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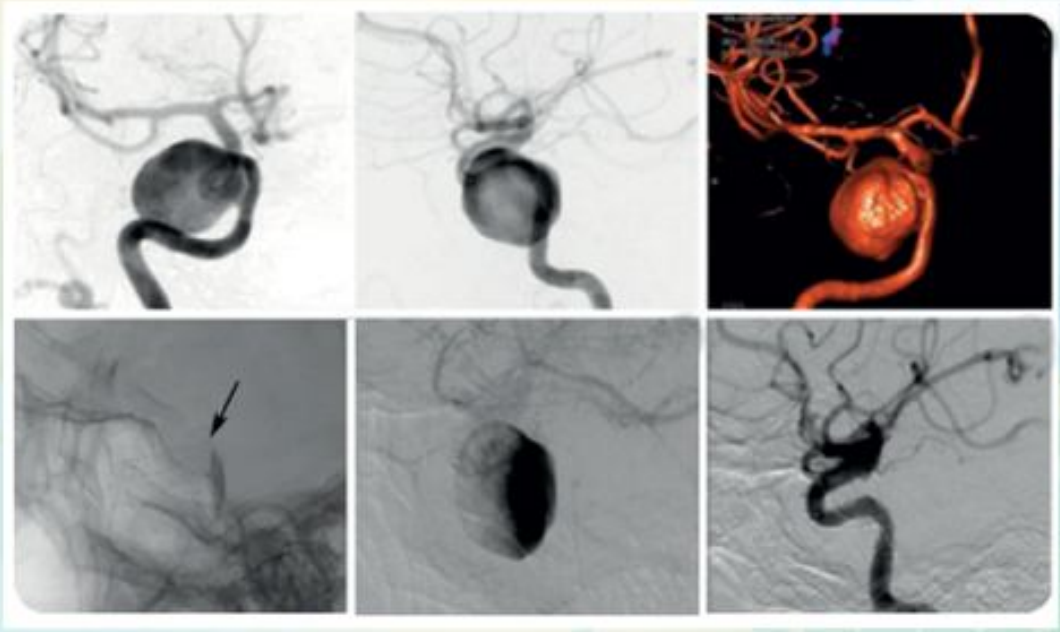

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(Chet Int Ferti Col 2014)

Date: Sunday, 21st September 2014

Venue: LH-3(Mini Auditorium), Chettinad Health City

CME credit points Awaited

Organized by

Department of Reproductive Medicine, Chettinad Hospital and Research Institute

Chettinad Health City

Rajiv Gandhi Salai, (OMR, Chennai), Kelambakkam, Kanchipuram Dist., - 603 103 Tamil Nadu.

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Chettinad Health City
MEDICAL JOURNAL

Contents

Editorial

This issue is dedicated to Cerebrovascular diseases which are one of the common non-communicable diseases and are a major cause of morbidity and mortality. A series of articles have been contributed by experts in the field, covering the various aspects which will provide a comprehensive review of the current status on the management of common cerebrovascular diseases.

The core articles on this subject include a brief review of the current guidelines for management of aneurysmal subarachnoid hemorrhage, endovascular management, anesthetic and surgical management of intracranial aneurysms. There are also reports of our Institute's experience in surgery of intracranial aneurysms and arterio-venous malformations. There is a classroom article on thrombolytic therapy of acute ischemic stroke.

The original article is from the field of regional anesthesia. This is a study on the use of buprenorphine as an adjuvant for brachial plexus block using bupivacaine.

Other case reports include Non-secretory multiple myeloma and an unusual case of hypotension during anesthesia due to an anaphylactic response.

A fond remembrance of the doyen of Indian Neurosurgery, Prof. B. Ramamurthi, is outlined in the pages of history section.

Medical updates from all over the world highlights the importance of diet in maintaining health and in prevention of disease. An interesting ECG completes the issue.

We hope this special issue on cerebrovascular diseases will be interesting and informative to one and all. We welcome your valuable comments and suggestions.

Dr. V. G. Ramesh

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Original Article

Buprenorphine as an Adjuvant to Bupivacaine in Supraclavicular Brachial Plexus Block

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Abstract

Background and aims : Adjuvants used in peripheral nerve blocks prolong duration of analgesia without prolonging motor blockade or causing systemic side effects. The current study was conducted to evaluate the efficacy of buprenorphine as an adjuvant to bupivacaine in supraclavicular brachial plexus block.

Methodology : A prospective randomised double blind study was conducted on 50 adult patients between 20- 60 years, weighing > 60 kgs, belonging to American Society of Anaesthesiology class I and II, scheduled to undergo elective upper limb orthopaedic procedures. Patients were randomised into 2 groups of 25 each. Patients in group A (n=25) received supraclavicular brachial plexus block with 25 ml 0.5% bupivacaine and group B (n=25) patients received supraclavicular brachial plexus block with 25 ml 0.5% bupivacaine and 3 mcg/ kg of buprenorphine. Onset of sensory and motor blockade, duration of analgesia and postoperative VAS scores were noted.

Results : Duration of analgesia was significantly longer in group B (13.24 hrs) compared to group A (6.68 hrs), with a p value <0.000. No statistical difference was found in the mean onset time of sensory and motor blockade, postoperative VAS scores or postoperative morphine consumption. No side effects were noted.

Conclusion : Addition of buprenorphine 3 mcg/ kg as an adjuvant to 0.5% bupivacaine in supraclavicular brachial plexus block prolongs postoperative analgesia without causing systemic side effects.

Key Words: Adjuvants, Buprenorphine, Supraclavicular brachial plexus block, Analgesia

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Introduction

Peripheral nerve blocks provide ideal operating conditions during surgery by reducing stress response, with minimal interference to physiological functions of the body. General anaesthesia requires polypharmacy, whereas peripheral nerve blocks, with minimal drugs provide excellent intraoperative and post operative analgesia preserving an alert, awake and cooperative patient. The problem solely with local anaesthetics is that they cannot provide prolonged postoperative analgesia. Several adjuvants have been tried with local anaesthetics to prolong the duration of postoperative analgesia without prolonging motor blockade or causing systemic side effects.The demonstration that opioid receptors are present in the peripheral nervous system by Fields et al[1] in 1980 prompted recent investigations on the use of opioids either alone or combined with local anaesthetics for regional anaesthesia procedures like brachial plexus block. Important factors determining the duration of action include lipid solubility and the affinity of different opioids for their receptors. Opioids like morphine, tramadol, buprenorphine etc. are used as adjuvants. Several studies have shown that the addition of buprenorphine, an agonist antagonist opioid to bupivacaine[2,3,4,5] produces longer postoperative analgesia compared to other opioids.The aim of this randominized double blind prospective study was to clinically evaluate the efficacy of buprenorphine as an adjuvant to bupivacaine in a dose of 3 mcg/kg body weight for supraclavicular brachial plexus block in patients undergoing upper limb orthopaedic procedures with regards to the onset and duration of both sensory and motor blockade.

Materials and methods

After obtaining institutional ethics committee approval and written informed consent, 50 adult patients in the age group of 20-60 years, weighing > 60kg,without any neurological deficit and local sepsis, belonging to ASA I & II scheduled to undergo elective upper limb orthopaedic procedures were chosen. All the patients were assessed and those with normal clinical, biochemical, hematological and radiological parameters were selected. Patient with history of allergy to local anaesthetics and those with cardiovascular and respiratory disorders ,and extremely obese patients with difficult landmarks were excluded from the study. Informed written consent was obtained from all the patients. All the patients were randomly allocated into group A or group B using a computer generated random table.Group A(n=25) : patients undergoing supraclavicular brachial plexus block by

This is an abridged version of the dissertation submitted to Annamalai University as part of the M.D Anaesthesia course.

subclavian perivascular technique with 25 ml of 0.5% bupivacaine. Group B(n=25) : patients undergoing supraclavicular brachial plexus block by subclavian perivascular technique with 25 ml of 0.5% bupivacaine and 3mcg/kg of buprenorphine.

On arrival of the patient in the operating room pulse oximetry, non invasive blood pressure and electrocardiogram were connected and baseline values of heart rate, blood pressure, respiratory rate and oxygen saturation were recorded. An intravenous access was obtained in the opposite arm. According to group allocation, the test solution was prepared by an anaesthetist who did not participate further in the study. The patients were given supraclavicular brachial plexus block by the subclavian perivascular technique under aseptic precautions using nerve stimulator guidance. 25ml of the test solution, either 0.5% bupivacaine alone or 0.5% bupivacaine with 3 mcg/kg buprenorphine was injected after careful negative aspiration.

Non invasive blood pressure and heart rate were measured every minute for the first 10 minutes and every 5 minutes thereafter throughout the intra operative period. Heart rate and rhythm by electrocardiogram and oxygen saturation by pulse oximetry were monitored continuously. They were documented at 1, 2, 5, 10, 15,30 minutes and every 30 minutes thereafter. Following the administration of the drug patients were evaluated every minute till the onset of sensory and motor blockade.Time of onset of sensory blockade was tested by the time in minutes from the injection of the drug to the lack of appreciation of pin prick sensation at C_5 dermatome with a 26G hollow needle.Onset of motor blockade was assessed by the time in minutes from the time of drug injection to the loss of shoulder abduction. Failure of the block to appear in 20 minutes was taken as failure and the patients were administered general anaesthesia and were excluded from the study. After confirmation that the block has taken up, surgery was started. During the surgical procedure, the degree of pain was assessed with a 3 point verbal rating score. The verbal rating score utilizes objectives to describe the intensity of pain such as no pain, pain and unbearable pain and was scored as 0 =no pain, 1 = mildpain ,2 = unbearable pain. If verbal rating score was > 1, patients were administered general anaesthesia to complete the surgery and were excluded from the study. Local anaesthetic toxic reactions including subjective and objective manifestations like circumoral numbness, tinnitus, twitching, convulsions, etc., were looked for and appropriate measures were planned. Complications associated with the technique like intravascular injection, intrathecal injection, epidural injection and pneumothorax were looked for and appropriate measures were planned.Duration of analgesia was tested post operatively using the visual analogue score (0-10) every 1/2 hour for the first 6 hours thereafter every 2 hours till 24 hours thereafter every 3 hours till 48 hours. Patients were given rescue analgesia with intravenous morphine 3 mg when VAS≥4 upto a maximum of 30 mgs in 24 hrs. Side effects of opioids like nausea and vomiting, pruritus, urinary retention, hypotension, headache, respiratory depression defined as respiratory rate < 10/minute and any other neurological depression were monitored for 48 hours.

Duration of analgesia is the time in hours from the onset of analgesia to the time of administration of rescue analgesia. Side effects of buprenorphine were monitored for a period of 48 hours from the time of administration of the drug.

The parameters of age, weight and duration of surgery were analysed using the ANOVA test. The sex distribution in the two groups were analysed with the Pearson's Chi - Square test. Onset time for motor and sensory blockade were analysed using the ANOVA test. Duration of analgesia in the two groups was analysed with the t-test and the statistical significance estimated. A p value of < 0.05 was considered statistically significant.

Observations and Results

The patients included in this study were divided into two groups consisting of 25 patients each.

Group A (n=25) received 0.5% bupivacaine

Group B (n=25) received 0.5% bupivacaine + 3mcg/kg of buprenorphine.

Table 1- Demographic parameters

PARAMETERS	GROUP A N = 25	GROUP B N = 25
Mean Age in years (S.D)	37 (1.44)	37 (1.44)
Sex ratio Male: Female	20:5	20:5
Mean Weight in kg (S.D)	63.5 (1.44)	63.5 (1.44)

Table 2- Type of surgical procedure and mean duration of surgey

Parameters	Group A	Group B
Type of surgery	ORIF-25	ORIF-25
Duration of surgery (mins)	127.60± 6.64	128.60± 7.14

ORIF – Open reduction and internal fixation

Table 3. Mean onset time of motor & sensory blockade

PARAMETERS	GROUP A N=25 (S.D)	GROUP B N=25 (S.D)
MOTOR BLOCKADE	3.18 (0.061)	3.25 (0.086)
SENSORY BLOCKADE	6.31 (0.080)	6.17 (0.081)

Table 4. Duration of Analgesia in Hours

Group	N	Mean (hours)	SD	p Value
A	25	6.68	0.082	<0.000
B	25	13.24	0.081	

There was no statistically significant difference in age, sex ratio or weight among the two groups (Table 1).

The two groups were well matched for the type of surgical procedure and duration of surgery, suggesting postoperative pain of similar intensity (table 2).

Onset of sensory and motor blockade in the two groups was comparable and there was no statistically significant difference among the two groups (Table 3).

Patients in group B had a longer duration of analgesia than patients in group A and the difference was statistically significant (Table 4).

There was no statistically significant difference in the vital signs like heart rate, systolic blood pressure, and diastolic blood pressure from the baseline throughout the surgery in the two groups. The groups did not show statistical difference in the postoperative VAS scores or postoperative morphine consumption. None of the patients in the two groups developed nausea, vomiting, pruritus, hypotension, respiratory depression or any other neurological depression.

Discussion

The subclavian perivascular approach to the brachial plexus has gained popularity because of the satisfactory anaesthesia and less failure rate with this approach. Franco CD, Vieira ZE[6] in their study on subclavian perivascular brachial plexus block found that the subclavian perivascular block provides an effective block for the surgery on the upper extremity. They also concluded that at the site of injection with this technique the plexus is reduced to its smallest components and the sheath is reduced to its smallest volume, which explains in greater part the success obtained with this block. Lanz[7] and his colleagues in their study on the extent of blockade following various techniques of brachial plexus block demonstrated that the subclavian perivascular approach to the brachial plexus resulted in a homogenous blockade of the nerves of the brachial plexus.With the interscalene approach to the brachial plexus, made at the level of the nerve roots, C8 and Tl are likely to be missed because of the vertical arrangement of the roots. Thus the interscalene approach tends to fail on the ulnar side of the limb in a dermatomal distribution.In contrast, the axillary approach is made at the level of the terminal nerves and the musculocutaneous and radial nerves are the most likely nerves to be inadequately blocked resulting in failure within a terminal nerve distribution.

With the supraclavicular technique these complications are not seen. There is a 0.6 - 25% incidence of pneumothorax, which is usually asymptomatic.With the interscalene approach, dangerous and potentially lethal complications like vertebral artery injection and subarachnoid or epidural injection can occur. Therefore, in this study the subclavian perivascular approach to the brachial plexus was used.

Cheryl et al[8] in their comparative study of 0.25% bupivacaine and 0.25% ropivacaine for brachial plexus block demonstrated a higher incidence of required supplementation. Therefore, they recommend using 0.5% concentration of these local anaesthetics to provide brachial plexus anaesthesia. Therefore, in this study 0.5% bupivacaine was used. However in a study by Gupta et al, ED 50 dose of bupivacaine was not dependent on concentration. The median effective volume for 0.25%, 0.375% and 0.5% bupivacaine for supraclavicular block was 26.8, 18.1 and 12.0 ml respectively. Lowering concentration led to increase in volume required for block. The block in this study was done under ultrasound guidance[9]. In our study, we used nerve stimulator guidance for giving the block. So a higher volume of drug was selected.

According to Franco CD, Vieira ZE[6] in the subclavian perivascular technique the solution is delivered at a point in which the trunks are compactly arranged. So a volume of 20-30 ml of local anaesthetic solution is sufficient. Therefore, in this study a volume of 25 ml was used.

The demonstration of opioid receptors in the peripheral nervous system by Fields et al[1] in 1980 prompted recent investigations on the use of opioids either alone or combined with local anaesthetics for regional anaesthesia procedures like brachial plexus block. In this study, the efficacy of buprenorphine as an adjuvant to bupivacaine in brachial plexus block was evaluated. Buprenorphine in a dose of 3 mcg/ kg is used in supraclavicular block, and is found to be effective[10,11]. Even in a dose of 0.3 mg added to local anaesthetic in supraclavicular block, no adverse effects have been encountered[12,13]. In our study, the mean weight of patients selected was 63.50+/_1.44Kgs and buprenorphine was used on a weight basis at 3mcg/kg with 25ml (0.5%) bupivacaine for subclavian perivascular brachial plexus blockade.

Onset of sensory and motor blockade : The onset of sensory analgesia was tested by loss of pinprick sensation in the C5 dermatome. In this study the mean onset of sensory analgesia was 6.31 minutes in group A and 6.17 minutes in group B. The difference was not statistically significant among the groups.

The onset of motor blockade was tested by loss of shoulder abduction. In this study the mean onset time for motor blockade was 3.18 minutes in group A and 3.25 minutes in group B. The onset time for motor blockade was thus similar in the two groups, the difference being statistically insignificant. The data and results reported by Ashok Jadon[10] and his colleagues and Amol Singam et al[12] on the addition of buprenorphine to bupivacaine for brachial plexus block were similar to these findings and support these observations. In these studies also the onset of motor block was earlier than the onset of sensory block, which can be explained by the "core and mantle" concept by Winnie and Ramamoorthy[14]. However, in the study by Bharat Paliwal et al the onset of sensory blockade was 8.25+ 3.93 mins. 0.25% bupivacaine was used in their study, and the delay might be attributed to the difference in concentration of the local anaesthetic used. Also in their study, motor blockade followed sensory blockade[13].

Duration of analgesia : In this study the mean duration of sensory blockade in group A was found to be 6.68 hours and 13.24 hours in group B . Thus the addition of buprenorphine 3 mcg/kg significantly prolongs the duration of analgesia.

In the study by Kenneth D.Candido[15] and colleagues the addition of 0.3mg of buprenorphine conferred a mean duration of post operative analgesia of 22.3 hours compared to 6.6 hours with the local anesthetic alone. In another study[16] by the same authors, the mean duration of post operative analgesia was found to be 5.3 hours with the local anaesthetic alone as compared with 17.4 hours when 0.3mg of buprenorphine was added.In both these studies a volume of 40 ml of local anaesthetic was used, and 0.3 mgs buprenorphine was used, both of which are higher than the volume and dosage used in our study. This might explain the longer duration of analgesia attained in their study compared to our study. In the study by Singam et al[12], addition of 0.3 mg buprenorphine to 38 ml of 0.25% bupivacaine produced significantly longer sensory blockade (647.83= 55.7 mins) compared to bupivacione alone (322.16= 31.80 mins). Though a large volume of drug was used in this study, the concentration of drug used was less, which might explain similarity in the duration of sensory blockade with our study. In the study by Ashok Jadon[10] and his colleagues the addition of 3mcg/Kg of buprenorphine as an adjuvant to 30ml of 0.3% bupivacaine for subclavian perivascular brachial plexus blockade conferred a mean duration of 680.6 +/_86.27 minutes as compared to 331.2 +/_ 33.54 minutes with 30ml of 0.3% bupivacaine alone, similar to our study.

Side effects and Hemodynamic parameters : None of the patients in the two groups showed any of the side effects like nausea, vomiting, pruritus, urinary retention, hypotension, headache, sedation or respiratory depression. In the study performed by Kenneth D.Candido[16] there was a 5% incidence of nausea, vomiting and pruritus when buprenorphine was added to the local anesthetic.In the study of 20 patients by J.E.Bazin et al[17] 1 patient reported drowsiness, 4 patients reported pruritus, 6 patients had nausea and 4 patients had vomiting.

In this study there was no significant change in the hemodynamic parameters from the baseline in all the groups.

Conclusion

The addition of 3mcg/kg of buprenorphine to 0.5% bupivacaine in supraclavicular brachial plexus block provides a significant advantage over plain bupivacaine in terms of postoperative analgesia without any systemic side effects.

Conflict of Interest: Authors declare no conflict of interest.

References

1) Fields HL, Emson PC, Leigh BK, Gilbert RFT, Iversen LL. Multiple opiate receptor sites on primary afferent fibres. Nature 1980; 284:351-353

2) Wylie and Churchill Davidson. A practice of Anaesthesia. Sixth Edition. The pharmacology of local anaesthetics, Physiology of nerve conduction. 1996: 72-188

3) Ronald D.Miller. Anaesthesia. Fifth edition. Pharmacology of local anaesthetics ;491-521 Pharmacology of buprenorphine ;346 Peripheral nerve blockade ;1520-1527

4) Tripathi KD Essentials of medical pharmacology.Fifth edition. Local Anaesthetics ; 351-364 Opioid analgesics and antagonists ; 453-468

5) Alfred Goodman, Gilman. The pharmacological basis of therapeutics. Pharmacology of bupivacaine; 369-386. Pharmacology of buprenorphine ;575-576

6) Franco CD, Vieira ZE. Subclavian brachial plexus blocks: success with a nerve stimulator. Regional anesthesia and pain medicine 2000; 25(1) :41-46

7) Lanz E,Theiss D, Jankovic D. The extent of blockade following various techniques of brachial plexus block. Anesthesia and analgesia 1983; 62 (1) :55-58

8) Hickey R, Rowley CL, Candido KD et al,. A comparative study of 0.25% bupivacaine and 0.25% ropivacaine for brachial plexus block. Regional anesthesia and pain medicine 1992;75 (40): 604-611

9) Gupta PK, Hopkins PM.Effect of concentration of local anaesthetic solution on the ED of bupivacaine for supraclavicular brachial plexus block.Br J Anaesth. 2013 Aug;111(2):293-6.

10) Jadon A, Panigrahi M, Parida S, Chakraborty S, Panda A. Buprenorphine improves the efficacy of bupivacaine in subclavian perivascular brachial plexus block.The internet journal of anaesthesiology 2008; 16 (2)

11) Dixit R, Chakole V, Tadwalkar GV. Effect of buprenorphine on post operative analgesia in supraclavicular brachial plexus block using peripheral nerve locator. Journal of Evolution of Medical and Dental Sciences 2013; 2(2): 114-118

12) Singam A, Chaudhari A, Nagrale M. Buprenorphine as an adjuvant in supraclavicular brachialplexus block. IJBAR. 2012;03(07)

13) Paliwal B, Karnawat R. Comparative study of effects of buprenorphine or clonidine as adjuvants to local anesthetics (bupivacaine 0.25%) for supraclavicular brachial plexus block Journal of Dental and Medical Sciences. 2013; 4(3): 30-39

14) Winnie AP, Ramamoorthy S, Tay CH, Patel KP, Durrani Z. Pharmacokinetics of local anaesthetics during brachial plexus blocks. Anesthesia and Analgesia 1977;56:852-861

15) Candido KD, Franco CD, Khan MA, Winnie AP, Raja DS. Buprenorphine added to the local anaesthetic for brachial plexus block to provide post operative analgesia in out patients. Regional anesthesia and pain medicine 2001;26:352-356

16) Candido KD, Winnie AP, Ghaleb AH, Fattouh MW, Franco CD. Buprenorphine added to the local anaesthetic for axillary brachial plexus block prolongs post operative analgesia. Regional anesthesia and pain medicine 2002;27:162-167

17) Bazin JE, Massoni C, Bruelle P, Fenies V, Groslier D, Schoeffler P. The addition of opioids to local anasethedcs in brachial plexus block: The comparative effects of morphine, buprenorphine and sufentanil. Anaesthesia 1997;52:858-862

Pulse your way to healthy living!

Overweight and obesity are worldwide problems. Together, they affect more than a third of world's population. The need to keep the weight in check has spawned a whole lot of dietary regimens and novel exercises. Now in a new systematic review and meta-analysis (Siying S. Li et al. Dietary pulses, satiety and food intake: A systematic review and meta-analysis of acute feeding trials. Obesity, 2014; 22 (8): 1773 DOI: 10.1002/oby.20782) published in the latest issue of Obesity, the authors claim that consumption of about 160 g of pulses (peas, lentils, beans, chickpeas) everyday might help to regulate your weight much better. The pulses are relatively rich in protein and have low glycaemic index. They can adequately replace animal protein and trans-fats in our regular diet. Besides pulses make people feel fuller with less quantities. The benefit is fairly uniform across all age groups and body mass indexes.

- Dr. K. Ramesh Rao

Red Hot Chilli Peppers Keep Your Bowel Healthy

If you are a chilli lover, you should rejoice! For your love may prevent colorectal cancer. Chilli peppers contain an active ingredient called Capsaicin. In a new experimental study carried out in University of California, San Diego (Petrus R. de Jong et al. Ion channel TRPV1-dependent activation of PTP1B suppresses EGFR-associated intestinal tumorigenesis. Journal of Clinical Investigation, 2014; DOI: 10.1172/JCI72340) the investigators administered capsaicin to mice genetically predisposed to develop colonic tumours. They found that capsaicin caused reduction in the tumour burden and prolonged the lifespan of the mice by 30%. This effect was potentiated by simultaneous administration of COX 2 inhibitors. Capsaicin activates a receptor/ion channel called TRPV1. TRPV1 has been called the molecular pain receptor. When it is activated it causes feedback inhibition of EGFR, thus acting as a tumour suppressor. So, chilli peppers don't just spice up your food, they spruce up your bowel too!

- Dr. K. Ramesh Rao

Review Article

Management of Aneurysmal Subarachnoid Hemorrhage: A Brief Outline of The Present Guidelines

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Abstract

Aneurysmal subarachnoid hemorrhage is one of the significant causes of major morbidity and mortality throughout the world. Early diagnosis and management have considerably reduced the mortality. American Heart Association and American Stroke Association have recently compiled the guidelines for the management of aneurysmal subarachnoid hemorrhage. This article gives a brief overview on the management of aneurysmal subarachnoid hemorrhage, based on the above guidelines.

Key Words: Aneurysms, subarachnoid hemorrhage, management of aneurysms

Chettinad Health City Medical Journal 2014; 3(2): 44 - 45

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a common cerebro-vascular problem, presenting acutely, with often devastating sequelae. Early diagnosis and management are imperative to reduce the mortality. Advances in the diagnostic modalities, improved surgical techniques and endovascular procedures have resulted in significant reduction in mortality in aSAH. In many countries, aSAH is regarded as a major public health problem and this has resulted in increased awareness among the healthcare professionals. It is essential that every medical professional is aware of this problem and principles in the management. Recently, American Heart Association and American Stroke Association have compiled the present day recommendations in the management of aSAH in the form of guidelines, based on literature search and metaanalysis[1,2,3]. A brief outline of management of aSAH based on these guidelines is discussed in the following.

Risk Factors and Prevention of aSAH

Hypertension is considered as a major risk factor in the development of aneurysm and aSAH. Treatment of hypertension and consumption of vegetable rich diet may reduce the risk of aSAH. Tobacco and alcohol consumption are known risk factors of aSAH.

Natural History and Outcome of aSAH

The clinical grading systems proposed by Hunt and Hess and World Federation of Neurological Surgeons (WFNS) provide accurate determination of severity of aSAH and they also help in planning treatment and predicting outcome. Since the risk of rebleeding in the first 24 hours and in the first week is very high, urgent evaluation and management of aSAH is recommended.

Clinical Manifestations and Diagnosis of aSAH

Any patient presenting with acute onset severe headache ("thunderclap" headache) should be suspected to be having aSAH and all measures are to be undertaken to diagnose/exclude aSAH in these patients. Diagnostic workup should include noncontrast CT scan. Lumbar puncture is indicated when the CT is non-diagnostic. 64 slice CT angiography (CTA) may be used for the diagnostic work up of aneurysm and planning treatment. When CTA is inconclusive, Digital Subtraction Angiography (DSA) is recommended. Fluid-attenuated inversion recovery (FLAIR), proton density and diffusion-weighted MRI may be used for the diagnosis of aSAH when the CT scan is negative. DSA with 3-dimensional rotational angiography is the gold standard and indicated for detection of aneurysm in patients with aSAH and for planning treatment, except when the aneurysm has already been diagnosed with a non-invasive angiogram.

Medical Measures to Prevent Rebleeding After aSAH

The blood pressure should be controlled with titratable agent to keep the systolic pressure <160 mm Hg to prevent the risk of rebleeding, stroke and to maintain the cerebral perfusion. Short term use for less than 72

hours, of tranexamic acid or aminocaproic acid may be considered to prevent the risk of early aneurysm rebleeding, when there is unavoidable delay in the definitive management of aneurysms.

Surgical and Endovascular Methods for Treatment of Ruptured Cerebral Aneurysms

Measures to obliterate aneurysms (clipping or coiling) should be undertaken as early as possible to prevent rebleeding after aSAH. A multidisciplinary approach involving both cerebrovascular surgeons and endovascular specialists, is required for planning the treatment of aneurysms based on the patient factors and the anatomy. If the aneurysm is equally amenable to neurosurgical clipping and endovascular coiling, then coiling should be considered. In patients presenting with large (>50 ml) intraparenchymal hematomas and middle cerebral artery aneurysms, neurosurgical clipping is preferred. In the old patients(>70 years of age), in those presenting with poor-grade (WFNS grade IV and V) aSAH, and in those with aneurysms of the basilar apex, endovascular coiling is preferable. Stenting of a ruptured aneurysm is associated with increased morbidity and mortality, and should only be considered when less risky options have been excluded.

Management of Cerebral Vasospasm and Delayed Cerebral Ischemia after aSAH

Oral nimodipine has been shown to improve neurological outcome and is strongly recommended in aSAH. Maintenance of euvolemia is recommended to prevent delayed cerebral ischemia (DCI) in contrast to the earlier recommendation of triple H therapy (hypervolemia). Use of the other agents like statins, endothelin-1 anagonists (clazosentan), magnesium sulphate, etc., has not found much favour. Prophylactic balloon angioplasty before the development of vasospasm is not recommended. Transcrainal Doppler for monitoring the development of vasospasm, perfusion imaging with CT or MRI to identify the regions of potential brain ischemia may be used. Induction of hypertension (triple H therapy) is recommended in patients with DCI, unless the blood pressure is already elevated or the cardiac status is a contraindication. Cerebral angioplasty and/or intra-arterial vasodilator therapy is indicated in patients with symptomatic vasospasm not responding to hypertensive therapy.

Management of Hydrocephalus associated with aSAH

Acute symptomatic hydrocephalus is managed by external ventricular drainage (EVD) or lumbar drainage depending on the clinical picture. Chronic symptomatic hydrocephalus should be treated by shunting. Routine fenestration of lamina terminalis has no value in preventing hydrocephalus and is not recommended.

Management of Seizures Associated With aSAH

Use of prophylactic anticonvulsants is recommended in the acute phase of aSAH and in the long-term for patients with prior seizure, intracerebral hematoma, infarction, middle cerebral artery aneurysm, etc.

Management of Medical Complications Associated With aSAH

Hyponatremia is a very common condition after aSAH, commonly due to cerebral salt wasting syndrome and this affects the outcome adversely. The use of hypertonic saline and fludrocortisone is recommended in the management of hyponatremia. Avoidance of hypoglycemia and aggressive control of fever in the acute phase aSAH is advocated.

Conclusions

The management of aSAH is complex and involves multi-disciplinary approach. The knowledge about pathophysiology and management are continuously evolving and requires periodic updating.

References

1) Mayberg MR, Batjer HH, Dacey R, Diringer M, Haley EC, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Circulation. 1994; 90: 2592–2605.

2) Bederson JB, Connolly ES Jr., Batjer HH, Dacey RG, Dion JE, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke. 2009;40:994–1025.

3) Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2012;43:1711–1737.

Review Article

Endovascular Treatment of Intracranial Aneurysms

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Introduction

Aneurysms of the cranial vessels are more prevalent (3% - 4%)[1] than it was thought before (1% -2%)[2,3]. They are mostly asymptomatic until they rupture[4] and unruptured aneurysms are increasingly detected in clinical practice as use of CT and MRI is becoming more common. The risk of aneurysm rupture is about 1% (0.05%-2%) per year and may vary with location, size, and shape[5]. The aneurysm rupture account for about 80–85% of non-traumatic subarachnoid hemorrhages[6] and can also cause intraparenchymal and intraventricular hemorrhage. Most aneurysms in both ruptured and unruptured setting are managed by endovascular means. We review here the current role of endovascular management of intracranial aneurysms.

Evolution

Craniotomy for clip ligation was first successfully performed by Walter Dandy in 1937[7] and has been the treatment of choice for intracranial aneurysms since then. Following in the footsteps of the pioneering work of Serbinenko in Russia in the mid-1970s on management of vascular malformations of cranium using Balloon catheterization[8], Higashida et al, attempted to treat posterior circulation aneurysms with detachable balloons by placing the balloon within the aneurysm and filling it with polymer intended to solidify over 40–60 minutes to provide a permanent solid filling of the aneurysm[9]. However, high rate of complications eventually led to this procedure being abandoned, but this experience demonstrated the feasibility of the endovascular route in the treatment of intracranial aneurysms[10]. The search for a more suitable material to fill an aneurysmal sac eventually led to the development of the detachable coil by Guglielmi et al, in 1990[11-13]. Though the initial coils were relatively stiff, and their intra-aneurysmal deployment was poorly controlled it led to the breakthrough that revolutionized the field and provided a real endovascular alternative to surgical clipping. The original Guglielmi detachable coil consisted of a stainless steel delivery wire attached to a soft, radiopaque platinum coil that was delivered into the aneurysm and detached by electrolysis. Subsequent development of variable stiffness microcatheters and steerable microwires capable of navigating the tortuous intracranial circulation, led to an exponential growth in the field of endovascular neurosurgery. A multitude of different coils with various sizes (diameters and lengths), predetermined shapes, degrees of softness, delivery systems, and biological coatings have since been developed. In a brief time span, endovascular coiling became the preferred treatment modality for most ruptured and unruptured intracranial aneurysms.

The International Subarachnoid Aneurysm Trial (ISAT), a randomized, controlled, prospective study comparing both endovascular and surgical aneurysm treatment options revealed survival free of disability at 1 year is significantly better with endovascular coiling. The data also suggested that the long-term risks of further bleeding from the treated aneurysm are low with either therapy, although somewhat more frequent with endovascular coiling[14].

Recently published BRAT study evaluating the superiority in safety and efficacy of clipping versus endovascular coiling for the treatment of ruptured cerebral aneurysms also observed a better 1-year outcome in patients treated with coil embolization in comparison to microsurgical clipping and no recurrent hemorrhage was seen after aneurysmal coil embolization[15].

Today, endovascular treatment has become the treatment of choice for both ruptured and unruptured intracranial aneurysms. Over the past two decades, the access system, microcatheters, microguide wires and embolic materials along with management strategies have significantly improved and are still evolving.

Decision making in Intracranial Aneurysm Treatment

Intracranial aneurysms are quite heterogeneous with regards to patients age, their status at presentation (ruptured versus unruptured), aneurysm shape (fusiform versus saccular) and location (aneurysm geometry in relationship to parent artery), their size (small/large/giant), the size of their neck (small/

large), and associated systemic disorders. The heterogeneity is made more complex by the availability of various treatment options including surgery and rapidly improving endovascular treatment options.

In general, any ruptured aneurysm warrants treatment provided patient is in a fair neurological status. Decision-making on treatment of unruptured intracranial aneurysm is difficult. The following principles serve as guidelines in the treatment of most simple aneurysms[16].

Patients under the age of 60 years

For small (<7 mm) anterior circulation aneurysms, conservative medical management, with aggressive treatment of risk factors such as smoking and hypertension, can be considered. Exceptions include patients with a strong family history of subarachnoid hemorrhage, a symptomatic aneurysm, a daughter sac, or aneurysms at potentially high-risk locations, including the posterior communicating artery origin and possibly the anterior communicating artery.

For small (<7mm) posterior circulation aneurysm, treatment should be considered if it could be undertaken with a low risk of complications.

For those aneurysms that are 7 mm or greater in size, treatment is typically recommended; the choice of intervention is dependent on aneurysm size, location, and other morphology characteristics, and the patient's clinical state.

Interventional treatment should probably be undertaken for large unruptured intracranial aneurysms and those that are symptomatic, particularly in young patients.

As intervention risks generally increase with age, a conservative approach to treatment of elderly patients is indicated, particularly for small aneurysms. Surgical morbidity is lowest under the age of 50–60 years.

In patients undergoing endovascular therapy, age is not as strongly related to risk of morbidity and mortality.

Patients over the age of 60 Years

For small (<7 mm) aneurysms, conservative management is usually recommended except in those with a strong family history of subarachnoid hemorrhage or a symptomatic aneurysm.

For aneurysms of 7–12 mm in diameter, management is individualized. Aneurysms in the anterior circulation can be considered for conservative management. Aneurysms in the posterior circulation or posterior communicating artery should be strongly considered for interventional management.

For aneurysms greater than 12 mm in diameter, an interventional procedure should be strongly considered, taking into account the patient's overall health status and presence of factors that might increase surgical or endovascular risks.

Patients treated conservatively should be counseled about potential risk factors for aneurysm growth and rupture. These risk factors include hypertension and tobacco use. Aggressive control of hypertension and smoking cessation should be strongly advocated for all such patients. They should also be advocated on the need for follow up vascular imaging using CT angiogram or MR angiogram.

Endovascular Treatment

Endovascular embolization is the treatment of choice for intracranial aneurysm. Since the introduction of electrolytically detachable platinum coils, coil embolization is accepted as an optimal minimally invasive treatment option. Initial large series showed acceptable mortality and morbidity (4%-9%), related mostly to thromboembolic complications and intraoperative rupture[17,18]. Further larger series confirmed the feasibility of aneurysm coiling (96.9% in ruptured aneurysms and 94.0% in unruptured aneurysms), with acceptable procedural mortality (1.4% in ruptured and 1.7% in unruptured aneurysms) and morbidity rates (8.6% in ruptured and 7.7% in unruptured aneurysms)[19,20]. Various treatment options include-

1. Coil embolization.
2. Balloon assisted coil embolization(BAC)
3. Stent assisted coil embolization (SAC)
4. Flow diversion
5. Flow disruption
6. Embolization using liquid embolic agents (LEA)
7. Parent artery occlusion

Coil embolization

Most aneurysms (about 75%) have narrow neck with dome to neck ratio (maximum dome width/maximum neck width) of more than 1.6 which is amenable for endovascular CE without any assistance[21]. Endovascular access is gained via placement of a femoral sheath. This approach is a minimally invasive technique in which a microcatheter is placed into the aneurysm lumen and platinum coils that come in different shapes, sizes, softness and coil diameters are delivered to support thrombus formation. Detachment of the coils occurs either mechanically or electrolytically. Initially framing coils followed by filling coils are used to achieve good packing of the aneurysm. During aneurysm coiling, the most frequent complication that can happen includes thromboembolic complications and intraoperative rupture of the aneurysm. In unruptured aneurysms, the rates of thromboembolic complications and intraoperative rupture were reported at 7.3% and 2.0%, respectively[22] while, in ruptured aneurysms, they were higher at 13.3% and 3.7%, respectively[23]. To prevent thromboembolic complications, most operators use intravenous heparin before coil deployment in unruptured aneurysm and after the first few coils in ruptured aneurysm[24] (Fig 1).

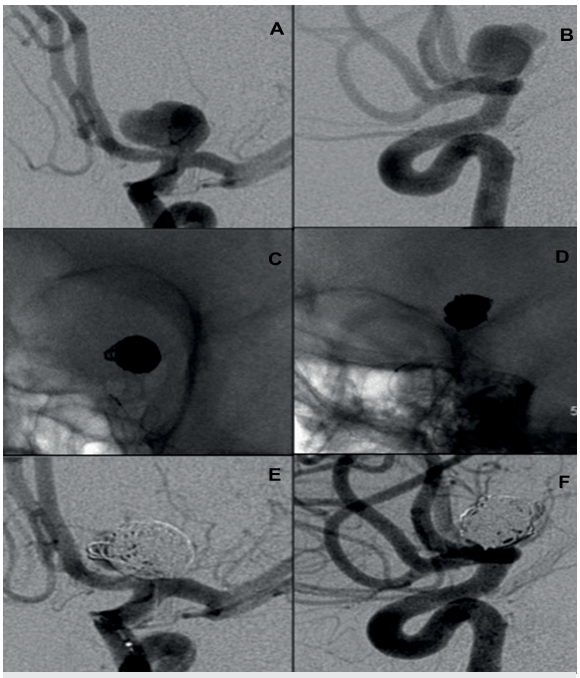

Fig 1: Internal carotid artery bifurcation aneurysm with a narrow neck AP (A) and Lateral view (B). Treated by primary coil embolization and the radio opaque coil mass is seen in native images (C & D). Immediate post treatment angiogram shows the obliteration of aneurysm with stagnation of residual flow in the aneurysm. (E & F).

Following coil embolization, persistent and durable occlusion is not achieved in all aneurysms. It is estimated by systematic review that aneurysm recanalization occurs in up to 25% and retreatment in 10.3% of cases[25]. Recanalization of the aneurysm may be due to coil compaction or regrowth of the aneurysm and various factors that may be associated with this include high blood pressure, smoking, aneurysm diameter and neck size, and quality of immediate postoperative aneurysm occlusion as decided by coil packing density[26-30]. To reduce the recanalization rate various modifications were made, that include: Coating of the coil with bioactive Polyglycolic/polylactic acid (PGLA), absorbable copolymer (matrix coil), interwoven PGLA microfilaments (Nexus coils), filling the inner core with hydrogel (Hydro coil) that swell on exposure to blood to improve packing density. Mid and long term follow up evaluation of these coils in multicenter series showed no benefit in preventing recanalization compared to bare platinum coils[9,31-33]. Incompletely coiled or recanalized aneurysms have an increased risk of rehemorrhage compared with those that are completely occluded and therefore require long-term follow-up angiography. Post procedural rebleeding is an infrequent complication and carries a high mortality[34, 35].

Balloon assisted coil embolization (BAC)

Aneurysms with dome to neck ratio of less than 1.6 require some assistance at the base of the aneurysm either temporarily during coiling or permanently for successful embolization. In 1997, Moret et al described the technique to coiling wide neck aneurysm with remodeling using balloon. Since then balloon remodeling has been used in different locations including bifurcation aneurysm and for different shapes of the aneurysm. The balloon is inflated during the coil placement and deflated right after. During inflation of the balloon, there is temporary occlusion of the parent artery so the patient needs to be adequately anti-coagulated to prevent thromboembolic complications. Initially a round balloon was used, now in most cases, a hyper-compliant sausage shaped balloon is used. Recently a double lumen balloon was introduced that enables the use of stent in the end if the coils placed within the aneurysm remain unstable and also prevents the coils from prolapsing between the stent struts. BAC is not only used to enable coiling, but also as a bailout in case of an intraoperative aneurysm rupture during coiling. The balloon stays deflated across the neck of the aneurysm and is inflated only in case of intraoperative rupture. Santillan et al have demonstrated that in the setting of intraoperative rupture, BAC was associated with a higher probability of unchanged or improved clinical outcome as compared with standard coiling[36]. The rates of thromboembolic events in both ruptured and unruptured aneurysms are the same with or without balloon use during the procedure. But, the rupture rate is relatively higher in the balloon group (3.2% vs. 2.2%)[37]. In general, if used judiciously in selected cases, it is a safe and useful tool for better treatment in wide neck aneurysms as it avoids the use of stent and long-term antiplatelet treatment (Fig 2&3).

Stent assisted Coil embolization (SAC)

Stent is a metal scaffold placed across the neck of the aneurysm for effective embolization of wide neck, large to giant, and fusiform aneurysms. Initially coronary stents were used and the reports date back to as early as 1998. Later dedicated neurovascular stent systems were developed using much thinner and lightweight titanium metal.

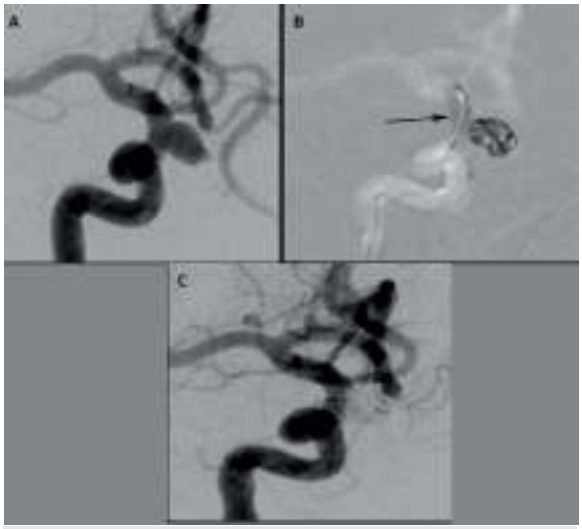

Fig 2: Oblique angiogram of internal carotid artery showing a broad based superior hypophyseal artery aneurysm (A). Balloon assisted embolization is performed (B), the inflated balloon in the parent artery is shown with an arrow. Post embolization angiogram shows complete obliteration of the aneurysm (C).

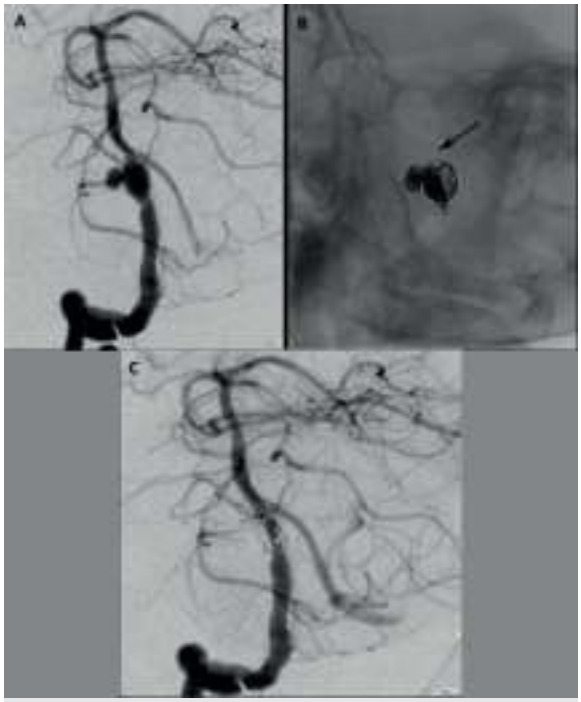

Fig 3: Dysplastic ruptured vertebral artery aneurysm (A) is treated by stent assisted coil embolization. The radio opaque stent struts are shown with an arrow (B). Post embolization angiogram shows complete obliteration of the aneurysm with preserved flow in the parent artery. (C)

In general, stent is avoided in patients with acutely ruptured aneurysm and reserved for patients with unruptured aneurysm. A foreign body left in blood stream will result in thrombosis, and in order to prevent it, preoperative and postoperative antiplatelet treatment is essential. Aspirin and Clopidogrel are the preferred anti-platelets and their inhibition of platelet function is monitored to assess their therapeutic effect. In resistant patients Prasugrel is the next choice anti-platelet. Stent assistance allows the surgeon to spack the aneurysm better along with the residual tiffness of the stent resulting in reorientation of the vessel and reduction in hemodynamic stress contributes to lesser recanalization. In one of the early largest series, though stent was used for difficult and complex aneurysms, stent use was associated with higher rates of permanent neurological complications (7.4%) as compared with standard coiling (3.8%). Procedure related mortality in the stenting group was 4.6% versus 1.2% in the non-stenting group. However the recurrence was significantly lower in the stenting group 14.9% as against 33.5% in the non-stenting group[38].

More recently multicenter studies from United States and Europe show better and similar results. Periprocedural complication rate was around 12% in particular thromboembolic events happened in 4.4% and 3.7% respectively. The complete occlusion rate after the procedure was 60% to 66.4%, respectively. An additional 14% of the treated aneurysms showed a progressive occlusion at 12 to 18 months follow-up; aneurysm recurrence rate was around 10%. Subsequently 8% and 4% and of the aneurysms were retreated in respective studies[39, 40].

Now, with gaining experience during the past years, stenting is more frequently used in acutely ruptured aneurysms however, the hemorrhagic complications are higher with this approach. One of the reviews have noted intracranial hemorrhagic complications in 8% including EVDs related hemorrhages. Clinically significant thromboembolic events occurred in 6%. Sixty-seven percent of patients had favorable clinical outcomes, 14% had poor outcomes, and 19% died[41].

Flow Diversion

Flow diverters have expanded the therapeutic options for treatment of cerebral aneurysms and represent a welcomed paradigm shift. Previously untreatable intracranial aneurysms can now be safely treated.

Flow diverters are low porosity, tight meshed tubular stents when placed in the parent artery across the base of the aneurysm result in parent vessel reconstruction, aneurysm obliteration with preservation of side branches. Preclinical studies have shown good clinical efficacy[42]. The mesh has a metal coverage of about 30% to 40% of the surface area and the pores are strategized to provide flow redirection ie, increased impedance of the stent reduces the blood flow into the aneurysm leading to slow, progressive and stable thrombus formation along with diversion of flow into the parent artery. High flow and demand in the side branches keep them open. Over time, the meshwork provides a scaffold for neo-endothelialization across the aneurysm neck. In contrast to the traditional intrasaccular aneurysm treatment, there often remains a residual post-interventional filling of the aneurysm sac, which will subside over a period of months (Fig 4).

Flow diverters are used to treat complex aneurysms, including wide neck, large and giant aneurysms, fusiform aneurysms, dysplastic and recanalized aneurysms following previous treatment. Currently four flow diverters are available for clinical use. Pipeline Embolization Device (EV3-MTI, Irvine, CA), Silk (Balt, Montmorency, France), Surpass (Stryker, Fremont, CA) and FRED (Microvention, Tustin, CA). Initial small series from one or few centers were promising with technical feasibility and its safety with acceptable complication rate[43-47]. Subsequent large series both retrospective and prospective from single and multicenter have shown similar results to substantiate its clinical use[48-50]. Recently a prospective multinational multicenter series confirmed the high efficacy of flow diverters with technical feasibility of 99.1% with acceptable safety profile (5.6% of patients had major ipsilateral stroke or neurological death)[51].

Flow diverter use currently is limited for difficult unruptured aneurysms, as it requires dual antiplatelet medication. However, there is a series to suggest its use in small-ruptured blister like aneurysm that cannot be treated by standard coil embolization[52]. Due to the higher metal coverage in Flow diverters, there is an increased incidence of thromboembolism in spite of the dual antiplatelet. Delayed rupture of the aneurysm has been reported and its incidence is about 1% but its mechanism is unknown. Hemodynamic alteration leading to altered focal stress within the aneurysm,

along with large unstable aneurysmal thrombus created by flow reduction, may result in inflammation and weakening of the aneurysm wall, have been proposed as mechanisms and it largely remains speculative[53,54]. To prevent delayed rupture, suggestions have been made to place coils within the aneurysm and use of periprocedural steroids have been proposed.

Delayed and remote ipsilateral intraparenchymal hemorrhage is reported and its incidence is not known. Its mechanism is largely unknown but the proposed mechanisms include hemorrhagic transformation of small ischemic lesions, higher blood flow with altered auto regulation, along with dual antiplatelets contribute to massive hemorrhage.

Flow diverters have been in clinical use only for the past few years, the initial experience is promising and has provided effective and simple solution to complex and difficult aneurysms. The safety profile is acceptable in such high-risk situations. Its use for simple aneurysms is yet to be proven. Flow diverters use has reignited the need for research of safer and more efficacious use of antiplatelet in elective and emergent endovascular techniques (Fig 5&6).

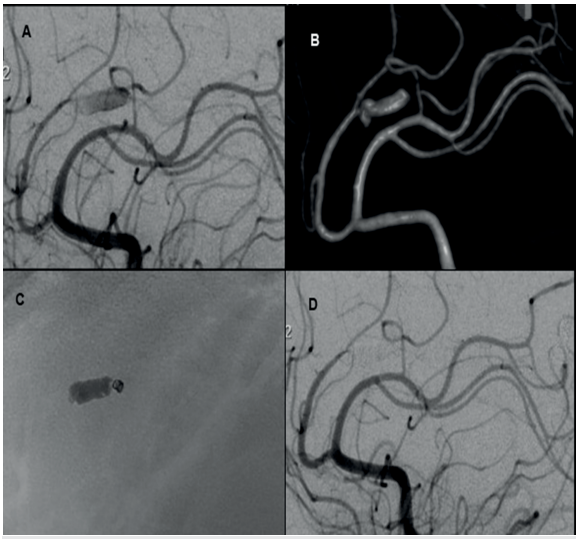

Fig 5: Pericallosal dysplastic mycotic aneurysm (A) in lateral angiogram and 3D angiogram (B) treated by n-BCA embolization with coils to prevent forward migration of the liquid embolic (C). Control angiogram reveals total obliteration of the aneurysm and the dysplastic segment of the artery (D).

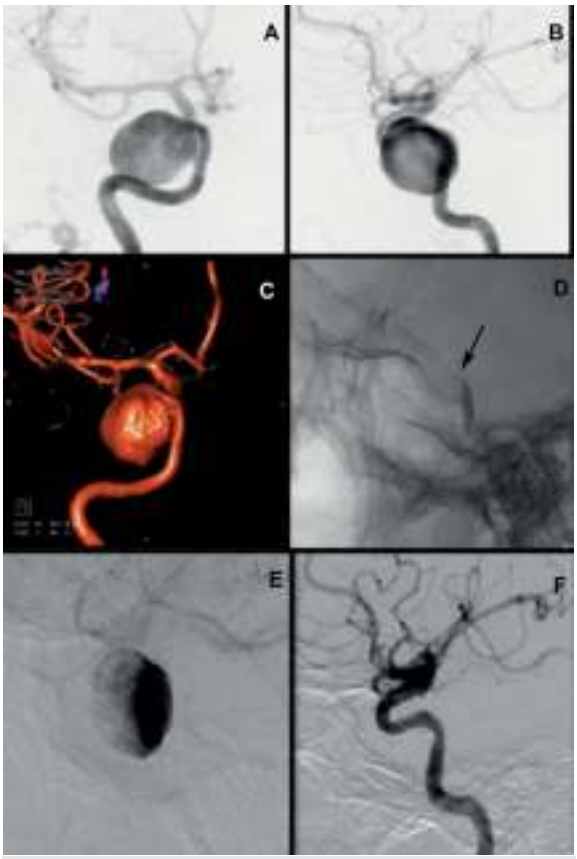

Fig 4: Giant cavernous carotid artery aneurysm presented with ocular cranial neuropathy in shown AP (A), Lateral (B) and 3D projections (C). The aneurysm was treated by flow diverter, which is shown in the native image with an arrow (D). Immediate post treatment angiogram shows contrast stagnation within the aneurysm (E). Six months follow up angiogram shows complete obliteration of the aneurysm with remodeling of the parent artery (F).

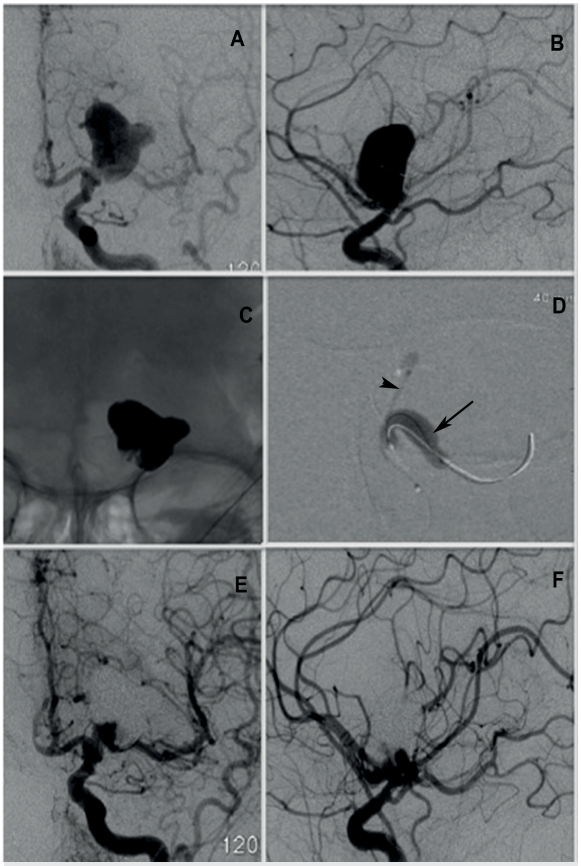

Fig 6: M1 segment large aneurysm with broad base in AP (A) and Lateral (B) projections. The aneurysm is treated by balloon assisted Onyx embolization (D), the inflated balloon is shown by arrow and the Onyx injection catheter is shown by arrow head. Final Onyx cast in native image (C) is shown. Post embolization angiogram reveals obliteration of the aneurysm with minimal residual filling at the base of the aneurysm in AP (E) and Lateral (F) projections.

Intra aneurysmal flow diversion or Flow Disruption

Intra-aneurysmal flow disruption or flow diversion is an endovascular approach where a device is deployed within the aneurysm to create blood flow stasis with subsequent thrombosis. There is no need for antiplatelet medication and therefore can be safely used for ruptured aneurysms. Preclinical studies have shown the feasibility of this approach as well as its safety and efficacy[55]. Currently available devices include WEB and Luna. The WEB device is well suited for the treatment of wide-neck bifurcation aneurysms of the basilar artery, the middle cerebral artery, the anterior communicating artery, and the internal carotid artery. In an initial retrospective, multicenter series using WEB device the technical success rate was 100% with an acceptable morbidity of 4.8%[56]. Subsequent prospective, single-center series showed similar results[57].

Embolization With Liquid Embolic Material

An aneurysm being a 3 dimensional space, volume filling with a liquid that will subsequently become solid to take the shape of the aneurysm is the most definitive way to achieve maximal occlusion. With this concept, High density Onyx (ethylene vinyl alcohol copolymer dissolved in dimethyl sulfoxide) - a liquid embolic system, was developed and used for the treatment of intracranial aneurysms[58-60]. Its use involves placement of a balloon across the neck of the aneurysm while Onyx is injected endosaccularly. This procedure is technically challenging with significant limitations. The challenges include: leakage across the balloon into the parent artery resulting in narrowing of the parent artery, catheter entrapment, potential space between the onyx cast and aneurysmal wall as Onyx is more cohesive than adhesive[61]. Though initial results in complex aneurysms were acceptable with good safety and efficacy[62] technical challenges and safety concerns interrupted the development of this technique[63].

Parent artery Occlusion

Giant and dysplastic aneurysms are difficult aneurysms to treat. Parent vessel occlusion following balloon test occlusion with or without extra cranial and intracranial bypass is considered as an acceptable solution. Now, with the introduction of flow diverters most such aneurysms are treated effectively without vessel sacrifice. Parent occlusion has become almost obsolete with few exceptions like distally located mycotic aneurysms, high-flow caroticocavernous fistula due to ruptured cavernous aneurysms, flow related pre-nidal aneurysms in the feeder of an AVM.

Complications associated with endovascular treatment of intracranial aneurysms

Endovascular treatment of intracranial aneurysm is a demanding procedure that requires a specific skill set and attention to finer details during the procedure to avoid complications related to the procedure. It may be mild or have devastating consequences if not identified or no corrective measures are taken. Overall complication rates varies significantly based on the experience of the surgeon and has been reported to range from 11.3%-19.4%[64].

Aneurysm Perforation

Aneurysm perforation can occur during any part of the procedure, typically occuring in a small aneurysm during intra aneurysmal manipulation with microwire, microcatheter, or coil. Aneurysm perforation has been reported in 2.5%-5.4%. A meta-analysis by Cloft et al found the risk of perforation to be significantly higher in ruptured aneurysms than in unruptured aneurysms (4.1% vs. 0.7%)[65]. In a more recent meta-analysis in patients with aneurysms of ≤3 mm, the intraprocedural rupture rate in unruptured aneurysms was found to be 5.0% compared to 10.7% in small-ruptured aneurysms[66].

In the event of an intra-procedural aneurysm rupture, there is sudden systemic hemodynamic alteration. Confirmation is done by angiogram that reveal leakage of contrast. The heparin on board is reversed with Protamine. The goal in this situation is to rapidly occlude the aneurysm, by placing coils taking into account that a segment of the coil may extrude into the sub arachnoid space. If balloon assistance is in place, taking advantage to inflate the balloon will help to temporarily arrest bleeding.

Thromboembolic Events

Thromboembolic events are commonest complication of an endovascular aneurysmal treatment. This includes silent DWI changes seen following aneurysm coiling that occurs in about 42% of patients[67]. Periprocedural thromboembolic events do happen as the coils we use for occlusion is highly thrombogenic. They mostly happen at the base of the aneurysm extending into the parent artery. As a preventive measure, the patient is heparinized to maintain the ACT at 2-3 times the normal range. In ruptured aneurysms heparin is given after the placement of first coil. Factors that influence thrombosis as evidenced by the CLARITY study, a higher rate of thromboembolic events was observed in patients with large aneurysms (>10 mm), in smokers, and in aneurysms with a neck larger than 4 mm[68]. managed by using, abciximab (ReoPro), a glycoprotein IIb/IIIa receptor antagonist that inhibits platelet aggregation. It has a short plasma half-life. Platelet aggregation returns to normal in about 96-120 hours after discontinuation. Interventional techniques like the Penumbra aspiration catheter with separator or stent-trievers can also be used to re-open an occluded vessel.

Device Failure

Stretching: Currently the coils used for coiling are all stretch resistant with tiny filaments extending between the two ends of the coil to prevent it from unraveling unintentionally when pulled on. Excess manipulation can result in stretching of the coil and the reported rate during embolization varies between 0.2%-6.5%[19,69].

Failure to detach and premature detachment of the coils: Failure of the coil to detach is easily managed as the coil can still be retrieved while premature coil detachment can lead to coil being lodged in the parent artery. In such a situation, it can be pushed into the aneurysm with a pusher wire but repositioning is impossible.

Coil herniation: Coil herniation happens when the coil is extruded out of the aneurysm into the parent artery during coiling. The reported incidence is 2.4%-4.2%[69]. It is associated with detachment of unstable coil moving with pulsatile blood flow, larger or longer coils, excessive packing of the aneurysm and wide neck aneurysm. Coil herniation can induce parent artery thrombosis, emboli and lead to ischemic complications[70,71].

Coil migration: Coil migration happens in wide-necked aneurysms due to unstable coil position, undersized coils and under packing of the aneurysm. Its incidence is reported in about 0.5%-1.7%.[17,72] Stent- or balloon-assistance can reduce the risk of coil herniation or migration.

Dissection

A dissection develops due to tear in the tunica intima, the innermost layer of the arterial wall and blood enters this newly formed space leading to progressive separation of the inner lining and may cause stenosis or even complete occlusion of the true vessel lumen. Periprocedurally, vessel dissection is caused by catheter and wire manipulation and has been reported in 0.26% of cases[73]. If the dissection is flow limiting with poor collaterals, it is necessary to place a stent else most dissections are treated with heparin in the acute phase and later with aspirin or clopidogrel.

Conclusion

In summary, most intracranial aneurysms today can be treated by endovascular technique. Endovascular approaches available for the treatment include standard coiling, balloon assisted coiling, stent assisted coiling, flow diversion, flow disruption, embolization by liquid embolic agents and parent artery occlusion. Ruptured aneurysms are treated emergently to prevent rebleeding and effectively manage complications associated with subarachnoid hemorrhage like vasospasm and hydrocephalus. Not all unruptured aneurysms need to be treated. Management decisions are made on a case-by-case basis, taking into account clinical presentation, age, associated comorbidities as well as aneurysm location, morphology and size. In general, aneurysms with small neck are treated by standard coiling or balloon assisted coiling while wide neck, large and giant, and fusiform, aneurysms, are treated by stent assisted coiling, or by use of flow diverter or flow disruption. Advances in imaging technology and device manufacturing have resulted in safe and effective management of most intracranial aneurysms by endovascular route.

References

1) Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. Lancet neurology. 2011;10(7):626-36.

2) Jellinger K. Pathology of intracerebral hemorrhage. Zentralblatt fur Neurochirurgie. 1977;38(1):29-42.

3) Jakubowski J, Kendall B. Coincidental aneurysms with tumours of pituitary origin. Journal of neurology, neurosurgery, and psychiatry. 1978;41(11):972-9.

4) Wardlaw JM, White PM. The detection and management of unruptured intracranial aneurysms. Brain : a journal of neurology. 2000;123 (Pt 2):205-21

5) Morita A, Kirino T, Hashi K, Aoki N, Fukuhara S, et al. The natural course of unruptured cerebral aneurysms in a Japanese cohort. The New England journal of medicine. 2012;366(26):2474-82.

6) Kassell NF, Torner JC, Jane JA, Haley EC, Jr., Adams HP. The International Cooperative Study on the Timing of Aneurysm Surgery. Part 2: Surgical results. Journal of neurosurgery. 1990;73(1):37-47.

7) Dandy WE. Intracranial Aneurysm of the Internal Carotid Artery: Cured by Operation. Annals of surgery. 1938;107(5):654-9.

8) Serbinenko FA. Balloon catheterization and occlusion of major cerebral vessels. Journal of neurosurgery. 1974;41(2):125-45.

9) White PM, Lewis SC, Gholkar A, Sellar RJ, Nahser H, Cognard C, et al. Hydrogel-coated coils versus bare platinum coils for the endovascular treatment of intracranial aneurysms (HELPS): a randomised controlled trial. Lancet. 2011;377(9778):1655-62.

10) Higashida RT, Halbach VV, Cahan LD, Hieshima GB, Konishi Y. Detachable balloon embolization therapy of posterior circulation intracranial aneurysms. Journal of neurosurgery. 1989;71(4):512-9.

11) Guglielmi G, Vinuela F, Dion J, Duckwiler G. Electrothrombosis of saccular aneurysms via endovascular approach. Part 2: Preliminary clinical experience. Journal of neurosurgery. 1991;75(1):8-14.

12) Guglielmi G, Vinuela F, Sepetka I, Macellari V. Electrothrombosis of saccular aneurysms via endovascular approach. Part 1: Electrochemical basis, technique, and experimental results. Journal of neurosurgery. 1991;75(1):1-7.

13) Guglielmi G. History of the genesis of detachable coils. A review. Journal of neurosurgery. 2009;111(1):1-8.

14) Molyneux A, Kerr R, Stratton I, Sandercock P, Clarke M, Shrimpton J, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet. 2002;360(9342):1267-74.

15) McDougall CG, Spetzler RF, Zabramski JM, Partovi S, Hills NK, Nakaji P, et al. The Barrow Ruptured Aneurysm Trial. Journal of neurosurgery. 2012;116(1):135-44.

16) Brown RD, Jr., Broderick JP. Unruptured intracranial aneurysms: epidemiology, natural history, management options, and familial screening. Lancet neurology. 2014;13(4):393-404.

17) Vinuela F, Duckwiler G, Mawad M. Guglielmi detachable coil embolization of acute intracranial aneurysm: perioperative anatomical and clinical outcome in 403 patients. Journal of neurosurgery. 1997;86(3):475-82.

18) Cognard C, Weill A, Castaings L, Rey A, Moret J. Intracranial berry aneurysms: angiographic and clinical results after endovascular treatment. Radiology. 1998;206(2):499-510.

19) Gallas S, Pasco A, Cottier JP, Gabrillargues J, Drouineau J, Cognard C, et al. A multicenter study of 705 ruptured intracranial aneurysms treated with Guglielmi detachable coils. AJNR 2005;26(7):1723-31.

20) Gallas S, Drouineau J, Gabrillargues J, Pasco A, Cognard C, Pierot L, et al. Feasibility, procedural morbidity and mortality, and long-term follow-up of endovascular treatment of 321 unruptured aneurysms. AJNR 2008;29(1):63-8.

21) Brinjikji W, Cloft HJ, Kallmes DF. Difficult aneurysms for endovascular treatment: overwide or undertall? AJNR 2009;30(8):1513-7.

22) Pierot L, Spelle L, Vitry F, Investigators A. Immediate clinical outcome of patients harboring unruptured intracranial aneurysms treated by endovascular approach: results of the ATENA study. Stroke; a journal of cerebral circulation. 2008;39(9):2497-504.

23) Cognard C, Weill A, Spelle L, Piotin M, Castaings L, Rey A, et al. Long-term angiographic follow-up of 169 intracranial berry aneurysms occluded with detachable coils. Radiology. 1999;212(2):348-56.

24) Ries T, Buhk JH, Kucinski T, Goebell E, Grzyska U, Zeumer H, et al. Intravenous administration of acetylsalicylic acid during endovascular treatment of cerebral aneurysms reduces the rate of thromboembolic events. Stroke; a journal of cerebral circulation. 2006;37(7):1816-21.

25) Ferns SP, Sprengers ME, van Rooij WJ, Rinkel GJ, van Rijn JC, Bipat S, et al. Coiling of intracranial aneurysms: a systematic review on initial occlusion and reopening and retreatment rates. Stroke; a journal of cerebral circulation. 2009;40(8):e523-9.

26) Hope JK, Byrne JV, Molyneux AJ. Factors influencing successful angiographic occlusion of aneurysms treated by coil embolization. AJNR 1999;20(3):391-9.

27) Ortiz R, Stefanski M, Rosenwasser R, Veznedaroglu E. Cigarette smoking as a risk factor for recurrence of aneurysms treated by endosaccular occlusion. Journal of neurosurgery. 2008;108(4):672-5.

28) Choi DS, Kim MC, Lee SK, Willinsky RA, Terbrugge KG. Clinical and angiographic long-term follow-up of completely coiled intracranial aneurysms using endovascular technique. Journal of neurosurgery. 2010;112(3):575-81.

29) Wakhloo AK, Gounis MJ, Sandhu JS, Akkawi N, Schenck AE, Linfante I. Complex-shaped platinum coils for brain aneurysms: higher packing density, improved biomechanical stability, and midterm angiographic outcome. AJNR 2007;28(7):1395-400.

30) Pierot L, Cognard C, Anxionnat R, Ricolfi F, Investigators C. Endovascular treatment of ruptured intracranial aneurysms: factors affecting midterm quality anatomic results: analysis in a prospective, multicenter series of patients (CLARITY). AJNR 2012;33(8):1475-80.

31) Pierot L, Cognard C, Ricolfi F, Anxionnat R, investigators C. Mid-term anatomic results after endovascular treatment of ruptured intracranial aneurysms with Guglielmi detachable coils and Matrix coils: analysis of the CLARITY series. AJNR 2012;33(3):469-73.

32) Molyneux AJ, Clarke A, Sneade M, Mehta Z, Coley S, Roy D, et al. Cerecyte coil trial: angiographic outcomes of a prospective randomized trial comparing endovascular coiling of cerebral aneurysms with either cerecyte or bare platinum coils. Stroke; a journal of cerebral circulation. 2012;43(10):2544-50.

33) Roth C, Struffert T, Grunwald IQ, Romeike BF, Krick C, Papanagiotou P, et al. Long-term results with Matrix coils vs. GDC: an angiographic and histopathological comparison. Neuroradiology. 2008;50(8):693-9.

34) Elijovich L, Higashida RT, Lawton MT, Duckwiler G, Giannotta S, Johnston SC, et al. Predictors and outcomes of intraprocedural rupture in patients treated for ruptured intracranial aneurysms: the

CARAT study. Stroke; a journal of cerebral circulation. 2008;39(5):1501-6.

35) Aikawa H, Kazekawa K, Nagata S, Onizuka M, Iko M, Tsutsumi M, et al. Rebleeding after endovascular embolization of ruptured cerebral aneurysms. Neurologia medico-chirurgica. 2007;47(10):439-45; discussion 46-7.

36) Santillan A, Gobin YP, Greenberg ED, Leng LZ, Riina HA, Stieg PE, et al. Intraprocedural aneurysmal rupture during coil embolization of brain aneurysms: role of balloon-assisted coiling. AJNR 2012;33(10):2017-21.

37) Pierot L, Spelle L, Leclerc X, Cognard C, Bonafe A, Moret J. Endovascular treatment of unruptured intracranial aneurysms: comparison of safety of remodeling technique and standard treatment with coils. Radiology. 2009;251(3):846-55.

38) Piotin M, Blanc R, Spelle L, Mounayer C, Piantino R, Schmidt PJ, et al. Stent-assisted coiling of intracranial aneurysms: clinical and angiographic results in 216 consecutive aneurysms. Stroke; a journal of cerebral circulation. 2010;41(1):110-5.

39) Fargen KM, Hoh BL, Welch BG, Pride GL, Lanzino G, Boulos AS, et al. Long-term results of enterprise stent-assisted coiling of cerebral aneurysms. Neurosurgery. 2012;71(2):239-44; discussion 44.

40) Gentric JC, Biondi A, Piotin M, Mounayer C, Lobotesis K, Bonafe A, et al. Safety and efficacy of neuroform for treatment of intracranial aneurysms: a prospective, consecutive, French multicentric study. AJNR 2013;34(6):1203-8.

41) Bodily KD, Cloft HJ, Lanzino G, Fiorella DJ, White PM, Kallmes DF. Stent-assisted coiling in acutely ruptured intracranial aneurysms: a qualitative, systematic review of the literature. AJNR 2011;32(7):1232-6.

42) Sadasivan C, Cesar L, Seong J, Rakian A, Hao Q, Tio FO, et al. An original flow diversion device for the treatment of intracranial aneurysms: evaluation in the rabbit elastase-induced model. Stroke; a journal of cerebral circulation. 2009;40(3):952-8.

43) Lylyk P, Miranda C, Ceratto R, Ferrario A, Scrivano E, Luna HR, et al. Curative endovascular reconstruction of cerebral aneurysms with the pipeline embolization device: the Buenos Aires experience. Neurosurgery. 2009;64(4):632-42; discussion 42-3; quiz N6.

44) Szikora I, Berentei Z, Kulcsar Z, Marosfoi M, Vajda ZS, Lee W, et al. Treatment of intracranial aneurysms by functional reconstruction of the parent artery: the Budapest experience with the pipeline embolization device. AJNR 2010;31(6):1139-47.

45) Byrne JV, Beltechi R, Yarnold JA, Birks J, Kamran M. Early experience in the treatment of intra-cranial aneurysms by endovascular flow diversion: a multicentre prospective study. PloS one. 2010;5(9).

46) Lubicz B, Collignon L, Raphaeli G, Pruvo JP, Bruneau M, De Witte O, et al. Flow-diverter stent for the endovascular treatment of intracranial aneurysms: a prospective study in 29 patients with 34 aneurysms. Stroke; a journal of cerebral circulation. 2010;41(10):2247-53.

47) Berge J, Biondi A, Machi P, Brunel H, Pierot L, Gabrillargues J, et al. Flow-diverter silk stent for the treatment of intracranial aneurysms: 1-year follow-up in a multicenter study. AJNR 2012;33(6):1150-5.

48) Kan P, Siddiqui AH, Veznedaroglu E, Liebman KM, Binning MJ, Dumont TM, et al. Early postmarket results after treatment of intracranial aneurysms with the pipeline embolization device: a U.S. multicenter experience. Neurosurgery. 2012;71(6):1080-7; discussion 7-8.

49) Piano M, Valvassori L, Quilici L, Pero G, Boccardi E. Midterm and long-term follow-up of cerebral aneurysms treated with flow diverter devices: a single-center experience. Journal of neurosurgery. 2013;118(2):408-16.

50) O'Kelly CJ, Spears J, Chow M, Wong J, Boulton M, Weill A, et al. Canadian experience with the pipeline embolization device for repair of unruptured intracranial aneurysms. AJNR 2013;34(2):381-7.

51) Becske T, Kallmes DF, Saatci I, McDougall CG, Szikora I, Lanzino G, et al. Pipeline for uncoilable or failed aneurysms: results from a multicenter clinical trial. Radiology. 2013;267(3):858-68.

52) Kulcsar Z, Wetzel SG, Augsburger L, Gruber A, Wanke I, Rufenacht DA. Effect of flow diversion treatment on very small ruptured aneurysms. Neurosurgery. 2010;67(3):789-93.

53) Cebral JR, Mut F, Raschi M, Scrivano E, Ceratto R, Lylyk P, et al. Aneurysm rupture following treatment with flow-diverting stents: computational hemodynamics analysis of treatment. AJNR 2011;32(1):27-33.

54) Berge J, Tourdias T, Moreau JF, Barreau X, Dousset V. Perianeurysmal brain inflammation after flow-diversion treatment. AJNR 2011;32(10):1930-4.

55) Ding YH, Lewis DA, Kadirvel R, Dai D, Kallmes DF. The Woven EndoBridge: a new aneurysm occlusion device. AJNR 2011;32(3):607-11.

56) Pierot L, Liebig T, Sychra V, Kadziolka K, Dorn F, Strasilla C, et al. Intrasaccular flow-disruption treatment of intracranial aneurysms: preliminary

results of a multicenter clinical study. AJNR 2012;33(7):1232-8.

57) Lubicz B, Mine B, Collignon L, Brisbois D, Duckwiler G, Strother C. WEB device for endovascular treatment of wide-neck bifurcation aneurysms. AJNR 2013;34(6):1209-14.

58) Cekirge HS, Saatci I, Ozturk MH, Cil B, Arat A, Mawad M, et al. Late angiographic and clinical follow-up results of 100 consecutive aneurysms treated with Onyx reconstruction: largest single-center experience. Neuroradiology. 2006;48(2):113-26.

59) Dalyai RT, Randazzo C, Ghobrial G, Gonzalez LF, Tjoumakaris SI, Dumont AS, et al. Redefining Onyx HD 500 in the Flow Diversion Era. International journal of vascular medicine. 2012;2012:435-490.

60) Tevah J, Senf R, Cruz J, Fava M. Endovascular treatment of complex cerebral aneurysms with onyx hd-500(R) in 38 patients. Journal of neuroradiology Journal de neuroradiologie. 2011;38(5):283-90.

61) Struffert T, Roth C, Romeike B, Grunwald IO, Reith W. Onyx in an experimental aneurysm model: histological and angiographic results. Journal of neurosurgery. 2008;109(1):77-82.

62) Molyneux AJ, Cekirge S, Saatci I, Gal G. Cerebral Aneurysm Multicenter European Onyx (CAMEO) trial: results of a prospective observational study in 20 European centers. AJNR 2004;25(1):39-51.

63) Carlson AP, Alaraj A, Amin-Hanjani S, Charbel FT, Aletich VA. Continued concern about parent vessel steno-occlusive progression with Onyx HD-500 and the utility of quantitative magnetic resonance imaging in serial assessment. Neurosurgery. 2013;72(3):341-52; discussion 52.

64) Henkes H, Fischer S, Weber W, Miloslavski E, Felber S, Brew S, et al. Endovascular coil occlusion of 1811 intracranial aneurysms: early angiographic and clinical results. Neurosurgery. 2004;54(2):268-80; discussion 80-5.

65) Cloft HJ, Kallmes DF. Cerebral aneurysm perforations complicating therapy with Guglielmi detachable coils: a meta-analysis. AJNR 2002;23(10):1706-9.

66) Brinjikji W, Lanzino G, Cloft HJ, Rabinstein A, Kallmes DF. Endovascular treatment of very small (3 mm or smaller) intracranial aneurysms: report of a consecutive series and a meta-analysis. Stroke; a journal of cerebral circulation. 2010;41(1):116-21.

67) Grunwald IQ, Papanagiotou P, Politi M, Struffert T, Roth C, Reith W. Endovascular treatment of unruptured intracranial aneurysms: occurrence of thromboembolic events. Neurosurgery. 2006;58(4):612-8; discussion -8.

68) Pierot L, Cognard C, Anxionnat R, Ricolfi F, Investigators C. Ruptured intracranial aneurysms: factors affecting the rate and outcome of endovascular treatment complications in a series of 782 patients (CLARITY study). Radiology. 2010;256(3):916-23.

69) Im SH, Han MH, Kwon OK, Kwon BJ, Kim SH, Kim JE, et al. Endovascular coil embolization of 435 small asymptomatic unruptured intracranial aneurysms: procedural morbidity and patient outcome. AJNR 2009;30(1):79-84.

70) Kim BM, Park SI, Kim DJ, Kim DI, Suh SH, Kwon TH, et al. Endovascular coil embolization of aneurysms with a branch incorporated into the sac. AJNR 2010;31(1):145-51.

71) Dinc H, Kuzeyli K, Kosucu P, Sari A, Cekirge S. Retrieval of prolapsed coils during endovascular treatment of cerebral aneurysms. Neuroradiology. 2006;48(4):269-72.

72) Park HK, Horowitz M, Jungreis C, Genevro J, Koebbe C, Levy E, et al. Periprocedural morbidity and mortality associated with endovascular treatment of intracranial aneurysms. AJNR 2005;26(3):506-14.

73) Paramasivam S, Leesch W, Fifi J, Ortiz R, Niimi Y, Berenstein A. Iatrogenic dissection during neurointerventional procedures: a retrospective analysis. Journal of neurointerventional surgery. 2012;4(5):331-5.

Review Article

Perioperative Management of Intracranial Aneurysms

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Abstract

A ruptured intra-cranial aneurysm and the ensuing subarachnoid haemorrhage have a dramatic clinical presentation and are associated with high morbidity and mortality. The diagnosis and perioperative management of this condition extending from the intensive care unit to the neurosurgical OT or catheterization laboratory (for surgical clipping or endovascular coiling) are discussed in detail. Recent recommendations in the anaesthetic management of this condition are also covered in this review article.

Key Words: Aneurysmal SAH, Anaesthesia, Surgical clipping, Endovascular coiling.

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Epidemiology

Intracranial aneurysms affect 5-10% of the general population[1]. The rate of rupture of an intracranial aneurysm is 0.05% to 6% per year. Smoking, hypertension, heavy alcohol intake and sympathomimetic drug abuse are risk factors for aneurysm rupture. Aneurysmal rupture may occur during exertion although in most cases there is no associated relationship. They are 11 times more likely to rupture in patients with a history of previous subarachnoid haemorrhage(SAH) than in those who do not. Around 20% of patients have more than one aneurysm. There is a male preponderance in the age group below 40 years but females are more affected than males in the age group above 40 years with a ratio of 3:2[1]. The main mode of presentation of a ruptured intracranial aneurysm is subarachnoid haemorrhage (SAH).

The overall incidence of SAH is around 9.0 – 10.5 / 100000 population / year[2]. Finland and Japan have the highest incidence of SAH in the world[2,3,4]. The incidence in these countries varies from 15.1 – 29.8 / 100000 population / year. The incidence in India is reported to be around 3 – 4 /100000 population / year[5]. The incidence of SAH is 1.24 – 1.60 times more common in women compared to men. It is higher in Hispanics and blacks compared to caucasians. The incidence of SAH is similar in males and females under 50 years, but is higher in females over 50 years of age.

Types of Aneurysms:

- Saccular aneurysms are usually less than 2.5 cm in diameter. They are the most common.
- Fusiform aneurysms are usually associated with severe atherosclerosis.
- Dissecting aneurysms are due to an endothelial tear
- Traumatic aneurysms usually follow traumatic brain injury
- Mycotic aneurysms are caused by vessel wall infection due to haematogenous spread
- Giant aneurysms are those over 2.5cm in diameter.

Genetics

Connective tissue disorders which have been associated with cerebral aneurysms include polycystic kidney disease, Ehler-Danlos syndrome type IV, Marfans syndrome, Neurofibromatosis type I, Pseudoxanthoma elasticum and Alpha-1 antitrypsin deficiency. There is defective synthesis of collagen and elastin in the arterial walls in these patients.

Aetiology of SAH

Traumatic brain injury is the most common cause of SAH. Aneurysmal rupture constitutes 70 – 75 % of all non-traumatic causes of SAH, as listed in Table 1. All the rare causes together constitute less than 5 %.

Table – 1: Non-Traumatic causes of SAH	
Vascular – Ruptured Aneurysms	70 – 75 %
AV Malformations	5 %
Haemorrhage from Tumours	Rare
Pituitary Apoplexy	Rare
Vasculopathy–Collagen vascular disease	Rare
Amyloid angiopathy	Rare
Arterial dissection	Rare
Haematological – Anticoagulant Treatment	Rare
Leukaemia	Rare
Coagulopathy (Liver disease)	Rare
Drugs – Ephedrine, Cocaine, Amphetamine	Rare
Undefined	15 %

Clinical features

Ruptured aneurysms present as subarachnoid haemorrhage. Sentinel symptoms like headache, retro-bulbar pain and nuchal pain and are seen in 60-70% of patients before rupture.Some patients however have a minor bleed before the major haemorrhage. This is associated with mild headache, nausea and vomiting. These sentinel bleeds occur in 40 – 50 % of cases of SAH and are usually seen 2 – 8 weeks prior to the major haemorrhage[6,7]. Only 49% of unruptured aneurysms were symptomatic[8]. Neurological symptoms of unruptured aneurysms are given in table 2.

Table 2 : Neurological symptoms of unruptured aneurysms	
Acute Symptoms (17 %)	
Headache	~ 37 %
Cerebral ischaemia	~37 %
Seizures	~18 %
Cranial neuropathies	~12 %
Chronic Symptoms (32 %)	
Headache	51 %
Visual defects	29 %
Weakness	11 %
Facial pain	9 %

The severity of symptoms in SAH is related to the severity of the bleed. The most common and classical symptom of aneurysmal SAH is a severe headache of sudden onset (Thunderclap headache). A period of loss of consciousness or epileptic seizures may immediately follow. Nausea and vomiting occur commonly. The headache is acute in onset, peaks rapidly and persists for days in spite of treatment. In some patients, neck pain may predominate over other symptoms. Fifty percent of patients suffering from SAH have nuchal rigidity due to meningeal irritation by the blood. It develops 3 – 12 hours after the SAH. The Kernigs sign may also be positive. Examination of the fundus may reveal papilloedema as well as retinal, pre-retinal or subhyaloid haemorrhages. Visual symptoms may occur due to SAH from ACOM aneurysms while rupture of PCOM aneurysms cause third cranial nerve palsy. Diabetes insipidus and hypothalamic dysfunction may be seen in patients with ruptured ACOM aneurysms. A reactive systemic hypertension may develop even in previously normotensive individuals and the BP may take several days to return to normal levels. A severe fluctuating pyrexia may reflect ischaemic hypothalamic damage. SAH is a true medical emergency. 10 – 15 % of patients suffering from SAH die before reaching the hospital. About 40 % die within 30 days[9]. Of all patients suffering from SAH, roughly one third die acutely, one third survive with significant neurological deficits and one third recover well[10].

Clinical grading of SAH

Botterell in 1956 introduced a system for grading patients after SAH to facilitate assessment of surgical risk, prediction of outcome and prompt evaluation of the patient's condition. This system was modified in 1968 by Hunt and Hess to include a provision for the effect of serious systemic illness[11] (Table-3). When there is any associated serious systemic illness like hypertension, diabetes, COPD or angiographically-demonstrated vasospasm, the patient is placed in the next less favourable Hunt and Hess grade.

Table 3: Hunt and Hess clinical grading of SAH		
Grade	Description	Mortality
Grade 0	Unruptured aneurysm	0
Grade 1	Asymptomatic or minimal headache with normal neurological examination	2 %
Grade 2	Moderate to severe headache, nuchal rigidity, no other neurological deficit other than cranial nerve palsy	5 %
Grade 3	Lethargy, confusion or mild focal deficit	15-20 %
Grade 4	Stupor, moderate to severe hemiparesis, early decerebrate rigidity, vegetative disturbances	30-40 %
Grade 5	Deep coma, decerebrate rigidity, moribund state	50-80 %

The World Federation of Neurological Surgeons (WFNS)grading scale, based on the GCS was introduced in 1988, demonstrated that the preoperative level of consciousness correlated most directly with outcome[12] (Table-4).

Table 4: WFNS Grading Scale		
Clinical Grade	**GCS Score**	**Motor Deficit**
I	15	Absent
II	14-13	Absent
III	14-13	Present
IV	12-7	Present or absent
V	6-3	Present or absent

Investigative approach to aneurysmal SAH

CT Scan – Any patient suffering from a severe headache of acute onset for the first time in their life should undergo an immediate CT scan of the brain. A subarachnoid bleed will be evident in 95-98 % of patients in the first 24 hours post bleed[13]. This declines to 58 % by the fifth day and to 50 % by the seventh day[14].The location of SAH may give information about the probable aneurysm site (Table-5).

Table – 5: Correlation of CT scan location of SAH and site of aneurysm	
Location of SAH on CT Scan	**Probable site of ruptured aneurysm**
Anterior Interhemispheric fissure	ACA aneurysm
Distal Interhemispheric fissure	Distal ACA aneurysm
Unilateral sylvian fissure	MCA aneurysm
Suprasellar cisterns	ICA aneurysm
Interpeduncular cistern	Basilar top aneurysm
Prepontine/Cerebellopontine cisterns	Basilar trunk/Vertebrobasilar aneurysm
Isolated intraventricular bleed	Distal PICA aneurysm, Basilar top aneurysm, Post.superiorly directed ACOM aneurysm
Frontal ICH	A1, ACOM, M1, IC bifurcation aneurysm
Temporal ICH	MCA aneurysm

Fischer et al have graded subarachnoid haemorrhage based on the CT scan appearance (Table-6) and this can be used to predict the outcome of patients with SAH[15]. The amount of blood in the subarachnoid space directly correlates with the risk of vasospasm with Fischer grade 3 SAH carrying the highest risk.

Table 6: Fischer Grading of SAH based on CT scan appearance	
Grade 1	No detectable blood on CT scan
Grade 2	Diffuse thin SAH (vertical layers < 1 mm thickness)
Grade 3	Localised clot / thick SAH (vertical layers > 1 mm thickness)
Grade 4	Intraventricular / Intracerebral clot with diffuse or no SAH

Lumbar Puncture

CT scan is often considered the investigation of first choice since it has a high sensitivity for detecting SAH. A lumbar puncture is indicated when a clinical diagnosis of SAH has been made and CT scan turns out to be negative. It is usually done 6 – 12 hours after SAH to allow formation of haemoglobin metabolites. CSF that is uniformly blood stained when collected in four separate tubes is highly suggestive of SAH. If the lumbar puncture is done a few days after SAH, CSF analysis will reveal xanthochromia, RBC's, WBC's and bilirubin. A sentinel bleed can be ruled out and a favourable outcome expected if both CT scan and CSF results are negative after a history of severe headache of sudden onset.

Cerebral Angiography

Four vessel catheter angiography is the gold standard for detection of aneurysms. It gives the exact location, size and configuration of the aneurysm with good visualisation of the neck. It establishes the cause of SAH in 85 % of cases. Cerebral angiography does not delineate thrombosed aneurysms. The procedure carries a complication rate of 7 %, the majority being puncture site haematomas.

CT Angiography

This is a rapid, non-invasive technique for the detection of aneurysms. The procedure has a sensitivity of 95-100% for detecting aneurysms of over 5 mm in size. The sensitivity is significantly lesser in detecting aneurysms of less than 5 mm in size[16]. CT angiography is less effective in detecting mild to moderate vasospasm and is not useful in patients whose aneurysms have already been clipped or coiled because of artefacts. CT angiography in combination with catheter angiography can demonstrate intraluminal thrombosis in aneurysms, calcification of the aneurysmal wall and its relationship to intracerebral haemorrhage and bony landmarks.

MRI Scan / MR Angiography

MR angiography is useful in demonstrating the size and shape of the aneurysm and its relationship to important structures, the amount of clot inside the aneurysmal lumen and any recent or old haematomas. MR angiography has a sensitivity of 85-100 % in detecting aneurysms over 5 mm in size. This falls to 56 % for aneurysms smaller than 5 mm[17]. MR angiography does not require ionizing radiation or radiocontrast and hence is safe to use in pregnant women.

MRI scans performed several days after the bleed may provide greater sensitivity than CT scans in detecting small areas of subarachnoid clot and help determine the particular lesion responsible in patients with multiple aneurysms. MRI scans are also useful in the detection of arteriovenous malformations of the brain and spine resulting in SAH.

Management of SAH

Mortality following SAH is high even in those patients reaching hospitals with adequate facilities to manage these cases. Approximately 10 % die before reaching the hospital and 25 % die in the first 24 hours[18]. The main causes of death are re-bleeding, vasospasm induced ischaemia, raised ICP, acute hydrocephalus, intra-cerebral haemorrhage, myocardial ischaemia, cardiac arrhythmias, pulmonary oedema and respiratory failure. The Hunt & Hess or WFNS score at admission is the most important predictor of outcome and mortality.

Patients with SAH have to be managed in intensive care units by trained nurses in hospitals with adequate expertise to treat these cases. The ICU's should be dimly lit since most of these patients suffer from photophobia. Complete bed rest is an essential part of the management of these cases. Sedatives may be given to control agitation and analgesics administered for treating headache. Laxatives should be prescribed to avoid straining at stools. Pneumatic compression devices and TED stockings may be used for DVT prophylaxis.

SAH adult patients require 3000 to 4000 ml of fluids to maintain normovolaemia. In addition to hypovolaemia, these patients also demonstrate hyponatremia, hypokalemia, hypocalcemia and hypomagnesemia. Hypomagnesemia may be associated with vasospasm and poor outcome. A large placebo controlled trial of treatment with a continuous infusion of magnesium sulphate suggested that the administration of magnesium may reduce delayed cerebral ischaemia by 34 % and decrease poor outcome at 3 months by 23 %[19]. Hyponatremia, which occurs due to release of atrial natriuretic peptide from the hypothalamus, should be corrected with normal or hypertonic saline.

Hypothalamic disturbances following SAH result in elevated levels of catecholamines and renin which causes arterial hypertension. Moderate hypertension with a MAP of less than 120 mm Hg need not be treated. Control of pain and agitation may be sufficient to lower the blood pressure in these patients.

Following SAH, responsiveness of the cerebral vasculature to changes in CO_2 tension is usually preserved. However SAH interferes with cerebral autoregulation. The main CNS complications following SAH are seizures and hydrocephalus.

The incidence of seizures in patients with SAH is 3 – 26% and usually occurs during the first 24 hours. The associated rise in blood pressure may precipitate re-bleeding from the aneurysm. Patients who have lobar intra-cerebral haemorrhage or a thick layer of cisternal blood have the highest risk of developing seizures. Other risk factors are given in Table 7.

Table-7 :Risk factors for developing seizures in SAH
Re-bleeding
Vasospasm and delayed ischaemic deficit
MCA aneurysms
Subdural Haemorrhage
Intraparenchymal haematoma
Cerebral infarction
Medical hypertensive disease
Chronic neurological impairment

What is more disturbing is the development of non-convulsive seizures in stuporous patients which can be detected only by EEG monitoring. Hence it is common practice to provide seizure prophylaxis in these patients with fosphenytoin or levetiracetam, since phenytoin administration is associated with a worsened cognitive function at 3 months post SAH.

Acute hydrocephalus is seen in 20 – 30 % of patients with SAH and usually occurs within 72 hours of the bleed. A communicating hydrocephalus is due to blood clot within the basal cisterns and obstruction of the arachnoid villi. An obstructive hydrocephalus is due to a blood clot within the ventricular system. Associations of acute hydrocephalus are given in Table 8.

Table – 8: Associations of acute hydrocephalus in SAH
Early onset of lethargy and coma
Lower WFNS grade
Higher Fischer grade
Thicker subarachnoid clot
Intraventricular haemorrhage
Alcoholism
Female gender / Elderly
Larger aneurysms
Medical Hypertensive disease
Meningitis

Symptoms of acute hydrocephalus include headache, impaired consciousness, dementia, incontinence and gait ataxia. Subacute hydrocephalus occurs a few days after the bleed and is characterised by a gradual decline in the sensorium. Delayed hydrocephalus occurs weeks to months after the bleed and the main manifestation is subacute dementia. Acute hydrocephalus resolves spontaneously in most patients. However some may require temporary CSF diversion (EVD insertion). There is however a risk of re-bleeding on sudden decompression of the ventricle. Predictors of the requirement of shunting include a lower WFNS grade, intra-ventricular haemorrhage and re-bleeding. Delayed hydrocephalus develops in 25 % of SAH survivors and is treated by permanent shunting.

Raised ICP following SAH causes a depression in the sensorium. The causes include cerebral oedema, intra-cerebral haematoma, intra-ventricular haematoma and hydrocephalus. Raised ICP is managed by head end elevation, fluid balance, antioedema measures, correction of hyponatremia, prevention of hypoventilation and hypocapnia and treatment of fever and agitation. Specific measures include evacuation of intra-cerebral haematoma and temporary or permanent shunting for hydrocephalus.

Re-bleeding after the initial SAH is one of the main causes of neurological deterioration in these cases. It is usually more severe than the original bleed. The size of the re-bleed haematoma is the most important factor determining outcome. Other indicators of a poor prognosis are a marked midline shift, a large subdural haematoma, intra-cerebral haematoma and intra-ventricular haemorrhage. Re-bleeding is characterised by deterioration in the level of consciousness, development of focal neurological deficits like hemiplegia and aphasia, hypertension, bradycardia, irregular breathing and presence of haemorrhages on fundoscopic examination. Factors predisposing to re-bleeding include the female gender, elderly patients, systemic hypertension, abnormal clotting parameters, posterior circulation aneurysms, increased time to treatment, intra-cerebral and intra-ventricular haematomas and large volume of blood in the sub-arachnoid space after the initial bleed. Approximately 20 – 30 % of SAH patients re-bleed within the first 30 days and upto 50 % by 6 months. The definitive prevention of re-bleeding is by early aneurysm clipping or endovascular coiling (within 24 – 48 hours of SAH). Systolic hypertension and interventions that cause an increase in the transmural pressure gradient (TMPG) should be avoided. These patients are usually on nimodipine for vasospasm and this has to be taken into consideration when adding an infusion of labetalol or esmolol for BP control. Hypotension, which can lead to cerebral ischaemia in the presence of vasospasm, should be avoided at all costs.

Antifibrinolytic drugs like tranexamic acid reduce the rate of re-bleeding following SAH. There is however an increase in the incidence of cerebral ischaemia and infarction. Currently it is recommended to administer a short course of antifibrinolytic therapy in combination with early definitive treatment of the aneurysm. Management of re-bleeding after SAH is designed to maintain CPP, limit ICP, decrease intracranial volume, control systemic BP, reduce TMPG across the wall of the aneurysm and maintain cerebral oxygen delivery.

Vasospasm is a dreaded complication following SAH and mainly affects the larger conducting arteries in the sub-arachnoid space. It is induced by the breakdown products of red blood cells in clots. It causes ischaemic deficits and cerebral infarction and is a major cause of disability and death. The incidence of vasospasm peaks between the 4th and 9th day after SAH and subsequently decreases. Vasospasm is suspected by the appearance of new focal neurological deficits and progressive impairment in the level of consciousness and is usually seen four days after the initial SAH and which cannot be linked to a structural or metabolic cause.

Transcranial Doppler studies reveal blood flow velocities > 120 cm / sec which correlates with angiographically demonstrated vasospasm. A rapid

increase in blood flow velocity of 50 cm / sec from baseline in 24 hours also indicates development of vasospasm. A peak flow velocity of 140 – 200 cm / sec indicates moderate vasospasm while values > 200 cm / sec indicates severe vasospasm. Cerebral angiography is the most reliable investigation for diagnosing and evaluating vasospasm. Angiographically severe vasospasm is defined as a reduction in the diameter of the arterial lumen by > 50 %. Xenon enhanced CT demonstrates decreases in regional blood flow in patients with vasospasm. Jugular bulb oximetry detects an increase in AV DO2 as early as 24 hours before vasospasm sets in and a decreasing value reflects the patient's response to treatment. Positron Emission Tomography(PET) may be used to measure CBF and shows a fall in CMRO2 after SAH. Single Photon Emission Computed Tomography (SPECT) may reveal regions of hypoperfusion associated with vasospasm.

The definitive treatment of vasospasm involves early clipping or coiling of the aneurysm. If the surgical modality is used, fresh clot may be removed by irrigation and suction. Recombinant TPA may be instilled to remove residual clot keeping in mind that normal clot may also get lysed causing re-bleeding.

The prophylactic use of nimodipine is universally accepted in the prevention of development of vasospasm following SAH. Enoxaparin in a dose of 20 mg / day has been shown to improve overall outcome at one year after SAH. Statins like simvastatin and pravastatin have been shown to reduce vasospasm and associated mortality.

Hypertensive Hypervolaemic Haemodilution (Triple-H therapy) is used to augment perfusion in the vasospastic areas of the brain. Crystalloids are infused to attain a CVP of 10 – 12 mm Hg. Haemodilution to a haematocrit of 30 – 35 % helps to improve blood flow through the cerebral microvasculature. An infusion of vasopressor drugs like dopamine or phenylephrine maybe required to increase the blood pressure, the target being 120 – 160 mm Hg before the aneurysm is clipped or coiled and then a higher level of 160 – 200 mm Hg afterwards. The complications of Triple-H therapy are given in Table 9.

Table-9 Complications of Triple-H therapy
Re-bleeding
Haemorrhagic transformation of infarct
Cerebral / Pulmonary oedema
Raised intra cranial pressure
Hypertensive encephalopathy
Myocardial Infarction
Congestive cardiac failure
Dilutional hyponatremia
Coagulopathy
Complications of CVP access

In transluminal balloon angioplasty, the vasospastic segment is selectively catheterised and dilated. Selective intra-arterial injection of vasodilators like verapamil, nimodipine, nicardipine and papaverine may be done. The last drug is falling out of favour since it is neurotoxic.

Cardiac abnormalities following SAH include T-wave inversion, ST segment depression, U waves, QT prolongation and prominent Q waves in the ECG. Rhythm disturbances include PVC's, Sinus bradycardia, Sinus tachycardia, AV blocks, Atrial ectopics, Atrial fibrillation, Brady/Tachyarrythmias, Ventricular tachycardia and Ventricular fibrillation. They are usually seen during the first 7 days following SAH with a peak occurrence on the 2nd and 3rd day. Cardiogenic pulmonary oedema may also be seen in some cases.

Medical complications are responsible for 25 % of all deaths following SAH out of which 50 % are due to pulmonary causes. Pulmonary complications following SAH include neurogenic pulmonary oedema, pneumonia, ARDS and pulmonary embolism. Hepatitis and hepatic failure are seen in 25 % of cases, renal dysfunction in 8 % of cases and thrombocytopaenia in 4 % of cases following SAH. Gastrointestinal bleeding is seen in 5 % of cases of SAH and should be suspected if unexplained hypotension and tachycardia occur.

Management of Aneurysms: 85 % of all intracranial aneurysms originate in the anterior circulation and 10 % in the vertebro-basilar (Posterior) circulation. About 4% of aneurysms arise from the superior cerebellar artery and anterior inferior cerebellar artery. The common locations of aneurysms are given in Table – 10.

Table – 10 Common locations of intra-cranial aneurysms	
Location	Incidence
ACOM	~ 30 %
Junction of ICA and PCOM	~ 25 %
Bifurcation of MCA	~ 20 %
Bifurcation of ICA	~ 7.5 %
Basilar artery bifurcation	~ 7 %
Pericallosal-Callosomarginal artery Junction	~ 4 %
Origin of PICA	~ 3 %

Ruptured intracranial aneurysms should be treated as soon as possible after the haemorrhage to prevent re-bleeding and provide adequate medical treatment of vasospasm. Aneurysms can be managed surgically by clipping or endovascularly using Gugliemi Detachable Coils (GDC). Patients with large intra- parenchymal haematomas (> 50 ml) and MCA aneurysms benefit from clipping[20]. Early surgical clipping allows removal of blood clots from the sub-arachnoid space and the safe institution of Triple H therapy (Fig 1,2,3) .

Table-11 Indications for endovascular coiling
Age > 70 Years
Aneurysm is not amenable to surgical clipping
Patient is unable to tolerate surgery
Poor clinical grades (WFNS IV / V)
Basilar top aneurysm
Partially clipped aneurysm
Patient refusal for surgery

Fig 1: Aneurysm clips and applicator

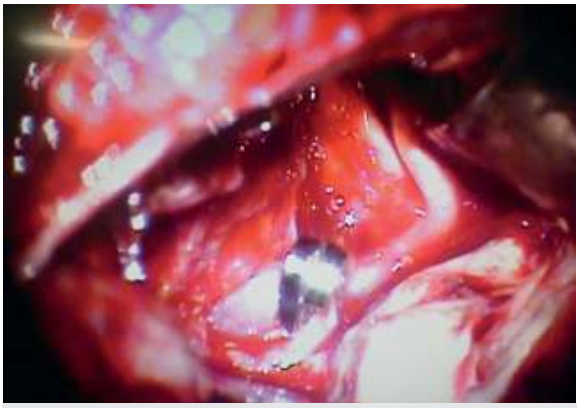

Fig 2: Clipped ACOM aneurysm

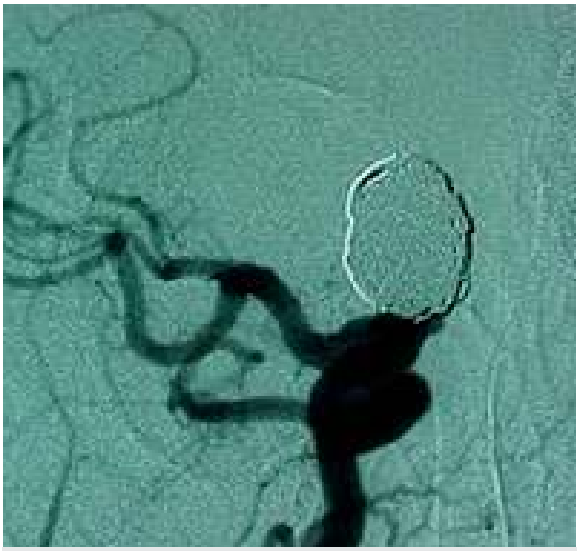

Fig 3: Coiled ICA aneurysm

The goal of endovascular coiling is to fill the aneurysmal lumen with Gugliemi Detachable Coils (GDC) which then initiates secondary thrombosis of the aneurysm. These are soft platinum coils which are placed inside the aneurysm. The coils are threaded through a micro-catheter placed in the aneurysmal lumen through the femoral artery. If the aneurysm is amenable to both clipping and coiling, coiling should be preferred. Elderly patients, patients with poor WFNS grades (IV and V) and those with a basilar top aneurysm benefit from endovascular coiling[20]. Broad necked aneurysms may be managed with balloon remodelling techniques and using bioactive coils which promote complete neck endothelialisation.

The complications of endovascular coiling include aneurysmal perforation, thromboembolic events and occlusion of the parent vessel from coil herniation. New technologies like enhanced coil construction, intracranial stents, balloon remodelling and two catheter techniques have evolved to enhance safety during endovascular coiling.

The management of aneurysmal SAH has changed considerably since the publication of the International Subarachnoid Aneurysm Trial (ISAT)[21]. This is a randomized controlled trial which compared endovascular coiling with surgical clipping in patients with ruptured aneurysms who were suitable for either treatment. A total of 2143 patients with ruptured intracranial aneurysms were included in the study. Primary outcome was death or dependence at 1 year. Secondary outcomes included re-bleeding from the treated aneurysm and risk of seizures. 23.5 % of patients (250 / 1063) allocated to endovascular coiling were dead or dependant at 1 year compared to 30.9 % of patients (326 / 1055) allocated to neurosurgery, an absolute risk reduction of 7.4 % (p=0.0001). The early survival advantage was maintained up to 7 years (p=0.03). The risk of epilepsy was substantially lower in patients allocated to endovascular treatment, but the risk of re-bleeding was higher. There were 13 re-bleeds from the treated aneurysms on long term follow up out of which 10 were in the endovascular group and 3 in the neurosurgical group (p=0.06)[22]. ISAT was criticised on a number of factors mainly related to the randomisation of the patient population. The patient population was on average younger and the majority had aneurysms under 10 mm and in the anterior circulation. In order to address these criticisms, a new randomised multi-centric trial (ISAT 2) is currently under way.

Anaesthesia for surgical clipping of aneurysms

Anaesthesia in these patients should ensure the preservation of adequate cerebral perfusion and oxygenation, avoidance of sudden changes in blood pressure and ICP, satisfactory surgical exposure and prompt emergence for early neurological assessment. Pre-operative evaluation of these patients includes a review of the radiological investigations, detailed history and a focused neurological examination. The relationship between hypotension and appearance of symptoms of neurological deterioration should be evaluated. The fluid and electrolyte balance and the cardiac function should be assessed. The patient's drug regimen should be evaluated.

Premedication in these patients includes drugs to reduce gastric acidity and prokinetic agents like metoclopramide. Calcium channel blockers, anticonvulsants and steroids should be continued in the perioperative period. Sedatives, hypnotics, anxiolytics and opioids are generally avoided since they may cause respiratory depression and mask neurological deterioration.

Monitoring in the perioperative period includes the usual monitors along with direct arterial blood pressure, central venous pressure, PCWP (if indicated), Trans-oesophageal echocardiography, Trans-cranial Doppler, Electroencephalogram, Jugular venous oximetry and arterial blood gases. The exact combination of monitoring may be selected based on requirement and availability.

Two large bore intravenous cannulae should be inserted and checked for free flow. A femoral venous sheath may be inserted in addition for rapid replacement of large volumes. During induction of anaesthesia, the hypertensive response to laryngoscopy and intubation should be blunted in all patients using adequate depth of anaesthesia, Beta-blockers [Esmolol (0.5 mg/Kg); Metoprolol (2-5 mg); Labetalol (2.5-5.0 mg/Kg)] or additional doses of Propofol (1-2 mg/Kg), Fentanyl (3-5 mcg/Kg), Lignocaine (1.5 mg/Kg) or Midazolam (0.1-0.2 mg/Kg).Sevoflurane or Isoflurane may be introduced to deepen the plane of anaesthesia before laryngoscopy. Other maneuvers that increase the blood pressure include application of skull pins, positioning for surgery and elevation of the bone flap.

Mild hypotension can be used in good grade patients (WFNS Grades 0, I, II) during induction since their ICP is usually not elevated and there is no evidence of cerebral ischaemia. It should be avoided in poor grade patients (WFNS Grades IV, V). Good grade patients may be ventilated normally, but poor grade patients with elevated ICP benefit from moderate hyperventilation to a pCO_2 of 30 mm Hg.

Maintenance of anaesthesia may be done with intravenous or inhalational agents or a combination of the two. An infusion of Fentanyl (bolus 25-50 mcg followed by an infusion of 1-2 mcg / Kg / Hr) may be combined with an infusion of Propofol (40-60 mcg/Kg/mt) and/or an inhalational agent like sevoflurane or isoflurane. Thiopentone at a dose of 3 mg/Kg/hr may be used in the presence of a tight brain. However its use is associated with delayed recovery and difficulty in early neurological assessment. Sevoflurane has minimal effects on cerebral haemodynamics and ICP. Isoflurane and desflurane can increase ICP when used at higher concentrations. Nitrous oxide is avoided in patients with poor intracranial compliance as it can further increase the ICP.Muscle relaxants that have minimal effect on cerebral haemodynamics like vecuronium, rocuronium and cis-atracurium may be used for intubation and maintenance.

In order to achieve brain relaxation to facilitate surgical access to the aneurysm, various measures may be adopted. These include moderate hyperventilation to a pCO_2 of 30-35 mm Hg (unless vasospasm is present), Mannitol at a dose of 0.25-1.0 GM/Kg (given after the dura is opened), Furosemide at a dose of 0.25-1.0 mg/Kg (potentiates mannitol), drainage of CSF through a lumbar sub-arachnoid catheter and using total intravenous anaesthesia (TIVA).

Patients with SAH are hypovolaemic and require more fluids compared to a patient with an unruptured aneurysm. Normovolaemia should be maintained in good grade patients till the aneurysm is clipped and then Triple-H therapy guided by invasive monitoring of the volume status should be instituted. Dextrose containing solutions are generally avoided since ischaemic deficits are exacerbated by hyperglycaemia. Ringers lactate is hypotonic to plasma and can contribute to cerebral oedema, hence it should be avoided. Blood and blood products should be utilized to maintain a haematocrit of 30 – 35 %. Blood should be available in the operation theatre before the dissection of the aneurysm starts. Hetastarch can interfere with haemostasis and might cause intracranial bleeding.

Good grade patients may be reversed and extubated at the end of the procedure taking care to avoid coughing, straining, hypercapnia and hypertension. Hypertension in the immediate post-operative period, unless existing before surgery, usually returns to normal within 12 hours. The various reasons for post-operative hypertension include pain, urinary retention and hypercapnia secondary to residual anaesthesia. The blood pressure should be maintained 10-20 % above preoperative values in patients at risk of developing delayed ischaemic deficits. The blood pressure of patients whose aneurysms have been wrapped rather than clipped should be maintained within 20 % of their normal range during recovery from anaesthesia. Patients with poor grades and who have brain swelling or those with intraoperative rupture of their aneurysm should be sedated and electively ventilated post-operatively. If a patient fails to wake up from anaesthesia or develops a new neurological deficit, all administered sedative, analgesic and anaesthetic drugs should be reversed, the pCO_2 normalized and hypoxia and hyponatremia ruled out or treated. If the patient still doesn't recover, an urgent CT scan should be ordered to diagnose a haematoma, hydrocephalus, pneumocephalus, cerebral infarct or cerebral oedema.

Most modern neurosurgeons prefer to avoid induced hypotension during dissection of the aneurysm because of increased incidence of vasospasm, cerebral ischaemia, infarcts and post-operative neurological deficits. Induced hypotension is however indicated if the aneurysm ruptures during dissection in order to gain control of the parent vessel. Use of induced hypotension could lead to increased risk of early and delayed neurological deficits[23,24]. Induced hypotension is relatively contraindicated in the presence of cerebrovascular occlusive disease, coronary artery disease, renal dysfunction and anaemia.

Temporary proximal clipping of the parent artery of the aneurysm may be used to reduce the risk of rupture during dissection. Blood flow in the collateral blood vessels may be enhanced during temporary (if required for > 120 seconds) by maintaining the patient's blood pressure in the high normal range. An infusion of dopamine or phenylephrine may be used for achieving this. The duration of temporary occlusion should be less than 20 minutes in order to minimize the risk of cerebral ischaemia and infarction, cerebral oedema and damage to the parent artery. A dose of Propofol or Thiopentone may be administered to achieve EEG burst suppression immediately before temporary occlusion. Mannitol may also be administered to reduce the incidence of cerebral oedema. None of the pharmacological agents

used for cerebral protection have been shown to improve neurological outcome in these patients.

Mild hypothermia (32-34°C) during surgery is not associated with a beneficial effect in mortality or neurological outcome among patients with good grade SAH[25]. In addition, intraoperative hypothermia had no beneficial effects on neuro-psychological function after SAH[26]. Intra-operative hyperglycaemia is associated with long term decline in cognition and gross neurological function[27].

The incidence of aneurysm rupture during induction of anaesthesia is 0.5 – 2.0 % while intraoperative rupture occurs in 6 – 18 %. The causes of intraoperative rupture include aneurysmal dissection, brain retraction, haematoma evacuation and dural opening. Aneurysm rupture during induction of anaesthesia and surgical dissection of the aneurysm carries a very high mortality and morbidity because of cerebral ischaemia from hypotension and attempts to clip the aneurysm on an urgent basis. Rupture during induction is associated with a sudden rise in ICP and systemic hypertension with or without bradycardia. A ruptured aneurysm is treated by normalizing the intravascular volume using crystalloids, colloids or cross matched blood, maintaining cerebral perfusion, controlling ICP and reducing bleeding by lowering the systemic BP. Definitive surgical repair should be carried out immediately and the aneurysm clipped after reducing the MAP to 40-50 mm Hg or using temporary proximal and distal occlusion of the parent vessel.

Anaesthesia for endovascular coiling of aneurysms

Patients undergo endovascular coiling in catheterization laboratories that are often located in remote areas of the hospital. The anaesthetist must be familiar with the intervention planned for the patient as well as the anticoagulation plan (degree, duration and timing of reversal). The baseline renal function should be evaluated as IV contrast will be used. The anaesthetist should also be ready to provide intra-procedural hypotension, hypertension and hypercapnia when required. Intravenous access and monitoring should be similar to that used in the neurosurgical operation theatre. Direct arterial BP monitoring is mandatory if manipulation of the blood pressure is anticipated.

The patient should be given a comfortable pillow and pressure points should be padded if conscious sedation is used since they may have to stay immobile for long periods of time. The main advantage of conscious sedation is that it allows the physician to perform periodic neurological examinations. Conscious sedation is also used to check adequacy of collateral circulation during trial balloon occlusion of parent vessel in patients with giant aneurysms. This is followed by trapping the aneurysm by coiling the parent vessel both proximal and distal to the aneurysm. General anaesthesia negates patient movement and improves image quality on radiological screening. Since access to the airway is difficult once the procedure starts, it is important to intubate the patient beforehand.

Induction and maintenance of anaesthesia is similar to that described for aneurysm clipping. Total intravenous anaesthesia may be used if the ICP is elevated. The systemic BP should be adjusted to maintain CPP and wide swings that can cause the aneurysm to rupture, should be avoided. Use high normal levels of blood pressure if the patient has vasospasm. Heparin should be given at the start of the procedure and reversed once it ends. This will help prevent thromboembolic events.

If the patient has a perforation during the procedure, it may manifest as headache, nausea, vomiting, systemic hypertension, bradycardia and change in the level of consciousness. This should be immediately treated with protamine (to reverse the heparin) and then maintaining the blood pressure in the normal range. Since aggressive treatment of hypertension may induce ischaemia, only extreme elevations should be treated. Platelets may be transfused if the patient is on aspirin, clopidogrel or glycoprotein IIb / IIIa receptor antagonists. If occlusive problems like thromboembolism or vasospasm develop, deliberate hypertension guided by neurological examination with or without direct thrombolysis or angioplasty to improve distal perfusion, should be undertaken.Other measures include volume expansion, head up tilt, hyperventilation, diuretics, anticonvulsants, mild hypothermia, cerebral protection and cerebral vasodilators.

Conclusion

The perioperative management of intracranial aneurysms has evolved over the past decades with advances in endovascular coiling and management of subarachnoid haemorrhage. Evidence based recommendations published by the American Heart Association and the American Stroke Association (most recently updated in 2012) have resulted in standardisation of the management of aneurysmal SAH[20]. The initial Hunt & Hess or WFNS score is a good indicator of the outcome following aneurysmal SAH. Since re-bleeding is associated with high mortality, all measures should be taken to prevent it.

Recovery following treatment of an intracranial aneurysm depends whether it has bled or not and the type of treatment administered. For patients with ruptured aneurysms, the hospital stay and recovery is typically stormy compared to unruptured aneurysms. Endovascular therapy, being less invasive compared to surgical clipping, is associated with a shorter hospital stay and a more rapid return to previous activities. Because of the higher risk of recurrence of aneurysms following endovascular therapy, these patients have to undergo follow up angiography at periodic intervals. Many of the patients recovering from SAH go on to develop mood disorders like depression and anxiety and this should also be addressed.

References

1) Linn FH, Rinkel GJ, Algra A. Incidence of subarachanoid haemorrhage: Role of region, year and rate of computed tomography: A metaanalysis. Stroke. 1996; 27(4): 625 – 39.

2) De Rooij NK, Linn FH, Van Der Plas JA. Incidence of subarachanoid haemorrhage: A systemic review with emphasis on region, gender and time trends. J Neurol Neurosurg Psychiatry. 2007; 78: 1365 – 72.

3) Fogelholm R. Subarachanoid haemorrhage in middle Finland. Incidence, early prognosis and indications for neurosurgical treatment. Stroke. 1981; 12: 296 – 301.

4) Ingall T, Asplund K, Mahonen M. A multinational comparison of subarachanoid haemorrhage epidemiology in the WHO MONICA stroke study. Stroke. 2000; 31: 1054 – 61.

5) Bhagwati SN. Incidence of subarachanoid haemorrhage from aneurysmal rupture in India. Neurol Med Chir (Tokyo); 1998; 38: 128 – 30.

6) Leblanc R. The minor leak preceding subarachanoid haemorrhage. J Neurosurg. 1987; 66: 35 – 39.

7) Okawara SH. Warning signs prior to rupture of an intracranial aneurysm. J Neurosurg. 1973; 38: 575 – 580.

8) Raps EC, Roger JD, Galetta SI. Clinical spectrum of unruptured intracranial aneurysms. Arch Neurol. 1993; 50(3): 265 – 68.

9) Broderick JP, Brott TG, Duldner JE. Initial and recurrent bleeding are the major causes of death following subarachanoid haemorrhage. Stroke. 1994; 25: 1342 – 47.

10) Longstretch WT, Nelson LM, Koepsell TD. Clinical course of spontaneous subarachanoid haemorrhage: A population based study in Kings county, Washington. Neurology. 1993;43:712–18.

11) Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. J Neurosurg. 1968; 28: 14 – 20.

12) Drake CG, Hunt WE, Kassel N. Report of world federation of neurological surgeons committee on a universal subarachnoid haemorrhage grading scale. J Neurosurg. 1988; 68: 985 – 86.

13) Kassel NF, Torner JC, Haley EC. The international cooperative study on the timing of aneurysm surgery. J Neurosurg. 1990; 73: 18 – 47.

14) Van Gijn J, Van Dongen KJ. The time course of aneurysmal haemorrhage on computed tomograms. Neuroradiology. 1982; 23: 153 – 56.

15) Fischer C, Kistler J, Davis J. Relation of cerebral vasospasm to subarachnoid haemorrhage visualised by CT scanning. Neurosurgery. 1980; 6: 1 – 9.

16) Vieco PT, Shuman WP, Alsofrom GF. Detection of circle of willis aneurysms in patients with acute subarachanoid haemorrhage. A comparison of CT angiography and digital subtraction angiography. Am J Roentgenol. 1995; 165: 425 – 430.

17) Huston J III, Nichols DA, Luetmer PH. Blinded prospective evaluation of sensitivity of MR angiography to known intracranial aneurysms: Importance of aneurysm size. Am J Neuroradiol. 1994; 15: 1607 – 14.

18) Arboix A, Marti Vilata JL. Predictive clinical factors of very early in hospital mortality in sub arachanoid haemorrhage. Clinical NeurolNeurosurg. 1999; 101: 100 -105.

19) Van den Bergh WM, Algra A, Van Kooten F. Magnesium sulphate in aneurysmal subarachnoid haemorrhage: A randomised controlled trial. Stroke. 2005; 36: 1011 – 1015.

20) E Sander Connolley, Alejandro A Rabinstein, Ricardo Carhuapoma, Colin P Derdeyn, Jaques Dion. Guidelines for the management of aneurysmal subarachnoid haemorrhage. A guideline for healthcare professionals from the American Heart Association / American Stroke Association. Stroke. 2012; 43: 1711 – 1737.

21) Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M. International subarachanoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, re-bleeding, subgroups and aneurysm occlusion. Lancet. 2005 Sep; 366(9488) 809 – 17.

22) Molyneux AJ, Kerr RS, Birks J, Ramzi N, Yarnold J. Risk of recurrent subarachnoid haemorrhage, death or dependence and standardised mortality ratios after clipping or coiling of an intracranial aneurysm in the international subarachanoid aneurysm trial (ISAT): long term follow-up. Lancet Neurol.2009 May; 8(5): 427-33.

23) Farrar JK, Gamache FW, Ferguson GG, Barker J, Varkey GP. Effects of profound hypotension on cerebral blood flow during surgery for intracranial aneurysms. J Neurosurg. 1981; 55: 857 – 64.

24) Hitchcock ER, Tsementzis SA, Dow AA. Short and long term prognosis of patients with a subarachanoid haemorrhage in relation to intraoperative period of hypotension. ActaNeurochir (Wien). 1984; 70: 235 – 42.

25) Todd MM, Hindman BJ, Clarke WR, Torner JC. Intraoperative hypothermia for aneurysm surgery trial (IHAST) investigators. Mild intraoperative hypothermia during surgery for intracranial aneurysm. NEJM. 2005; 352: 135 – 45.

26) Clarke WR, Torner JC. IHAST investigators. Effects of intraoperative hypothermia on neurophysiological outcomes after intracranial aneurysm surgery. Ann Neurol. 2006;60:518 –27.

27) Pasternak JJ, McgGregor DG, Shroeder DR, Laniel WL, Shi Q. IHAST investigators. Hyperglycaemia in patients undergoing cerebral aneurysm surgery: its association with long term gross neurologic and neuropsychological function. Mayo Clin Proc. 2008; 83: 406 – 17.

Review Article

Cerebral Aneurysms

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Abstract

Intra cranial aneurysms are abnormal outpouchings of vessel wall occurring at major vessel bifurcations. Majority of them occur in the anterior circulation and most commonly present with sub arachnoid hemorrhage. Various radiological investigations are presently available to accurately localize the aneurysm and identify the morphology. The 2 major treatment modalities are surgical clipping and endovascular coiling and each have their own merits and demerits. While the treatment mainly focuses on exclusion of the aneurysm from the circulation to prevent recurrent bleed, the other major goal of management is treatment of cerebral vasospasm associated with subarachnoid hemorrhage. Little is known about the pathophysiology of vasospasm and thus the treatment remains mainly symptomatic by raising the blood pressure and adequately hydrating the patient during the peak period of vasospasm. While the surgical clipping of aneurysms is standardized, the endovascular coiling techniques continue to evolve and may be the mainstay of management in the future. Microsurgery would be restricted to a small cohort of patients requiring vascular bypasses. The long term outcome of coiling is a matter of concern as recanalization of previously coiled aneurysms is an issue which has to be worked upon.

Key Words: Aneurysm, Clipping, Endovascular coiling, Vasospasm, Sub arachnoid hemorrhage, Vasospasm

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Introduction

Cerebral aneurysm is defined as an abnormal focal dilatation of a cerebral artery with attenuation of the vessel wall[1].Intracranial aneurysms are generally classified according to their shape as saccular (berry shaped) and fusiform (dissecting, infectious, atherosclerotic and traumatic) aneurysms. They can be solitary or multiple (Fig 1). Saccular aneurysms constitute 90% of all cerebral aneurysms and are located at the major branch points of large arteries[2]. Fusiform aneurysms are elongated outpouchings of arteries and account for 7% of all cerebral aneurysms. Mycotic aneurysms are found peripherally and comprise 0.5% of all cerebral aneurysms.

Aneurysms arising from anterior circulation constitute 85%. Multiple aneurysms are noted in 20-30% of patients[3] (Fig 1b). They present most commonly with subarachnoid haemorrhage (SAH). They may also cause intraparenchymal, intraventricular, or subdural haemorrhage. Giant aneurysms(Figure 2) (size greater than 25 mm in diameter) represent 3-5% of all intracranial aneurysms and present with mass effect and distal thromboembolism (Fig 1a).

Pathogenesis

The basic pathology of aneurysmal formation is defect in the internal elastic lamina with associated elastic defects in the adjacent layers of the tunica media and adventitia. As such, intra cranial vessels lack external elastic lamina which may account for the higher prevalence of aneurysms in this region. Focal turbulence and discontinuity of the normal architecture at vessel bifurcations contribute to occurrence of aneurysms at these locations. Recent evidence suggests that arterial wall proteolysis by matrix metalloproteinases, apoptosis, and chronic inflammation play a key role in the pathogenesis and disease progression of intracranial aneurysms[4,5].

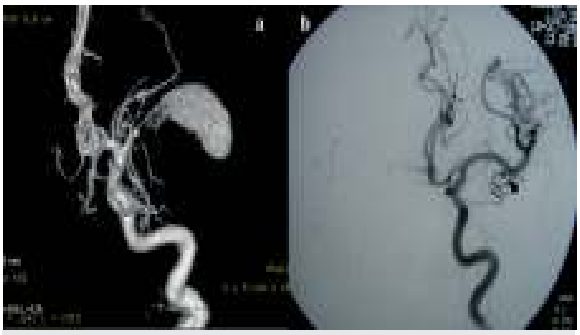

Figure 1 :

a – Large single middle cerebral artery aneurysm seen on a 3D reconstructed CT angiogram image.

b – Multiple aneurysms. The thin arrow points to a distal anterior cerebral artery aneurysm and the short thick arrow points to a left middle cerebral artery aneurysm.

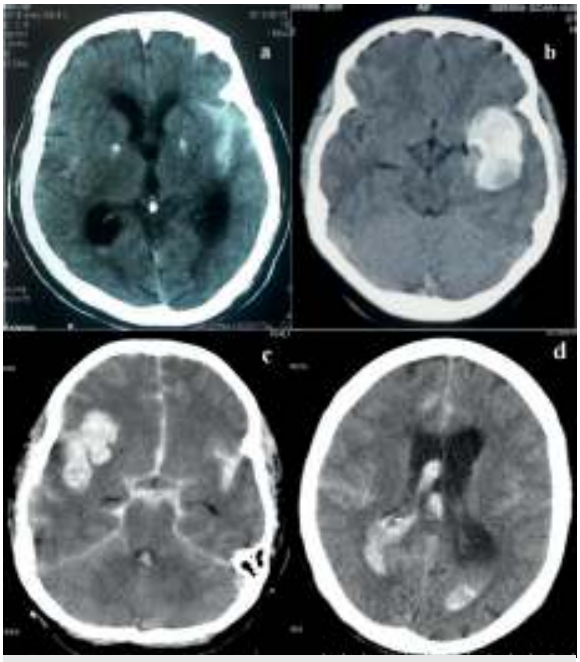

Figure 2 : Subarachnoid hemorrhage.
a – Plain CT showing localized SAH in the left Sylvian fissure.
b – A large intraparenchymal hematoma in the left temporal lobe, caused by a left middle cerebral artery aneurysm.
c – A combination of subarachnoid hemorrhage and intra-parenchymal hematoma arising from a single right middle cerebral artery aneurysm.
d – Intraventricular hemorrhage arising from rupture of an anterior communicating artery aneurysm.

Most aneurysms are developmental and the major contributory factors are atherosclerosis and hypertension. Rarely, aneurysms may be congenital due to collagen deficiency such as seen in fibro muscular dysplasia, Marfan syndrome, Ehlers-Danlos syndrome etc. Adult polycystic kidney disease is one of the co-existing lesion in intra cranial aneurysms[6]. Cigarette smoking increases the ratio of elastase to alpha 1 - antitrypsin levels in cerebral arterial walls, which may contribute to formation or rupture of aneurysm in smokers[7,8].

Mycotic aneurysms are of infective etiology and are most often encountered in infective endocarditis[9]. The seedling of infective vegetation containing pathogens like *Staphylococcus aureus* results in degradation of vessel wall resulting in aneurysmal formation. They are mostly seen in peripheral branches of middle cerebral artery and may be multiple. They have high propensity to bleed due to thin and friable wall than the saccular aneurysms[9].

Other rare causes of aneurysms are trauma, tumor emboli, high flow state like arteriovenous malformation, Moya Moya disease etc.

Risk factors for rupture of aneurysm

The treatment of an unruptured intracranial aneurysm is based on the likelihood of its rupture during the patient's lifetime. The risk factors associated with rupture of aneurysm are aneurysmal size, location, shape, significant family history, multiple aneurysms and prior history of aneurysmal subarachnoid hemorrhage[8].

Aneurysms are historically classified as small (<10 mm), large (10–24 mm), and giant (≥25 mm). Studies have concluded that there is a correlation between aneurysm size and risk of rupture. ISUIA (International Study of Unruptured Intracranial Aneurysms) I 1998 and ISUIA II 2003 have studied the relationship between aneurysm size and risk of rupture and showed that rupture rates are high with larger sizes[10,11]. Clinical and autopsy studies have shown that, aneurysms between 7 and 10 mm size are more likely to bleed, but many are smaller than 7 mm in size; the exact size beyond which an aneurysm becomes "dangerous" is unclear.

Rinkel and colleagues showed that the relative risk for aneurysm rupture was higher for posterior circulation aneurysms like basilar tip, vertebrobasilar and posterior cerebral compared to anterior circulation aneurysms with a relative risk of 4.1%[12,13]. ISUIA studies showed that posterior circulation aneurysms, especially basilar apex aneurysms and posterior communicating (Pcom) artery aneurysms from anterior circulation have a higher relative rupture rate compared to those at other sites (Fig 3).

Studies suggest that aneurysms with irregular morphology, particularly those that are multilobed with daughter domes, are more likely to bleed compared to smooth-walled lesions. Several studies suggest that ruptured aneurysms have higher aspect ratios (aneurysm height/neck width) compared to unruptured aneurysms[13,14].

The aneurysm's risk of rupture is higher and may occur at an earlier age in individuals who have multiple family members with intracranial aneurysms, compared to aneurysms that arise in individuals with no known family history[15].

Several studies showed that multiple unruptured intracranial aneurysms are associated with a higher risk for hemorrhage than solitary lesion[14]. Yasui et al demonstrated an annual rupture rate of 6.8% and Rinkel et al found that the relative risk for rupture is 1.7 in patients with multiple lesions compared to single unruptured intracranial aneurysm[16,17].

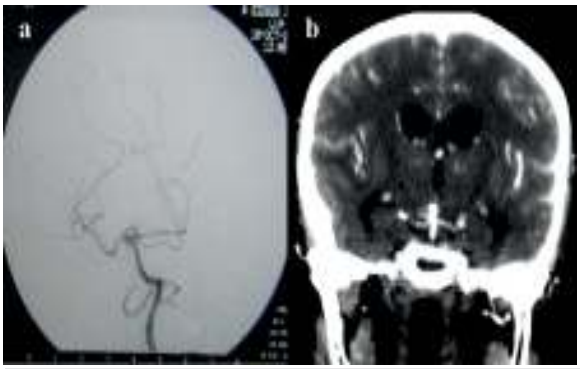

Figure 3 : Posterior circulation aneurysms
a – Digital subtraction angiogram of a right superior cerebellar artery aneurysm.
b – CT angiogram (coronal) of a basilar apex aneurysm.

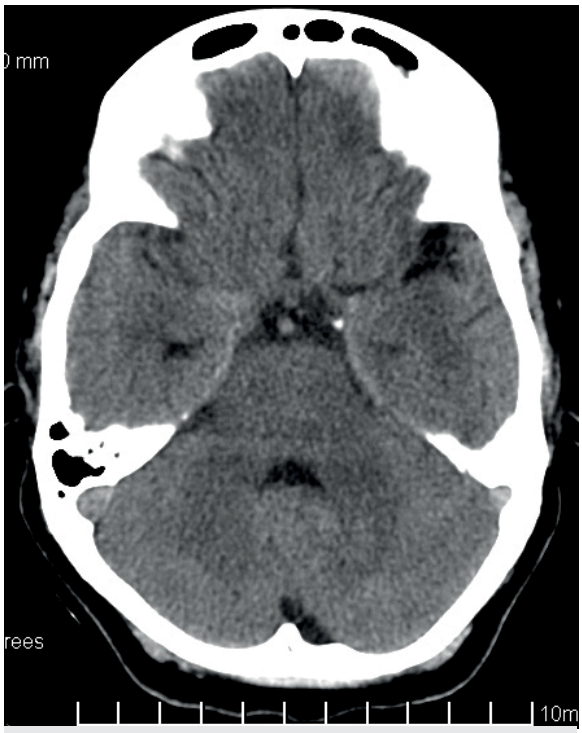

Figure 4:
Very small quantity of SAH seen in the left sylvian fissure. LP was positive for SAH in this case, with crenated RBCs and supernatant xanthochromia.

ISUIA showed that patient with a history of subarachnoid hemorrhage from a different aneurysm had a tenfold increase in the risk of rupture from a small unruptured aneurysm, compared to a patient with no history of subarachnoid hemorrhage[10,11].

The reported mortality of patients in whom subarachnoid hemorrhage is diagnosed is about 40% within the first 30 days. Among those who survive, less than 25% have a good functional outcome[18,19].

The volume of blood escaping during rupture of an aneurysm varies from a negligible amount constituting a "warning leak" to massive amounts (≥150 mL) associated with immediate death (Fig 2c). When the intra cranial pressure equals the mean arterial pressure, temporary circulatory arrest occurs which stops the aneurysmal bleeding. This transient global ischemia causes loss of consciousness as seen in most patients with acute sub arachnoid haemorrhage. Because many patients do not lose consciousness, normal clotting mechanisms may probably also contribute to arrest of the haemorrhage[20].

Clinical presentation

The characteristic presentation of SAH is a sudden, severe headache, as seen in more than 80% of patients, which often is described by the patient as the "worst headache of my life"[21]. Headache is usually associated with vomiting and followed by loss of consciousness. Patients might deteriorate rapidly resulting in death or continue to have altered sensorium. The rapidity of the clinical deterioration and resulting death depends on the severity of the bleed. Patients with minor bleed the sensorium can even improve to normal following the brief episode of loss of consciousness. Other symptoms include seizures, dysphasia, limb weakness, vision loss and double vision[22].

The associated symptoms may give a clue to the location of aneurysms. Bilateral lower limb weakness may be due to aneurysm in the anterior cerebral artery territory. Middle cerebral artery aneurysm may be associated with hemiparesis or dysphasia. Ptosis is seen with aneurysms in the posterior communicating artery or rarely superior cerebellar artery due to direct compression of cisternal part of third nerve by the aneurysm fundus.

Large unruptured aneurysms can cause symptoms due to local mass effect and embolic episodes due to dislodgement of thrombi from the aneurysm. Giant middle cerebral artery aneurysm may cause limb weakness due to embolic infarct in the motor area or internal capsule. Large vertebro-basilar thrombosed aneurysms can present with lower cranial nerve palsy and brain stem symptoms due to direct compression or due to brain stem infarcts.

Fusiform aneurysms mostly arise due to atherosclerotic aetiology[8]. They are most commonly seen in posterior circulation. The entire vessel wall becomes dilated and do not have the neck or fundus as seen in saccular aneurysms. They contain laminated thrombus which may result in thrombo embolic stroke. They rarely cause subarachnoid haemorrhage and typically present with mass effect on brainstem and cranial nerves.

On examination meningismus along with altered sensorium and focal deficits are commonly noted among patients with aneurysmal rupture. Funduscopy might reveal subhyaloid haemorrhage and vitreous haemorrhage (Terson syndrome)[23]. Depending on the GCS and the presence of focal deficits, patients with aneurysmal SAH are graded by WFNS (World federation of Neurological surgeons) grading system and modified Hunt and Hess clinical grading system. The higher the grade, poorer is the prognosis.

Investigations

A plain cranial CT is the investigation of choice in patients with suspected SAH. It has a high sensitivity and can be positive in 92% of the cases, if done on the day of ictus. The sensitivity gradually decreases in the subsequent days due to clearance of blood in the subarachnoid spaces by the CSF. After 1 week, the sensitivity drops to less than 5%[24]. In addition to subarachnoid blood, CT scan can detect intra parenchymal haemorrhage, intra ventricular haemorrhage, cerebral edema, hydrocephalus and infarcts in the parent vessel territory (Fig 2).Fischer's grading helps to estimate the amount of blood in the subarachnoid space and is thus of prognostic value in predicting vasospasm, one of the most adverse side effects of sub arachnoid haemorrhage[25]. Recent studies suggest that the rate of clearance of blood is more important than the amount of blood in subarachnoid space for predicting vasospasm.

Lumbar puncture is indicated if there is strong suspicion of sub arachnoid haemorrhage and Cranial CT is

normal (Fig 4). This can happen when the bleed is negligible or when the patient presents to physician at a later date. Supernatant xanthochromia and presence of crenated RBCs are very reliable signs of sub arachnoid haemorrhage[26]. Uniform blood staining of CSF helps to differentiate sub arachnoid haemorrhage from traumatic tap in which CSF clears in serial drainage.

CT Angiography

CT angiography (CTA) has sensitivities of 77% to 97% and specificities of 87% to 100% for detection of intracranial aneurysms larger than 3mm in maximal diameter[27] (Fig 3a, b). 3D TOF MRA has sensitivity of 87% and specificity of 95%. CTA is less time consuming and provides additional information on the 3-D anatomy of the vessel with respect to the adjacent bony structures. MRA is superior than CTA in follow up imaging of aneurysms treated with coiling due to lesser artefacts. MRI is also essential in imaging large thrombosed aneurysms[28] (Fig 5).

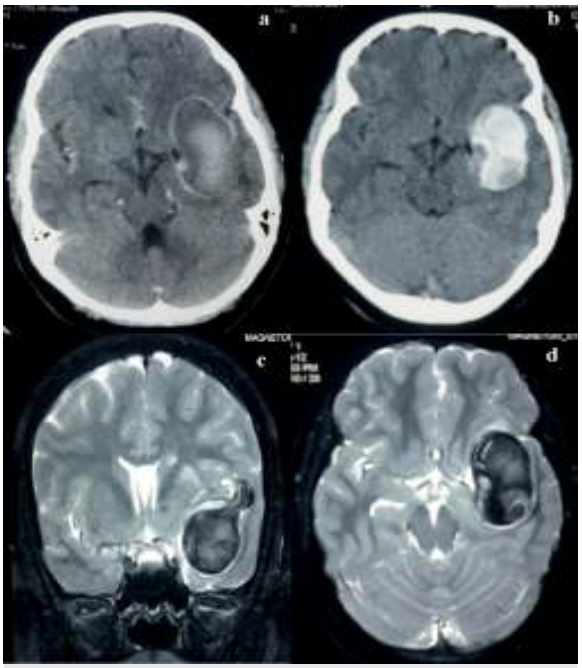

Figure 5 : Posterior circulation aneurysms

a – Plain CT scan outlining the giant left middle cerebral artery aneurysm.

b – CT showing the hematoma within the aneurysm after it bled.

MRI of the same aneurysm, T2 coronal (c) and axial (d) images, showing the hypointense hematoma within the large fundus.

Digital subtraction angiography (DSA)

DSA is still considered to be the gold standard for detecting intracranial aneurysms and defining its anatomy despite its invasiveness. The risk for permanent and transient neurological complication associated with DSA during the diagnosis of unruptured and ruptured aneurysms is 0.3% and 1.8%, respectively. DSA is sensitive for even aneurysms smaller than 3mm[29] (Fig 6c & d). It can provide information about the cross circulation across different arterial territories. The greatest advantage of DSA at present day scenario is the possibility of simultaneous endovascular intervention whenever feasible.

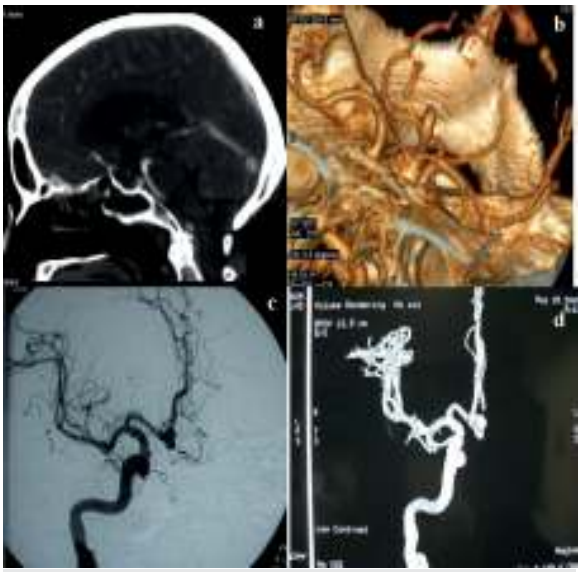

Figure 6: - Imaging modalities for aneurysms.

a – CT angio sagittal image showing a basilar apex aneurysm.

b – 3D reconstruction of the same image, showing the aneurysm and its relationship to the surrounding vessels.

c - Digital subtraction angiogram showing an anterior communicating artery aneurysm.

d – 3D reconstruction of the same aneurysm.

Surgical management

The main goal of surgical management of aneurysm is to exclude it from circulation thereby preventing rebleed and at the same time preserve the continuity of the parent vessel and its branches. This can be accomplished by passing a clip across the aneurysm neck (Fig 7). For aneurysms in inaccessible locations or for those lesions, whose morphology prevent passing of clip, alternative strategies have to be done. These include proximal or Hunterian ligation, wrapping the aneurysm, and trapping (combined proximal and distal vessel occlusion). For giant aneurysms, in addition to exclusion from circulation, the other goal is to reduce the mass effect by opening the fundus, remove the thrombus and decompress it from surrounding neurovascular structures.

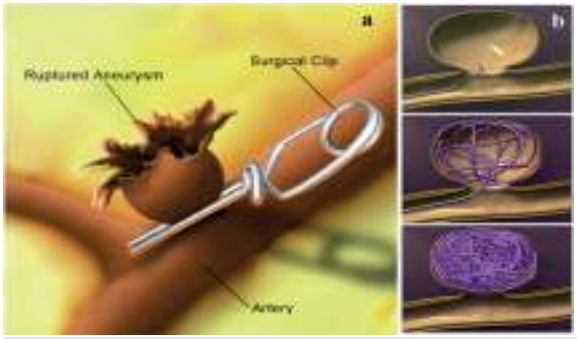

Figure 7 : Techniques of eliminating an aneurysm from the circulation.

a – Schematic of aneurysm clipping.

b – Schematic of aneurysm coiling.

Principles of Aneurysm surgery

Anaesthesia: The main goal of anaesthesia for aneurysm surgery is cerebral protection during temporary clipping. The other goal is maintain normotension, euvolemia and adequate analgesia throughout the surgery to prevent intra operative aneurysm rupture. It is of paramount importance that the brain is lax during surgery by giving osmotic diuretics and hyperventilation.

Positioning: The goal is to position the head such that the operative site is above the level of the cardia and avoiding flexion of the neck thereby reducing venous congestion. In basal approaches, a good extension can enable the cerebrum to fall with gravity thereby eliminating manual retraction. This is especially important while operating on acute SAH (Fig 8).

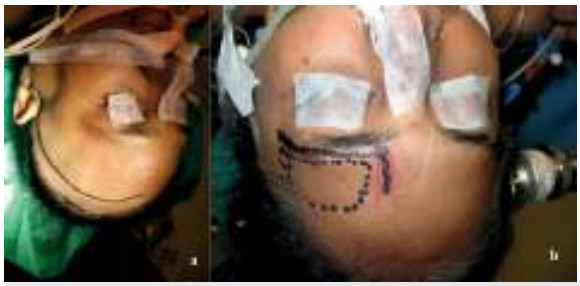

Figure 8 : Positioning a patient for aneurysm surgery.
a – Position for a conventional pterional craniotomy.
b – Position and incision for a suprabrow mini-craniotomy approach.

Craniotomy: The selection of craniotomy depends on the location of aneurysm. Most anterior circulation aneurysms are operated upon by using pterional craniotomy as described by Yasargil. With this approach, majority of the aneurysms along internal carotid artery, Posterior communicating artery, anterior communicating artery, middle cerebral artery can be clipped. The essential steps include removal of small portion of bone centring pterion, removal of the lateral sphenoid ridge adequately to expose 5*5 cm dura overlying sylvian fissure. After dural opening, the frontal lobe is retracted in the long axis of optic nerve initially to release CSF from carotico optic cistern. This will ensure laxity of the brain for further dissection.

Then a self-retaining Retractor is placed on the basal part of frontal lobe to stretch the sylvian fissure. Opening of the sylvian fissure is done from lateral to medial direction by meticulous technique under high magnification. Once the fissure opening is completed, the axis of retraction is changed and the retractor is placed along long axis of the internal carotid artery. The mainstay of aneurysm surgery is extensive arachnoid opening to clear all the subarachnoid clots and inspecting the arteries related to the aneurysm location.

Further dissection depends on the location of aneurysm. The general principles are proper exposure of the parent vessel to aid placement of temporary clip if necessary, dissecting the neck of the aneurysm (the fundus region is not usually dissected to avoid premature rupture), identification of all the perforating branches in close vicinity of the neck and the major branching vessels beyond the aneurysm. Sharp dissection using micro scissors is preferred over blunt dissection throughout exposure of the aneurysm. Once the neck of the aneurysm is exposed, the appropriate clip is selected which can slide along with ease and does not compromise the lumen of parent vessel. Various shapes of clips like straight, curved, right angled, left or right curve etc, are available and have to be chosen accordingly. Fenestrated clips are sometimes used in specific situations when a major artery is in the axis of neck precluding safe placement. In such instances, the fenestration can be used around the artery and clip blades across the neck. Various clipping techniques are described which are to be tailored according to the morphology of the aneurysm (Fig 9).

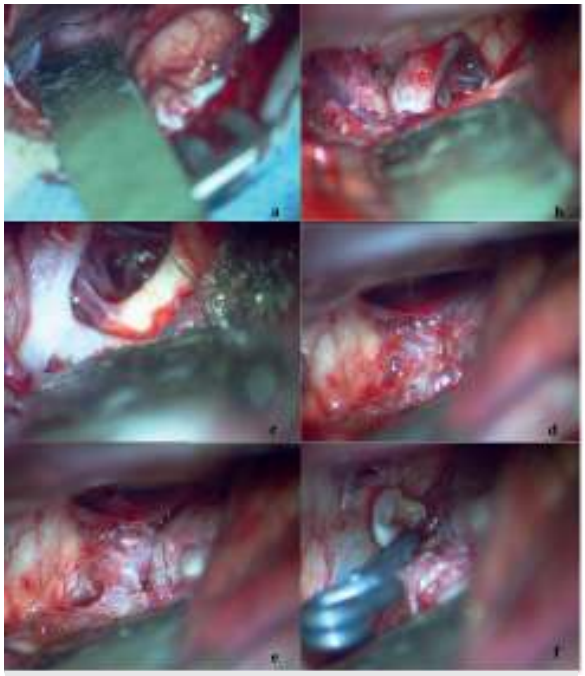

Figure 9 : - Steps in clipping an anterior communicating artery aneurysm.
a - Intra operative picture showing retraction of basifrontal lobe exposing optico carotid cistern
b - Showing exposure of optic nerve and ICA
c - Showing exposure of ICA bifurcation
d – Showing exposure of Acom aneurysm covered by arachnoid
e - Showing exposure of neck of Acom aneurysm after opening the arachnoid
f - Showing the clip across the neck.

It is important to confirm the complete exclusion of aneurysm and the patency of parent vessel before closing the dura. Various techniques are described from microsurgical inspection of the pulsation, puncturing the fundus etc. These are crude methods and the better way to do is using micro Doppler probe which can signal the presence of flow. Latest in technology is Indo cyanine green angiography (ICG) which can intra operatively visualize the vessels in the field and can be used with high precision[30]. The difficulty is to make sure that perforators are not caught in the clip on the back wall of the aneurysm neck. Both ICG angiography and Micro Doppler are not less useful in this situation.

Using a 30 degree endoscope can inspect the back wall of neck to identify patency of the perforators which are not visualized by microscope angle.

Following clipping, the subarachnoid clots are cleared by using copious saline irrigation and the lamina terminalis is opened to establish communication of third ventricle to basal cisterns. This may obviate the need of CSF diversion at later date in some patients and also accelerate the clearance of subarachnoid clots thereby preventing vasospasm.

Specific circumstances - Skull base approaches: While most anterior circulation aneurysms can be dealt with pterional craniotomy, some aneurysms close to the base of skull requires removal of the portions of basal bones to enhance exposure as in paraclinoidal ICA aneurysms and carotico- ophthalmic aneurysms. These aneurysms can be safely clipped following removal of anterior clinoid process.

Posterior circulation aneurysms: Basilar bifurcation aneurysms are better approached by pterional approach if they lie in the normal plane (Opposite dorsum sella). A high bifurcation usually requires orbito zygomatic approach and a low bifurcation is better dealt via sub-temporal trans tentorial approach.

Vertebral-PICA aneurysms can be operated through far lateral, retro sigmoid or midline occipital approaches depending on the location of the aneurysms.

Complications

Vasospasm: The major complication of subarachnoid haemorrhage is vasospasm (also called delayed ischemic neurological deficit)[31]. The onset of vasospasm starts 3 days following SAH and peaks during 7-9 days. Thereafter, the risk gradually reduces until about 3 weeks. Angiographic vasospasm is seen on vascular imaging and is high in incidence (60-70%). Clinical vasospasm is seen in roughly half of these patients. The risk is directly proportional to the amount of blood clots in the sub arachnoid cisterns. The exact pathogenesis is unclear and various hypothesis relate to imbalance between nitric oxide synthase (potential vasodilator) and Endothelin I (vasoconstrictor). While angiography can exactly identify the vasospasm, it can also be reasonably diagnosed with good precision by trans cranial Doppler, a non-invasive tool used more frequently nowadays.

The mainstay of preventing vasospasm is hydrating the patient adequately and maintaining a high blood pressure with the help of inotropic agents[32]. Reducing the viscosity of blood by administering low molecular weight dextran may also help perfuse the brain through narrow perforator vessels by improving the rheology. These three measures together constitutes the HHH regime (Hypertension, Hypervolemia & Haemodilution) and the most important component is hypertension. Generally, a target of 160-180 mmHg of systolic pressure, 110-120 mmHg of diastolic pressure, central venous pressure of 8-10 mmHg and a haematocrit of 10 is achieved to prevent vasospasm.

The main pharmacological agent used for vasospasm is Nimodepine, a calcium channel blocker which has selective action on intra cranial vessels with no peripheral action[33]. Though the exact mechanism by which it acts is unknown, the speculation is that it acts as a cerebral protectant by preventing neuronal intra cellular calcium influx rather than by vasodilatation. It is administered orally as 60 mg 4th hourly. It can also be administered intra venously in severe cases of vasospasm.

Endovascular treatment of Vasospasm: If conservative measures fail to improve the vasospasm within 12 hours, one should resort to emergency endovascular procedures. Balloon angioplasty is ideally performed if proximal major vessels(ACA, MCA and PCA) are involved[34]. The complications are minimal if carefully performed but occasionally can cause rupture of the vessel. If distal vessels are involved in spasm, then balloon angioplasty is not advocated and chemical angioplasty can be performed by injecting papaverine (1 in 10 dilution) or Nimodepine. The effects are however short lasting (maximum of 6 hours) and may have to leave the intra-arterial catheter in situ for repeat injections with the potential risks of thromboembolism if anticoagulation is not effectively used.

Hydrocephalus: Ventricular dilatation warranting CSF diversion can be seen upto 15-20% of patients following sub arachnoid haemorrhage. It is seen after 4-6 weeks and is due to blockade of arachnoid villi by the degradation products of haemoglobin. Patients with intra ventricular blood has a higher chance of developing hydrocephalus. Opening of lamina terminalis and adequate washing of sub arachnoid blood clots intra operatively may help in reducing the incidence of hydrocephalus[35] (Fig 10).

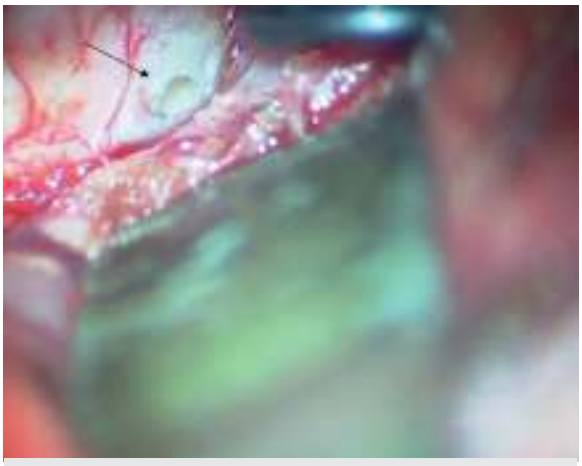

Figure 10 : - Opening of lamina terminalis after clipping to prevent hydrocephalus.

Seizures: Seizures can occur in 20% of patients following sub arachnoid haemorrhage[36]. Patients with middle cerebral artery aneurysms have a higher tendency to develop seizures. Early prevention of seizures by pharmacological measures may reduce the risk for developing late seizures by preventing kindling.

Fluid and electrolyte disturbances: The most frequent electrolyte abnormality seen following sub arachnoid haemorrhage is hyponatremia (up to 40%)[37]. This is

also called cerebral salt wasting, which occurs due to release of cerebral atrial natriuretic peptide resulting in loss of both sodium and water in urine. The treatment is by replacing both water and sodium (ideally hypertonic saline). In refractory cases, a mineralocorticoid like fludrocortisone is administered orally in 0.1-0.15 mg twice a day[38].

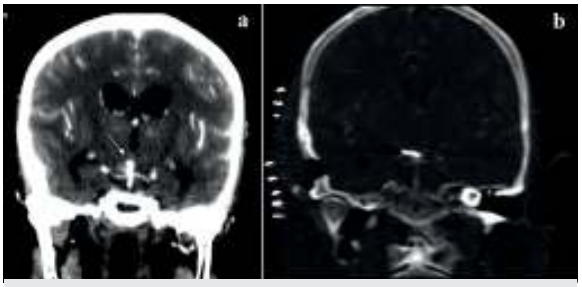

Figure 11 : - Complete aneurysm obliteration by clipping

a – Coronal image CT angiogram showing a basilar apex aneurysm

b – Postop coronal image showing a clip across the aneurysm neck and complete obliteration of the aneurysm.

Controversies

Timing of Surgery: In the past, there was a great controversy regarding the timing of surgical intervention. One school of thought was to perform delayed surgery after 2-3 weeks of subarachnoid haemorrhage so that the cerebral edema subsides and the subarachnoid cisterns are clear of blood thereby facilitating surgical clipping. But, the major drawback was the high rebleed rate and inadequate measures to combat vasospasm. According to the international co-operative study on Timing of aneurysm surgery, the peak risk of rebleed was within 24 hours (4%). The subsequent risk is 1.5% per day with a cumulative risk of 19% in the first 2 weeks. Rebleed was associated with mortality of more than 75%. Thus, by delaying the surgery for 2 weeks, the patients are deprived of their protection against rebleed and hence the evidence is in favour of early surgery[39]. Some studies even advocate ultra-early surgery (within 6 hours of SAH) to improve the final outcome.

Microsurgery Versus Endovascular surgery: The other major controversy is whether to subject the patient for surgical clipping or endovascular coiling(Fig 7). The International Sub arachnoid aneurysm trial (ISAT) which randomised patients to clipping versus coiling in situations where both management modalities deemed appropriate, demonstrated a marginal benefit of cognitive outcome in patients who had undergone coiling at 1 year follow up[40]. However, the long term outcome in subsequent studies revealed that the rate of recanalization and recurrence of aneurysm formation is between 15-50% when the patients were followed up several years after treatment[41]. On the contrary, more than 90% of patients who had undergone microsurgical clipping showed complete occlusion of aneurysms in the long term follow up (Fig 11). Thus, though the mortality is slightly higher in the surgical group, the combined mortality and severe morbidity is equivalent in both clipping and coiling group[42]. To summarise, endovascular coiling is an attractive option in acutely ruptured aneurysms with poor grade, especially in the older age group. Posterior circulation aneurysms are preferred for coiling than clipping.

Conclusion

The management of intra cranial aneurysm can be complex and challenging. Various factors have to be considered before contemplating the ideal treatment. Good knowledge of the anatomy and pathophysiology guides the accurate line of management. While the technology of managing these complex lesions are still evolving, a major insight into the pathophysiology and management of cerebral vasospasm still needs to be identified. As the technology of endovascular treatment is rapidly progressing, majority of the aneurysms would be managed with this modality in the future and microsurgery would be restricted to cases with previously failed coiling and vascular bypasses for giant and complex aneurysms.

References

1) Meyers PM, Schumacher HC, Higashida RT, Derdeyn CP, Nesbit GM, Sacks D, Wechsler LR, Bederson JB, Lavine SD, Rasmussen P. Reporting standards for endovascular repair of saccular intracranial cerebral aneurysms. Stroke. 2009 May;40(5):e366-79.

2) Parlea L, Fahrig R, Holdsworth DW, Lownie SP. An analysis of the geometry of saccular intracranial aneurysms. AJNR Am J Neuroradiol. 1999 Jun-Jul;20(6):1079-89.

3) Wiebers DO, Whisnant JP, Sundt TM Jr, et al.: The significance of unruptured intracranial saccular aneurysms. J Neurosurg.1987 Jan;66(1):23-29.

4) Drăghia F, Drăghia AC, Onicescu D. Electron microscopic study of the arterial wall in the cerebral aneurysms. Rom J Morphol Embryol. 2008; 49(1):101-3.

5) Santiago-Sim T, Kim DH. Pathobiology of intracranial aneurysms Youmans Neurological Surgery(Winn HR, ed), 6th ed. Vol. 4 Philadelphia, PA: Elsevier, Saunders; 2011:3747–3755.

6) Schievink WI.Genetics of intracranial aneurysms.Neurosurgery. 1997 Apr;40(4):651-62.

7) Baker CJ, Fiore A, Connolly ES Jr, Baker KZ, Solomon RA. Serum elastase and alpha-1-antitrypsin levels in patients with ruptured and unruptured cerebral aneurysms. Neurosurgery. 1995;37:56–62.

8) Juvela S, Poussa K, Porras M.Factors affecting formation and growth of intracranial aneurysms: a long-term follow-up study.Stroke. 2001 Feb;32(2):485-91.

9) Masuda J, Yutani C, Waki R, Ogata J, Kuriyama Y,

Yamaguchi T. Histopathological analysis of the mechanisms of intracranial hemorrhage complicating infective endocarditis. Stroke. 1992;23:843-850.

10) International Study of Unruptured Intracranial Aneurysms Investigators: Unruptured intracranial aneurysms—risk of rupture and risks of surgical intervention. N Engl J Med. 1998;339:1725-1733.

11) Wiebers DO, Whisnant JP, Huston J 3rd, Meissner I, Brown RD Jr, Piepgras DG, Forbes GS, Thielen K, Nichols D, O'Fallon WM, Peacock J, Jaeger L, Kassell NF, Kongable-Beckman GL, Torner JC; International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet. 2003 Jul 12;362(9378):103-10.

12) Bromberg JE, Rinkel GJ, Algra A, et al. Subarachnoid haemorrhage in first and second degree relatives of patients with subarachnoid haemorrhage. BMJ. 1995;311:288-289.

13) Juvela S, Porras M, Poussa K. Natural history of unruptured intracranial aneurysms: probability of and risk factors for aneurysm rupture. J Neurosurg. 2000;93:379-387.

14) Lall RR, Eddleman CS, Bendok BR, et al. Unruptured intracranial aneurysms and the assessment of rupture risk based on anatomical and morphological factors: sifting through the sands of data. Neurosurg Focus. 2009;26(E2):1-7.

15) Broderick JP, Brown RD, Sauerbeck L, et al. Greater rupture risk for familial as compared to sporadic unruptured intracranial aneurysms. Stroke. 2009;40:1952-1957.

16) Yasui N, Suzuki A, Nishimura H, et al.: Long-term follow-up study of unruptured intracranial aneurysms. Neurosurgery. 1997;40:1155-1159.

17) Rinkel GJ, Djibuti M, Algra A, et al.: Prevalence and risk of rupture of intracranial aneurysms: a systematic review. Stroke. 1998;29:251-256.

18) Risselada R, Lingsma HF, Bauer-Mehren A, Friedrich CM, Molyneux AJ, Kerr RS, Yarnold J, Sneade M, Steyerberg EW, Sturkenboom MC. Prediction of 60 day case-fatality after aneurysmal subarachnoid haemorrhage: results from the International Subarachnoid Aneurysm Trial (ISAT). Eur J Epidemiol. 2010 Apr;25(4):261-6.

19) Hop JW, Rinkel GJ, Algra A, et al. Case-fatality rates and functional outcome after subarachnoid hemorrhage: a systematic review. Stroke. 1997;28:660-664.

20) Lee VH, Oh JK, Mulvagh SL, Wijdicks EF. Mechanisms in neurogenic stress cardiomyopathy after aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2006;5(3):243-9.

21) Bassi P, Bandera R, Loiero M, Tognoni G, Mangoni A. Warning signs in subarachnoid hemorrhage: a cooperative study. Acta Neurol Scand. 1991; 84: 277–281.

22) Fontanarosa PB. Recognition of subarachnoid hemorrhage. Ann Emerg Med. 1989; 18: 1199–1205.

23) McCarron MO, Alberts MJ, McCarron P. A systematic review of Terson's syndrome: frequency and prognosis after subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry. 2004;75:491-493.

24) Brown SC, Brew S, Madigan J. Investigating suspected subarachnoid haemorrhage in adults. BMJ. 2011;342:d2644.

25) Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Connolly ES Jr, MacDonald RL, Mayer SA.Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale.Neurosurgery. 2006 Jul;59(1):21-7; discussion 21-7.

26) Jonathan A. Edlow, Louis R. Caplan. Avoiding pitfalls in the diagnosis of subarachnoid haemorrhage. N Engl J Med, 2000; 342:29-36

27) Westerlaan HE, van Dijk JM, Jansen-van der Weide MC, de Groot JC, Groen RJ, Mooij JJ, Oudkerk M. Intracranial aneurysms in patients with subarachnoid hemorrhage: CT angiography as a primary examination tool for diagnosis: systematic review and meta-analysis. Radiology. 2011; 258: 134–145.

28) White PM, Teasdale EM, Wardlaw JM, Easton V. Intracranial aneurysms: CT angiography and MR angiography for detection prospective blinded comparison in a large patient cohort. Radiology. 2001; 219(3): p. 739-49.

29) Ishihara H, Kato S, Akimura T, Suehiro E, Oku T, Suzuki M. Angiogram-negative subarachnoid hemorrhage in the era of three dimensional rotational angiography. J ClinNeurosci.2007; 14: 252–255.

30) Hardesty DA, Thind H, Zabramski JM, Spetzler RF, Nakaji P. Safety, efficacy, and cost of intraoperative indocyanine green angiography compared to intraoperative catheter angiography in cerebral aneurysm surgery. J ClinNeurosci. 2014 Aug;21(8):1377-82.

31) Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdicks EF, Muizelaar JP, Mendelow AD, Juvela S, Yonas H, Terbrugge KG, Macdonald RL, Diringer MN, Broderick JP, Dreier JP, Roos YB. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. Stroke.2010; 41: 2391–2395.

32) Lennihan L, Mayer SA, Fink ME, Beckford A, Paik MC, Zhang H, Wu YC, Klebanoff LM, Raps EC, Solomon RA. Effect of hypervolemic therapy on cerebral blood flow after subarachnoid hemorrhage: a randomized controlled trial. Stroke.2000; 31: 383–391.

33) DorhoutMees SM, Rinkel GJ, Feigin VL, Algra A, van den Bergh WM, Vermeulen M, van Gijn J. Calcium antagonists for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD000277.

34) Zwienenberg-Lee M, Hartman J, Rudisill N, Madden LK, Smith K, Eskridge J, Newell D, Verweij B, Bullock MR, Baker A, Coplin W, Mericle R, Dai J, Rocke D, Muizelaar JP; Balloon Prophylaxis for Aneurysmal Vasospasm (BPAV) Study Group. Effect of prophylactic transluminal balloon angioplasty on cerebral vasospasm and outcome in patients with Fisher grade III subarachnoid hemorrhage: results of a phase II multicenter, randomized, clinical trial. Stroke.2008; 39: 1759–1765.

35) Komotar RJ, Hahn DK, Kim GH, Khandji J, Mocco J, Mayer SA, Connolly ES Jr..The impact of microsurgical fenestration of the lamina terminalis on shunt-dependent hydrocephalus and vasospasm after aneurysmal subarachnoid hemorrhage.Neurosurgery.2008; 62: 123–132.

36) Choi KS, Chun HJ, Yi HJ, Ko Y, Kim YS, Kim JM. Seizures and epilepsy following aneurysmal subarachnoid hemorrhage: incidence and risk factors. J Korean Neurosurg Soc. 2009; 46: 93–98.

37) Disney L, Weir B, Grace M, Roberts P. Trends in blood pressure, osmolality and electrolytes after subarachnoid hemorrhage from aneurysms. Can J Neurol Sci. 1989; 16: 299–304.

38) Mori T, Katayama Y, Kawamata T, Hirayama T. Improved efficiency of hypervolemic therapy with inhibition of natriuresis by fludrocortisone in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg.1999; 91: 947–952.

39) Whitfield PC, Kirkpatrick PJ. Timing of surgery for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev. 2001;(2):CD001697.

40) Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA, Sandercock P; International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet.2005; 366: 809–817.

41) Uda K, Murayama Y, Gobin YP, Duckwiler GR, Viñuela F. Endovascular treatment of basilar artery trunk aneurysms with Guglielmi detachable coils: clinical experience with 41 aneurysms in 39 patients. J Neurosurg.2001; 95: 624–632.

42) Bakker NA, Metzemaekers JD, Groen RJ, Mooij JJ, Van Dijk JM. International Subarachnoid Aneurysm Trial 2009: endovascular coiling of ruptured intracranial aneurysms has no significant advantage over neurosurgical clipping. Neurosurgery.2010; 66: 961–962.

No Link between Sleep Apnoea and Cancer

Several studies have claimed that obstructive sleep apnoea (OSA) influences cancer progression. As 2 – 10% of the population worldwide is afflicted with sleep apnoea, this claimed association assumes clinical and epidemiological significance. However, a new study carried out on 10,149 apnoea patients over a period of 16 years (1994-2010), failed to find any association between OSA & Cancer (Tetyana Kendzerska, et al., Obstructive sleep apnoea and the prevalence and incidence of cancer, CMAJ, DOI:10.1503/cmaj.140238, published online 5 August 2014). The patients were followed up for an average period of 7.8 years. During that period, 6.5% developed cancer (lung, prostate, breast or colorectal). But when all the known risk factors were accounted for, there was no causal link between sleep apnoea & cancer. The authors are confident that their results are correct as the earlier studies were done on very small number of subjects. It is also likely that profound hypoxia (a known promoter of growth) in earlier studies might have skewed the results.

- Dr. K. Ramesh Rao

Case Report

Microsurgical Aneurysm Clipping - Our Experience

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Abstract

Microsurgical clipping of aneurysms is a challenging procedure for any neurosurgeon. It requires in depth knowledge of microanatomy, microsurgical skills, experienced neuro anaesthetists and dedicated specialised postoperative care. We present our experience in aneurysmal clipping.

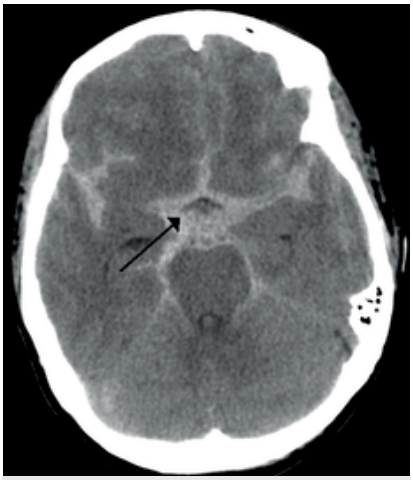
Key Words: Aneurysm, SAH, Giant, Clipping

Chettinad Health City Medical Journal 2014; 3(2): 74 - 76

Case Report

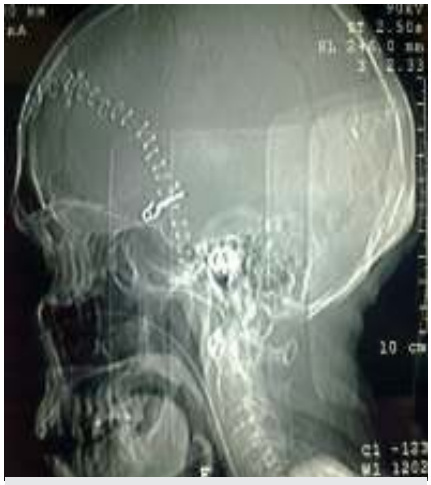
We have limited experience in aneurysmal clipping since 2012 in our institute. During this period we successfully clipped 5 aneurysms in various locations and with different World Federation of Neurologists Societies(WFNS) grades.

Case 1: A 53 year old known non hypertensive lady presented with sudden onset headache followed by seizure and altered sensorium. On admission her GCS was 7/15 with and right hemiplegia. (WFNS Grade 5). CT Brain showed diffuse SAH in all basal cisterns with mild hydrocephalus(Hunt-Hess Grade IV) (Fig 1). MRI with MR Angio and CT Angio showed large saccular aneurysm in the left Internal Carotid Artery (ICA) bifurcation measuring 29mm with neck width of 7 mm (Fig 2). Patient underwent left pterional craniotomy and sphenoid wing was drilled to make it accessible with meticulous arachnoidal dissection and clearing the subarachnoidal clots, a giant saccular thin walled aneurysm at the Left ICA was identified. Neck was dissected all around and a 11 mm slightly curved clip was applied at the neck. During application the thin neck ruptured and second clip of 11mm straight was applied below the first one and augmented with muscle patch. The bleeding stopped. Postoperative patient had dense right hemiplegia and aphasia. Patient slowly improved over a period of 6 weeks with neuro rehabilitation. At the time of discharge patient was aphasic and walking with minimal support. At 3 months follow up patient's aphasia improved and was walking without support and doing her daily activities independently (Fig 3).

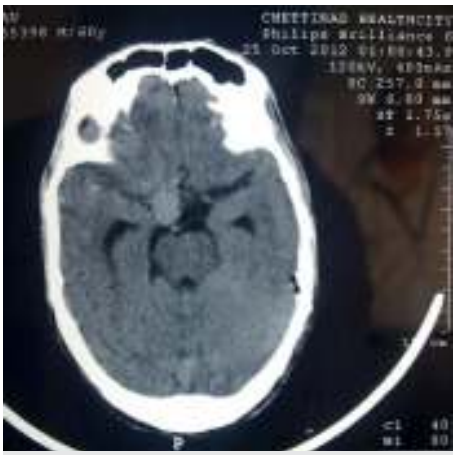


Case 1 - Image 1
Preoperative CT brain showing diffuse SAH

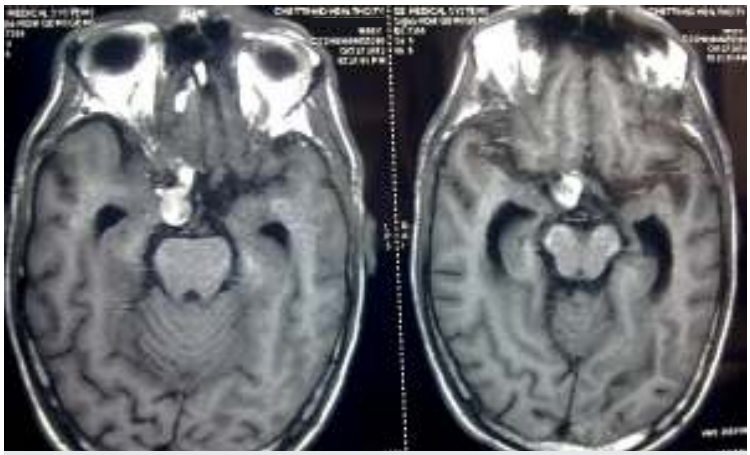
Case 1 - Image 2
Preoperative MRA showing left ICA bifurcation sacular



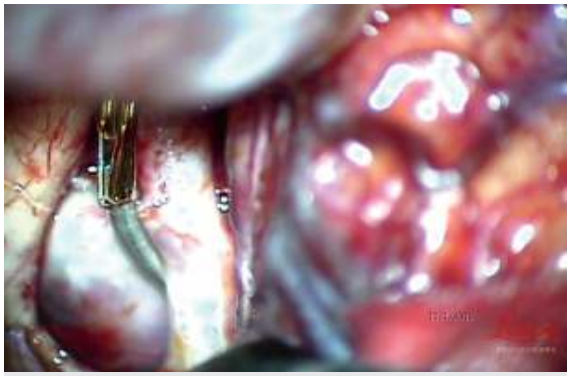
Case 1 - Image 3
Postoperative Xray showing clip in position aneurysm



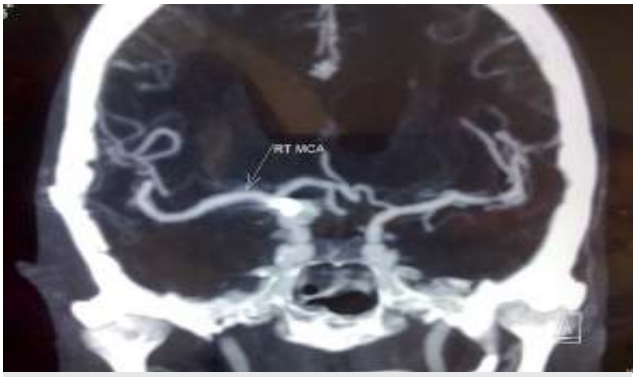
Case 2 - Image 1
Preoperatice CT showing thrombosed Right ICA bifurcation Aneurysm



Case 2 - Image 1
Preoperative MRI showing thrombosed aneurysm at Right ICA bifurcation



Case 2 - Image 3
Intra operative image showing clipped aneurysm



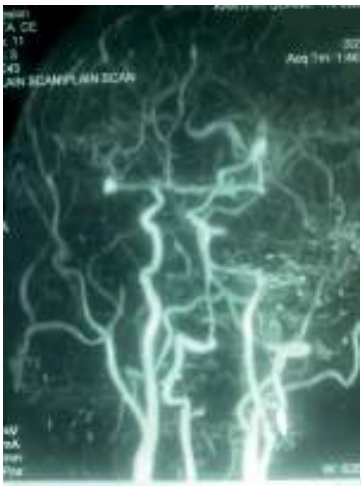
Case 2 - Image 4
Post operative CT angio after 6 months showing clipped aneurysm

Case 2: A 60 year old hypertensive patient presented with five days of headache and altered sensorioum. On examination his GCS was 13/15 with minimal left hemiparesis. (WFNS grade 3). CT brain showed no SAH but there wss a well circumscribed blobular lesion in right ICA bifurcation not enhancing with contrast, probably a thrombosed aneurysm noted (Fig 1). MR Angio also confirmed that the size is around 24mm with a neck width of 5mm (Fig 2). Patient underwent right pterional craniotomy and with meticulous microscopic arachnoidal dissection there was a large thrombosed hard aneurysmal sac at the right ICA bifurcation with relatively small neck. Neck was dissected all around and clipped with 8mm straight clip (Fig 3). Post operative period was uneventful and patient improved well and 6 weeks post operative CT angio showed satisfactory clipping and occlusion of the neck (Fig 4).

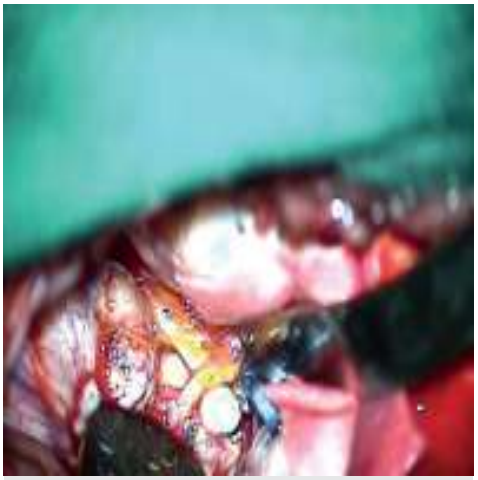
Case 3: A 35 year old gentleman presented with one month old severe headache, vomiting for couple of days and he took symptomatic treatment .Then he ws evaluated later and referred to us with CT angiogram which showed Right MCA bifurcation 5 mm aneurysm which was thrombosed (WFNS Grade 1) (Fig 5). Patient underwent right pterional craniotomy and clipping with 7mm straight clip (Fig 2). Post operative period was uneventful and follow up angiogram showed perfect occlusion (Fig 3).

Case 4: A 40 year old lady non hypertensive presented with sudden headache ,seizure and unconsciousness, on examination her GCS was 10/15.CT brain showed diffuse SAH in suprasellar cistern and interhemispheric fissure and a small ICH in right frontal lobe with diffuse edema.(WFNS Grade 4) (Fig 1). MR angiogram showed ACOM(Anterior Communicating) aneursym with the neck on left side and the fundus towards right frontal lode (Fig 2). Patient underwent left pterional craniotomy and with meticulos arachnoidal dissection all the perforators around the neck were excluded and both A1 and A2 on both sides excluded and a 5mm straight clip was applied (Fig 3). Post operatively her recovery was slow and post op CT showed left side ACA partial infarct. After two weeks patient recovered well and on discharge patient GCS was 15 with no motor deficit but she had minimal behavioral disturbance.3 months follow up CT angio showed clipping in situ (Fig4).

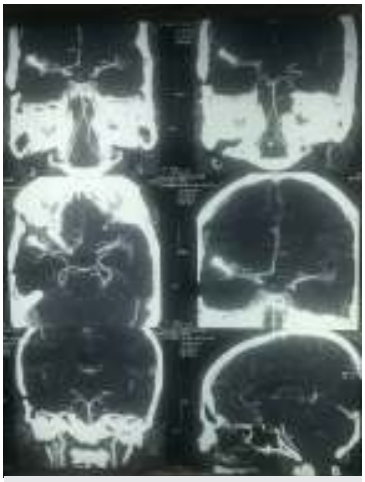
Case 5: 48 year old hypertensive man referred to us as a case of ACOM(Anterior communicating artery) aneurysm (WFNS Grade1). He had history of frquent headaches only .Neurologically his GCS was 15 and no deficit. CT angio showed a narrow necked ACOM aneurysm of 9 mm in size (Fig 1 & 2). He underwent conventional right pterional craniotomy and clipping. Post operative period was uneventful (Fig 3).



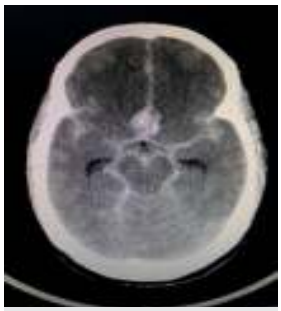
Case 3 - Image 1
Pre operative Angio showing Rt MCA bifurcation Aneurysm



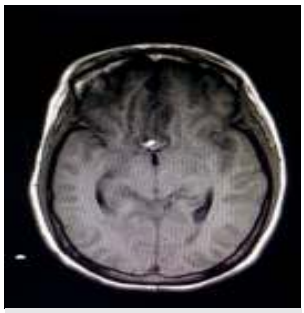
Case 3 - Image 2
Intra operative image showing clipped aneurysm



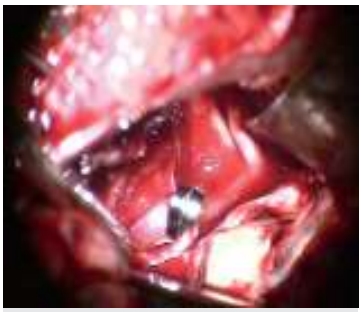
Case 3 - Image 3
Postop CT angio showing clipped aneurysm



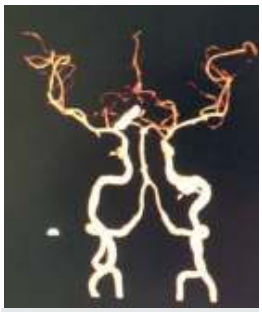
Case 4 - Image 1
CT Brain showing diffuse SAH with IVH and ICH



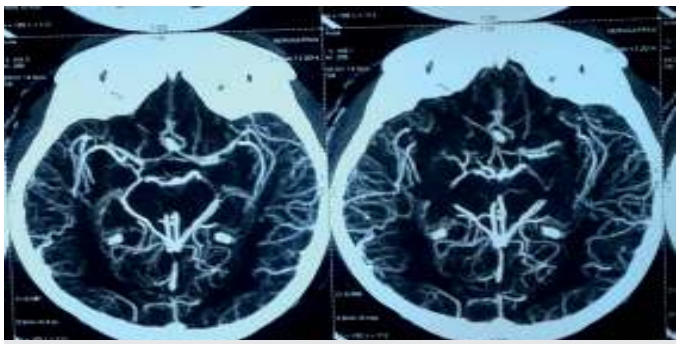
Case 4 - Image 2
Preoperative MR angio showing Narrow necked aneurysm at ACOMand CH



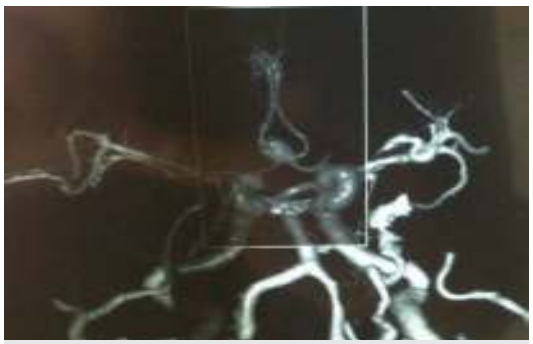
Case 4 - Image 3
Intra operative image showing clip in situ



Case 4 - Image 4
Post operative CT angio 3D reconstruction showing clip insitu



Case 5 - Image 1
CT angiogram showing narrow necked ACOM aneurysm



Case 5 - Image 2
3D reconstruction shows the Aneurysm

Case 5 - Image 3
Immediate post operative X ray showing clip in situ

Conclusion

With our limited experience we achieved a 100 percent success after clipping with no mortality and minimal morbidity. Though conventional 4 vessel angio is the gold standard test, due to limited availability in our institute CT angio served as an alternative tool in diagnosing .Effective post operative care is essential in ruptured aneurysm to overcome the complications of subarachnoid haemorrhage.

Case Report

Giant Cerebral Arterio-Venous Malformation Excision

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Abstract

Arteriovenous malformations(AVM) are the most commonly seen surgical vascular lesions. It accounts for about 0.68 per 100000 person-years. Mean age of presentation is about 33-45 years with no sex predisposition. Approximately half of the patients suffer from intracranial haemorrhage (ICH) during their lifetime. Inspite of many treatment options available for AVM, surgery is the gold standard treatment though it poses a great challenge. Here we present one such case.

Key Words: AVM`s, Craniotomy, Radiosurgery, Embolization.

Chettinad Health City Medical Journal 2014; 3(2): 77 - 79

Introduction

Arteriovenous Malformations(AVMs) are the second most common intracranial vascular malformations. They are believed to be congenital. Multiple AVMs are rare and so are familial AVMs. 90% of AVMs are supra-tentorial. AVMs consist of a bunch of vessels called `nidus`, which is made up of vessels of variable diameter and vessel wall thickness. The AVM may be fed by one or more branches from cortical and deep branches of all major arteries, such as- Anterior cerebral artery, middle cerebral artery and posterior cerebral artery. Brain surrounding the AVM, may show area of gliosis due to ischemia secondary to 'steal' phenomenon. Common presentations of brain-AVM are haemorrhage, epilepsy, progressive neurological deficit, migraine and intractable headache. Clinical signs depend on location of the malformation and the venous drainage.

Case Report

A 61 year old lady presented with complaints of headache, speech disturbance and difficulty in using right upper limb and lower limb for a duration of 3 weeks. Patient also had a history of difficulty in holding objects with the right upper limb, difficulty in walking (3 week duration) and history of seizures (5 episodes-last episode of seizure was 3 days before admission, started in the right upper limb with secondary generalization and loss of consciousness).On examination, patient had expressive dysphasia with decreased word output with normal comprehension, cranial nerves were intact. Patient had right hemiparesis with power of grade 3 to 4.Deep tendon reflexes were brisk on the right side and plantar was extensor on the right side. CT Angio (Fig.1) and MR Angio (Fig.2 a,b) showed subcortical left temporal lobe arteriovenous malformation fed by middle cerebral artery, posterior cerebral artery and draining veins into superficial middle cerebral vein and transverse sinus. Patient was graded pre-operatively as grade 3(based on Spetzler and Martin grading system - Table 1). Patient was started on anticonvulsants and other supportive treatments. Patient was offered embolization and excision of AVM or excision of AVM alone, but patient wanted to directly undergo Excision of AVM, hence craniotomy was planned to excise the AVM.

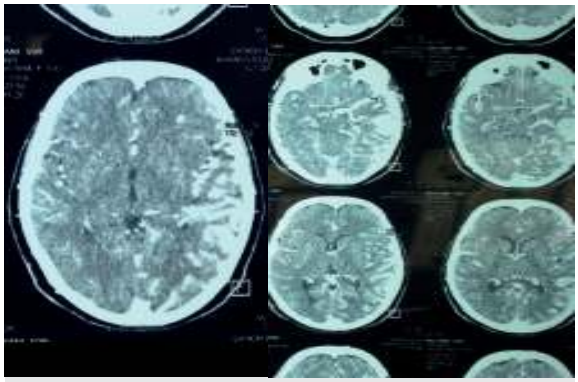


Fig 1 - CT-Angio showing sub cortical left temporal lobe Arteriovenous Malformation.

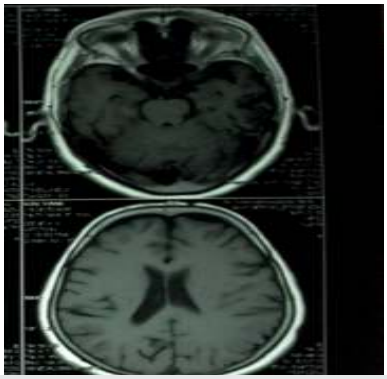


Fig 2a . MRI showing flow voids and nidus suggestive of AVM.

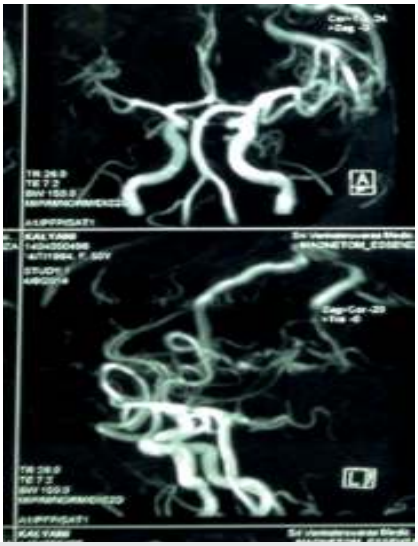


Fig 2b. MRI MR-Angio showing Sub Cortical Left Temporal Lobe AVM of size 4.5cms fed by Middle cerebral artery and Posterior cerebral artery and draining veins into Transverse sinus, no intra-nidal aneurysm seen (Grade III AVM).

Patient was placed in a supine position with face turned to right side, left frontotemperoparietal craniotomy was performed. A large arteriovenous malformation measuring 4.5cms was seen in the left posterior temporal lobe with adhesion to dura which was removed, after identifying the feeders. Arterial feeders were first coagulated and divided while venous feeders were clipped and divided at the end and AVM was excised in toto (Fig.3). Postoperative period was uneventful, patient's deficits improved. Post operative CT scan showed complete excision of AVM (Fig.4).

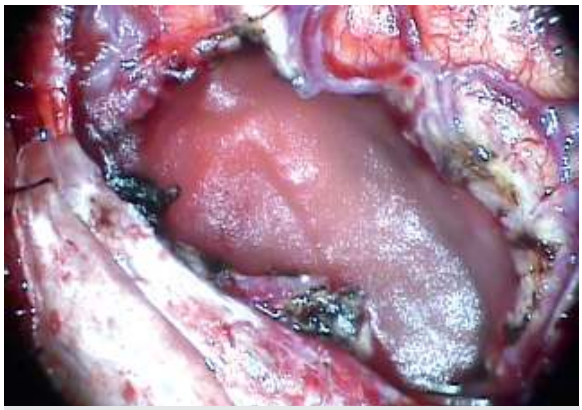


Fig 3. Intra-Operative picture showing complete excision of the AVM.

Discussion

The term arteriovenous malformation is commonly used to describe all types of vascular malformations of the brain. Though numerous classifications have been proposed, widely accepted is the one by McCormik in 1966[1] and is based on the morphology of the competent vessels. This was subsequently modified by him in 1978[2] as:

- AVM
- Cavernous angiomas
- Venous angiomas
- Capillary telangiectasia
- Transitional forms

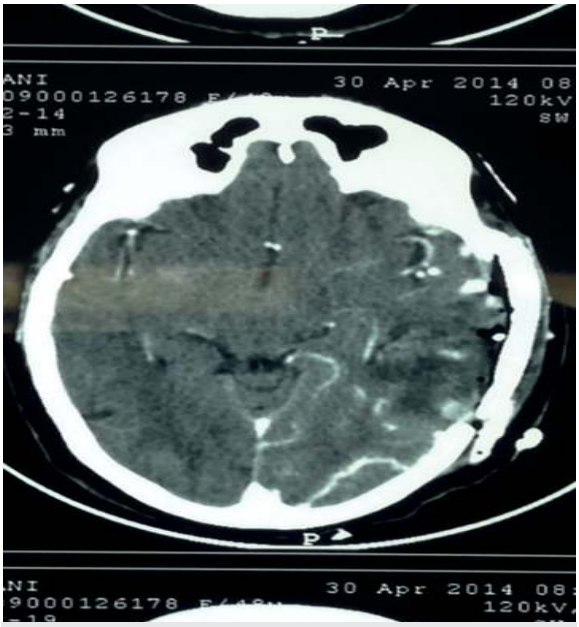


Fig 4. Post-Operative Contrast-CT showing complete excision of AVM.

AVMs are the commonest of these lesions. AVMs are the congenital lesions which develop during the late somite stage, between 4th and 8th week of embryonic life. They rank second to aneurysms among the intracranial vascular lesions that produce subarachnoid haemorrhage. Treatment options available are excisional surgery which is the gold standard, endovascular treatment, radiosurgery and/or combination of the above.

Total surgical resection of an AVM is determined by many factors[3]-

- Age and neurological status of the patient.
- Size (small, medium, large, giant)
- Location, especially with respect to eloquent areas of the brain.
- Configuration of the nidus.
- Number, size, type and source of arterial feeders.
- Nature of venous drainage (superficial, deep or both) and number of draining veins.
- Haemodynamics of the AVM.

Spetzler and Martin grading system[4], which takes into consideration- size, venous drainage and eloquence of adjacent brain. A score between 1 - 5 estimates the risk of surgery.

Table 1

1. Size of the AVM
   - Small (less than 3cm)- 1 point.
   - Medium (3-6 cms)- 2 points.
   - Large (more than 6 cms)- 3 points.
2. Eloquence of adjacent brain -
   - Non-eloquent- 0 point.
   - Eloquent- 1 point.
3. Pattern of venous drainage -
   - Superficial only- 0 point.
   - Deep-1 point.

Based on this system:

Grade 1 has good prognosis.

Grade 5 has worst prognosis.

Up to grade 3, excision is the treatment of choice.

Grade 4 and 5 endovascular treatment is the treatment of choice.

A 3-tier classification of cerebral AVMs in which -

Class-A combines Grade I and II AVM`s.

Class-B Grade III AVM`s.

Class-C[5] combines Grade IV and V AVM`s.

Recommended management is Surgery for Class-A, Multi-Modality treatment for Class-B, and Observation for Class-C.

The first complete surgical excision of cerebral AVM was made by the famous French Surgeon Pean.

Total surgical excision remains the gold standard in the treatment of AVM. The aim of surgical excision is to interrupt the natural history of the disease, and to prevent future haemorrhage, decrease cerebral steal, improve neurological deficits and to achieve seizure control. Main principle of surgical treatment is that arterial feeders are attacked first followed by excision of nidus and finally resection of the draining veins[6]. Care should be taken to preserve veins until the very end of surgery. Large high flow AVM's are often a surgical challenge for one stage surgical resection.

Current indications for embolization are - Pre-surgical embolization for large or giant cortical AVM[7] and embolization before radiosurgical intervention to reduce the nidus size. Embolic materials used are divided into solid and liquid agents, solid agents includes microcoils and microballons, liquid agents includes 1-butyl cyano acrylate(IBCA), N-butyl cyanoacrylate(NBCA) and ethylene vinyl alcohol(EVAI).

Radiosurgery-gamma knife (Co-60) is useful in small(2-3cms), deeply located inaccessible AVM in eloquent areas of brain with multiple small feeders, in combination with surgery or embolization for large AVM's, inaccessible or unresectable residual AVM's and in patients who are not willing for surgery or poor candidates because of concomitent medical illness. Radio surgery is useful; it is successful in treatment of majority of paediatric patients, suffering from AVM`s and morbidity levels are minimal[8].

References

1) Mc Cormick WF. The pathology of vascular (arteriovenous) maldormations. J.Neurosurg. 1966; 24(4) : 807-16.

2) Mc Cormick WF. The pathology of Angiomas – In: Fein JM, Flamn ES(Eds) Vascular Surgery IV. New York : Springler Verlag ; 1985:1073.

3) Drake CG. Cerebral Arteriovenous Malformations : Considerations for and experience with surgical treatment in 166 cases. Clin.Neurosurg.1979; 26:145-208.

4) Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. J.Neurosurg. 1986; 65(4): 476-83.

5) Robert F.Spetzler, Francisco A.Ponce, A 3-tier classification of cerebral arteriovenous malformations - Clinical article : Journal of Neurosurgery. March 2011; vol.114 (3) : 842-849.

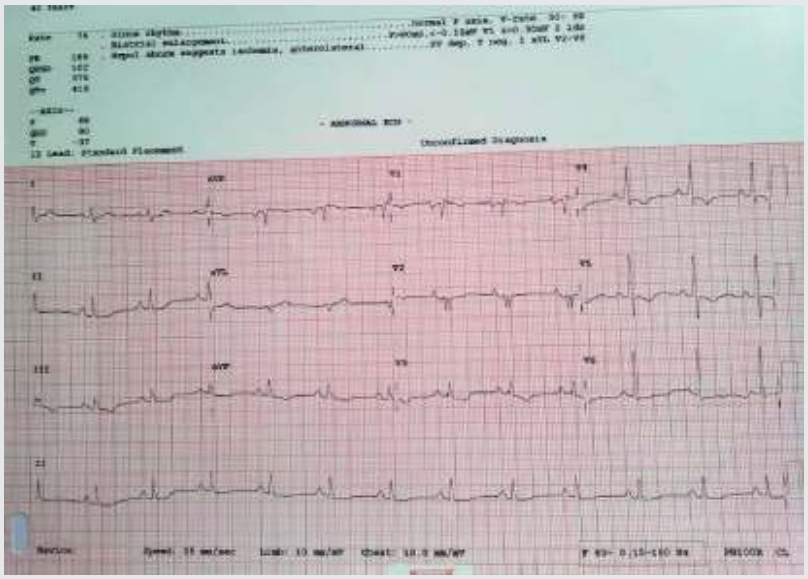
6) Yasargill MD (Ed.) MicroNeurosurgery. Stuttgart : Georg Thieme Verlag; 1988.

7) Robert F.Spetzler, Neil A.Martin, L Philip.Carter, Richard A.Flour. Surgical Management of Large AVM`s by staged embolization and operative excision. : Journal of Neurosurgery. July 1987; vol.67(1): 17-28.

8) Aaron.A.Cohen-Gadal, Bruce E.Pollock. Radiosurgery for arteriovenous malformations in children. Journal of Neurosurgery : Paediatrics. June 2006;vol.104 (6) : 388-391.

Diagnose the condition

A 40 year old male presented with gradually progressive dyspnoea.



Dr. M.Chokkalingam, Consultant Cardiology, CSSH.

Answer in page : 85

Review Article with Case Study

Non-Secretory Multiple Myeloma- An Unusual Presentation With Review of Literature

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Abstract

Multiple myeloma is a B-cell malignancy caused by monoclonal proliferation of plasma cells which secrete immunoglobulins leading to a "M" protein spike on immunoelectrophoresis and lytic bone lesions or renal involvement or anaemia or hypercalcaemia and is not associated with organomegaly.Here we present a case with non-secretory multiple myeloma with lymphadenopathy and hepatosplenomegaly with review of literature.

A 75 year old male presented with low back pain, recurrent anaemia, recurrent pneumonia,raised ESR,lymphadenopathy and hepatosplenomegaly. With a haematological malignancy in mind, a bone marrow examination was done which revealed plasma cells which were CD 138 and monoclonal kappa chain positivity on immunohistochemistry. The serum protein electrophoresis with immunofixation did not show a "M" spike. Lytic lesions were seen on X-ray.Hence, a diagnosis of non-secretory multiple myeloma(NSMM) was made. However,the patient expired after four cycles of chemotherapy due to persistent pneumonia.

NSMM has varied clinical manifestations like plasma cell leukaemia, a higher incidence of neurological presentation, minimal lytic bone disease, a lower median percentage of plasma cells in the marrow and a lower incidence of hypogammaglobulinaemia.Various studies have differing experiences on the survival of patients with NSMM.Morphologically,plasma cells have shown rough endoplasmic reticulum and a clear Golgi apparatus on electron microscopy or with distended endoplasmic reticulum.A case of NSMM presenting with pancytopenia has been reported. This patient had plasma cell infiltration of the bone-marrow. The plasma cells were multinucleated and showed erythrophagocytosis and phagocytosis of granulocytes.These are true non-secretors who do not excrete the light chains and can be identified by immunohistochemistry using CD 138 and kappa and lambda light chain.The conventional methods of detection of free light chains(FLC) are not sensitive ;hence,FLC assay is now used for the detection of light chains in oligo-secretors.Patients are prone to infections especially with Pneumococcus.Amyloidosis has also been reported in secretory cases.

A high degree of suspicion for a haematological malignancy is warranted in a case of recurrent anaemia despite blood transfusions,repeated infections,generalised lymphadenopathy and hepatosplenomegaly.A bone-marrow examination with immunohistochemistry is helpful in such cases,which can be supported by ancilliary tests like serum protein electrophoresis with immunofixation, Free-Light Chain assay and X-ray for lytic lesions in bone, where indicated.

Key Words: Non-secretory multiple myeloma, M-band, Anaemia, Recurrent pneumonia, Lytic bone lesions, Plasmacytosis.

Chettinad Health City Medical Journal 2014; 3(2): 80 - 85

Introduction

Multiple myeloma is a B-cell malignancy caused by monoclonal proliferation of plasma cells which secrete immunoglobulins leading to "M" protein spike on immunoelectrophoresis and lytic bone lesions or renal involvement or anaemia or hypercalcaemia and is not associated with organomegaly.

Non secretory multiple myeloma is a rare disease (1-5% of all myelomas) and is characterised by the increase in plasma cells, lytic bone lesions with or without hypercalcaemia and renal involvement. There is absence of M band in the serum or urine[1].The diagnosis rests on the demonstration of plasma cells in the bone-marrow. A search in "PubMed", showed less than 80 case reports since 1972 following which the incidence of non-secretory multiple myeloma has declined, probably as a result of more sensitive methods of detection of light chains. A high index of suspicion is needed to diagnose such cases[1]. We report here a rare

case of non-secretory multiple myeloma with an unusual presentation of lymphadenopathy and hepato-splenomegaly,lytic bone lesions and a bone-marrow plasmacytosis. A literature review of cases of non-secretory multiple myeloma, its clinical manifestations and investigations has been done.

Case report

A 75 yr old male came with complaints of fever and cough for 20 days, shortness of breath for four days, history of chest pain, left sided, non radiating, not associated with sweating. There was no history of palpitations or pedal oedema.

Patient had a past history of Hansen's disease 40 years ago,which was treated with dapsone and clofazimine. Patient was operated for epigastric hernia one year back when he was treated for anaemia while admitted in surgical ward.Six units of packed RBC was transfused.He had a past history of recurrent pneumonias.He was a non smoker and a non-alcoholic.

On examination,the patient was pale,had bilateral pitting oedema and bilateral lymph node enlargement , cervical & inguinal group of nodes,1-1.5cm in size,firm in consistency.His blood pressure was 140/80 mm hg,respiratory rate was 32 / min.Patient was dyspnoeic. His abdomen was distended. He had hepatomegaly, 5 cm below right costal margin and splenomegaly 7cm below the costal margin. On auscultation, bilateral fine basal crepitations were heard. Heart sounds were normal.CNS examination showed no focal neurological deficit.

Laboratory investigations revealed anaemia(Hb – 6.3 g/dl), neutrophilic leucocytosis (Tlc – 14,900, Dc - N-87.1,E-0.6,L-10.6,M-1.7,B-0). He had slight thrombocytopenia (platelet count – 1.30 lac/cu.mm). The ESR was 136 mm at one hour. His renal parameters and serum electrolytes were normal. Urine analysis revealed- albumin 1+, pus cells 5-10/hpf, epithelial cell- 2-4/hpf. His liver function tests revealed mild hyperbilirubinemia(total bilirubin-2.2mg/dl,direct bilirubin-0.3 mg/dl) with mild increase of serum alkaline phosphatase – 177 u/l. The total protein(7.4 g/dl) was normal with a lowered serum albumin(2.2 g/dl). The serum globulin was raised (5.2 g/dl). The serum LDH was slightly raised at 257 u/l. The reticulocyte count was slightly raised at 3.2%, the indirect Coombs test being negative. HIV 1 & 2 and HBsAg were non reactive.The echocardiography showed normal LV function and no regional wall abnormality.

In view of the raised temperature,breathlessness and elevated WBC counts the patient was started on oxygen,diuretics and antibiotics.The breathlessness suddenly increased and saturation dropped to less than 60%,at which point he was intubated and put on ventilator. The repeat haemoglobin was 7.5 gm/dl and repeat total leucocyte count was 60,000 cells/cu mm of blood. ABG revealed hypoxaemia & hypercapnia. Blood culture and sensitivity showed no growth. Urine culture showed insignificant bacteriuria.Endotracheal tube aspirate Gram stain showed few pus cells, occasional Gram positive cocci in pairs, numerous Gram negative bacilli.

On re-evaluation of patient's history & examination,with history of chronic low back pain, recurrent pneumonia,generalised lymphadenopathy, hepatosplenomegaly, anemia despite repeated blood transfusions & taking into consideration other lab parameters,serum protein electrophoresis with immunofixation was done. The total protein was 6.61 g/dl,albumin – 3 g/dl,alpha 1 globulin – 0.13 g/dl,alpha 2 globulin – 0.35 g/dl, gamma globulin – 0.36 g/dl. The immunoelectrophoresis did not show a M Band. With clinical features pointing to hematological malignancy,i.e,high ESR (136 mm), a bone marrow aspiration and biopsy were performed. The bone marrow showed a hypercellular marrow with an increase in plasma cells,plasma blasts, binucleated plasma cells with a bone marrow plasmacytosis (25%) (Figs 1&2).

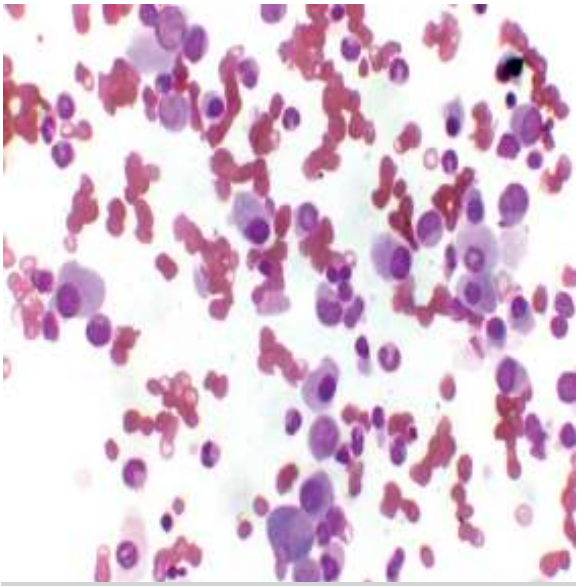

Fig 1- Bone marrow aspiration showing infiltration by plasma cells (Leishman's stain 40X10X)

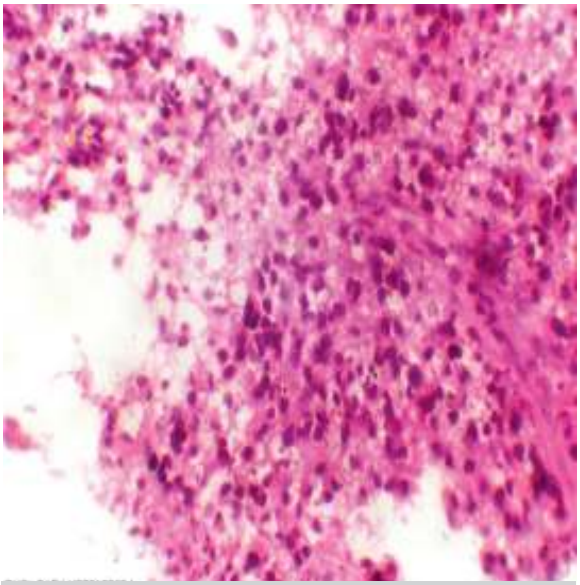

Fig 2- Bone marrow trephine biopsy showing plasma cells infiltrating the marrow (Haematoxylin and eosin staining 40X10X)

The erythroid series was normoblastic & myelopoiesis was normal.Immunohistochemistry on the bone marrow biopsy showed CD 138 and monoclonal kappa chain positive cells. The X-ray skull showed a lytic lesion.The urine did not show the presence of light chains or M protein spike.In view of the raised ESR,bone marrow plasmacytosis and an absence of M band on serum immune-electrophoresis, a diagnosis of non-secretory multiple myeloma was made.The serum calcium and renal parameters were normal. Ultrasound of the liver showed diffuse homogenous deposition and amyloidosis was suspected.However,an abdominal fat biopsy was negative for amyloid. The patient was started on melphalan,prednisolone & allopurinol.After 4 cycles of chemotherapy the patient passed away due to persistent pneumonia.

Discussion

Multiple myeloma is the malignant disorder of plasma cells accounting for 10-15% of all haematological malignancies and one to two percent of all malignancies. Non secretory multiple myeloma is characterized by bone marrow plasmacytosis,lytic bone lesions and an absent M band either in the serum or urine on immuno electrophoresis with or without organ damage[2].Two cases of NSMM below the age of 30 years have been described in literature.The monoclonal immunoglobulins were demonstrated by immunohistochemistry[3]. The disease has a varying presentation ranging from low grade bodyache,backpain ,pathological fractures,repeated infections to other non-specific complaints.About 10-40%are asymptomatic[1]. Our patient had anaemia not corrected by repeated transfusions,repeated respiratory infections, generalized lymphadenopathy and hepatosplenomegaly with normal serum calcium levels and normal renal parameters.

An occasional patient presenting with plasma cell leukaemia has been described. The authors postulate that these cases may be more aggressive as immature plasma cells do not have the capacity to synthesize or secrete complete immunoglobulins. Hepatomegaly was seen infrequently as compared to plasma cell leukaemia and no patients had splenomegaly or peripheral lymphadenopathy at the time of diagnosis. They also used fluorescein-conjugated antisera against immunoglobulins to demonstrate free kappa chains in the cytoplasm of the plasma cells as was seen in our case.They described two categories of patients- one group of patients with positive immunofluorescence in plasma cells (secretory, non-excretory MM) and the other group with negative immunofluorescence (true nonsecretory MM)[4,5,6].

The clinical features of 13 patients with non-secretory multiple myeloma(NSMM) from a series of 172 consecutive multiple myelomas were studied. The non-secretors survived longer than the secretors, median 46 months versus 21 months (p-value< 0.01). Non-secretory myeloma was associated with a higher incidence of neurological presentation, lesser incidence of lytic bone lesions, a lower percentage of plasma cells in the marrow and a lower incidence of hypogammaglobulinaemia. The superior survival of non-secretors was thus thought to be due to earlier presentation possibly as a result of a tendency to form symptomatic local tumours.A retrospective immunoperoxidase staining of the archived tissue was performed in nine cases. Monoclonal immunoglobulin was detected in eight cases. Thus,immunoperoxidase staining helps in establishing the diagnosis of non-secretory multiple myeloma[7].

Non-secretory multiple myeloma is an aggressive disease as illustrated by a case-report where the patient had 4 relapses after multiple therapeutic regimens including conventional chemotherapy,high dose chemotherapy with autologous stem cell transplantation and the more potent, novel anti-myeloma agents. The last relapse was a nodular infiltration of liver following which the patient expired[8].

Non-secretory multiple myeloma was first described in 1958 by Serre[1].It has since been postulated that either there is a reduced production or reduced secretion of immunoglobulins. In such cases intra-cytoplasmic immunoglobulins are detected by immunohistochemistry as was seen in our case where the kappa chain positive plasma cells were seen[1].

The morphology of plasma cells are characteristed by a perinuclear halo and rough endoplasmic reticulum and a clear Golgi apparatus on electron microscopy. A case report of NSMM with azurophilic granules in the cytoplasm had been reported,which were identified as phagocytic vacuoles on electron microscopy. Immunohistochemical staining showed positivity for myeloma cells, B-cell associated markers, myeloid and stem cell markers. Such cases may present a diagnostic dilemma where electron microscopy may demonstrate the characteristic morphology[9].

A case of NSMM presenting with pancytopenia had been reported. This patient had plasma cell infiltration of the bone-marrow. The plasma cells were multinucleated and showed erythrophagocytosis and phagocytosis of granulocytes. The patient lacked lytic lesions. The plasma cells were aberrantly positive for CD117 and CD13 and lacked expression of CD56 and were positive for kappa chains. The patient improved on dexamethasone therapy though haemophagocytosis persisted[10].

A case report of NSMM showed plasma cells with distended rough endoplasmic reticulum containing cytoplasmic colloid. On immunoperoxidase staining, the cells showed IgA heavy and kappa light chain positivity. This distension of the endoplasmic reticulum may suggest either active synthesis or block in their excretion[11].

Also, the conventional methods of detection of immunoglobulins and light chains are not sensitive enough to detect these chains. The newer serum immunoglobulin-free light chain assay(FLC) detects the light chains not detectable by the earlier assays. Patients with non-secretory multiple myeloma have less involvement of the kidney as free chains are not excreted in the urine. Few reports claim a better survival for patients with NSMM because of lower

incidence of involvement of the kidney, but prognosis is guarded in such cases as the diagnosis is delayed because of the absence of M protein in the serum or the urine[1].

The presenting features of non-secretory myeloma are similar to those in patients with a detectable M-protein, except for the absence of renal function impairment. The response to therapy and survival of patients with non-secretory myeloma are similar to those of patients with measurable M-protein[12] though there are case reports of NSMM with hypercalcemic acute renal failure[13].

Intact and fragmented intracellular immunoglobulin and kappa chain in the plasma cells in a case of non-secretory myeloma have been demonstrated by polyacrylamide gel electrophoresis before the introduction of FLC assay[14]. Another method which was tried was by immunoisoelectric focusing. These methods have been replaced by the introduction of the FLC assay[15].

The serum free light-chain (FLC) assay (Freelite™, The Binding Site Limited, Birmingham, U.K.) is a nephalometric assay that can be performed on automated chemistry analysers and allows quantification of free kappa (κ) and lambda (λ) chains (i.e., light chains that are not bound to intact immunoglobulin) secreted by plasma cells. An abnormal kappa/lambda FLC ratio indicates an excess of one light chain type versus the other, and is interpreted as a surrogate for clonal expansion of plasma cells. The assay is used to monitor patients with oligo-secretory or non-secretory myeloma and primary amyloidosis[16,17].

Asymptomatic myeloma with a high risk of progression to symptomatic disease is identified by the presence of extensive bone marrow (BM) infiltration, abnormal free light chain (FLC) ratio and serum monoclonal (M)-protein >3 gr/dl whereas the type of heavy (IgG vs IgA) or light chain or immunoparesis of the uninvolved immunoglobulins were not. Abnormal marrow signal of magnetic resonance imaging of the spine was associated with a significant risk of progression (median 15 months, p=0.001). Extensive BM infiltration >60% (hazard ratio, HR: 13.7, p<0.001) and FLC ratio>100 (HR: 9, p=0.003) independently identified a 'very high-risk' group[18].

The quantitative assay for free light chains (FLCs) is a recently introduced commercial test reported to be sensitive and specific for detecting FLC diseases such as primary systemic amyloidosis (AL), light chain deposition disease (LCDD), non-secretory multiple myeloma (NSMM), and light chain multiple myeloma. The authors performed the FLC assay and found the results to be consistent with published data[19].

Serum free light chains (FLC) are present in the serum and urine of many patients with monoclonal gammopathies and is useful in the management of light chain MM, non-secretory MM and AL amyloidosis. It cannot be recommended for monitoring intact immunoglobulin multiple myeloma[20,21].

The serum immunoglobulin-free light chain (FLC) assay measures levels of free kappa and lambda immunoglobulin light chains. There are three major indications for the FLC assay in the evaluation and management of multiple myeloma and related plasma cell disorders (PCD). In the context of screening, the serum FLC assay in combination with serum protein electrophoresis (PEL) and immunofixation yields high sensitivity, and negates the need for 24-h urine studies for diagnoses other than light chain amyloidosis (AL). Second, the baseline FLC measurement is of major prognostic value in virtually every PCD. Third, the FLC assay allows for quantitative monitoring of patients with oligosecretory PCD, including AL, oligosecretory myeloma and nearly two-thirds of patients who had previously been diagnosed to have non-secretory myeloma. In AL patients, serial FLC measurements outperformed PEL and immunofixation. In oligosecretory myeloma patients, serial FLC measurements reduce the need for frequent bone marrow biopsies. In contrast, there is no data supporting the use of FLC assay in place of 24-h urine PEL for monitoring or for serial measurements in PCD with measurable disease by serum or urine PEL. This paper provides consensus guidelines for the use of this important assay, in the diagnosis and management of clonal PCD[22,23,24].

Our case had diffuse homogenous deposition in the liver prompting suspicion of amyloidosis which was disproved on further biopsy of the abdominal fat which was negative for amyloid. There are few reports of NSMM being associated with amyloidosis. An attempt has been made to explain the lack of monoclonal immunoglobulins in the serum and urine, although extensive organ amyloidosis of AL type (kappa-light chains) has been found. The immunoglobulins get degraded on excretion or pathologic immunoglobulins are secreted as amyloid proteins which polymerize into amyloid fibrils[25,26].

Patients with multiple myeloma and NSMM are prone to having infections due to decreased levels of polyclonal serum immunoglobulis.*Pneumococcal, Haemophilus influenzae B*, and *Pneumocystis carinii* infections are seen commonly with myeloma[27]. Infections are the main cause of morbidity and mortality in multiple myeloma due to impaired humoral immunity. Infections of the urinary tract with *Escherichia coli, Pseudomonas, Proteus and Klebsiella* are common. These infections result in sepsis and the resultant sepsis can be fatal in nearly 20% of patients [28].

An increased reactivation of *Herpes simplex and Herpes zoster* infections in patients treated with novel anti-myeloma drugs like bortezomib has been seen. Stem cell transplantation, which is being used for treatment of multiple myeloma is associated with an increased risk of infection with *Clostridium difficile*, cytomegalovirus and opportunistic moulds[29]. After diagnosis, gram negative bacilli and *Staphylococcus aureus* infection increases markedly and are responsible for >90% deaths from infection[30].

Conclusion

A high degree of suspicion for a haematological malignancy is warranted in a case of recurrent anaemia despite blood transfusions,repeated infections, generalised lymphadenopathy and hepatosplenomegaly. A bone-marrow examination with immunohistochemistry is helpful in such cases to establish haematological malignancy, which can be supported by ancillary tests like serum protein electrophoresis with immunofixation, Free-Light Chain assay and X-ray for lytic lesions in bone,where indicated.

References

1) Middela Seshikanth , Kanse Prakash. Nonsecretory multiple myeloma. Indian Journal of Orthopaedics.2009; 43(4):408-411.

2) Amir J, Forman WB, Rassiga A, Bernier GM. Nonsynthetizing multiple myeloma. Haematologia (Budap).1977;11(1-2):73-7.

3) Ishida T, Dorfman HD. Plasma cell myeloma in unusually young patients: a report of two cases and review of the literature. Skeletal Radiol. 1995 Jan;24(1):47-51.

4) Sureda A, Pais J.R, Pascual J, Perez Vaquero MA, Hernando' JC. Non-secretory multiple myeloma presenting as primary plasma cell leukaemia. Postgrad Med J. 1992; 68: 470 - 472

5) Cavo M, Galieni P, Gobbi M, Baldrati L, Leardini L, Baccarani M, Tura S. Nonsecretory multiple myeloma. Presenting findings,clinical course and prognosis. Acta Haematol. 1985;74(1):27-30.

6) Rubio-Felix D, Giralt M, Giraldo MP, Martinez-Peñuela JM, Oyarzabal F, Sala F, Raichs A. Nonsecretory multiple myeloma. Cancer. 1987 May 15;59(10):1847-52.

7) Smith DB, Harris M, Gowland E, Chang J, Scarffe JH. Non-secretory multiple myeloma: a report of 13 cases with a review of the literature. Hematol Oncol. 1986 Oct-Dec;4(4):307-13.

8) da Silva Rodrigo Lopes, Monteiro Alexandra, Veiga Joana. Non-Secretory Multiple Myeloma Relapsing as Extramedullary Liver Plasmacytomas. J Gastrointestin Liver Dis. 2011; 20(1): 81-83.

9) Kuyama J, Kosugi S, Take H, Matsuyama T, Kanayama Y. Non-secretory multiple myeloma with azurophilic granules and vacuoles: an immunological and ultrastructural study. Intern Med. 2004 Jul;43(7):590-4.

10) Savage DG, Zipin D, Bhagat G, Alobeid B. Hemophagocytic, non-secretory multiple myeloma. Leuk Lymphoma. 2004 May;45(5):1061-4.

11) Raubenheimer EJ, Dauth J, Senekal JC. Non-secretory IgA kappa myeloma with distended endoplasmic reticulum: a case report.Histopathology. 1991 Oct;19(4):380-2.

12) Bladé J, Kyle RA Nonsecretory myeloma, immunoglobulin D myeloma, and plasma cell leukemia. Hematol Oncol Clin North Am. 1999 Dec;13(6):1259-72.

13) Prakash MS, Baliga KV, Singh AP, Mishra DK. Non-secretory multiple myeloma with hypercalcemic acute renal failure. J Assoc Physicians India. 2002 Oct;50:1330-1.

14) Whicher JT, Davies JD, Grayburn JA. Intact and fragmented intracellular immunoglobulin in a case of non-secretory myeloma. J Clin. Path.1975;28:54-59

15) Sheehan T, Sinclair D, Tansey TP, O'Donnell JR. Demonstration of serum monoclonal immunoglobulin in a case of non-secretory myeloma by immunoisoelectric focusing. J Clin Pathol 1985;38:806-809.

16) Rajkumar S. Vincent. Multiple Myeloma. Curr Probl Cancer. 2009 Jan–Feb; 33(1): 7–64.

17) Viroj Wiwanitkit. Nonsecretory multiple myeloma, how to make a diagnosis? Indian J Orthop. 2010 Jan-Mar; 44(1): 112.

18) Kastritis E, Terpos E, Moulopoulos L, Spyropoulou-Vlachou M, Kanellias N, Eleftherakis-Papaiakovou E, Gkotzamanidou M, Migkou M, Gavriatopoulou M,Roussou M, Tasidou A, Dimopoulos MA. Extensive bone marrow infiltration and abnormal free light chain ratio identifies patients with asymptomatic myeloma at high risk for progression to symptomatic disease. Leukemia. 2013 Apr;27(4):947-53.

19) Katzmann JA, Abraham RS, Dispenzieri A, Lust JA, Kyle RA. Diagnostic performance of quantitative kappa and lambda free light chain assays in clinical practice. Clin Chem. 2005 May;51(5):878-81. Epub 2005 Mar 17.

20) Guenet L, Decaux O, Lechartier H, Ropert M, Grosbois B. Usefulness of a free light chain immunoassay in serum for the diagnosis and the follow-up of monoclonal gammopathy. [Article in French]. Rev Med Interne. 2007 Oct;28(10):689-97. Epub 2007 May 25.

21) Jung S, Kim M, Lim J, Kim Y, Han K, Min CK, Min WS.Serum free light chains for diagnosis and follow-up of multiple myeloma.[Article in Korean] Korean J Lab Med. 2008 Jun;28(3):169-73.

22) Dispenzieri A, Kyle R, Merlini G, Miguel JS, Ludwig H, Hajek R, Palumbo A, Jagannath S, Blade J, Lonial S, Dimopoulos M, Comenzo R, Einsele H, Barlogie B, Anderson K, Gertz M, Harousseau JL, Attal M, Tosi P, Sonneveld P,

Boccadoro M, Morgan G, Richardson P, Sezer O, Mateos MV, Cavo M, Joshua D, Turesson I, Chen W, Shimizu K, Powles R, Rajkumar SV, Durie BG; International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders. Leukemia. 2009 Feb;23(2):215-24. Epub 2008 Nov 20.

23) Sthaneshwar P, Nadarajan V, Maniam JA, Nordin N, Gin Gin G. Serum free light chains: diagnostic and prognostic value in multiple myeloma.Clin Chem Lab Med. 2009;47(9):1101-7.

24) Radovic V, Mijuskovic Z, Tukic Lj, Djurdjevic P, Stojanovic J, Zlatkovic M. Free light chains ratio as a marker to estimate prognosis and survival in patients with multiple myeloma and primary amyloidosis. J BUON. 2012 Jan-Mar;17(1):110-5.

25) Richter S, Makovitzky J.Case report: amyloid tumors in a case of non-secretory multiple myeloma. Acta Histochem. 2006;108(3):221-6. Epub 2006 May 22.

26) Gafumbegete E, Richter S, Jonas L, Nizze H, Makovitzky J. Nonsecretory multiple myeloma with amyloidosis. A case report and review of the literature. Virchows Arch. 2004 Nov;445(5):531-6. Epub 2004 Jul 29.

27) Nau Konrad C, Lewis William D. Multiple Myeloma: Diagnosis and Treatment. Am Fam Physician. 2008;78(7):853-859, 860

28) Kang J, Kumar, A, Monteleone C. Multiple Myeloma Presenting as Recurrent Sinopulmonary Infections. Southern Medical J. 2010;103(3): 260-261.

29) Nucci Marcio, Anaissie Elias. Infections in Patients with Multiple Myeloma in the Era of High-Dose Therapy. Clin Infect Dis. 2009;49 (8):1211-1225.

30) Dispenzeieri A,Lacy MQ,Greipp PR. Multiple Myeloma. Wintrobe's Clinical Hematology. Philadelphia;Lippincott Williams and Wilkins:Vol II,2nd Edition;2009:Pg 2377.

Answer to : **Diagnose the condition**

ECG shows Normal sinus rhythm; Tall peaked P waves were seen more evident in lead V2 and II. QRS is broad and splintered suggesting an intraventricular conduction defect. The patient was diagnosed to have Ebsteins anomaly on Echocardiogram.

Ebsteins anomaly: It is a congenital anomaly of the right heart, where the septal tricuspid leaflet is apically displaced and right atrium is large due to atrialisation of right ventricle. ECG is seldom normal even in mild anomaly. A confident diagnosis can be made on the ECG per se. These tall P waves are characteristically described as Himalayan P waves, occuring due to right atrial conduction disturbance. Prolongation of QRS is due to prolonged activation of the atrialised RV, which leads to Bizzare second QRS attached to first normal QRS. Other common ECG findings of the condition include, prolonged PR, atrial flutter/fibrillation, type B WPW pattern.

- **Dr.M.Chokkalingam,** Consultant Cardiology, CSSH.

"Whey" to Relief in Type II Diabetes

Post-prandial glucose surge is considered to be responsible for most of the type II diabetes complications such as, cardiovascular disease, retinopathy, renal damage and dementia. A study conducted in Tel Aviv University has found a new solution to these post meal glucose surges: consumption of "Whey" protein concentrate (Daniela Jakubowiczet al. Incretin, insulinotropic and glucose-lowering effects of whey protein pre-load intype 2 diabetes: a randomised clinical trial. Diabetologia, 2014; 57 (9): 1807 DOI: 10.1007/s00125-014-3305-x).Whey is the watery portion of curdled milk. In the study, whey protein concentrate was administered 30 minutes before a high glycaemic breakfast. Blood glucose, insulin and intact Glucagon-like Protein 1 (GLP-1) levels were estimated at half hourly intervals for 3 hours following the breakfast. The study found that glucose levels were 28% lower, and insulin/GLP-1 levels higher, in whey protein treated individuals than in controls. Whey protein acts by stimulating the release of GLP-1 which in turn increases the levels of insulin. Whey protein concentrate promises to be a novel solution to a difficult problem.

- Dr. K. Ramesh Rao

Case Report

Unexplained Hypotension Under General Anaesthesia

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Case Report

A 39 years aged young male with hypertension and ischemic heart disease of 4 years duration on medical management, presented with lumbar canal stenosis involving L3-L4 and L4-L5 levels for surgical decompression. Routine preoperative assessment including cardiac evaluation revealed regional wall motion abnormality in the echocardiogram with LVEF of 56%. He had moderate effort tolerance and was planned for surgery under ASA grade II. The patient was adequately fasted and pre-medicated with a benzodiazapine and H2-antagonist. He was advised to skip ACE inhibitors on the morning of surgery and to continue with antiplatelet agents. The patient was monitored as per ASA standard including invasive BP (right radial artery) monitoring. He had a stable induction with IV Fentanyl 100 mcg and IV Propofol 180 mg and was intubated after muscle relaxation with IV Vecuronium 8 mg. In addition the patient was also given 10mg of IV Esmolol to attenuate the stress response due to larngoscopy and intubation.

The surgery was done in the prone position and anaesthesia was maintained with Isoflurane, air and oxygen. Since the patient's intraoperative BP was gradually dropping and the urine output was falling, he was managed initially with 2 litres of intravenous crystalloids and then 500ml of colloid(Gelofusine) to maintain the MAP above 70-80 mmHg. However, following administration of the colloid, there was sudden drop in BP to 60/40 mmHg. He was given additional intravenous boluses of crystalloids. IV Ephedrine 6 mg boluses (to a total of 36 mg) and IV Phenylephrine 100 mcg boluses (to a total of 300 mcg)were administered and then a dopamine infusion was started at 10 mcg $kg^{-1}min^{-1}$ with no improvement in the BP. Given his past medical history, a cardiac etiology was suspected for the hypotension.

At the end of surgery (in about 10 minutes time), when the drapes were removed and the skin was exposed, extensive erythrodermic rashes were noticed over the thorax, abdomen, arms and legs raising the doubt of a possible hypersensitivity reaction to one of the anaesthetic agents. We suspected anaphylaxis and the patient was immediately given IV Adrenaline (1 cc of 1:10000 solution), IV Chloramphenicramine 25 mg and IV Hydrocortisone 100 mg. The BP rapidly improved to 100/72 mmHg with a stable heart rate. Other signs of anaphylaxis were ruled out. The patient was extubated after adequate reversal and shifted to the ICU in a stable condition for observation.

after adequate reversal and shifted to the ICU in a stable condition for observation.

Discussion

Anaphylactic and anaphylactoid reactions are sudden and dose independent. They occur mostly in individuals who are already sensitized but may occur even on first exposure to any of the anaesthetic drugs or colloids used during the surgery. The manifestation of anaphylactic and anaphylactoid reactions are clinically indistinguishable. Anaphylactic reactions are IgE mediated and are detected by the presence of positive in-vitro and in-vivo tests and the release of tryptase, a mast cell protease enzyme during the reactions. Anaphylactoid reactions occur through a direct nonimmune mediated release of mediators or complement activation. Though they are IgE independent anaphylactoid reactions can be associated with activation of mast cells and/or basophils and raised tryptase levels[1]. Though anaphylactic reactions are rare in occurrence, they may occur intra-operatively in patients under anaesthesia which often go unnoticed.

Since the main features of anaphylaxis such as hypotension and bronchospasm have many other common causes, the recognition of such hypersensitivity reactions during anaesthesia is usually delayed. Anaphylactic reactions in operation rooms can occur due to various allergens, particularly drugs like muscle relaxants, NSAIDS, antibiotics, hypnotics and certain intravenous colloid solutions. Natural rubber latex materials like gloves and the Foley catheter are also common trigger factors for hypersensitivity reactions. In this case we had not given any antibiotics or NSAIDS intra-operatively, so it was thought that either the muscle relaxant or the colloid solution could have been the trigger for anaphylactic reaction. Muscle relaxant was given at induction and was associated with no haemodynamic changes. But the sudden hypotension following the administration of intravenous gelofusine lead us to conclude that the colloid solution was the cause of anaphylaxis. There are very few reports of colloids causing anaphylaxis. Polyzoiset al[2] has reported a similar kind of anaphylactic reaction due to gelofusine during an orthopedic surgical procedure.

Plasma expanders such as colloids are commonly used during major surgeries with excessive blood loss. They play a major role in resuscitation of the severely hypovolaemic patients. The incidence rate of anaphylactoid reaction to gelofusine that contains

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succinylated gelatin and other plasma expanders varies between 0.07–0.15%[3,4]. However with increasing use of such plasma expanders, the reports of such adverse reactions are increasing in the literature[5-8].

In a large multi-centred prospective trial involving 2,00,906 infusions of colloid substitutes conducted by Ring and Messner, 69 cases of anaphylactoid reactions were observed. Specifically, the incidence of severe reactions such as shock, cardiac and/or respiratory arrest was found to be 0.003% for plasma protein solutions, 0.006% for hydroxyethylstarch, 0.008% for dextran and 0.038% for gelatin solutions[4]. Vervloet et al, reported 3 cases of anaphylaxis due to Plasmagel, a modified fluid gelatin. One of these occurred on first exposure during the surgery and in another patient a repeated infusion of plasmagel caused anaphylactic shock[6].

Diagnosis

The sudden increase in serum tryptase levels are indicative of mast cell degranulation and are the only indicative test to narrow down the diagnosis to anaphylaxis. Concentrations peak after an hour of the hypersensitivity reaction and usually last for several hours thereafter. Serial measurements are more specific and sensitive than a single measurement in the confirmation of anaphylaxis. The collected blood samples are needed to be refrigerated before sending to the laboratory. Comparison with the baseline values, taken during convalescence may confirm or exclude the diagnosis. In this case we did not check the serum tryptase level since it was not available in the institute. The activated basophils express lysosomal membrane glycoprotein CD63 on their surface which can be detected in a method called basophil activation test(BAT). Apostolou et al[9] have reported the use of basophil activation test as a reliable assay to detect gelofusine sensitivity. In addition anaesthesiologists should also recognize other possible non-allergic causes for the reaction.

Management

Initial management of anaphylaxis should follow the ABC approach, limb elevation and discontinuation of the suspected drug or intravenous colloid solution. Adrenaline (epinephrine) is the most effective drug in anaphylaxis and should be given as early as possible. It effectively reverses peripheral vasodilation and reduces oedema. Its beta-receptor stimulation helps in dilatation of the bronchial airways, potentiates myocardial contraction, and suppresses the release of histamine and leukotriene. Early administration of adrenaline attenuates the severity of IgE-mediated allergic reactions. There is greater margin of safety for the intramuscular route though experienced specialists give adrenaline 1mcg Kg-1 intravenously for anaphylaxis. Subcutaneous or inhaled route for adrenaline may not be effective and is not recommended.

Intravenous fluid challenge with crystalloids 20ml Kg-1 and oxygen supplementation should be administered as soon as possible. Antihistamines (H1-antihistamine) as a second line drug in the management of anaphylaxis may help counter histamine-mediated vasodilation and bronchoconstriction. Corticosteroids may help prevent or control the reactions. The dose of IV hydrocortisone varies from 100-200mg depending on the age and weight of the patient. In case of severe bradycardia which develops in some patients after an anaphylactic reaction IV atropine may be considered. Glucagon may be considered to treat an anaphylactic reaction in patients on beta-blockers.

Conclusion

Anaesthesiologists and surgeons should always be suspicious and vigilant to diagnose rare causes of uncontrolled hypotension which may be hidden under the surgical drapes like in this case. A portion of the skin has to be made visible to be observed by the anaesthesiologist through the duration of surgery irrespective of the nature of the surgery and position of the patient. Though anaphylactoid reactions occur commonly with drugs used during anaesthesia, the colloid plasma expanders also carry the risk of hypersensitivity reactions. Plasma expanders provide intravascular volume expansion and help reduce transfusion requirements. However, these agents should be handled with caution. A high index of suspicion and a prompt diagnosis should ensure successful resuscitation in the event of anaphylaxis.

References

1) Hepner DL, Castells MC. Anaphylaxis during the perioperative period. Anesth Analg 2003; 7:1381-95.

2) Polyzois I, Lampard A, Mohanlal P, Tsiridis E, Manidakis N, Tsiridis E. Intraoperative anaphylaxis due to gelofusine in a patient undergoing intramedullary nailing of the femur: a case report. Cases Journal 2009; 2:12.

3) Mishler JMt. Synthetic plasma volume expanders – their pharmacology,safety and clinical efficacy. Clin aematol 1984; 13:75-92.

4) Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. Lancet 1977; 1:466-9.

5) Jenkins SC, Clifton MA: Gelofusine allergy – the need for identification jewellery. Ann R Coll Surg Engl 2002; 84:206-7.

6) Vervloet D, Senft M, Dugue P, Arnaud A, Charpin J. Anaphylactic reactions to modified fluid gelatins. J Allergy Clin Immunol 1983; 71:535-40.

7) Freeman MK. Fatal reaction to haemaccel. Anaesthesia 1979; 34:341-3.

8) Prevedoros HP, Bradburn NT, Harrison GA. Three cases of anaphylactoid reaction to Haemaccel. Anaesth Intensive Care 1990; 18:409-12.

9) Apostolou E, Deckert K, Puy R, Sandrini A, de Leon MP, Douglass JA, et al. Anaphylaxis to Gelofusine confirmed by in vitro basophil activation test: a case series. Anaesthesia 2006;61:264-8.

Class Room

Management of Acute Ischemic stroke

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Introduction

Ischemic stroke is a major devastating neurological problem which may result in severe disability and can lead to mortality at times. It is frequently associated with diabetes mellitus, hypertension, hyperlipidemias and cardiac diseases. The advent of acute thrombolysis and endovascular interventions[1] is showing good results in the outcome of acute stroke. There is a limited time window for acute intervention as ischemic tissue may not be salvageable if irreversible damage to the ischemic region sets in. Hence time is very precious in acute management; the concept of "Brain attack", like heart attack is gaining popularity to stress emergency treatment.

Emergency room management

Acute thrombolysis[2,3,4] is possible only with teamwork involving public, ambulance personnel, emergency physicians, neurologist, intensivists and the nursing staff. The treatment cascade includes selection of cases, evaluation and acute treatment protocol.

When patients with suspected stroke/TIA (Transient Ischemic attack) are received at the emergency department, the stroke team must be activated to ensure adequate and timely evaluation of the high risk patients. Vitals of the patient including pulse oximetry should be monitored, and if need be oxygen therapy has to be instituted. If the patient is hypotensive, normotension has to be established; however, hypertension should not be treated unless there is suspicion of intracranial haemorrhage. Intravenous access should be established. 12- lead ECG should be obtained and patient's capillary blood glucose has to be monitored frequently. Blood should also be sent to test for renal function, serum electrolytes, serum glucose, coagulation (PT, INR, aPTT) and cardiac enzymes (CK, CK-MB, Trop).

Detailed history including the symptoms and time of onset and evolution should be obtained as it is essential for planning and initiating the treatment. Previous treatment history, particularly related to anti-coagulants and antiplatelet agents, previous history of stroke, head injury, previous episode of any brain haemorrhage and major surgeries undergone recently should also be obtained. History related to co-morbidities such as hypertension and diabetes mellitus and their recent values and medication history should be included. A quick neurological examination should be conducted that includes level of consciousness, focal neurological deficit including arm/leg weakness, speech and visual disturbances and sensory impairment. Carotid pulsations should be felt on both sides to check any reduction or diminished pulsation and also should be auscultated for any bruit. Heart sounds must be auscultated for murmurs, if present.

Neurological Evaluation

The important phases in the management of patients presenting with stroke like symptoms include suspicion of the diagnosis of stroke based on clinical features, confirmation of the diagnosis, determining the stroke type, etiology and management planning.

When a patient is evaluated for any of the thrombolytic therapies, it is vital to evaluate the patient as soon as practicable. The severity of stroke is quickly evaluated through the NIHSS (National Institute of Health Stroke Scale), which plays an important role in the criteria for intra venous TPA (Tissue Plasminogen Activator), in acute ischemic stroke patients (Table 1).

Investigations recommended before initiating reperfusion therapy are chest X-Ray to rule out aortic dissection which can mimic stroke, routine blood investigations and urine analysis and coagulation studies. Other investigations are required if there is a family history of recurrent miscarriages and vasculo-embolic events including anti-Thrombin III, Protein C and S, G20210A prothrombin gene mutation, APLA (Anti Phospholipid Antibodies) and Factor V Leidin. Pregnancy test should be done, since CT and intravenous thrombolysis is contra-indicated in pregnant women. Blood culture should be done if endocarditis is suspected. Lumbar puncture is mandatory during the hyper acute phase to confirm the diagnosis.

Neuro Imaging

Early diagnosis of brain hemorrhage can be life-saving. Imaging of brain parenchyma is crucial to exclude or confirm the presence of cerebral hemorrhage. It is essential to assess the extent of brain injury and to select the patients who are likely to benefit from reperfusion

therapy. Imaging of vasculature can identify the vascular lesion responsible for cerebral ischemia.

Stroke patients presenting within the therapeutic time window should receive intravenous r-tPA and vascular imaging should be performed once r-tPA is started to determine the nature and location of arterial occlusion.

Table 1 - NIHSS

Level of Consciousness	Alertness (0 – 3) Orientation (0 – 2) Ability to follow commands (0 – 2)
Gaze	Normal eye movements (0) Gaze palsy (1) Forced eye deviation (2)
Vision	Normal (0) Partial hemianopia (1) Complete hemianopia (2) Blindness (3)
Facial palsy	Symmetric face (0) Mild paralysis (1) Partial paralysis (2) Complete paralysis (3)
Motor strength (Arms and Legs)	Separate score for each limb- No drift (Can hold limb up for 10 seconds) (0) Drift present (1) Some effort against gravity (2) No effort against gravity (3) No detectable movements (4)
Limb ataxia	Only scored, if out of proportion to weakness – Absent (0) Present in one limb (1) Present in two limbs (2)
Sensory loss	Measured to pin-prick or noxious stimuli present (0) Mild to moderate loss of sensation (1) Severe to total loss of sensation (2)
Best language	Testing both expressive and receptive aphasia and dysarthria- No Aphasia (0) Mild to Moderate Aphasia (1) Severe Aphasia (2) Global Aphasia/Mute (3)
Dysarthria	Normal Speech (0) Mild to Moderate slurred speech (1) Severe, unintelligible slurred speech (2)
Extinction and Inattention	No Neglect (0) Neglects Visual, tactile, auditory, spatial stimuli(1) Has profound hemi-attention/ does not recognize own body part (2)

minimum score = 0.

maximum score (maximum disability i.e., coma) = 42.

minimum disability is by nihss score of less than 4.

maximum disability is reflected by a NIHSS score of more than 20.

Thrombolysis

Once a diagnosis of ischemic stroke is made, patient`s eligibility for re-perfusion therapy is to be assessed. Re-perfusion therapy include:

- Intravenous thrombolysis.
- Intra-arterial thrombolysis.
- Endovascular treatment.
- Combination therapy.
- Hypertensive therapy.

Thrombolysis is indicated in patients more than 18yrs of age, in cases of ischemic stroke causing a measurable neurological deficit (NIHSS) and when stroke onset to needle time is less than 3 hours (Table 1).

Absolute contra-indications include minor or rapidly resolving stroke symptoms, other stroke or serious head trauma within the past 3 months, major surgeries within 14 days, known history of intracranial hemorrhage, sustained systolic blood pressure of more than 185 mmHg or diastolic blood pressure of more than 110 mmHg, symptoms suggestive of SAH, gastrointestinal or urinary tract hemorrhage within the past 21 days, arterial puncture at non compressible site within the past 7 days, heparin therapy within the last 48 hours and platelet count less than 1, 00,000/cu.mm. Relative contra-indications include seizure at the onset of stroke, serum glucose < 50mg/dl or >400mg/dl, haemorrhagic eye disorder, myocardial infarction in the past 6 weeks, suspected septic embolism, infective endocarditis and International Normalized ratio (INR) > 1.7.

IV Thrombolysis

If an acute stroke patient fulfills all the inclusion and none of the absolute exclusion criteria, treatment with IV r-tPA at a dose of 0.9mg/kg. (max.Dose of 90mg) with a 10 % bolus over 1 min and remaining dose over 60 minutes should be considered. After administration, BP should be kept within the above parameters & ICU admission with neurological examination, monitoring every hour is essential for atleast 24 hours. Nasogastric tube, foley's catheter and central line should be avoided for 24 hours after thrombolytics are given. There are around seven major trials evaluating the use of thrombolytic agents in the treatment of acute ischemic stroke.

IA Thrombolysis

Intra-arterial (IA) r-tPA is not superior to intravenous (IV) treatment. IA is particularly helpful when IV is contra-indicated, for example, in post-operative stroke. Studies suggest that IA thromobolysis is an effective and relatively safe therapy in patients with large vessel occlusions who are otherwise expected to have poor re-cannulation with IV thrombolytic agents. Mechanical disruption of the clot can be used with IA thrombolysis and it is helpful when IV is contra-indicated.

New re-perfusion therapies are Desmoteplase, a plasminogen activator, Abciximab, glycoprotein IIb, IIIa receptor inhibitor, use of external Trans cranial

Doppler (TCD), permissive hypertensive therapy and high dose albumin. Use of aspirin 160-300 mg daily and IV heparin can be useful in patients who are not eligible for reperfusion therapy.

Management of hydration and fluid status

Hypovolemia should be avoided in embolic and carotid strokes. Isotonic crystalloids (0.9 % NS) can be used. Hypotonic fluids (0.45 % saline or D5W) aggravate cerebral edema and should be avoided. Also, hypervolemia should be avoided in hemorrhagic or large strokes.

Management of blood sugar

Hyperglycemia promotes anaerobic metabolism and lactic acidosis within the ischemic tissue, thus worsening outcome. It also increases the risk of hemorrhagic transformation after thrombolysis. Hyperglycemia is best managed by short acting insulin and the target glucose level should be less than 200 mg /dl.

Management of blood pressure

Most of the time high blood pressure comes down spontaneously. There is no need to lower BP urgently. Anti-hypertensive drugs are required if systolic BP is more than 210 and diastolic BP more than 110. There are certain situations in which BP has to be brought down, like thrombolysis, aortic dissection, myocardial infarction and heart failure.

Conclusion

Initial few hours are critical in the outcome of acute ischemic stroke. An expert team working quickly and efficiently can minimize the mortality and morbidity. Newer therapeutic options like endovascular technology improves stroke outcome.

References

1) Huded V, Nair RR, de Souza R, Vyas DD. Endovascular treatment of acute ischemic stroke: An Indian experience from a tertiary care centre. Neurol India. 2014 May-Jun; 62(3):276-9. doi: 10.4103/0028-3886.136919.

2) Higashida T. Thrombolysis in acute ischemic stroke. Intra-arterial and intra-venous. Interv Neuroradiol. 2003 Oct 10; 9(2):39-40.

3) Devos D, Sevin M, De Gaalon S, Lintia-Gaultier A, Guillon B. Management of ischemic stroke in the hyperacute phase. Panminerva Med. 2013 Mar; 55(1):59-78.

4) Calvet D, Bracard S, Mas JL.Treatment of arterial and venous stroke. Experts'recommendations: stroke managementin the intensive care unit.French Society of Intensive Care. Rev Neurol (Paris) 2012 Jun;168(6-7):512-21. doi: 10.1016/j.neurol.2012.01.587.

5) Alonso de Leciñana M, Egido JA, Casado I, Ribó M, Dávalos A, Masjuan J, Caniego JL, et al., Guidelines for the treatment of acute ischaemic stroke. Neurologia. 2014 Mar; 29(2):102-22. doi: 10.1016/j.nrl.2011.09.012.

Baked Fish is Brain's relish!

As the average lifespan of humans lengthens, dreaded diseases of the advancing age like dementia (particularly Alzheimer's) are becoming more common. According to one estimate, there will be around 80 million people with dementia by 2040. So, how to retain a healthy brain as we grow older? Several past studies have linked high intake of omega-3 fatty acid rich foods (fish, nuts, certain vegetable oils) to improved brain health. Until now it was considered to be due to the anti-oxidant properties of fish irrespective of how it was consumed. But now in a new study carried out in UCLA (Cyrus A. Raji et.al , Regular Fish Consumption and Age-Related Brain Gray Matter Loss. American Journal of Preventive Medicine, 2014; DOI: 0.1016/j.amepre.2014.05.037), the investigators found that individuals who ate fish baked or broiled at least once a week, had enlarged grey matter in the regions of brain connected with cognition and memory and were also more likely to have college education compared with those who did not eat fish. This was not related to the levels of omega-3 fatty acid. So, life style (how we eat) also contributes to brain health. Remember to eat your fish baked or broiled, so that you can remember!

- Dr. K. Ramesh Rao

From the Pages of History

Prof. B. Ramamurthi (1922-2003), The Pioneer Neurosurgeon

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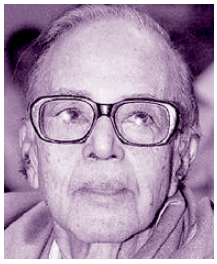

Prof. B. Ramamurthi

Professor B. Ramamurthi (popularly known as BRM), was the pioneer Neurosurgeon, recognized as the Father of Indian Neurosurgery. He was born on 31st January, 1922 at Sirkali in Tamil Nadu. He completed his MBBS in 1943, MS (General Surgery) in 1947 from Madras Medical College and FRCS (Ed) thereafter. He was sent for training in Neurosurgery by the Government of Madras to Newcastle (UK) in 1949 at a time when Neurosurgery was not known in India. He was trained under Prof. G. F. Rowbotham at Newcastle. He also spent time with doyens of Neurosurgery like Prof. Geoffrey Jefferson (Manchester), Prof. Krayenbuhl (Zurich), Dr. Edward Busch (Copenhagen), Prof. Olivecrona (Stockholm) and Prof. Wilder Penfield (Montreal). He returned to Madras in 1950, bringing back with him the traditions of the British, American, Canadian and European schools of Neurosurgery and started Neurosurgery in Madras General Hospital and Madras Medical College on October 24th (Vijayadasami day). This was the second Neurosurgery department to be started in India(Prof. Jacob Chandy had started his department at Christian Medical College, Vellore a year earlier). Against great odds and difficulties, Dr B. Ramamurthi built and developed the neurosurgical department, which later developed into the Institute of Neurology at the Government General Hospital, where he was the Professor and Head till his retirement in 1978. After his retirement from the Government Service, he started the Dr. A. Lakshmipathi Neurosurgical Centre, at the Voluntary Health Services Hospital, which he established in 1978. Both these centers have turned out to be institutes of academic excellence and are the major postgraduate neurosurgical training centers. He continued his untiring work till 2003, when he passed away on December 13th at the age of 81.

Major contributions to Neurosurgery and Neurosciences:

- He established Neurosurgery as a speciality in India, when very little was known about brain tumours and other surgical conditions of nervous system.
- He started Stereotactic and Functional Neurosurgery in Madras, along with his team comprising Drs. V. Balasubramaniam, S. Kalyanaraman, T. S. Kanaka and his Neurology colleagues Drs. G. Arjundas and K. Jagannathan. Madras Institute of Neurology became one of the major centers for Stereotactic Surgery and several pioneering original work was done here, which have won international acclaim.
- His work on the Surgery for Tuberculoma of brain, Angiographic appearance of brain tuberculoma, Delayed decompression for spinal cord injury, Management of growing fractures of skull are recognized internationally.
- He has trained many Neurosurgeons, who have won a place for themselves all over India and around the world.
- He along with Drs. Jacob Chandy, S. T. Narasimhan, and Baldev Singh started the Neurological Society of India (NSI) in 1951 at Madras and was its Founder-Secretary.
- He along with Prof. P.N.Tandon edited the Indian Textbook of Neurosurgery.
- He was instrumental in the establishment of the National Board of Examinations and National Brain Research Centre at Manesar, near Delhi.

Awards and Honours:

- He was awarded the prestigious Padma Bhushan, Dhanvantri awards and was made honorary Brigadier of the Indian Army.
- He was made Fellow of National Academy of Medical Sciences (1962), Fellow of the Academy of Sciences (1972), Fellow of the Indian National Science Academy (1981) and Fellow of the Royal Society of Medicine of London (1983)
- He was the President of the World Federation of Neurosurgical Societies in 1989.

References

1. Ramamurthi B: Uphill all the way - the Autobiography, 2000.
2. Sridhar K. Prof. B. Ramamurthi: The legend and his legacy. Neurol India 2004;52:27-31.

Perchlorate and IQ

It is a common knowledge that our environment carries a variety of potentially harmful chemicals. Many of these chemicals may accumulate within our blood leading to abnormally high levels. One such chemical is the common perchlorate. It is ubiquitous. Several earlier studies have established its anti-thyroid effect. It contaminates many foods and drinking water. The researchers from Boston University medical school, using the data from Controlled Antenatal Thyroid Study Cohort (Cats), examined 487 mother-child pairs and 50 women with highest perchlorate level in the body (Peter N Taylor et al. Maternal perchlorate levels in women with borderlinethyroid function during pregnancy and the cognitive development of their offspring; Data from the Controlled Antenatal Thyroid Study. The Journal of Clinical Endocrinology & Metabolism, 2014; jc.2014-1901MLA APA ChicagoBoston University Medical Center. DOI: 10.1210/jc.2014-1901) found that off-springs of such women have a subnormal IQ compared to controls. Earlier it was believed to be due to their hypothyroid state; now it appears to be due to abnormally high maternal perchlorate levels.

- Dr. K. Ramesh Rao

Chettinad
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(Deemed to be University Under Section 3 of the UGC Act 1956)

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B.Sc. Medical Bionanotechnology (3 Years)
B.Sc. Medical Biotechnology (3 Years)
B.Sc. Medical Genetics (3 Years)

II. Post Graduate Courses

Medical Post Graduate Courses - M.D. Pre and Para Clinical (3 years)

M.D. (Anatomy)
M.D. (Physiology)
M.D. (Biochemistry)
M.D. (Pathology)
M.D. (Microbiology)
M.D. (Pharmacology)
M.D. (Community Medicine)

Medical Post Graduate Courses - M.D./M.S. Clinical Courses (3 years)

M.D. (General Medicine)
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M.D. (Dermatology, Venerology and Leprosy)
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M.D. (Radio-diagnosis)
M.S. (Otorhinolaryngology)
M.S. (General Surgery)
M.S. (Obstetrics and Gynecology)

Post Graduate Courses (2 years)

M.Sc. Tissue Engineering & Regenerative Medicine
M.Sc. Medical Genetics & Molecular Diagnostics
M.Sc. Medical Bionanotechnology
M.Sc. Medical Biotechnology
M.Sc. Clinical Research & Experimental Medicine
M.Sc. Marine Pharmacology
M.Sc. Human Nutrition
M.Sc. Occupational Health & Industrial Safety
M.Sc. Health & Yoga therapy
M.Sc. Computational Biology
M.Sc. Bioinformatics
M.Sc. Counseling Psychology
M.Sc. Pharamaceutical Chemistry

Post Graduate - Super Speciality Courses D.M. / M.Ch Courses (3 years)

D.M. (Cardiology)
D.M. (Neurology)
D.M. (Neonatology)
M.Ch. (Cardio Vascular & Thoracic Surgery)
M.Ch. (Neuro Surgery)
M.Ch. (Urology)
D.M. (Medical Gastroenterology) - LOP awaited

M.Sc. - Allied Health Sciences (2 years)

Echocardiography & Cardiovascular Imaging Technology
Radiology and Imaging Science Technology

Post Graduate Courses in Nursing (2 years)

M.Sc. Medical Surgical Nursing
(Cardio Vascular and Thoracic Nursing)

Postgraduate Courses in Nursing (2 Years)

M.Sc. Medical Surgical Nursing
(Cardio Vascular and Thoracic Nursing)

III. POSTGRADUATE DIPLOMA COURSES

Postgraduate Diploma in Clinical Embryology (1 year)

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Post Basic B.Sc Nursing (2 years)

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