantly predict aVSP-infarction [OR 19.3 (3.2-116.6) P = 0.0012]. Large aVSP infarction [OR 19.0 (1.7-216.4) 0.0179] and poor WFNS grade [OR 6.6 (1.3-33.9) P = 0.0233] were significant predictors of poor outcome on multivariate analysis.

6.1.4 Conclusion

This approach may result in low rates of aVSP-infarction and encouraging rates of favourable outcome when compared to literature benchmarks. Delayed

presentation, however, predicts infarction and large infarct and poor initial grade significantly influence functional outcome.

6.3 Introduction

Cerebral infarction is strongly associated with poor outcome following SAH (Furgusson & Macdonald, 2007, Vergowen *et al*, 2011b). Aetiologies include the acute injury (Wartenberg *et al*, 2011), aneurysm treatment, or delayed ischaemia (Rowland *et al*, 2012). Proposed mechanisms for delayed ischaemia, either alone or in combination (Pluta *et al*, 2009; Rowland *et al*, 2012), include microthrombosis, spreading depolarisation with cortical ischaemia and angiographic vasospasm (aVSP). The contribution of the latter is controversial (Pluta *et al*, 2009; Macdonald, 2013; Hou & Zhang, 2013), largely stemming from the finding that endothelin-receptor antagonists reduce the rate of moderate-severe aVSP but not the rate of poor outcome (Macdonald *et al*, 2008; Macdonald *et al*, 2011). However, there is a strong correlation between the severity of aVSP and infarct incidence (Crowley *et al*, 2011). The majority of delayed infarcts occur in association with aVSP (Crowley *et al*, 2011; Wagner *et al*, 2013; Brown *et al*, 2013), mostly with severe aVSP (Weidauer *et al*, 2007; Crowley *et al*, 2011, Inagawa et al 2014), which results in the most significant perfusion deficits (Weidauer *et al*, 2007; Dankbaar *et al*, 2009; Vatter *et al*, 2011; Dhar *et al*, 2012). Severe aVSP is associated with poor cognition, worse patient-relevant outcomes, and greater inpatient healthcare resource use (Macdonald *et al*, 2012).

Two endovascular approaches have been employed to treat vasospasm; prophylactic TBA before vasospasm onset (Zwienenberg-Lee *et al*, 2009) or, use of TBA and/or IA vasodilators as a rescue procedure in patients who deteriorate despite medical therapy. The former approach may result in unnecessary treatments. The latter relies on early detection of clinical deterioration. However, these patients are often poor grade, comatose or sedated and difficult to assess. They may suffer silent infarction that itself has a negative impact on outcome (Shimoda *et al*, 2001; Schmidt *et al*, 2008; Macdonald *et al*, 2013). An alternative approach is to screen for vasospasm with the intention of treating it while it is minimally symptomatic. We routinely undertake a program of angiographic surveillance at days 5-7 post-ictus, at or just before the time that most patients become symptomatic (Suarez *et al*, 2002; Ionita *et al*, 2010) with subsequent endovascular treatment (multiple procedures where necessary) based on symptomology and radiographic features. We

hypothesised that using this approach and comparing to benchmarks in the literature, rates of infarction and clinical outcomes were favourable.

6.4 Methods

This was a dual-centre retrospective observational study of patients with severe aVSP following aneurysmal SAH treated between November 2009 and December 2013. The study was approved by the regional ethics committee.

Patients included were defined as having severe aVSP on the basis of > 66% arterial narrowing (Crowley *et al*, 2011) on initial screening or subsequent DSAs. Statistical analysis was performed using Openstat software, 2013. Univariate analysis of nonparametric variables and their relationship to infarction and unfavourable outcome (mRS 3-6) was calculated using χ^2. For variables that demonstrated P <0 0.1 on univariate analysis, multivariate binary logistic regression was undertaken with statistical significance defined as $P < 0.05$. Patients were managed in line with published protocols (Mortimer *et al*, 2015c). Significant aVSP was treated using IA verapamil or TBA, with a repeat angiogram the following day. Papaverine was used as a second-line IA vasodilator. Decision to use vasodilators or TBA was undertaken on a case-by-case risk/benefit basis. Vasodilators were used for distal (M2/3MCA, A2/3-ACA and PCA) disease. Severe proximal (VA, BA, ICA, M1-MCA or A1-ACA) vasospasm was treated with TBA where possible. For refractory vasospasm, daily treatments were undertaken until either vasospasm was no longer significant or vasospasm proved to be unsatisfactorily treated with this regime. For multiple treatments the groin sheath was sutured in situ, replaced daily and side alternated after 3-4 days.

A neuroradiologist assessed presenting CT and CTs performed during the treatment period and at 2 to 6 weeks' follow-up. The initial CT was interpreted for extent and distribution of haemorrhage and hydrocephalus. The initial DSA was interpreted for the site and size of the aneurysm. Vasospasm distribution and severity was then recorded from subsequent angiography. Severe vasospasm was defined as arterial narrowing of >66% relative to the angiogram performed within 72 hours of ictus. For late presenters, severe vasospasm was defined as ICA, BA, M1-MCA and A1-ACA vessel diameters of ≤ 2 mm, ≤ 1.5 mm, ≤ 1.5 mm and ≤ 1 mm respectively.

Delayed CT scans were interpreted in conjunction with DSA to record the rate and characteristics of aVSP-related infarction. This was defined as hypodensity

in a vascular territory or watershed distribution correlating with the distribution of aVSP. Infarcts were classified as proximal (M1 or M2-MCA, A1-ACA, or P1-PCA), watershed, perforator or distal branch. Hypodensities present prior to the development of vasospasm, relating to EVD insertion or hydrocephalus, lying adjacent to haematomas or relating to aneurysm treatment were excluded. Clinical outcome was graded through means of a modified Rankin Scale score (mRS) at mean 16 ± 4 months' follow-up.

6.5 Results

Fifty-seven patients were included: 18 males (31.6%) and 39 females (68.4%) of mean age 50.4 ± 3.0 years. Clinico-radiological features at presentation are shown in table 6.1. Twenty-two patients (38.6%) were clipped and 35 patients (61.4%) were coiled. The aneurysm responsible for the haemorrhage was anterior circulation in 47 (82.5%) [ACA 24, ICA 14 and MCA 9] and posterior circulation in 10 (17.5%). Seven aneurysms (12.3%) were large (≥ 10 mm) and one was giant. Eleven patients (19.3%) presented >72 hours and had vasospasm on initial angiography. Clinical state when commencing treatment for vasospasm was GCS 3-6 in 16 patients (28.1%), GCS 7-12 in 16 (28.1%), GCS 13-14 in 17 (29.8%) and GCS 15 in 4 (7%). Four patients (7%) were sedated for raised intracranial pressure and could not be assessed. Thirteen patients (22.8%) underwent decompressive craniectomy.

6.5.1 Distribution of aVSP

The distribution of severe aVSP is shown in figure 6.1. Severe aVSP was seen in 1 vessel (ICA, MCA, ACA, VA or BA), in 11 patients (19.3%), 2 vessels in 17 patients (29.8%), 3 vessels in 10 (17.5%), 4 vessels in 11 (19.3%) and 5-7 vessels in 8 patients (14.1%). All patients had at least one proximal segment treated during the course of their surveillance. Only one patient was treated prior to the screening window of 5-7 days.

WFNS grade	**1**	**2**	**3**	**4**	**5**
	11 (19.3)	8 (14)	6 (10.5)	13 (22.8)	19 (33.3)
Fisher grade	1	2	3	4	
	0 (0)	1 (1.8)	50 (87.7)	6 (10.5)	
Maximal clot thickness	≤5mm	5-10mm	11-15mm	>15mm	
	6 (10.5)	13 (22.8)	20 (35.1)	18 (31.6)	
Intraventricular haemorrhage	46 (80.7)				
Intraparenchymal extension of haemorrhage	28 (49.1)				
Hydrocephalus	48 (84.2)				
Hypertension	18 (31.5)				
Diabetes mellitus	2 (3.5)				
History of smoking	22 (38.5)				

Table 6.1 Clinico-radiological features at presentation (%).

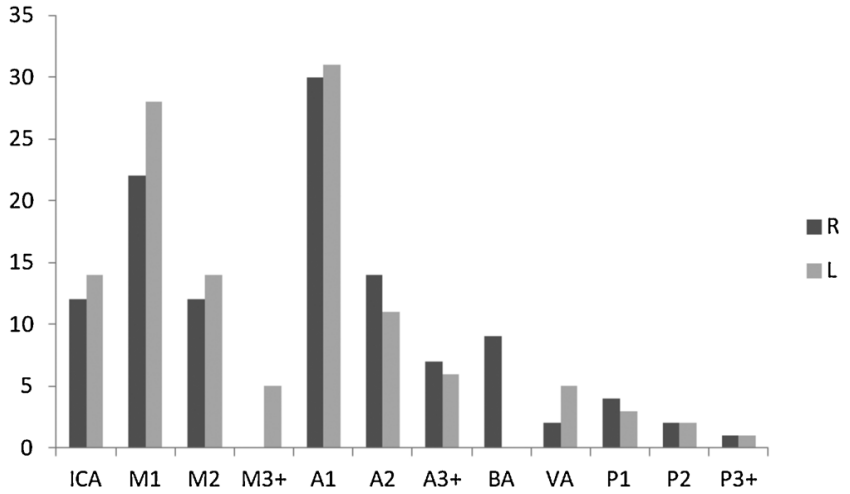

Figure 6.1 Distribution of severe aVSP in the treated cohort.

6.5.2 Endovascular treatment

The mean number of procedures/patient was 5.87 ± 0.77 (2-13 per patient). All patients had at least one verapamil infusion. Doses administered are displayed in table 6.2. Mean day of first treatment was 6. Papaverine was used as a second-line treatment in 21 patients with 64 infusions; 30 were selective microcatheter

injections. The mean dose was 133.68 ± 19.67 mg and mean number of infusions 2.17 (1-6 per patient). Thirty-one patients (52.6%) underwent TBA. Vessels angioplastied are shown in figure 6.2. Of the 89 vessels angioplastied, one required retreatment with TBA (1.1%).

Vessel	Mean dose (mg)	Range (mg)	Mean number of treatments	Range
RICA	14.39+/-0.78	8.33-22	5	1-12
LICA	14.21+/-0.83	8.5-20.7	4.7	1-13
RVA	11.87+/-1.83	5.0-17.0	3.36	1-15
LVA	12.59+/-1.33	10.0-15.0	2.58	1-6

Table 6.2 Dose and number of Verapamil infusions by vessel.

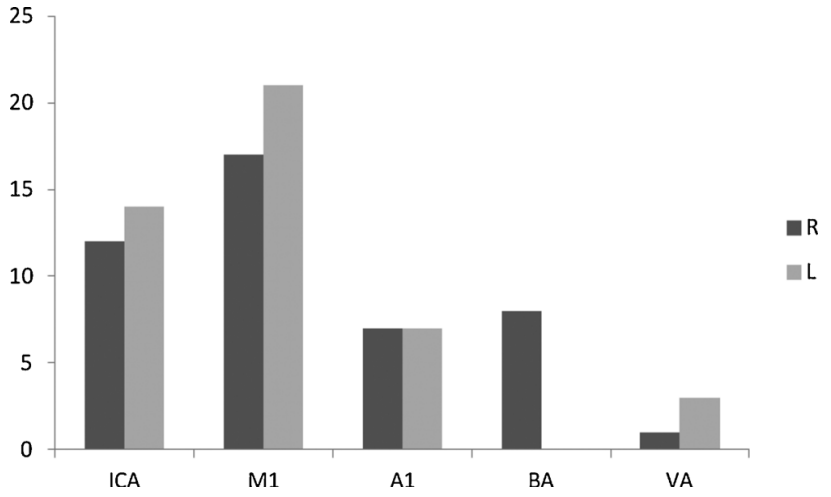

Figure 6.2 Vessels treated with TBA.

6.5.3 Complications

Fifty-seven patients underwent 335 procedures. Complications included two asymptomatic external iliac dissections, one symptomatic external iliac dissection requiring stenting, two asymptomatic grade 1 ICA dissections and one thromboembolism treated with thrombectomy. No complication had permanent sequaele but the serious complication rate was 3.5% (patient-specific) and 0.6% (procedure-specific).

6.5.4 Vasospasm-related infarction

Follow-up imaging was not available in 1 patient. The rate of proximal territory infarction in patients presenting <72 hours from ictus was 3/45 (6.7%). If smaller infarcts were included, infarction was demonstrated in 8/45 patients (17.8%). Eight of 11 patients (72.7%) who presented with aVSP on initial angiography at >72 hours suffered aVSP infarction. Delayed presentation was a significant risk factor for infarction on univariate analysis (8/16; 50% versus 3/40; 7.5%, $P = 0.0002$) and on multivariate analysis (OR 19.3, 3.2—116.6, $P = 0.0012$). Of those patients who developed large infarcts, 4/7 presented at >72 hours. Of the overall cohort, 9/16 infarcts were small (4 perforator, 2 watershed and 3 distal branch infarcts).

Vasospasm involving ≥4 vessels significantly increased the risk of developing aVSP-related infarction on univariate analysis (10/16; 68.8% versus 9/40; 25%, $P = 0.0042$). This trended to significance on multivariate analysis (OR 4.2, 0.9—18.0, $P = 0.0634$). Although fewer good grade patients suffered aVSP-related infarction, (21% versus 32%) this was not significant. No significant difference in the rate of aVSP-related infarction was noted for clipped versus coiled patients, age ≤ 50, gender, intraventricular haemorrhage, hydrocephalus, intraparenchymal extension of haemorrhage, use of TBA plus vasodilators versus vasodilators alone, or maximal clot thickness ≥ 10 mm.

6.5.5 Clinical outcomes

Outcomes for the overall cohort are displayed in table 6.3 and outcomes by grade are displayed in table 6.4 and figure 6.3. For WFNS grades 1-4, favourable outcome (mRS 0-2) was seen in 28/38 (73.7%). WFNS grade and proximal vessel aVSP-related infarction significantly impacted on outcome on both univariate and multivariate analysis (table 6.5). No significant difference in the rate of unfavourable outcome was seen for age, sex, clip/coiling, presentation beyond 72 hours, hydrocephalus, intraventricular or intraparenchymal haemorrhage or vasospasm treatment modality (TBA and vasodilators versus vasodilators alone).

mRS	0	1	2	3	4	5	6
N (%)	15 (26.3)	14 (24.6)	4 (7.0)	6 (10.5)	4 (7.0)	5 (8.8)	9 (15.8)

Table 6.3 Distribution of clinical outcomes in the overall cohort.

Grade Clinical Outcome	WFNS 1-2	WFNS 3-4	WFNS 5
Good (mRS 0-2)	16 (84.2)	12 (63.2)	5 (26.3)
Moderate (mRS 3)	0	1 (5.3)	5 (26.3)
Poor (mRS 4-6)	3 (15.8)	6 (31.6)	9 (47.4)

Table 6.4 The distribution of clinical outcome by presenting WFNS grades.

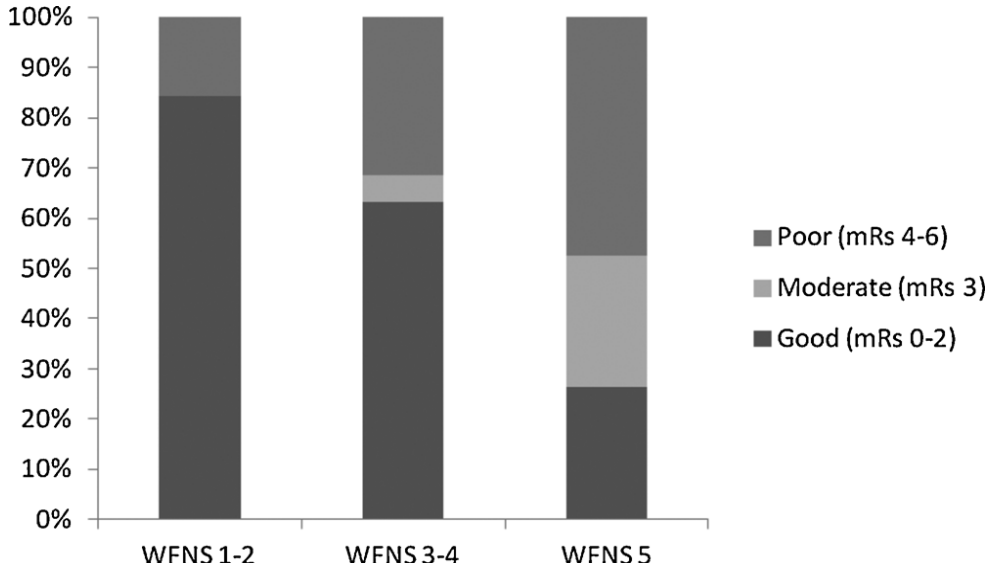

Figure 6.3 The distribution of clinical outcomes by WFNS grade.

Variable	Unfavourable outcome (%)	Favourable outcome (%)	P	Multivariate OR (95% CI)	P
Vasospasm-infarction (large)	6/23 (26.1)	1/33 (3.0)	0.0102	19.0 (1.7-216.4)	0.0179
Poor grade (WFNS 3-5)	21/24 (87.5)	17/33 (51.5)	0.0043	6.6 (1.3-33.9)	0.0233

Table 6.5 Significant predictors of unfavourable outcome (mRS 3-6).

6.6 Discussion

Two established philosophies exist for endovascular vasospasm management: prophylactic TBA or rescue therapy. We use an intermediate paradigm, identifying aVSP and commencing treatment prior to neurological deterioration or whilst the patient is minimally symptomatic. Rates of cerebral infarction and clinical outcome were assessed. Rates of infarction associated with severe aVSP range from 46-81% (see table 6.6) (Crowley *et al*, 2011; Inagawa *et al*, 2014; Weidauer *et al*, 2014). In contrast, when patients presented within 72 hours and were treated using our algorithm, the rate of proximal territory infarction was 6.7%. However, presenting after 72 hours was a significant predictor of infarction. This suggests that securing the aneurysm, nimodipine administration and therapeutic hypertension is effective in protecting against infarction. More diffuse severe aVSP involving ≥4 vessels was significantly associated with infarction on univariate analysis and tended to significance on multivariate analysis (perhaps not reaching significance as the study was underpowered). Most infarcts were small (watershed, distal branch or perforator). Proximal infarction significantly predicted poor outcome, underlining the need for prevention.

Study/Modality	Severity of aVSP	Infarct rate (%)
Cowley et al (2011)/CT	Mild (<34%)	1
	Moderate (34-66%)	9
	Severe (>66%)	46
Inagawa et al (2014)/CT	Mild-moderate (<50%)	5
	Severe (>50%)	63
Weidauer et al (2007)/MR	Mild (10-33%)	3
	Moderate (34-66%)	16
	Severe (>66%)	81
Present study/CT	Severe (>66%)	18

Table 6.6 Rates of vasospasm related infarction relative to degree of vasospasm.

TBA and IA verapamil may be effective since both have been shown to significantly increase vessel diameters in the setting of aVSP (Higashida *et al*, 1989; Firlik *et al*, 1997; Rosenwasser *et al*, 1999; Sehy *et al*, 2010). Improvements in CBF have demonstrated using perfusion imaging following TBA and IA vasodilators (Firlik *et al*, 1997; Elliott *et al*, 1998; Beck *et al*, 2006; Hanggi *et al*, 2008). Jestaedt et al (2008) also demonstrated a reduction in the infarction rate in angioplastied MCA versus non-angioplastied ACA territories (7% versus 38% respectively). The use of IA vasodilators and TBA has previously been reviewed by Pierot et al (2010d).

There is limited data available defining the natural history for those with severe aVSP. The CONSCIOUS-1 trial results suggested that of WFNS grades 1-4 patients with moderate-severe aVSP (> 33% narrowing), the rate of favourable outcome was 40% in symptomatic patients and 65% in asymptomatic patients, equating to 54.1% overall (Vergouwen *et al*, 2011a). More specifically, 43% of those with severe aVSP had a favourable outcome (mRS 0-2) [R.L. Macdonald 2014, unpublished data]. Functional status scores remained significantly worse after adjustment for age and grade (Macdonald *et al*, 2012). Our results suggest that the majority of patients (73% of WFNS grades 1-4) with treated severe aVSP can achieve favourable outcome (mRS 0-2). Outcomes by grade compared favourably with those of a large SAH population, despite the detriment of severe aVSP (see table 6.7) (Rosen *et al*, 2004). In an analysis of prospective trial data, we have demonstrated that there is no significant difference in outcome for patients with treated severe vasospasm versus those without significant vasospasm (Mortimer *et al*, 2015c). We noted two severe angiographic complications equating to a patient-specific rate of 3.5% and a procedure-related rate of 0.6%. Although it is recognised that elevated intracranial pressure, systemic hypotension and seizures may complicate infusion of either agent (Abruzzo *et al*, 2012), this was not encountered in this series. Recognised complications of TBA include vessel dissection, perforation, occlusion and rupture, reperfusion haemorrhage, infarction and clip displacement (Rahme *et al*, 2013). Older series had documented rupture rates as high as 4-5% but with modern compliant balloons the rupture rate is probably in the order of 1% (Pierot *et al*, 2010d, Abruzzo *et al*, 2012).

Retrospective analyses at hospital and nationwide levels have suggested that institutions that offer endovascular treatment for vasospasm may have lower rates of unfavourable outcome (Khatri *et al*, 2011a; Khatri *et al*, 2011b). However, the decision to treat, timing and number of treatments is crucial and this study differs from others (Jun *et al*, 2010; Chalouhi *et al*, 2014; Hayashi *et al*, 2014) in the approach. DSA was used to screen. It is often stated that DSA is the gold standard tool for vasospasm evaluation and can be used to institute treatment but is invasive with recognised complication rate; repeated procedures carry the risk of significant radiation exposure. Others have developed local expertise with TCD and CT perfusion and each may be valid to guide a similar algorithm. Both are non-invasive tools; CT perfusion may play a more prominent role in the future (Lefournier *et al*, 2010). TCD is operator dependant and limited in its ability to assess the ACA, posterior circulation and distal vasospasm.

WFNS grade	**Favourable outcome**	
	Rosen et al (2004): all patients with SAH (GOS 4-5)	Present study: patients with treated severe aVSP (mRS 0-2)
1-2	82.1%	84.2%
3-4	48.1%	63.1%
5	33.0%	26.3%

.

Table 6.7 Comparison of outcomes by grade to those seen in the Tirilizad trials (Rosen *et al*, 2004)

It is our current policy to base the decision to treat principally on radiographic features of severe aVSP prior to significant deterioration. We employ daily treatments (mean 5 per patient for the anterior circulation). We suspect that, although the duration of action of vasodilators is temporary, in concert with induced hypertension, this combats the sustained ischaemia of persisting vasospasm. Although controversial, the approach of treating the radio-graphic appearances is used by others (Bulsara *et al*, 2015). Whilst it is commonly quoted that approximately half of patients with aVSP become symptomatic, severe aVSP is associated with a higher incidence of symptoms (Dankbaar *et al*, 2009; Inagawa *et*

al, 2014), and patients without acute deterioration but severe aVSP may still develop infarction (Shimoda *et al*, 2001; Schmidt *et al*, 2008), which is our justification for managing severe aVSP, an independent predictor of poor outcome (Vergouwen *et al*, 2011a). This approach differs from prophylactic TBA or rescue treatment.

Prophylactic TBA was investigated in a multicentre randomised trial (Zwienenberg-Lee *et al*, 2009). Fisher grade 3 patients were randomised to receiving prophylactic TBA before the typical vasospasm window, or maximal medical therapy. Clinical outcomes were no different between the TBA-treated patients and controls. There was no difference in the rate of TCD defined vasospasm, length of ICU or hospital stay. However, the incidence of delayed ischaemic deficit, trended towards significant reduction (24% of TBA patients versus 32% of controls). A significant reduction in rescue angioplasty was demonstrated, (12% of TBA patients versus 26% of controls), perhaps reflecting a lower incidence of severe, medically refractory vasospasm. Furthermore, for good grade patients (Hunt and Hess 1 and 2), there was a 9.5% reduction in unfavourable outcome. We suggest that the treatment algorithm was suboptimal as it did not select patients with documented vasospasm for treatment thereby diluting the effect of interventional therapy. Identifying patients with significant aVSP prior to deterioration may be more suitable. It is possible that TBA has a more sustainable result when used in vessels that are vasospastic. Histological analysis of post-angioplasty vessels suggests that the mechanism for the long-lasting effects is stretching and disruption of degenerative muscle and proliferative non-muscle components of the vasospastic vessels (Honma *et al*, 1995).

Following the more traditional rescue approach, reported rates of clinical improvement vary widely between studies for both TBA and IA vasodilators: 30% to 80% for TBA and 0 to 66% for IA verapamil (Higashida *et al*, 1989; Coyne *et al*, 1994; Firlik *et al*, 1997; Bejjani *et al*, 1998; Feng *et al*, 2002; Keuskamp *et al*, 2008; Stuart *et al*, 2011). In the largest study comprising 645 patients undergoing TBA and/or IA vasodilators, 64.7% exhibited neurological improvement (Hayashi *et al*, 2014). The differences in rates of improvement likely stem from the contribution of the acute injury to the patient's status and the timing of treatment relative to infarction: a number of series have failed to demonstrate improvements in poor grade patients (Higashida *et al*, 1989; Coyne *et al*, 1994; Stuart *et al*, 2011), suggesting

that the acute injury may mask overt clinical benefit in some. However, since infarct size is inversely proportional to outcome (Attyé *et al*, 2012), minimising infarct development/growth may be a reasonable end-point, potentially allowing favourable outcome after rehabilitation.

The impact of timing is highlighted by a study showing that TBA within 2 hours of symptom onset was associated with 70% clinical improvement compared to only 40% when performed later (Rosenwasser *et al*, 1999). In the JR-NET2 audit (Hayashi *et al*, 2014), early treatment was associated with neurological improvement on multivariate analysis. Polin *et al* (2000) showed no improvement for TBA-treated patients but more than half underwent procedures after 6 hours. Interestingly, 22/29 patients who had follow-up imaging available had large hemispheric infarcts, suggesting that delayed treatment in symptomatic patients is futile. Detection of neurological worsening, particularly in the presence of sedation or for non-eloquent areas of ischaemia is a challenge and these patients may be at risk of silent infarction if a rescue approach is employed. This was a single-arm retrospective analysis of a small sample with heterogeneity in the distribution of vasospasm and the treatment employed. There was no control group and only surrogate comparisons with the literature could be made. Assessment of infarction was made via analysis of CT, which is less sensitive than MRI. Our outcome observations may have benefited from late clinical evaluation (mean 16 months) and after a period of rehabilitation; this needs to be acknowledged when performing inter-study comparisons. We were unable to extract the relative benefit of endovascular therapy over medical therapy including hypertension; the benefit of this approach remains unknown but it was associated with relatively low morbidity and is clinically feasible, so further evaluation with comparison to a control population in a prospective study is warranted.

6.7 Conclusion

This study suggests that an intensive endovascular approach of TBA and multiple IA verapamil infusions can result in low rates of vasospasm-associated infarction and encouraging rates of favourable outcome when compared to literature benchmarks if treatment is instituted early when the patient is minimally symptomatic. Delayed presentation, however, predicts infarction and large infarct and poor initial grade significantly influence functional outcome. Further investigation is needed to fully evaluate the efficacy of this approach.

6.8 Acknowledgements

Professor R.L. Macdonald (university of Toronto) and Actelion (San Francisco, California, USA) for providing clinical outcome data for patients with severe angiographic vasospasm in the CONSCIOUS-1 trial.

CHAPTER 7

THE DETRIMENTAL CLINICAL IMPACT OF SEVERE ANGIOGRAPHIC VASOSPASM MAY BE DIMINISHED BY MAXIMAL MEDICAL THERAPY AND INTENSIVE ENDOVASCULAR TREATMENT

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7.1 Abstract

7.1.1 Background

Severe angiographic vasospasm (aVSP) is a risk factor for poor functional outcome following subarachnoid haemorrhage. We investigated the impact of angiographic surveillance and intensive endovascular treatment using transluminal balloon angioplasty (TBA) and/or verapamil infusion for severe aVSP through comparison of clinical outcomes in patients of similar presenting grade but with no/mild vasospasm.

7.1.2 Methods

This was an analysis of prospectively acquired clinical trial data. World Federation of Neurosurgical Societies (WFNS) grade 1–2 patients presenting within 72 hours were included. Angiographic screening for vasospasm was undertaken at days 5–7 or in response to clinical deterioration. Severe aVSP was defined as >50% luminal narrowing on digital subtraction angiography. Treatment was instituted on the basis of radiographic findings and/or clinical deterioration. Discharge destination and favourable clinical outcomes (discharge Glasgow Outcome Score (GOS) 4–5, 90 day modified Rankin Scale (mRS) score 0–2, and GOS 4–5) for patients with severe aVSP were compared with those without significant vasospasm. Statistical analysis was undertaken using Fisher's exact test.

7.1.3 Results

Sixty-three WFNS grade 1–2 patients with minimal vasospasm were compared with 17 WFNS grade 1–2 patients with severe aVSP treated with induced hypertension and endovascular therapy. Results were available in 62 and 16 patients, respectively. Rates of favourable outcome did not differ significantly between the two groups. For patients with treated severe vasospasm, 90 day mRS 0–2 was seen in 15/17 (88.2%) and GOS 4–5 was achieved in 16/17 (94.1%).

7.1.4 Conclusion

An intensive endovascular approach of TBA and/or intra-arterial verapamil in combination with induced hypertension for severe aVSP may result in comparable clinical outcomes to those without vasospasm.

7.2 Introduction

Angiographic vasospasm (aVSP) is an independent predictor of poor outcome following subarachnoid haemorrhage (SAH) (Vergouwen *et al*, 2011a). There is a strong correlation between the severity of aVSP and the incidence of cerebral infarction (Crowley *et al*, 2011), which itself is strongly associated with poor outcome following SAH (Furgusson & Macdonald, 2007; Vergouwen *et al*, 2011b). The majority of delayed infarcts are related to severe aVSP (Weidauer *et al*, 2007; Crowley *et al*, 2011; Brown *et al*, 2013; Inagawa *et al*, 2014) which results in the most severe perfusion deficits (Weidauer *et al*, 2007; Vatter *et al*, 2011; Dakbaar *et al*, 2009; Dhar *et al*; 2012). The goal of endovascular therapy, using either transluminal balloon angioplasty (TBA) or intra-arterial vasodilators, is to improve cerebral blood flow and therefore to reduce the risk of infarction. Endovascular methods are most commonly employed as 'rescue' procedures. This has been shown to be effective in case series but neurological improvement is maximal if treatment is performed early in this setting (Rosenwasser *et al*, 1999; Hayashi *et al*, 2014). Delayed endovascular treatment following development of symptoms is probably of limited clinical benefit (Polin *et al*, 2000). The use of prophylactic TBA undertaken prior to development of vasospasm has also been investigated in a multicenter randomised trial (Zwienenberg-Lee *et al*, 2009). Although there were significant reductions in the rate of patients requiring rescue therapy in the treatment arm and possible outcome benefits in the good grade patients, overall clinical outcome was not significantly different in those treated with prophylactic TBA.

An alternative approach is to screen for vasospasm at or just before the time when the majority of patients develop symptoms (Suarez *et al*, 2002; Ionita *et al*, 2010). The goal of this practice is to identify those patients with significant angiographic vasospasm who may benefit from treatment prior to development of symptoms or who are at risk of silent infarction as they are clinically too difficult to accurately assess (Schmidt *et al*, 2008). We routinely undertake a program of angiographic surveillance at days 5-7 post ictus, at or just before the time point that most patients become symptomatic (Suarez *et al*, 2002; Ionita *et al*, 2010), with subsequent endovascular treatment and multiple procedures where necessary based not only on symptomology but also on radiographic features.

We analysed prospectively collected trial data obtained at our institution to assess the clinical efficacy of this approach through comparison of outcomes of patients with treated severe aVSP with those of similar presenting grade who did not develop significant aVSP.

7. 3 Methods

7.3.1 Study design and inclusion/exclusion criteria

This was an analysis of prospectively acquired clinical trial data obtained primarily for the assessment of clinical outcomes and aVSP severity and incidence in patients treated with magnesium following aneurysmal SAH (Bradford *et al*, 2013). The primary aim of this study was to compare clinical outcomes for patients with either no aVSP or mild aVSP (<25% arterial narrowing) treated with medical therapy only, with those patients with severe aVSP (>50% arterial narrowing) treated using an intensive combined medical and endovascular approach involving induced hypertension, TBA, and/or intra-arterial infusion of verapamil.

Patients admitted to a tertiary hospital (Royal North Shore Hospital) between April 1, 2005 and February 1, 2010, presenting within 72 hours of SAH confirmed by CT, were included. The study was confined to those presenting with World Federation of Neurosurgical Societies (WFNS) grades 1–2 to minimize the confounding impact of poor grade/acute injury on outcomes. Exclusion criteria included age <18 years, serum creatinine >200 mmol/L, if death was thought imminent within 72 h, if the patient had myasthenia gravis or was pregnant, or if aVSP was present prior to inclusion in the study. The study was approved by the Northern Sydney Ethics Committee and written informed consent was obtained from each patient or legal surrogate.

7.3.2 Patient management

All patients were managed on the neurointensive care unit with routine insertion of arterial and central lines. After admission, digital subtraction angiography or CT angiography was performed, and the aneurysm responsible for the bleeding was occluded by operative or endovascular means within 48 h. Following clipping or coiling of the aneurysm, systolic blood pressure was maintained between 120 and 150 mm Hg. A nimodipine infusion of 20 mg/kg/h was commenced on arrival in the ICU. All patients received nimodipine for 21 days, with at least 10 days of intravenous administration. For body temperature, the aim was to maintain the temperature below 37.5°C. Oxygen saturation was monitored continuously by pulse oximetry and maintained at >95%. Angiographic screening

for vasospasm was performed routinely at days 5-7. In the event that vasospasm was suspected at an earlier time point, hydrocephalus was excluded with CT and angiographic investigation was brought forward. If felt to be clinically deteriorating secondary to aVSP, patients were managed with adequate hydration, systolic blood pressure maintained between 140–160 mm Hg, and continued nimodipine infusion.

7.3.3 Endovascular technique

Digital subtraction angiography was performed via a femoral approach using a 5 F system. Vasospasm was defined as none, mild (<25%), moderate (25–50%), and severe (>50%) by two neuroradiologists by consensus. If significant aVSP was identified, this was treated using either chemical or balloon angioplasty, and a repeat angiogram was undertaken the following day. In cases of severe refractory vasospasm, multiple treatments were undertaken. Angiography was repeated daily until either aVSP was no longer significant or aVSP proved to be unsatisfactorily treated with this regimen. In the event that multiple treatments were required, the groin sheath was sutured in situ, replaced at each sitting, and femoral angiography was performed at daily intervals to screen for external iliac artery dissection. The side of the sheath was routinely changed after 4 days if further treatments were required.

The decision to treat and mode of treatment were based on the degree and site of arterial narrowing in conjunction with the clinical state of the patient, with treatment generally reserved for moderate–severe aVSP. Severe proximal aVSP involving the vertebral artery (VA), basilar artery, internal carotid artery (ICA), M1 middle cerebral artery, or A1 anterior cerebral artery was treated with TBA where possible. M2 middle cerebral artery and distal vasospasm was treated with intra-arterial vasodilators. Verapamil was delivered via a 5 F catheter positioned in the proximal ICA or VA at a rate of 1 mg/min, typically 10–15 mg total to a maximum dose of 25 mg per territory. Papaverine (used as a second line agent) was delivered via a microcatheter positioned proximally within the target vessel. Arterial monitoring was used during the procedure to augment blood pressure control through slowing of the vasodilator administration and/or titration of inotropic support.

Patients undergoing TBA were systemically anticoagulated using intravenous heparin (typically 5000 U total) with a goal of doubling baseline activated clotting time. A guiding catheter was placed on heparinised saline drip in either the cervical

ICA or cervical VA. Next, a compliant balloon microcatheter (HyperGlide, ev3, Irvine, California) was navigated over a compatible 0.010 inch microwire to the most distal aspect of the spastic vessel segment to be treated (i.e. the smallest spastic arterial branch farthest from the femoral access site). A single, gentle, brief (<30 s) inflation with iodinated contrast material were performed to achieve at least 70% of the expected baseline vascular luminal diameter. If the response was inadequate, further balloon inflations were performed.

7.3.4 Data collected and analysis

Baseline variables were collected, including demographic data, history of smoking, hypertension, use of statins, use of trial magnesium, previous SAH or stroke, and Acute Physiology and Chronic Health Evaluation (APACHE II) score. WFNS grade was assessed at admission. Aneurysm site and presence of hydrocephalus were recorded through assessment of angiographic and CT imaging, respectively. Clinical outcomes, including discharge Glasgow Outcome Score (GOS), discharge destination, and 90 day GOS and modified Rankin Scale (mRS) score were obtained, acquired by independent assessors. Secondary outcome measures, including length of ITU stay and length of hospital stay, were also assessed.

Statistical analysis was performed using Medcalc statistical software. Non-parametric data (sex, WFNS grade, history of smoking, hypertension, SAH, cardiovascular event, magnesium or statin use, hydrocephalus, aneurysm location, and aneurysm securing modality) were compared using Fisher's exact test, and parametric data (age, APACHE II score, ITU days, ventilated days, hospital days, and noradrenaline dose) were compared using analysis of variance. Statistical significance was defined as $p<0.05$.

7.4 Results

Analysis of the trial database identified 80 patients; 63 patients with either no aVSP or mild aVSP who were treated with medical therapy only and 17 patients with severe aVSP who were treated with medical therapy and endovascular treatment. Fifteen patients with moderate aVSP were also identified but these patients were variably treated with endovascular therapy and were therefore not included in the analysis. Two patients with severe vasospasm who were not treated using endovascular therapy were not included in the analysis. Baseline variables are displayed in table 7.1. There was no significant difference in baseline characteristics between the two groups, including sex, age, history of smoking, hypertension, previous stroke or SAH, magnesium or statin use, APACHE II score, or incidence of hydrocephalus (table 7.1). Patients in the severe aVSP group tended to be younger, although this did not reach statistical significance. There were significantly more WFNS grade 2 patients in the severe aVSP group. No significant difference in the distribution of responsible aneurysm or aneurysm securing treatment method (endovascular vs surgical clipping) was demonstrated.

	None/Mild aVSP (n=63)	Treated severe aVSP (n=17)	P
Females	40 (63.5)	14 (77.7)	0.2422
Age (years) (mean +/- 95% CI)	56.5 +/-3.5	48.9 +/-6.2	0.0818
WFNS grade 2	17 (30.0)	11 (64.7)	0.0083
Smoking history	18 (28.6)	5 (29.4)	1.0000
Hypertension	20 (31.7)	5 (29.4)	1.0000
Previous CVE	3 (4.8)	0	1.0000
Previous SAH	2 (3.2)	0	1.0000
Prior Statin use	15 (23.8)	4 (23.5)	1.0000
APACHE II score (mean and 95% CI)	11.4 +/-1.4	11.1 +/- 2.7	0.8239
Ruptured aneurysm location			
Posterior	9 (14.3)	2 (11.8)	1.0000
Anterior	42 (66.7)	14 (82.4)	1.0000
Unknown	12 (19.0)	1 (5.9)	0.2781
Hydrocephalus at 24 hours	3 (4.8)	3 (17.6)	0.1067
Coiled	30 (47.6)	7 (41.2)	0.7855
Treated with magnesium	33 (52.4)	7 (41.2)	0.5856

Table 7.1 Baseline characteristics. APACHE, Acute Physiology and Chronic Health Evaluation; aVSP, angiographic vasospasm; CVE, cardiovascular event; SAH, subarachnoid haemorrhage; WFNS, World Federation of Neurosurgical Societies.

Patients with severe aVSP had a significantly greater ITU and hospital stay and spent significantly more days ventilated. They had a significantly increased total noradrenaline dose (table 7.2). The mean first day of vasospasm treatment following haemorrhage was 6.6±1.5. For those with severe aVSP, mean duration of aVSP was 6.5±2.5 days. Of those with severe aVSP, 8/17 patients (47%) underwent TBA with a total of 15 procedures. Seventeen patients underwent verapamil chemical angioplasty with a total of 67 procedures. The mean total dose of verapamil that any one patient received at each procedure was 20.3 ±2.3 mg (range 5–40 mg). Four patients were additionally treated with intra-arterial papaverine (mean dose 90 mg; range 60–120 mg) with a total of eight infusions. The distribution of severe

vasospasm and treatment employed for each patient in the study population are shown in table 7.3.

	None/Mild aVSP (Mean +/- 95% CI)	Treated severe aVSP (Mean +/-95% CI)	P
Noradrenaline dose (mg)	61.9+/-29.7	118.1+/-98.4	0.0002
Ventilated days	1.8+/-2.9	5.4+/-4.0	0.0122
ITU days	12.3 +/-2.4	20.2 +/-2.7	<0.0001
Hospital days	21.5+/-3.4	27.1+/-3.6	0.0392

Table 7.2 Differences in care between the two populations studied. aVSP, angiographic vasospasm.

Clinical outcome data are shown in tables 7.4 and 7.5 and figures 7.1 and 7.2. Clinical outcomes were available for 62 patients with none or mild aVSP and for 16 patients with treated severe vasospasm. No significant difference in discharge GOS, proportion of patients discharged home, mortality, 90 day GOS, or 90 day mRS was demonstrated between the two groups if favourable outcome was dichotomised as GOS 4–5 or mRS 0–2. Patients with no/mild aVSP achieved a 90 day GOS 4–5 and mRS 0–2 of 83.9% and 82.2%, respectively. Of those with aggressively treated severe vasospasm, 90 day GOS and mRS were 94.1% and 88.2%, respectively. If favourable outcome was dichotomised as mRS 0-1, there tended to be more favourable outcomes in the no/mild vasospasm group but this did not reach significance (p=0.2693). However, there were significantly more WFNS grade 2 patients in the severe aVSP group (10/17, 64.7% v 17/63, 30%) confounding this. When outcomes were assessed by grade, this difference was less apparent (see table 7.4.6). For example, for WFNS grade 2 patients without significant spasm, favourable outcome was 7/17 (41.2%) mRS 0-1 and 13/17 (76.5%) mRS 0-2. Outcomes for WFNS grade 2 patients with treated severe aVSP were 4/11 (36.4%) mRS 0–1 and 10/11 (90.9%) mRS 0-2. Furthermore, if favourable outcome was dichotomised by GOS 5, no significant difference was demonstrated.

Patient	Location of severe vasospasm	Treatment	Number of Treatments
1	Bilateral ICA and MCA	TBA	2
2	Left MCA	Verapamil Papaverine	2
3	Left MCA	Verapamil	1
4	Left ICA and MCA Right ACA	TBA Verapamil Papaverine	8
5	Left ICA and MCA	TBA Verapamil Papaverine	8
6	Left ICA, MCA and ACA, Right MCA	TBA Verapamil	6
7	Bilateral ICA and MCA	Verapamil	2
8	Left ICA and MCA and right ACA	TBA Verapamil	3
9	BA	Verapamil	1
10	Right MCA and ACA	TBA Verapamil	3
11	Bilateral ICA, MCA and ACA	TBA Verapamil Papaverine	7
12	Bilateral ACA	Verapamil	4
13	Bilateral MCA and left ACA	TBA Verapamil	7
14	Right MCA and bilateral ACA	Verapamil	1
15	Bilateral MCA, PCA, SCA	Verapamil	5
16	Right ICA and MCA	Verapamil	5
17	Bilateral ACA	Verapamil	2

Table 7.3 Distribution of vasospasm and treatments used. ACA, anterior cerebral artery; BA, basilar artery; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; SCA, superior cerebellar artery; TBA, transluminal balloon angioplasty.

Outcome measure	None/Mild aVSP (n=63 (%))	Treated severe aVSP (n=17 (%))	P
Discharge GOS 4-5	35 (55.5)	8 (47.1)	0.5910
Discharge to home	41 (65.1)	12 (70.5)	0.7777
90 day GOS 4-5	52 (82.5)	16 (94.1)	0.4444
90 day GOS 5	30 (47.6)	7 (41.2)	0.7855
90 day mRS 0-2	51 (81.0)	15 (88.2)	0.7224
90 day mRS 0-1	40 (63.5)	8 (47.1)	0.2693
Mortality	2 (3.2)	0	1.0000
Missing data	1	1	-

Table 7.4 Outcomes for each of the two populations studied. aVSP, angiographic vasospasm; GOS, Glasgow Outcome Score.

90 day mRS n (%)			**90 day GOS n (%)**		
	No/Mild aVSP	Severe aVSP		No/Mild aVSP	Severe aVSP
0	13 (20.6)	2 (11.8)	5	30 (47.6)	7 (41.2)
1	27 (42.8)	6 (35.3)	4	22 (34.9)	9 (52.9)
2	11 (17.5)	7 (41.7)	3	8 (12.7)	0
3	6 (9.5)	0	2	0	0
4	3 (4.8)	1 (5.9)	1	2 (3.2)	0
5	0	0			
6	2 (3.2)	0			
Missing data	1 (1.6)	1 (5.9)	Missing data	1 (1.6)	1 (5.9)

Table 7.5 Clinical outcomes at 90 days by modified Rankin Scale and Glasgow Outcome Scale. aVSP, angiographic vasospasm; GOS, Glasgow Outcome Score; mRS, modified Rankin Scale.

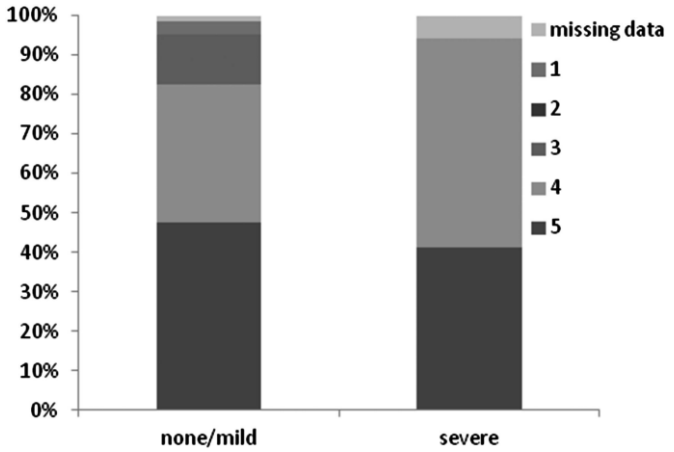

Figure 7.1 Ninety day Glasgow Outcome Score for patients with minimal or severe vasospasm.

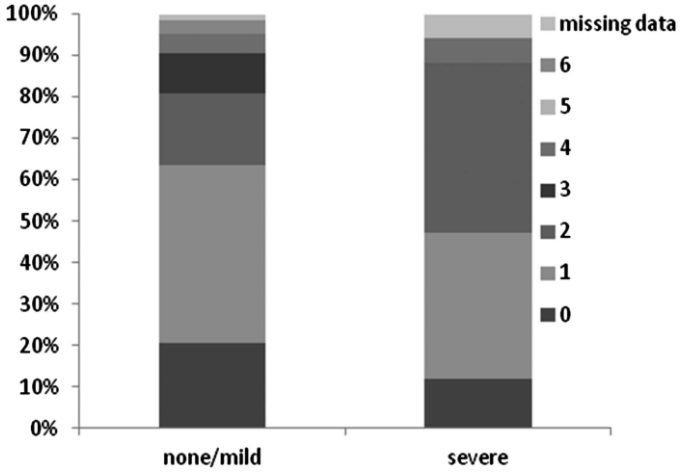

Figure 7.2 Ninety day modified Rankin Scale scores for patients with minimal or severe vasospasm.

WFNS grade	No/mild aVSP n, (%)		Severe aVSP n, (%)	
	mRS 0-1	mRS 0-2	mRS 0-1	mRS 0-2
1	33/46 (71.7)	41/46 (89.1)	4/6 (66.7)	5/6 (83.3)
2	7/17 (41.2)	13/17 (76.5)	4/11 (36.4)	10/11 (90/9)

Table 7.6 Favourable outcomes by World Federation of Neurosurgical Societies grade. aVSP, angiographic vasospasm; mRS, modified Rankin Scale; WFNS, World Federation of Neurosurgical Societies.

Complications included one thromboembolic event treated using intravenous abciximab with prompt angiographic resolution. This equated to a procedural risk of 1.5% and a patient specific risk of 5.9% but there was no permanent morbidity or mortality related to the treatment.

7.5 Discussion

We have demonstrated that for good grade SAH patients (WFNS 1–2) who subsequently develop the complication of severe cerebral vasospasm and are treated aggressively with a combination of induced hypertension and intensive endovascular management, comparable clinical outcomes can be obtained with patients who do not develop this complication. No significant difference in discharge GOS, the proportion of patients discharged home, 90 day mRS, or 90 day GOS was demonstrated for those with severe vasospasm undergoing treatment compared with those without vasospasm, whose outcomes were in line with those published in previous trials (Rosen *et al*, 2004). Of patients with severe vasospasm, 88% achieved mRS 0–2. Similarly, in a retrospective analysis of the period spanning 2009 and 2013 demonstrated that 84% of WFNS grade 1-2 patients with severe vasospasm achieved mRS 0-2 (Mortimer *et al*, 2015b). In an earlier study spanning 1992–1998 (Morgan *et al*, 2000), in which a similar protocol based on papaverine angioplasty was used, favourable clinical outcomes for good grade patients who developed significant vasospasm were seen in 93%. There are two possible conclusions that can be drawn from these data. Firstly, it could be argued that angiographic vasospasm has no impact on patient outcome and that these favourable outcomes are incidental. Secondly, it could be argued that intensive efforts to improve cerebral blood flow have a beneficial impact on clinical outcomes in patients afflicted by severe vasospasm.

Critics of this approach to treating angiographic vasospasm may cite uncertainty regarding the role of aVSP in delayed cerebral ischemia (Pluta *et al*, 2009; Macdonald, 2013; Hou & Zhang, 2013). A number of clinical trials of pharmaceutical agents have demonstrated improvement in the rate of moderate–severe vasospasm but not in the rate of favourable outcome (Macdonald *et al*, 2008; Macdonald *et al*, 2011). Likewise, while nimodipine remains the only pharmacological treatment to improve outcomes, this benefit is achieved without angiographic evidence of cerebral vasodilation (Petruk *et al*, 1988; Feigin *et al*, 1998). As a result of this, there has recently been much emphasis on the role of alternative mechanisms of delayed ischemia, including microthrombosis and spreading depolarization with cortical ischemia, that may act separately or in combination with aVSP. However, analysis of the CONSCIOUS-1 trial has

demonstrated that moderate–severe angiographic vasospasm is an independent predictor of poor functional outcome (OR 2.62 (1.58–4.36), p<0.0001) (Vergouwen *et al*, 2011a). In that study, 46% of patients with moderate to severe aVSP (>33% arterial narrowing) had a poor outcome at 3 months. The International Co-operative Study on the Timing of Aneurysm Surgery found that vasospasm was more often the cause of death or disability than any other factor, including the direct effect of the initial bleed (Kassell *et al*, 1990).

Intuitively, the impact of vasospasm on outcome stems from an increased risk of cerebral infarction, which itself is strongly associated with poor outcome (Furgusson & Macdonald, 2007; Vergouwen *et al*, 2011b). There is a strong correlation between the severity of aVSP and the incidence of cerebral infarction (Crowley *et al*, 2011). The more severe the vasospasm, the more severe the perfusion deficit (Weidauer *et al*, 2007; Dankbaar *et al*, 2009; Vatter *et al*, 2011; Dhar *et al*, 2012), and we believe strongly that the haemodynamic effects of vasospasm are appropriate to target to reduce the risk of associate infarction. While it is commonly quoted that approximately half of patients with vasospasm will be 'symptomatic', the severity of vasospasm correlates with symptomology, and even if asymptomatic, angiographic vasospasm can result in infarction (Vergouwen *et al*, 2011a; Inagawa *et al*, 2014). Although we were unable to analyse the rate of aVSP associated infarction in this study, we have analysed this in a separate cohort of WFNS grade 1-5 patients (Mortimer *et al*, 2015b), and for those presenting within 72 h of ictus, 6.7% suffered proximal vessel infarction if treated using the same regimen used in this study. If smaller perforator infarcts and watershed infarcts were included, the overall rate of infarction was 17.8%, but if this is compared with other reported rates of infarction in the region of 46–81% for severe vasospasm (Weidauer *et al*, 2007; Crowley *et al*, 2011; Inagawa *et al*, 2014), the results are promising.

The Poiseuille equation states that flow is directly proportional to the pressure gradient and radius to the fourth power and inversely proportional to the fluid viscosity and vessel length. This formula forms the basis for hypertensive treatment in the intensive care unit but also for attempts to improve flow through an increase in vessel diameter. While flow will increase with a change in pressure, it will increase markedly with a change in vessel diameter. Both TBA (Higashida *et al*, 1989; Firlik *et al*, 1997; Rosenwasser *et al*, 1999) and (more modestly) verapamil (Sehy *et al*, 2010) have been shown to significantly increase vessel diameter in the

setting of aVSP (albeit with a lag of approximately 30 min with the latter). TBA and intra-arterial calcium channel antagonists result in significant improvements in cerebral blood flow (Firlik *et al*, 1997; Elliot *et al*, 1998; Beck *et al*, 2006; Hänggi *et al*, 2008). While TBA has a relatively durable effect (Honma *et al*, 1995; Abruzzo *et al*, 2012), the duration of action of verapamil on the cerebral circulation remains unknown and further investigation is required to elucidate this. We have evolved a system of performing daily vasodilator infusions where necessary and in a number of patients, multiple procedures, as previously discussed (Rosen *et al*, 2004). Others have experimented with indwelling microcatheters (Albanese *et al*, 2010) although we are reluctant to employ this approach because of the potential risk of thromboembolic complication.

In this study, patients with severe angiographic vasospasm had a significantly increased ITU stay and ventilated days. This can be explained partly by the impact of vasospasm on clinical status, partly by local protocols which centre on hypertensive therapy in patients with vasospasm, and partly on the need for inotropic support in patients treated with high dose verapamil. Indeed, the total noradrenaline dose was significantly higher for those with severe vasospasm. We were unable to elucidate the relative benefit of endovascular therapy over hypertensive therapy but these finding suggest that a combined approach of endovascular therapy and induced hypertension may have a role in the prevention of delayed cerebral infarction following the development of severe aVSP and further lends support for design of a trial to test this hypothesis and to elucidate the relative impact of each facet of treatment.

The approach used in the study was different to that often previously published which centres on either prophylactic TBA prior to development of significant vasospasm or rescue therapy in patients who deteriorate despite maximal medical therapy or who cannot tolerate medical therapy. Our aim has been to identify significant vasospasm prior to neurological deterioration.

This is controversial but is employed by other centres surveyed in a recent US national questionnaire (Bulsara *et al*, 2015). The use of prophylactic TBA has been investigated in a multicentre randomised trial (Zwienenberg-Lee *et al*, 2009). Fisher grade 3 patients were randomised to receiving either prophylactic TBA at a mean 51 hours (range 19–94 hours) post SAH, prior to the typical vasospasm

window, or maximal medical therapy. Balloons were inflated to the vessel diameter until apposition of the balloon to the vessel wall was identified fluoroscopically.

The primary outcome measure (dichotomised GOS score at 3 months after haemorrhage) was no different between patients treated with prophylactic TBA and controls. There was no difference in the secondary outcome measures of vasospasm (defined by transcranial Doppler (TCD), length of stay in the ICU, or total length of hospitalization). However, the secondary outcome measure, incidence of delayed ischemic deficit, trended toward significance, with 24% of prophylactic TBA patients developing a deficit versus 32% of controls. A significant difference was identified in the need for rescue angioplasty, with only 12% of prophylactic TBA patients requiring this procedure compared with 26% of controls, perhaps reflecting a lower incidence of severe medically refractory vasospasm in the prophylactic TBA group. Furthermore, for good grade patients (Hunt and Hess grades 1 and 2), there was a 9.5% reduction in unfavourable outcome.

We suggest that the treatment algorithm of this trial was suboptimal as it did not select patients with documented cerebral vasospasm for treatment, thereby diluting the treatment effect of prophylactic TBA. Selection based purely on Fisher grade is likely to result in a proportion of patients undergoing unnecessary treatment. Furthermore, 56% of the prophylactic TBA group developed vasospasm by TCD criteria, which suggests that TBA may not be as effective in non-spastic vessels (TBA seems to be effective through stretching and disruption of both the degenerative muscle and the proliferative non-muscle components, mainly in the media of the vasospastic vessels (Honma *et al*, 1995)) and there remains the problem of more distal vasospasm. We suggest that identifying patients with significant angiographic vasospasm and selecting these patients for treatment prior to significant deterioration may be a more suitable approach.

The approach of reserving endovascular treatment for use as a rescue therapy alone following clinical deterioration suffers from two major limitations. Firstly, the therapeutic window is narrow (Rosenwasser *et al*, 1999; Hayashi *et al*, 2014) (this probably accounts for a limited number of patients showing neurological improvement with vasodilator therapy or TBA) (Coyne *et al*, 1994; Bejjani *et al*, 1998; Feng *et al*, 2002; Keuskamp *et al*; 2008; Stuart *et al*, 2011; Macdonald, 2013; Hou & Zhang, 2013) and secondly, patients may suffer infarction in the absence of acute deterioration (especially if poor grade and difficult to assess) which itself is

associated with a poor eventual outcome (Ionita *et al*, 2010). A process of screening for and treating severe aVSP may allow more timely intervention prior to more severe ischemia but the risks of this approach need to be justified, and critical to this is the safety of the screening method and chemical and balloon angioplasty. In this study, there was one transient thromboembolic complication. This equates to a procedural risk of 1.5% but patient risk of 5.9%, although with no permanent morbidity and mortality relating to the procedure. However, the group sizes in this study are probably too small to draw firm conclusions. The feared complications of TBA are vessel rupture and thromboembolic events. In a recent review of the literature, it has been suggested that the procedural risk of rupture for TBA with modern compliant balloons is approximately 1%, and thromboembolic complications have been reported in 4–5% (Abruzzo *et al*, 2012). For chemical angioplasty, the risks are related to the angiographic procedure and also to the agent being used. We now rely on verapamil as the first line vasodilator. In our experience, it is associated with a low rate of complications but there are reports in the literature of elevated intracranial pressure (Feng *et al*, 2002; Keuskamp *et al*, 2008). We manage these patients with inotropic support as required and titrate the rate of administration of verapamil with blood pressure to limit systemic hypotension. Papaverine use is now second line both at our institution and at other surveyed centres (Bulsara *et al*, 2015) owing to its side effect profile (Abruzzo *et al*, 2012).

The approach of investigating for vasospasm with digital subtraction angiography utilizes the gold standard imaging modality for detection of vasospasm and allows therapeutic intervention but does carry with it a small but not insignificant procedural risk. Others have developed local expertise in the use of TCD and CT angiography/perfusion. Each may be a valid method of evaluation either alone or in combination to guide a treatment algorithm of similar philosophy. Both TCD and CT angiography/perfusion are non-invasive tools. TCD is operator dependant and is limited in its ability to assess the anterior cerebral artery and posterior circulation as well as distal vasospasm. CT angiography and CT perfusion may play a more prominent role in vasospasm diagnosis in the future. CT angiography has limits in demonstration of distal vasospasm and vessels adjacent to clip or coil artefact, and CT perfusion can be limited by the amount of brain volume coverage, radiation exposure, and clip or coil artefact (Greenberg *et al*, 2010; Mir *et*

al, 2014). Accurate quantification with CT perfusion is also dependent on an intact blood– brain barrier, which may not be the case with ischemic tissue.

This was a post hoc analysis of trial data that was not specifically collected to answer the question of the impact of endovascular treatment or hypertensive therapy from available data. The study group with severe aVSP contained a small sample of only 17 patients and there was considerable difference in the size of the study group compared with the control population without spasm, comprising 63 patients. There was no control population with severe aVSP who did not undergo endovascular therapy with which to compare, and as a result we are unable to report on the additional benefit of endovascular treatment over hypertensive therapy.

7.6 Conclusion

The results of this prospectively acquired single institution study suggest that clinical outcomes for patients with severe angiographic vasospasm are similar to those without vasospasm if treated with induced hypertension and an intensive endovascular regimen of TBA and/or chemical angioplasty based on a verapamil protocol. Further trials are necessary to fully elucidate the individual impact of medical treatment and endovascular therapy on the natural history of vasospasm with patients receiving medical and timely interventional treatment versus matched controls receiving medical management alone.

CHAPTER 8

IS LONG-TERM FOLLOW-UP OF ADEQUATELY COIL-OCCLUDED RUPTURED CEREBRAL ANEURYSMS ALWAYS NECESSARY? A SINGLE-CENTRE STUDY OF RECURRENCES AFTER ENDOVASCULAR TREATMENT

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8.1 Abstract

8.1.1 Background

Aneurysm recurrence following coil occlusion is well recognised. However, there is controversy as to how long these patients should be followed up after coiling to detect reopening. We aimed to identify the rate of late reopening and the risk factors for reopening in a large single-centre cohort of ruptured aneurysms that appeared adequately occluded at 6 months. We also aimed to assess whether rates of recurrence have altered over time with improving coil and angiographic technology.

8.1.2 Methods

Patients treated between 1996 and 2010 were assessed and those with both 6-month initial and subsequent long-term follow-up with either digital subtraction angiography or magnetic resonance angiography were included. Aneurysms were stratified by features such as size, neck width, anatomical location and time of treatment: 1996–2005 (cohort 1) and 2006–2010 (cohort 2). ORs for risk of recurrence were calculated for aneurysm features and rates of recurrence in each cohort were compared using a χ^2 test.

8.1.3 Results

437 patients with 458 adequately occluded aneurysms at 6 months had mean long-term follow-up of 31 months; 57 (12.4%) were large (≥10 mm) and 104 (22.7%) were wide-necked (>4 mm). Nine aneurysms (2%) showed significant late anatomical deterioration whereby retreatment was considered or undertaken. The risk was greater for large aneurysms (≥10 mm) (OR 15.61, 95% CI 3.79 to 64.33, p=0.0001) or wide-necked aneurysms (>4 mm) (OR 12.70, 95% CI 2.60 to 62.13, p=0.0017). The frequency of significant late anatomical deterioration and retreatment was also less common in those treated in cohort 2 ($p<0.05$). No completely occluded aneurysm at 6 months demonstrated significant late recurrence.

8.1.4 Conclusion

Most aneurysms adequately occluded at 6 months did not show evidence of late recurrence. Large and wide-neck aneurysms are, however, at greater risk of later recurrence.

8.2 Introduction

Endovascular coiling is the preferred treatment for ruptured cerebral aneurysms, but systematic review of the literature suggests that approximately 20% of aneurysms will show reopening or recurrence following treatment (Ferns *et al,* 2009). Intuitively, the principal indication for following aneurysms with imaging after coil occlusion is to identify aneurysm recurrence (either through coil compaction, migration into thrombus or aneurysm regrowth) and to pre-empt rehaemorrhage through retreatment. A number of studies have demonstrated an inverse relationship between the degree of occlusion and the risk of rerupture (Johnston *et al,* 2008; Sherif *et al,* 2012). However, there is little consensus in the literature as to the most appropriate timing of follow-up or length of follow-up, and long-term follow-up is not without detriment; there is evidence that those patients are more prone to anxiety and depression (Ferns *et al,* 2011a). Follow-up also brings with it a financial cost either to health systems or patients.

Although previous series with variable initial follow-up time have suggested that long-term follow-up is mandatory to detect late aneurysm reopening (Cognard, *et al,* 1999; Piotin *et al,* 2007; Campi *et al*; 2007), recent evidence provided by a study using a fixed initial follow-up date of 6-months post-treatment in adequately occluded aneurysms suggests differently (Ferns *et al,* 2011b). In 400 patients with 440 aneurysms, the rate of aneurysm reopening was very low (2.6%) on long-term follow-up (mean 6 years) and consequently the risk of delayed rebleeding in adequately treated aneurysms is reported to be extremely low (Gallas *et al,* 2005; Johnston *et al,* 2008; Molyneux *et al,* 2009). An additional question is whether some aneurysms (e.g. large, wide-necked or those at specific anatomical locations) are more prone to recurrence than others, even when adequately occluded at 6 months, and it may be that longer follow-up should be focused on these subgroups.

At our centre we follow aneurysms routinely at 6 months and then at 30 months, but continue for longer until stability is achieved or a remnant is retreated. We aimed to assess the rate of late reopening in adequately occluded aneurysms (defined as those either completely occluded or with a small neck remnant at 6-months' follow-up) in patients treated between 1996 and 2010 to assess whether late follow-up was necessary in all of these patients. We also aimed to assess whether

reopening or retreatment rates for patients with adequately occluded aneurysms at initial follow-up have changed with evolving coil and angiographic technology.

8.3 Methods

Patient details were retrieved from two institutional databases containing all ruptured aneurysms coiled at our institution between 1996 and 2005 (cohort 1) and all those coiled between 2006 and 2010 (cohort 2). Only patients with both short- and long-term imaging follow-up were included in the primary study population. These patients were stratified into those with adequately occluded aneurysms (complete occlusion or only a small neck remnant) at 6-month angiographic follow-up and those with an aneurysmal remnant; this was determined by occlusion status as recorded on the neuroradiological reports. Subsequent long-term digital subtraction angiography (DSA) or magnetic resonance angiography (MRA) follow-up was then assessed for evidence of anatomical deterioration. Occlusion status was re-adjudicated by the study personnel through consensus between two neuroradiologists (AMM and SAR). Further retreatment was also recorded.

8.3.1 The endovascular procedure

All procedures were performed by consultant interventional neuroradiologists (SAR and MDB). The aim was to place coils sequentially into the aneurysmal sac to the point of angiographic occlusion. The vast majority of coils deployed were bare platinum (Boston Scientific (now Stryker), Kalamazoo, Michigan, USA; Micrus (now Codman Neurovascular), Raynham, Massachusetts, USA; ev3 (now Covidien), Dublin, Ireland). A minority of aneurysms in the study cohort were coiled with balloon remodelling and none with stent assistance. In only a small number of aneurysms were bioactive coils used. The coiling technique did not alter over the study period. The aneurysm responsible for haemorrhage was identified by blood distribution on CT, aneurysm appearance, and vasospasm distribution. If it was not possible to clearly identify the ruptured aneurysm, all possible candidates were treated and aneurysms were classified as ruptured. The degree of initial aneurysm occlusion was recorded on the basis of post-coiling angiography.

8.3.2 Imaging follow-up protocol

Prior to 2005 we followed aneurysms with DSA. After 2005 our institutional protocol changed to following with 3D time-of-flight (TOF) MRA, often favoured as a non-invasive tool for detection of reopening (Weng *et al*, 2008; Wee *et al*, 2007;

van Amerongen *et al*, 2013). MRI examinations were performed on 1.5 T or 3 T systems (Philips Healthcare). The MRI protocol included axial T2-weighted fast spin echo and multiple overlapping thin slab acquisition 3D TOF MRA sequences. Axial images and triplanar maximum intensity projections were assessed. If the initial MRA was performed using 1.5 T, the subsequent scan would have been either 1.5 T or 3 T. If the initial scan was 3 T, subsequent scans were also at 3 T. A 3 T scan never preceded a 1.5 T scan.

Anatomical deterioration was defined as increased flow on DSA or MRA at the base or within the aneurysm, either caused by compaction of the coil mesh or by aneurysm growth, when compared with the initial MRA. The aneurysms were dichotomised between adequately occluded aneurysms (completely occluded or small neck remnant) and incompletely occluded aneurysms. Mild deterioration (but continued adequate occlusion) was classified as deterioration to a small neck remnant or mild enlargement of a neck remnant (see figure 8.1). Significant deterioration was classified as deterioration to aneurysm residuum (see figure 8.2).

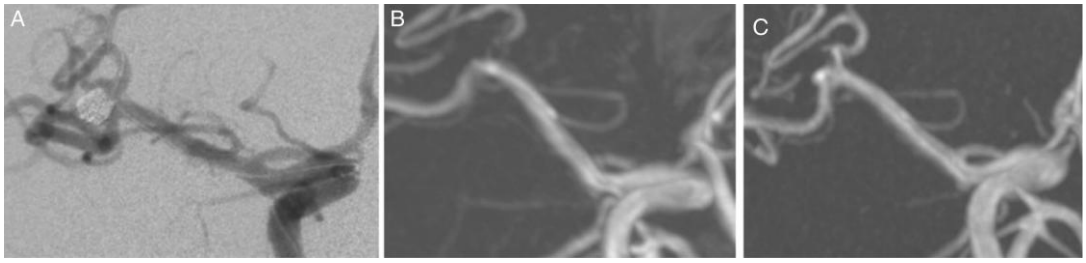

Figure 8.1 Mild anatomical deterioration. Right middle cerebral artery aneurysm completely occluded on immediate angiography (A) and at 6-month follow-up magnetic resonance angiography (B), but showing a small neck remnant at 30 months (C).

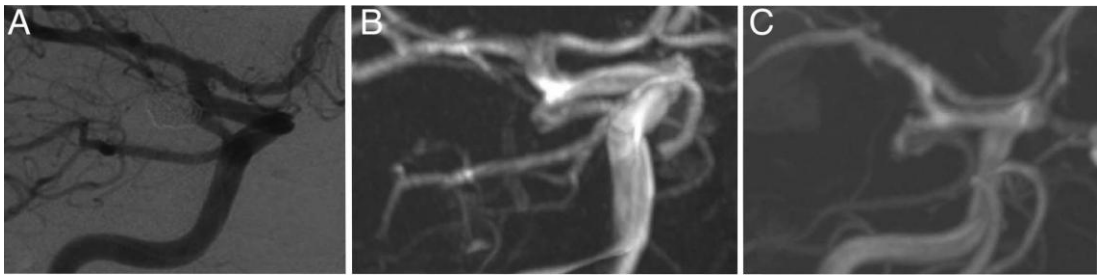

Figure 8.2 Significant anatomical deterioration. Foetal posterior communicating artery aneurysm showing complete occlusion at immediate angiography (A), a neck remnant at 6-months magnetic resonance angiography (B), but aneurysmal residuum at 30 months (C).

8.3.4 Statistical analysis

The results were compared statistically (Medcalc V.12.4.0, Ostend, Belgium). ORs were used to compare patients with and without aneurysm reopening in terms of factors such as aneurysm size and neck width, early recanalization and location. Analysis of variance was used for comparison of age between the two cohorts. χ^2 test was used for statistical comparison of proportions for patient sex, aneurysm size ≥10 mm, neck size >4 mm, aneurysm location and rates of recurrence in each of the two cohorts selected on the basis of year of procedure.

8.4 Results

A summary of patient selection is shown in figure 8.3. Between 1996 and 2010, 1106 patients with subarachnoid haemorrhage underwent endovascular coiling. The primary study population included 437 patients with 458 adequately occluded aneurysms at 6 months with mean long-term follow-up of 31 months. This population was subdivided into those aneurysms treated between 1996 and 2005 (cohort 1; 197 patients with 198 aneurysms) and those treated between 2006 and 2010 (cohort 2; 241 patients with 260 aneurysms).

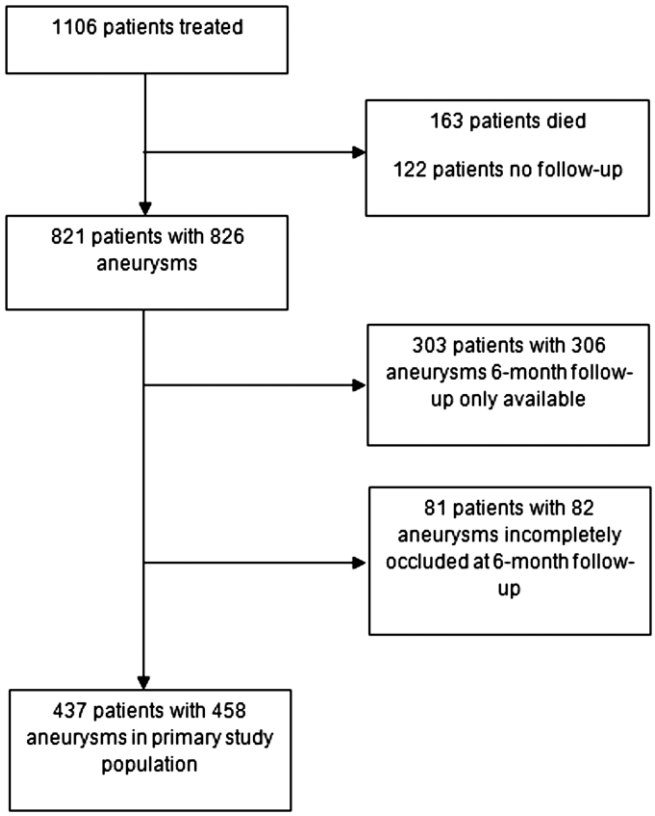

Figure 8.3 Summary of patient selection for the study population.

8.4.1 Patients not included in the primary study population

A total of 669 patients were not included in the primary study population for the following reasons: (1) no angiographic follow-up; (2) follow-up at 6 months only; (3) aneurysms incompletely occluded at 6 months.

Two hundred and eighty-five patients had no follow-up; 163 patients died in the acute period and 122 had no follow-up for the following reasons: advanced age (37), severe clinical outcome (24), out of region follow-up (14), and other reasons (19). Twenty-eight patients refused follow-up. Three hundred and three patients with 306 aneurysms had a single follow-up DSA or MRA available for assessment. The occlusion grades at initial follow-up in these aneurysms were complete occlusion 80.4% (246/306) and small neck remnant 19.3% (59/306). All but one patient was therefore adequately occluded. There was no subsequent follow-up available for reasons such as advanced age, out of region follow-up, severe outcome, and patient choice.

Eighty-one patients with 82 aneurysms were deemed incompletely occluded at initial 6-month follow-up. Of these, 70 had shown anatomical deterioration and 12 were stable but incompletely occluded. Wide neck and large size represented significant risk factors for incomplete occlusion at 6 months: 31 (37.8%) were large compared with 95 of the 764 (12.4%) adequately occluded aneurysms at initial follow-up (OR 4.28, 95% CI 2.61 to 7.03, $p<0.0001$) and 38 (46%) were wide-necked compared with 190 of the 764 (24.9%) adequately occluded aneurysms at initial follow-up (OR 2.61, 95% CI 1.64 to 4.15, $p=0.0001$). Fifty-five of these aneurysms (67% of incompletely occluded aneurysms as adjudged at 6 months) were retreated. Those that were not retreated were managed conservatively for reasons such as patient age, anatomical configuration, and estimated procedural risk.

Analysis of the primary study population: overall outcomes for adequately occluded aneurysms at 6 months A total of 437 patients with 458 adequately occluded aneurysms at 6 months had mean long-term follow-up of 31 months. Two hundred and ninety-nine (68.4%) were women. Mean age was 50.3 years. Table 8.1 summarizes the aneurysm characteristics: 57 (12.4%) were large (≥10 mm) and 104 (22.7%) were wide-necked (>4 mm).

Characteristic	N	%
Anterior circulation	390	85.1
ACA	180	39.3
MCA	79	17.2
ICA **-PCom**	131 88	28.6 19.2
Posterior circulation **-Basilar tip**	68 38	14.8 8.3
Size ≥10mm	57	12.4
Neck >4mm	104	22.7
Immediate complete occlusion	314	68.4
Immediate small neck remnant	134	29.1
Immediate aneurysmal remnant	10	02.2
6-month complete occlusion	290	63.2
6-month small neck remnant	169	36.8

Table 8.1 Characteristics of the total primary study population (n=458).

Immediate post-coiling angiography demonstrated adequate occlusion in 97.8%. In cohort 1, adequate occlusion was 97.4% (193/198 aneurysms) and, in cohort 2, adequate coiling was 98.1% (255/260 aneurysms). Therefore, although immediate angiography suggested some residual aneurysm in a minority, by definition, all went on to adequate occlusion by 6 months.

Overall, 28 aneurysms (6%) showed any anatomical deterioration between 6 months and 30 months of follow-up, but most remained adequately occluded at late follow-up with only nine (2.0%) showing significant deterioration to aneurysmal remnant whereby retreatment was either considered or performed. Six of the nine were retreated, one which was stable between 30 and 42 months opted for neurosurgical clipping, and the other two continue to be followed.

In the group that deteriorated to aneurysmal remnant, seven of nine (78%) were wide-necked (OR 12.70, 95% CI 2.60 to 62.13, p=0.0017) and six (60%) were

large (OR 15.61, 95% CI 3.79 to 64.33, p=0.0001). The anatomical locations were as follows: two in the anterior communicating artery (22.2%), two in the posterior communicating artery (22.2%), two in the basilar tip (22.2%, OR 3.28, 95% CI 0.66 to 16.37, p=0.1479), and one each in the ophthalmic artery, posterior inferior cerebellar artery, and distal anterior cerebral artery.

Sixty-one of the 430 aneurysms (14.2%) that had long-term stability showed minor deterioration between the initial post-coiling angiogram and 6-month follow-up compared with five of the 28 aneurysms (17.9%) that did show late deterioration (OR 1.32, 95% CI 0.48 to 3.59, p=0.5930).

8.4.2 Outcomes for completely occluded aneurysms

In all, 290 aneurysms were completely occluded at 6 months (see table 8.2), 50 (17.2%) of which were wide-necked and 27 (9.3%) were large; 16 (5.5%) of these aneurysms showed deterioration to small neck remnant on late follow-up, but none of these aneurysms required retreatment. All remain adequately occluded. Three of these aneurysms were large (OR 2.40, 95% CI 0.64 to 9.03, p=0.1940), two were wide-necked, and six of the 16 were posterior communicating artery aneurysms (OR 2.50, 95% CI 0.87 to 7.19, p=0.0886). There have been no cases of delayed rebleeding from aneurysms completely occluded at 6 months initially treated from January 1996 to date.

	No recurrence		**Mild recurrence**	
Characteristic	**N**	**%**	**N**	**%**
Neck >4mm	48	16.6	2	12.5
Size ≥10mm	24	8.3	3	18.8
Anterior circulation	252	86.9	14	87.5
ACA	111	38.3	4	25.0
MCA	57	19.7	3	18.8
ICA	84	30.0	7	43.8
-PCom	53	18.3	6	37.5
Posterior circulation	38	13.1	2	12.5

Table 8.2 Characteristics of those aneurysms that were completely occluded (n=290).

8.4.3 Comparison of anatomical outcomes over time

A summary of the populations treated between 1996 and 2005 (cohort 1) and 2006 and 2010 (cohort 2) is shown in table 8.3. There was no significant difference in either patient or aneurysm characteristics. In cohort 1, 16 aneurysms showed late anatomical deterioration (8%). Seven showed significant deterioration to the aneurysm residuum and six (3%) were retreated. In cohort 2, 12 aneurysms showed late anatomical deterioration (4.6%). Only two of these cases (0.8%) showed significant deterioration, both stable on later follow-up, but one awaits neurosurgical clipping. The difference in the rate of significant late recurrence reached significance (p=0.0345), with a smaller number of significant deteriorations in cohort 2. The rate of retreatment was also significantly lower in cohort 2 (p=0.0221). Comparison of aneurysms that exhibited reopening versus those that did not within each cohort is displayed in table 8.4. In cohort 1, aneurysm size ≥10 mm significantly predisposed to any recurrence (OR 4.72, 95% CI 1.46 to 15.27, p=0.0097) and in cohort 2 aneurysm size ≥10 mm also increased the risk of recurrence significantly (OR 3.38, 95% CI 1.02 to 12.51, p=0.0474). In cohort 2, posterior communicating artery aneurysms tended to show more recurrence and anterior cerebral artery aneurysms showed less recurrence, but this was not reproduced in cohort 1 so the validity of this is questionable.

Characteristic	Cohort 1					Cohort 2					P
	197 patients with 198 aneurysms 1996-2005					241 patients with 260 aneurysms 2006-2010					
	Mean (SD)	N	%	Median (IQR)	Range	Mean (SD)	N	%	Median (IQR)	Range	
Women		133	67.5				166	68.9			0.7598
Age Y	50.6 (10.5)			51 (13)	16-76	49.9 (12.5)			51 (17)	17-76	0.6557
Size ≥10mm		21	10.6				36	13.5			0.2980
Neck >4mm		52	26.3				52	20.0			0.1129
Anterior circulation		165	83.3				225	86.5			0.3392
ACA		78	39.4				102	39.2			0.9717
MCA		28	14.1				51	19.6			0.1244
ICA		59	29.8				72	27.7			0.6213
Posterior circulation		33	16.7				35	13.5			0.3392

Table 8.3 A summary of the characteristics of the two cohorts. ACA, anterior cerebral artery, ICA, interior carotid artery, MCA, middle cerebral artery.

	Cohort 1							Cohort 2						
	No reopening		All Reopening					No reopening		All reopening				
	180 patients with 182 aneurysms Mean age 50.8, SD 10.5		16 patients with 16 aneurysms Mean age 48.4, SD 10.8					230 patients with 248 aneurysms Mean age 49.7 SD 12.5		11 patients with 12 aneurysms Mean age 51.1 SD 8.7				
	N	**%**	**N**	**%**	**OR**	**95% conf int**	**P**	**N**	**%**	**N**	**%**	**OR**	**95% conf int**	**P**
Women	123	67.9	11	68.8	0.95	0.31-2.85	0.9237	157	68.3	9		2.09	0.44-9.93	0.3527
Size ≥10mm	16	8.8	5	31.3	4.72	1.46-15.27	0.0097	32	12.9	4	33.3	3.38	1.05-12.51	0.0474
Neck >4mm	46	25.3	6	37.5	1.77	0.61-5.15	0.2919	50	15.7	2	16.7	0.80	0.17-3.73	0.7682
ACA	71	39	6	37.5	0.94	0.33-2.69	0.9054	101	40.7	1	8.3	0.13	0.02-1.04	0.0546
MCA	28	15.4	0	00.0	0.16	0.01-2.82	0.2129	49	19.8	3	25.0	1.44	0.37-5.50	0.5979
ICA	53	29.1	6	37.5	0.56	0.15-2.05	0.3828	66	26.6	6	50.0	2.76	0.86-8.85	0.0882
-PCom	39	21.4	4	25.0	1.22	0.37-4.00	0.7401	(33)	(13.3)	(4)	(33.3)	3.29	0.94-11.53	0.0630
Posterior circulation	31	17.0	3	18.8	1.12	0.30-4.18	0.8615	19	7.7	2	16.7	2.54	0.52-12.42	0.2507

Table 8.4 Comparison of aneurysms that exhibited re-opening versus those that did not within each cohort.

8.5 Discussion

The results of this study suggest that the vast majority of patients with adequately coil-occluded cerebral aneurysms at initial follow-up of 6 months remain well occluded at long-term follow-up. Overall the rate of any reopening was 6%, but the majority of these remained well occluded and only 2% showed significant deterioration to aneurysmal remnant. Completely occluded aneurysms showed no cases of significant deterioration (5.5% showed mild deterioration but they remained well occluded), and the rate of significant deterioration in all adequately occluded aneurysms was lower in those aneurysms treated after 2006 with only one case in this cohort awaiting retreatment. Our results are broadly in agreement with those of a recent investigation of 400 patients with 440 aneurysms followed for a mean period of 6 years (Ferns *et al*, 2011b). This investigation found that the rate of aneurysm reopening after adequate initial occlusion identified at 6 months with 3 T TOF MRA was 2.6% (11 patients) and only three patients were retreated. In a series of 126 patients with fixed follow-up intervals of 6 and 18 months after coiling, all reopened aneurysms were found at 6-month angiography (Sluzewski *et al*, 2003). In another study, 111 aneurysms adequately occluded at 6 months underwent 3 T MRA 5–11 years after coiling. Three showed minor reopening and only one aneurysm, which initially contained intraluminal thrombus, showed major reopening (Sprengers *et al*, 2008). A difference between these studies and our own is that they included patients with both ruptured and unruptured aneurysms whereas we confined our analysis to ruptured aneurysms that, in theory, may be more prone to recurrence due to a thinner more friable wall and associated thrombus. Our results suggest that this is not necessarily the case. Likewise, a study by Gallas et al (2005) reported that 96% of ruptured aneurysms completely occluded at 1 year remained stable, with a mean follow-up period of 36 months. They also reported that no patient with a completely occluded aneurysm at 2 years demonstrated recanalization at 3 years.

Several studies (Cognard *et al*, 1999; Piotin *et al*, 2007; Campi *et al*, 2007; Wee *et al*, 2007) have reached conclusions that contradict the findings of our study and that of Ferns *et al* (2011b). In these studies, prolonged imaging follow-up was recommended to detect more first-time recurrences, but the findings of these studies are hindered by wide variations in the time intervals of follow-up angiography; it is possible that initial reopening may have been identified sooner with earlier follow-up. When initial follow-up is fixed at 6 months, very few recurrences are first

recognised beyond the 6-month follow-up (Sluzewski *et al*, 2003; Ferns *et al*, 2011b).

Aneurysm rupture (Hope *et al*, 1999; Raymond *et al*, 2003; Tan *et al*, 2011), larger aneurysm size (Hope *et al*, 1999; Raymond *et al*, 2003; Tan *et al*, 2011), wide aneurysm neck (Hope *et al*, 1999; Raymond *et al*, 2003; Ries *et al*, 2007; Ferns *et al*, 2009; Tan *et al*, 2011; Pierot *et al*, 2012a), posterior circulation location (Ferns *et al*, 2009), intraluminal thrombus (Sprengers *et al*, 2008), low packing density (Sluzewski *et al*, 2004; Slob *et al*, 2005), and initial incomplete occlusion (Piotin *et al*, 2007) have previously been implicated in conferring a greater risk for aneurysm recurrence. We found that large aneurysm size (≥10 mm) ($p<0.001$) and wide aneurysm neck (>4 mm) ($p=0.0001$) were significant risk factors for early recurrence. We have also demonstrated that aneurysms of ≥10 mm size ($p=0.0001$) and neck width >4 mm ($p=0.0017$) are significant risk factors for significant late recurrence (reopening to residual aneurysm). Any influence of aneurysm location on the predisposition to recurrence is more controversial (Cognard *et al*, 1999; Pierot *et al*, 2012a). We noted that the posterior communicating artery location tended to confer an increased risk, but this is of debatable significance.

Our results suggest that, for adequately occluded aneurysms, the rate of late recurrence was lower in those coiled between 2006 and 2010 than in those coiled between 1995 and 2005 ($p<0.05$). We speculate that this coincided with the introduction of a biplane unit and 3D rotational angiography to our department that we feel has improved assessment of the aneurysm neck and local anatomy and also the introduction of next generation coil technology including 360 (Boston, now Stryker) and Axium 3D (eV3/Covidien) coils. Although we did not formally assess packing density, complex-shaped platinum coils have been shown to increase packing density (Wakhloo *et al*, 2007). Nevertheless, we accept that there are multiple flaws in comparing the data of these two cohorts, not least that the imaging modalities used were different, that the missing data could have altered the results, and that attitudes to retreatment may have changed over time. This therefore limits the conclusions that can be drawn.

The results do indicate that, for adequately occluded aneurysms at 6 months, long-term follow-up may not be necessary for all aneurysms. Patients with small narrow-necked aneurysms that are completely occluded at 6 months may not necessarily benefit from long-term follow-up. Indeed, through evaluation of the

effects on mood and level of anxiety from long-term follow-up MRA in comparison to general population norms, aneurysm follow-up has been implicated in prolonging patient anxiety (Ferns *et al*, 2011a), although there are no data about follow-up imaging and depression levels in a ruptured aneurysm population between those who underwent imaging and those who did not.

The purpose of detecting recurrence is to identify those patients who may benefit from retreatment in order to reduce the risk of haemorrhage. Although this is a well-accepted concept, only a small number of studies have related the degree of aneurysm coil occlusion to the subsequent risk of rehaemorrhage. The CARAT investigators (Johnston *et al*, 2008) demonstrated that the risk of rehaemorrhage in completely occluded aneurysms was 1.1%, but was as high as 17.6% for those with <70% occlusion. Similarly, Sherif and colleagues (2012) demonstrated that the risk of rebleeding ranged from 0% for completely occluded aneurysms to 16.7% for those with <70% occlusion. Furthermore, the risk of rehaemorrhage is greatest in the first year following treatment (Johnston *et al*, 2008). Current evidence suggests that the risk of rehaemorrhage beyond the first year is low and lies between 0.11% and 0.21% per year (Johnston *et al*, 2008; Molyneux *et al*, 2009). The very low incidence of aneurysm rebleeding therefore questions the validity and cost-effectiveness of performing routine long-term follow-up imaging of intracranial aneurysms completely obliterated after 6–12 months. Indeed, in the International Subarachnoid Aneurysm Trial (ISAT), two of 988 patients had rehaemorrhage from an aneurysm that was completely occluded at 6-month follow-up angiography (Molyneux *et al*, 2005). What confounds this argument is the effects of retreatment (7.7% in the first year and 4.5% in the second year in CARAT (Johnston *et al*, 2008) and 17.4% overall in ISAT (Campi *et al*, 2007) that requires a robust follow-up system to guide the need for re-intervention. In this study we specifically investigated those aneurysms that were adequately occluded at 6 months. In ISAT, 5.8% of 584 aneurysms that were well occluded at 6-month angiographic follow-up were retreated. If retreatment is used as a surrogate measure of recurrence, this somewhat contradicts the findings of our study, particularly as the mean time to retreatment was 17 months, but what is difficult to quantify is the effect of retreatment in this group on the rate of rehaemorrhage. It is noticeable that there may now be a trend to manage small recurrences or neck remnants more conservatively. This trend may be reflected in the proportion of retreated patients in

the more recent Cerecyte (Molyneux *et al*, 2012) and HELPS (HydroCoil Endovascular Aneurysm Occlusion and Packing Study) (White *et al*, 2011) trials compared with ISAT (5.5% and 3%, respectively, vs 17.4%).

Some suggest that an additional reason for following patients with treated cerebral aneurysms is also to detect de novo aneurysms and to depict growth of untreated aneurysms. This is an unresolved issue. We have not detected any de novo aneurysms in our cohort of patients imaged using MRA (unpublished observations), nor have we observed the growth of additional small untreated aneurysms. The results of previous large follow-up studies indicate that, in the first 5 years after coiling (and probably also in the first 10 years), both the risk of de novo aneurysm formation and the risk of growth of existing untreated aneurysms is very low. Gallas et al (2009) found five de novo aneurysms in 731 patients over a 5-year period of follow-up and Sprengers et al (2009) describe a 1.5% incidence after 5 years. The risk of subarachnoid haemorrhage from such aneurysms is extremely low (Wermer *et al*, 2005; Gallas *et al*, 2009; Sprengers *et al*, 2009). There is no evidence that treatment of small unruptured aneurysms is beneficial. Where appropriate at our institution, additional aneurysms are treated either at the time of the initial procedure or 3–6 months after the subarachnoid haemorrhage, following recovery.

There are multiple problems with the methodology employed in this study and other retrospective observational studies that have reached similar conclusions (Sluzewski *et al*, 2003; Gallas *et al*, 2005; Sprengers *et al*, 2008; Ferns *et al*, 2011b). Each study has been relatively small and suffered from missing data. This has previously been thoroughly critically appraised by Raymond (2009). Grading of aneurysm occlusion was initially based on operator reports. It is well-accepted that there is wide variation in the reporting of aneurysm occlusion between operators and independent assessors (Nagarra *et al*, 2010; Daugherty *et al*, 2011; Tollard *et al*, 2012). We used different imaging modalities to follow patients (DSA prior to 2005 and 1.5 T or 3 T TOF MRA for follow-up after 2005). This could well have impacted on our comparison of the two cohorts. It is generally accepted that DSA is the most sensitive method of detection for recurrence and therefore any differences in the rate of reported recurrence between the two cohorts should take into account the inherent differences in the sensitivity of DSA and MRA. The evidence is conflicting with regard to the differences between 1.5 and 3 T MRA and is probably not significant (Kaufmann *et al*, 2010; Pierot *et al*, 2012c). The study could also

have been skewed by missing data. A total of 122 patients were not followed up (11% of the overall population treated) and 303 patients with 306 aneurysms (27% of the overall population treated) had only 6-month follow-up available for review and were therefore not included in the primary study cohort, so limiting our ability to draw firm conclusions on the basis of the available data: we may have failed to capture all recurrences or alternatively, the rate of recurrence may have been overestimated since many of the aneurysms that underwent only 6-month follow-up were completely occluded at that stage. An additional limitation is that long-term follow-up in most cases was limited to only 30 months. It is possible that later reopening could have occurred but would not have been identified by the timing of our follow-up. Significantly, however, no cases of rebleeding have occurred from the two cohorts of adequately coil-occluded aneurysms.

8.6 Conclusion

This study concurs with others and proposes that most aneurysms adequately occluded at 6 months do not require further follow-up. However, current data suggest that this policy should perhaps be reserved for small, narrow-necked and completely occluded aneurysms while large and wide-necked aneurysms are at greater risk of recurrence.

CHAPTER 9

AVENUES FOR FUTURE RESEARCH

9.1 Introduction

The findings of the investigations included in this thesis suggest that EVC is a suitable first line treatment for MCA aneurysms; that the injury sustained by brain regions heavily involved with cognition is significantly greater in patients with ACOM aneurysms treated with clipping; that clinical outcomes in patients with more severe physiological derangement are superior for coiled patients; that invasive imaging may be unnecessary in patients with PMSAH; that aggressive endovascular treatment of vasospasm results in low rates of cerebral infarction and may negate its clinical impact; and finally that long term follow-up of adequately occluded coiled aneurysms is probably not necessary.

9.2 Treatment of middle cerebral and anterior communicating artery aneurysms

Many critics of the ISAT study (Molyneux *et al*, 2002) state that a large proportion of the ruptured aneurysms encountered in routine practice are not characteristic of those included in the study in which equipoise for clipping or coiling was required. Although the BRAT study (McDougall *et al*, 2012), was designed to answer whether either modality was superior for all-comers the study design has been heavily criticised so this remains an area of controversy.

The findings of this large case series of endovascularly treated MCA aneurysms suggest that the clinical results, anatomical occlusion rates and complication rates are similar to those for aneurysms at other locations. Furthermore, results are comparable to those published for the best surgical series and the endovascular results are reproducible. There will remain some doubt, however, from proponents of surgery and since surgery in many institutions is reserved for more anatomically challenging lesions, a trial of surgery versus endovascular treatment using adjunctive endovascular treatments may well be of use to the neurovascular team. Balloon-assistance allows treatment of almost all ruptured cerebral aneurysms and current evidence suggests this can be achieved without a significant increased risk to the patient (Pierot *et al,* 2012b). Balloon-assistance was used in a handful of cases in the present series and very few of the ISAT cohort so a trial of balloon-assisted coiling versus surgery for more complex lesions is feasible. Complex unruptured lesions can now be treated with stent-assistance, flow diversion and the recent development of intra-aneurysmal flow

diverters. An additional study that would therefore be useful is a trial of surgery versus newer flow-diverting techniques.

The results of the present radiological observational study addressing rates of ischaemic injury following clipping or coiling of ACOM artery aneurysms demonstrated a marked predisposition to basal forebrain and septal/subcallosal region injury in the clipped patients. These areas are heavily involved in cognition and it is likely that this injury is responsible for inferior cognitive outcomes following surgery. Again, it could be argued by proponents of surgery that the more anatomically challenging lesions may require clipping for treatment but as the neurointerventionalist's armamentarium increases, a trial of flow diversion/stent-assisted coiling versus surgery would be fascinating.

To improve the application of endovascular techniques in the context of subarachnoid haemorrhage, there is a need for development of stent devices that do not necessitate the use of dual anti-platelet therapy.

9.3 Aneurysm treatment modality and physiological status

The ISAT cohort was mostly of good clinical grade but we have no information on the physiological status of the patients. The results of the present work suggest that there is a relationship between treatment modality, physiological status and outcome. Clipping results in worse clinical outcomes in physiologically sicker patients. Other work has suggested that clipping is associated with higher rates of medical and perioperative complications (Vergouwen *et al*, 2011c; Ayling *et al*, 2015). Physiological information should probably be included in the data collection of trials designed to answer whether surgical or endovascular options are superior for different groups of patients that were less well represented in the ISAT trial including those with more complex aneurysms requiring adjunctive endovascular options including stents and intra-aneurysmal flow diverters or patients of poorer clinical grade.

9.4 Invasive imaging in patients with perimesencephalic haemorrhage

The results of the present work suggest that DSA may not be required for investigation of perimesencephalic haemorrhage. CT angiography may be a suitable definitive investigation. Although other authors have reached similar conclusions, the validity of this investigation algorithm needs to be confirmed with higher level of evidence. A prospective study is probably required to achieve more universal acceptance. The author is presently undertaking a prospective study investigating the clinical course in patients with perimesencephalic haemorrhage investigated with CT angiography alone read by two experienced neuroradiologists.

9.5 Treatment of cerebral vasospasm using endovascular techniques

The use of endovascular techniques to treat cerebral vasospasm and the role of cerebral vasospasm in delayed ischaemia remains controversial. International guidelines state that it is reasonable to consider endovascular options in cases where medical therapy has failed (Bederson *et al*, 2009). The approach in the present studies was slightly different: endovascular treatment was started early in patients exhibiting significant angiographic vasospasm so as to prevent clinical deterioration. The adoption of this protocol will be limited in many health systems including that in the United Kingdom due to resource implications. What would be more pertinent would be to address the efficacy of endovascular treatment options in situations in which maximal medical therapy has failed to show clinical improvement. Many neurointerventionalists are reluctant to undertake balloon angioplasty for the risk of vessel rupture and in view of this, the use of intra-arterial vasodilators would seem a useful treatment option with relatively low risk. A multicentre trial comparing various intra-arterial vasodilators is in process (Chen, 2015). However, there is much work to be done on a basic science level. For example, what is the dose-response for the various agents that are commonly in clinical use? Furthermore, what is the effect of these agents on the other dominant mechanism of delayed ischaemia, spreading cortical depression? The author is in the process of designing a study using electro-encephalography to assess these interactions and also the interaction between both angiographic vasospasm and spreading cortical depression in order to fully elucidate the pathophysiology of this disease.

9.6 The necessity of long term follow-up of coiled cerebral aneurysms

The present work also suggests that long term imaging follow up beyond 6 months may not be necessary in patients with well coil-occluded cerebral aneurysms. However, this evidence was single-centre and of a retrospective nature. For this notion to gain acceptance, the level of evidence needs to be greater. This would necessitate a multicentre, prospective study in which anatomical outcomes are independently assessed with long term follow-up beyond that of 2.5 years used in the present work.

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APPENDIX 1

SUPPLEMENTARY IMAGES FOR CHAPTER 5

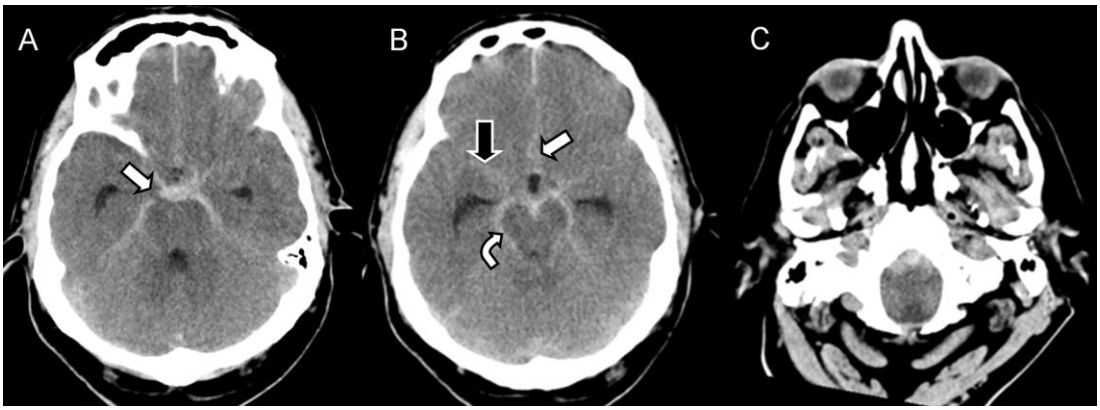

Figure A1 The definition of perimesencephalic haemorrhage: Hemorrhage centered anterior to the midbrain and/or pons within the pre-pontine and interpeduncular cisterns (A, white arrow), with possible extension to the quadrigeminal or ambient cisterns (B, curved arrow). No deep extension into the anterior interhemispheric fissure (B, white arrow). Possible extension into the basal parts of the sylvian fissures with no extension into the lateral sylvian fissures (B, black arrow). 4. Possible extension to the cisterna magna but not centered on the cisterna magna (C). The latter feature was associated with a possible vertebral dissection in this study (see figure A2) and removal of this criterion resulted in a NPV of 100% for CTA, suggesting that cisterna magna haemorrhage should not be present if DSA is no be avoided.

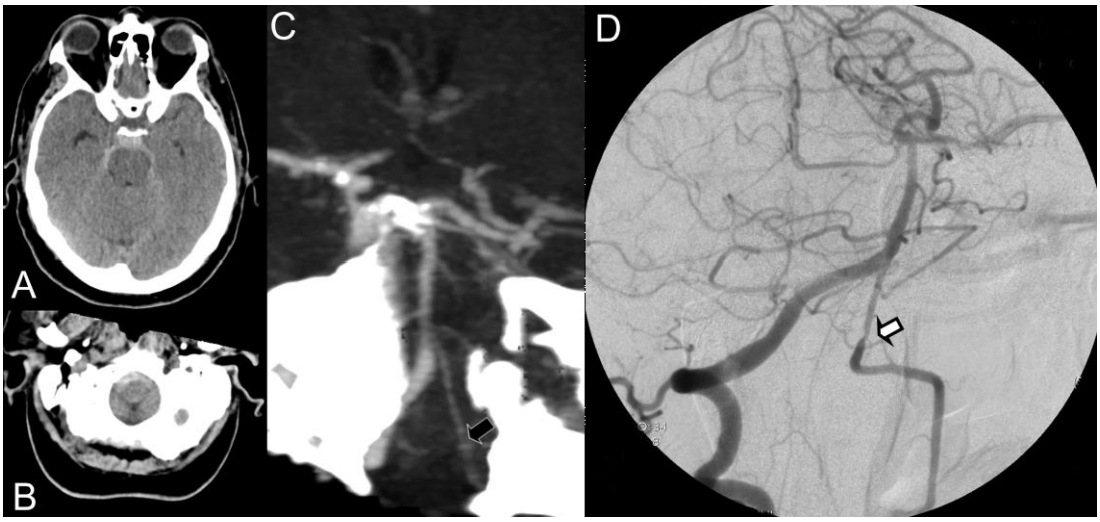

Figure A2 An abnormality beyond detection with CTA in a patient with a perimesencephalic pattern of haemorrhage with extension to the foramen magnum. Non contrast CT (A and B) demonstrating a perimesencephalic pattern of SAH with extension to the foramen magnum. Coronal CTA (C) demonstrating minimal detectable abnormality of a hypoplastic V4 segment of left vertebral artery (black arrow). Oblique frontal projection DSA (D) demonstraing an irregular stenosis of the left vertebral artery (white arrow) interpereted as a potential dissection at time of angiography.

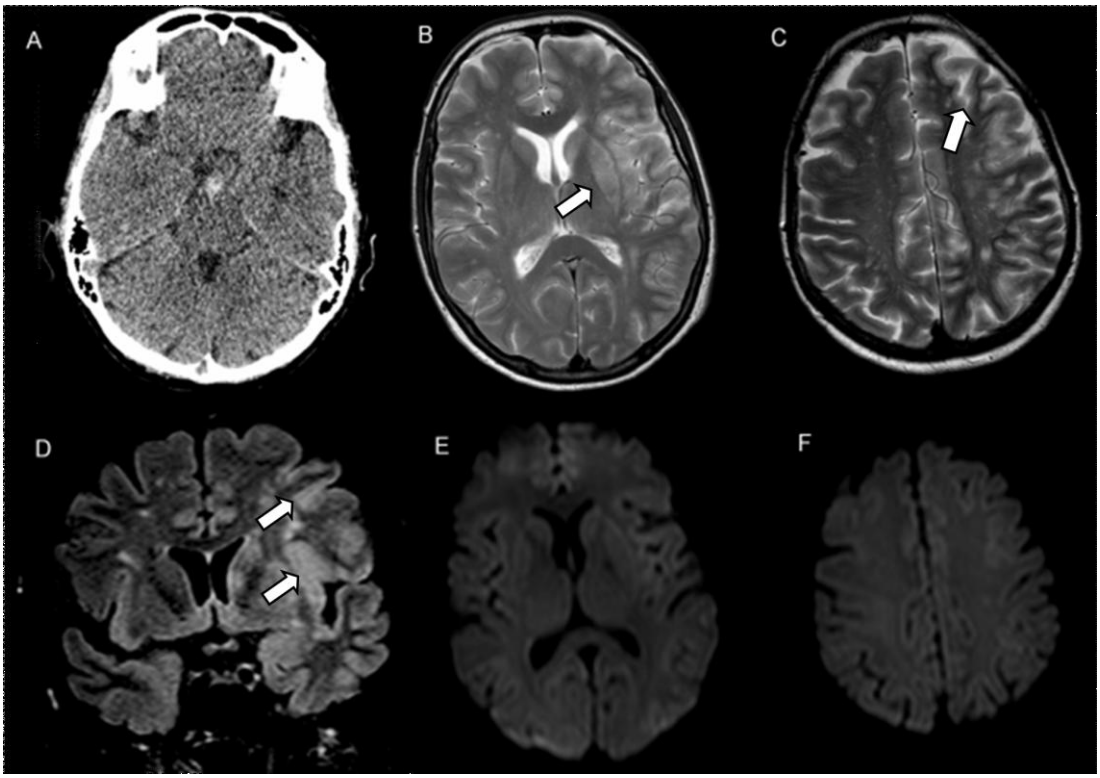

Figure A3 A rare complication of cerebral angiography as a result of possible contrast toxicity. A female patient presented with a small pre-pontine haemorrhage (A). Shortly after cerebral angiography she developed a right hemiparesis with subsequent coma. Repeat angiography was normal. MRI performed within 3 hours showed minimal changes but a second MRI performed at 24 hours showed widespread, predominantly left hemisphere cortical and basal ganglia hyperintesity on T2-weighted and FLAIR sequences (B, C and D, arrows). No diffusion restriction was evident suggesting that this was not a thrombo-embolic process (E, F). The patient made a full recovery after supportive care.