COMPARISON OF IMMEDIATE POST-OPERATIVE CT ANGIOGRAPHY WITH DELAYED ANGIOGRAPHY TO DETECT ANEURYSM REMNANT: A CROSS-SECTIONAL STUDY IN HSAJB

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List of Abbreviations

1	CTA	Computed tomography angiography
2	DSA	Digital subtraction angiography
3	MCA	Middle cerebral artery
4	ICA	Internal carotid artery
5	ACOM	Anterior communicating artery
6	PCOM	Posterior communicating artery
7	ACA	Anterior communicating artery
8	HDU	High dependency unit
9	NSC	Neurosurgical Clinic
10	HSAJB	Hospital Sultanah Aminah Johor Bahru
11	WFNS	World Federation Of Neurosurgical societies
12	mRS	Modified Rankin Score
13	EVD	External ventricular drainage
14	iCT	Intraoperative Computed Tomography
15	OT	Operating theatre
16	GCS	Glasgow Coma Scale

ABSTRAK

Latar Belakang dan Objektif

Aneurisma otak pecah adalah penyebab utama strok yang menyebabkan morbiditi dan kematian tinggi. Walaupun terdapat kemajuan dalam pengurusan pembedahan aneurisma pecah, imbasan selanjut pasca operasi masih berbeza dan tidak ada kesepakatan. Pada masa ini, beberapa pusat menggunakan imbasan CT pasca operasi segera untuk mengesan baki aneurisma. Oleh itu, kami bertujuan untuk menguji kepentingan dan kebolehpercayaan CTA pasca operasi segera.

Kaedah

Ini adalah kajian keratan rentas pusat tunggal. Sebanyak 54 pesakit berusia antara 18 hingga 80 tahun dimasukkan ke Jabatan Bedah Saraf, Hospital Sultanah Aminah Johor Bahru (HSAJB) dari 1 Januari 2019 hingga 31 Mei 2020 kerana aneurisma pecah yang memenuhi kriteria kemasukan dimasukkan dalam kajian ini. Data demografi termasuk umur, jantina, jenis aneurisma, skor WFNS, jenis pengimejan diagnostik dan keperluan EVD dikumpulkan. Pesakit kemudian menjalani pembedahan dan menjalani CTA segera. Kemudian pesakit menindaklanjuti dan menjalani angiografi yang tertunda dari 3 - 6 bulan. Data dianalisis dan perbandingan kedua-dua pengimejan dibandingkan.

Keputusan

Seramai 54 pesakit dengan usia rata-rata 51.87 ± 12.34 tahun dimasukkan dan menjalani pembedahan kliping. 66.7% (n = 36) dimasukkan dengan skor WFNS yang baik. Aneurisma Acom adalah yang paling kerap (31.5% (n = 17)). Secara amnya, ia memerlukan waktu min 4.85 hari dari hari kemasukan hingga hari pembedahan. Semasa pembedahan 27.8% (n = 15) mengalami pecah semula aneurisma. 4 kes dapat mengesan

sisa-sisa aneurisma dengan CTA segera manakala 8 kes dikesan melalui angiografi yang tertunda. Ujian Cohen Kappa menunjukkan nilai 0.63, yang menunjukkan persetujuan kukuh antara angiografi segera dan tertunda. Terdapat hubungan yang signifikan antara isyarat Doppler intraoperatif dan pengesanan vasospasme di CTA ($p < 0.001$). Juga mendapati bahawa terdapat hubungan yang signifikan antara CTA vasospasm dan pecah semasa pembedahan ($p = 0.006$). Hasil umum pesakit yang diukur dengan median skor mRS semasa rawatan susulan pertama adalah 2.

Kesimpulan

Terdapat persetujuan kukuh antara CTA segera dengan angiografi tertunda dalam mengesan sisa aneurisma. Oleh itu, menggunakan CTA segera sebagai alat pengimbasan awal pasca-kliping membolehkan kita membuat strategi rawatan seterusnya. Pada masa yang sama, jika bergabung dengan Doppler dalam pembedahan, ia boleh menjadi berguna dalam mengesan vasospasme.

Kata Kunci

Aneurisma, pendarahan subarachnoid, CTA segera, baki aneurisma, vasospasme

ABSTRACT

Background and Objective

Ruptured intracranial aneurysm is a common cause of stroke leading to high morbidity and mortality. Despite there are advancements in the surgical management of ruptured aneurysms, post-operative follow-up imaging still varies, and no consensus. Currently, some centers are utilising an immediate post-operative CT scan to detect residual aneurysm. Hence, we aim to test the significance and reliability of immediate post-operative CTA.

Methods

This was a single-center cross-sectional study. A total of 54 patients aged between 18 to 80 years old were admitted to the Department of Neurosurgery, Hospital Sultanah Aminah Johor Bahru (HSAJB) from 1st January 2019 to 31st May 2020 for ruptured aneurysm who fulfilled the inclusion criteria were included in this study. Demographic data including age, gender, type of aneurysm, WFNS score, type of diagnostic imaging, and requirement of EVD were collected. The patients subsequently underwent surgical clipping and subjected to immediate CTA. Then the patients followed up and proceeded with delayed angiography from 3 – 6 months. Data were analysed and the finding of both imaging compared.

Results

A total of 54 patients with a mean age of 51.87 ± 12.34 years were admitted and subjected to clipping surgery. 66.7% (n=36) admitted with good WFNS score. ACOM aneurysm was the commonest (31.5% (n=17)). Generally, it required a mean time of

4.85days from the day of admission until clipping. Intraoperatively 27.8% (n=15) had re-rupture of the aneurysm. 4 cases (7.4%) were able to detect aneurysm remnants with immediate CTA while 8 cases (14.8%) were detected via delayed angiography. Cohen's Kappa test showed a value of 0.63, which indicates substantial agreement between immediate and delayed angiography. There is a significant association between intraoperative Doppler signal and detection of vasospasm in CTA ($p < 0.001$). There is also a significant association between CTA vasospasm and intraoperative rupture ($p = 0.006$). The general outcome of the patient measured with the mRS score during the 1st follow-up at the mean duration of 53 days was a median of 2.

Conclusion

There is substantial agreement between immediate CTA and delayed angiography in detecting aneurysm remnants. Therefore using immediate CTA as an early imaging tool post-clipping enables us to tabulate subsequent management strategy. At the same time, if combine with intraoperative Doppler, it can be useful in detecting vasospasm.

Keywords

Aneurysm, Subarachnoid hemorrhage, Immediate CTA, aneurysm remnants, vasospasm

1. LITERATURE REVIEW

Aneurysmal subarachnoid hemorrhages still being among the major cause of morbidity and mortality related to intracranial pathology. SAH accounts for about 10 percent of total stroke incidence. The prevalence of brain aneurysm in general population globally range from 1-5% (1). Saccular aneurysms are the commonest cause of non-traumatic SAH. Although recent systematic review and meta-analysis of the global incidence of aneurysmal SAH show declining trend and mortality related to aneurysmal SAH also reducing trend, overall mortality rates reaching 50% with significant neurological deficit in survivors of aneurysmal SAH (2). Malaysian data in the late 80s reveals that the incidence of spontaneous SAH in Malaysia was 37 per 100000 hospital admissions with 9 per 100000 admissions were due to ruptured aneurysms (3,4). Due to the high weightage of aneurysm incidence and the related morbidity and mortality, advances in the management of ruptured aneurysms showing consistent progress.

For the diagnosis of an aneurysm, CT angiogram, MR angiogram, and digital subtraction angiography are among the choices of imaging. Each modality has its pros and cons. CTA being the commonest modality provides the fastest imaging modality for the diagnosis of an aneurysm. MRA is a good non-invasive modality with acceptable sensitivity and specificity for the diagnosis of intracranial aneurysm with a size of >3mm (5). But, as a gold standard, intra-arterial digital subtraction angiography still plays important role in the detection of an aneurysm. However, a recent analysis of imagings shows multislice CTA has a sensitivity similar to DSA even for aneurysms with size < 3mm(1). At the same time, it is reported that aneurysm >5mm CTA has a higher diagnostic value than MRA (1). Surgical clipping and endovascular coiling are the most commonly used techniques for aneurysm treatment. In many cases, anatomic

considerations, such as size, location, and other morphological features determine which treatment is most suitable for the patient. Surgical aneurysm clipping is carried out when it is feasible and the facility is available. Completeness of occlusion of the aneurysm is important in both endovascular coiling and surgical clipping. CARAT study suggests that the degree of aneurysm occlusion after the initial treatment is a strong predictor of the risk of subsequent rupture in patients presenting with subarachnoid hemorrhage, which justifies attempts to completely occlude aneurysms(6).

Detection of aneurysm remnant is vital. As it carries weight in the patient's future management. According to Sindou et al, they have classified aneurysm remnants into 5 categories in which only grade IV and V requires retreatment (7). Aneurysmal rest are classified into 5 grades in which grade I is less than 50% of neck size, grade II is more than 50% of neck size, grade III is the residual lobe of a multilobulated sac, grade IV is the residual sac of less than 75% of the aneurysmal size and grade V is the residual sac of more than 75% of aneurysmal size (7). Thus post clipping imaging to detect residual aneurysm neck is important to facilitate subsequent management for complete occlusion of the residual neck. Post-surgical clipping, to detect the aneurysm rest, commonly CTA or DSA is carried out.

CTA an emerging preferable modality, it's important to understand the limitation of the CTA in a treated aneurysm. Even though the current usage of titanium clips has lesser artifacts than previously used cobalt clips, titanium clips can create artifacts that influence the outcome of the study (8). It is found that a perpendicularly placed clip to the parent artery has fewer artifacts. Furthermore, if a clip lies oblique to the scanning plane, it will create lesser artifacts(8).

For aneurysms treated via endovascular means, commonly there is a guideline on imaging follow-up. However, when comes to the surgically clipped aneurysm, the follow-up management is still in a grey area. The duration of postoperative imaging varies from center to center and is based on surgeons' experience, local guidelines, and available modalities (9,10). Currently, in HS JB, a post-operative CT scan was done immediately post clipping in the brainsuite and subsequently after 3 to 6 months as an outpatient. While in Malaysia, neurosurgical centers without brainsuite facility, repeat imaging is adjusted based on their available resources. However, there is no standard accepted guideline available locally for any reference. But According to N.Scheer et al, four centers in Netherland did not routinely perform early postoperative imaging (44.4%) and seven did not routinely perform late imaging (77.8%) while three centers performed neither routine early nor routine late postoperative imaging (33.3%) (10). Thus, it's better to have scientific evidence to support our current practice and to adjust the practice according to evidence-based medicine.

Overview of the management of Aneurysmal SAH in Hospital Sultanah Aminah Johor Bahru

Hospital Sultanah Aminah Johor Bahru caters neurosurgical services for the whole state of Johor. Thus Department of Neurosurgery HSAJB receives the patient load from centers with imaging facilities such as Batu Pahat, Muar, Kluang, Segamat, and Hospital Sultan Ismail and facilities without imaging such as Kulai, Kota Tinggi, Mersing, and Pontian. Occasionally it does receives cases from private medical facilities from throughout Johor. All patients with SAH will be admitted and depending on the WFNS grading and existing pathology patient will be managed accordingly. On average HSA receives about 4-8 cases per month with annual admission of 50-80 cases per year.

Patients that are diagnosed with spontaneous SAH based on CT brain, will be admitted and managed as per ruptured aneurysms until completely exclude the ruptured aneurysm. The patient will be placed on nimodipine, an anti-epileptic agent, and closely observed in Neuro HDU. If the patient shows symptoms of increased intracranial pressure with hydrocephalus, the patient will be subjected to external ventricular drainage (EVD). Subsequently, the patient will be investigated preferably with intra-arterial digital subtraction angiography and in circumstances of unable to proceed with DSA then with CTA brain.

Based on positive angiogram finding patient will be planned for further management either surgical clipping or endovascular coiling. Patients planned for clipping will be subjected to surgery once consented to the next available operating time. Surgery will be conducted in Brainsuite iCT in HSAJB where an intraoperative CT facility is available. It is a standard operating procedure, where patients post clipping will be subjected to immediate CT brain and CT Angiogram within the operating theater before the patient being extubated or being transferred to Neuro HDU for weaning of ventilation.

Subsequent management will be individualized to patients and commonly will be aimed at weaning of ventilation with the continuation of nimodipine for 21 days. After the patient is discharged, the patient will be followed up in the neurosurgical clinic. A repeat cerebral angiogram (DSA) or CTA will be planned in 3 to 6 months duration to assess aneurysm remnant. Depending on the CTA / DSA further management plan will be decided.

It has been a routine to perform immediate CTA and also delayed CTA /DSA to detect aneurysm remnant. However no data or study available to look into the significance of performing immediate CTA. By conducting this study, we can look into the clinical relevance of performing immediate CTA and correlate it with its subsequent management.

2. STUDY PROTOCOL

This was the single-center cross-sectional study among patients with spontaneous SAH secondary to ruptured aneurysm admitted to the Department of Neurosurgery, Hospital Sultanah Aminah (HSAJB), Johor Bahru during the period of 1st January 2018 until 31st May 2020 who fulfilled all the inclusion criteria. This study aims to test reliability between immediate CTA with delayed angiography in detecting aneurysm rest. In addition to that, this study aims to analyse the factors associated with radiological vasospasm. The inclusion criteria for patients in this study were those aged between 18 to 80 years, who underwent clipping of cerebral aneurysm in Brainsuite ICT, HSAJB, and subjected for immediate post clipping CTA and delayed angiography. The exclusion criteria were namely pregnant women, patients with established chronic kidney diseases, patients with raised creatinine of more than 120, the patient who succumbed related to primary disease/post clipping, and the patient who missed follow-up and never done delayed repeat CTA / DSA. This study incorporating the standard operating procedure of the department into the study protocol in which patients will be subjected to intraoperative Doppler ultrasound, immediate post-operative CTA, and delayed CTA/DSA

Approval for this study was obtained from the Medical Research & Ethics Committee of the Ministry of Health Malaysia and registered in the national register for clinical trials registration ID: NMRR-19-1943-49275.

Sample Size

Universal sampling was used in this study. All the adult population age from 18 to 80-year-old who underwent craniotomy and clipping of aneurysm with immediate intraoperative CTA in brainsuite ICT Hospital Sultanah Aminah from January 2018 to May 2020. The sample size estimation was calculated using the population proportion formulae (Lemeshow, Hosmer, Klar, Lwanga & Organization 1990). Prior data indicate that the proportion is 0.18 and the population size is 50. If the type 1 error probability and precision are 0.05 and 0.05, we will need to study 42 samples. With an additional 10% dropout rate, the sample size is 47 samples. However, we manage to collect a total of 54 cases throughout the study period.

Declaration of Interest Conflict

There was no conflict of interest in this study. The standard operating procedure of management of ruptured aneurysm was incorporated into this study protocol

This study was conducted in compliance with the ethical principles outlined in the Declaration of Helsinki (2013) and the Malaysian Good Clinical Practice Guideline (2016). Approval was obtained before the initiation of this study. As this was a retrospective and prospective study, therefore the consent of patients and their relatives

was obtained when prospective data is collected. Names of patients were kept in a password-protected database and linked only via a study identification number during this research. The patient identification numbers rather than patient identifiers were used on datasheets. All data were entered into a computer that was password protected. On the completion of this study, the data in the computer will be copied to a USB drive and other soft copies will be erased while the hardcopy data will be kept and locked in the office cabinet located in the Department of Neurosurgery, Hospital Sultanah Aminah, Johor Bahru.

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3.2 Abstract

Background and Objective

Ruptured intracranial aneurysm is a common cause of stroke leading to high morbidity and mortality. Despite there are advancements in the surgical management of ruptured aneurysms, post-operative follow-up imaging still varies, and no consensus. Currently, some centres are utilising an immediate post-operative CT scan to detect residual aneurysms. Hence, we aim to test the significance and reliability of immediate post-operative CTA.

Methods

This was a single centre cross-sectional study. A total of 54 patients aged between 18 to 80 years old were admitted to the Department of Neurosurgery, Hospital Sultanah Aminah Johor Bahru (HSAJB) from 1st January 2019 to 31st May 2020 for ruptured aneurysm who fulfilled the inclusion criteria were included in this study. Demographic data including age, gender, type of aneurysm, WFNS score, type of diagnostic imaging, and requirement of EVD were collected. The patients subsequently underwent surgical clipping and subjected to immediate CTA. Then the patients followed up and proceeded with delayed angiography from 3 – 6 months. Data were analysed and the finding of both imaging compared.

Results

A total of 54 patients with a mean age of 51.87 ± 12.34 years were admitted and subjected to clipping surgery. 66.7% (n=36) admitted with good WFNS score. ACOM aneurysm was the commonest (31.5% (n=17)). Generally, it required a mean time of

4.85days from the day of admission until clipping. Intraoperatively 27.8% (n=15) had re-rupture of the aneurysm. 4 cases were able to detect aneurysm remnants with immediate CTA while 8 cases were detected via delayed angiography. Cohen's Kappa test showed a value of 0.63, which indicates substantial agreement between immediate and delayed angiography. There is a significant association between intraoperative Doppler signal and detection of vasospasm in CTA ($p < 0.001$). Also found that there is a significant association between CTA vasospasm and intraoperative rupture ($p = 0.006$). The general outcome of the patient measured with the mRS score during the 1st follow-up was a median of 2.

Conclusion

There is substantial agreement between immediate CTA and delayed angiography in detecting aneurysm remnants. Therefore using immediate CTA as an early imaging tool post-clipping enabled us to tabulate subsequent management strategy. At the same time, if combined with intraoperative Doppler, it can be useful in detecting vasospasm.

Keywords

Aneurysm, Subarachnoid hemorrhage, Immediate CTA, aneurysm remnants, vasospasm

3.3 Introduction

Aneurysmal subarachnoid hemorrhages still being among the major cause of morbidity and mortality. It's a major cause of stroke and accounts for about 10 percent of total stroke incidence. Although recent systematic review and meta-analysis of the global incidence of aneurysmal SAH show declining trend and mortality related to aneurysmal SAH also reducing trend, overall mortality rates reaching 50% with significant neurological deficit in survivors of aneurysmal SAH (2). Malaysian data in the late 80s reveals that the incidence of spontaneous SAH in Malaysia was 37 per 100000 hospital admissions with 9 per 100000 admissions were due to ruptured aneurysms (3,4). Due to the high weightage of aneurysm incidence and the related morbidity and mortality, advances in the management of ruptured aneurysms showing consistent progress.

For the diagnosis of an aneurysm, different modality of imaging is used with each has its pros and cons. Despite being the gold standard, DSA still requires certain expertise and it's invasive. Thus trend toward CTA is recently surging due to ready availability, fast, cheap, and non-invasive with accountable reliability. Surgical clipping and endovascular coiling are the most commonly used techniques for aneurysm treatment. In many cases, anatomic considerations, such as size, location, and other morphological features determine the choice of treatment. Surgical aneurysm clipping is carried out when it is feasible and the facility is available. Completeness of aneurysm occlusion is important in both endovascular coiling and surgical clipping. CARAT study suggests that the degree of aneurysm occlusion is a strong predictor of the risk of subsequent rupture, which justifies attempts to completely occlude aneurysms (6).

To date, there is no consensus on the modality and timing of imaging on post-operative screening. It's important to detect residual aneurysm to facilitate subsequent

management. Post-clipping, to detect the aneurysm rest, commonly CTA or DSA is carried out. The duration of postoperative imaging varies from centre to centre and is based on surgeons' experience, local guidelines, and available modalities (9,10). Currently, in HSAJB, a post-operative CT scan is done immediately post clipping in the brainsuite and subsequently after 3 months as an outpatient. While in Malaysia, neurosurgical centres without brainsuite facility, repeat imaging is adjusted based on their available resources. According to N.Scheer et al, four centres in Netherland did not routinely perform early postoperative imaging (44.4%) and seven did not routinely perform late imaging (77.8%) while three centres performed neither routine early nor routine late postoperative imaging (33.3%) (10). Thus, it's better to have scientific evidence to support our current practice and to adjust the practice according to evidence-based medicine. This study aims to test reliability between immediate CTA with delayed angiography in detecting aneurysm rest. In addition to that, this study aims to analyse the factors associated with radiological vasospasm.

3.4 Methodology

3.4.1 Research design

This was the single centre cross-sectional study where patients with spontaneous SAH secondary to ruptured aneurysm admitted to the Department of Neurosurgery, Hospital Sultanah Aminah (HSAJB), Johor Bahru who fulfilled the inclusion criteria. This study aims to test reliability between immediate CTA with delayed angiography in detecting aneurysm rest. In addition to that, this study aims to analyse the factors associated with radiological vasospasm.

Approval for this study was obtained from the Medical Research & Ethics Committee of the Ministry of Health Malaysia and registered in the national register for clinical trials registration ID: NMRR-19-1943-49275.

3.4.2 Research location and duration

Patients who fulfilled the inclusion criteria among those admitted to the Department of Neurosurgery HSAJB for the treatment of ruptured aneurysm during the period of 1st January 2018 until 31st May 2020. The Department of Neurosurgery, HSAJB is the only neurosurgical centre in the southern region with 2 operative theatres, 10-beds NeuroHDU, and 2 neurosurgery wards with 30 beds. Apart from that, this centre is led by consultant neurosurgeons who able to facilitate the treatment of ruptured aneurysms and provide guidance in terms of surgical skills and academic expertise to all the residents in this region. At the same time with the interventional facility provided by radiologists enables integrated multidisciplinary care for ruptured aneurysm patients.

3.4.3 Study population and sample size

Universal sampling was used in this study. All the adult population age from 18 to 80-year-old who underwent craniotomy and clipping of aneurysm with immediate intraoperative CTA in brainsuite ICT Hospital Sultanah Aminah from January 2018 to May 2020. The exclusion criteria were: pregnant woman, patients with established chronic kidney diseases, patients with raised creatinine of more than 120, the patient who succumbed related to primary disease/post clipping, and the patient who missed follow up and never done delayed repeat CTA / DSA.

The sample size estimation was calculated using the population proportion formulae (Lemeshow, Hosmer, Klar, Lwanga & Organization 1990). Prior data indicate that the

proportion is 0.18 and the population size is 50. If the type 1 error probability and precision are 0.05 and 0.05, we will need to study 42 samples. With an additional 10% dropout rate, the sample size is 47 samples.

3.4.4 Method of research

Details of all patients who were admitted were entered into the data collection form (Appendix 1). The study design is incorporating the existing usual standard operating procedure for the Neurosurgical department for the patient with a ruptured aneurysm. Once a patient is admitted to neuroHDU / ward for spontaneous SAH then the patient will be subjected to CTA / DSA for the detection of the cause of spontaneous SAH. Based on the positive imaging, the patient will be planned for the clipping of an aneurysm. Intraoperatively, the aneurysm will be tested with an intracranial 8MHz surgical Doppler system (Mizuho Vascular Doppler System with bayonet probe, manufactured by Mizuho Medical Co.Ltd, Japan) over the dome and the distal flow pre and post clipping of aneurysm. Subsequently, the craniotomy flap is closed and the patient will be subjected to immediate post-operative computed tomography angiogram and subsequently standard postoperative care given in Neurosurgical HDU. Immediate CTA will be done using iCT machine type Siemens CT Somatom Definition AS (128 slices) with Omnipaque (300mg I/ML) as a contrast agent. The patient will be managed accordingly and will be discharged home once the patient is fit to be discharged. Routinely repeat imaging either with CTA or intra-arterial DSA will be conducted from 3 to 6 months depending on the patient's general condition. The discharged patient will be followed up in the neurosurgical clinic in 1, 3, and 6 month period, and repeat imaging will be reviewed in the clinic. If the presence of an aneurysm rests then the patient will be managed accordingly.

In summary, we are incorporating the standard operating procedure of the department into the study protocol in which patients will be subjected to intraoperative Doppler ultrasound, immediate post-operative CTA, and delayed CTA/DSA. Standard treatment for ruptured aneurysm and post clipping care including triple H therapy and weaning of ventilation given and the patient will be followed-up for 1st, 3rd, and 6th month post clipping. During this study period, all the reporting of the CTA – immediate and delayed will be reported by the radiologist. There is no management difference between standard management and the study protocol.

3.4.5 Statistical analysis

The data obtained were analysed using SPSS version 26. The descriptive statistic was used in which categorical variables were analysed by frequency and percentage while numerical variables were analysed by a central tendency either mean, median, standard deviation, and inter-quartile range. This analysis was presented in the table. The main objective was tested with the Cohen Kappa test to check reliability and agreement between the two modalities. Another statistical analysis used in this study was chi-square and independent t-test. They were used to test the association between two independent samples.

3.5 RESULTS

3.5.1 Demographic and Clinical Characteristics

A total of 62 patients underwent craniotomy and clipping of aneurysm in Hospital Sultanah Aminah Johor Bahru from January 2018 until May 2020 and of these total of 54 patients enrolled in this study and 8 were excluded from this study. Reasons for exclusions

(Table 3) were as follows: no follow-up imaging was done due to poor neurological status (4 cases), the patient passed away during the post-op period (3 patients) and the patient defaulted follow-up (1 case). Clinical characteristic of patients being included (n=54) is summarized in Table 4. Out of 54 patients, 19 (35.2%) were males and 35 (64.8%) were females with male to female ratio was 1:1.84. The mean age of the patients recruited was 51.87 ± 12.34 with the youngest patient was 27 years old while the oldest was 80 years old. A total of 36 (66.7%) patients were admitted with good WFNS grade (Grade 1, 2, 3) while 18 (33.3%) patients were admitted with poor WFNS grade (Grade 4, 5)**.** Of 54 patients, 40 (74.1%) were not having any underlying medical problem while 10 (18.5%) had one comorbidity and 4 (7.4%) had two comorbidities. 17 (31.5%) patients were required to undergo external ventricular drainage before craniotomy for clipping of aneurysm.

Regarding the preoperative choice of imaging, 46 (85.2%) patients underwent digital subtraction angiography while 8 (14.8%) initially underwent CT angiography followed by digital subtraction angiography.

3.5.2 Aneurysm and Surgery

Based on preoperative imaging it is found that ACOM is the commonest aneurysm which accounts for 17 (31.5%) cases followed by PCOM which is about 13 (24.1%) cases. Others including ICA 11 (20.4%), MCA 8 (14.8%) and ACA 5 (9.3%). The overall patient required a mean time of 4.85 days from admission until surgery for clipping of aneurysm. Meanwhile, it takes a mean time of 2.87 days from the day of angiography until craniotomy for clipping. Character analysis of aneurysm shows mean sizes as follows: width was 4.48mm, height was 5.4mm and neck size was 2.92mm. Table 4 summarises the clinical characteristics of the patient and the aneurysms. It took a mean

time of 350 minutes for the craniotomy and clipping of the aneurysm. Out of 54 aneurysm surgeries, 37 cases had no intra-operative complications, while 15 (27.8%) cases had intraoperative rupture of an aneurysm, a case had vessel injury, and another case of cranial nerve injury during surgery.

3.5.3 Post-Operative Imaging & Follow up

All 54 cases underwent immediate post-op CT angiography in brain suite iCT. Immediate post-op CTA was analysed for the presence of vasospasm, finding of the residual aneurysm, infarct, and new intracranial bleed. Residual aneurysm visualised in 4 (7.4%) cases. Vasospasm is seen in 11(20.4%) cases. While infarct was seen in 2 (3.7%) cases and hemorrhage seen in 11 (20.4%) cases. These immediate post-operative angiographies were compared with delayed angiographies. Delayed angiography was either CTA or DSA. The decision in the choice of imaging was depending on the treating surgeon or patient's request. 92.6% of cases were decided by the surgeon while only 7.4% were based on the patient's request. Of 54 cases, 40 (74.1%) underwent delayed DSA while 14 (25.9%) underwent delayed CTA. The median time for delayed angiography was 90 days from the day of surgical clipping.

Analysing the post-operative residual aneurysm and the reliability of tests, a total of 8 (14.8%) aneurysm remnants were detected during delayed postoperative angiography. Out of 8, 4 were picked up earlier in immediate post-operative CTA. Only 4 (7.4%) were detected in delayed angiography. Those 4 detected through delayed angiography were all with DSA and none with CTA. Statistical analysis is required to compare agreement between both immediate post-op CTA and delayed angiography. Cohen's Kappa statistical analysis was used to test the reliability between immediate post-op CTA with

delayed angiography. Cohen's Kappa (Table 5) showed substantial agreement or reliability between immediate angiography and delayed angiography with a kappa value of 0.630 ($p < 0.001$ and 95% CI). Comparing immediate CTA to delayed angiography, immediate post-op CTA found to have a sensitivity of 50% (95% CI = 0.16-0.84) and specificity of 100%, it's positive predictive value 100% and negative predictive value 97.96% (95% CI=0.96-0.99). There is no significant association between the intraoperative rupture of an aneurysm, vasospasm, and duration of surgery to the detection of a residual aneurysm in CTA. Analysis of delayed imaging showed aneurysm remnants were located mainly in ACOM 4 (50%), MCA 2 (25%), and PCOM 2 (25%). The mean size of all aneurysm remnants was 1.84 mm (width), 1.68 mm (neck), and 1.8mm (height). Aneurysm remnants are categorised based on Sindou grading and found to be 3 are in Grade 1 and 5 are grade 2. Out of these 8 aneurysm remnants, only 1 showed an increase in size during follow-up angiography (12months post clipping) and which required endovascular treatment which was done at the 13th-month post clipping. Aneurysm remnants were analysed and summarised in table 7.

Analysis of the intraoperative Doppler and immediate post-operative CTA findings, it was found that there is a direct association between the absence of Doppler in distal circulation with the presence of vasospasm in CTA in where an absence of Doppler signal in distal flow suggestive of vasospasm. Based on the Pearson chi-square there is an association between those two with a p-value < 0.001. This is shown in table 6. Out of 11 cases with immediate imaging vasospasm, 7 cases had intraoperative rupture of the aneurysm. It shows there is a significant association between intraoperative rupture with the detection of vasospasm (P=0.006). However, there was no significant association between the duration of surgery (P=0.479) with the detection of vasospasm in immediate post-op CTA.

Post-clipping patients were reviewed in the neurosurgical clinic with the earliest 7 days and the latest 129 days with median time for 1st follow-up was 51 days. Most patients were found to have an mRS score of 2 (21%) and only 1 (1.9%) patient noted to have an mRS score of 5. THE median MRS score during 1st follow up found to be 2.

3.6 Discussion

Being a common cause of hemorrhagic stroke with an incidence of 1.1 – 1.7 per 100000 population-based on a study conducted by Chee and Loh in 1988 (3,4), ruptured aneurysm carries a significant burden to our healthcare system (11). This prompts us to create a systematic and guided management strategy to optimise care. Currently, there is still a lack of consensus on post-clipping imaging strategies (10). Various centres have their preferences and even within the same centre, it varies among surgeons (10). Being the major referral and tertiary neurosurgical centre, Hospital Sultanah Aminah Johor Bahru serves as the only largest referral centre for aneurysm cases in the entire state of Johor and the southern region of peninsular Malaysia. Thus we aim to focus on post-operative management in the line of imaging modalities. Our cross-sectional study focuses on the role and reliability of immediate post-clipping CT angiogram in HSAJB utilising the Brainsuite iCT.

3.6.1 Patient Demographic

A total of 62 cases operated over 29 months which averages about 2 cases per month. This number is similar to the previous study conducted by L.Chee et al from the year 2011 to 2016 which quotes about 2 cases per month (12). The majority of our patients are females ranging from 33 to 80 years old with predominantly in the menopausal age group >45years old. This probably due to a decrement in blood estrogen level which can potentiate ramification in arterial integrity which can lead to aneurysm formation (13).

Most of the patients about 74.1% of cases have no underlying medical problem. However, among those with a medical problem, diabetes mellitus type 2 or hypertension were the commonest medical problem which accounts for 85.71%. Long-standing diabetes and hypertension are well-known factors for atherosclerosis formation. Similar histological and biochemical properties of aneurysms and atherosclerotic lesions may suggest that atherosclerosis may play role in the mechanism of intracranial aneurysm formation (14). Thus predictably that our pool of patients with medical problems was mainly diabetic or hypertensive patients. In our centre, all patients underwent DSA before surgery. As a gold standard and to determine the dynamic flow of the aneurysm, DSA has been the choice of the imaging preoperatively. DSA is done by our radiologist, is readily available service during office hours (8 am to 5 pm) and weekdays (Sunday to Thursday).

3.6.2 Aneurysm and Surgery

The mean waiting time from admission to clipping was about 4.85 days were influenced by multiple factors such as patient's waiting time for the angiogram, limited OT time, time is taken to stabilise, and time to improve from poor WFNS grade as the only patient with improvement to good WFNS grade are subjected for surgery. Once required imaging is done and the patient is eligible for surgery, the case will be usually posted under a semi-emergency list for surgery. Once a case is being posted, the actual waiting time is about 2.87 days. According to Marcos et al, intermediate surgery between day 3- 10 carries a similar outcome with those subjected to early surgery (1-2days) (15). Thus mean surgical time between 4 – 5 days is considered acceptable. The incidence of intraoperative rupture was about 27.8% which is higher compare to the CARAT study (16). But when compare to dichotomised study based on duration in Lakićević N. et al, those aneurysm clipped between day 3-10 has a percentage of 24.27% which is similar to our centre (17). Early

clipping is associated with a higher rate of intraoperative rupture but it was reported as having benefit over later surgery by preventing uncontrolled re-rupture and high mortality among untreated patients (17).

3.6.3 Post-Operative Imaging & Follow up

CTA as a tool of post-operative imaging to detect remnant aneurysms is still being a doubt for many neurosurgeons worldwide due to potential artifacts caused by aneurysmal clips. Wallace et al suggest that CTA can effectively show aneurysm remnants and able to use it for follow-up of the remnant (8). They recommended that CTA is beneficial in detecting post-operative vasospasm, patency of vessel, and even stenosis thus it is useful as surveillance of entire cerebral vasculature even for de novo aneurysm after clipping surgery (8).

The main objective of our study is to test the immediate CTA reliability and comparing it to delayed angiography in detecting aneurysm remnants. Thus in our study, a total of 54 immediate post-op CTA was analysed. It was able to pick up 4 cases with aneurysm remnant. While delayed angiography showed 8 cases with aneurysm remnants in which 4 cases already showed in the previous CTA. Agreement between immediate CTA and delayed angiography is tested with Cohen's Kappa coefficient. The results show a k value of 0.63 which means a substantial agreement between the two imaging studies (18). Substantial agreement between both tests suggests the reliability of the immediate CTA comparing to delayed angiography is acceptable. Immediate CTA shows specificity of 100 % which means the probability that the CTA will be negative when no remnant is 100%. While it has a sensitivity of 50% suggests the probability of CTA showing remnant aneurysm is 50% if there is any actual remnant. This low sensitivity of the CTA

but high specificity is mainly contributed by the smaller sample size. By increasing the total number of cases over a longer period of study may improve the sensitivity value of this test. Sindou et al classified aneurysm remnant into 5 grades. Only grade IV and V are subjected to direct retreatment while grade I to III are recommended to follow up with additional angiography study. In the case of remnant regrowth, the patient was subjected to retreatment (7,19). All 8 cases with remnant were followed up with additional DSA and only 1 was found with remnant regrowth which required endovascular intervention. That particular case required retreatment was also detected in immediate CTA and was classified as Sindou grade II. Furthermore, in this study, we found the rate of the remnant aneurysm is 14.81% which is slightly lower than Soon-Seob Ahn reported in their paper which was about 19.3%. So literally only 1.9% of total clipped patients required retreatment in this study. Based on this analysis, we have substantial evidence that immediate post-operative CTA is adequate as post-operative imaging to detect aneurysm remnants that will be requiring retreatment. Hence, we can conclude that immediate CTA is a reliable tool for detecting aneurysm remnants. Performing immediate post-op CTA in Brainsuite iCT leads to minimal transport of patient for subsequent imaging which reduces patient transfer-related risk. Contrary to Sunil et al, who reported that intraoperative rupture of the aneurysm is not associated with increased risk of vasospasm (20), we found that there is a significant association between intraoperative rupture and vasospasm with a p-value = 0.006. This probably due to the usage of a temporary clip for temporary occlusion of proximal circulation which has reported the potential to aggravate vasospasm (21). However, there is no clear evidence or association between the duration of surgery and the occurrence of vasospasm (22).

8MHz surgical Doppler system is regularly used in our aneurysm surgery as an audio blood flow detector. Intraoperative distal to aneurysm circulation is checked for audible

blood flow and correlated with immediate CTA vasospasm. The absence of distal flow correlated with the presence of vasospasm in CTA and noted a significant p-value <0.001. Consequently, we suggest that combining multimodality of intraoperative Doppler and immediate CTA which enables us to predict the occurrence of vasospasm. Therefore, necessary treatment can be initiated to minimise poor outcomes by the delayed ischemic neurological deficit. The sensitivity of CTA alone as a DIND predictor drop to 50% (23). Ergo, by combining intraoperative Doppler we can increase the sensitivity of immediate CTA.

The follow-up date for the patient is given depending on the clinical status of the individual patient accordingly, and it varies from weeks to months, and it records median as 51days. Dichotomised mRS score into favourable (MRS 0-2) and non-favourable (MRS 3-6) shows, 64.8% are in a favourable group which is higher than Lai et all which is about 59.1% (12). This may suggest improvement in intensive post-operative care with subsequent remarkable rehabilitation and physiotherapy (4,12)

3.7 Study Limitations and Recommendations

The main limitation of the study is the limited number of aneurysm clipping cases. Even though it was a cross-sectional study, to increase the number of samples we could have extended the retrospective duration longer. However, due to previous technical issues, iCT wasn't used as an immediate post-operative CTA until early 2018. At the same time, even during the study period, we had an issue with the contrast injector which made the immediate CTA unable to be done. Thus it reduced the overall pool of population that was potential. Furthermore, it was a short duration of the study period. A longer duration of the study period is preferable in the future to increase the sample size and strengthen the results of the study. In addition to that, this study was only confined to

a single centre. Even though the results of the study showed statistical significance in various aspects, a multicentre study will maximise the variables and improve the study's statistical value. Hence, a multicentre study is needed in the future. For the intraoperative Doppler, an 8MHz system was used that provides audio blood flow, which tends to be subjective depending on the operating surgeon. A trained clinician with the availability of colour duplex sonography will increase the reliability of the intraoperative Doppler finding.

3.8 Conclusion

Being the first cross-sectional study conducted in Malaysia by assessing the reliability of immediate post-operative CT angiogram in post-clipping patients utilising the brain suite iCT, we managed to collect significant data on immediate CTA findings and associations. Study analysis showed there is substantial agreement between immediate CTA and delayed angiography in detecting aneurysm remnants. Therefore, using CTA as an early imaging tool post-clipping enables us to tabulate the subsequent management strategy. However, in circumstances of incomplete CTA, suspicious or non-conclusive, it is always recommended to complement with additional gold standard DSA. Apart from detecting aneurysm remnants, immediate CTA can be utilized together with intraoperative Doppler in detecting vasospasm too which can prompt us to initiate crucial early intervention for vasospasm.