GIANT INTRA-DURAL ANEURYSMS: CLINICO-MORPHOLOGICAL FEATURES, NATURAL HISTORY AND TREATMENT OUTCOMES

THESIS

SUBMITTED IN PART FULFILLMENT OF THE DEGREE OF
DM (NEUROIMAGING & INTERVENTIONAL NEURORADIOLOGY)

OF THE

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY, THIRUVANANTHAPURAM, INDIA

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Certificate

This is to certify that the work incorporated in this thesis titled **"Giant Intra-dural aneurysms : Clincomorphological features, natural history and treatment outcomes"** for the degree of DM (Neuroimaging and Interventional Neuroradiology) has been carried out by **Dr Aneesh Mohimen** under my supervision and guidance. The work carried out in connection with this thesis has been carried out by the candidate himself and is genuine.

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DECLARATION

I hereby declare that this thesis titled "**Giant Intra-dural aneurysms : Clincomorphological features, natural history and treatment outcomes**'' has been prepared by me under the supervision and guidance of Dr Santhosh K, (Associate Professor), Dr Jayadevan E.R (Co-Guide) and Dr. Kapilamoorthy T R, (Professor & Head), Department of Imaging Sciences and Interventional Radiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram.

Date: 03/10/2016 **(Dr Aneesh Mohimen)**

Place: Thiruvananthapuram

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I would specially like to acknowledge my gratitude to my past and present colleagues for their valuable co-operation and guidance.

I wish to sincerely thank the entire staff of the Department of Imaging Sciences and Interventional Radiology at our institute for their constant support and assistance.

I would also like to extend my special gratitude to my family members for being so supportive and patient throughout the years of my medical education and particularly during the work on my thesis.

Last but most important, I am grateful to all my patients & their relatives who have been the very basis of this study.

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Introduction

Intra-cranial aneurysms (IA) are the commonest cause of non-traumatic sub-arachnoid haemorrhage (1). These are ominous entities with aneurysmal SAH being associated with significant morbidity and mortality. The prevalence of IA in literature has been reported as approximately 2% of the general population (2) . IA have been differently classified as per morphology into saccular, fusiform and serpentine or as per size into small (less than 10 mm), large (10-25 mm) and giant aneurysms (>25 mm).

Giant aneurysms (GA) are defined as those aneurysms with largest dimension exceeding 25 mm (3). GA pose clinical conundrums and management dilemmas significantly different to those of smaller IA. They present with a myriad of varying manifestations ranging from completely asymptomatic to life threatening SAH. Pressure effects of adjacent structures leading to cranial nerve palsies, seizure disorders, ischemic neurologic events are not uncommon presentations (4). Natural history of GA is not clearly understood due to the lack of adequate literature describing the evolution of untreated aneurysms. A few short case series which do exist claim an ominous prognosis with high mortality (5,6).

GA can affect the carotid and vertebro-basilar systems (7) at any location (intra-dural or extra-dural), with the cavernous ICA being one of the commonest sites. It is well established that cavernous ICA aneurysms (commonest extra-dural aneurysms) have an entirely different clinical spectrum and approach to management as opposed to their intra-dural counterparts (8), predominantly because an extra-dural location largely prevents potentially life threatening SAH. Thus it stands to logic that giant intra-dural aneurysms (GIDA) will have similarly different clinical manifestations than their extra-dural counterparts. Furthermore, the more proximal location of the extra-dural aneurysms is likely to affect the treatment modality and outcome due to

less likelihood of essential branches and perforating arteries arising from intra-dural segments of the arteries.

Surgical treatment has been the time honoured and most durable technique for definite management of IA with aneurysm clipping being the most favoured treatment modality (9). Giant aneurysms due their bizarre morphology, incorporation of branch vessels into the aneurysm, and the presence of thrombus; make clipping often a difficult procedure (10). Other techniques like aneurysm wrapping, aneurysmoraphy or excision and surgical bypass procedures are required more frequently for GA with an overall poorer outcome as compared to smaller aneurysms.

Endovascular (EV) techniques have progressively gained popularity in the treatment of IA since the development of detachable coils (11). The International Sub-Arachnoid Haemorrhage trial (ISAT) showed significantly improved clinical outcomes for ruptured aneurysms as compared to surgical methods (12). The development of neck support devices such as balloons and coils has further improved the armamentarium of the interventionist in tackling aneurysms, however the results of EV treatment of GA have not been met with the same degree of success and good outcomes as those of smaller aneurysms (13). The conventional EV methods of treatment of GA are aneurysm coiling and parent artery occlusion. While coiling has been associated with high rates of recurrence (14) , parent artery occlusion may not be suitable for all patients depending upon aneurysm location and the presence of collateral flow (15)

Flow diverters (FD) are recently introduced stents with high mesh density and are currently gaining popularity in the management of large and complex aneurysms (16).

While these devices achieve better aneurysm occlusion, there are concerns about the immediate and long term outcomes, especially for GA (17).

Presently, there are considerable lacunae in the understanding of the clinico-morphological correlates of GA and particularly about the natural history of these entities. GIDA have never previously been studied as a homogenous group with a view to ascertain immediate and long term treatment outcomes or the natural history. Our study aims to evaluate these aspects of GIDA and compare the results against the existing literature on GA.

Aims & Objectives

Our study is a prospective – retrospective study aimed at analysing the clinic-morphological features, natural history and treatment outcomes of Giant Intra-dural aneurysms (GIDA) in patients who have had out-patient or in-patient management at out institute between 01 January 2005 to 31 July 2016.

The specific objectives of the study are as detailed below:

a) To study the morphological features of GIDA and their correlation with clinical presentation and outcome.

b) To study the treatment strategies adopted along with their immediate and long term outcome.

c) To study the natural history of the GIDA in patients who have been managed using a conservative approach.

d) To review the clinico-morphological features and treatment results at our centre and compare the same with available data in International literature.

e) To make appropriate recommendations on future directions of research and management of GIDA.

Review of Literature

Intra-dural aneurysms (IA) have been recognized since decades as a major contributor of life threatening sub-arachnoid haemorrhage (SAH). Approximately 75%-85% cases of spontaneous (non-traumatic) SAH have been ascribed to IA (1). Aneurysmal SAH is also well-established for its propensity to cause high mortality and significant neurological disability as well as harbouring an increased risk of subsequent future rupture (18,19). In addition to the risk of SAH, aneurysms may manifest clinically with ischemic symptoms and symptoms arising from local mass effect. Neurosurgical management has for decades been an established and time honoured method of treatment for all IA. The rapid development of endovascular techniques in aneurysm management and their wide acceptance has placed this modality of treatment at par with surgery. A clinical conundrum now faces every treating surgeon / interventionist in the selection of the treatment modality which is likely to provide the best risk-benefit ratio to the patient.

Intra-cranial aneurysms: Overview of etiopathogenesis and classification systems

The most commonly followed systems in aneurysmal literature classify aneurysms based upon morphology , size or on etiopathogenetic basis. (4,20,21).

a) Morphological classification :

   a. Saccular aneurysms (SA)

   b. Non-Saccular

      i. Fusiform

      ii. Serpentine

b) Size based classification (based upon maximum aneurysm dimension):

a. Small (<10 mm)

b. Large (10 to 24 mm)

c. Giant (> 25 mm)

Some authors also use the term very large aneurysms to sub-classify aneurysms between 20 to 24 mm in size (22).

c) Etiopathological classification:

a. Classic saccular

b. Segmental Ectasia

c. Atherosclerotic

d. Traumatic

e. Mycotic

f. Dissection with aneurysm

g. Immunodeficiency related

The above mentioned classification systems do not provide a true idea about the natural history and the potential rupture risk and consequently, the need and urgency for management. In addition, there is a tremendous heterogeneity in the usage of classification systems with different authors using different terminologies. Aneurysm size has consistently reported to have an association with rupture risk with larger aneurysms being more prone to rupture in addition to several etiological factors which have also been implicated in increasing rupture risk (23,24).

Giant Aneurysms:

By simple definition, any intra-cranial aneurysm measuring more than 25 mm in its maximum dimension is labelled as giant (3) . The criteria of 25 mm is an arbitrary cut-off and has been traditionally used to imply a higher rupture risk than smaller aneurysms. The International Study of Unruptured Intracranial Aneurysms (ISUIA) data show an 8% and 10 % annual rupture risks for GA of the anterior and posterior circulation respectively (24). The term "giant" is purely a size based terminology and conveys no information with regard to the etiology or the morphology. The term is widely used in neurovascular parlance to convey an aneurysm which, irrespective of morphology or etiology, confers high morbidity and mortality and probably merits early definitive treatment.

Giant intra-dural aneurysms:

Multiple studies and case series have found a significant proportion of giant aneurysms to be extra-dural in location (7,10) with the commonest extra-dural location being the cavernous segment of the internal carotid artery (ICA). If the ISUIA data and the significantly increased risk of giant aneurysm rupture is to be studied separately, distinction has to be made of the extra and intra-dural locations of the aneurysms. Giant intra-dural aneurysms (GIDA) have thus not been separately studied or published in any large series and hence there is paucity of natural history data on these entities. A few of the possible reasons for this could be due to higher rates of mortality and morbidity due to rupture, early surgical / endovascular treatment due to the perceived risk of rupture and initial detection several years after aneurysm origin due to absence of clinical symptoms prior to initial manifestation.

Formation and Growth of Giant Aneurysms

The history of intra-cranial aneurysm pathology usually tends to distinguish between true saccular (berry aneurysms) as opposed to non-saccular aneurysms due to a difference in both the aneurysm origin and the subsequent aneurysm growth. In very large and giant aneurysms, it may be difficult to make the true distinction between saccular and non-saccular aneurysms due to aneurysm size. However, this classification system is still useful in understanding aneurysm growth and morphology due to different etiological factors and subsequently to predict eventual aneurysm behaviour.

Before delving into the topic of aneurysm formation and growth, it is essential to understand certain histological peculiarities of the intra-cranial vessels which make them particularly prone to aneurysm formation.

The 2 basic structural differences between the arterial wall in intra-cranial arteries as compared to other arteries is the lack of an external elastic lamina and a significantly thinner adventitia. (20). Intra-cranial arteries also have a lesser wall: lumen ratio compared to their extra-cranial counterparts (25,26). Intra-cranial extra-dural arteries on the other hand are histologically similar to large arteries in other parts of the body. Intra-dural arteries, in addition to the histological peculiarities detailed above, are surrounded by cerebrospinal fluid (CSF) in contrast to other arteries which are invested by soft tissue structures.

a) Giant Saccular (berry) aneurysms:

The origin of the classical berry aneurysms was a matter of controversy during the formative years of neurovascular pathological understanding. Two main schools of

thought arose, one which posited that these aneurysms were congenital and grew slowly right from infancy, and the other which theorized that SA were due to acquired abnormalities in the arterial wall such as degenerative changes (27). Over the years, the acquired theory has gained acceptance. SA have a very low incidence in neonates and infants, and the cases which have been reported usually show strong evidence of underlying predisposing factors such as infection, trauma, associated hereditary vasculopathies or high flow shunts (28). Several gene linkages and polymorphisms have been described, yet no definite strong genetic associations to the development of isolated SA have been documented till date. While it is well known that the conditions such as Marfan syndrome, Ehlers Danlos syndrome, and autosomal dominant polycystic kidney disease predispose to aneurysm formation, the majority of incidentally detected or symptomatic SA are not associated with definite predisposing aneurysmal vasculopathy (29).

The natural history of SA have broadly been divided into 3 stages, namely aneurysm initiation, aneurysm growth and subsequent stabilization or rupture. Both aneurysm origin and subsequent growth of SA, are ascribed to an interplay of two pathological processes (29).

a) Weakening of the arterial wall

b) Abnormal hemodynamic stress at the point of aneurysm initiation.

Intra-cranial arteries in humans have a thinner adventitia and tunica media due to a relative paucity of elastin content, along with fenestrations in the internal elastic lamina , making the arterial walls inherently weaker as compared to other mammalian arteries (20,30). A number of associated factors have been implicated in aneurysm initiation & growth such as inflammatory cell recruitment, disruption of the elastic

laminae, and damage to smooth muscle cells in the tunica media (31). A number of hemodynamic factors have been found to have a strong association with the prevalence of SA such as hypertension, anomalies of the circle of Willis and associated arterio-venous shunts (32,33). In recent years there has been much interest in experimental models, especially involving computational fluid dynamics (CFD) to explain aneurysm pathology (34,35). A number of CFD related parameters have been shown (36) to have an association with both aneurysm prevalence and rupture, however the highest emphasis till date has been given to wall shear stress (WSS). WSS is defined as the tangential force created on the arterial wall by flowing blood within the lumen (37). Although various CFD related studies have separately implicated both high and low WSS in aneurysmal pathology, in a recent attempt to unify all theoretical and experimental evidence on the same, Meng et al have proposed that both high and low WSS have a role in the natural history of SA (38). Initial high WSS is responsible for vascular wall changes which lead to aneurysm initiation. Subsequent aneurysm propagation or growth is dependent on high or low WSS. The former is proposed to trigger an arterial mural cell mediated mechanism and the latter is implicated in the trigger of an inflammatory cell mediated mechanism. Both mechanisms lead to subsequent aneurysm growth. There is a relative equilibrium between the disruptive forces on the aneurysm wall and attempted repair mechanisms which prevent aneurysm rupture. Meng et al suggest that a shift in this delicate equilibrium towards the disruptive forces is responsible for eventual aneurysm rupture. Whatever be the initial pathological mechanisms at work, the factors that needs to be subsequently examined are those that lead to giant SA formation and the potential risk factors for rupture of saccular GIDA.

While growth of SA is well recognized as an independent risk factor for rupture (23), it is also established that all unruptured SA do no grow to giant size. Hemodynamic factors aside , vessel wall inflammatory changes have also been postulated to have a crucial role in aneurysm growth with activation of enzymes such as mitogen activated protein kinases which subsequently upregulate factors affecting cellular proliferation and growth leading to remodelling of the aneurysm wall and eventual enlargement of size (39).

Non-Saccular Giant Aneurysms:

Classically, non-saccular aneurysms have been loosely classified as fusiform or serpentine. The criterion for this classification is purely morphological and reveals no insight whatsoever into the etiopathogenesis or natural history of the entity. In reality however, there is a great degree of overlap between the 2 entities and even between the morphology of giant saccular and non-saccular aneurysms. Different authors have proposed different theories about their origin and growth, with no definite unifying hypothesis or classification system.

Fusiform aneurysms:

In terms of simple definition, a fusiform aneurysm implies a complete circumferential enlargement of the arterial lumen due to pathological affliction of the entire vascular wall (40) . Some authors have also extended this definition to include a relatively short length of afflicted arterial wall (41). When viewed externally, these aneurysms impart a spindle like appearance with apparently normal arterial diameter proximal and distal to the dilated segment.

The term “fusiform” is a purely morphological description and imparts no information about the etiopathogenesis of these entities. There are a variety of ultimately overlapping and conflicting theories which attempt to described the pathogenesis, the two most common etiologies being dissection and atherosclerosis. In a post-surgical histopathological analysis of fusiform aneurysms (with exclusion of dissecting and atherosclerotic aneurysms), Nakatomi et al (42) propounded that development of fusiform aneurysms is due to a cyclical chain of events that originate with disruption of the internal elastic lamina (IEL) followed by intima media thickening (IMT), neovascularization and recurrent haemorrhage which leads to a further increase in IMT. The authors also mention that while histopathological changes noted by them were similar in certain cases to atherosclerotic lesions, they advocate defining fusiform aneurysms as separate from atherosclerotic or dissecting aneurysms. Day et al (43) ascribed arterial dissection as the primary inciting event in all fusiform aneurysms. In yet another series Park et al (40) used a broader criteria including atherosclerotic lesions in their series of 22 fusiform aneurysms , though the series did not include histopathological data.

Serpentine aneurysms:

The term “serpentine aneurysm” was first coined in 1977 by Segal and McLaurin who used the term to define a morphological variant of large and giant saccular aneurysms (44). To be termed a serpentine aneurysm, 2 morphological criteria must be fulfilled (21). First, the aneurysm should have a tortuous and patent lumen which imparts the classical “snake-like” appearance and secondly, the vessel lumen should show a spatially separate entry and exit site (the latter criteria to distinguish it from large and giant saccular aneurysms). The vessel wall surrounding this serpentine lumen usually

shows variable degree of circumferential thrombus, which may or may not show areas of calcification (45).

The etiopathogenesis of serpentine aneurysms is an even greater conundrum in comparison to saccular or fusiform aneurysms. They have been variously propounded to either develop from saccular or fusiform aneurysms (or from both) or as pathological entities separate from the aforementioned ones. The formation of the tortuous 'serpentine' luminal channel has been ascribed to a hemodynamic phenomenon called the "Coanda / Boundary wall effect" (21). This phenomenon occurs when a jet of blood flow, created across a proximal vessel stenosis, is deflected to one particular wall of the vessel. The subsequent turbulent flow changes are buffered by the low pressure zone in the vessel distal to the stenosis and creates the so-called serpentine channel.

Giant Aneurysms: Role of Dissection and intra-luminal thrombus.

The term GA implies purely a size of more than 25 mm in the maximum dimension of the aneurysm and conveys no further information whatsoever of the morphology or the etiology of the aneurysm. One of the most widely and heterogeneously used terms in association with GA has been dissection. Different authors have chosen to convey a different meaning from the primary etiology being an arterial dissection leading to secondary aneurysm formation to recurrent dissection leading to growth and morphological changes in a pre-existing aneurysm. As per its basic pathological definition (46), a dissection is an entry of intra-luminal blood beyond the confines of the lumen into the vessel wall (at any depth from sub-intimal to sub-adventitial). This dissection may occur at any stage depending on the hemodynamic and other external factors such as trauma. A dissection in a normal vessel (e.g. iatrogenic, traumatic) has

an entirely different pathophysiological perspective to a dissection occurring within a preformed saccular aneurysm, due to the hemodynamic changes coupled with constant vessel wall remodelling.

Mizutani et al have sought to dispel this existing confusion in the use of the term dissection in the nomenclature of GA, by sub-classifying aneurysms into 4 causal subtypes (47).

1. Acute dissecting aneurysms:

   These aneurysms were defined by classical location at non-branching points on arteries and evidence of intra-mural hematoma (typically in the form of T1 hyperintense signal on MRI). Morphologically these aneurysms show a focal constriction followed by luminal ectasia. These entities are most likely to present with acute SAH and are more common in the posterior circulation but are unlikely to reach a giant size to likelihood of rupture at smaller sizes.

2. Segmental fusiform ectasia:

   These entities are the classical fusiform aneurysms and are defined as a spindle shaped arterial dilatation without demonstrable necks or evidence of mural thrombus.

3. Mural bleeding ectasia: These aneurysms show evidence of chronic intra-mural hematoma and are postulated to occur from recurrent haemorrhages within the aneurysm wall. Mizutani et al proposed an association of atherosclerosis with these type three lesions.

4. Saccular aneurysms

These aneurysms probably derive from the classical "berry" aneurysms, and retain certain morphological characteristics. They may be noted either at arterial branching points or at the side-walls.

Histological reports of thrombosed giant aneurysms demonstrate clots of different ages with the relatively recent haemorrhage situated between the older thrombus and the aneurysm wall. In addition with clefts of fresh blood have been noted, suggestive of a dissection of the aneurysmal wall caused by luminal blood flow (48,49).

Epidemiology and clinical features of GA:

GA are extremely rare entities and constitute approximately 5% of all intra-cranial aneurysms (50,51). Although their subsequent growth might generally evolve over several years or even decades, these aneurysms usually come to clinical notice in the fifth and sixth decades of life. Most reports indicate a female predominance (52). No other definite epidemiological associations such as vascular risk factors, smoking or alcohol consumption have been noted.

An approximately 2:1 distribution of GA are found in the anterior and posterior circulation respectively. In the anterior circulation, the aneurysms are usually saccular in morphology and are noted in the proximal ICA (cavernous and supra-clinoid) with the proximal MCA being the next commonest location. Atherosclerotic and dissecting aneurysms may assume fusiform or serpentine morphology though these appearances as considerably rarer as compared to the posterior circulation. Aneurysms of the distal vessels including the cortical branches of the ACA and MCA are much rarer and may be formed as sequelae of infection or dissection (53).

GA manifest clinically in one of four different spectra.

(a) Rupture with acute sub-arachnoid haemorrhage (SAH) / intra-parenchymal haemorrhage.

(b) Symptoms of Mass effect due to direct compression of brain, cranial nerves, pain sensitive structures etc.

(c) Thromboembolic events with ischemic stroke / TIA.

(d) Incidentally detected during evaluation of unrelated symptomatology / pathology.

Though initial reports suggested that GA might be relatively resistant to rupture, subsequent series in larger patient groups have found that these entities have higher rupture risks than aneurysms of smaller sizes. Different series have cited rupture risks ranging from 20 to 70% (54,55). The ISUIA investigators have reported 5 year rupture risks of 40% and 50% for anterior and posterior circulation aneurysms respectively (24). Respective annual rupture risks of 8 and 10 % have been reported in the same study. Khurana et al reported a rebleeding rate of 18.4 % within the first 2 weeks after hospitalization with an overall 33% in-hospital mortality (56).

Non-SAH headache is most frequent presenting symptom in unruptured GA (57), with the etiology of headache presumably being due to the compression of adjacent pain sensitive intra-cranial structures such as the cranial dura. Other compressive symptoms depend on the location of the aneurysms and their relation to neighbouring structures. Supra-clinoid ICA aneurysms may present with a variety of symptoms ranging from visual field defects, ophthalmoplegia, pituitary symptoms and occasionally even personality changes due to frontal lobe compression (4,58,59). Posterior circulation aneurysms present with bulbar symptoms or ataxia due to

brainstem and cerebellar compression, cranial nerve neuropathies due to compression of the cisternal segments of cranial nerves or rarely obstructive hydrocephalus due to 4^{th} ventricular compression (49) .

Thromboembolic complications are relatively rarer but potentially devastating manifestations of GA. GA have also reported as having higher risk of ischemic strokes with different studies reporting incidences between 2.7% to 10.8% (7,22). This can be attributable to a number of factors ranging from complete thrombosis, distal embolization from partial intra-aneurysmal thrombus to compression of adjacent vessels (e.g. perforators).

Natural History of Intra-cranial aneurysms:

Studies aimed at understanding of the natural history of IA have been conducted over decades with often insufficient or widely contradictory results. The main focus of all studies has been to pinpoint specific determinants of aneurysm rupture, as it is associated with the maximum mortality and morbidity burden. Approximately 50% of all diagnosed aneurysms present after rupture with acute sub-arachnoid haemorrhage which has an incidence of approximately 6 to 10 per 100,000 people every year (9). Acute aneurysmal SAH has a 30 day mortality between 30 to 42% and permanent neurological disability rates of upto 50% (1). There is a high risk of re-bleed in acutely ruptured aneurysms with reported rates of 4 to 13.6% in the first 24 hours (60). The direction of research has therefore been towards predicting behaviour of unruptured aneurysms and further predicting their growth rate, risk of rupture and other complications in order to arrive at a consensus on deciding the indications for surgical / endovascular treatment. In a systematic review of 56304 patients (described in 23 studies), from 1955 to 1995 , Rinkel et al found an overall IA prevalence of

approximately 2% (in adults without additional risk factors) with only 8% aneurysms greater than 10 mm in size (2). In their overall review they found an annual rupture risk of 0.7%. The salient findings of subsequent newer studies analysing the natural history of IA have been detailed in Table 3.1.

Table 3.1 : Selected Studies reporting Natural History of IA.

Study		**Type**	**Patient Number**	**Number of aneurysms**	**Total FU (months)**	**Determinants of Rupture**
ISUIA	Retrospective (61)	Retrospective	1449	1937	99.6	Size Location
	Prospective (24)	Prospective	4062 (1692 untreated)	2686 (untreated)	49.2	-
Small Unruptured Aneurysm Verification Study (62)		Prospective	374	448	41	Age (>50) Size (>4mm) Multiplicity HTN
Unruptured cerebral aneurysm study (63)		Prospective	5720	4305 (without early treatment)	11660 aneurysm years	Size Location Daughter sac

The most consistent risk factors which emerge from these studies are aneurysm size (larger aneurysms being more prone to rupture), history of previous aneurysmal SAH and location, with posterior circulation aneurysms described as having higher rupture rates as compared to anterior circulation aneurysms. Other risk factors such as female sex, presence of hypertension. Female sex, smoking and hypertension have also been cited as independent risk factors for aneurysm rupture (64).

Natural History of GA and GIDA:

GA, as had been previously described, are the end result of a number of pathological changes occurring within the aneurysm lumen and the vessel wall, irrespective of the initial etiological origin of the aneurysm. As opposed to smaller aneurysms, which manifest predominantly with features of SAH due to rupture, GA have protean clinical manifestations ranging from rupture and SAH / ICH, thromboembolic complications and a myriad of symptoms due to direct compression of adjacent structures. As opposed to smaller aneurysms (predominantly saccular), natural history data on GA is conspicuous by its scarcity. In the prospective arm of the ISUIA study, only 3.2 % of the total untreated aneurysms were GA. In addition, fusiform aneurysms were excluded from the study making it an incomplete cohort in assessment of GA as a whole (24). The investigators reported five-year rupture risks of 40% for anterior circulation aneurysms and 50% for posterior circulation aneurysms. The Japanese UCAS study had even smaller percentage of GA (0.4%) in their cohort (63). Michael et al reported a 100% mortality in their series of 7 posterior circulation large-giant aneurysms mimicking tumours over a maximum follow up period of two years (5) while Kodama et al (6) reported a 75% SAH related morality in untreated GA. In a 2003 review , Choi et al state that GA have a 50% rupture risk and 60% overall mortality risk at 2 years (4).

Apart from the pure size considerations and associated rupture risk, another pathological factor affecting the overall prognosis in patients with GA is a unique pattern of aneurysm growth. While smaller aneurysms grow centrifugally from within the lumen predominantly under hemodynamic influences, GA have a tendency for

extra-luminal growth (65). The principal reason for this is the presence of a thrombosed component with associated inflammatory response (66).

The natural history of partially thrombosed aneurysms has been a matter of considerable debate and speculation. Some authors have mentioned that presence of a thrombosed component protects the aneurysm from due to reinforcement of the vessel wall but manifest predominantly with either mass effect due to local compression or due to thromboembolic complications (46,67).

Imaging of GA:

While digital subtraction angiography (DSA) remains the gold standard for the evaluation and treatment planning of all aneurysms including GA, computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) also serve as excellent non-invasive techniques for follow up and assessment of aneurysm growth or recanalization after treatment.

GA offer certain anatomic peculiarities which mandate imaging with other cross-sectional modalities. The size of the aneurysm and compression on adjacent neural structures is best evaluated on MRI. MRI also serves to evaluate the thrombosed component of the aneurysm which is a unique feature of large and giant aneurysms.

With specific neuroimaging parameters, it is possible to differentiate between GA where the lumen is fully perfused and the so-called “partially thrombosed” entities, in which the maximal aneurysmal as detected by cross-sectional imaging is larger than that of the patent aneurysm lumen which shows contrast / flow within. The partially thrombosed aneurysms often show distinct imaging appearances and are often regarded by various authors as separate entities. The unique features of these

aneurysms are the tendency to grow regardless of their size (68), with some showing increase in size even after complete parent artery occlusion and cessation of flow to the aneurysm (69). They are also more prone to present with mass effect (70) and on MRI, show typical features of thrombi of varying ages in a laminated (onion-peel) fashion with a smaller or even absent patent lumen. Due to sudden progress of the thrombosed component, these aneurysms may exhibit a sudden rapid increase in size on serial imaging with compression of the adjacent neuro-parenchyma and associated oedema (71). An enhancing rim can be also be perceived which may be due to either one of , or a combination of peri-aneurysmal inflammatory change and neovascularization with proliferation of the vasa-vasorum (67,72).

Management of GA

The ideal treatment of any aneurysm is to completely exclude it from the circulation while maintaining full patency of the parent artery and all its branches. Surgical methods for GA (as for all IA) are the older and time honoured methods. Endovascular procedures have gained widespread acceptance over the past two and half decades.

Surgical Techniques:

Microsurgical clipping is the surgical technique of choice and wherever feasible offers the most durable and physiological treatment option. Success of surgical clipping depends on the anatomic complexity and the aneurysm morphology with the ideal requirement being the presence of a well-defined aneurysm neck. The clip is positioned in such that it apposes the vessel walls at the aneurysm neck while preserving the luminal patency (73). Simple clipping of fusiform aneurysms with no definable neck and origin of vessels from the aneurysmal segment is often impossible

and clip reconstruction techniques are frequently required to exclude these aneurysms from the circulation. A significant risk of mass effect may necessitate aneurysm opening and thrombus evacuation after it has been eliminated completely from the circulation (74).

Temporary proximal clipping prevents inadvertent premature rupture, allows visualization of perforating vessels and also permits readjustment of the clips (54).

When clipping is not feasible due to aneurysm size, morphology or location, other surgical options come to the fore. These include aneurysm trapping and proximal parent artery occlusion (with or without bypass). While the former excludes the aneurysm completely from circulation, proximal artery occlusion causes reduced retrograde flow into the aneurysm and promotes thrombosis.

Various bypass techniques have been described such as direct vessel re-implantation, side- to-side anastomosis, low-flow bypass of extracranial-intracranial arteries and high-flow bypasses using the radial artery or the saphenous vein grafts (75–77).

Endovascular Methods:

There are essentially two physiological forms of endovascular treatment of IA.

1. Reconstructive: The aneurysm is excluded from the circulation while preserving parent artery flow.
    a. Primary aneurysm coiling (with neck support devices)
    b. Flow diversion
2. Deconstructive: Eliminating the aneurysm and parent artery circulation with parent artery occlusion (with or without aneurysm trapping).

Aneurysm Coiling:

The development of dedicated intra-cranial detachable coils by de Guglielmi (78) have revolutionised the management of intra-cranial aneurysms. Since the early days, advancements in the coil technology as well as in the coil delivery devices and support devices have led to endovascular management being an indispensable tool in the treatment of IA. In comparison to smaller aneurysm, giant aneurysms and their morphological peculiarities bring with them a set of unique challenges to endovascular coiling.

Coils are linear wires of specialised metallic alloys which are tightly wound around a core wire called the stock wire, which are packaged by the manufacturer in sheaths which restrict the coils (79). Once unrestricted, the coils occupy a variety of shapes and configurations in 3-dimensional space with the diameter and the length of every individual coil determining the volume that will be occupied. The commonest alloy used for coil manufacture is Platinum/Tungsten (92% : 8%). The earliest developed detachable coils were simple helical 2-dimensional coils. Subsequent research has seen the development of 3-dimensional coils with varying softness as well as a variety of bioactive coils (11).

As with the variety of coil designs, a number of different detachment mechanisms have also been developed. The earliest GDC coils were eletrolytically detachable. Current coil detachment mechanisms are either electrolytic, mechanical or hydrostatic.

Based on the stage of aneurysm coiling coils can be further sub-classified into framing coils, filling coils and finishing coils. While framing coils provide a relatively sturdy 3-dimensional skeleton within the aneurysm, subsequent filling and finishing

coils are usually softer coils meant for filling of the interstitial spaces and ensuring adequate packing density.

Coils are delivered into the aneurysm through microcatheters. Standard coiling microcatheters vary between sizes of 1.5 to 2.1 on the French (Fr) scale (outer diameter). These microcatheters have 2 distal markers, one at the tip and another 3 cm proximal to the tip (80). The latter marker is used to identify the proximal marker of the coil and ensure complete unrestriction of the coil before detachment. The current microcatheters used for aneurysm coiling have variable degree of metallic braiding which ensures better response to push and torque as well as better stability. The "coiling catheters" need to be navigated over dedicated intra-cranial microwires (usually of 0.014" diameter).

Assisted Coiling:

The initial method of intra-cranial aneurysms coiling was simple coiling of the aneurysm sac by introducing a microcatheter within the aneurysm. It was soon noted that while the technique in itself was a novelty, there was much scope for refinement. Most notably, there was a tendency of the coil mass to prolapse into the vessel wall, thereby causing risk of thromboembolic complications. There was also a risk of complete coil displacement from the aneurysm with distal migration and occlusion of smaller arteries. The risks of coil prolapse are highest with wide necked aneurysms. These entities are defined based on either a neck diameter greater than 4 mm or a neck: dome ratio less than 1: 2 (81). Giant aneurysms, in view of their large size are usually demonstrate wide necks and thus are unsuitable for simple coiling. The two commonly used techniques for aneurysm neck support during coiling are balloon assistance and stent assistance.

Balloon assisted coiling (BAC):

The basic principle of BAC is inflating a non-detachable balloon across the aneurysm neck to protect the parent vessel while deploying coils inside the aneurysm sac through a separate microcatheter. After completion of the procedure, the balloon is deflated, removed and no permanent device is left within the native vessel.

Intra-cranial balloons in current use are made of polyurethane and mounted over specialised delivery microcatheters. Different balloon delivery systems have different microguidewire diameter compatibility. Depending upon the configuration of the microcatheter, the balloons may be classified as single lumen or double lumen balloons. (81).

Single Lumen Balloons:

These devices have a single internal lumen and the balloon is inflated with the microwire in situ. The central lumen of the catheter has a variable number of side holes which allow for balloon inflation with contrast once the wire has been passed through the distal tip of the catheter. Commonly used single lumen balloon are the Hyperglide / Hyperform (Ev3) and the Transform (Stryker) balloons. The former are compatible with 0.010" microwires while the latter are compatible with 0.014" microwires. Balloon catheters with smaller wire profiles induce less deformation or the native vessels during navigation but are also less stable during navigation and inflation.

Dual-Lumen Balloons:

The microcatheter assembly of dual lumen balloons have separate channels for wire navigation and balloon inflation. Commonly used double lumen balloons are the

Scepter C / XC (Microvention, Tustin CA) and the Ascent (Codman) balloons. The Ascent balloon also contains a 3 cm marker proximal to the distal tip which can be utilised in exceptional circumstances for coiling directly through the balloon microcatheter. Commercially available dual lumen balloons are compatible with 0.014" microwires.

Balloon Compliance:

Compliance is a term use to define the mechanical property of the balloon by which the inflated balloon moulds its 3-dimensional morphology according to the configuration of the parent artery in which it is being deployed. Based upon a relatively higher or lower degree of compliance, the balloons are classified as compliant or super-compliant balloons. Compliant balloons are designed for use in distal vasculature and across complex bifurcation aneurysms due to their tendency to cause less parent vessel deformation.

Techniques of Balloon Assisted Coiling:

Safety concerns were initially noted in balloon assisted techniques due to the fear of thrombo-embolic complications as well as vessel wall injuries due to balloon inflation. Shapiro et al in a systematic review of 23 studies between 1997 and 2006 compared the safety profiles and outcomes of 867 simple coiling procedures and 273 balloon assisted coiling procedures (82). The study found no statistically significant difference in the risk of thromboembolic complications or procedure related vessel injury between the two groups. In addition, they found higher rates of initial and long term aneurysm occlusion with balloon assisted techniques. Apart from providing better angiographic outcomes, balloons are also an invaluable tool in the emergency management of intra-procedural vessel or aneurysm rupture. Immediate balloon

inflation and flow arrest allows the interventionist to plan a definitive management and reduce a catastrophic intra-cranial bleed (83). Indeed, in the setting of acutely ruptured aneurysms where stents are not preferred, balloon assisted coiling forms the first line method of treatment, both to ensure optimal packing and as a remedial measure in case of an inadvertent rupture.

Stent Assisted Coiling:

While the use of balloon assistance for aneurysm coiling greatly reduced the problems of recanalization and coil prolapse after simple coiling, it did not completely eliminate these issues. To further reduce the incidence of these issues, the use of stents was looked into to bridge the aneurysm neck while coiling. Stents have three technical advantages over balloons during assisted coiling (84). First, it provides more rigid support to the aneurysm neck during coiling, thus enabling lesser catheter kickback and allowing for tighter packing. Secondly, as the stent is left in situ after coiling, it prevents delayed coil prolapse and migration into the parent vessel. Finally, the stent brings a unique property known as flow diversion by which there is a mechanical reduction of flow into the aneurysm merely because of the structure of the stent across the aneurysm. In the long term, the stent surface undergoes endothelialisation, thus further reducing the chances of recanalization of the aneurysm.

In the absence of dedicated intra-cranial stents, the first report of stent assisted coiling using a coronary balloon expanding stent was published by Higashida et al (85). After this report a number of case reports and series were published describing the use of coronary stents for aneurysm coiling. While reporting better angiographic outcomes, the use of balloon mounted stents had a relatively higher incidence of morbidity and mortality arising out of intra-procedural complications (84). These stents were also

more difficult to navigate across tortuous intra-cranial arteries thus creating higher rates of unsuccessful procedures. A combination of the above described factors led to research veering in the direction of development of dedicated intra-cranial stents.

Intra-Cranial Self Expanding Stents:

All currently available intra-cranial stents are manufactured with Nitinol, which has the unique property of memory shape. All stents are self-expanding and delivered through specialised delivery systems suited for navigation through tortuous anatomy. The Neuroform (Boston Scientific Neurovascular, Fremont, California, USA) was the first stent approved by Food and drug administration (FDA). It has an open cell Nitinol design providing 6.5 to 9.5% metal coverage across the aneurysm neck (84) . Newer generations of neuroform stents have subsequently been marketed, predominantly based on advances in the delivery and detachment mechanisms (Neuroform 2, Neuroform 3 and Neuroform EZ). A number of commercially available stents have since been developed which are broadly classified based upon the strut design as having open cell or closed cell configurations (86).

Open Cell Stents : Neuroform, Wingspan.

Closed Cell Stents: Enterprise, Leo, LVIS, Solitaire.

Low Profile Stents:

These devices have been developed to fit smaller sized feeding arteries (upto 1.5 mm in diameter). In addition, these stents are can be delivered through smaller microcatheters (internal diameter of 0.0165”), which greatly eases the navigability of the device through tortuous arteries (87), (88). The commercially available low profile

stents are the LVIS junior (Microvention, Tustin CA) and the Leo Baby (Balt, Montmorency, France) stents.

Issues & complications with Stent assisted coiling:

The most obvious complication in relation to use of stents is a higher incidence of thromboembolic complications. As the stent is a permanent indwelling metallic foreign body layered along the vascular intima, it incites higher risk of local thrombus formation, which may occlude the stent completely or cause distal emboli. As a result, all stents are used with the patient under dual anti-platelet medication cover (Thromboxane A2 inhibitors and P2Y12 receptor antagonists). Usual practice consists of pre-treating patients with 5 to 7 days with anti-platelet drugs before performing the procedure. The obvious issue of anti-platelet drug pre-treatment concerns the use of stents in acutely ruptured aneurysms in which there is higher risk of aneurysm re-bleed.

Different techniques have been practiced to overcome this difficulty such as administering intra-venous anti-platelet medications after securing the aneurysm dome with the first coil, administering a loading dose of anti-platelet medications on the day of the procedure, and / or usage of platelet aggregation inhibitor (GpIIb/IIIa inhibitors) to manage intra-procedural thrombotic complications. Other authors advise an initial balloon assisted partial coiling during the acutely ruptured phase to secure the aneurysm and prevent re-bleed followed by later elective stent assisted coiling.

Techniques of Stent Assisted Coiling: A variety of different techniques have been described for SAC, each having its own set of advantages and limitations. Based upon individual angiographic anatomy, a technique is chosen on an individual basis to best

optimise the results of the intervention. Some of the techniques described in literature are as follows (81) :

Sidewall Aneurysms: A variety of techniques have been described for SAC of side wall aneurysms. The stent may be deployed before or after coiling of the aneurysmal sac (finishing and rescue stent techniques).

(a) Finishing Stent and Rescue Stent Techniques: In these techniques, the stent is deployed after completion of coiling, often as a bailout procedure to push a prolapsed coil mass into the aneurysm sack (stent jack technique). The term "Rescue stent" is specifically used for a bailout procedure when a coil loop has prolapsed into the parent vessel. In this case, a stent is deployed to trap the coil loop between the vessel wall and the stent, hence preventing it from coming in contact with freely flowing blood in the arterial lumen.

(b) "Jailed" Microcatheter technique: In this technique, the coiling microcatheter is passed into the aneurysm prior to deployment of the stent. As a result, deployment of the stent results in trapping or "jailing" of the microcatheter between the vessel wall and the stent. This offer more stability to the microcatheter during coiling and is prone to less 'kickback' of the microcatheter. The drawback of this technique is difficulty in regaining access into the aneurysm in case of inadvertent catheter kickback.

(c) "Through the Struts" coiling technique: In this technique, the stent is deployed first and the microcatheter is then navigated into the aneurysm through the stent struts. The disadvantage of the technique is difficulty in accessing the aneurysm through the struts and a higher risk of microcatheter kickback.

(d) Semi-Jailing Technique: In this method, after initial cannulation of the aneurysm, the stent is partially deployed. To provide neck support during coiling. Usually a retrievable stent (e.g. Solitaire AB) is used, which may either be completely deployed and detached or withdrawn if the coil mass remains stable after completion of coiling. The technique of removal of a partially deployed stent after coiling is known as temporary stenting.

Specialised techniques for SAC in Bifurcation aneurysms: Stenting techniques for bifurcation aneurysm are dictated by two factors, the width of the neck and the complexity of the vascular anatomy. Based on the above factors, different techniques have been described.

(a) Single stent: deployed across the proximal vessel into one of the branches, usually the larger or more easily accessible branch.

(b) "Y" Stent: Initial deployment of an open cell stent into one of the branch vessels, followed by deployment of a 2^{nd} stent through the struts of the 1^{st} stent into the other vessel.

(c) "Double Barrel" technique: 2 stents are deployed as in the "Y technique, but the proximal ends of the stent lie side by side in the proximal vessel instead of one within the other.

(d) Waffle Cone Technique: In exceptionally difficult bifurcation aneurysms, the distal end of the stent is deployed into the aneurysms, which then flares within the aneurysm dome and supports the subsequently deployed coil mass.

(e) "X" Stenting: Used in crossing anatomy such as Anterior communicating artery (ACoM) aneurysms. 2 crossing stents are deployed in an "X" shaped manner from one proximal artery to the contralateral distal artery.

Complications of aneurysm coiling – Comparison of different methods:

Sluzewski et al in a 2006 publication, cited that balloon assisted coiling was wrought with significant risk of complications and advised that the procedure should be performed only if simple coiling was impossible or had been unsuccessful (89). A subsequent literature review by Shapiro et al did not validate these findings and the authors found no significant differences in complication rates between BAC and simple coiling with higher angiographic occlusion rates reported in BAC (82). The Analysis of Treatment by Endovascular Approach of Nonruptured Aneurysms (ATENA) study and the Clinical and Anatomic Results in the Treatment of Ruptured Intracranial Aneurysms (CLARITY) study were multi-center prospective studies aimed at analysing the safety and efficacy of balloon remodelling techniques in aneurysm treatment (90,91).

The ATENA study reported an overall morbidity of 2.2% in the simple coiling group and 2.3% in the BAC group and mortality of 0.9% and 1.4% respectively. The CLARITY series reported morbidity of 3.9% and 2.5% and mortality of 1.2% and 1.3% respectively for the coiling and balloon remodelling groups. Pierot et al in a 2012 review (92) of the technique stated that except for one early study (89), all other subsequent publications have shown no significant difference in the safety profile of simple and balloon assisted coiling with better aneurysm occlusion rates in the balloon remodelling technique .

Yang et al performed a comparative study on the outcomes of simple coiling and endovascular coiling on a total of 512 patients over a 1 year period and reported comparable procedure related complication (6.2 % in coiling group and 6.3% in the SAC group) with a lower recurrence in the SAC group (5.2 % against 16.5%, p=0.002). They also reported comparable mortality (1.2% in coiling and 1.5% in SAC) and morbidity (1.6% in coiling and 1.1% in SAC) figures in each group (93). In a similar analysis on 416 aneurysms treated over a 9 year period, Ghinda et al compared the results of SAC and non-stent assisted coiling (94). The study showed insignificant differences in good outcome rates (93.6 % in the non-SAC group against 98.2% in the SAC group) with a significant difference in recanalization rates (9.5% in the non-SAC group against 11.3% in the SAC group). Zhao et al performed a systematic review and meta-analysis including 38 studies on 2556 wide neck aneurysms (in 2446 patients) and examined the results of SAC and non-SAC. They reported an overall complete occlusion rate of 74.5% with long term good outcome of 91.4% and recanalization and retreatment rates of 5.8% (95).

The safety of SAC is questionable in the setting of acutely ruptured aneurysms in view of the need for anti-platelet medication to prevent in-stent thrombosis and the inability to pre-medicate the patient before securing the aneurysm. While some studies have mentioned that platelet aggregation inhibitors like tirofiban are a safe alternative in the treatment for such aneurysms, use of stents in ruptured aneurysms (96), remains very much a last resort option in the practice of most endovascular surgeons .

Challenges in Coiling of Giant Aneurysms:

Most giant aneurysms have wide necks and hence are not suitable for simple coiling due to high risk of coil prolapse into the parent arteries. Even classical berry aneurysms often incorporate large lengths of the parent vessel within the aneurysm wall making complete coil embolization practically impossible. The large size of the aneurysms heralds a higher likelihood of coil compaction and subsequent aneurysm recanalization (13). Aneurysms which harbour large volumes of intra-luminal thrombi are also at a higher risk of recanalization after coiling. This happens because of 2 phenomena: First, the coil mass may migrate into the relatively soft thrombus leading to opening of spaces within the previously coiled aneurysm lumen (97). Secondly, there may be peripheral dissolution of the thrombus leading to recanalization peripheral to the coil mass.

Deconstructive technique – Parent Artery Occlusion:

Deconstructive method of aneurysm treatment is by occluding the parent artery supplying the aneurysm. When feasible, this procedure is relatively simple with a good safety profile and provides a long term durable aneurysm occlusion. Parent vessel occlusion (PAO) can be performed in proximal arteries such as the ICA, unilateral or bilateral vertebral arteries and the proximal basilar trunk as well as on intracranial arteries distal to the circle of Willis.

In the ICA, parent artery occlusion is feasible for cavernous and proximal supra-clinoid (ophthalmic segment) aneurysms, though more distal ICA occlusion may be considered if the posterior communicating artery (PCOM) is absent and collateral flow is only across the anterior communicating artery (ACoM). The mandatory procedure prior to performing a therapeutic ICA occlusion is the balloon occlusion

test to assess for tolerance to vessel sacrifice. Though a number of provocative techniques spanning different modalities are available but the clinic-angiographic assessment over a 30-minute balloon occlusion is currently the most accepted technique. The angiographic tolerance of balloon occlusion is assessed by measuring the cerebral circulation time on the occluded side as compared to the contralateral side. Different authors have cited different acceptable delay times from 1s to 2s (98,99).

Clarencon et al in their series of 26 cases reported 100 % good outcome with permanent occlusion in 17 of 18 cases with available follow up (100). Laberyie et al in a series of 56 consecutive carotid siphon aneurysms treated with PAO reported zero mortality with 5% morbidity and a 91% aneurysm retraction rate. The authors have advised aneurysm trapping as the method of choice as opposed to only proximal parent artery occlusion (15).

In the posterior circulation, vertebral artery (VA) aneurysms proximal to the PICA can usually safely be treated with aneurysm sac coiling along with proximal vessel coil occlusion (101). Basilar trunk or distal VA aneurysms have in the past been treated with VA and proximal BA occlusion, however the safety profile of the techniques is yet to be established (102,103).

Occasionally giant and large aneurysms may be located in arteries distal to the circle of Willis. There aneurysms are usually fusiform or serpentine in morphology and are often the sequelae of processes like dissection or infection. Due to the morphology and their distal location, the flow in these arteries is usually impaired, with the distal territories gaining perfusion across collateral vessels (53). In such circumstances, occlusion of the artery becomes the ideal treatment modality. van Rooij et al state,

that if feasible, the parent artery sacrifice may be undertaken after a balloon occlusion test to check for tolerance (104). In case a provocative occlusion test is not feasible, the artery may be sacrificed weighing the benefits of aneurysm occlusion against the risk of a distal territorial infarct (105).

Flow Diverters:

Flow diverters (FD) are essentially intra-cranial bare metal stents (usually manufactured from Nitinol or cobalt chromium alloys) which have high mesh density and low porosity. While conventional intra-cranial stents have mesh density less than 10%, flow diverting stents have density varying between 25 to 50%. This higher mesh density serves to selectively divert blood flow away from the aneurysm sac (when the stent is deployed across the neck).

FD- Concept & Development:

The earliest conceptual origin of the principle of 'flow diversion' was noted in-vitro models where studies using techniques like image velocimetry and laser induced fluorescence demonstrated that deployment of a stent across aneurysms caused a shift in blood flow from within the aneurysm sac and redirected it distally into the native vessel (106). Wakhloo et al (107) deployed first generation stents across experimentally produced aneurysms in canine arteries and subsequent autopsy studied showed both progressive aneurysm thrombosis as well as preserved stent patency along with an absence of significant thromboembolic complications.

Subsequent research showed two factors that predicted the degree of flow diversion and eventual aneurysm occlusion, FD properties and hemodynamic factors.

Flow diverter properties: 3 closely related terms are used to describe the physical attributes of flow diverting stents – the mesh density, which is the percentage of metallic coverage provided over any unit area of the stent; the porosity of the stent which is the inverse of the mesh density and the pore density (108,109). The latter factor refers to the number of pores in a stent over a given unit of surface area. Experimental studies have shown that a mesh density above 20 % (porosity < 80%) provides adequate flow diversion effect to induce intra-aneurysmal thrombosis (110,111). Conventional intra-cranial stents provide mesh density of less than 10%, however in exceptional circumstances and in small aneurysms, they too have been noted to cause complete aneurysm thrombosis due to flow diverting effect. Commercially available FD have mesh density varying between 25 % to 45 % (112). The trade-off in deploying stents with higher mesh density is the progressively increased risk of perforator and side-branch occlusion as well as an increased risk of thromboembolic complications.

Hemodynamic factors : CFD studies have shown that flow diverting effects of stents is more pronounced in side-wall aneurysms as compared to those located on a curve of a vessel. The reason for the same is that in the former, the predominant flow is shear driven whereas in the latter the predominant flow is inertia driven (113,114).

FD – Side branch and perforator preservation: The logical question which arises out of deploying a stent across an aneurysm is the potential coverage of smaller branches and perforator vessels with the resultant risk of occlusion of these vessels. A number of in-vitro studies (115,116) have shown than even with smaller branch vessel coverage of greater than 90%, there is a less than 10% reduction in flow within these vessels. The explanation of this phenomenon is the existence of a pressure gradient which drives blood flow from the parent artery into side branches. This gradient is negligibly affected even with a considerable degree of metal coverage across the

branch vessel ostium hence preserving flow within the vessel (109). As has been detailed previously, the gradient begins to drop with a progressive increase in mesh density and decrease in porosity thus thereby increasing the chances of branch vessel occlusion. It is for this reason that commercially available FD maintain mesh density between 25 to 45 % (porosity between 75% to 55%).

FD: Clinical and technical issues:

As with other intra-cranial stents, FD are highly thrombogenic and are routinely advised to be deployed with the patient under dual anti-platelet (DAP) medication cover. Due to higher metal coverage over the vessel wall, which causes a higher risk of thrombogenicity, many authors routinely advise performance of platelet function tests, before and after starting DAP to ensure optimal platelet suppression. Routine use of Aspirin (150 mg) and clopidogrel (75 mg) for 5 days is usually sufficient to provide adequate platelet suppression. However in cases of clopidogrel resistance (confirmed on platelet function test), the patient may be switched over to a different P2Y12 receptor antagonist (e.g. Prasugrel, Ticagrelor) prior to performing the procedure.

FD are deployed across larger microcatheters (ID between 0.021 to 0.027"). The microcatheter is first used to cross the aneurysm neck using a 0.014" microwire and advanced distally till a position of stability is reached. Subsequently, the stent is passed through the microcatheter and deployed across the aneurysm neck. Optimal stent size (in terms of diameter and length) has to be selected to ensure adequate neck coverage as well as optimal sizing to fit the vessel diameter.

Technical issues which arise during FD deployment are usually difficulty in crossing the aneurysm neck in case of wide necked and fusi-saccular aneurysms, difficulty in navigating the device across tortuous intra-cranial vasculature, inadequate stent

apposition to the vessel wall and stent migration after deployment. Microwire or microcatheter access should be maintained through the stent into the distal artery till the procedure is successfully completed. In case of inadvertent stent migration, a 2nd device may then be passed and telescoped across the initial stent to cover the aneurysm neck.

Commercially Available FD: The SILK FD was the first to be developed and commercially marketed followed by the Pipeline embolization device (PED). Table 3.2 lists the major properties of the commonly available FD.

Table 3.2 : Major Commercially available flow diverters

Name	Vendor	Material	Design	Resheathability
Silk	Balt Extrusion, Montmorency, France	Nitinol	48 braided nitinol strands and 35-µm platinum microfilaments. 45-60% porosity	90%
Pipeline (PED)	ev3/Covidien, Irvine,CA, USA	25 % platinum and 75 % nickel–cobalt–chromium alloy	65 to 70% porosity.	Zero
FRED	Microvention, Tustin, CA, USA	Nitinol	Dual layer, stent within stent design.	50%
SURPASS	Neurovascular, Fremont, CA, USA	Cobalt chromium alloy	Porosity 70% Uniform pore density	80%
p64	Phenox, Bochum , Germany	Nitinol	Braided mesh tube of 64 strands Controlled mechanical detachment	100%

Results of FD studies: Angiographic and clinical outcomes of different studies and trials with flow diverters are summarized below.

PED was successfully deployed in 107/108 patients (99.1%) in the Pipeline for uncoilable or failed aneurysm (PUFS trial) with an 86% complete occlusion rate (117). An international study, the International Retrospective study of the Pipeline embolization device (IntrePED) retrospectively collected data from 793 patients with 906 aneurysms (118). The study showed relatively low neurologic morbidity and mortality (7.4%). Higher incidence of adverse effects was noted in large, ruptured, and posterior circulation aneurysms. Ischemic stroke was the majority of complications (4.7%) with relatively uncommon occurrence of delayed aneurysms rupture (0.6%). Wakhloo et al published the results of a prospective, single-armed, multi-center clinical study of the Surpass flow diverter (119). The authors reported successful placement in 161 of 186 aneurysms (98%), and neurologic death or any stroke within 6 months in 18 patients (12%). In a clinical study published by Mohlenbruch et al (120), 29 patients with 34 aneurysms were treated with the FRED device with 100% successful placement and no complications in 26 cases (89%). Briganti et al examined the results of p64 device deployed in 40 patients with 50 aneurysms in six Italian centres (121). The authors reported permanent aneurysm occlusion rates of 88% with one single ischemic stroke (2.5% morbidity) and zero mortality.

Ye at al performed a meta-analysis of 48 studies with 2508 patients with 2826 intra-cranial aneurysms (122). The total occlusion rate at a mean follow up duration of 6.3 months was 77.9%. Morbidity and mortality rates of 9.8% and 3.8% were reported. Rates of spontaneous aneurysm rupture, intra-parenchymal haemorrhage and ischemic

strokes were 2.0%, 2.5% and 5.5% respectively. The authors did notice significantly worse outcomes in giant aneurysms as well as in posterior circulation aneurysms.

FD – Safety Issues:

Treatment of aneurysms with FD is perhaps the most physiological method as it reconstructs the vessel lumen with exclusion of flow into the aneurysm sac. Early results have been promising, in that a more durable aneurysm occlusion is obtained as compared to coiling. As a result, there has been a tremendous upsurge of research in this field with the development of multiple devices and emergence of various studies citing their efficacy.

However, FD still have a number of safety related issues that cloud their status as the true panacea of intra-cranial aneurysm treatment.

These devices are highly thrombogenic due to the high metal coverage and necessitate long term dual anti-platelet therapy and lifelong single anti-platelet therapy. The requirement of anti-platelet medication precludes avid use of these stents in acutely ruptured aneurysms. In spite of the use of anti-platelet medications, there is a definite higher risk of device occlusion and thromboembolic complications after the deployment of FD (123).

Technique of stent deployment is critical as improper wall apposition may reduce flow and incite thrombus formation (124) . In the early post deployment period, there is significant turbulence and stasis of blood within the aneurysm sac leading to fresh "red" thrombus formation. A combination of these factors along with release of lytic enzymes due to platelet aggregation may cause aneurysm rupture and SAH. Peri-aneurysmal inflammatory changes coupled with the altered hemodynamics after FD deployment may lead to sudden increase in aneurysm size and transient worsening of

clinical symptoms (125). Another poorly understood but dreaded complications of FD is delayed intra-cerebral haemorrhage This entity is rare and is usually noted after uneventful procedures. It has been explained by some authors as a sequelae of small micro-emboli in the distal circulation with haemorrhagic transformation of the resultant small infarcts. Other authors have attempted to explain it by the phenomenon of dampened flow with increased distal arteriolar pulsatality and rupture (126).

Specific areas of concern in the use of flow diverters are GA and posterior circulation aneurysms. In GA, safety concerns arise out of higher incidences of haemorrhagic complications and incomplete occlusion. Both the PUFS and the IntrePED studies showed poorer outcomes in patients with GA as compared to those with smaller aneurysms (117,118). Furthermore, fusi-saccular GA may necessitate use of 2 or more telescoped flow diverters with requirement of prolonged wire and catheter manipulation within the aneurysm which may further increase the risks of intra-procedural rupture.

The major posterior circulation arteries (VA, BA and PCA) are perforator rich arteries. In addition, there is a higher incidence of non-saccular aneurysms at these locations. The factors combine to make the use of FD in posterior circulation aneurysms more challenging and with serious safety concerns. In one of the early studies, Siddiqui et al reported the results of FD placement in 7 posterior circulation aneurysms, of which 4 patients died after the procedure and only 2 patients had a good outcome (127). In a recent meta-analysis, Wang et al pooled the results of 14 studies with FD placement in 225 posterior circulation aneurysms on 220 patients (128). Although an overall aneurysm occlusion rate of 84% was noted, there was a significantly higher mortality rate for giant and basilar aneurysms (15%). Higher complication rates were also noted with 11% incidence of ischemic strokes, 7% perforator territory infarcts and 7% overall haemorrhagic complications (SAH and

delayed). There have also been concerns about the deployment and use of FD in giant middle cerebral artery aneurysms. PAO in these aneurysms is not an option unless accompanied by an associated bypass procedure. Huang et al state that compared to more proximal aneurysms, there is greater technical difficulty in navigating the devices across the aneurysm in the MCA along with a higher risk of haemorrhagic complications (129).

Combined Surgical and Endovascular Treatment:

The complex and bizzare morphology and location of GA occasionally precludes treatment by a single modality. In such circumstances , a number of combined surgical and endovascular techniques have been described for optimal outcome (130). These include coiling of the aneurysm dome (in a acutely ruptured setting) flowed by neck clipping, proximal control of flow using a temporary balloon inflation, proximal endovascular vessel occlusion prior to aneurysm excision, Hybrid endovascular and surgical suites facilitate these procedures with simultaneous or sequential performance of both surgical and endovascular procedures (131). Lawton et al described their results in a series of patients treated with combined surgical and endovascular approaches and reported total angiographic occlusion in 95% cases and good outcomes in 86% cases (132).

To summarize, the management of GA is still a work in progress, with both surgical and endovascular techniques having a collaborative role. Ongoing research and development in the field might eventually yield or perfect a technique which offers the best long term angiographic as well as clinical outcome but currently such a technique is still lacking. Hence, treatment of these complex entities requires a combined inter-disciplinary approach aimed at targeting each individual lesion in isolation rather than attempting treatment from a generic perspective.

Materials &

Methods

Data Collection:

The study was planned as a retrospective-prospective descriptive study and appropriate institutional ethics committee clearance was obtained. Institutional medical records from 2005 were reviewed with key word search combinations of "Giant aneurysm", "Large aneurysm" and "fusiform aneurysm" and "intracranial" and "intradural". The imaging data of the search results were reviewed and patients were selected for the study who fit the following inclusion criteria.

1. Largest aneurysm dimension > 25 mm.
2. Intra-dural or transitional zone aneurysms.

The following criteria were used to exclude patients from the study:

1. Patients with the largest aneurysm dimension < 2.5 cm.
2. Purely extra-dural aneurysms.
3. Post-traumatic / iatrogenic / infective pseudoaneurysms.
4. Patients with unavailable imaging or clinical records

The prospective arm of the study was started in June 2014 and patients were enrolled from the Neurology, Neurosurgery and Neuroradiology out-patient departments (OPD). After obtaining informed consent the patient data and the imaging parameters were evaluated for baseline assessment.

The patient demographics such as age at presentation, sex and the presence of co-morbidities like diabetes mellitus (DM) and hypertension (HTN) were recorded. The patients were then classified based on the initial clinical presentation into 4 sub-groups.

1. Sub-arachnoid haemorrhage (SAH)
2. Mass effect
3. Thromboembolic events
4. Other / incidental

The clinical status of the patients were also recorded as per the modified Rankin Score (mRS) (133). This system is described in table 4.1.

Table 4.1: Modified Rankin Score (mRS) for assessment of clinical severity of symptoms.

Score	Assessment
0	Asymptomatic
1	Mild symptoms but able to carry out all usual activities
2	Slight disability. Unable to perform all usual tasks but able to perform own affairs without assistance
3	Moderate disability. Able to walk unassisted but requires some help for daily activities.
4	Moderately severe disability. Not able to walk without assistance and requires hep to attend to personal bodily needs.
5	Severe disability requiring constant nursing case. Bedbound and incontinent.
6	Dead

The initial and all subsequent follow up imaging data of the patients were reviewed. Based on the imaging, the aneurysms were described according their shape, size, location and the presence or absence of thrombus.

Based upon their morphology, GIDA were classified into saccular, fusiform and serpentine types. Aneurysm location was described based upon involvement of the anterior circulation (ICA, ACA, MCA) or the posterior circulation (VA, BA, PCA).

Analysis of treatment modalities

Patients were categorized into three groups based on the treatment modality adopted.

A. Conservative.

B. Surgical.

C. Endovascular.

The reasons for the selection of a particular modality of treatment along with future follow up of the patients were used to study the clinical effectiveness of the treatment modality as well as the natural progression of the disease entity.

A. Conservative:

The clinical documents of all patients were reviewed along with OPD follow up. Follow up imaging data, if available was analysed for serial growth. mRS at final OPD follow up was noted. In case of patients lost to clinical follow up, attempts were attempted to contact the patient or his / her relatives over the telephone.

B. Surgical:

The types of surgical procedure, peri-procedural complication and mRS at discharge and final OPD follow up were noted with reasons for death in fatal cases. Angiographic follow up is not routinely done in the post-surgical cases at our institute and hence the same was not available for analysis.

C. Endovascular:

3 types of endovascular procedure are routinely performed at our institute

i) Aneurysm Coiling

ii) Parent artery occlusion

iii) Flow diverter (FD) placement

The type of procedure with the resultant post procedural complications (if any) were noted. Angiographic outcome was noted immediately after the procedure and at available follow up. Follow up vascular imaging was either computed tomographic angiography (CTA), magnetic resonance angiography (MRA) and digital subtraction angiography (DSA). 2 scales of angiographic occlusion were used to report outcome. The modified Raymond scale was used to report outcomes after aneurysm coiling and parent artery occlusion (Table 4.2). The O'Kelly Marotta (OKM) scale (134) was used to report outcomes after FD placement (Table 4.3) .

Table 4.2: Modified Raymond score for assessment of aneurysm occlusion after endovascular aneurysm treatment.

Score	Angiographic Feature
1	Complete aneurysms obliteration including neck
2	Neck opacification without sac opacification
3	Sac opacification

Table 4.3 : O'Kelley Marotta Scale for angiographic occlusion after FD placement.

Degree of Aneurysm Filling	**Persistence of Contrast in Angiographic phase**		
	Arterial Phase 1	**Capillary Phase 2**	**Venous Phase 3**
A Total Filling	A1	A2	A3
B Sub-total filling	B1	B2	B3
C Entry Remnant	C1	C2	C3
D No filling	D		

Statistical Analysis:

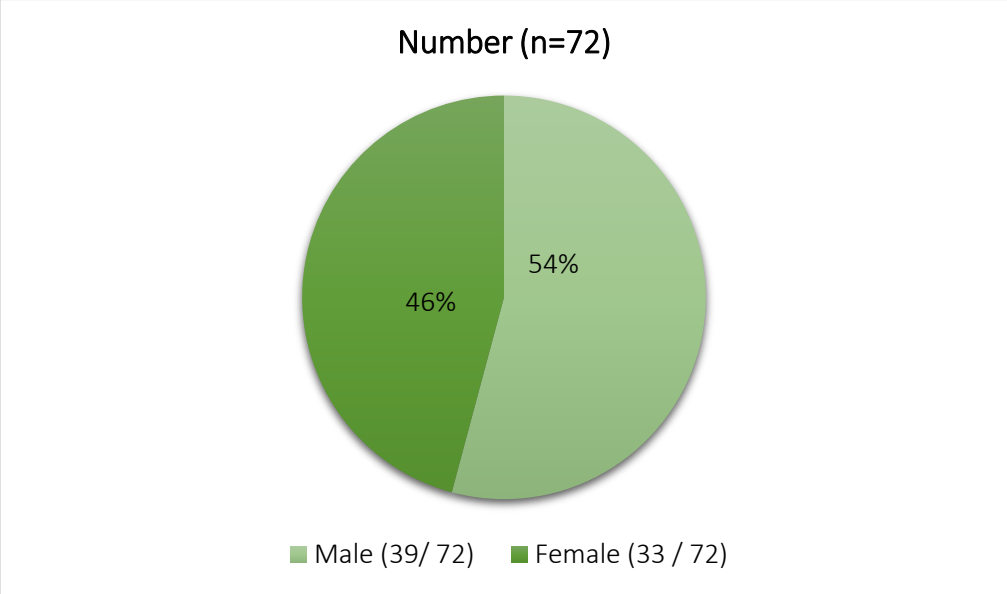
Univariate analysis was performed of the different demographic and morphological parameters with aneurysm location, initial clinical symptoms and clinical state at presentation. Multivariate analysis could not be performed due to small numbers of multiple variables. Long term clinical outcomes and mortality were analysed based upon treatment modality adopted and the initial clinical state. All statistical analyses were performed on SPSS Version 22, IBM corporation, USA. A p value of 0.05 or lesser was considered significant.

Results

Patient profile:

A total of 72 patients with 72 GIDA were identified and evaluated in the study. The sex distribution of the patients was as detailed in Fig 5.1.

Fig 5.1: Sex distribution of patients



The age wise distribution of patients was as per table 5.1 The mean age of the patients was 46 years within the range of 4 years to 82 years.

Table 5.1: Age wise distribution of patients

Age Group (in yrs)	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
Number of patients	2	5	6	9	12	26	9	2	1

20 of the 72 patients (27.7%) had hypertension (HTN) while 7 patients (9.7%) had co-existing diabetes mellitus (DM).

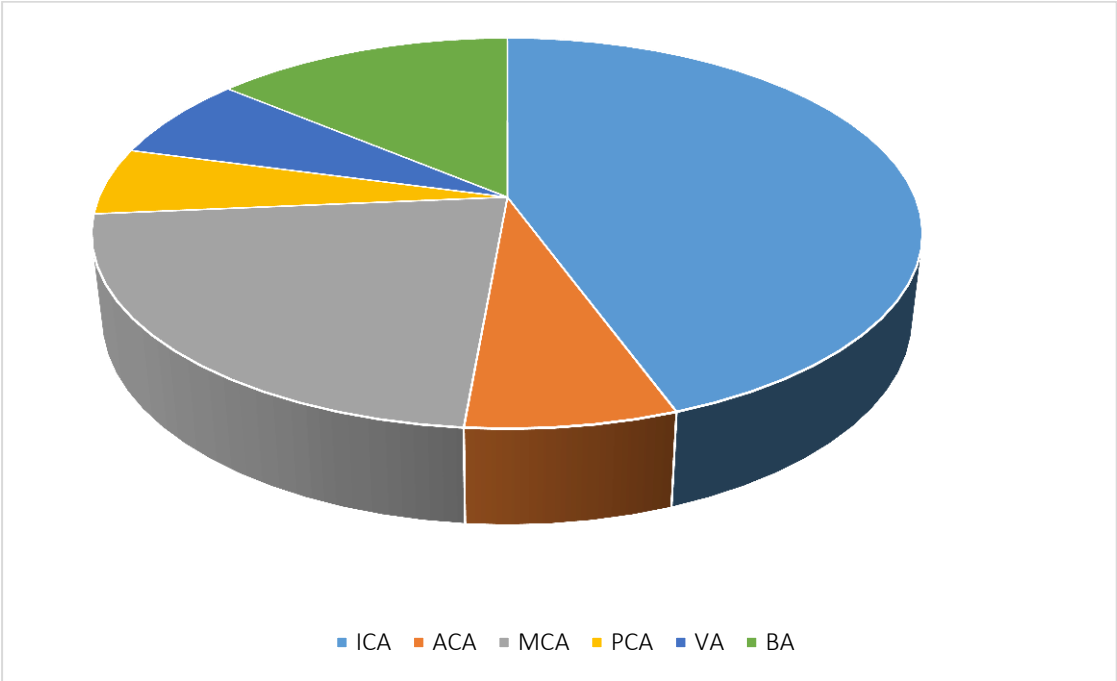
Aneurysm Location:

53 GIDA (73.6%) were located in the anterior circulation while 19 (26.4 %) were located in the posterior circulation. The artery-wise distribution of aneurysms in the anterior and posterior circulation are detailed in table and figure 5.2.

Table 5.2 : Location of Aneurysms

	Anterior Circulation (53)			Posterior Circulation (19)		
Location	ICA	MCA	ACA	PCA	VA	BA
Number	32	16	5	4	5	10

Fig 5.2: Pie chart depicting distribution of GIDA based on location.



Morphological characteristics of Aneurysms

Table 5.3 and Fig 5.3 shows the distribution of morphological characteristics of the GIDA. Of the non-saccular aneurysms, 10 were fusiform and 3 were serpentine. Due to a paucity of serpentine aneurysms, they were analysed together along with fusiform aneurysms under the group of non-saccular aneurysms.

Fig 5.3: Distribution of Aneurysms as per morphology

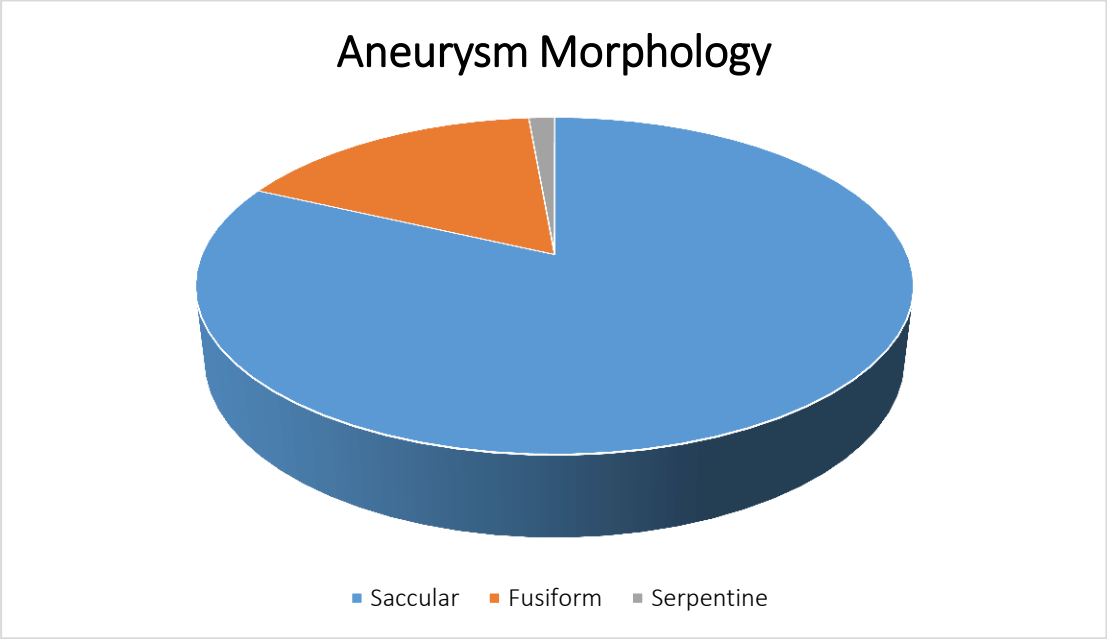


Table 5.3: Morphological characteristics of aneurysms

Aneurysm Morphology	Number of Aneurysms	Percentage of Total
Saccular	59	81.9
Fusiform	13	18.1
Aneurysm	1	1.4

Determinants of Initial Clinical Presentation:

Table 5.4 and Fig 5.4 shows the distribution of clinical events within the patients in the study.

Table 5.4: Distribution of Clinical events

Clinical Event	Number of Patients	Percentage of Total
Mass Effect	47	65.3
SAH	8	11.1
Thromboembolic	14	19.4
Other / Incidental	3	4.2

Fig 5.4: Distribution of Clinical events

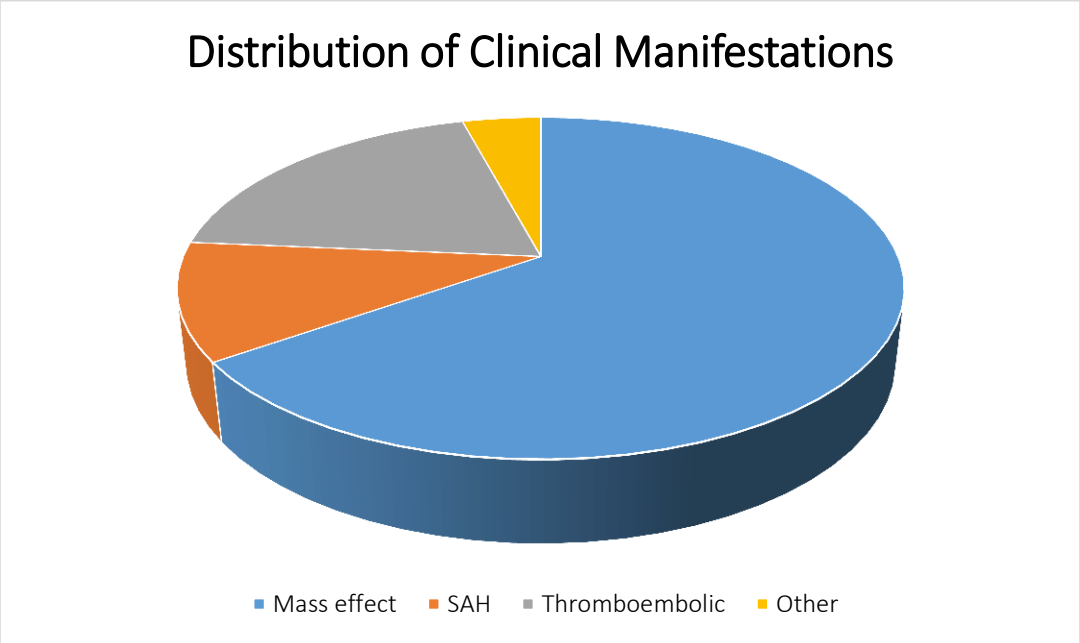
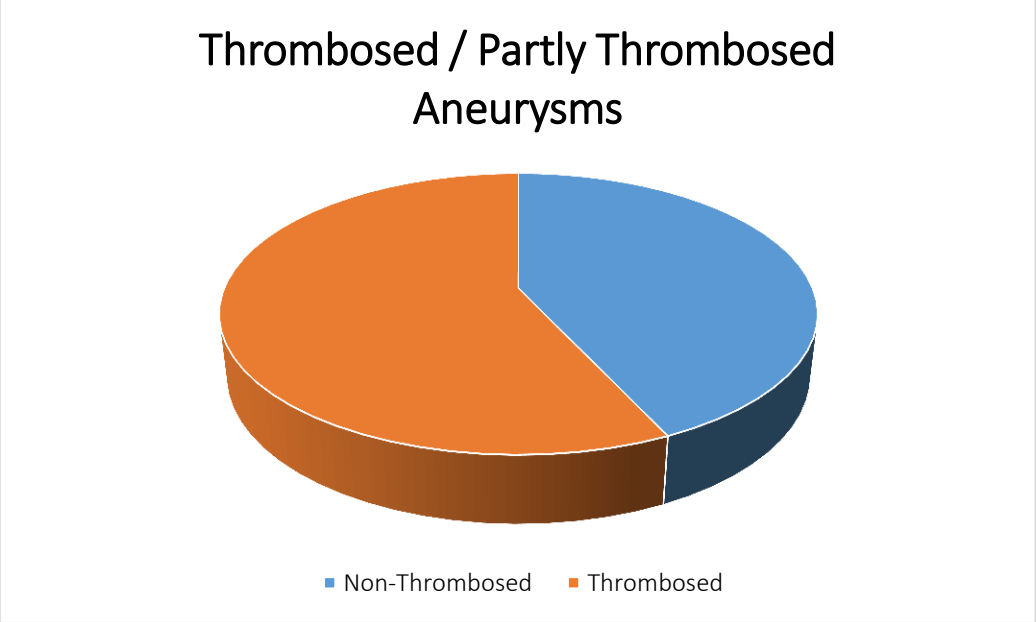


Table 5.5 and Fig 5.5 show the distribution of thrombosed / partly thrombosed and non-thrombosed aneurysms in the patient set.

Table 5.5: Distribution & Percentages of thrombosed and non-thrombosed aneurysms

Presence of Thrombus	Number of Aneurysms	Percentage of Total
No	31	43.1
Yes	41	56.9

Fig 5.5: Distribution of thrombosed and non-thrombosed aneurysms



Bivariate analysis of clinical and morphological parameters

Table 5.6 shows the bivariate analysis of the different clinical parameters (Sex, DM, HTN), morphological parameters and aneurysm location with the initial clinical presentation. Significant association was noted with the presence of intra-aneurysmal

thrombus and clinical manifestation with thrombosed / partly thrombosed aneurysms showing a significantly lesser incidence of SAH as initial presentation and showing higher incidence of presentation with thromboembolic symptoms. 11 of 14 (78.6 %) patients with thromboembolic symptoms had thrombosed / partially thrombosed aneurysms as opposed to 1 of 8 (12.5%) patients who presented with SAH.

Table 5.6: Comparison of epidemiological and aneurysm characteristics with initial clinical manifestation.

Variable		**Clinical Presentation**				**Total**	**p Value**
		Mass Effect	SAH	Thromboembolic	Other		
Sex	Male	23 (59.0%)	6 (15.4%)	9 (23.1%)	1 (2.6%)	39	0.389
	Female	24 (72.7%)	2 (6.1%)	5 (15.2%)	2 (6.1%)	33	
Co-Morbidities	HTN	12 (60.0%)	2 (10%)	4 (20%)	2 (10%)	20	0.491
	DM	4 (57.1%)	0	2 (28.6%)	1 (14.3%)	7	0.365
Presence of Thrombus		27 (65.9%)	1 (2.4%)	11 (26.8%)	2 (4.9%)	41	***0.026***
Aneurysm Morphology	Saccular	39 (66.1%)	7 (11.9%)	10 (16.9%)	3 (5.1%)	59	0.389
	Non-Saccular	8 (61.5%)	1 (7.7%)	4 (30.8%)	0	13	
Location	Anterior Circulation	36 (67.9%)	8 (15.1%)	6 (11.3 %)	3 (5.7%)	53	***0.012***
	Posterior Circulation	11 (57.9%)	0	8 (42.1%)	0	19	

Table 5.7 shows the cross tabulation of aneurysm morphology, presence of thrombus and location with the initial presentation with SAH or non SAH symptoms. Significant association of non-thrombosed aneurysms with presentation as SAH was noted (p = 0.007). None of the posterior circulation aneurysms in our series presented primarily with SAH. Although the p value did not show significance, this is probably due to lesser number or cases in each individual cell. No significant association of SAH with aneurysm morphology was noted.

Table 5.7: Comparison of aneurysm characteristics with initial presentation as SAH.

Variable		**Presentation as SAH**		**Total**	**p Value**
		SAH (8)	Non-SAH (64)		
Presence of Thrombus	**Thrombus present**	1 (2.4%)	40 (97.6%)	41	***0.007***
	No thrombus	7 (22.6%)	24 (77.4%)	31	
Aneurysm Morphology	Saccular	7 (11.9%)	52 (88.1%)	59	0.665
	Non-Saccular	1 (7.7%)	12 (92.3%)	13	
Location	Anterior Circulation	8 (15.1%)	45 (84.9%)	53	0.070
	Posterior Circulation	0	19 (100%)	19	

Table 5.8 shows the cross tabulation of different patient epidemiological data and aneurysm characteristics with clinical status (mRS) during initial presentation. No statistically significant association was noted, although there was a trend towards poorer initial clinical status in males (33%) as opposed to females (15.2%). A trend towards poorer initial clinical state was also noted for posterior circulation aneurysms (36.8%) in comparison with anterior circulation aneurysms (20.8%).

Table 5.8: Comparison of epidemiological and aneurysm characteristics with clinical status at initial presentation.

		Grade of Initial Clinical Presentation		**Total**	**p Value**
		Good (mRS <=2)	Poor (mRS 3 to 5)		
Sex	Male	26 (66.7%)	13 (33.3%)	39	0.076
	Female	28 (84.8%)	5 (15.2%)	33	
Co-Morbidities	HTN	14 (70.0%)	6 (30.0%)	20	0.543
	DM	4 (57.1%)	3 (42.9%)	7	0.356
Presence of Thrombus		32 (78.0%)	9 (22.0%)	41	0.389
Aneurysm Morphology	Saccular	43 (72.9%)	16 (27.1%)	59	0.376
	Non-Saccular	11 (84.6%)	2 (15.4%)	13	
Location	Anterior Circulation	42 (79.2%)	11 (20.8%)	53	0.165
	Posterior Circulation	12 (63.2%)	7 (36.8%)	19	

Aneurysm Location:

Table 5.9 Shows the comparison of different patient and aneurysm characteristics with aneurysm location. There was a trend towards females having higher incidence of anterior circulation aneurysms (84.8%) in comparison to males (66.7%). As compared to anterior circulation aneurysms (3.8%), 57.9% of posterior circulation aneurysms were non-saccular in morphology. The presence of thrombus in anterior and posterior circulation aneurysms was not significant.

Table 5.9: Comparison of patient and aneurysm characteristics with aneurysm location

Variable		**Location**		**p Value**
		Anterior Circulation	Posterior Circulation	
Sex	Male	26 (66.7%)	13 (33.3%)	0.076
	Female	28 (84.8%)	5 (15.2%)	
Presence of Thrombus		32 (78.0%)	9 (22.0%)	0.389
Aneurysm Morphology	Saccular	51 (96.2%)	8 (42.1%)	***<0.001***
	Non-Saccular	2 (3.8%)	11 (57.9%)	

Clinical Presentation:

Table 5.10 shows the distribution of different clinical manifestations with clinical state (in mRS) during initial presentation. As can be seen from the table, the majority of patients who presented with symptoms of mass effect (89.4%) were in good clinical state as opposed to patients who presented with SAH (50%) and thromboembolic events (42.9%). Table 5.11 shows the comparison of bled and unbled aneurysms based upon mRS at presentation.

Table 5.10 : Cross tabulation of initial clinical manifestations with clinical state during initial presentation ($p < 0.001$).

Clinical Event	Initial mRS		Total
	Good (<=2)	Poor (3 to 5)	
Mass Effect	42 (89.4%)	5 (10.6%)	47
SAH	4 (50%)	4 (50%)	8
Thromboembolic	6 (42.9%)	8 (57.1%)	14
Other	2 (66.7%)	1 (33.3%)	3

Table 5.11: Comparison of ruptured and unruptured aneurysms with initial clinical state (mRS) p = 0.083

Clinical Event	Initial mRS		Total
	Good (<=2)	Poor (3 to 5)	
SAH	4 (50%)	4 (50%)	8
Non-SAH	50 (78.1%)	14 (21.9%)	64

Natural History:

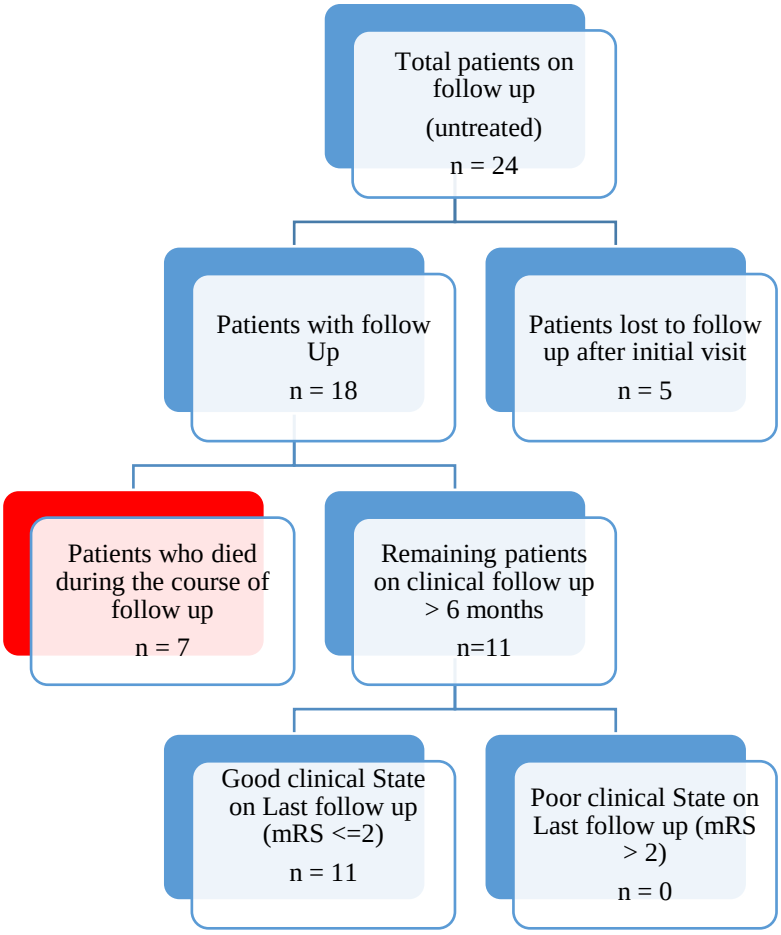
A total of 24 patients did not undergo surgical or endovascular procedures and were placed on follow up. The reasons for not performing procedures was a high risk of potential procedure related morbidity and mortality or patients refusing procedures due to either financial or other constraints. The follow-up details of the patients who did not undergo treatment are depicted in Fig 5.6.

Of the 24 patients, 5 patients were lost to follow-up after the initial hospital visit. Of the remaining 18 patients, 7 patients died due to aneurysm related complications.

Clinical follow up of more than 6 months was available for the remaining 11 patients. The longest follow-up duration was available for a patient with 216 months. The shortest follow up duration was 6 months. The mean follow-up duration among these 12 patients was 30.6 months. The mean follow-up of 11 patients, excluding the patient with follow up of 216 months, was 15.2 months.

None of the above mentioned 11 patients had worsening of clinical status during the period of follow-up with no new clinical events.

Fig 5.6: Flowchart depicting follow-up and outcome of patients who did not undergo surgical or endovascular treatment.



The patient on long term follow up had presented with headache and had been diagnosed with a giant supra-clinoid ICA aneurysm in 1998. He had declined treatment and had subsequently been on out-patient follow up till 2016 when he presented with a minor MCA territory infarct. All 11 patients on long term follow up were in good clinical condition (mRS<=2) at initial presentation. Only 1 patient (on 216 month follow up) had worsening on mRS by 1 point on long term follow up. The other 11 patients remained clinically stable with no worsening on mRS.

Location of Aneurysm on patients with follow up are as detailed below.

Anterior Circulation (7): ICA - 6 , MCA – 1

Posterior Circulation (4) : VA - 2 , BA - 2

9 of the 11 (81.8%) aneurysms were partly or completely thrombosed. 7 aneurysms were saccular while 4 were non-saccular. 3 patients had presented with thromboembolic complications while 8 had presented with symptoms of mass effect. None on the patients on long term follow up with good outcome had presented with initial SAH. The sub-division of aneurysm location, initial clinical presentation and mRS at initial presentation are detailed in Table 5.12.

Table 5.12: Outcome of Untreated Patients

	Aneurysm Location	**Initial Presentation**	**Initial Clinical State**
Good Final Outcome (11)	Anterior : 7 Posterior : 4	Bleed : 0 Mass effect : 8 TE : 3	Good : 11 (mRS<=2)
Poor Final Outcome (Mortality) (7)	Anterior : 4 Posterior : 3	Bleed : 1 Mass Effect : 4 TE : 2	Good : 2 Poor : 5

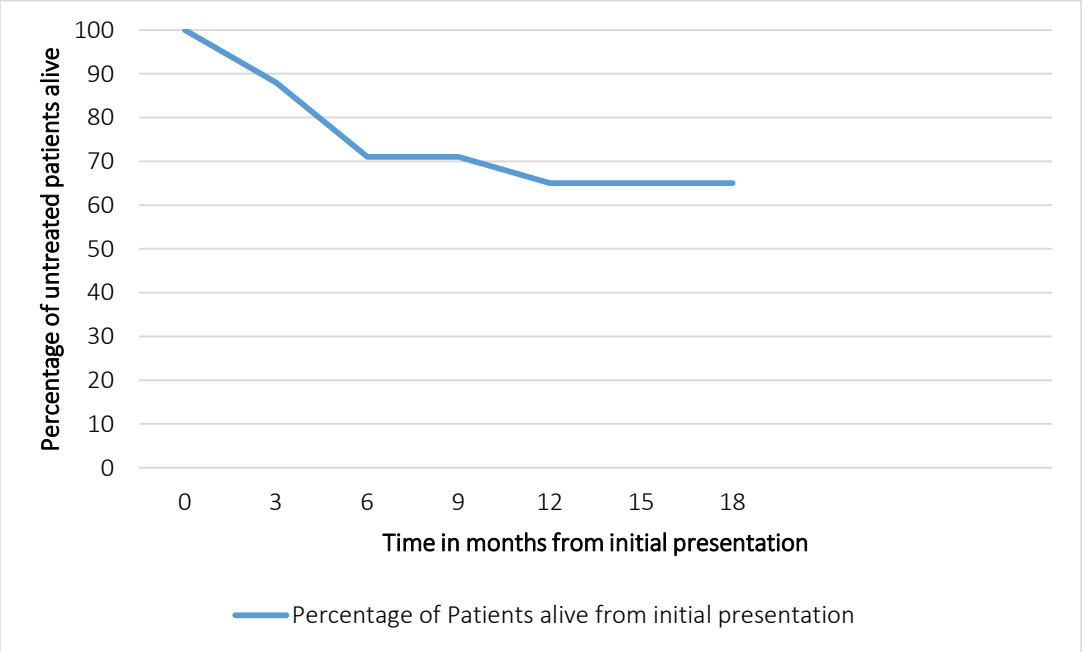
Mortality in the Untreated Group:

7 patients in the conservative arm died due to aneurysm related causes. 1 patient who presented with an acute SAH died in the hospital on the 3rd day after ictus. Mean survival time from onset of diagnosis in the other 6 patients was 6 months (range 3 m to 12 m).

4 patients had giant ICA aneurysms while 3 had basilar artery aneurysms. 1 patient had presented with SAH, 2 patients with symptoms of mass effect while 3 patients

had presented with ischemic symptoms. 5 of the 7 patients had poor clinical status (mRS at presentation 4 to 5). 1 patient with an ICA aneurysm who had presented with mass effect in initial good clinical state (mRS of 1), suffered an aneurysmal rupture with SAH and died due to associated complications 5 months after initial diagnosis. Another patient with an ICA aneurysm initial good clinical state died due to sudden loss of consciousness and associated complications but the exact cause of death could not be determined due to absence of imaging at the time of ictus. Both patients with initial good clinical state who subsequently had deterioration had non-thrombosed aneurysms at initial presentation. Fig 5.7 plots the mortality of untreated patients as per against time since initial presentation. As can be noted from the table, all fatal events happened within 12 months from initial diagnosis with the 6/7 (85.7%) occurring within the first 6 months. None of the patients on follow up beyond 12 months had a fatal event or significant worsening of clinical state.

Fig 5.7 : Mortality in the untreated patient sub-group of follow up.



Endovascular Treatment

A total of 17 patients were planned for endovascular treatment and a total of 22 procedures were attempted in 16 patients (Table 5.13). 7 patients in the endovascular group had anterior circulation aneurysms (5: ICA, 2 : MCA) while 10 patients had posterior circulation aneurysms (2:VA, 5 :BA, 3 : PCA). The number of procedures and their results in anterior and posterior circulation aneurysms is detailed in Tables 5.13 to 5.15.

1 patient with a giant basilar top aneurysm was planned for flow diversion and started on dual anti-platelet medications but developed modified Fisher Grade 4 SAH due to aneurysm rupture on the 2nd day. He eventually died 3 days after the event without a procedure being performed.

Of the 22 procedures, 11 were aneurysm coiling (10 with balloon assistance and 1 with stent assistance), 5 patients each underwent parent artery occlusion and attempted flow diverter placement respectively. 18 of the 22 attempted procedures were technically successful.

Table 5.13: Summary of Endovascular Procedures & Outcomes

Procedures	Number of Patients	Number of Procedures attempted	Procedural Success	Recanalization	Retreatment
Coiling	9	11	9 (81.2 %)	5 (45 %)	5 (45 %)
PV Occlusion	6	6	5 (83.3 %)	Nil	Nil
Flow Diverter	6	5	4 (80 %)	Nil	Nil
Total	17	22	18 (81.8 %)	5 (27.8 %)	5 (27.8 %)

Table 5.14: Procedures in Anterior Circulation Aneurysms

Procedures	Number of Patients	Number of Procedures attempted	Procedural Success	Recanalization	Retreatment
Coiling	4	6	5 (83.3 %)	3 (50 %)	3 (50 %)
PV Occlusion	1	1	1 (100 %)	Nil	Nil
Flow Diverter	5	5	4 (80 %)	Nil	Nil
Total	7	12	10 (83.3 %)	3 (25 %)	3 (25 %)

Table 5.15: Procedures in Posterior circulation aneurysms

Procedures	Number of Patients	Number of Procedures attempted	Procedural Success	Recanalization	Retreatment
Coiling	5	5	4 (80 %)	2 (40 %)	2 (20 %)
PV Occlusion	5	5	4 (80 %)	Nil	Nil
FD	1	0	-	-	-
Total	10	10	8 (80%)	2 (20%)	2 (20%)

Coiling:

Although coiling procedures were completed with a high degree of technical success (9 / 11) they were fraught with incidence of aneurysm recanalization and retreatment

(45% each). 2 procedures were technically unsuccessful, 1 due to unfavourable angiographic anatomy and another due to arterial dissection during the procedure.

Parent Artery Occlusion:

6 procedures of parent artery occlusion were attempted with 5 successful procedures. 5 of the 6 attempted procedures were for posterior circulation aneurysms. One parent artery occlusion was done for an ICA aneurysm after balloon occlusion test. The one unsuccessful procedure was of a PCA aneurysm which was planned for coiling along with parent artery occlusion. There was an intra-procedural aneurysm rupture with SAH upon which the procedure was abandoned and the patient was managed conservatively with external ventricular drain (EVD) and made a complete recovery with no residual deficits.

Flow Diverter:

Five procedures were attempted of which four were successful (80%). All procedures were attempted in anterior circulation aneurysms (5 ICA aneurysms, 1 MCA aneurysm). Single FD were deployed in 4 cases (all ICA), while 3 telescoped FD were placed in one giant MCA aneurysm. As can be seen from Table 5.13, the technical success rate of all procedures was similar (80 to 83%) with a total technical success of 81.8%. Patient who underwent coiling had a high rate of recanalization and retreatment (45%). No long term recanalization was noted in patients who underwent parent vessel occlusion or flow diverter placement. As per our results, 20% of the patients (1/5) who underwent flow diversion had poor outcome. However, of the 6 patients planned for FD placement, there was one mortality due to rupture after starting anti-platelet medication.

Mortality in Patients with Endovascular procedures:

A total of 2 cases of mortality were noted in patients who were planned for or underwent endovascular procedures. 1 patient with a giant basilar trunk aneurysm was planned for staged proximal parent artery occlusion to reduce aneurysm inflow. She underwent unilateral vertebral artery coil occlusion after a posterior circulation balloon occlusion test and the immediate post procedure period was uneventful. However, she developed a sudden drop in sensorium due to aneurysm rupture and modified Fisher grade 4 SAH and had to be intubated and mechanically ventilated. She subsequently died 2 days after the ictus.

The 2nd patient had a giant basilar top aneurysm and was planned for FD placement and started on anti-platelets. However, he developed SAH due to aneurysm rupture on the 2nd day after staring DAP and died on the 3rd day after ictus.

Procedural Complications:

Of the 22 procedures, intra or early post procedural complications were noted 6 patients, which are summarized in Table 5.16. Of the 6 patients, 4 recovered completely on conservative management without significant deficits or long term sequelae. 1 patient died due to an early post procedure aneurysm rupture. 1 patient had an intra-procedure rupture during flow diverter placement and underwent surgical hematoma evacuation. He developed hemiparesis in the immediate post-operative period with partial improvement on long term follow up (mRS 3).

Table 5.16 : List of complications after endovascular procedures

Aneurysm Location	Procedure	Complication	Management	Final Outcome
ICA	Flow diverter placement	Retroperitoneal hematoma	Conservative	Self limiting
BA	Proximal VA occlusion	Aneurysm rupture on 3rd post Op day	Conservative	Died
BA	Aneurysm coiling	Intra-procedural dissection	Conservative	Spontaneous aneurysm thrombosis – Patient asymptomatic on follow up
MCA	Flow diverter	Peri-aneurysmal bleed	Surgical evacuation	Hemiparesis
VA	Parent artery occlusion	Embolic infarcts	Conservative	No neurologic deficits
BA	Coiling with parent artery occlusion	Rupture with SAH	Conservative	No deficits

Angiographic Outcome:

Table 5.17 shows the immediate and delayed angiographic outcome after endovascular procedures. Of the 9 successful coiling procedures, complete occlusion was achieved in six, while neck remnant (Modified Raymond grade I) was noted in the other 3. Significant aneurysm recanalization was noted in 5 patients on delayed angiographic follow up, all of which mandated retreatment. All 5 patients with successful parent artery occlusion procedures showed complete occlusion at immediate and follow up angiograms with no requirement for retreatment.

Table 5.17 : Immediate and delayed angiographic outcome after endovascular procedures. (MR : Modified Raymond score ; OKM : O'Kelley Marotta score)

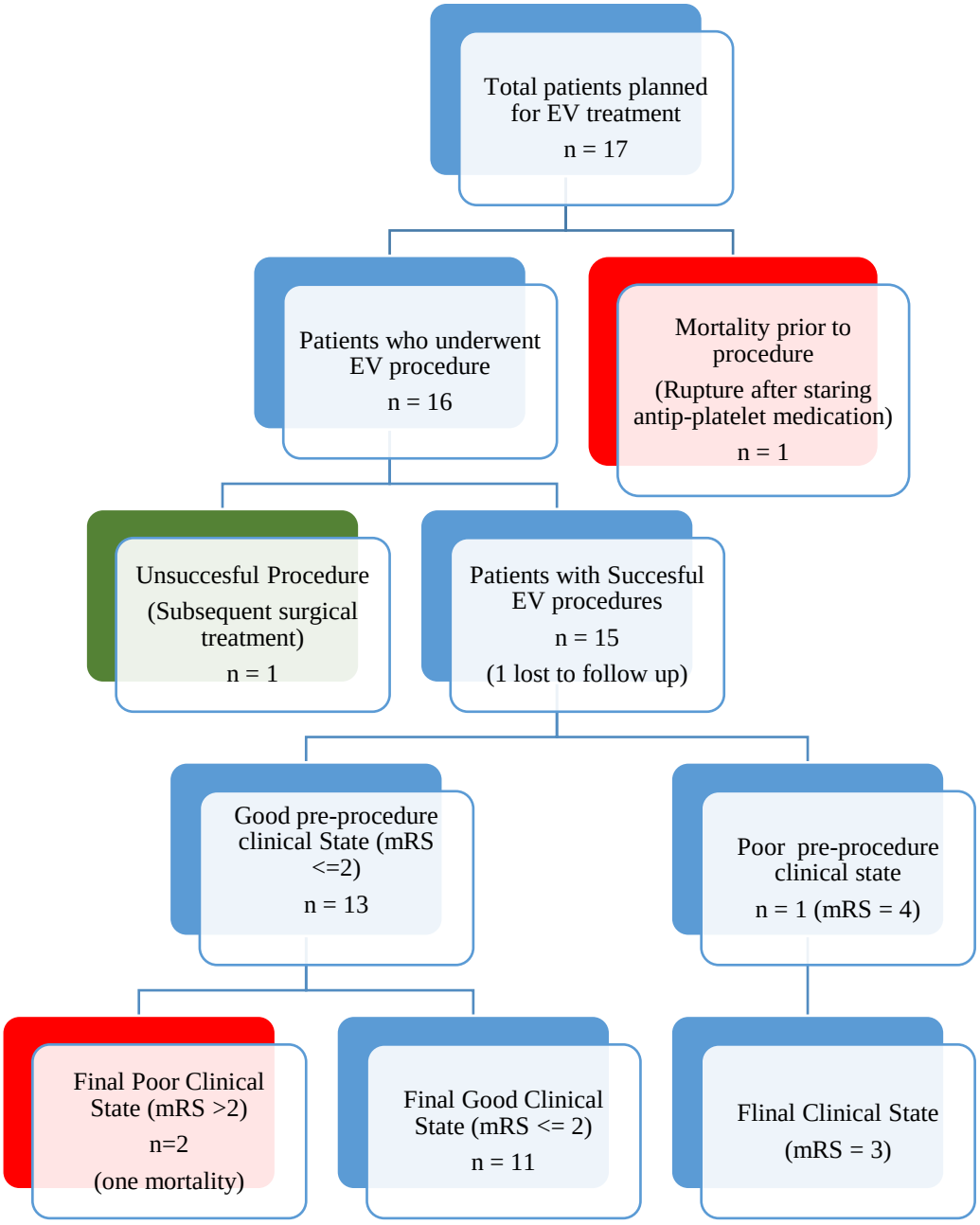
	Immediate	**Delayed**
Coiling	MR 0 : 6 MR 1 : 3	MR 0 : 3 MR 1 : 0 MR 2 : 5 (Total delayed FU 8)
Parent Artery Occlusion (5)	MR: 0	MR: 0
Flow Diversion (4)	OKM B3: 4	OKM D: 4

Clinical Outcome of EV treatment:

Fig 5.8 shows the follow up of patients who were planned for endovascular procedure. Of the 16 patients who underwent attempted EV treatment, ultimate procedural success was noted in 16 patients (Mean follow up duration of 20.4 months). 1 patient with an unsuccessful FD placement, subsequently underwent surgical treatment.

Of the 15 patients who underwent successful EV treatment, 14 were in good clinical state prior to the procedure, while 1 patient had a pre-procedural mRS of 4. On long term follow up only 1 patient showed significant worsening of clinical state (2 point worsening of mRS), while the other patients had either improved or stable clinical state. One patient died due to aneurysm rupture in the early post procedure period. Hence, good clinical outcome was noted in 12 of 15 patients (81.3%) with 2 cases of mortality (13.3%).

Fig 5.8: Flow chart depicting procedures and follow op of patient having undergone endovascular procedures.



Surgical Treatment:

A total of 35 patients underwent surgical procedures. All surgical procedures were performed on anterior circulation aneurysms with fifteen ICA and MCA aneurysms each and five ACA aneurysms. No surgical procedures were performed on posterior

circulation aneurysms. The summary of surgical procedures is given in Table 5.18. 71% of the surgical procedures were attempted clipping with a fewer number of other procedures as detailed in the table. Wrapping was performed predominantly as an interim procedure with 3 of the 5 patients who underwent wrapping subsequently undergoing definitive procedures (2 surgical and 1 endovascular). Surgical procedures had a high technical success rate and low retreatment rates. A total of 8 patients died after surgery, 7 of whom had undergone clipping and 1 patient who underwent trapping and bypass surgery.

Table 5.18: Summary of Surgical Procedures & Outcomes

	No of patients	**Total Procedures**	**Technical Success**	**Retreatment**	**Good Outcome**	**Mortality**
Clipping	25	27	25 (92.6 %)	0	15/23 (65.2 %)	7/25 (28 %)
Wrapping	5	5	5 (100%)	3 2 -surgical 1 - EV	5	Nil
Trapping	2	2	2	0	1	1
Bypass with aneurysmoraphy	1	1	1	0	NA	NA
Excision with / without anastomosis / bypass	3	3	3	0	3	0
Total	35	38	36 (94.7%)	3 (7.9 %)	20 / 32 (62.5 %)	8/32 (25%)

Surgical Complications:

Table 5.19 shows the number of surgical and post-surgical complications and sequelae. Infarcts were the commonest complication noted in 33% of the surgical group. 7/13 (53.8%) patients with surgery required decompressive surgery after development of infarct. All 8 patients who died after surgical procedures were due to post-operative infarcts. 6 of the 7 patients who underwent decompressive surgery died in the early post-operative period. Good long term outcome in patients with post-operative infarcts were noted in only 2 patients with long term follow up. Patients with other post-operative complications such as seizures, dyselectrolytemia and infections were managed conservatively and did not have poor outcomes on long term follow up.

Table 5.19 : Surgical Complications

Complication	Number
Infarct	13
Meningitis	2
Seizures	3
Dyselectrolytemia	2
Total	20 / 38 (52.6%)

Comparison of Treatment Outcomes:

Follow up of 47 patients treated with either surgical or endovascular means was available, with 2 patients having undergone both procedures. Table 5.20 shows the number of patients with good and poor clinical outcome after the respective treatment modality on long term follow up. The clinical outcome of none of the surgical or

endovascular patients worsened after the immediate post-procedural mRS (at the time of discharge).

Table 5.21 shows the number of patients who died after surgical or endovascular procedures. All cases of mortality died in the immediate peri-procedural period due to procedure related complications. None of the patients (on available follow up) died after discharge following the initial procedure.

Table 5.20 : Comparison of Outcomes between Surgical and Endovascular group (p = 0.346)

Treatment Modality	**Outcome at Last Follow Up**		**Total**
	Good Outcome	**Poor Outcome**	
Surgical	22 (66.7%)	11 (33.3%)	33
Endovascular	12 (80%)	3 (20%)	15
Total	34 (70.8%)	14 (29.2%)	48

Table 5.21: Comparison of mortality due to surgical & endovascular treatment on long term follow up (p= 0.388)

Treatment Modality			**Total**
	Alive at last follow up	**Dead**	
Surgical	25 (75.8%)	8 (25.2%)	33
Endovascular	13 (86.7%)	2 (13.3%)	15
Total	38 (79.2%)	10 (20.8%)	48

Table 5.22 shows the comparison of the different aspects of surgical and endovascular treatment outcomes with a higher success rate and lower retreatment rates noted for the surgical group as opposed to trend towards better outcome, lower mortality and lower post procedural complications in the endovascular group.

Table 5.22 : Comparison of Different aspects of Surgical and Endovascular treatment

	Surgical Treatment	Endovascular Treatment
Technical Success	94.7%	81.8%
Retreatment	7.9%	27.8%
Complication	52.6%	27.3 %
Mortality	25%	17.6%
Good Outcome	62.5%	68.8%

In our group of treated patients, all surgical cases were anterior circulation aneurysms with no patients with posterior circulation aneurysms having undergone surgical treatment. On the contrary, of the 17 patients in the endovascular arm, 10 had posterior circulation aneurysms while 7 had anterior circulation aneurysms.

Comparison of Outcomes of Treated versus untreated group:

The clinical outcomes at final follow up between the treated and untreated arm are detailed in Table 5.23. Table 5.24 shows the mortality figures of patients in the treatment group versus the untreated group.

Table 5.23: Outcomes of treated and untreated patients (p =0.595)

Treatment Modality	Outcome at Last Follow Up		Total
	Good Outcome	Poor Outcome	
Surgical/ Endovascular	32 (68.1%)	15 (31.9%)	47
Conservative	11 (61.1%)	7 (38.9%)	18
Total	43 (66.2%)	22 (33.8%)	

Table 5.24: Mortality in treated and untreated patients (p = 0.148)

	Alive at last follow up	Dead
Surgical/Endovascular treatment	37 (78.7%)	10 (21.3%)
Conservative	11 (61.1%)	7 (38.9%)
Total	48 (79.2%)	17 (20.8%)

Table 5.25 shows the relation of mRS at initial presentation to the final mRS. Irrespective of the modality of management, patients with a poor initial mRS had a significantly poorer final outcome as opposed to patients who presented with an initial good mRS.

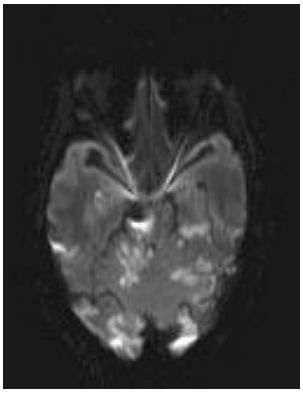
Table 5.25: Relation of intial mRS to final mRS (p = 0.002)

Initial mRS	Final mRS	
	Good (<=2)	**Poor (3 to 6)**
Good (<=2)	35 (74.5%)	12 (25.5%)
Poor (3 to 6)	6 (33.3%)	12 (66.7%)
Total	41 (63.1%)	24 (36.9%)

Representative Cases

Case 1:

50 year old lady presented with an acute posterior circulation stroke involving the PCA territories , cerebelllum and brainstem (Fig 6.1). CT angiography showed a fusi-saccular partially thrombosed giant basilar artery aneurysm (Fig 6.2). The patient was intubated and managed conservatively and died 10 days after the onset of symptoms without having undergone surgical or endovascular treatment.

 Fig 6.1(a)

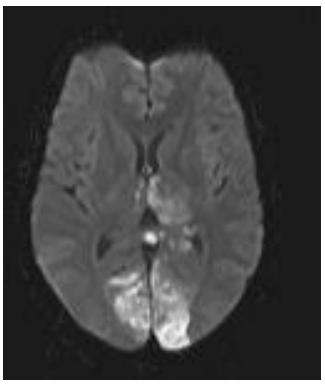
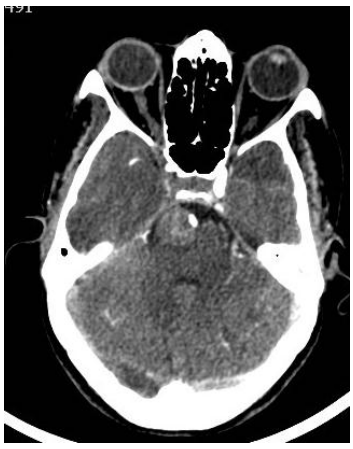
 Fig (b)

Fig 6.1 (a & b): Diffusion Weighted images showing multiple acute infarcts in bilateral PCA territories, cerebellar hemispheres and in the brainstem.

 Fig 6.2(a)

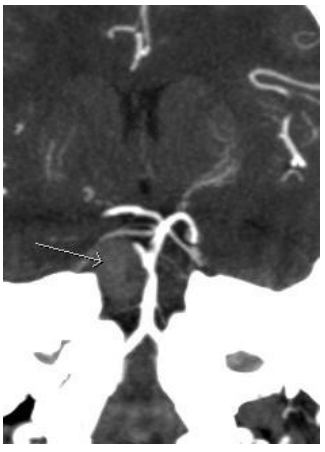
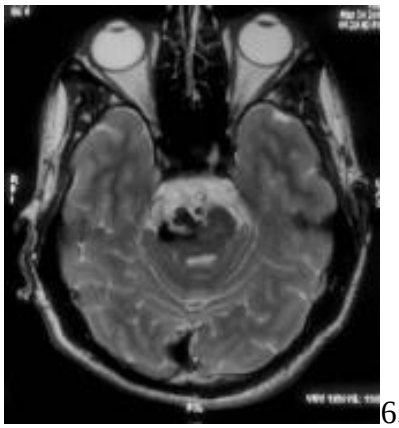
 Fig 6.2(b)

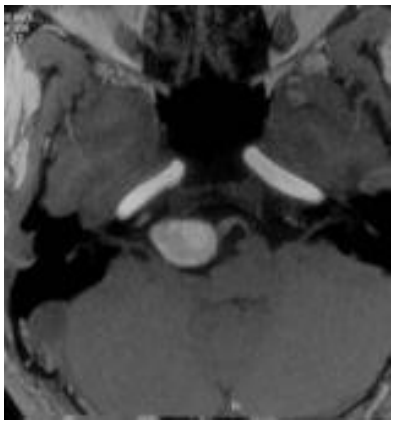
Fig 6.2 (a) & (b): CT angiogram showing partly thrombosed fusiform giant basilar artery aneurysm.

Case 2:

25 year old male presented with sub-acute onset of bulbar symptoms along with gait ataxia. Imaging (Fig 6.3 & 6.4) showed a thrombosed fusiform basilar artery aneurysm causing brainstem compression. The patient was placed on conservative follow up without surgical or endovascular treatment and had no significant worsening of symptoms over a follow up period of 18 months. Follow up angiogram at one year showed no recanalization of the aneurysm (Fig 6.5).

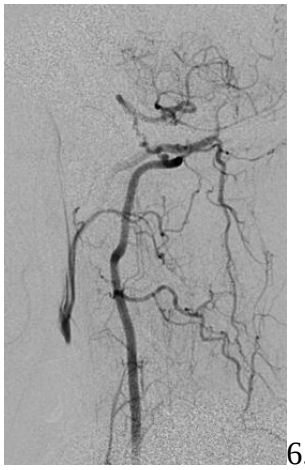


6.3(a)

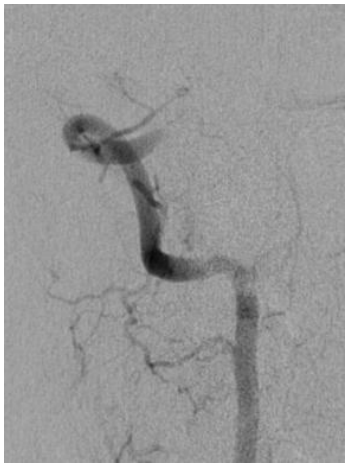


6.3(b)

Fig 6.3 : MRI (a) T2WI and (b) T1 post contrast axial images showing a thrombosed BA aneurysm with brainstem compression.

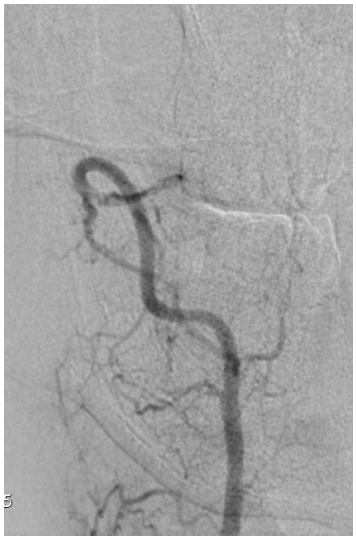


6.4(a)

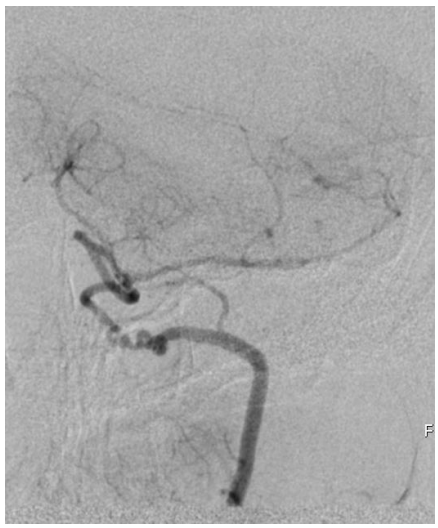


6.4(b)

Fig 6.4 : DSA (a) Left VA , lateral view and (b) right VA , frontal view ; showing complete aneurysmal thrombosis and non-opacification and non-filling of the basilar artery.



6.5(a)



6.5(b)

Fig 6.5: Follow up DSA after 1 year (a) Right VA, (b) left VA, frontal views; showing complete and persistent aneurysmal thrombosis and non-opacification and non-filling of the basilar artery.

Case 3:

64 year old lady presented with complaints of progressive new onset headache and episodic giddiness. Imaging revealed a giant, saccular non-thrombosed right MCA bifurcation aneurysm (Fig 6.6). The patient underwent right pterional craniotomy with aneurysm excision and side-side anastomosis of the parent artery (Fig 6.7). Post-operative period was uneventful and the patient remained asymptomatic till on 1 year follow up.

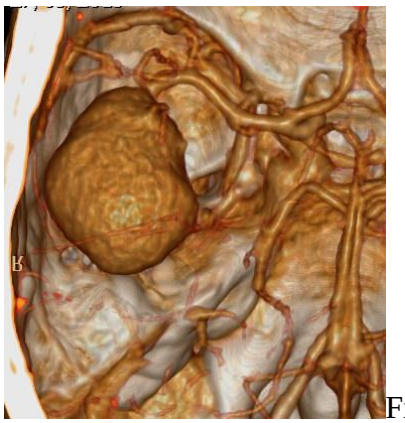
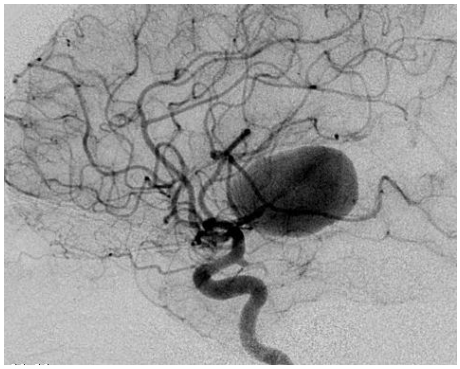


Fig 6.6(a)



6.6(b)

Fig 6.6 : (a) CT Angiogram (volume rendered image) and (b) DSA (right ICA lateral view) showing giant saccular right MCA bifurcation aneurysm.

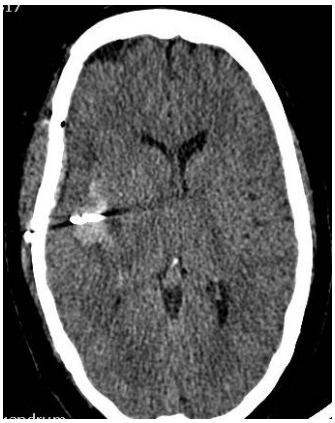


Fig 6.7

Fig 6.7 : Immediate post operative CT scan showing aneurysm clip in situ with mild post surgical hemorrhage in the right Sylvian fissure.

Case 4:

56 year old lady had presented with painless, progressive visual diminution of vision in the right eye over 6 months (Finger counting at 2 feet). Imaging evaluation for the same revealed a right supra-clinoid ICA aneurysm (Fig 6.10). She initially underwent balloon assisted coiling with residual neck remnant (Fig 6.11a). She developed symptoms in the form of right hemi-cranial headache two months after the procedure and repeat angiogram showed significant aneurysm recanalization (Fig 6.11b). She was subsequently treated with flow diversion by deploying single PED achieving post OKM grade B3 aneurysm filling (Fig 6.12a) on the immediate post procedural angiogram with check angiogram after 1 year (Fig 6.12b) showing complete aneurysm occlusion (OKM grade D).

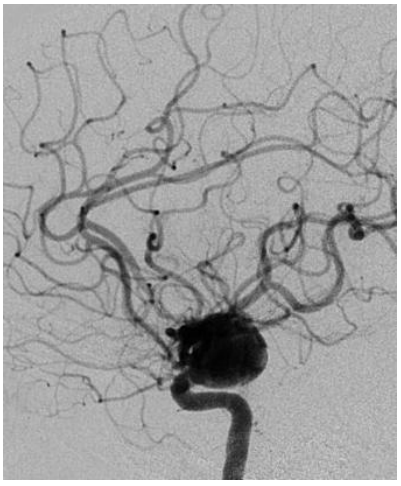


Fig 6.8(a)

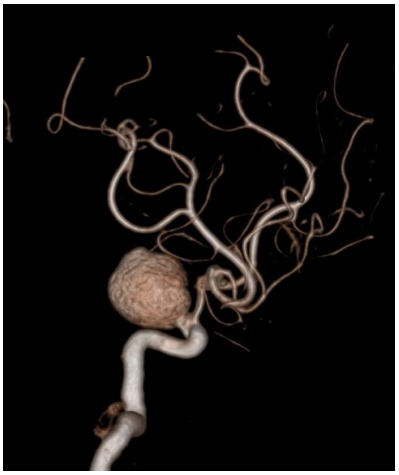


Fig 6.8(b)

Fig 6.8: (a) DSA (right ICA lateral view) and (b) 3D rotational angiogram, volume rendered image , showing a giant right supra-clinoid ICA aneurysm.

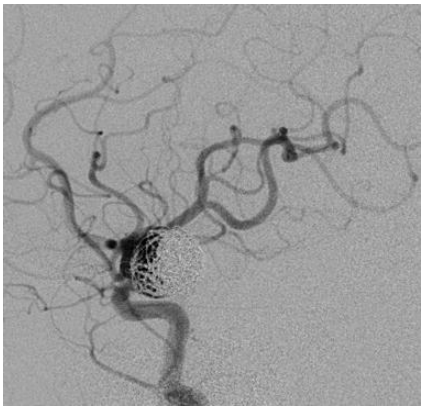


Fig 6.9(a)

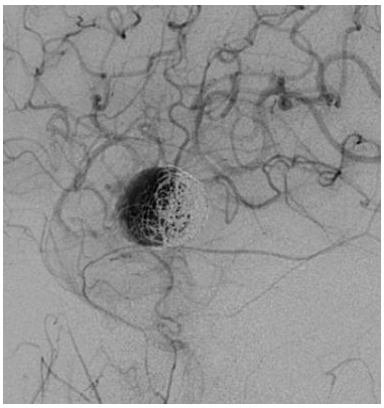


Fig 6.9(b)

Fig 6.9: (a) Immediate post coiling angiogram showing residual neck remnant and (b) Check DSA after 2 months showing significant sac recanalization.

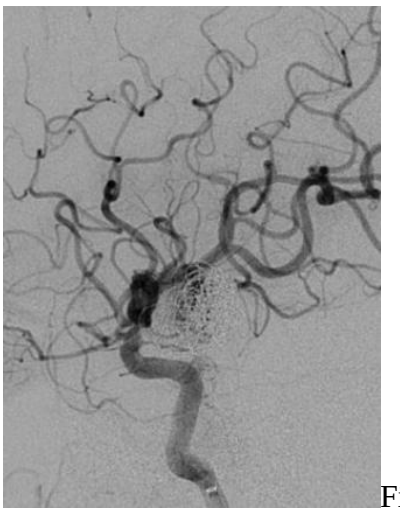


Fig 6.10(a)

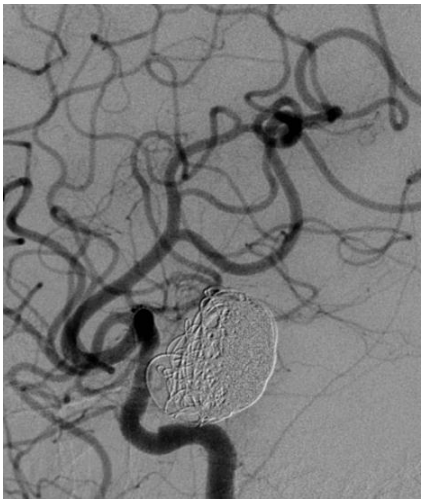


Fig 6.10(b)

Fig 6.10 : (a) Immediate post procedural angiogram after deployment of PED showing OKM grade B3 aneurysm filling. (b) Check angiogram after 12 months showing complete occlusion of the aneurysm (OKM grade D).

Case 5:

53 year old lady presented with episodic right hemi-cranial headache and ocular pain. Imaging showed a right ICA transitional aneurysm (16.13). She underwent balloon occlusion test followed by aneurysm trapping and parent artery occlusion with complete aneurysm exclusion. She had an uneventful post procedural period and no recurrence of symptoms or aneurysm recanalization on follow up.

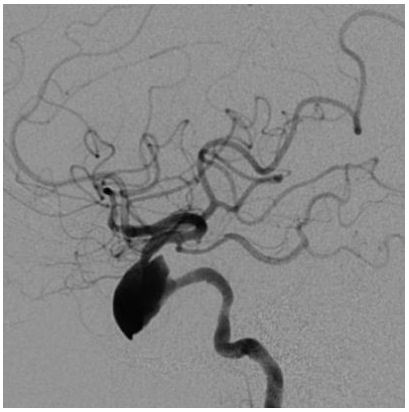


Fig 6.11(a)

Fig 6.11(b)

Fig 6.11: ICA angiogram (a) Lateral view and (b) 3D rotational angiogram, volume rendered image showing a saccular transitional aneurysm of the right ICA.

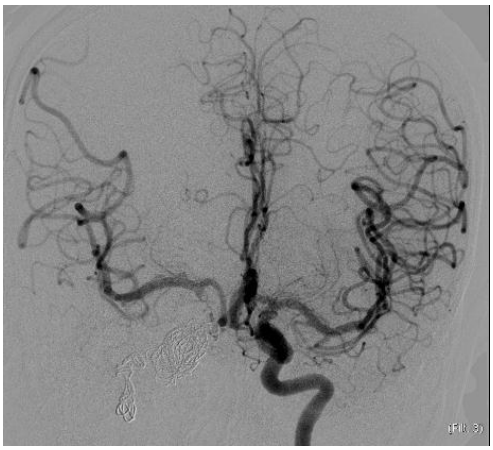


Fig 6.12

Fig 16.12: Post parent vessel occlusion check angiogram showing complete aneurysm exclusion with synchronus filling of bilateral MCA branches of contralateral (left) ICA injection.

Case 6:

57 year old female had presented with sudden severe sub-occipital headache with imaging showed a giant partially thrombosed proximal basilar artery aneurysm without evidence of SAH. FD treatment was considered but after being explained about the uncertain efficacy in view of peculiar angio-morphology of the aneurysm, she opted against FD treatment.

She was taken up for balloon assisted coiling but was detected to have a dissection during wire navigation with contrast extravasation into the aneurysm wall. The procedure was abandoned and the patient placed on follow up.

She presented one year later with increasing symptoms due to brainstem compression and repeat imaging showed complete exclusion of the aneurysms due to progressive occlusion of proximal basilar artery. She was managed conservatively with anti-edema measures and showed gradual improvement of clinical symptoms in the follow up period. She has subsequently remained in good clinical state with no symptomatic worsening over a follow up period of 24 months.

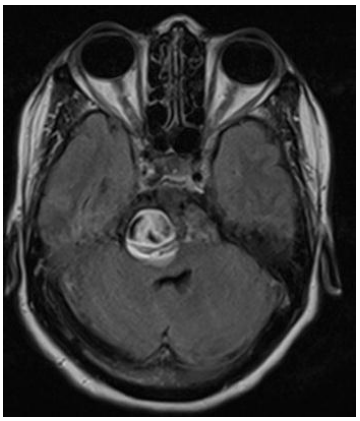


Fig 6.13

Fig 6.13: MRI showing Giant basilar aneurysm with brainstem compression.

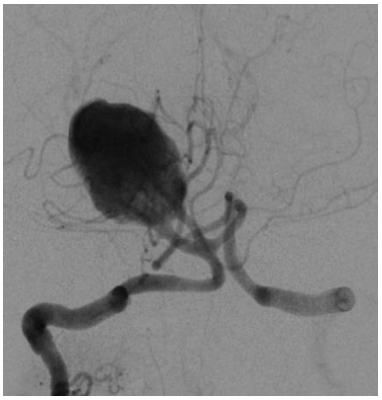


Fig 6.14(a)

Fig 6.14(b)

Fig 6.14: (a) Right VA angiogram (b) 3D rotational angiogram, volume rendered image; showing fenestration of proximal basilar artery with a giant aneurysm.

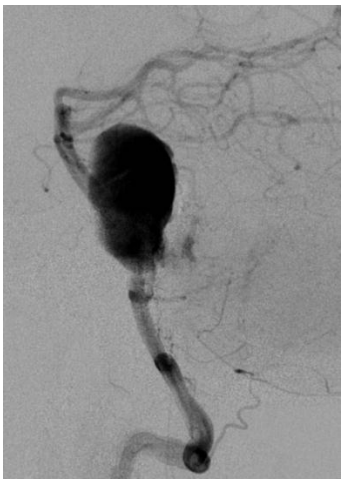


Fig 6.15 (a)

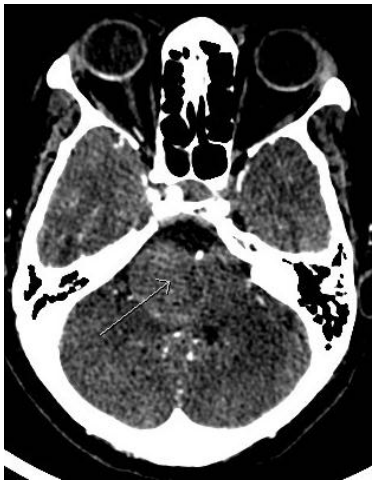


Fig 6.15(b)

Fig 6.15: (a) VA lateral view showing evidence of dissection with contrast extravasation beyond the confines of the aneurysms lumen. (b) Post procedural CT angiogram showing thrombosed aneurysm with no contrast filling.

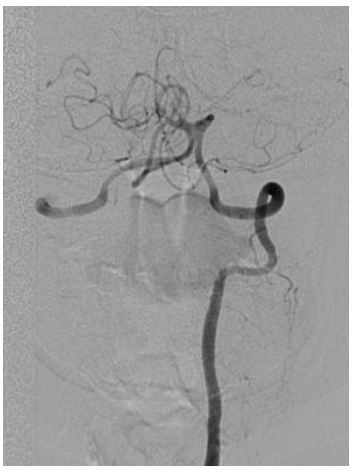


Fig 6.16(a)

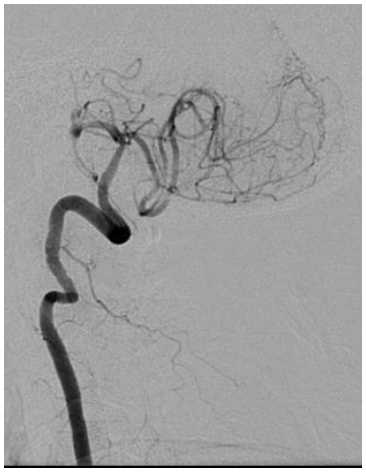


Fig 6.16(b)

Fig 6.16: Left VA angiogram after 1 year (a) frontal view (b) lateral view, showing persistently thrombosed aneurysm with no evidence of recanalization.

Case 7:

51 year old male, had been initially diagnosed with a giant left ICA bifurcation aneurysm in 1998 during evaluation for episodic headache. He had refused treatment and was relatively asymptomatic till April 2016 when he developed acute onset right upper limb weakness along with slurring of speech. Imaging showed a partially thrombosed left ICA bifurcation aneurysm with mass effect and in the left ganglio-capsular region. Over the next 5 days he recovered to his previous state of health (with no persistent neurological deficit). He was advised for flow diverter placement and discharged on follow up and planned for admission after conferring willingness for procedure.

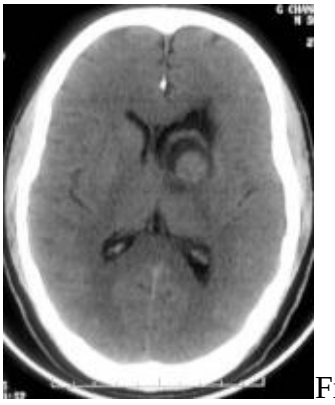


Fig 6.17(a)

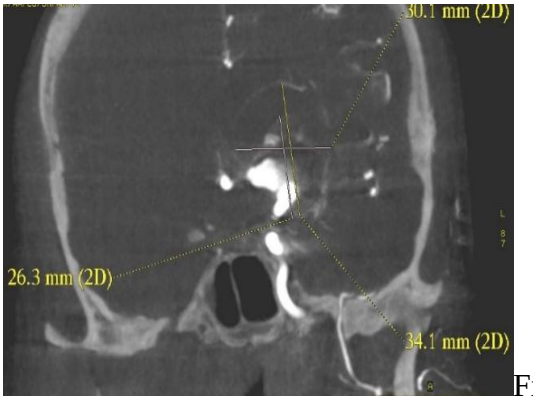


Fig 6.17(b)

Fig 6.17: (a) Plain CT head and (b) CT angiogram (coronal reformat) showing partially thrombosed giant left ICA bifrucation aneurysm with mass effect.

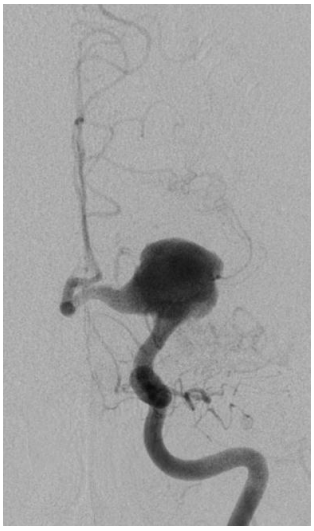


Fig 6.18(a)

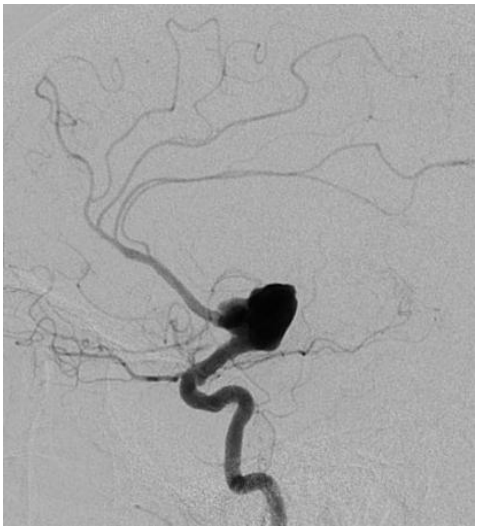


Fig 6.18(b)

Fig 6.18: Left ICA angiogram (a) frontal view and (b) Lateral view depicting the aneurysm.

Discussion

We performed a retrospective-prospective analysis of patient demographics, aneurysm morphology and clinical outcomes in patients with treated or untreated intra-dural giant aneurysms. This sub-set of purely intra-dural entities has never been previously reported in a single series. Different studies have reported differing rupture risks for GA with the prevailing consensus being that when diagnosed, all patients with GA should mandatorily be offered treatment. Furthermore, while natural history studies on IA in general are available, the same on GA are largely restricted to anecdotal case series. We also attempted to shed some light on this aspect of the disease entity, in our analysis of the clinical follow up of untreated patients.

Table 7.1 compares our current study with three similar large series (7,22,57). The three studies have many similarities in the inclusion criteria but are not identical to the criteria used in our study. These studies have described the clinico-morphological features of GA similar to our study. We also compared our results to the surgical series on GA published by Sharma et al (10). Although this study did not report the complete details of clinico-morphological features, the study was used for comparison as this was the largest available study on these entities in an Indian population.

All 3 studies have included intra and extra-dural aneurysms within their study population and have not described morphological characteristics separately for purely intra-dural aneurysms. Darsaut et al. used a size criterion of 20 mm and above for inclusion in their study. While they subsequently mentioned the number of very large (20 to 25 mm) and giant aneurysms (>25 mm) as 85 and 99 respectively, the study did not provide separate results for very large and giant aneurysms. Our study is the first of its kind to describe GA in an Indian population and there are certain demographic

differences to be noted from the other studies which have principally studied western population groups (USA, Finland and Brazil respectively). (7,22,57).

Table 7.1: Comparison of epidemiological and morphological results of current study with similar large series.

Study	Sex (M:F)	Mean Age	Size (Number)	Location (AC:PC)	Morphology (Saccular : non saccular)	Clinical presentation (SAH:Mass Effect : TE)
Darsaut et al (2011)(22)	62 :121 (1:2)	56.8	>20mm (184)	140 : 44 (3:1)	144: 40 (3.6:1)	64:89:5 (12.8: 17.8:1)
Nurminen et al (2014)(7)	59:66 (0.9:1)	53	>25 mm (129)	97:32 (3:1)	106 : 23 (4.6:1)	42: 31 :14 (3:2.2:1)
Dos Santos et al (2013)(57)	14:66 (1:4.7)	53	>25 mm (80)	72:8 (9:1)	85%:15% (5.6:1)	24:46:NA (1:2:NA)
Sharma et al (2008)(10)	1:1.5	5th decade	>25 mm (181)	168:13 (12.9:1)	-	31:11:1
Current Study	39:33 (1.2:1)	46	>25 mm	53:19 (2.8:1)	59:14 (4.2:1)	8:47:14 (1:5.8:1.8)

The mean age at initial diagnosis (46 years) was lower in our study as compared to the other studies (53 to 57 years). Sharma et al. reported a similar slightly lower age of initial presentation (5th decade) in their series (10). Our study had a slightly higher male population with male to female ratio of 1.2:1. In contrast, the studies by the US and Brazilian groups had an overwhelming female predominance (1:2 and 1:4.7 respectively) while the Finnish study had a slight female predominance (0.9 :1). Multiple previous demographic studies on IA have mentioned them to predominate in

females and the female sex has even been cited as a risk factor for development of aneurysms (29).

The ratio of anterior circulation to posterior circulation aneurysms (4.2 : 1) in our study was similar to the results published by Darsaut et al and Nurminen et al. Dos Santos et al published an even higher frequency of anterior circulation aneurysms in their study (9:1) while the highest incidence was reported by Sharma et al (12.9 : 1). It is possible that the higher incidence in the latter study is due to a selection bias as a result of it being a purely surgical series.

Compared to the other studies, our series showed the lowest proportion (1:9) of aneurysms presenting with SAH; with mass effect and thromboembolic events showing higher incidence. The others series have higher incidences of GA presenting with SAH (ranging from $1/3^{rd}$ to $2/3^{rd}$ of the total number of cases). At the outset, these results seem paradoxical as ours is the only series which reports purely intra-dural aneurysms and hence it might be expected that it would have a higher incidence of SAH.

Again a selection bias due to the inclusion of subjects from in-hospital patient data, as performed in some of the studies, might be one of the reason for this paradoxical observation. It is therefore likely that GA which were considered unsuitable for treatment were not hospitalized and hence excluded from the study. Some of these patients may have presented with non-SAH symptoms and would possibly not have been hospitalized. The results of these studies may henceforth not be truly generalizable to the entire prevailing population harbouring GA. In contrast, our study included all patients with GA who had been registered as outpatients in the hospital irrespective of subsequent admission and treatment. We believe that the

previously reported incidences of SAH in GA across different series may be due to this same selection bias and the true incidence could be much lower.

57% of aneurysms in our series were partially or completely thrombosed with relatively similar prevalence in saccular and non-saccular aneurysms (55.9 % and 61.5% respectively). Previous series have reported partial thrombosis in up to half the total number of diagnosed GA. Earlier studies have shown no significant predilection for thrombosis based upon either aneurysm morphology or location. The issue of thrombus within an aneurysm providing protection against rupture has been a contentious issue. We found a significant inverse association of partially thrombosed aneurysms with presentation with SAH. Various early studies and reports have suggested both, a protective action against rupture (135) as well as the absence of any such protection (136). Krings et al have postulated that haemorrhage which occurs in partially thrombosed aneurysms is at the periphery of the thrombus due to inflammatory change or bleeding from the vasa vasorum, and does not manifest as clinical SAH (67). One patient in our group of conservatively managed cases presented with acute compressive symptoms 18 years after the initial diagnosis of the aneurysm, with imaging showing perianeurysmal edema, mass effect and a focal infarct. These findings are in coherence with other reports of partially thrombosed aneurysms which state that acute worsening due to dissection and intra-mural thrombi result in sudden increase in size and worsening of compressive symptoms but are unlikely to present as SAH.

The few limited series which have described the follow up of untreated GA, report a dismal prognosis with mortality ranging from 60 - 100% (4–6). Sacho et al. published a series on fusiform intra-dural aneurysms less than 25 mm in size and described a

worse outcome for atherosclerotic aneurysms as opposed to non-atherosclerotic ones. They also concluded that fusiform intra-dural aneurysms are likely to have a benign clinical course unless symptomatic at presentation or greater than 7mm in diameter: a conclusion which precluded giant intra-dural fusiform aneurysms from having a benign clinical course. In our study of 18 untreated patients with clinical follow-up, there was a 38.9% mortality over a mean follow up period of 15.2 months with the rest of the patients having a good outcome with no clinical worsening over the period of follow-up. All patients who died, had the fatal event within 12 months of diagnosis with 86% (6/7) patients succumbing within the first 6 months. 4 of the 7 patients who died (57.1%) were in poor clinical state during initial presentation and eventually died due to associated complications. Of the three patients in initial good clinical state who eventually died, only one patient could be ascertained to have died due to an aneurysm rupture with the cause of death unknown in the other two.

Our series includes 19 aneurysms of the posterior circulation of which 11 were non-saccular (57.9%). This proportion of non-saccular posterior circulation GA was found to be of very high significance in the univariate analysis. In their series of 125 patients with GA, Nurminen et al. reported 34% of all fusiform aneurysms (11 /32) to be located in the posterior circulation while 50% of all posterior circulation aneurysms were fusiform (7). None of the patients with posterior circulation GA, in our series had presented primarily with SAH and only 1 patient eventually developed SAH after he was started on dual anti-platelet medication prior to planned FD placement.

Saliou et al in their series of 52 basilar trunk aneurysms (all sizes), reported a similar percentage of anterior and posterior circulation (34.5:64.5) aneurysms as in our series (137). They further sub-classified the aneurysms in their series based upon the

classification system proposed by Mizutani into 4 sub-types (47). Of the Mizutani categories, saccular and acute dissecting aneurysms were relatively smaller (median diameter of 5 and 8mm respectively). Segmental ectasia and mural bleeding ectasia were relatively larger (median diameters of 10 mm and 15 mm each). None of the larger aneurysms (segmental ectasia and acute bleeding ectasia) presented with acute SAH, with the predominant symptoms being compressive or thromboembolic and a combined 64% of these varieties were diagnosed incidentally. In contrast, smaller aneurysms (saccular or acute dissecting) had a higher tendency to present with SAH (83% and 38% respectively).

Saccular aneurysms of the posterior circulation have been described as being more prone to rupture as well as progressive increase in size with associated pressure effects or thromboembolic events (24,49) . The ISUI data ascribed a 50% five-year rupture risk for posterior circulation aneurysms larger than 25 mm in size. Ge at al reported 10 patients with saccular vertebrobasilar GA of which 3 patients were managed conservatively. All 3 patients died due to aneurysm rupture within 6 months of initial diagnosis (138). In addition, they reported that compressive symptoms or thromboembolic presentation also had a poor outcome irrespective of eventual successful treatment.

Surgery has been the time honoured treatment method for GA. Hosobhuci et al reported good outcomes in 80% of cases in their 1979 series on 40 GA with 15% procedure related mortality (136). Surgical techniques depend on the patient's clinical profile, aneurysm morphology, presence of cross circulation and intra-aneurysmal thrombus. The ideal modality is clipping and complete exclusion of the aneurysm with alternate strategies required on an individual patient basis. Posterior circulation

aneurysms and non-saccular aneurysm morphology make surgical treatment more difficult with higher rates of complication and mortality. Various studies reporting surgical treatment results have reported good outcomes in 58 to 84% cases and mortality in 14 to 22% cases (139–141). Sharma et al in their series of 181 aneurysms in 179 patients reported good clinical outcomes in 86% cases with 9% mortality (10).

Consistent with published literature, our surgical results showed good outcome in 66% cases with a 25% mortality. These results are a partly influenced by the fact that many surgical patients were in poor pre-operative clinical state, a fact that has previously been reiterated by Sharma et al in their study.

Endovascular coil embolization has been the mainstay of intra-cranial aneurysm treatment since the development of the technology in 1991(78) and publication of the ISAT trial results (142). While multiple trials have proven the safety of the technique for acutely ruptured aneurysms, there still remains questions on the durability, subsequent recanalization and need for retreatment. There is a direct relationship of aneurysm size and subsequent recanalization after coil embolization. While subsequent modified coils and neck support devices like stents and balloons have enabled tighter packing of the sac, use of the same has not seen a significant decrease in recanalization & retreatment rates in giant aneurysms (143). In addition, these techniques are associated with higher risks of complications such as thromboembolic events and in-stent stenosis. McLaughlin et al published a systematic review of 17 studies incorporating 656 patients with 702 aneurysms treated with stent assisted coiling (144). The authors noted that only 30-35% aneurysms could be described as having been satisfactorily treated, after factoring in aneurysm occlusion, recanalization, complication and delayed in-stent stenosis.

In our series, nine out of eleven (81.8%) coiling procedures were successfully completed but significant recanalization was noted in 45% of aneurysms, all of which necessitated retreatment. These results are similar to other studies on very large and giant aneurysms by Chalouhi et al , Sluzewski et al and Gao et al (Table 7.2) who have also reported high recanalization rates (14,145,146).

In their series of 31 very large and giant aneurysms treated primarily with coiling, Sluzewski et al reported only 7 aneurysms (23%) with complete occlusion on immediate post procedural angiogram. On follow up angiogram (at 6 months) aneurysm filling was noted in 69% of cases. Incomplete angiographic occlusion was noted in 41% of the 16 retreated cases in their series. Chalouhi et al in their series of coiled aneurysms greater than 10 mm in size, reported recanalization rates of 39% and retreatment rates of 33% (145).

Table 7.2 : Salient features of studies reporting results of coiling for very large and giant aneurysms and comparison with current study.

Study	Number	Size	Recanalization	Retreatment
Chalouhi et al (2014) (145)	21	>25 mm (subgroup of aneurysms >10mm)	52%	47.6%
Sluzewski et al (2003) (146)	31	>20 mm	Incomplete occlusion – 69%	16 (50%)
Gao et al (2012) (14)	31	>25 mm (subgroup of aneurysms >15mm)	46.4%	Not mentioned
Current Study	9	>25 mm (intra-dural only)	45%	45%

In their sub-group of GA, recanalization rate of 52% and retreatment rate of 47.6% were reported. Gao et al in their sub-group of all aneurysms larger than 15 mm treated with coiling reported 46.4% recanalization rates as opposed to 20.8% recanalization for aneurysms between 15 to 25 mm in size (14). Previous studies have also reported recanalization rates of up to 50% for aneurysms larger than 10 mm in size (147,148).

A number of potential causes of recanalization of coiled aneurysms have been propounded, the most consistent of which appears to be packing density of the coil mass in relation to the volume of the aneurysm. Studies have shown that packing density above 20 to 24% (149,150) lead to lower chances of aneurysm recanalization. However as aneurysm volume increases, attempts at increased packing may not substantially prevent recanalization and comes at an added increased rupture risk as opposed to smaller aneurysms (151). Furthermore, the complex and often bizarre morphology of very large and giant aneurysms make determination of packing density extremely difficult.

The other defined factor affecting long term recanalization in coiled aneurysms is the presence of intra-luminal thrombus. This occurs chiefly due to 2 mechanisms: first, due to migration of coil mass into the aneurysm and secondly due to gradual thrombus resorption after coiling (97). Ferns et al studied the results of endovascular treatment in 56 partially thrombosed aneurysms (30 treated with coiling and 26 with parent vessel occlusion) and found a high recanalization rate of 75% with 19 out of 30 patients treated with primary coiling requiring retreatment (58). The authors also noted that reduction in size of partially thrombosed GA was relatively infrequent even after complete coil occlusion, with a number of aneurysms even showing persistent growth.

Parent artery occlusion after balloon occlusion test has been reported as a durable and relatively safe treatment modality for anterior circulation aneurysms (proximal ICA) in multiple series (15,100). However, parent artery occlusion is more suitable for proximal (extra-dural ICA) aneurysms with a lesser number of intra-dural aneurysms treated with this modality. Of the total set of anterior circulation aneurysms treated with parent artery occlusion, intra-dural aneurysms comprised 40% and 29% in the series reported by Bechan et al and Clarencon et al respectively (100,152). Yang et al reported the results of parent artery occlusion versus isolated aneurysm sac exclusion for large and giant aneurysms (both surgical & endovascular) and reported 100% occlusion rates with no recanalization in the parent artery occlusion group as opposed to 30% recanalization and retreatment in the selective sac exclusion group (97). Kashiwazaki et al reported good outcomes and occlusion rates in PCA aneurysms treated with parent artery occlusion (153). Two patients with PCA aneurysms were treated with parent artery occlusion in our series with both showing good long term outcome.

Only one of our patients with a supra-clinoid IC aneurysm was treated with parent artery occlusion, who had a good clinical outcome and no aneurysm recanalization on subsequent long term follow up. There is no series comparing the results of balloon occlusion test for extra-dural and intra-dural ICA aneurysms but it is likely that the more distally an aneurysm is located in the ICA, the more difficult it is to perform an aneurysm trapping, especially in location near the bifurcation (152).

Of the 5 FD placement procedures in our series, 4 were successful. All procedures were attempted in anterior circulation aneurysms (4 in the ICA and 1 in the MCA). Single FD was used for all except 1 patient who treated with 3 telescoped FD for a

giant MCA aneurysm. All successfully treated cases had a 100% aneurysm occlusion on follow up angiogram with no recanalization on subsequent follow up, indicating the efficacious and durable nature of this modality. In a systematic review and meta-analysis of 59 studies reporting outcomes of 2493 aneurysms (no size or location criteria), Zhou et al reported a 97.4% technical success rate with an 82.5 % overall complete occlusion rate. The authors reported a 76% complete occlusion rate for GA (154) but did not report the technical success rate for GA separately in their analysis. In yet another meta-analysis of 48 studies incorporating 2508 patients with 2826 aneurysms, Ye et al reported complete occlusion, morbidity and mortality rates of 77.9%, 9.8% and 3.8% respectively. They reported a 72% occlusion rate for GA and higher rates of morbidity and mortality (122).

The Pipeline for Uncoilable or Failed Aneurysms (PUFS) trial was a multi-center prospective trial which analysed the efficacy and safety of the pipeline embolization device (PED) in the endovascular management of large and giant aneurysms with a wide neck (117). The primary safety outcome of the trial was death or ipsilateral major stroke within 180 days and the primary effectiveness endpoint was demonstration of total aneurysm exclusion and absence of stent stenosis at 180 days. The trial recruited 108 patients in ten centres with 22 (20.4%) giant aneurysms (>25 mm) and 85 (78.7%) large aneurysms (>10 mm). The complete occlusion rate was 73.6% at 180 days and 86.8% at one year. The authors reported a one-year angiographic occlusion rate of 86.8% with primary effectiveness endpoint of met by 76.8% of the patients and the primary safety endpoint met by 94.4% patients with 86% patients reported to have mRS of 1 or less on follow up. The trial, although a meticulously conducted prospective study, had certain caveats in the inclusion of only ICA aneurysms, use of only single devices and having proportion of GA as only 1/5th

of the study population. In a meta-analysis of studies reporting results of flow diverters, Ye et al found GA to have lower occlusion rates (72%) as opposed to small or large aneurysms (78.4%) with higher rates of neurological morbidity and mortality (122). There is very little available literature describing the results on FD in GA in isolation and no available reports on the purely intra-dural entities. Zhou et al described the best results till date for GA in their series of 28 patients with large and giant aneurysms treated with the turbridge flow diverter (155). The reported a 72% occlusion rate, 97% technical success rate along with zero mortality and long term morbidity rates.

Our reports on FD in GA are undoubtedly limited by small numbers, however we feel that these numbers are due to the stringent selection criteria of size more than 25 mm and purely intra-dural aneurysms. A number of authors have described the increased technical difficulty in deploying FD across GA and also the increased risk of complications. Another factor which cannot be ignored in our results is the unwillingness of patients to undergo FD placement, principally due to the enormous financial implications.

One intra-procedural complication which was observed in our series was a case of a patient with a giant MCA aneurysm who developed intra-parenchymal haemorrhage after placement of 3 telescoped FD. The possible reason for this was significantly increased wire and microcatheter manipulation within the aneurysm sac. Overall, flow diverters for GA, while still requiring long term prospective study, appear to achieve more durable aneurysm occlusion as compared to coiling at the cost of higher rates of complications and morbidity.

Since the inception of endovascular techniques for neurovascular pathology, there has been considerable debate in the scientific community about the optimal treatment strategies for IA. The ISAT trial was the first randomised control trial which compared the outcomes after surgical clipping and endovascular coiling in acutely ruptured aneurysms (12,142). However, the trial did not include unruptured aneurysms and only 7% and 8% of the aneurysms in the surgical and endovascular group respectively were greater than 11 mm in size. There is no mention of the number of giant aneurysms in the trial. The comparative results of surgical and endovascular treatment of GA are only available from single centre case series. In one such large series comparing surgical and endovascular results, Darasut et al reported the results of multi-modality treatment in 85 very large (size > 20mm) and giant aneurysms with 46% and 54% in each group respectively (22). 114 patients in their series underwent surgery, 60 patients underwent endovascular treatment and 9 patient underwent both surgical and endovascular treatment. They reported complication rates with neurological deficit of 15.8% and mortality of 12.2% for the surgical group and 18.3 % and 8.3% respectively for the endovascular group. These results compared favourably with our series, especially considering the authors included all patient with mRS of 3 or less as having a good outcome as compared the cut off of 2 or less used by us. They reported retreatment rates of 28.3% for the endovascular group and 6.1% for the surgical group which again are similar to the respective rates of 27.8% and 7.9% in our study. In our series, despite strict inclusion of only intra-dural aneurysms, no intra-procedural rupture was noted among the surgical patients. Among patients in the endovascular group, rupture was the most frequent complication noted in 4 patients (3 during or immediately after procedure and 1 after starting anti-platelet

medications). Of these 4 patients, 2 (50%) died and only one patient had a good outcome.

All ruptured aneurysms in our series were treated surgically. The endovascular treatment of giant ruptured aneurysms is still a work in progress with flow diverters needing anti-platelet medications due to high thrombogenicity and only a small proportion of patients with GA amenable for parent artery occlusion. Brikinji et al reported a series of 31 patients with large / giant ruptured aneurysms who were treated with initial coiling to reduce the risk of rebleed and subsequent staged flow diverter placement in 27 patients over a median time interval of 16 weeks (156) . They reported complete occlusion in 58.1% patients on an intention to treat basis and 63% patients who underwent flow diversion with overall good outcome of 80.6%.

Posterior circulation aneurysms formed 26.4% of all GIDA in our study and were managed either conservatively (9/19) or by endovascular means (10/19). Endovascular treatment was performed either by coiling or parent vessel occlusion with an 80% procedural success rate and 20% recanalization and retreatment rates each. There was one post procedural mortality in addition to one patient who died after starting anti-platelet medications prior to FD placement. All other patients had a good long term follow up. Previous reports in literature detailing endovascular treatment of giant posterior circulation aneurysms have small sample sizes similar to ours. Ge at al reported a series of 7 patients with giant saccular vertebrobasilar aneurysms with an extremely poor outcome (6 of 7 patients died over a 22 months follow up period (138). Qin et al reported 8 giant (saccular and non-saccular) aneurysms in their series of 59 PCA aneurysms treated by endovascular methods. Although they reported a good overall outcome (47 of 49 patients on long term follow

up) they did not further sub-classify their results based upon aneurysm size (157). Use of flow diverters for posterior circulation aneurysms has not been as enthusiastically practised as for their counterparts in the anterior circulation, principally due to the fear of ischemic complications arising out of deployment of high mesh density stent across the perforator rich posterior circulation arteries. Wang et al in a meta-analysis of 220 patients deployed with FD for posterior circulation aneurysms reported a procedure related mortality of 15% with significantly higher rates for giant and basilar artery aneurysms with an aneurysm occlusion rate of 84% (128).

After very early reports suggesting the benefits of conservative management, thus far GA have been considered as potentially life threatening entities which require early treatment. Natural history studies on GA have ascribed a high rupture risk. In our series of 72 patients, 50 (69.4%) underwent treatment while 22 (30.6%) were managed conservatively. The available follow up in 65 patients did not show significant differences in mortality or good clinical outcome in either group. While these results are insightful, they should be viewed with caution especially as the mean follow up period for untreated aneurysms was only 15 months and longer follow up was available for the treated patients. The lowest mortality was noted in the endovascular group with only one direct procedure related mortality (and one pre-procedural mortality). The single most important factor predicting eventual outcome irrespective of the type of management or the manner of clinical presentation was the clinical state at initial presentation with an initial mRS of 3 or more having more morbidity and mortality as compared to patients with mRS of 2 or less.

Dengler et al published at meta-analysis to review the outcomes of GA in a pooled analysis of 54 studies with 1269 aneurysms (158). None of the studies in the analysis

reported results of intra-dural aneurysms separately and only three studies had larger populations than ours. They included 27 study populations with endovascular treatment, 31 with surgical treatment and 6 with combined surgical and endovascular treatment. The investigators found an overall combined good outcome rate of 80.9% with no significant difference in outcomes of the surgical and endovascular groups. The authors also state that good outcomes rates reduced (70%) in studies of higher quality (similar to our results) as compared to rates of poorer quality studies (83.6%). Significantly poorer outcomes were noted for posterior circulation aneurysms and in older patients (more than 63 years). The study, though the first of its kind to pool and compare data on outcomes of GA , still do not delve into the territory of natural history. This is probably because of a striking lack of literature on the subject with our study providing the largest subset of patients hitherto described with follow up for untreated GA. Dengler's meta-analysis again, did not sub-classify intra and extra-dural aneurysms separately, which we feel is an important factor to consider when studying the outcomes of GA.

In view of our findings, we would make a guarded suggestion that patients in good clinical state with partially thrombosed GIDA (especially non saccular) which are considered high risk for either endovascular or surgical treatment may be observed conservatively with close clinical and imaging follow up with a decision to intervene at the signs of clinical worsening or significant aneurysmal growth. The results of the giant intra-cranial aneurysm registry may possibly validate our observations (159). This study is a prospective multi-center trial to compare 5 year outcomes after surgical, endovascular and conservative management of GA. The trial started recruitment in 2008 and the results are still awaited.

There were a few interesting anecdotal features in some of the cases in our series which are characterised by their rarity and deserve mention.

One patient with a saccular unruptured basilar artery aneurysm who was planned for flow diversion developed SAH due to aneurysm rupture two days after he was started on dual antiplatelet medications.

One patient had a proximal basilar aneurysm (fig 6.13 to 6.16) with fenestration of the artery proximal to the fenestration. Basilar artery fenestration has been reported to have an angiographic frequency of 0.022 to 1.7% with possible associations with thromboembolic events and aneurysm formation, though the rarity of the condition probably precludes definite statistical analysis (160). While spontaneous complete thrombosis in untreated GA, though rare , is well known and documented (161,162), we believe our case is the first such case of spontaneous thrombosis following an iatrogenic dissection.

One patient who had been diagnosed with a giant ICA bifurcation aneurysm and had refused treatment with subsequent loss of follow up. The patient subsequently presented 18 years after initial diagnosis with sudden onset monoparesis and the imaging evaluation showed that the aneurysm had significantly increased in size with a large thrombosed component causing surrounding pressure effects (Fig 6.17-6.18). His sudden worsening was presumed to be due to thromboembolic phenomenon. We did not find any similar references in published literature of such a long follow up of a giant aneurysm.

Although the above described cases are anecdotal, we feel that they provide insight into the pathophysiology and natural history of GA and possible stages of dormancy where the patient might remain symptom free for years. Inflammatory and

hemodynamic changes may cause sudden morphological changes such as thrombosis and possibly even rupture, years after initial diagnosis. As in our case, a previously apparently stable aneurysm might have a ‘tipping point’ such as use of anti-platelet medications, which may lead to potentially fatal rupture and SAH.

Our study had a number of limitations. First, in view of retrospective and prospective patient selection over a period of 11 years, it is possible that the same parameters for selection of patients for treatment were not uniform which could have affected our results. FD have now evolved as a viable and clinically proven method for treatment of aneurysms. The first FD placement in our institute was done in 2013, 8 years after the start of the study period. The indications for flow diverters has increased dramatically since their inception with a number of authors reporting good success rates and outcomes for posterior circulation aneurysms. Our surgical series was comprised totally of anterior circulation aneurysms, which have historically have shown better treatment outcomes as compared to those in the posterior circulation.

While number of patients with posterior and anterior circulation GIDA were advised for flow diversion, the procedures could not be performed due to financial restrictions, a fact which reduced the numbers of patients in the endovascular arm of the study. Coiling had to be performed in some patients due to the risk of aneurysm rupture in spite of high chances of recanalization and the inability of the patients to afford FD treatment. This factor is likely to have adversely affected the outcomes in the endovascular treatment group.

Mean follow up of 15 months was available for patients managed conservatively. It is well known that GIDA are dynamic entities with potential for delayed growth. Future research into the natural history may be conducted in large tertiary care centres by

reviewing the clinical outcomes of untreated patients with GA on follow up. We would like to continue the follow up of our cohort of patients to further validate our preliminary observations on the natural history. Future studies reporting treatment outcomes on GA should provide sub-group analysis for GIDA to compare the overall treatment outcomes as compared to all GA. Randomized control trials for GA while desirable are highly improbable due to the rarity of the situation and difficulty in finding cases of clinical equipoise for randomization. Prospective trials assessing the outcomes of the latest treatment modalities are likely to provide the highest level of evidence concerning these aneurysms.

As per the existing literature and our results, there is no panacea in the treatment of GIDA and every patient should be offered a particular management strategy after detailed counselling and a combined inter-disciplinary consensus. In this regard, we cannot emphasise too strongly the role of a multi-disciplinary effort in a tertiary care centre. Our team included dedicated neurointerventional radiologists, neurosurgeons, neuroanaesthesiologists and stroke neurologists and we feel that such multi-speciality teams are imperative in offering the best outcomes to patients.

Conclusion

Our study is the largest series from India to analyse multi-modal and inter-disciplinary treatment outcomes of GA in general and GIDA in particular, in addition to being the largest series analysing the natural history of these entities. The study shows angiographic occlusion rates similar to other larger series in literature (22,156) with the slightly poorer outcome rates possibly due to inclusion of pure intra-dural aneurysms and higher proportion of patients presenting with an initial poor clinical state. The natural history analysis from our patients on conservative management suggests that the outlook for untreated patients might not be as universally grim as that suggested by previous reports in smaller samples (5,6).

This series also helped us in reaching following inferences regarding the clinical perspectives and practical management based on observations and outcomes on analysis of data.

1. GIDA are a diverse group of pathological entities with varying morphological presentation which may not reflect the initial etiological event inciting aneurysm formation. There is no definite demographic parameter that bears significant relation to aneurysm morphology, location or clinical presentation.
2. Anterior circulation aneurysms are more likely to be saccular in morphology as compared to posterior circulation aneurysms. Giant posterior circulation aneurysms are less likely to rupture as compared to anterior circulation aneurysms.
3. The overall rupture risk in GIDA may be overestimated in previous studies due to selection of patients from hospital admission records. The intra-dural location of aneurysms as studied specifically by us, was not reflected by a

higher incidence of presentation with SAH as compared to GA in combined intra and extra-dural locations as reported in previous studies.

4. Absence of intra-aneurysmal thrombus and a saccular aneurysm morphology are likely to be factors predicting eventual aneurysm rupture.

5. Initial poor clinical state is the single most important clinical factor in predicting the final outcome and survival of the patient irrespective on the manner of clinical presentation (SAH or stroke) or the type of treatment undertaken.

6. Endovascular coiling of GIDA, though a relatively safe and efficacious technique, is associated with a higher risk or recanalization and retreatment and should be considered if other alternative methods such as PAO and FD placement are not feasible. PAO is a less feasible alternative in GIDA as compared to extra-dural aneurysms. FD is a relatively safe, efficacious and highly durable treatment option which should be considered among the first line modalities for all GIDA.

7. Based upon the follow-up of untreated patients, certain unruptured aneurysms, which are exceptionally difficult for surgical or endovascular management may be treated conservatively. Medium term follow-up suggested acceptable untoward clinical event rates in patients with good initial clinical status. However, subsequent studies with longer durations of follow up are required to further validate this observation.

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Annexures

Sree Chitra Tirunal Institute for Medical Sciences & Technology

Proforma for Giant Intra-Dural Aneurysms

A.GENERAL INFORMATION

1.1 Name

1.2 Age

1.3 Sex

1.4 Hospital No

1.9 Date of admission

1.11 Date of discharge/death

B.CLINICAL DETAILS

Mode of Presentation [Bleed/ Mass effect/thromboembolism/incidental/others]

Examination findings

On initial examination

Modified Rankin Score :

C. INVESTIGATIONS

Imaging (CT / MRI/ DSA)

Location:

- ICA
- ACA
- MCA
- PCA
- VA
- BA

SHAPE :

- SACCULAR
- FUSIFORM

- SERPENTINE

Presence of Thrombus:

- Yes
- No

Mass Effect :

Presence of SAH:

D. Management

1. Surgical
2. Endovascular
3. Conservative

- Date of procedure:
- Brief description of procedure:

5) Intra-procedural complications (if any):

E. COMPLICATIONS (elaborate if needed)

In case of Death :

- Time from initial presentation:
- Direct cause of death:
- Pre-treatment or post treatment:
- Whether death due to treatment related complication:
- If yes , elaborate the complication and duration of survival after treatment:

Clinical Follow Up: (modified Rankin score)

At Discharge :

Subsequent OPD Follow Up record (as available):

Plagiarism Check Report

Aneesh_Thesis.docx

ORIGINALITY REPORT

1%

SIMILARITY INDEX

PRIMARY SOURCES

1	Yoshimura. Shinichi. "Clinical Evidence of Flow Diverters". Journal of Neuroendovascular Therapy. 2016. Crossref	36 words — < 1%
2	Papagiannaki. C.. L. Spelle. A.- C. Januel. A. Benaissa. J.- Y. Gauvrit. V. Costalat. H. Desal. F. Turjman. S. Velasco. X. Barreau. P. Courtheoux. C. Cognard. D. Herbreteau. J. Moret. and L. Pierot. "WEB Intrasaccular Flow Disruptor--Prospective. Multicenter Experience in 83 Patients with 85 Aneurysms". American Journal of Neuroradiology. 2014. Crossref	23 words — < 1%
3	Sharma. B.S.. "Surgical management of giant intracranial aneurysms". Clinical Neurology and Neurosurgery. 200807 Crossref	23 words — < 1%
4	James Vincent Byrne. "Arterial Aneurysms". Tutorials in Endovascular Neurosurgery and Interventional Neuroradiology. 2012 Crossref	21 words — < 1%
5	Ye. Gengfan. Meng Zhang. Lin Deng. Xiaohui Chen. and Yunyan Wang. "Meta-Analysis of the Efficiency and Prognosis of Intracranial Aneurysm Treated with Flow Diverter Devices". Journal of Molecular Neuroscience. 2016. Crossref	20 words — < 1%
6	M. Sluzewski. "Endovascular Treatment of Large and Giant Aneurysms". American Journal of Neuroradiology. 08/21/2008 Crossref	16 words — < 1%
7	Sousa. Atos. José Sousa Filho. and Marcos Dellaretti Filho. "Treatment of Giant Intracranial Aneurysms: a Review Based on Experience from 286 Cases". Arquivos Brasileiros de Neurocirurgia Brazilian Neurosurgery. 2015. Crossref	15 words — < 1%

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EXCLUDE BIBLIOGRAPHY ON
EXCLUDE MATCHES OFF

CONSENT FORM

TITLE OF THE STUDY: **Giant intra-dural aneurysms – Analysis of clinico-morphological Features, natural history and treatment outcomes.**

I would like to conduct a study in about 70 patients who suffer from similar illness like you, about the disease and treatment method, results, complications etc. You are being requested to participate in this study which analyse clinical & radiological characteristics, efficacy of the treatment modality offered to you (surgical / endovascular / conservative), complications (if any) in patients with giant intra-dural aneurysms and the follow up patients subsequent to treatment.

What is an Aneurysm?

- An aneurysm is any abnormal enlargement of the walls of blood vessels called arteries, which supply blood from the heart to the tissues. The brain is one of the commonest sites for the development of the aneurysm. Intra-dural aneurysms are those aneurysms which lie within the outer covering of the brain called as the dura mater. Giant aneurysms are those aneurysms which are larger than 2.5 cm in their largest problems.

What problems can brain aneurysms cause ?

- Brain aneurysms can cause many problems. The most common of these is rupture of the aneurysm due to weakening of the walls of the artery in which the aneurysm forms. This gives rise to a condition called as sub-arachnoid haemorrhage, which carries a very high risk to life if not treated urgently. Sometimes aneurysms can become large enough to cause pressure effects on the adjoining brain tissue, the nerves of the brain and so on. Some aneurysms can get thrombosed (blocked) and these can cause stroke like symptoms. Occasionally aneurysms may remain totally asymptomatic and are discovered incidentally on brain imaging studies.

How are aneurysms treated ?

- Aneurysms can be treated by surgery or by interventional radiology (endovascular) methods. Surgery may entail blocking the parent vessel in which the aneurysm has formed or by placing a clip across the neck of the aneurysm. Endovascular methods entail taking a small pipe called catheter into the aneurysm through the thigh or arm arteries and placing small metal coils into the aneurysm thus obliterating its lumen. Newer methods of treatments include placing devices called flow diverters across the width of the aneurysm which do not permit blood from entering the aneurysm. The method of choice to treat an aneurysm is decided based on its location, shape , size, course of the parent vessels and various other factors. Some aneurysms may be left untreated altogether and the patients simply placed on follow up.

If you take part what will you have to do?

- For this study, we'll be using some of the data like history and other clinical details, Imaging details (CT/MRI/ CTA /MRA), Angiograms (DSA), treatment technique, outcome of the procedure(Immediate angiographic and clinical) , delayed follow up clinical and radiological regarding your disease and treatment which you undergo in this hospital.
- The natural history of disease, treatment options, cost, risks, benefits and other complications about the treatment is already explained to you by the treating physician.
- No additional cost will be incurred /no additional drugs will be used and there are no additional risks as a part of the research.
- Analysis of these data may or may not be useful for you later, but this is likely to give more understanding of this disease and treatment, for the benefit of future generation. You understand that strict confidentiality will be maintained.

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way. If you want to withdraw or need any more information, you can contact me in interventional Radiology OPD or in the telephone number 04712524518, 9447961100 or email: romianeesh@sctimst.ac.in.

Will your personal details be kept confidential?

- The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

Participant's name: Date of Birth / Age (in years):
I_____ _____,
Son/daughter of _____ (Please tick boxes) •
Declare that I have read the above information provide to me regarding
the study: G**iant intra-dural aneurysms: clinicomorphological features, natural history and treatment outcomes** and have clarified any doubts that I had. I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights.
• I also understand that study investigators will be using some of the data like history and other clinical details, Imaging details (CT/MRI/ CTA /MRA), Angiograms (DSA), treatment technique, outcome of the procedure(Immediate angiographic and clinical) , delayed follow up clinical and radiological regarding your disease and treatment which you undergo in hospital.
• I also understand that no additional cost will be incurred /no additional drugs will be used and there are no additional risks as a part of the research.
• I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access.
• I understand that my identity will not be revealed in any information released to third parties or published.
• I voluntarily agree to take part in this study.
• I received a copy of this signed consent form.

Name:

Signature:

Date:

Name of witness:

Relation to participant:

Date:

(Person Obtaining Consent) I attest that the requirements for informed consent for the medical research project described in this form have been satisfied. I have discussed the research project with the participant and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

_____ _____

Name and Signature of Person Obtaining Consent

Principal Investigator.

MASTER CHART

Sl No	Age	Sex		Clinical Presentation					LOCATION						thrombus		Morphology			treatment			Comorbidities		MRS at presentation
	(yrs)	Male	Fem	Bleed	Mass/E	TE	Incidental	Other	ICA	MCA	ACA	PCA	VA	BA	YES	no	Sacc	fusi	serp	surg	EV	Cons	DM	HTN	
1	50	1	0	0	1	0	0	0	1	0	0	0	0	0	1	0	1	0	0	1	0	0	0	0	1
2	53	1	0	0	1	0	0	0	1	0	0	0	0	0	1	0	1	0	0	1	0	0	0	0	1
3	36	0	1	0	1	0	0	0	1	0	0	0	0	0	1	0	1	0	0	1	0	0	0	1	2
4	42	1	0	0	1	0	0	0	0	1	0	0	0	0	1	0	1	0	0	1	0	0	0	0	1
5	56	1	0	1	0	0	0	0	0	1	0	0	0	0	0	1	1	0	0	1	0	0	0	0	5
6	38	1	0	0	1	1	0	0	1	0	0	0	0	0	1	0	1	0	0	1	0	0	0	0	5
7	35	0	1	0	0	0	0	1	1	0	0	0	0	0	1	0	1	0	0	1	0	0	0	0	0
8	51	0	1	0	1	0	0	0	1	0	0	0	0	0	0	1	1	0	0	1	0	0	0	0	2
9	37	1	0	1	0	0	0	0	0	0	1	0	0	0	0	1	1	0	0	1	0	0	0	0	1
10	48	1	0	0	1	0	0	0	0	0	1	0	0	0	1	0	1	0	0	1	0	0	0	1	2
11	55	0	1	0	1	0	0	0	0	0	0	0	0	1	1	0	0	1	0	0	1	0	0	1	2
12	57	0	1	0	1	0	0	0	1	0	0	0	0	0	0	1	1	0	0	0	1	0	0	0	1
13	12	1	0	0	1	0	0	0	0	1	0	0	0	0	0	1	1	0	0	1	0	0	0	0	1
14	48	0	1	0	1	0	0	0	1	0	0	0	0	0	1	0	1	0	0	1	0	0	0	0	2
15	35	1	0	0	1	0	0	0	0	0	1	0	0	0	1	0	1	0	0	1	0	0	0	0	1
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18	14	1	0	0	1	1	0	0	0	1	0	0	0	0	1	0	1	0	0	1	0	0	0	0	3
19	40	1	0	0	1	0	0	0	0	0	0	1	0	0	1	0	1	0	0	0	1	0	0	0	2
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21	58	1	0	1	0	0	0	0	0	1	0	0	0	0	0	1	1	0	0	1	0	0	0	1	3
22	43	0	1	0	1	0	0	0	1	0	0	0	0	0	0	1	1	0	0	0	0	1	0	0	1
23	29	1	0	0	1	1	0	0	0	0	0	1	0	0	0	1	0	1	0	0	1	0	0	0	1
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72	54	1	0	1	1	0	0	0	0	0	0	0	0	1	0	1	1	0	0	0	1	0	0	0	3

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Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013)

SCT/IEC/621/JUNE -2014 17-07-2014

Dr. Aneesh Mohimen
Senior Resident
Department of IS & IR,
SCTIMST.

Dear Dr. Aneesh Mohimen,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "GIANT INTRA-DURAL ANEURYSMS – ANALYSIS OF CLINICO-MORPHOLOGICAL FEATURES, NATURAL HISTORY AND TREATMENT OUTCOMES "(IEC/621) on 7th June, 2014.

The following documents were reviewed:

1. *Covering letter addressed to the Chairman, dated 27.05.2014 & IEC Application Form.*
2. *TAC Clearance letter.*
3. *Project proposal.*
4. *Proforma.*
5. *CVs of the PI and Co-PI.*
6. *Consent form (English and Malayalam).*
7. *Covering letter addressed to the Chairman, dated 14.07.2014.*
8. *Revised proposal including all revision suggested by IEC on July 7th, 2014.*

तार : चित्रमेट फोन फाक्स ई-मेइल
Grams : Chitramet Phone : 2443152 Fax : (91)471-2446433 E-mail : sct. @sctimst.ac.in

The following members of the Ethics Committee were present at the meeting held on 7th June, 2014 at G. Parthasarathi Board Room, AMCHSS, SCTIMST.

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Justice Gopinathan. P.S	BSc. LLB	Male	Legal Expert (Chairperson)	No
2.	Dr. J. M. Tharakan	MD	Male	Clinician (Cardiologist)	Yes
3.	Dr. O.S. Neelakandan Nair	BE	Male	Engineer	Yes
4.	Dr. Meenu Hariharan	DM	Female	Clinician (Gastro Enterologist)	No
5.	Dr. M.D. Gupte	MD, DPH	Male	Public Health	No
6.	Dr. Rema M. N	MD	Female	Pharmacologist	No
7.	Dr. R V G Menon	PhD	Male	Lay Person	No
8.	Smt. Sathi Nair	MA	Female	Lay Person	No
9.	Dr. K R S Krishnan	ME, PhD	Male	Biomedical Scientist/Engineer	No
10.	Dr. Kala Kesavan. P	MD	Female	Pharmacologist	No
11.	Dr. K. Jayakumar	MS, MCh	Male	Clinician (Surgeon)	Yes
12.	Dr. Mala Ramanathan	MSc, PhD, MA	Female	Ethicist/Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC