

## Vesico-Vaginal Fistula - Problems in Management

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The etiology of uro-genital fistulae varies geographically. In developed countries, the obstetric fistulae are practically non-existent, while in developing countries like India, still majority of fistulae are related to inappropriate care during childbirth. Most common obstetric fistulae are vesicovaginal fistulae (VVF) resulting from prolonged and obstructed labor. In few there may be associated rectovaginal, uretero-vaginal or urethro-vaginal fistulae. Obstetric fistulae are a reflection of standard of obstetric care currently available to our women.

In western world, most genital fistulae occur as a complication of gynaecological surgery (91%), radiotherapy (6%) or sometimes due to malignant process or severe pelvic disease<sup>1</sup>, while in developing countries over 80% cases follow neglected obstructed labor<sup>2</sup>, this being as high as 97-98% in northern Nigeria<sup>3</sup>.

Current data on the incidence of VVF are practically nonexistent. WHO estimates that there are two million women living with fistulae and an additional 50,000 to 100,000 new cases occur every year. The incidence of obstetric urogenital fistulae is 1.1 per 1000 births. The condition is associated with illiteracy and poorly supervised delivery. The peak incidence is in 15-19 years age group and more common in primiparas.

The overall burden of obstetric fistulae in developing world is immense, with significant social isolation and ongoing human suffering of these young women. Most patients become outcaste, many are divorced or abandoned and remain childless. The smell of urine or feces and the inability to stay dry are humiliating and uncomfortable.

Diagnosis is not difficult, but complete evaluation of bladder, ureters and kidneys and eradication of infection is essential before planning treatment. Fistulae can be surgically repaired. J. Marion Sims (1813-1884) has been called the "Father of Gynecology" for his revolutionary approach to treating the diseases of women, his major contribution being innovations in successful treatment for vesicovaginal fistula. Success rate for primary surgical repair ranges

from 88 to 93% and decreases with each successive attempt. Simple vesicovaginal fistulae can be easily repaired transvaginally, but 12-25% of complex fistulae<sup>4</sup> involving ureters, bladder, vagina and urethra, may require more difficult surgeries for their treatment<sup>5</sup>. Sometimes due to antecedent obstetric events, there is induration, fibrosis and constriction in the vagina with difficulty in mobilization of fistulous margins. For such situations, some additional reinforcement with tissue graft (Martius graft, labial fibrofatty tissue, omentum etc) is required. A careful post operative care with adequate hydration and continuous urinary drainage is important for successful outcome. Duration of bladder drainage is individualized and ranges from 1-4 weeks. Obstetric urogenital fistula can be prevented by the government's recognition of fistulae as a major public health concern, improving socio-economic condition, extending primary education particularly for girls and advice against teenage pregnancy. There is a need to have skilled birth attendant at every level, at least capable of recognizing difficult labor early and making an appropriate referral. We, as health providers can improve facilities and access for emergency obstetric care, provide social and psychological support to the patients and train doctors and nurses in the most affected parts of the world for reparative surgery.

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### ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH

The need for uniform ethical guidelines for research on human subjects is universally recognised. It has acquired a new sense of urgency as the ethical issues in the area of biogenetic research involving human subjects have become acute. Apart from the mandatory clinical trials on new drugs, a number of diagnostic procedures, therapeutic interventions and prevention measures including the use of vaccines, are being introduced which involve human subjects. Further the advent of new medical devices and radio-active materials and therapeutic benefits of recombinant DNA products have added a new dimension to the ethical issues that need to be considered before evaluating these for their efficacy, utility and safety.

Any research using the human beings as subjects shall bear in

mind the following principles of : (i) essentiality, (ii) voluntariness, informed consent, (iii) non-exploitation, (iv) privacy and confidentiality, (v) precaution and risk minimisation, (vi) professional competence, (vii) accountability & transparency, (viii) maximization of public interest and distributive justice (ix) institutional arrangements (x) public domain (xi) totality of responsibility and (xii) compliance.

Recent advances in the field of Assisted Reproductive technologies, organ transplantation, Human genome analysis and gene therapy promise unquestionable benefits to mankind. At the same time, they raise many questions of law and ethics, stimulating public interest and concern.

(Source : ICMR Publication, 2000)

## Genito-Urinary Fistula - A Review on 45 Cases

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**Abstract :** *In this prospective study of 45 cases, all the fistulas occurred outside our institution; 86.66% of them resulted from obstetric cause and the rest from gynaecological. 37.77% subjects were aged below 20 and 26.66% between 21-25 years. As high as in 48.88%, it followed first childbirth. Most of them having little or no education came from rural areas with poor socioeconomic background, 14 out of 39 obstetric fistulas had history of prolonged labour, 11 had eclampsia and 21 needed instrumental delivery. This reflects the poor obstetric care they received. We repaired the fistulas through vaginal route in 43 cases and abdominally in two women. Some cases needed repeat surgery. The overall success rate was 75.55%.*

### INTRODUCTION

The subjects with genitor-urinary fistulas suffer from constant discomfort from leakage of urine, mental agony, depression, marital disharmony and social isolation. In developing countries, most of them are young, illiterate and come from rural areas with a poor socioeconomic background.

The communication between the genital and urinary tract may be uterocervical, vesicovaginal and urethrovaginal and sometimes ureterovaginal, ureterocervical and ureterouterine. Of all these, vesicovaginal fistula is the commonest type in developing countries including ours. At the inaugural session of the XVIIth World Congress of FIGO on 02-11-2003 at Santiago, Chile, the President of FIGO, Prof. Sirish Seth, mentioned that 80,000 of genitourinary fistulas are being added every year in our planet. Such dismal picture deserves utmost attention of our fraternity. Mitigating their suffering is our moral and social obligation.

### MATERIALS AND METHODS

This prospective study was carried out in the Department of Obstetrics & Gynaecology, N.R.S. Medical College and Hospital, Kolkatta, from July 1992 to January 1998. During this period, we have treated 45 cases of genitourinary fistula. The duration of incontinence varied from one month to six years. Four cases came from Bangladesh.

### RESULTS

Of 45 cases 39 (86.66%) were obstetric in origin and 6 (13.33%) were gynaecological. Moreover 11 (28.2%) out of 39 obstetric fistulas suffered from eclampsia. Most of them having minimum or no education came from rural areas and received poor obstetric care.

**Age and Parity :** Of 45 cases, 17 (37.77%) were below the age of 20 years, 12 (26.66%) between 21-25 years, 7 (15.55%) 26-30 years, 4 (8.88%) 31-40 years and 5 cases (11.11%) above 40 years. The youngest patient in this series was aged only 12 years and the oldest 57 years. The young girl sustained street accident while moving on a bicycle and presented two years after the accident. She had fracture shaft of right femur and a spoke caused vulvo-

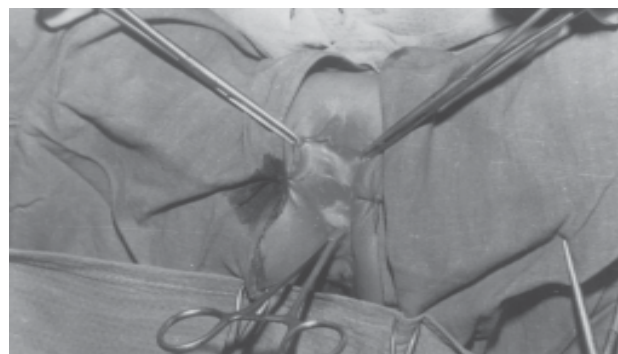
urethral injury. There was total avulsion of urethra (Fig.1). The bladder was full of brittle stones, which had to be evacuated thrice before operation. The urethra was reconstituted with vaginal flap. Table 1 shows that 22 cases (48.88%) were para 1 + 0 and seven of them lost their babies due to difficult delivery. One can imagine their mental and physical morbidity. Of 12 cases above para 3 + 0, only 5 had gynaecological fistula.

**Table - 1 : Parity Distribution (N+45)**

Parity	Number	Percentage
Unmarried	1	2.22
Para 1 + 0	22	48.88
Para 2 + 0	5	11.11
Para 3 + 0	5	11.11
Above 3	12*	26.66

\* Includes 5 gynaecological fistula

**Etiological Factors :** Out of 39 obstetric fistula, prolonged labour was responsible in 14 and instrumental delivery in 21 cases. There too was history of either prolonged or obstructed labour. Caesarean hysterectomy was responsible in 3 cases. Of gynaecological fistulas 4 resulted from abdominal and one from vaginal hysterectomy.



*Fig.1 : Urethrovaginal fistula*

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**Table - 2 : Etiological Factors (N=45)**

Obstetric Cause	Gynaecological Cause
Prolonged labour - 14	Street Accident - 1
Instrumental delivery - 21	Abdominal Hysterectomy - 4
Forceps - 17	Vaginal Hysterectomy - 1
Craniotomy - 4	
LUCS - 1	
C.S. hysterectomies - 3	
Obstetric - 39 (86.66%)	Gynaecological - 6 (13.33%)

**Preparative Investigations :** Besides routine investigations, urine culture and sensitivity was done in all the cases, EUA, swab and Dye test in 12 cases, cystoscopy in 6 and IVU in 2 cases.

**Fistula Location :** Table - 3 shows that in 17 cases (37.77%) the fistula was located in the lower third of vagina, midvaginal in 14 and in the upper third in another 14 cases. Table - 3 shows the other details as regards site, size, number and condition of surrounding tissues.

**Surgery :** The repair was done through vaginal route in 43 cases, by flap splitting technique in 42 and reconstruction of urethra in one. The oldest case, aged 57 years had Ward-Mayo's operation in a Sub-Divisional hospital and was referred to us in emergency situation with severe infection after one month. There was a rent of 2 fingers in anterior vaginal wall (Fig.2).

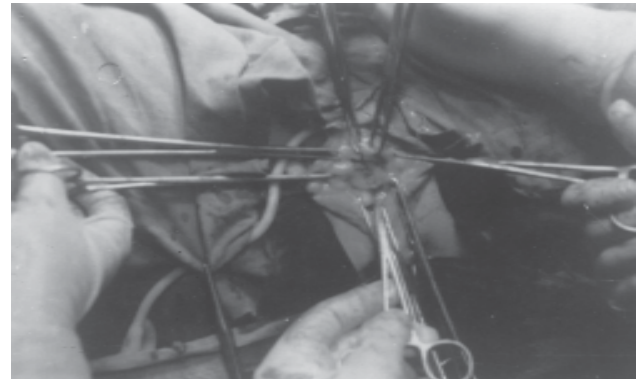
After 2 months and 9 days we had undertaken the repair which was successful. In two cases (vesicocervico-vaginal - 1, vault fistula - 1) the repair was done abdominally with the help of uro-surgeon. For bladder rent vicryl-000 was used and vicryl-00 for vagina.

**Table - 3 : Details (location) of the Fistula**

Site of Fistula	No.	Percent	Number of Fistula
Lower 1/3rd	17	37.77	Two in 5, three in 1
Juxtaurethral	15	33.33	and 4 in two cases size
Urethrovaginal	2		2 mm - 30 mm
Midvaginal	14	31.11	Bony margin 3 cases
Upper 1/3rd	14	31.11	Dense scarring - 8
Juxtacervical	6	13.33	Vaginal atresia - 2
Vesicocervico			
Vaginal	1		
Vault Fistula	7	15.55	

Martius graft (Bulbospongiosus) was used in 6 cases. As additional measure Kelly's operation was done in 4 cases for narrowing and to create angulation of vesico-urethral junction and trachelorrhaphy in one. Continuous bladder drainage was maintained for 2 weeks and intermittent clamping for 3 days.

**Results of Surgery :** Table - 4 shows results (success) of surgery. Eight cases needed repair for second time, three cases third time and one case for 4th time. The overall success rate was 75.55%.

**Fig.2 : Vesico-vaginal fistula****Table - 4 : Results of Surgery (N=45)**

No. of Attempts	n	Success Rate
First	45	28 (62.22%)
Second	8	4 (50%)
Third	3	1 (33.33%)
Fourth	1	1
Overall success		34 (75.55%)

## DISCUSSION

Genitourinary fistula is a severely demoralizing and disabling injury among women<sup>7</sup>. Majority of obstetric fistulas are preventable<sup>6</sup>. In our study 86.66% were obstetric fistula. Its incidence is very high in some African countries like Ethiopia, Somalia, Sudan, Ghana, Tanzania and Zambia<sup>6</sup>. In Bangladesh, it leads to 3.8% postnatal morbidity in women<sup>2</sup>.

As observed in this study, 37.77% of the sufferers were below 20 years and 26.66% between 21-25 years. In 48.88%, it followed first childbirth and 11.11% after second childbirth. Most of them coming from rural areas were either illiterate or with low education and poor socioeconomic background. Early child bearing, ignorance about proper antenatal care and inadequate access to quality intrapartum care are well-known contributory factors. This was also observed in Bangladesh among many other studies<sup>2</sup>. In our series, this is also substantiated by the fact that out of 39 obstetric fistulas 14 had prolonged labour, 21 needed instrumental deliveries and 3 had Caesarean hysterectomy (Table - 2). In a study of 1443 cases in northern Nigeria<sup>10</sup>, 83% of the fistulas resulted from obstructed labour and 13% from Gishiri cutting (tribal practice of cutting anterior vaginal wall for obstructed labour). In our series 4 cases of fistula occurred following hysterectomy (3 abdominal and one vaginal). In abdominal hysterectomy bladder injury usually happens while separating the bladder from the anterior surface of isthmus and supravaginal cervix. A meta-analysis of 22 centers (Melbourne institute) shows ureteral injury to be 1.6/1000 (range 0 - 14.6) and bladder injury 2.6(0.2 - 19.5/1000<sup>5</sup>. The key to success are careful dissection of bladder from vaginal wall, adequate haemostasis and proper repair in separate planes<sup>8</sup>. One has to ensure continuous bladder drainage in postoperative period<sup>9</sup>. In spite of all these, failure is not uncommon and repeat repair is



*Fig.3 : Successfully repaired VVF*

needed in a significant number of cases. In other words, repair of genitourinary fistula should be taken as a surgical challenge. In 43 cases out of 45 we adopted vaginal route. It is well-known that gynaecologists prefer vaginal approach<sup>4</sup> but urologists usually prefer abdominal route<sup>3,9</sup>. In 2 cases the repair was done transperitoneally. In several cases repeat surgery was needed (Table - 4). The overall success in our study was 75.55%. The condition of surrounding tissue was unfavourable in several cases. In a series of 132 patients<sup>1</sup>, initial success rate was 45% and after repeated attempts it was 81%. In another study of 64 cases<sup>4</sup>, the success rate was 85.9%.

## ACKNOWLEDGEMENT

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## Functional Endoscopic Sinus Surgery : 7 Year's Review

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**Abstract :** This study was conducted to assess the treatment results in patients undergoing functional endoscopic sinus surgery for chronic sinusitis, with evaluation of prognostic indicators of success and failure. A total of 266 patients who underwent Endoscopic Sinus Surgery for chronic sinusitis over a period of 7 years (from February 1995 to February 2002) were included. The diagnosis of chronic sinusitis was based on ongoing symptomatology for greater than 3 months and the presence of mucosal disease on radiological examination. A retrospective analysis was done looking at patient data, presenting symptoms, CT findings, operative details and outcome at 3 and 6 months follow up. The most common presenting complaints were olfactory disturbance followed by nasal obstruction and postnasal discharge. There was a positive history of asthma in 25.4% allergies in 13% and ASA triad in 3.3% patients. 41.7% patients had previous nasal surgeries in the past. Positive outcome was obtained in 81.0% at 3 months and 84.7% at 6 months. Revision operations were required in 7.9% patients. Minor complications were seen in 10.5% and major complications in 0.75%.

### INTRODUCTION

Chronic sinusitis is a common problem encountered by otolaryngologists worldwide. Treatment of chronic sinusitis is initially medical and those refractory to medical treatment are treated surgically. In 1901 Hirschmann<sup>1</sup> first used a modified Nitze cystoscope to examine the sinuses. Spielberg<sup>2</sup> was the first to use an endoscope to examine the maxillary sinus through the inferior meatus. Maltz<sup>3</sup> coined the term sinuscopy and used a specially made endoscope by Wolfe. The development of compact, straight and angled telescopes, plus the pioneering work of Messerklinger<sup>4</sup> Wigand et al<sup>5</sup> and others<sup>6</sup> sparked an interest in endoscopic sinus surgery. Functional endoscopic sinus surgery continues to gain popularity among otolaryngologists. This paper looks at symptoms, signs, surgical results and complications of 266 patients who underwent functional endoscopic sinus surgery in a district general hospital in UK.

### MATERIALS AND METHODS

Two hundred and sixty six (266) cases underwent clinic endoscopic evaluation and subsequent sinus surgery at the Staffordshire General Hospital, Stafford, UK, from February 1995 to February 2002. A uniform history was documented for each patient, including the location of facial pain, nasal discharge, allergic symptoms, nasal obstruction, congestion, anosmia, previous medical management and previous surgical interventions. All patients had unsuccessful medical therapy, which was usually intense.

Each patient was examined with nasal speculum and head mirror. 4 mm rigid endoscopes were used to examine the overall nasal cavity and meati. Information was recorded on the presence of a deviated nasal septum the presence of nasal discharge the character and appearance of middle and inferior turbinates the appearance of middle meatus and the presence of polyps. Diagnosis of chronic sinusitis was made on the basis of ongoing symptomatology, including nasal congestion/obstruction, facial pain/headaches and/

or olfactory disturbance greater than 3 months duration.

Initially patients were medically managed according to their symptoms and prior management. Patients who had received previous adequate medical management were evaluated with CT of the sinuses. Patients who had not received adequate medical management were started on appropriate regimen. Patient's were seen 6 weeks after medical management and if they were still symptomatic, a CT scan was performed.

### RESULTS

From February 1995 to February 2002, 289 patients underwent Functional Endoscopic Sinus Surgery (FESS). 266 case notes were available for review. Of these 266 patients 100 (37.6%) were female and 166 (62.4%) were male. The commonest presenting complaints were nasal obstruction (81.5%) and loss of sensation of smell (83.1%) followed by post nasal discharge (44.3%), headache (43.2%), sneezing bouts (38.7%), rhinorrhoea (35.7%) and midfacial pain (28.1%). A history of asthma was reported in 26.3% patients. 13.5% patients had some allergies. Aspirin sensitivity was present in 3.4% of patients. On examination 51.9% patients had deviated nasal septum, 81.2% had inferior turbinate hypertrophy, 60.9% had polyps and 62% had some pathology in middle meatus. 42.9% had previous nasal surgery. Ethmoids (anterior/posterior or both) were opened in 78.2% and frontal recess opened in 16.5% patients. In addition to FESS, septoplasty was performed in 15.8%, cauterization to inferior turbinates in 20.3% and both septoplasty and cauterization to inferior turbinates in 4.5% patients. Postoperatively no packs were put in 48.9% and moerocel pack in 18%. We had an overall complication rate of 10.9% of which 6% were immediate and 5.6% were late. We had only 1 major complication i.e. cerebro spinal fluid (CSF) leak in 1 patient (0.37%) which was recognised and dealt with at the time of operation. Minor complication rate was 10.5%. These were adhesions; primary (0.4%), reactionary (3%), secondary haemorrhage (4.1%); black eyes (0.4%), orbital fat prolapse (0.75%) and bradycardia (0.4%). Postoperatively 7.9% patients were given antibiotics, 36.5% decongestant drops and 41.7% steroid sprays.

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At 6 months *follow up* 81.9% patients were better, 10.5% same and 0.4% were worse. 7.14% patients were lost to follow up. 157 out of 266 patients were followed up after 12 months. Rest of the patients had been discharged at 6 monthly follow. At 12 months 84.7% were better and 13.4% were same. Total of 21 out of 266 (7.9%) had to undergo revision operations. 12 required 1 revision, 7 required 2 revisions and 2 required 3 revision operations. After revision FESS 13 out of 21 (61.9%) were better and 8 out of 21 (38%) were same. *Overall outcome* was 81.9% were better, 12% were same and 6% were lost to follow up.

## DISCUSSION

Family practitioners, general physicians, paediatricians, allergists and otolaryngologists see large numbers of patients with symptoms of facial pain, pressure, nasal obstruction and nasal discharge. According to the National Centre of Disease Statistics, sinusitis has become the number one chronic illness in the United States, surpassing arthritis<sup>7</sup>. For the majority of patients, sinonasal disease is a nuisance that causes absence from school, work and social functions. However it may exacerbate more serious illnesses such as asthma or chronic obstructive pulmonary disease, necessitating the use of long term daily steroids or increase in other pulmonary and cardiovascular medications. There are several ways to estimate treatment success when dealing with sinonasal disease. One is to examine the sinonasal area and see whether it is free of polypoid disease. Another is to determine patient satisfaction through relief of symptoms. Failure is determined by inability to rid patients of symptoms.

The use of endoscope as a functional tool was pioneered by Messerklinger in 1985 and has been popularised as the surgical treatment of choice for uncomplicated chronic inflammatory sinus disease. Much of the available literature concerns the theory, technique and complications of FESS. Both retrospective and prospective outcome analysis have been published with variable experimental designs, results and conclusions. The criteria used for success and failure, patient selection and the precise means and length of follow up are highly variable. Colclasure et al<sup>8</sup> had 300 patients with success rate of 94% and complications <1%. Ramadan<sup>9</sup> had 337 patients with minor complications rate of 15.1% and major complications of 1.5%. Nass et al<sup>9</sup> reported prospectively on 18 patients finding an 89% success rate postoperatively. Matthews et al<sup>10</sup> in their retrospective analysis of 155 patients determined outcome based on a subjective assessment of symptoms and physical examination. They had 90% success rate with minor complications of 1.5%.

In a prospective analysis of 250 patients Levine<sup>7</sup> found that the success of FESS (80.2%) was independent of preoperative extent of disease and concluded that patient satisfaction was the best

determinant of success. Royal College of Surgeons England audit<sup>8</sup> showed a success rate of 84% for blockage, 75% for pain relief and 96% for discharge after FESS. The overall complications were 1.4%.

Schaefer et al<sup>10</sup> reported an 83% success rate in 100 patients, using clinical improvement, complications and need for further surgery as criteria for outcome. In our patient group, the criteria for failure included recurrent or residual symptoms or the need for revision surgery with in the follow up period for 12 months. All patients who had a diagnosis of chronic sinusitis and underwent FESS were included in the study. Due to the retrospective design of the study, it was not possible to quantify the degree of improvement. We had an overall success rate of 81.9% for 266 patients, major complication rate of 0.37% and minor 10.5% 7.9% required revision surgeries and 61.9% were better after revision operations. These results are comparable to those in the literature. Factors affecting outcome included asthma, polyposis and pansinusitis. Functional Endoscopic Sinus Surgery has good results and little morbidity. Extent of disease as reflected by polyposis and pan sinusitis is the most important determinant of the outcome.

## CONCLUSION

Functional endoscopic sinus surgery has provided a safe, efficient method for dealing with identified disease. Surgery can be carried out safely and effectively. Nasal endoscopy provides an illuminated view into the nasal cavity so that chronic sinusitis and sinonasal polyposis can be managed with high success for alleviation of symptoms and improvement of disease with negligible morbidity.

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### Conference News

The Third IDDF-ADA Postgraduate Course on Diabetes will be held from 29th September to 1st October 2006 at Chennai, India. The meeting will be hosted by the Madras Diabetes Research Foundation, Chennai. For further details, contact : Dr. K. Mohan, M.D., FRCP, Ph.D., D.Sc. Madras Diabetes Research Foundation & Dr. Mohan Diabetes Specialities Centre, No.4 Gnananandam Road, Eppalam, Chennai-600086, India. Phone : (91 44) 28258042, 28258051, 28258051, Fax : (91 44) 28258055, E-mail : mdc@mdrf.com. Visit website at [www.mdrf-india.com](http://www.mdrf-india.com) or [www.drmoahanddiabetes.com](http://www.drmoahanddiabetes.com) for details regarding registration etc.

## Comparative Evaluation of Bupivacaine and Ketamine as Spinal Anesthetic Agents in Albino Rabbits

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**Abstract :** Spinal anesthetic effect of ketamine was compared with that of bupivacaine - alone as well as combination of two drugs in varying doses. The time taken for onset of spinal anesthetic effect was faster with bupivacaine as compared to ketamine; whereas the duration of effect was longer with the former. Not much difference was observed when two drugs were administered in combination in varying doses.

### INTRODUCTION

Domino et al<sup>1</sup>, reported first clinical use of ketamine more than 30 years ago; ketamine is commonly used as intravenous anesthetic agent for short surgical procedures. Ketamine acts by antagonising NMDA receptors in CNS; several investigators have reported its analgesic, anti-inflammatory, anticonvulsant, local anesthetic and neuroprotective actions<sup>2,3</sup>. The drug has no adverse effects on cardiovascular and respiratory systems. In animal studies, most investigators have found that ketamine - induced motor block was variable and short lived<sup>4</sup>.

The present study was undertaken to assess the spinal anesthetic action of ketamine and to compare it with bupivacaine, a standard spinal anesthetic agent. The present study also included assessment of any modifications in the duration of spinal anaesthesia with these two drugs.

### MATERIALS AND METHODS

**Animals :** Inbred healthy albino rabbits of either sex weighing 2.2-2.8 kg. were selected for the study. They were maintained separately on standard diet and water ad-libitum. These animals were randomly divided into five groups consisting of 6 animals in each group. Animals were kept fasting overnight. Experiment was carried out between 10 a.m. - 1 p.m, taking strict aseptic precautions.

**Preparation of the Animals :** After shaving the part the rabbit was wrapped in a towel and secured sideways by tying hind limbs on the rabbit board, leaving the area of spinal column exposed. Intervertebral space immediately above the line joining anterior superior iliac spines, was prepared for the injection.

**Methods :** After taking aseptic precautions, hypodermic needle of 26 no. was introduced in the above mentioned lumbar space, slightly off the midline at 45 angle till the needle pierced dural membrane which was indicated by appearance of CSF flowing out of the needle. The needle was connected to the tuberculine syringe containing the drug under examination. An equal volume of CSF was allowed to flow freely. Then the drug under study was injected; the volumes of injection was kept constant every time.

**Study Groups :** Following drugs were injected intrathecally in various groups.

**Group I** - Bupivacaine 2 mg/kg; **Group II** - Ketamine 20 mg/kg; **Group III** - Bupivacaine 1 mg/kg + Ketamine 10 mg/kg (50% +

50%); **Group IV** - Bupivacaine 1.5 mg/kg + Ketamine 5 mg/kg (75% + 25%) and **Group V** - Bupivacaine 0.5 mg/kg + Ketamine 15 mg/kg (25% + 75%)

Sensory loss was assessed by pin prick method on cleanly shaven areas on the flexor and extensor aspects of lower limbs and anterior and posterior aspects of the abdomen. Motor loss was assessed by loss and regain of righting reflex. Duration of spinal anesthesia was measured by the time of initiating sensory loss till the regain of the righting reflex.

**Drugs :** Bupivacaine (Anawin heavy 5 mg/ml - Neon laboratories) and ketamine (Anek 50 mg/ml - Neon laboratories) distilled water was used. The results were statistically evaluated by Student's "t" test.

### RESULTS

**Onset of Anaesthesia Effect :** The onset of anaesthesia effect occurred within 2.16+0.24 min in group I, 3.41+0.34 min in group II, 2.74+0.25 min in group III, 2.18+0.16 min in group IV. In group V. Bupivacaine + Ketamine produced spinal anesthesia in 3.79+0.46 min.

**Duration of Anaesthesia :** Duration of anesthesia was 110+1.38 min in group I as compared to 50+0.68 min in group II p<0, 75+1.67 min in group III, 88+1.6 min in group IV and 65+0.89 min in group V respectively.

Table compares the time taken for onset of action and duration of action of ketamine and bupivacaine.

**Table: Onset and Duration of Spinal Anaesthesia**

Group	Onset in Minutes	Duration in Minutes
I	2.16+0.24	110+1.38
II	3.41+0.34	50+0.68
III	2.75+0.25	75+1.67
IV	2.18+0.16	88+1.6
V	3.79+0.46	65+0.89

Intergroup comparison,  $p > 0.5$

**Intergroup Comparison :** In Group I where only Bupivacaine (2 mg/kg) was used, produced anesthesia of 110+1.38 min duration and in Group II (ketamine) produced anesthesia of 50+0.68 min only. As compared with Bupivacaine, Ketamine was less potent spinal anesthetic agent. There is no significant difference in duration of anesthesia effect with the varying dose combination of bupivacaine and ketamine.

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## DISCUSSION

Intrathecal administration of ketamine 20 mg/kg alone produced spinal anaesthesia in all the rabbits in Group II, the duration of which was 50+0.68 minutes and it was consistent. Hiroki et al studied spinal conduction block in dogs. While studying the mechanism of intrathecal ketamine analgesia on intraspinal evoked potential they found dose dependent decrease in the amplitude of Wave I and II. It indicated axonal block by ketamine in dose of 1-5 mg/kg. In the present study ketamine in the doses of 5-20 mg/kg resulted in loss of sensory and motor responses in all the rabbits. As compared with bupivacaine, ketamine was less potent spinal anaesthetic agent with regard to the duration of the spinal anaesthesia is concerned ( $p < 0.5$ ) and there was no significant modification in the duration of spinal anaesthesia with the different percentage combinations of bupivacaine and ketamine ( $p > 0.5$ ).

## ACKNOWLEDGEMENT

The authors are grateful to Pravara Medical Trust, Loni for providing the laboratory animals and the drugs to carry out these experiments.

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### Check-List

### Manuscript Submission : For JIMSA

- (i) Copyright statement/declaration (not submitted or published elsewhere) signed by all the authors.
- (ii) Three hand copies of manuscript with illustrations attached to each; floppy in addition will be desirable.
- (iii) Title page : Title of manuscript, Name(s) and affiliation of author(s); institution(s) and city(ies) address of corresponding author (Tel; Fax; e-mail).
- (iv) Abstract should highlight objectives, methods, results, conclusions.
- (v) Article (double-spaced on A4 size paper) : material & methods, results, discussions ; Indian literature must be

- (vi) referred, references numbered in text as they appear.
- (vi) References maximum number of references for update-20, original-10, Case reports-6.
- (vii) Each table on separate sheet, maximum number-4 in original article.
- (viii) Photographs/Figures in envelope, each marked figure number on reverse with legends on separate sheet. Number not to exceed 3, preferably.
- (ix) Statement regarding adherence to standard ethical/guidelines prescribed by ICMR 2000. (see page 25)

## Literature Review

**Tobacco habit in northern India.** Sandeep Kumar, Upendra Pandey, Nidhi Balal, *JIMA*.2006;104:19-24.

To study tobacco consumption practices in north-India population, a community-based, stratified sampling survey using validated interview schedule was performed in rural/urban areas of Lucknow, Uttar Pradesh. There were 432 tobacco users (385 men, 47 women, 276 urban, 156 rural) taken as subjects. Tobacco use practices i.e. chewing/smoking/rubbing/snuffing, fire control measures were all taken into consideration.

Single mode of tobacco use was reported by 277 subjects (64.1%) and the rest had a plethora of tobacco practices. Chewing was prevalent in 322 (74.5%), smoking in 256 (59.3%), rubbing in 32 (7.4%) and snuffing in 4 subjects (0.9%). Of the 10 preparations in the questionnaire, the "top 5" preferences ranked as tobacco-gutka, cigarette, bidi and khaini that remained unchanged between sexes, rural/urban people and age groups. Women significantly ( $p < 0.00001$ ) preferred smokeless tobacco and perceived social barrier for smoking. Gutka consumption was significantly higher in youngsters ( $< 25$  years,  $p < 0.0001$ ). Most subjects (235, 54.3%) used tobacco 7.24 times/day. Majority (259;60%) users started consuming tobacco before 21 years. The commonest context of tobacco use was with any refreshment (337, 78.0%). Of the 322 tobacco chewers, about half the subjects (178;52.2%) rotated the quid in their mouth, 313 (97.2%) later spat it out, 9 (2.1%) swallowed it and 15 (4.7%) admitted to sleep with quid in mouth. Tobacco along with alcohol was consumed by 82 (19%) and with opium by 33 subjects (7.6%). Social barrier to tobacco use was perceived by 231 subjects (53.5%), especially by smokers. Majority users (355;82.2%) did not have negative feelings of embarrassment in using tobacco. Most users (351,81.4%) said they would welcome legislative control on tobacco use.

**Detection of renal function decline in patients with diabetes and normal or elevated GFR by serial measurements of serum cystatin C concentration : results of a 4-year follow-up study.** Perking, BA; Nelson, RG; Betsy, EP. *J. Am. Soc. Nephrol.* 2003;6:1404-1412.

The serum concentration of cystatin C has recently been proposed as an endogenous marker of renal function that is accurate even at the low concentrations found when GFR is normal or elevated. Cystatin C is a nonglycosylated basic pro-tease inhibitor that is produced at a constant rate by all nucleated cells. It is freely filtered by the renal glomerulus and primarily catabolized in the renal tubules. Furthermore, levels are reported to be independent of gender, age and body mass. Diurnal variation is insignificant, levels are not altered by inflammatory conditions, and the concentration is stable in stored serum. Thirty participants with type 2 diabetes in the Diabetic Renal Disease Study met these three eligibility criteria GFR  $> 20$  ml/min per 1.73m<sup>2</sup> at baseline (based on cold iohalamate clearance), 4 year of follow-up and yearly measurements of iohalamate clearance and serum cystatin C. With the use of linear regression, each individual's trend in renal function over time, expressed as annual percentage change in iohalamate clearance, was determined. Serum cystatin C in mg/L was transformed to its reciprocal (100/cystatin C) and linear regression was used to determine each individual's trend over time, expressed as an annual percentage change. In paired comparisons of 100/cystatin C with iohalamate clearance at each examination, the two measures were numerically similar. More important, the trends in 100 cystatin C and iohalamate clearance were strongly correlated (Spearman  $r = 0.77$ ). All 20 participants with negative trends in iohalamate clearance (declining renal function) also had negative trends for 100/cystatin C. Results were discordant for only three participants. In contrast, the trends for three commonly used creatinine-based estimates of GFR compared poorly with trends in iohalamate clearance (Spearman  $r < 0.35$ ). Serial measures of serum cystatin C accurately detect trends in renal function in patients with normal or elevated GFR and provide means for studying early renal function decline in diabetes.

Compiled by Dr. .P.Chattree

## Dissection Room Reactions of First Year Medical Students

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**Abstract :** *The first sight of a cadaver can evoke negative influences in a new medical student and may constitute a substantial barrier to learning. To assess the physical and psychological reactions of students to this situation and find ways of dealing with those disadvantaged by negative experiences, a questionnaire was distributed to 200 first year female students of 18-20 year age group of LHMC. Physical symptoms, level of stress, factors that help them cope and any change in their attitude after dissection were elaborated. Any suggestions from their side were noted. The first sight of cadaver was very upsetting to 10% of students, 29% were not affected and the rest were moderately upset. 33% showed physical manifestations like nausea, loss of appetite etc. About 20% found the attitude of staff members of the department a helping tool in coping with the situation. 68% of students developed a deep sense of gratitude towards donors of cadavers and most felt that adequate preparation at institutional level prior to first dissection room visit would be a big morale booster. Counselling for stressed out students was also suggested.*

### INTRODUCTION

In the context of scientific study of human anatomy, dissection of a human cadaver forms an essential part of teaching and research. At the first sight of dissection room and the first dissection experience, a plethora of emotions are raised in students' mind. For some it may be anxiety provoking and for others death, formalin and smell together may be aesthetically repulsive as observed by Jones<sup>1</sup>. It has been suggested that these negative influences may constitute a substantial barrier to learning. Finkelstein and Mathers<sup>2</sup> reported marked disturbances like nightmares, intrusive visual images, insomnia and depression and learning impairments. A number of physical and psychological reactions have been observed by Penny<sup>3</sup> and Horne et al<sup>4</sup>. Charleton et al<sup>5</sup> had suggested that students learned to detach themselves from their feelings and in this way cope with dissection but this may have a detrimental effect on their subsequent ability to empathise with living patients. However O'Carroll et al<sup>6</sup> felt that many students may report a positive experience after the initial exposure to a cadaver.

The present study was undertaken to assess the reaction of students to cadavers, both positive as well as negative, so as to enable us to "dissect the pros and cons of dissection room experience and build up data about different views on the task of cadaveric dissection". The study may help us find ways of dealing with students disadvantaged by negative experiences with cadavers. With appropriate preparation, the anatomy room experience is sure to be positive with students stimulating them to think about fundamental questions and whenever possible remedial action can be taken.

### MATERIAL AND METHOD

A questionnaire was distributed to 200 first year female medical students, of India nationality and between 18-20 years of age. After noting any previous exposure to dead bodies and death of close relative in the near past, physical symptoms and level of stress resulting from exposure to dissection room were assessed.

The students were questioned on whether they were mentally prepared to face a cadaver, had any apprehensions in this regard and once in the dissection room, how upsetting was the first experience. They were asked to rate their physical symptoms and first reaction to the cadaver.

After the initial encounter, factors that helped them cope with the situation and any change in their attitude after dissection were elaborated. Any suggestions regarding dissection room experiences were noted.

### RESULTS

Table - 1: Student's Reaction (in percentage)

Students reaction	Yes	No
Exposure to dead body before introduction to dissection room	50	50
Death of a close relative in last 2 years	43	57
Apprehension before seeing a cadaver	26	74
Mental preparation for dissection	69	31
Interest in cadaver	43	57
Excitement	31	69
Anxiety, disgust, confusion	15	85
Anorexia nausea, loss of sleep, nightmares	23	77

**Student's Reaction** A 100% response to the questionnaire with all questions answered was obtained from the students. Half the respondents had seen a dead body before their introduction to dissection room and 43% reported death of close relative within last 2 years. Most of the students (74%) had no apprehension before facing the cadaver and 69% said they were mentally prepared for dissection. The first sight of cadaver was very upsetting to 10% of students, 29% were not at all affected and remaining were slightly to moderately upset. The degree to which the students were upset fell as they touched and gave their first incision. After a few sessions, only one student was still very upset and 47% had no problem.

**Physical Reaction and Stress :** The first reaction to cadaver during dissection was that of interest in 43% students followed by excitement

in 31%. There was detachment, anxiety, indifference, confusion and disgust in the range of 5-15%. There was feeling of horror and fascination in 2% while 12% had no particular emotional reaction. In the assessment of their physical reactions, 6% felt nauseous, 10% developed loss of sleep and nightmares and 7% had loss of appetite. There was no physical manifestation of any type among 77% of students. (Table 1)

**Coping Strategies** Students found different ways of coping with the situation. Roughly half of them found talking and sharing experiences with others helpful. About one fifth found that the attitude of the faculty and other staff members of the department of anatomy as well as black humor helped and 10% found solace by taking a detached and philosophical view on this subject.(Table 2).

**Table - 2 : Coping Strategies (in percentage)**

Coping Strategies	Yes	No
Talking and sharing experiences	50	50
Attitude of faculty & staff members and black humor	20	80
Detached and philosophical view	10	90

After a few sessions in the dissection room, there were a number of changes in the attitude of students (Table3). 68% felt a deep sense of gratitude towards to donors of cadavers and about 16% recalled awareness of own mortality and unwillingness for own or any close relative's body donation. About 12% of students felt that they had developed tendency to callousness.

**Table - 3 : Changes in Attitude (in percentages)**

Change in Attitude	Yes	No
Deep sense of gratitude towards donors	68	32
Awareness of own mortality	16	64
Tendency to callousness	12	88

**Suggestions:** Students were given opportunity to suggest means by which their experience with cadavers could be made less stressful. Most felt that adequate preparation at institutional level in the form of discussion on death, sharing of fears and knowledge of facts on donors and burials prior to first visit to dissection room would be a big help. About one fifth of them also suggested that there should be better handling and attitude of reverence to cadavers by the staff and information on embalming and preservation of cadavers would be appreciated. It would be helpful if arrangements could be made for counselling for stressed out students.

## DISCUSSION

It is important to determine whether students experience strong and persistent reactions to human dissection, severe enough to interfere with work or well being as suggested by Evans and Fitzgibbon<sup>7</sup>. This knowledge is a prerequisite for helping them to cope and for enabling staff to minimize the potential difficulties that students might experience.

Our study revealed that serious psychological distress from human dissection is rare. This is in agreement with findings of Evans and Fitzgibbon<sup>7</sup>. In contrast to Penney<sup>3</sup> who observed appreciable

apprehension in about 63% of students, our students (74% of them) showed no such reaction on their first exposure to a cadaver. There was anxiety, confusion and disgust in the range on 5-15% as against 30% anxiety reported by Penny<sup>3</sup>. 43% of our students showed interest in the cadaver but only 18% had a similar reaction in the study carried out by Penny<sup>3</sup>. In both the studies, same percentage (23%) of students showed physical reactions like nausea, loss of sleep, nightmares, etc. The present study showed that 20% of students used humor as a coping strategy, a finding in contrast to that reported by McGarvey et al<sup>8</sup>, Abu-Hijleh et al<sup>9</sup>, Evans and Fitzgibbon<sup>7</sup> and in keeping with the finding of Horne et al<sup>4</sup>. In assessing changes in attitude of students after a few sessions in the dissection room, 68% were observed to feel a deep sense of gratitude towards the donors of cadavers, a finding not observed in the literature cited.

The impact of anatomy course on the psychological and sometimes spiritual well-being of students can be an issue of long standing concern as reported by Gustafson<sup>10</sup>. McGarvey et al<sup>8</sup> reported that 27% of medical students felt the need for more preparation before first visit to the anatomy room. In our study majority were of similar view. It is seen that though initial cadaver dissection is experienced as significant emotional life event by many students, majority do adapt to the situation quickly. They feel that dissection room experience stimulates thoughts about mortality. This experience, with appropriate preparation, can be quite positive and help students to feel the need to balance comparison and objectivity.

Therefore, an orientation programme is recommended prior to first dissection with instructions regarding dissecting techniques and small group discussion with faculty members. They should be made aware of source of cadavers, their processing and arrangements regarding their reception and disposal. The students should be made to realize their responsibility towards the cadaver as well as their own health and safety. Finally, the students should abide by certain minimum standards of behaviour and procedure.

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## Haemangioma of Tongue

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**Abstract :** Hemangiomas are benign tumors of the vascular tissue. They can occur in any part of the body including head and neck region. In the tongue, hemangiomas are rare. They usually occur in childhood and are quite uncommon in the adult population. A rare case of tongue hemangiomas in an adult female, is being reported.

### INTRODUCTION

Hemangiomas of the head and neck region are relatively common, representing at least a third of all hemangiomas in humans. They are common in paediatric population but very rare in adults (0.8%)<sup>1,2</sup>.

### CASE REPORT

A 40 year old woman presented with complaints of tongue swelling and discolouration since 4 months. On examination there was a diffuse swelling over the tip and anterior part of the dorsum of tongue (Fig.). The overlying skin was showing bluish discoloration. On palpation the swelling was soft. The clinician suspected it to be either a hemangioma or a lymphangioma. The patient was referred for radiograph and ultrasound examination. A plain radiograph of the soft tissue of the face showed swelling of the tongue and phleboliths. USG revealed enlargement of the tongue with heterogenous echopattern and multiple hyperechoic foci with posterior acoustic shadowing consistent with calcification (phleboliths). There was a large anechoic channel within the lesion which on color doppler revealed the vascular nature of the lesion. Other anechoic areas were also filled up with colour. This was reported as a hemangioma. Contrast Enhanced CT was done which confirmed the gray scale and doppler findings, along with feeding enlarged lingual artery. The tumor was excised and biopsy of specimen showed a single line of endothelial cells with multiple blood vessels present in between the glandular tissue. There was no evidence of mitotic activity in the cells. This ruled out a malignant nature of the lesion and the diagnosis of hemangioma was confirmed.

### DISCUSSION

The oral or pharyngeal hemangioma occur in older age at diagnosis than lesions from other sites, in adults. The mucosal hemangioma most often arises from the frequently traumatized mucosal sites, commonly lip mucosa (63%), the buccal mucosa (14%) and the lateral borders of the tongue (14%), but it may occur at any oral or pharyngeal location. In population studies there is a strong (2:1) male predilection, although there is minimal

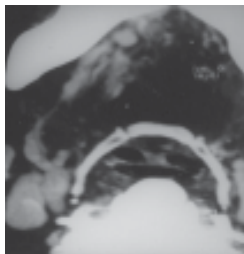


Fig.1: Open mouth view of tongue showing swelling on the top and interior part of dorsal surface.

gender predilection in hospital - based studies. The mucosal hemangioma is typically a soft, moderately well circumscribed painless mass which is red or blue in colouration.

Characterized by an excess of blood vessels, usually veins and capillaries, in a focal area of submucosal connective tissue; it is almost never encapsulated. Capillary hemangioma is the most common type and is comprised of numerous intertwining capillary - sized vessels lined by endothelium<sup>3</sup>. When lesional vascular channels are considerably enlarged, the term cavernous hemangioma has traditionally been applied. This differs from capillary hemangioma in that it is less well circumscribed, is larger and is usually deeper in submucosal tissues; sluggish blood flow may result in organized or dystrophically calcified thrombi within dilated vessels.

The tongue can be very well imaged with a high frequency probe the tip of the organ is better evaluated via a direct approach from its dorsal surface while the submental approach is used to examine the body and base of tongue<sup>4</sup>. The tongue appears as an elongated reflective structure bounded cranially by the air in the oral cavity. On USG, the echogenicity of a hemangioma is variable and depends on the size of the cystic component the tongue is usually enlarged and appears hypoechoic or more or less isochoic. They are highly compressible; color doppler study helps to detect the perfusion in the hemangioma and confirms the vascular nature of the lesion and helps to differentiate it from a lymphangioma<sup>5-7</sup>.

On CT, these tumors enhance; they are often lobular and may have phleboliths. The mass effect of the tumor on the surrounding tissues is relatively rare reflecting their soft nature.

MRI is an important non-invasive technique in the diagnosis of oral and maxillofacial venous malformations and evaluation of adjacent soft tissues. Direct sagittal and coronal images venous malformations show an isointensity or slight hyperintensity on T<sub>1</sub> weighed images and high hyperintensity due to the presence of enlarged venous lakes (slow-flowing blood) on T<sub>2</sub> weighed images on contrast-enhanced T<sub>1</sub> weighed images. A slow and homogeneous increase of signal intensity occurs. Signal homogeneity on both T<sub>1</sub> and T<sub>2</sub> sequences is sometimes interrupted by small hypointense foci and linear strands that correspond to phleboliths, flow void or septal partitions<sup>8</sup>.

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## Non-Hodgkin's Lymphoma of the Pleura Presenting as a Large Thoracoabdominal Mass - A Case Report

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**Abstract :** Primary pleuro-pulmonary non-Hodgkin lymphomas (NH<sub>2</sub>) are very rare tumors, possibly under diagnosed, with a very long, frequently asymptomatic evolution. It has been reported in patients with long standing pyothorax. Primary pleural non-Hodgkin's lymphoma in an immunocompetent patient without a history of chronic pyothorax is extremely rare. To the author's knowledge, very few cases have been described in the literature. A case of primary NHL of the pleura presenting as a large thoracoabdominal mass without a history of previous pyothorax is being reported.

### INTRODUCTION

Primary pleural lymphoma in immunocompetent patients without the setting of chronic pyothorax is very rare. These are asymptomatic tumors following an indolent course presenting with respiratory distress or chest wall mass. Thus, these tumors can reach enormous sizes and may become thoracoabdominal in location. Late in the disease, these tumors can involve the pulmonary parenchyma so that lung cannot be separately identified and the mass is recognized as a pleuropulmonary mass and the biopsy is required to make the definitive diagnosis. Hilar/mediastinal adenopathy is not a feature of this disease. The rarity of the disease has prompted us to report the case.

### CASE REPORT

A 35 years old female presented with a mass in the left upper abdomen and difficulty in breathing. On clinical examination, the patient had thoracoabdominal fullness on left side with shiny skin and prominent and dilated superficial veins. The respiratory movements were reduced on the affected side and the lower limit of the mass could not be reached. On the left lateral chest wall multiple nodular mass could be palpated. The patient had no previous history suggestive of long standing pyothorax on either side. The rest of the medical history and examination is unremarkable.

Laboratory investigations revealed increased ESR and reduced hemoglobin levels. Rest of the laboratory data was within normal limits. Plain radiograph of the chest revealed homogeneously opaque left hemithorax and hyperinflated right lung field with the mediastinal shift (heart and tracheal shadow) to the right side. Bony cage appears normal.

Ultrasound examination of the chest and abdomen revealed a large heteroechoic mass in the chest extending into the left hypochondrium but with the intervening intact left hemidiaphragm, thus pointing towards the thoracic origin of the mass. The abdominal viscera including left kidney, spleen, stomach and pancreas were displaced inferiorly. The mass is seen to extend

superiorly as far as the apex of the lung. At multiple points on the left lateral part of the chest wall, the mass was seen to project through the intercostal space into the subcutaneous planes.

Computed tomographic examination of the chest and abdomen of it revealed a large fairly well defined, heterogeneously but moderately enhancing mass completely occupying the left hemithorax with displacement of the mediastinal structures towards the right side (Fig.1). The left lung was engulfed in the mass. The mass was extending into the left upper abdomen with displacement of the abdominal viscera but with an intact intervening diaphragm (Fig.2). At several sites the mass was seen to extend its pseudopods through the intercostal spaces into the soft tissues of the chest wall. Pressure erosions of some ribs were noted on the bony window settings on the left side. No evidence of mediastinal, right hilar adenopathy was noted.

The histopathological examination revealed large cell type of non-Hodgkin's lymphoma of the pleura.

### DISCUSSION

Both Hodgkin's and non-Hodgkin's lymphomas can involve the pleura. The tumor is seldom the solitary at initial presentation<sup>1,2</sup>, mediastinal nodal and sometimes pulmonary parenchymal involvement.

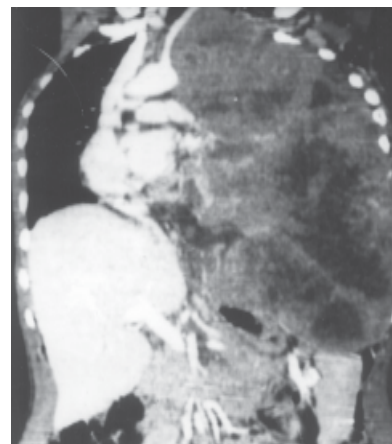


Fig.1 : Coronal MPR CT scan of the thorax reveals a large, heterogeneous, mass in the left hemithorax with mediastinal shift to the right side with complete loss of pulmonary parenchyma

Three (3) are often present patients with non-Hodgkin's lymphoma (NHL) involving the lung or chest wall following a long-standing empyema were reported by Kamesaki H. et al<sup>3</sup>. All patients had tuberculous pleuritis or received artificial pneumothorax for pulmonary tuberculosis 30 years or more previously. The NHL of these patients developed in or close to the thickened pleura. Histological examination showed diffuse large cell type (LSG classification) in all cases. Non-Hodgkin's lymphoma of the pleural cavity with long-standing pyothorax was described by Iuchi K, et al<sup>4</sup>. This study suggested a close relation between a preceding chronic tuberculous pyothorax and the development of non-Hodgkin's lymphoma (NHL) in the pleural cavity. Primary pleuro-pulmonary lymphomas are very rare and pose<sup>5</sup>.

Very few cases of NHL of pleura without the history of chronic empyema has been described in the literature<sup>6,7</sup>. Radiological features of primary NHL of the pleura have been described in the childhood<sup>8,9</sup>.

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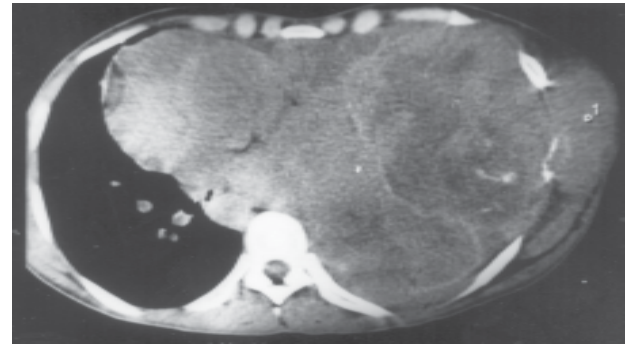


Fig.2 : Transaxial CT scan showing a left hemithoracic mass with bony destruction and extension into the soft tissues

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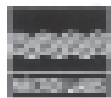
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## Oxidative Stress in Male Infertility : Role of Anti-Oxidants

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**Abstract :** The medical treatment of the infertile male has been largely empirical and unrewarding. The cost and complexity of sophisticated techniques don't represent a final solution to the infertile male. Oxidative stress (OS) precipitates a range of pathologies that affect the male reproduction. The development of rational approaches to treatment must be based on this cellular pathology that results in defective spermatozoa. Cellular damage in the semen is the result of positive oxidative stress status (OSS) because of either excess ROS or diminished anti-oxidants. The generation of ROS has become a real concern because of their potential toxic effects at high levels on sperm quality and function. The administration of antioxidants in patients with 'male factor' infertility has begun to attract considerable interest. Unfortunately, the clinical use of antioxidants is still in its infancy. Adequate randomized controlled trials to base any firm recommendations for clinical practice of antioxidants are lacking.

### INTRODUCTION

In general, the medical treatment of the infertile male has been largely empirical and unrewarding, while surgical treatment has limited applicability, with the possible exception of varicocele ligation or embolization. In contrast, the past two years have seen remarkable achievements in the application of techniques of assisted reproduction in the treatment of couples with 'male factor' infertility. The pragmatic clinical application of the sophisticated techniques of micro-assisted fertilization has yielded clinically outstanding results. Unfortunately, its cost and complexity is such that it cannot represent a final solution to the problem of the infertile male.

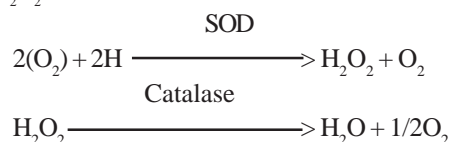
The development of rational approaches to diagnosis and treatment must be based upon an understanding of the cellular pathologies that result in the production of defective spermatozoa. "Oxidative stress" (OS) precipitates a range of pathologies that currently are thought to afflict the reproductive function<sup>1</sup>. OS is a condition associated with an increased rate of cellular damage induced by oxygen and oxygen-derived oxidants commonly known as reactive oxygen species (ROS). 25% to 40% of infertile men had high levels of ROS in semen samples. The generation of ROS has become a real concern because of their potential toxic effects at high levels on sperm quality and function.

### ROS AND ANTIOXIDANTS

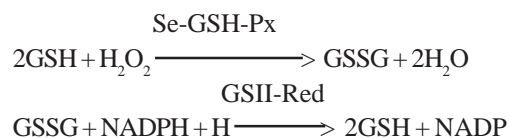
ROS are highly reactive oxidizing agents belonging to the group of free radicals. They have a tendency toward chain reaction. Most common of those having potential implications in reproductive biology include superoxide ( $O_2^-$ ) anion, hydrogen peroxide ( $H_2O_2$ ), peroxy radical (ROO) radical and the very reactive hydroxyl (OH) radical. The nitrogen derived free radical nitric oxide (NO) and peroxynitrite anion (ONOO) also appear to play a significant role in the reproduction and fertilization.

Seminal plasma is endowed with an array of antioxidants to

continuously inactivate ROS to keep only a small amount necessary to maintain normal cell function. Among the well-known biological antioxidants, SOD and its two isozymes and catalase have a significant role in seminal plasma. SOD spontaneously dismutates ( $O_2^-$ ) anion to form  $O_2$  and  $H_2O_2$  while catalase converts  $H_2O_2$  to  $O_2$  and  $H_2O$ .



SOD protects spermatozoa against spontaneous  $O_2^-$  toxicity and lipid peroxidation (LPO)<sup>2</sup>. SOD and catalase also remove ( $O_2^-$ ) generated by NADPH-oxidase in neutrophils and may play an important role in decreasing LPO and protecting spermatozoa during genitourinary inflammation. Glutathione peroxidase (Se-GSH-Px) with glutathione (GSH) as the electron donor removes peroxy (ROO) radicals from various peroxides including  $H_2O_2$ <sup>3</sup>. Glutathione reductase (GSH-Red) then regenerates reduced GSH from GSSG as shown in the following equation :



A selenium-associated polypeptide, presumably Se-GSH-Px, has been demonstrated in rat sperm mitochondria, which plays a significant role in this peroxy scavenging mechanism and in maintaining sperm mortality. In addition, Se-GSH-Px and GSH-Red directly act as antioxidant enzymes involved in the inhibition of sperm lipid peroxidation (LPO)<sup>3</sup>. GSH has a likely role in sperm nucleus decondensation and may alter spindle microtubule formation in the ovum, thus affecting the outcome of pregnancy. A high GSH/GSSG ratio will help spermatozoa to combat oxidative insult.

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## ROS AND SPERM FUNCTION

Small amounts of ROS are necessary for spermatozoa to acquire fertilizing capabilities<sup>4</sup>. Low levels of ROS can enhance the ability of human spermatozoa to bind with zona pellucida. Incubating spermatozoa with low concentrations of hydrogen peroxide stimulates sperm capacitation, hyper activation, acrosome reaction and oocytes fusion<sup>5</sup>. ROS other than hydrogen peroxide such as nitric oxide and superoxide anion promote sperm capacitation and acrosome reaction<sup>5</sup>. Cellular damage in the semen is the result of positive oxidative stress status (OSS), a situation in which there is a shift towards pro-oxidants, because of either excess ROS or diminished anti-oxidants. Pathological levels of ROS detected in semen from infertile men are more likely a result of increased ROS production rather than reduced antioxidant capacity. Mammalian spermatozoa are rich in polyunsaturated fatty acids and, thus, are very susceptible to ROS attack. Spermatozoa, unlike other cells, are unique in structure, function and susceptibility to damage by LPO<sup>2</sup>. Spermatozoa are unable to repair the damage induced by excessive ROS because they lack the cytoplasmic enzyme systems that are required to accomplish this repair. This is one of the features that make spermatozoa unique in their susceptibility to oxidative insult<sup>5</sup>.

LPO of sperm membrane is considered to be the key mechanism of this ROS-induced sperm damage leading to infertility. The most significant effect of LPO is the perturbation of membrane (cellular and organellar) structure and function (transport processes, maintenance of ion and metabolite gradients, receptor mediated signal transduction, etc.). It results in decreased sperm motility, presumably by a rapid loss on intracellular ATP leading to axonemal damage, decreased sperm viability and increased midpiece morphology defects with deleterious effects on sperm capacitation and acrosome reaction<sup>6</sup>.

The increased formation of ROS has been correlated with a reduction of sperm motility<sup>6</sup> due to decrease in axonemal protein phosphorylation and sperm immobilization, both of which results in reduced membrane fluidity necessary for sperm oocyte fusion. H<sub>2</sub>O<sub>2</sub> can diffuse cross the membranes into the cells and inhibit the activity of some enzymes such as glucose 6-phosphate dehydrogenase (G6PD). Inhibition of glucose-6 phosphate dehydrogenase (G6PD) leads to less NADPH, a source of electrons by spermatozoa to fuel the generation of ROS by an enzyme system known as NADPH oxidase and a concomitant accumulation of oxidized glutathione, which in turn can reduce the antioxidant defenses of the spermatozoa and peroxidation of membrane lipids<sup>7</sup>. The oxidative damage to mitochondrial DNA is well known to occur in all aerobic cells, which are rich in mitochondria and this may include spermatozoa. Sperm DNA is protected from oxidative insult by its characteristic tight packing and the antioxidants<sup>8</sup>. ROS induces DNA damage in the form of base modifications, production of base-free sites, deletions, frameshifts, DNA cross-links through covalent binding to malondialdehyde (MDA), chromosomal rearrangements, single and double DNA strand breaks and oxidation of critical -SH groups in proteins and DNA which will alter structure and function of spermatozoa with an increased susceptibility to attack by macrophages<sup>9,10</sup>.

Redox status affects phosphorylation and ATP generation of human

spermatozoa with a profound influence on its fertilizing potential<sup>9</sup>. The oxidizing conditions increase tyrosine phosphorylation with enhanced sperm function while reducing conditions have the opposite effect. High levels of ROS disrupt the inner and outer mitochondrial membranes resulting in release of cytochrome-C protein from the mitochondria that activates the caspases and induces apoptosis<sup>10</sup>.

## ANTIOXIDANT THERAPY

Antioxidants, in general, are compounds and reactions which dispose, scavenge and suppress the formation of ROS, or oppose their actions. They provide protection against the toxic effects of ROS. They must reach their target at the right time and in the right concentration. Also, the scavenger radicals formed during the interaction of the scavenger with toxic radical intermediate should be less reactive (i.e. have a long half-life) than the radical they attack. Antioxidants attack in different phases of LPO. They may :

- \* *Inhibit the initiation process* (abstracting the allylic hydrogen from the alpha-methylene carbon atom), e.g. vitamin E.
- \* *Inhibit the formation of hydro peroxides* (chain breakers like vitamin F and C).
- \* *Degrade the hydro peroxides* formed without producing radicals (e.g. glutathione peroxidase, thiols).
- \* *Act as metal chelating substances* (inhibiting the metal catalysis accelerating the decomposition of hydro peroxides), e.g. D-penicillamine.
- \* *Remove the free radical* (scavenger activity), e.g. vitamin E and A.

Vitamin C acts as prooxidant (facilitates LPO) in low concentrations in the presence of trace amounts of transition metals (iron, copper) either free or chelates because it reduces the metals, thereby promoting the metallic catalysis of LPO. In high concentrations, when there is sufficient number of metal binding sites, it act as antioxidant. It acts by interrupting the chain reaction: losing hydrogen, reacting with the peroxy radicals and stable monohydroascorbate is produced. In addition, it also has direct O<sub>2</sub> and OH scavenger action. When vitamin C interacts with reactive oxygen intermediates, the product is a mixture of monodehydroascorbate and dehydroascorbic acid<sup>11</sup>. Concentration of vitamin C in seminal plasma directly reflects dietary intake, and its lower levels leads to infertility and increased damage to the sperm's genetic material. Supplementation of vitamin C improves the fertility of men<sup>12</sup>. It protects sperm from oxidative damage, sperm agglutination and improves the quality of sperm and steroidogenesis<sup>13</sup>.

Vitamin E, a chain breaking antioxidant inhibits LPO in membranes by scavenging peroxy (RO) and alkoxy (ROO) radicals. The main lipid phase antioxidant activity of vitamin E in the cell membrane occurs via hydrogen donation to hydro peroxides, thus formation of hydro peroxides is prevented, the chain reaction is terminated and the extension of the pathological free radical reduction in the plasma membrane depends on the recycling of vitamin E by external reducing agents such as ascorbate or thiols. In this way, it is able to function again as a free radical chain breaking antioxidant, even

though its concentration is low. Oral supplementation of vitamin E significantly decreased LPO and improved sperm motility. Kessopoulou et al<sup>14</sup>, found that the zona binding test, a sperm function assay, was significantly improved with vitamin E administration. Its combination with selenium significantly increased sperm motility and the overall percentage of normal spermatozoa. Vitamin E supplementation improves fertility in humans and animals by decreasing free-radical damage to sperm cells.

Glutathione is vital to sperm antioxidant defenses and has demonstrated a positive effect on sperm motility<sup>15</sup>. Selenium and glutathione are essential to the formation of phospholipid hydroperoxide glutathione peroxidase, an enzyme present in spermatids which becomes a structural protein comprising over 50 percent of the mitochondrial capsule in the mid-piece of mature spermatozoa. Deficiencies of either substance can lead to instability of the mid-piece, resulting in defective motility<sup>16</sup>. Glutathione demonstrated a statistically significant effect on sperm motility, especially increasing the percentage of forward motility and on sperm morphology improving quality<sup>17</sup>. Treatment with selenium significantly improved sperm motility; however, sperm density was unaffected. Treatment with GSH resulted in significant increase in the observed content of long chain polyunsaturated fatty acids. This appeared to be associated with a fall in the lipid peroxidation potential of the spermatozoa of the treated infertile subjects, and an increase in sperm motility<sup>18</sup>. The findings of these studies indicate that glutathione therapy could represent a possible therapeutical tool in cases where ROS or exposure to toxins is the probable cause of infertility.

In sperm cells, coenzyme Q10 (CoQ10) in the mitochondrial mid-piece involved in energy production functions as an antioxidant, preventing lipid peroxidation of sperm membranes. It is a nutrient used by the body in the production of energy. While its exact role in the formation of sperm is unknown, there is evidence that as little as 10 mg per day (over a two-week period) will increase sperm count and motility. CoQ10 significantly increased sperm motility and count<sup>19</sup>. Clearly additional studies will be needed to evaluate the possible role of coenzyme Q10 in the treatment of male infertility.

## CONCLUSION

Oxygen toxicity is an inherent challenge to aerobic life forms, including the spermatozoa. Increased oxidative damage to sperm membranes (indicated by increased LPO), proteins and DNA is associated with alterations in signal transduction mechanisms that affect fertility. Spermatozoa possess an inherent but limited capacity to generate ROS which may help the fertilization process. A variety of defense mechanisms encompassing antioxidant enzymes (SOD, catalase, glutathione peroxidase and reductase), vitamins (E,C and carotenoids) and biomolecules (glutathione and ubiquinol) are involved in biological systems. A balance between the benefits and

risks from ROS and antioxidants appears to be necessary for the survival and normal functioning of spermatozoa. The administration of antioxidants, like vitamin C, vitamin E, glutathione and CoQ10 showed improvements in the sperm physiology. Unfortunately, the clinical use of antioxidants is still in its infancy. Adequate randomized controlled trials to base any firm recommendations for clinical practice of antioxidants are lacking.

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## Probiotics - Revisted

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**Abstract :** Probiotics are non-pathogenic micro-organisms which confer health benefits to the recipient. The derangement for normal body flora is responsible for various disorders which need treatment with probiotics because of their ability to supplement normal body flora. They are safe, cheap and widely prescribed. However, there may be chances of transferring resistance to other microbes including pathogens as well as occasional reports of systemic fungemia especially in immunocompromised and severely debilitated patients with the use of probiotics. Larger studies are required to document their definite role both therapeutically and prophylactically.

### INTRODUCTION

Probiotics are nonpathogenic micro-organisms or microbial mixtures used to improve the microbial balance and to confer health benefits to the recipient. The use of the term 'Probiotic' in greek means 'for life'. The derangement of normal body flora causes various disorders. Many revolutionary changes have taken place in the treatment of infectious diseases with the introduction of antibiotics. But there is risk of increased incidence of drug resistance and opportunistic infections with the use of antimicrobial agents<sup>1</sup>. This can be avoided if the use of antimicrobial therapy is minimized. The practice of probiotics via fermented milk products in animals was first documented by Weese et al<sup>2</sup>. Fuller (1991)<sup>3</sup> defined probiotics as a live microbial feed supplement which beneficially affects the host animal by improving its microbial balance. A review of probiotics in health and diseases<sup>4-6</sup> has been carried out by various workers. In this article, an attempt has been made to further review the currently used probiotics in health and disease in great details.

### WHY ARE THEY IN DEMAND?

More than 500 different bacterial species (some of which having important health functions) are present in the gastrointestinal (GIT) tract. Normally a protective gut microflora develops and thus there is no need for bacterial supplement. But due to many factors like excessive use of antibacterial agents, change in life style and food habits, consumption of processed food, drug resistance and opportunistic infections, the probiotics always remain in great demand to the consumer for better therapies.

### PROBIOTICS IN USE

The probiotics are increasingly used in various clinical conditions<sup>3</sup>. Lactobacillus and bifidobacterium are the commonest bacteria used as probiotics as described under

- (a) **Bacteria :** i) *Lactobacillus* - examples are *acidophilus*, *plantarum*, *sporogenes*, *rhamnosum*, *lactis*, *casei*, *reuteri*, ii) *Bifidobacterium* - examples are *bifidum*, *infantis*, *longum*, *thermophilum*, iii) *Streptococcus* - examples are *lactis*, *intermedius*, *alivarius* sub sp *thermophilus*, iv) *Enterococcus* - e.g. *faecium*, v) *Prophionibacterium*, vi) *Leuconostoc*, vii) *Pediococcus*, viii) *Bacillus*,  
 (b) **Moulds and Yeast;** i) *A. niger*, ii) *A. cerevisiae*, iii) *C. pintolopesii*, iv) *Saccharomyces boulardii*,

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### PRE-REQUISITES OF PROBIOTICS

These are : i) Non pathogenic and nontoxogenic, ii) Human origin iii) Stable in acid and bile, iv) Able to survive transit through GIT, v) Able to adhere to human intestinal mucosa, vi) Able to colonise in human GIT, vii) Should retain viability during storage and use<sup>4</sup>, viii) Production of antimicrobial substances towards pathogens, ix) Beneficial effects on human health,

*L.rhamnosum* strain GG is one of the most thoroughly explored lactic acid bacteria and meets most of these criteria. The plantarum species among lactobacillus has got many advantages like unique adhesiveness to the mucosa and tolerate low pH, whereby potential pathological micro-organisms fail to grow and thus microbial translocation is prevented.

### BENEFICIAL CLAIMS OF PROBIOTICS

The therapeutic and prophylactic claims of probiotics are depicted in Table - 2<sup>7</sup>

**Table - 2** Benefits of Probiotics

- |   |
|---|
| <b>A. Intestinal disorders :</b>  |
| <b>Diarrhoea:</b> a) Infectious diarrhoea, b) antibiotic associated diarrhoea (AAD), c) traveller's diarrhoea, d) lactose malabsorption associated diarrhoea (lactose intolerance), e) infantile diarrhoea, |
| <b>B. Other Uses :</b>  |
| a) Urogenital infections-vaginitis, b) hypercholesterolemia, c) cirrhosis liver, d) food allergy, e) hypertension, f) renal stones, g) cancer, h) vaccine adjuvant, i) growth and well being,               |
| <b>C. Miscellaneous Uses :</b>  |
| a) stabilization of flora, b) recolonization of bowel after antibiotic therapy,   |

### DIARRHOEA

a) **Infectable diarrhoea including infantile diarrhoea :** In developing countries, incidence of infectious diarrhoea is very high due to poor nutrition and sanitation. Diarrhoea is a major cause of death in infants in developing countries. Thus the use of probiotics has a definitive role in addition to improving sanitation and nutrition. Lactobacilli GG, bifidobacterium and streptococcus thermophilus have been shown to reduce the incidence of diarrhoea as compared

to control groups<sup>8,9</sup>. The supplementation of infant milk with *B. bifidum* and *S. thermophilus* reduced rotavirus shedding and episodes of diarrhoea in children<sup>9</sup>. The recovery (in terms of reduction in duration of diarrhoea) from acute diarrhoea has been reported to be good by lactobacilli GG, *L. reuteri*, *L. casei* and *S. boulardii*<sup>10</sup>. The infants are more susceptible to get diarrhoea because of immature intestinal mucosal barrier, low immunity and poor growth of intestinal bacterial flora, which takes 1 year to reach adult level and composition<sup>11</sup>. In AIDS associated diarrhoea, *S. boulardii* has been shown to resolve symptoms in 10 of 18 patients as opposed to 1 of 11 in placebo when given for 1 week<sup>12</sup>. *E. faecium* SF 68 has been shown to be effective in reducing diarrhoea in adults when given for 1 week<sup>13</sup>.

**(b) Antibiotic associated diarrhoea (AAD) :** Diarrhoea is one of the most common adverse effect of antimicrobial agents. Its incidence in children ranges from 20% to 40%<sup>14</sup>. It is mostly related to disturbances in normal intestinal flora leading to many changes like (i) Loss of carbohydrates digesting gut bacteria resulting in osmotic diarrhoea<sup>15</sup>; (ii) Direct stimulation of gut motility. For example erythromycin acts as motilin agonist to cause diarrhoea<sup>16</sup>; (iii) Decrease in colonic fermentation to short chain fatty acids, which are required for the nutrition of the enterocyte as well as for absorption of water and electrolytes<sup>17</sup>; (iv) Overgrowth by pathogens, (v) Invasion and translocation of toxins by life threatening infections e.g. *C. difficile*. *C. difficile* leads to 20% of AAD<sup>18</sup> and has been reported to colonise 21% of hospitalized patients<sup>14</sup>. Longum in the form of fermented Yogurt has been reported to be useful if tetracyclines or Beta-lactam antibiotics<sup>19-20</sup>. *B. Longum* in combination with lactobacillus acidophilus has been shown to be more effective in clindamycin induced diarrhoea than when given alone<sup>21</sup>. *C. difficile* diarrhoea (CDD) is characterized by simple diarrhoea which may progress to colitis, pseudomembranous colitis and toxic megacolon<sup>14</sup>. Its prevention lies in consumption of probiotic containing both lactobacilli and bifidobacterium<sup>22</sup>. As far as treatment of CDD is concerned, a significant reduction in first episode of CDD or recurrences has been reported in various studies using *S. boulardii* given as 1 G/day for 4 weeks along with standard course of metronidazole or vancomycin<sup>23</sup> and another study using standard dose of *S. boulardii* for 4 weeks and vancomycin 2 G/day for 10 days<sup>24</sup>. Another probiotic *L. plantarum* is useful in recurrent CDD<sup>25</sup>. Although probiotics have shown beneficial effects in CDD, yet they are not recommended for routine prophylactic use a larger trials are needed.

**(c) Traveller's diarrhoea :** In traveller's diarrhoea, *L. rhamnosus* GG<sup>26</sup>, *S. Boulardii*<sup>27</sup>, lactobacilli GG<sup>28,29</sup> have been found to be useful. Lactic acid bacterial in the gut are helpful in replenishing the suppressed bacterial and inhibiting the growth of pathogenic bacteria<sup>30</sup>. Volatile fatty acids produced by some lactic acid bacteria control the colonization of gut by *S. sonnet* and *E. coli*<sup>31</sup>. Probiotics like *S. faecalis*, *C. butyricum* and *B. mesentericus* liberate butyrate and acetate, which by lowering intestinal pH, make a harmful environment for pathogenic *E. coli*, salmonella and methicillin resistant *S. aureus*<sup>32</sup>. The metabolites like butyrate and acetate help in intestinal epithelial cells proliferation<sup>33</sup> and glutamine produced by *B. mesentericus* plays a major role in maintaining intestinal mucosal barrier damaged by endotoxins<sup>34</sup>.

**(d) Lactose intolerance :** 90% of Africans, Asians and South Americans lack enzyme lactase, which utilizes lactose. Lactase disappears after weaning. Utilization of dairy products in such persons cause lactose intolerance characterised by flatulence and loose motions<sup>35</sup>. *S. thermophilus* and lactobacilli *delbrueckii* in live yogurt cultures has been found to be useful in lactose digestion<sup>36</sup>. *Lactobacillus acidophilus* as dietary adjunct for milk has been documented to assist lactose digestion in humans<sup>37</sup>. *L. rhamnosus* GG has been found to stimulate local IgA secretion in human intestine in rotavirus infection<sup>38</sup> while *S. boulardii* stimulate IgA secretion in rats intestine<sup>39</sup>. *E. acidophilus* has been shown to inhibit the attachment of *E. coli* to mucosal cells in pig ileum<sup>40</sup>. *L. rhamnosus* GG and *L. reuters* have been shown to produce inhibitory substances like microcin<sup>41</sup> and reuterin<sup>42</sup> respectively, which are harmful to pathogens. *S. boulardii* destroys *C. difficile* toxin A receptor in rat ileum<sup>43</sup>. *Bifidobacterium* produces butyrate which stimulates the proliferation of normal intestinal epithelium and maintains mucosal barrier defences<sup>4</sup>.

**II) H. Pylori infections :** *Helicobacter pylori* (microaerophilic and gram negative bacilli) organisms lead to atrophic gastritis, gastric ulcers and gastric cancer. Lactobacilli *johnsonii* strain produce antibacterial substances which inhibit the growth, colonization and survival of *H. pylori*<sup>44</sup>. But lactobacilli GG<sup>45</sup> and *Bacillus clausii*<sup>46</sup> have been shown to be helpful in *H. pylori* infection but more studies are needed to establish their role in such infections.

**III) Inflammatory bowel disease (IBD) :** IBD is caused by luminal commensal bacterial flora (antigen) and immunological responses<sup>47</sup>. Because of immunomodulatory and bowel flora manipulating properties, probiotics have been shown to be beneficial in IBD<sup>48</sup>. In Crohn's disease, commensal *E. coli* strain stimulate the release of tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-8 (IL-8) by inflamed mucosa. *Lactobacillus casei* has been shown to downregulate the release of TNF- $\alpha$  by the inflamed mucosa and also inflammatory response by *E. coli*<sup>49</sup>. Kruis et al<sup>50</sup> reported relapse rates and 11.3% with mesalazine and 16% with *E. coli* when they were given for maintenance remission therapy for a period of 12 weeks in ulcerative colitis. Gioncetti P. et al<sup>51</sup> reported remission in 80% patients of ulcerative colitis with the use of probiotics given for 1 year. Another probiotic *S. boulardii* when given in patients with quiescent Crohn's disease as adjuvant therapy with mesalazine, produced lower clinical relapse rate as compared to mesalazine alone<sup>52</sup>. Gionchetti et al<sup>53</sup> has reported diminished occurrence of pouchitis, a common inflammatory condition which occurs in surgically created ileal reservoirs after total proctocolectomy for ulcerative colitis. More studies are required to evaluate the role of probiotics for the treatment of chronic IBD.

## OTHER USES

**Urogenital Infections :** Probiotics have been found to be useful in the management of nonsexually transmitted urogenital infections like urinary tract infections (UTI), bacterial vaginosis (BV) and vaginal candidiasis. Intravaginal insertion and perineal implantation of lactobacilli GR I strain twice weekly in patients suffering from recurrent UTI have been found to result in infection free period ranging from 4 weeks to 6 months<sup>54</sup>. The administration of

lactobacilli as vaginal suppositories significantly reduced recurrent UTI<sup>55</sup>. Lactobacilli rhamnosus GR-I and L-fermentum RC-14 significantly alter and improve vaginal flora as well as decrease yeast, bacteria and coliform count<sup>56,57</sup>. Lactobacilli acidophilus Yogurt two doses given for 7 days have been found to be useful in pregnancy bacterial vaginosis<sup>58</sup>. Vaginal flora prevents vaginal infections by creating unfavourable vaginal conditions for pathogens by producing H<sub>2</sub>O<sub>2</sub> and fermenting glycogen to produce lactic acid and an acidic pH. Since only few strains of lactobacilli have been shown to be beneficial in bacterial vaginosis and vaginal candidiasis, more studies are needed before probiotics can be recommended for routine prophylactic use in such conditions<sup>59</sup>.

**Hypercholesterolemia** : Consumption of Yogurt containing E.faecium is effective in lowering LDL and total cholesterol<sup>60</sup>. Maan GV et al<sup>61</sup> have also documented the beneficial effect of probiotics in lowering cholesterol. A study by Kiebling et al<sup>62</sup> has reported increase in HDL levels with the use of probiotics and fall in the ratio of LDL to HDL from 3.24 to 2.48. The proposed mechanisms include direct assimilation of cholesterol by bacterial cells, deconjugation of bile acids by bacterial acid hydrolases and inhibition of hepatic cholesterol synthesis<sup>63</sup>.

**Cirrhosis Liver** : Various studies<sup>64,65</sup> have reported that endotoxemia secondary to bacterial infection is responsible for hemodynamic alterations leading to cirrhosis liver, esophageal varices and portal hypertension. Administration of lactic acid bacteria in liver cirrhosis has been shown to increase mean blood velocity and flow in portal vein and reduction in splenic vein by way of fall in endotoxin levels<sup>66</sup>.

**Food allergy** : The colonic microbiota affects both the mucosal as well as systemic immunity in the host through modulation of both cellular and humoral mechanisms<sup>64</sup>. Administration of probiotics has been shown to be associated with disappearance of food allergy manifestations with decreased concentration of IgE in the serum<sup>67</sup>. Bifidobacteria and lactobacilli have been shown to increase IgA production in Peyer's patches in response to harmful agents<sup>68</sup>. This enhanced IgA response prevents some potentially allergenic dietary antigens from invading the intestinal mucosa and further alleviates intestinal inflammation and downregulates inflammatory responses<sup>69</sup> as well as induction of regulating T cells and counterregulation of Th 1 cells<sup>70</sup>. Lactobacilli also modify immunomodulatory properties of native food protein<sup>71</sup>.

Casein, a milk protein, upregulates the production of IL-4 and IFN- $\gamma$  in milk hypersensitive atopic infants but LGG degraded casein downregulates IL-4 production with no effect on TNF- $\alpha$  release. These facts highlight that probiotics potentially inhibit aberrant IgE secretion and eosinophil activation hypertension.

**Hypertension** : There are limited studies of the utility of probiotics in hypertension. A study by Hata Y et al<sup>72</sup> has reported that milk fermented with lactobacilli helveticus and saccharomyces cerevisiae, reduced systolic blood pressure by 9.4 mmHg and 14.1 mmHg after 4 and 8 weeks respectively and diastolic BP by 6.9 mm after 8 weeks of consumption in known hypertensives. The proposed mechanism may be due to bacterial cell wall component or ACE inhibiting peptides released by probiotics<sup>44</sup>.

**Renal Stones** : Increased levels of oxalate in the urine is a risk

factor for the development of kidney stones. An intestinal microbe known as oxalobacter-formigenes can degrade oxalate through the enzyme oxalate - CoA decarboxylase and thus decreases its absorption. Patients with calcium oxalate stone have been shown to have lower rate of colonization with oxalobacter formigenes. Absence of intestinal oxalobacter among stone formers correlates with higher oxalate concentration and increased risk of hyperoxaluria<sup>73</sup>. Bifidobacterium has been found to be useful as a probiotic in oxalate stone diseases for prophylaxis against new stone formation<sup>74</sup>.

**Cancer** : Colorectal cancer is one of the leading causes of mortality in both men and women<sup>75</sup>. Probiotics have been found to be useful in the prevention and suppression of colonic cancer. In humans, administration of fermented dairy products containing lactobacilli or B. Longum has been found to be beneficial in colon cancer<sup>76,77</sup> and breast cancer<sup>78</sup>.

The proposed mechanisms include :

- detoxification of ingested carcinogens.
- Production of enzymes like Beta-glucuronidase, nitroreductase, Beta-glucosidase and urease by enteropathogens such as E.coli and C.perfringens.
- Lowering of intestinal pH creates bacteriocidal environment.
- Colonization at the expense of enteropathogens may bind the ultimate carcinogen by physically removing it via faeces.
- Stimulating immune system to defend better against cancer cell proliferation.
- Producing metabolic products (like butyrate) which improve programmed cell death (apoptosis).

One of the earliest genetic alterations associated with human cancer especially colonic cancer is Ras activation<sup>79</sup>. Increased levels of Ras p-21 have been correlated with increased cell proliferation, histologic grade, nuclear atypia and degree of undifferentiation<sup>80</sup>. Consumption of dietary B. longum cultures significantly suppressed the expression of total and mutated Ras p-21 in the colonic mucosa and tumours compared with control diet<sup>81</sup>. The proposed mechanism of inhibition of Ras activation by R. longum cultures includes modulation of induction of methyl guanine repair protein called O6 methylguanine DNA methyltransferase, which acts as a suicidal enzyme and accepts a methyl group on itself from guanine by demethylation and restores the original guanine in DNA. The administration of L.casie fermented milk in humans has been shown to significantly reduce the recurrence of bladder cancer<sup>82</sup>.

**Vaccine adjuvant** : Increase in rota virus specific IgM secreting cells was reported in a study<sup>83</sup> when children were given lactobacillus GG as an adjuvant to an oral vaccine to rotavirus compared to placebo on 8th vaccination day. Still more studies are required in this field.

**Growth and well being** : The administration of 50 ml of fermented curd for 6 months in malnourished children has shown gain in weight, height, lower incidence of diarrhoea and fever<sup>84</sup>. Administration of milk formulae supplemented with bifidobacterium lactis and streptococcus thermophilus reduced the occurrence of colic and irritability in infants as compared to control group<sup>85</sup>. A study by Robinson and Thompson<sup>86</sup> has reported that bottle fed infants during the first month of life gained an average

21.9 ozs weight when fed a standard formula and 26.5 ozs weight when *L.acidophilus* was added to the formula. The proposed mechanism of this enhanced growth includes infection control and increased bioavailability of nutrients.

**Various problems associated with probiotic use :** The major problem with probiotics is the maintenance of their viability to produce beneficial effects to the consumer. The probiotics need to survive in many environments like processing treatments, storage condition and human body condition (especially gastric acidity and action of bile salts). The ability to live through the stressful acidic conditions and bile solutions in human body varies among the strains of probiotic bacteria. Only those strains, which tolerate these adverse conditions, should be preferred. Storage at 4°C temperature is reported to be a most important factor in keeping probiotic bifidobacterium viable during 4 weeks storage time<sup>87</sup>. Viability of lactobacilli has been enhanced by encapsulation in artificial sesame oil for storage and in simulated high gastric or bile salt condition as compared to free cells<sup>88</sup>. The use of prebiotics like 150 maltoligosaccharides has been found to be associated with higher level of probiotics like lactobacillus and bifidobacterium after 1 month storage<sup>89</sup>. Still more studies are required in the field of viability.

#### Safety of probiotics

Fermented dairy products and cereals have been in use for centuries. Generally, probiotics are considered non-pathogenic but occasional isolated reports of their adverse effects have cropped up including liver abscess<sup>90</sup> and lactobacillemia<sup>91</sup>. *S.boulardii* has been used without complications in AIDS patients with chronic diarrhoea<sup>92</sup>. *L.plantarum* can be safely given in AIDS patients including immunosuppressed individuals. Salminen et al<sup>94</sup> reviewed the safety data and found no evidence of probiotics being involved in human infections. This is supported by epidemiological data on safety of dairy products<sup>95</sup>. But other limitations include risk of transfer of resistance via probiotics because these agents have to be resistant to antibiotics since they are to be used concurrently. Yet another limitation is depletion of nutrients, which are essential for the proliferation of pathogens. An example is the depletion of monosaccharides, which is essential for *C.difficile*<sup>96</sup>.

**Areas for future research** include ;

- (a) Regulation of intestinal motility
- (b) Modulation of intestinal and systemic immune response
- (c) Reduction and protection of radiotherapy associated intestinal dysfunction
- (d) Prevention of intestinal cancers
- (e) Characterisation of the possible antimicrobial properties and their metabolic activities
- (f) Competitive exclusion
- (g) Cholesterol lowering effect

#### CONCLUSION

Various above mentioned studies have documented the beneficial effects of probiotics as preventive and therapeutic agents in various disorders including diarrhoeal diseases, urogenital infections, hypertension, hypercholesterolemia, oxalate renal stones, allergy, cancer and in children as growth promoters. However further larger

studies are needed to establish their role in the management of these conditions. On account of worldwide epidemic of resistant bacterial and increasing competition for health care resources, the use of cost effective microbial interference therapy should be a top priority. Some major limitations in establishing their role in the therapeutics may be lack of adequate knowledge about them among prescribers and probably the preparations available in the market contain non-viable organisms or strains which possess no antipathogenic activity. Probiotics are likely to emerge as alternative to conventional antimicrobial therapy since they are relatively cheap and may have lower risk of resistance.

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## Innovative Training Programmes for Health Workers

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**Abstract :** *Explosion of knowledge and technology in health care has a profound impact on education and practice of health workers. They are expected to demonstrate an expanded practice base requiring a higher level of competency. They have a responsibility to patients, a professional responsibility to organization and an individual responsibility to maintain high level of current and relevant knowledge and skills. The current situation with regard to need and expectation of knowledge and skills of these professionals is dismal. It is therefore of utmost importance that the entire approach towards training and education is reviewed in terms of national needs and priorities. In order to keep pace with current and potential health care reforms, health professionals need to maintain competency through continuing education. Traditional systems of education involves travel time, travel expenses, time away from work place and home and lack of adequate resources and facilities. Therefore it becomes increasingly important to provide educational offerings in different forms and ensure relevant training programmes as per the needs and requirements of the fast changing society. An innovative task ahead is to come out of the existing rigid frame work and traditional culture of training, generating expertise, capacity building, competency enhancement and collaborative working for enhancement and to transform the existing system of education and training for increasing access, quality and cost effectiveness. This will necessitate the designing and delivering of innovative ways of training to the large group of these health functionaries.*

### INTRODUCTION

Indian education system in general and professional education in particular faces the challenge of widening access to larger numbers particularly disadvantaged groups. ANMs who man the rural health structure in remote corners of our country in a sub centre catering to 5000 populations are most unreached group of health functionaries. The ANM has to perform multiple health care activities as per the national priorities and community needs. In view of her expanded role training assumes special significance with regard to its effectiveness and quality.

The effective delivery of health care services largely depends on nature of education training, retraining and appropriate orientation towards community health of all medical, nursing and allied health professionals and their ability to function as an integrated team. The current situation with regard to need and expectation of knowledge and skills of these professionals is dismal. It is therefore of utmost importance that the entire approach towards training and education is reviewed in terms of national needs and priorities.

The need of the hour is to ensure relevant training programmes as per the needs and requirements of the fast changing society, offer quality education of high standard and ensure equity and social justice in the provision of educational opportunities. The numbers involve lakhs of these functionaries hence cost effectiveness and efficiency need to be achieved. The modern information and communication technologies provide excellent opportunity for extending the out reach education by ensuring high quality.

An innovative task ahead is to come out of the existing rigid frame work and traditional culture of training, generating expertise, developing capacity, competency and collaborative working for enhancing and to transform the existing system of education and training for increasing access, quality and cost effectiveness. This will necessitate the designing and delivering of innovative ways of training to the large group of these health functionaries.

### NEED OF TRAINING

(1) ANM and other public health nursing personnel are disadvantaged group of health workers, (2) There is a need for widening the access to continuing professional education, (3) They have to perform multiple functions and expanded role as per national policies and programmes, (4) There is a need to provide services for consumer satisfaction, (5) Training is like an apprenticeship and there are inadequate residential and hostel facilities, (6) The present institutional infrastructure is limited, (7) There is non-availability of provision for continuing education and (8) Non involvement of trainers in continuing education

### ISSUES TO BE ADDRESSED

- |                                 |   |
|---------------------------------|---|
| (a) National priorities & goals | (f) Quality training                            |
| (b) Access and equity           | (g) Availability                                |
| (c) Cost effectiveness          | (h) Time factor                                 |
| (d) Large numbers               | (i) Readiness for training and getting training |
| (e) Application in practice     | (j) Field training                              |

### CURRENT SCENARIO OF TRAINING

At present there are 340 training schools of ANM providing basic training for 18 months. 42 promotional training centres - rural health training centres - district training centres and family welfare training centres. But the quality and coverage in real sense is cause of concern. Although a lot of efforts have been taken to train the workers from time to time as per the country needs. Yet the accessibility has been limited.

### IMPACT OF TRAINING

A closer look at basic training programme of ANM reveals that there are many handicaps in the training

- (i) Training is more like an apprenticeship, (ii) Living conditions and facilities are inadequate, (iii) Residential place is over crowded, (iv) P o o r sanitary facilities and their maintenance, (v) Inadequate stipend, (vi) Inadequate diet facility in hostel,

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A question arise what impact can be made on quality of training without concurrently thinking of improvement in physical facilities and living conditions. How best can an ANM be trained so that she has comfortable environment of stay and greater opportunity to work in the field for which she is trained.

### **INNOVATIVE TEACHING LEARNING STRATEGIES**

A number of innovative training techniques are used for general and professional clientele at local, regional, state and central level to address training requirement of public or private institutes, government and non-governmental organizations. The teaching learning strategies in these programmes may include following (Gibbs, 1992). The fine tuning strategy involves the modification of conventional practices or existing structures in order to increase motivation, learner activity and interaction, and to utilize a well-structured knowledge base. Changes in methods may take place in

- \* Lectures, by introducing active learning tasks and peer group discussions in typically passive lecture classes. Buzz pairs where students discuss their response to a question with the next to them is an effective strategy for involving students in the lecture situation.
- \* Reading through the use of reading guides or the division of background reading between members of small teams, followed by peer tutoring. This is called a jigsaw strategy. Self-directed learning materials are another effective way to guide students' reading and to provide a background for group discussion (Chalmers, 1995).
- \* Seminars or tutorials through the use of tutorless tutorial groups, student led discussions, and group. Self-directed study materials can also guide student work in group work and tutorless tutorials.
- \* Laboratory work by replacing selected tutor designed laboratory tasks with student designed laboratory tasks and with peer review of the work.
- \* Field work by introducing independent student designed fieldwork within a given framework.

The independent learning strategy involves giving students more autonomy and control over the subject matter, learning methods, pace of study and the formal assessment of learning. Teaching methods include the use of learning contracts, self and peer assessment, project work and self directed learning materials. The personal development strategy emphasizes motivational aspects of learning, especially students' personal involvement in learning. Teaching methods include group work, discussion and various other methods that allow for students' expression of feelings and covering the course content. The problem based strategy involves learning through tackling relevant problems. Teaching methods include the use of learning diaries, reflective exercises and the use of video, audio and observers to provide feedback on performance of skills. The independent group work strategy focuses on interaction between students. Teaching methods include group based project work and peer tutoring. It can include other strategies such as problem based learning or conventional inclass activities such as student led seminar groups. The learning by doing strategy utilizes experiential learning and emphasizes learning activity. The focus is on the deliberate introduction of concrete experience of real world tasks to encourage students to become more involved, more active

and more aware of their existing knowledge base and its use in their concrete experience. Teaching methods include the use of games, simulations, role plays, visits and practical work and work experience.

### **ADOPTING COST EFFECTIVE TRAINING STRATEGIES**

The most viable alternative to quality and cost effective training is using open and distance learning system which may include multimedia/multiple media/and or mixed media such as print media (self instructional material), audio video cassettes, telecast and broadcast, satellite - one way video and two way audio teleconferencing, two way video eleconferencing, interactive radio counselling, computer aid learning - integrated multimedia CD room and online learning. India and many countries in Asia have opted to extend range of educational opportunities by adopting the distance and open education and have set up for this purpose higher educational institutions of distance teaching and learning. The information in technology revolution has made these educational programmes and methodologies easier, more effective, enjoyable and highly customized. It is essential that these approaches be economical and efficient so as not further deplete the limited available community and government educational resources.

### **INNOVATIVE TRAINING PROGRAMMES - A REVIEW**

A variety of innovative training methods have been used to impart training to the inservice learners. Review of these innovative programmes revealed that following strategies are being adopted by various institutions / organizations (Dec. 2004).

IGNOU adopts an integrated multimedia approach which includes self instructional material supplemented by face to face counselling, practical contact sessions, hands on training, audio-video programmes, teleconferencing, telecast, broadcast and interactive radio counselling for training of inservice doctors and nurses. For Distance Education Programmes of primary school teachers all over the country IGNOU uses innovative methods such as self-instructional print material, lecturers, demonstrations, role-plays, simulations, AV aids, audio-video cassettes, counselling, workshops, radio and TV, satellite and integrated multimedia CD. BRAOU State Open University, Hyderabad uses self-instructional material face to face counselling, audio-visual / radio lessons, summer and winter schools, hands on Lab based practicals, teleconferencing and broad cast. Kota Open University, Rajasthan uses self-instructional material, audio/visual aids, face to face counselling, radio counselling in Doordarshan etc. Nalanda Open University, Patna uses self-instructional material and audio video mainly. Yashwant Rao Chavan Maharashtra Open University, Nasik uses self-instructional material, face to face counselling, audio-video, CD Rom, Radio and television broadcast and online education through internet and use of Krishi Prayog Parwar a community learning centre for learners which helps in exchanging their experience for interaction learning. MP Bhoj Open University, Bhopal uses self-instructional material, audio-visual aids, face to face counselling, hands on lab based practical, telecasts, broadcast internet for instructions and satellite. Baba Saheb Ambedkar University, Ahmedabad uses self-instructional material, audio visual aids, face to face counselling, interactive radio counselling for delivery of programmes, satellite, mobile computer and laboratory for hands

on practice in remote and rural areas. Karnataka State Open University, uses self-instructional print material, face to face counselling, audio video aids, radio counselling. Netaji Subhash Open University, Calcutta uses self-instructional material, face to face counselling, audio visual aids, radio counselling. Rajarshie Tandon Open University, West UP uses self-instructional material, face to face counselling, audio video.

It is evident from the above discussion that for training a large number of learners through distance open learning system, the main methods of instructions are self-instructional material, face to face counselling and audio video. Satellite communication is also emerging as an important media for training the learners in large numbers.

NIIPCCD uses a variety of innovative training techniques for refresher training of officers which include lectures, demonstrations, discussions, simulations, role play, etc. Similarly state ICDS centres use demonstration. AV aids, focus group discussion, mock assignments, mobile training and supervised practice training etc. A few states such as Bhopal and Hyderabad have also been using satellite based training for different ICDS workers and officers.

National Institute of Open Schooling uses self-instructional print material, audio and video programme, face to face counselling and contact sessions and delivery kits, etc. NCERT uses print material, networking, satellite training for inservice training of teachers and vocational courses. Krishi Vigyan Kendra use variety of training techniques to train the farmers, extension workers and other staff which include teaching by doing and learning by doing, summer schools, experiential learning. Front line demonstration, discussions and hands on training in collaboration with State Agricultural Department and Agriculture University.

Police Training Institutions use mainly group demonstration and case studies, simulations, role play. Integrated approach and said model discussions are also rarely used. For training probationary officers a variety of innovative methods are used such as case studies, role play simulation, exercises, demonstrations, panel discussions, group discussions, project report, field visits, individual presentations, book reviews and syndicate reports, use of films, slides, video cassettes, flow charts, electronic black boards, video projector, director projector, making of synoptic notes during indoor lectures, debates, public speaking competitions on police subjects, interactions with eminent personalities from police as well as other discipline and also self study.

#### **SUGGESTED MODELS OF INNOVATIVE TRAINING**

A large number of innovative methods can be adopted to train ANMs without removing them from workplace. These may include:

- \* **Satellite based field training model**
- \* **Integrated multimedia model IGNOU**
- \* **Classroom based, supportive and field training model**
- \* **Learner facilitator / mentor model**
- \* **Interactive multimedia CD / cum field experience**
- \* **Convenient Workshop model**

**Satellite Training Model :** The application of satellite technology in support of training will be useful both in terms of quantity and quality as it becomes possible to send message from one point to multipoint locations simultaneously. It can serve as interactive educational tool and facilitate ideal educational transactions. The

satellite system can address separate regions or audiences widely dispersed but professionally united. Training becomes possible on a large scale without uprooting the learners from their place of work. It can serve as an effective tool of training ANMs because of multiple *advantages*.

- \* It is a fast communication medium through which the expertise of the faculty or the specialist can be made available to a large group of learners across the country or even world
- \* The satellite can facilitate the information of inputs from various sources
- \* Visual lexicon can add a new dimension to the learning process, it can be an experiment in a laboratory or a novel technique in a hospitals
- \* The reach of radio and television can be increased and their round the clock quality ensured
- \* Satellite is flexible since its links can be changed as desired
- \* It offers medium diversity
- \* The links are reliable and clear
- \* The costs are distant independent
- \* Remote areas, islands, mountains regions and difficult terrain can be easily covered.

To achieve this human and machine can be pooled and the entire audience in the network can have the benefit of a good teacher or a good visual experience. The satellite delivery uses one or two way video where an instructor and a group of learners in one classroom can be linked to several other remote classrooms (designated as receiver sites). The instructor can see and hear every one at each site and the participants in each site can hear not only the instructor but the participants in every other site. The classroom presentation can be delivered live to other learners sitting at distant sites. They can participate in the class by a telephone, fax, computers etc. By this way all the learners can complete the same requirements as on campus learners on the same schedule. Practical demonstrations and activities can be shown by pre-recorded role plays. Each programme reception site has to be equipped with the appropriate technology so that participants are able to interact or talk back with the presentations. The television, telephones, fax machines and computer that can provide verbal and written interactions are available in most of the institutions. In view of challenging task of providing training to ever increasing number of ANMs and upgrading the knowledge and skills on a massive scale we cannot ignore to use the satellite. The case of satellite training medium therefore needs to be examined on merits for training the large number of ANMs. However the satellite alone would not be able to deliver the educational message. Actually the best results will be obtained by mixing of satellite and other traditional modes of learning mainly providing practical training in the field under continuous supervision facilitating demonstrations and return demonstrations.

**Integrated multimedia model IGNOU :** This model includes innovative self-learning modules teleconferencing, greater reliance on practicum especially hands on experience, tutorials, phone in facility and academic as well as personal counselling, T.V. broadcast and greater use of audio video cassettes to upgrade the knowledge and competencies without leaving their work place. Providing inservice training to ANMs through the distance mode can be a strong supplement to interactive face to face component in context of issue of quality, access and need to address the needs of large

number of ANMs. In this system training centres are established in existing training institutions for providing classroom and field training to make use of existing infrastructure for cost consideration. However additional training facilities and resources are provided for carrying out extra load of training. The distance education inputs and materials will facilitate the training of ANM/FHW by the networking and collaborations with NGOs and existing institutions could provide a befalling response to the challenge of training large number of ANMs.

**Classroom and field training model :** This could be a viable model for training of large number of ANMs at state level. Where variety of methods can be used viz use of satellite to connect the classroom to various distance sites for wider coverage. Mobile training teams resource person can be identified and training for providing hands on in the field on continuous basis.

**Learning Facilitator mentor model :** In this approach one or two facilitators / trainers can be identified from a particular district and trained in RCH for taking the charge of training ANMs / Public Health Nurses of that area availing the facility of identified centres, providing feedback and follow up.

**Interactive Multimedia CD Rom cum Field Training Model :** In this an interactive CD can be prepared which include, training content, simulations from actual field training, video clippings, audio clippings, recorded actual demonstrations and presentations by expert trainers. This method can take the major load of training. In addition, hands on training can be provided for a minimum required period either with the help of mobile training teams or providing training in selected centres during the meeting days at district headquarters.

**Convenient Workshop model :** In this model an intensive training programme both in classroom and the field is provided in workshop method. An intensive workshop can be organised in each centre to provide theoretical training inputs and hands on training.

In order to answer the question of coverage of large number of ANMs for training in RCH, technological support is the only answer. Therefore, it is advisable to adopt collaborative effort with IGNOU and other State Open Universities for providing this support. The academy can take leading role with the advice of Department of Family Welfare and UNFPA.

## TRAINING INPUTS

- (i) Development of teaching / learning materials and notebooks,
- (ii) Materials for teleconferencing, audio materials and CDs,
- (iii) Video clips on various procedures, (iv) Video recording of teleconferencing, (v) Capacity building, (vi) Trainers training programme in relevant areas, (vii) Resource persons for organizing training programmes, (viii) Strengthening of institutions,
- (viii) Providing print material and audio video-materials, (ix) Internet devices and internet faculty, (x) Television with audio CD and video player,

## METHODOLOGY OF TRAINING

**Production of competency based materials :** A team of experts will be identified and trained to prepare training/learning materials which include print material, audio video cassettes and CDs. Print material plays a vital role in teaching learning and is preferred to all other instructional media. Similarly, the audio, video, TV and radio programmes need to be developed as these can prove to be an effective and viable tool of training in terms of cost effectiveness and access. These are more effective than chalk and talk method.

**Identifying training centres :** Training has to be made available in the various regions. For this purpose district centres will be identified either in NGOs, existing district training centres etc. which will cater to the training requirements of the concerned district. Large number of such centres have to be established to provide timely training in cost effective manner for large coverage of learners.

**Identifying resource person :** A teaching resource person including the district training coordinator can be identified either on contrast or selecting from among the identified centres exclusive for the purpose of the training. These resource person will be trained to carry out training.

**Establishing the link with satellite centres :** It will be a costly affair to invest on these centres. Therefore collaboration is made with other universities / institutions for using the existing facility. This will help to train a large number of ANMs in a small duration of time across the country and benefit them with expertise of the resource persons. A well established university/NGO can take a leading role and IGNOU can be an important collaborative agency to undertake the task of training by adopting various approaches.

**Networking of the Institutions :** The institutions offering inservice training of health workers will be strengthened and used for providing field training. A team of trainers will be identified and trained to provide the hands on training in actual field under supervision. The field training teams can either be identified at from various districts or a core team of trainers will be identified and trained for providing mobile training.

**Evaluation and Follow up :** At the end of training a centralized examination can be conducted. Appropriate evaluation procedure shall be adopted to evaluate the learners and certificate will be offered.

## ADVOCACY GROUPS AND INTERACTIONS

- (a) IGNOU (b) NIHFV (c) State Open Universities/Distance Learning Institutions (d) NCERT (e) NIPCID (f) Selected NGO's and (g) National Institute of Open Schooling

## RECOMMENDATIONS

- \* Collaboration with institutions of excellence for imparting training.
- \* Creating resource learning centres at local, regional and national level to monitor the quality of training
- \* Provide adequate infrastructural facilities for learners such as PC, telephone facility, etc.
- \* Training a team of master trainers on continuous basis
- \* Create continuing education cells in each ANM and GNM schools and make provision for funding such programmes on continuous basis
- \* Appoint local block and district resource persons / coordinators among the trained master trainers in each resource centres to take responsibility of training in their area.

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## Systemic Sclerosis ----- Diffuse Form

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Systemic sclerosis (SSC) is a chronic multi system disorder of unknown etiology characterized clinically by thickening of skin caused by accumulation of connective tissue. A 27 year old female patient (Fig.1), presented with swelling and stiffness of fingers of both hands with limitation of movements (Fig.2), difficulty in opening mouth fully (Fig.3), difficulty in clenching fist (Fig.4), slight difficulty in swallowing solids and epigastric fullness, cough and history of dyspareunia since one year. She had difficulty in getting up from the squatting position since 10 months. She had a 9 year old daughter and her second daughter died at the age of 1 year in 2003. Her past history revealed bluishness of nails and tip of nose on exposure to cold with history of pallor followed by rewarming associated with coldness and numbness of fingers. There was no involvement of lower extremities. Her examination of hands revealed areas of depigmentation on dorsal aspect of fingers (Figs.4&5), flexion deformities (Figs.5&6), as well as presence of syndactyly (Figs.2,5&6). She had expressionless dark pigmented face with loss of wrinkles and pinched up nose (Figs.1-3). There were also areas of depigmentation on both forearms (Figs.7,8&9). The skin was tightly bound to subcutaneous tissue (hidebound skin) (Figs.7,8&9). Her chest examination revealed end inspiratory crepitations. CVS examination was normal. BP 130/80 . Her laboratory profile revealed Hb 8gm%. TLC 9000/mm<sup>3</sup>, DLC P<sub>68</sub> L<sub>30</sub> E<sub>1</sub> B<sub>1</sub>, ESR 70 mm/ 1st hour, ANA +ve. The above features were suggestive of SSC. She was put on D-pencillamine, H<sub>2</sub> blockers, antianemic and supportive therapy. She responded satisfactorily and is on regular follow up.



Figs.1&2



Figs.5&6



Figs.3&4



Figs.7,8&9

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## 'BRAIN ATTACK' : PRACTICAL ISSUES

## Editorial

## Stroke or Brain Attack

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The World Health Organisation defines stroke as "the rapidly developing clinical symptoms and/or signs of focal [at times global] disturbance of cerebral function, with symptoms lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin. The term 'Brain attack' is recently being used to describe the same clinical syndrome as stroke but within 24 hours of onset, when it is not possible to classify them into TIA (Transient ischaemic attack) or stroke.

**Magnitude of Problem**

According to WHO Survey in 1990, out of 9.4 million deaths in India, 19,000 were due to stroke. Thus, mortality rate in India due to stroke is 7.3/1, 00,000. As such, deaths due to stroke were 22 times higher than malaria, 1.4 times that due to tuberculosis, 4 times that due to rheumatic heart disease and almost equal to that of ischemic heart disease. These figures suggest that stroke mortality in India is significantly higher compared to Caucasians. Moreover, incidence of stroke is likely to increase in our country because of increasing population, increasing life expectancy and changing lifestyles (urbanization, smoking, salt/alcohol intake, stress, physical activity). WHO estimates for India show is expected that number of deaths from stroke to increase from 598000 in 2000 to 945000 in year 2020. Another disturbing fact is the relatively higher incidence of stroke in young persons in our country. The problem is further aggravated by the fact that the survivors are left with devastating disabilities with inability to lead a normal lifestyle.

Patients and their families have in the past felt frustrated and even the medical community had limited treatment to offer in these cases. However, recently there have been many advances with improvement in prevention and treatment of these disorders.

**Stroke centre** is a hospital or part of a hospital that (nearly) exclusively takes care of stroke patients with specialized staff with multidisciplinary approach to treatment and care. Care by stroke teams (including neurologists, neurosurgeons, interventional and diagnostic neuroradiologists) or by stroke units decrease the number of deaths and increase the number of independent survivors<sup>1</sup>. Patients with stroke need to undergo intensive evaluation and treatment to prevent further episodes of strokes.

**Thrombolysis** - Stroke is a medical emergency because brain cells start dying quickly and the treatment is most effective when given promptly<sup>2</sup>. It is a known fact that there is a zone around core of the infarct with cells, which though not functional can be revived with reperfusion. This zone known as "penumbra" can exist even after many hours after the onset of ischaemia. This is the target zone of recanalization (thrombolytic) therapies. Appropriate patients with ischaemic stroke can be treated by thrombolysis, which can result in significant improvement in prognosis in a portion of patients<sup>2</sup>. Intravenous thrombolysis can be performed upto 3-hours after the

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onset of stroke while intra-arterial therapy can be performed upto 6-hours or even longer in posterior circulation after onset of stroke and may be more effective in large vessel occlusion<sup>3</sup>. Advances in diagnostic imaging such as MR/CT angiography and diffusion/perfusion imaging are playing ever increasing role in precise diagnosis in these cases enabling well directed treatment.

**Interventional Neuroradiology** is a branch in which minimally invasive endovascular procedures of cerebrovascular disorders are performed. This minimally invasive approach ensures minimal injury to normal brain and interventional neuroradiologists are playing an ever increasing role in treatment of these patients. *Carotid artery stenting* can be performed to treat carotid stenosis. Similarly *vertebral and intracranial angioplasty* can be done to prevent strokes. Patients with subarachnoid haemorrhage need rapid evaluation and treatment for *intracranial aneurysms* because these cases have a very bad prognosis if not treated, mostly because of re-rupture of aneurysm. Endovascular treatment of the aneurysms can be performed and has been shown in a prospective multicentre trial to have better clinical outcome as compared to surgical clipping<sup>4</sup>. Intracranial arteriovenous malformations can also be treated by this minimally invasive method.

**Conclusion**

- \* The outcomes after stroke can be improved with development of centres with multi-disciplinary teams working according to well defined protocols with facilities to perform thrombolysis and endovascular neurointerventions.
- \* Early referral and prompt treatment at appropriate stroke centres - "Time is brain."
- \* Considerable effort is needed to increase public awareness early identification of stroke, is to be emphasized.
- \* CME programmes are needed to educate the medical community Usage of term "Brain attack" should be encouraged so as to promote a sense of urgency in management.

Purpose of this Symposium is to present a comprehensive review of various practical issues concerning management of patients suffering from cerebrovascular disorders. We hope that this effort of various contributors will play a role in creating awareness about this stupendous medical problem, preventing in the community.

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## Subarachnoid Haemorrhage (SAH) - What Should We Know?

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**Abstract :** Subarachnoid haemorrhage (SAH) is bleeding within the cerebrospinal fluid-filled spaces surrounding the brain which occurs most commonly due to trauma, rupture of intracranial aneurysms is the most common cause of non-traumatic SAH. SAH is always an emergency because untreated ruptured cerebral aneurysms have a bad prognosis. The outcome in these patients can be improved significantly by early treatment. Rebleed due to rerupture of aneurysm is a very important factor, which makes early treatment all the more important. Although, aneurysms have been treated traditionally surgical techniques, minimally invasive method such as endovascular coil embolization is feasible in most of these patients. Management in a centre with a team of doctors specializing in different aspects is important because patients with SAH are prone to secondary complications, like vasospasm and hydrocephalus.

### WHAT IS SUBARACHNOID HAEMORRHAGE (SAH) AND HOW IS IT DIFFERENT FROM OTHER TYPES OF INTRACRANIAL HAEMORRHAGE?

Based on location, the intracranial haemorrhages are roughly classified into intra-axial or extra-axial haemorrhages.

**Intra-axial haemorrhage** is bleeding within the brain itself. This category includes Intraparenchymal haemorrhage (bleeding within the brain tissue) and intraventricular haemorrhage (bleeding within the brain's ventricles).

**Extra-axial haemorrhage** is the bleeding that occurs within the skull but outside the brain tissue. It is classified into three subtypes :

*Extradural haemorrhage* is usually caused by trauma and results from laceration of an artery, most commonly the middle meningeal artery.

*Subdural haemorrhage* usually results from traumatic tearing of the bridging veins in the subdural space between the dura and arachnoid mater.

**Subarachnoid haemorrhage** is bleeding between the middle membrane covering of the brain and the brain itself. Specifically, it occurs within the cerebrospinal fluid-filled spaces surrounding the brain (also known as the subarachnoid space) from some pathologic process. The most common cause of SAH is head injury<sup>1</sup>. The medical use of the term SAH here refers to the nontraumatic types of haemorrhages, which most commonly occurs due to rupture of a berry aneurysm. However, it must be realized that not all SAH are due to aneurysm rupture of a berry aneurysm. However, it must be realized that not all SAH are due to aneurysm rupture and not all aneurysm ruptures are primarily into the subarachnoid space. Subarachnoid haemorrhage due to aneurysm rupture is a very important entity to recognize because if not treated early, it has a bad prognosis. However, good grade patients treated in specialized centers have a good prognosis. The annual incidence of SAH varies from 6-10 per 100,000 in different populations<sup>2</sup>.

### WHY IS TREATMENT OF SAH AN EMERGENCY?

SAH is always an emergency because ruptured cerebral aneurysms

continue to be a significant cause of death as well as a health and economic problem which can be significantly reduced if treated early. It is an important cause of mortality and morbidity because young and middle-aged adults are most often affected. Studies to date show peaks at various ages in the 40-70 year range<sup>3</sup>. An estimated 12% of patients die before reaching the hospital<sup>4</sup>. Epidemiological studies estimate that about 40% of those reaching hospital die<sup>4</sup>.

Rebleed due to rerupture of aneurysm is a very important factor, which makes early treatment all the more important. With modern surgical and interventional (endovascular) techniques, most of the aneurysm can be treated with reasonable safety. Early treatment reduces the risk of rebleed and facilitates the treatment of vasospasm by increasing the safety of hemodynamic manipulations. The peak risk of rebleed is within the first 24 hours after SAH thereafter the rate declines to 1.5% per day, with a cumulative risk of 19% in the first two weeks<sup>5</sup>. Early treatment in selected cases not only prevents morbidity and mortality due to rebleed but also enables aggressive treatment of secondary complications such as vasospasm and hydrocephalus.

### WHAT ARE THE COMMON SIGNS AND SYMPTOMS OF SAH?

Hallmark of SAH is sudden severe headache in 80% patients<sup>6</sup>. Sentinel headaches may occur a few hours to a few months before the rupture, with a reported median of 2 weeks prior to diagnosis of SAH. Headache of SAH is usually typical but sometimes is variable as to render the diagnosis difficult. Most common incorrect diagnosis in order of decreasing frequency are systemic infection or viral illness, migraine, hypertensive crisis, cervical spine disorder such as arthritis or herniated disc, brain tumor, aseptic meningitis, sinusitis and alcohol intoxication<sup>7</sup>. Therefore, a high degree of suspicion should be kept in this condition so as not to misdiagnose it as a more benign cause of headache. Ominous features associated with headache are vomiting (77%), alteration in consciousness (53%), meningism (35%), seizure (20%) or focal neurologic deficit<sup>8</sup>. Physical examination findings may be normal, or the clinician may find some focal neurological deficits. There might be varying degrees of impaired consciousness depending on the grade of the patient.

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Patients usually have nuchal rigidity as a sign of meningism. The *focal deficit* usually pertains to the vascular territory involved like bilateral lower limb weakness in anterior cerebral artery territory or hemiparesis in middle cerebral artery territory or third nerve palsy in posterior communicating artery territory<sup>9</sup>. Hence, it should be realized that the clinical presentation of a patient of SAH can be anywhere in a large spectrum of presentations. There has to be a high degree of suspicion and such patients should be urgently investigated to prove or rule out SAH. It needs to be emphasized again that this condition should be recognized and treated early to improve the outcome and avoid complications.

#### WHAT ARE THE INVESTIGATIONS NEEDED?

First investigation in any patient with clinical suspicion of SAH should be CT scan of brain. Every physician should be aware of the fact that CT is much more sensitive for detection of haemorrhage than routine MRI.

**Computed tomography (CT)** : this test should be the first investigation to be performed particularly to look for presence of bleeding. Most of the cases CT will show evidence of blood in subarachnoid space although one should be aware that 3% of patients might have normal scans within 24 hours of confirmed SAH<sup>10</sup>. CT scan also helps in diagnosis of associated intraventricular haemorrhage, intracerebral haemorrhage, as well as for presence of mass effect, ischemic changes and hydrocephalus. With passage of time, sensitivity of CT to detect SAH in a patient decreases and by day 5, significant number of patients may have normal CT in spite of presence of bleed and aneurysm<sup>10</sup>. This fact should be kept in mind in evaluation of patients presenting many days after the episode of headache. In patients with indeterminate CT, lumbar puncture or angiography may have to be done.

**Lumbar puncture (LP)** : Lumbar puncture is done to detect RBCs and xanthochromia as an evidence of SAH. LP is indicated in case where the clinical history is strongly suggestive of SAH with a negative CT<sup>9</sup> or the patient presents many days after the episode with a negative CT scan. It is contraindicated in case of abnormal coagulation profile, increased intracranial pressure and suspected spinal arteriovenous malformation (AVM) or infection at puncture site. It is important to differentiate a *traumatic tap* from SAH. Xanthochromia is a very reliable sign of SAH in CSF obtained more than 12 hrs. after SAH. It is a yellow discoloration of a centrifuged CSF sample due to hemoglobin and its breakdown products released by hemolysis of erythrocytes.

**Catheter angiography (DSA - digital subtraction angiography)** : This is the most accurate investigations in diagnosis and evaluation of aneurysms causing the SAH. Cerebral angiography is performed once the diagnosis of SAH is made. This study assess the ruptured aneurysm, vascular anatomy, presence of other aneurysms and secondary vasospasm.

This study helps in planning operative/interventional options. In spite of development of CT/MR angiography, DSA is needed in these cases to detect and assess the aneurysm. In particular, 3-D DSA is most accurate in evaluating assessment of intracranial aneurysms. Catheter angiography (DSA) findings can be negative in 10-20% of patients with SAH. If negative, it is advisable to repeat angiography a few weeks later. Magnetic resonance imaging

(MRI) is also performed if no lesion is found on angiography to evaluate for unusual parenchymal pathologies causing SAH like arteriovenous malformation, dural arteriovenous malformation, cavernomas, tumors or vasculitis.

**Magnetic resonance imaging (MRI)** : Although some reports show that MR can detect acute haemorrhage, CT should always be done first to rule out haemorrhage.

**CT/MR angiography** : Although MR angiography can detect intracranial aneurysms, its sensitivity in detection of small intracranial aneurysm is poor. CT angiography is performed after intravenous injection of contrast and is a useful procedure for detection of aneurysm and for arterial blockage/stenosis. Although CT angiography has improved significantly in recent times, 3-D DSA remains the gold standard in detection and evaluation of intracranial aneurysms.

#### WHAT ARE THE VARIOUS TYPES OF TREATMENT OF INTRACRANIAL ANEURYSMS?

Aneurysms can be treated by endovascular and surgical techniques. The primary goal of treatment is complete, permanent and safe aneurysm occlusion.

**Surgery** : Surgery has been the conventional method of aneurysm treatment. Surgery entails direct exposure of the aneurysm, the parent vessel(s) and surrounding structures. The aneurysm is then secured by the placement of a metallic clip along the neck thereby excluding it from the circulation. Problems with surgery include invasiveness and trauma to normal brain parenchyma. Surgery has an edge over endovascular method in cases of large haematoma or hydrocephalous where a decompression would always benefit the patient<sup>11</sup>.

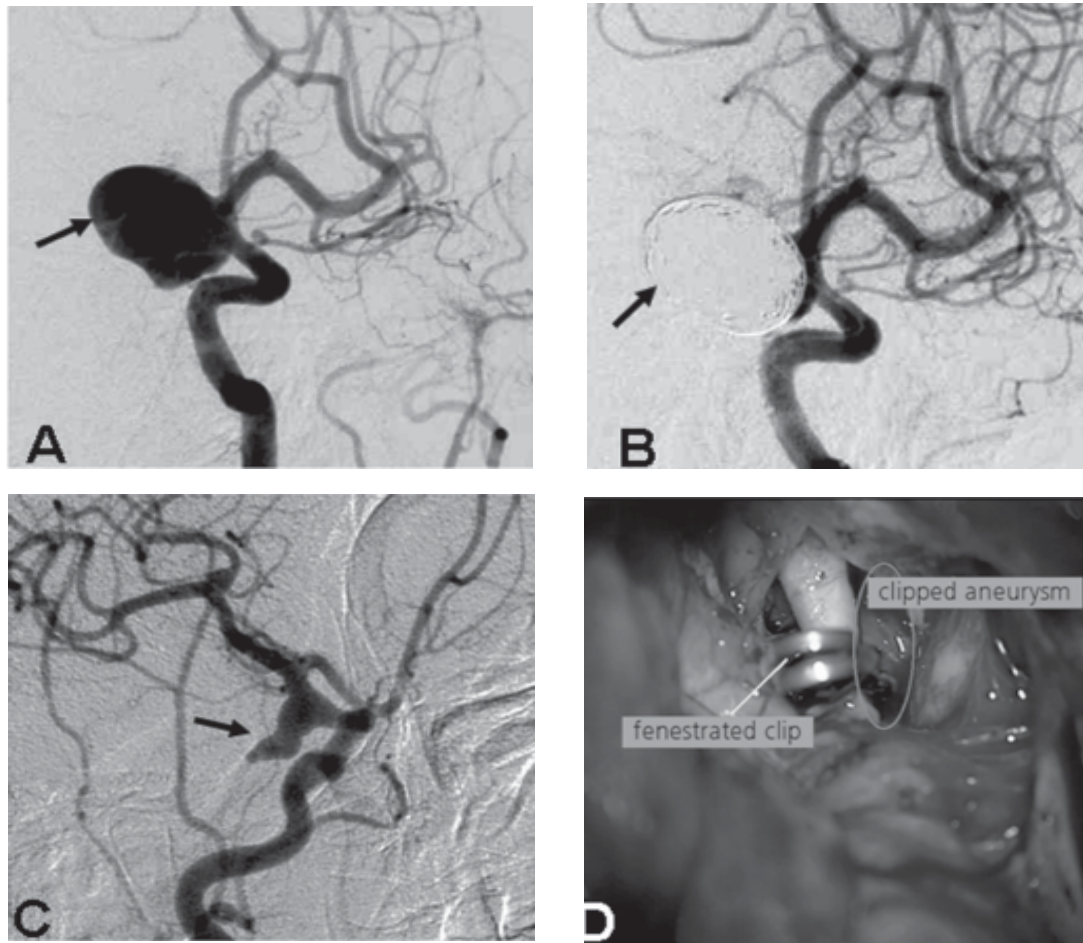
**Endovascular Coiling of Aneurysms** : In this treatment a microcatheter is placed from one of the leg arteries in to the aneurysm, which is then occluded with coils (usually detachable platinum coils) so as to prevent repeat bleeding. A recent randomized, multicentre trial conducted in Europe and North America has shown that long-term clinical results were better with embolization than open surgery in certain subset of patients<sup>12</sup>. Endovascular treatment and is usually the treatment of choice of patients with surgically poorly accessible aneurysms (posterior circulation, cavernous ICA aneurysms), in patients with medical risk factors and in patients with poor clinical status after the bleed.

Therefore, it is most important to have physicians with expertise in both treatment methods in any centre treating patients with SAH.

#### WHY IS IT IMPORTANT TO MANAGE SUCH PATIENTS IN SPECIALIZED CENTRES?

**Concept of stroke centers, stroke units, stroke team and stroke ICU** : A comprehensive stroke centre is defined as a facility or system with the necessary personnel, infrastructure, expertise and programs to diagnose and treat patients who require a high intensity of medical and surgical care, specialized tests, or interventional therapies. This kind of a centre has :

- \* Stroke team/physicians
- \* Diagnostic techniques such as MRI, CT (with CT angiography), Digital subtraction Angiography (DSA) and transcranial Doppler
- \* Surgical and interventional therapies well established surgical



*Fig.1 : Case 1 (Fig. A&B) - A 45 year old female presented with sAH due to alarge internal carotid artery aneurysm (arrow Fig. A). The aneurysm was embolized with almost complete occlusion (Arrow, Fig.B). Case 2 (Fig. C & D) - A 62 year old female presented with SAH due to a broad neck aneurysm of ICA (Fig.c). Due to unfavourable anatomy for embolization the aneurysm was clipped (Fig.D). Both aneurysms were treated with a gap of few days in our hospital. The decision making in both cases was made collectively by team of surgeon as well as interventional neuroradiologist*

procedures such as hematoma removal, clipping of aneurysms as well as interventional neuroradiology and endovascular therapy

\* Infrastructure such as Stroke ICU, neurosurgical ICU, and round-the-clock interventional and surgical facilities.

Studies have shown that patients treated in stroke centers have better outcomes as compared to patients treated in regular hospitals<sup>13</sup>. This holds true even for patients, which are managed medically and not treated by advanced interventional/surgical treatments. Results of both surgery and intervention are also largely dependent upon the expertise of the treating physician.

Management in a centre with a team of doctors specializing in different aspects is important because patients with SAH are prone to *secondary complications*, which can cause delayed onset of worsening after SAH. These include :

(i) Cerebral ischemia due to vsospasm - Symptomatic vasospasm is narrowing of vessels that have resulted in cerebral ischemia with

clinical symptoms and signs<sup>14</sup>. Angiographic vasospasm is arterial narrowing demonstrated on angiography after SAH and overall incidence of this is about 50%<sup>15</sup>. Almost 60% of patients with thick clots develop moderate or severe angiographic vasospasm in at least one major artery; (ii) Hydrocephalus; (iii) Hyponatremia; (iv) Hypoxia/hypotension from cardiopulmonary complications; (v) Systemic sepsis, meningitis and (vi) Cardiovascular complications - such as ECG abnormalities are quite common in these patients. Usually, they may be associated with underlying cardiac damage manifest as contraction band necrosis and elevated cardiac enzymes.

#### **HOW SHOULD A TEAM OF DOCTORS BE FORMED TO TREAT SAH AND WHO ARE THE INDIVIDUALS INVOLVED IN TREATMENT OF SAH?**

As outlined above a team of doctors and support staff enables best outcome in these cases. **Specialists** involved in treatment of

patients with SAH include :

- \* **Neurosurgeon** - performs surgical treatments such as hematoma evacuation, aneurysm clipping, arteriovenous malformation excision and endarterectomy for carotid artery stenosis
- \* **Interventional neuroradiologist** - Interventional neuroradiology/endovascular surgery is a branch in which minimally invasive diagnostic and therapeutic procedures of cerebrovascular disorders are performed. These procedures are carried by very thin catheters/wires etc. placed through groin vessels to reach the site of the abnormal vessels. This minimally invasive approach ensures minimal injury to normal brain, with less complications, better outcome and shorter hospital stay.
- \* **Diagnostic neuroradiologist** - specializes in diagnosis of stroke using modalities such as CT, MRI and Doppler etc.
- \* **Neuroanaesthetist** and critical care physicians.
- \* Nurses trained in management of stroke patients, physical therapists.

#### WHAT ARE THE LIKELY FUTURE DEVELOPMENTS IN TREATMENT OF SAH?

- \* **Advances in endovascular treatment (embolization) of intracranial aneurysms** - The technology of endovascular techniques is improving and evolving all the time.

**Stent/balloon-assisted coiling** : The endovascular treatment of cerebral aneurysm poses technical challenges in wide-necked aneurysms. Stent placement across the neck of the aneurysm has been used in these cases to prevent prolapse of the coils outside the aneurysm (Fig.3). Many stents meant for intracranial use are being introduced and in future use of these devices is likely to increase. Many compliant balloons are also available to perform coil placement in wide neck cerebral aneurysms<sup>16</sup>.

**Coils** - Wide ranges of coil shapes and sizes (including 3-D and 2-D) and much softer coils have been introduced to improve the range and effectiveness of the device. Unlike the bare metal coils initially available for endovascular treatment of aneurysms, bioabsorbable polymeric coils, have been introduced which promotes healing inside the aneurysm and may prevent recanalization<sup>17</sup>.

**Advances in technology** : The advances in DSA (Digital subtraction angiography) technology which makes this kind of procedure safer and effective are :

**The 3D technology**<sup>13</sup> allows construction of 3-D images format, which helps in accurate assessment of diseases affecting blood vessels such as stenosis, aneurysms and vascular malformations.

**The flat panel DSA technology** helps in having high-resolution images with decreased radiation exposure. This is achieved by using a digital system rather than the older optical systems.

**Genetics** : Genetic factors play an important role in pathogenesis of SAH and intracranial aneurysms. The different incidence of SAH in different parts of the world and different type of populations indicate the role of genetic factors. Elastin and collagen type 1A2 are most promising of all the genes because allelic association with intracranial aneurysms has been shown for them. However, genetic variations only explain a small proportion of all the factors involved in intracranial aneurysms<sup>19</sup>. In future, genetics screening may help in detecting patients who are more prone to have aneurysms as well as to predict the patients more prone to rupture of aneurysm.

#### CONCLUSION

- \* SAH is a bleeding in subarachnoid space which is most commonly due to rupture of intracranial aneurysms
- \* Untreated patients have a very bad prognosis. However if treated early can lead to cure with a favourable outcome. Treatment is an emergency because early recognition and treatment can prevent a wide range of complications including rebleeding. Therefore, a high degree of suspicion is mandatory to diagnose these patients.
- \* Multidisciplinary teams in stroke centers including neurosurgeons as well as interventional neuroradiologists best perform treatment.
- \* Minimally invasive method such as endovascular coil embolization is feasible in many of these patients.

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## Role of Interventional Neuroradiology in Intracranial and Spinal Vascular Disorder

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**Abstract :** Interventional neuroradiology (also known as endovascular neurosurgery) is a branch in which minimally invasive diagnostic and therapeutic procedures of cerebrovascular disorders are performed under radiological guidance. The endovascular, minimally invasive approach ensures minimal injury to normal brain as compared to open surgery. With advancement in technology, there has been remarkable growth of this medical speciality and interventional neuroradiologist plays a crucial role in treatment of intracranial and spinal vascular disorders. Diseases like aneurysms, arteriovenous malformations, arterial stenosis and thrombotic vascular occlusion can be treated by endovascular approach.

### BRAIN ATTACK “STROKE”

Stroke is third leading cause of death and disability worldwide. The patients who survive this disorder are many times disabled with inability to lead independent life resulting in huge social costs. In India, the incidence of stroke is likely to increase in future because of increasing population, increasing life expectancy and changing lifestyles (urbanization, smoking, salt/alcohol intake, stress, physical activity). WHO estimates that in India the number of deaths from stroke are likely to significantly in coming years. Recently, there have been many advances in treatment of patients suffering from this disorder. Interventional Neuroradiology is one of the medical specialities which are playing more and more important role in treatment of stroke.

### INTERVENTIONAL NEURORADIOLOGY - INDUCTION

Interventional neuroradiology (also known as endovascular neurosurgery) is a branch in which minimally invasive diagnostic and therapeutic procedures of cerebrovascular disorders are performed under radiological guidance. In these procedures very thin catheters/wires etc. are placed usually through the femoral artery and are navigated within the vessels to the site of the abnormality, followed by diagnostic or therapeutic procedures. The endovascular, minimally invasive approach ensures minimal injury to normal brain, with less complications, better outcome and shorter hospital stay.

Growth of endovascular treatment of cerebrovascular disorders has been slower than as compared with interventions in cardiovascular diseases. Brain is a highly specialized organ as compared to heart and even a small area of cerebral injury can result in marked deficits. Another fact which differentiates stroke from heart attack is short window of time available for any intervention in cases of stroke and high chances of complications if case selection is not appropriate. However, recent advances in implements used for neurointervention such as in catheters, coils, stents, etc. as well as

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in knowledge and attitude regarding brain attack has resulted in rapid growth of the medical speciality of interventional neuroradiology. These procedures are usually performed by trained interventional neuroradiologists who work as a team with neurosurgeons and neurologists.

### HAEMORRHAGIC “BRAIN ATTACK”

Intracranial haemorrhage can occur due to hypertension, aneurysms, vascular malformations, tumors, coagulopathies, vasculitides, amyloid angiopathy etc. In every case determination of exact cause is necessary for treatment planning.

One should remember that excluding trauma, aneurysm rupture is most common cause of subarachnoid haemorrhage. Whenever an aneurysm or an arteriovenous malformation is suspected, digital subtraction angiogram (DSA) is mandatory to detection and planning of treatment. At present, CT and MR angiograms are not accurate enough to replace DSA. However, these modalities are used when DSA facilities are not available.

**Intracranial aneurysms (Fig.1) :** Intracranial aneurysms usually present due to subarachnoid haemorrhage (SAH). Aneurysms can also present due to mass effect, thrombo-embolism or may be discovered incidentally. High morbidity and mortality is seen in untreated patients with SAH, most commonly because of re-rupture of the aneurysm<sup>1</sup>.

Although traditionally the aneurysms have been treated by surgery, recent advances have made endovascular treatment of aneurysms feasible as well as safer than open surgery in many circumstances. In fact, a recent randomized, multicentre trial conducted in Europe and North America has shown that long-term clinical results were better with embolization than open surgery<sup>2</sup>.

Endovascular embolization is most commonly performed by placing a microcatheter by endovascular route into the aneurysm followed by occlusion of the aneurysm with platinum coils (Fig.1). Recent advances such as retrievable balloons and intracranial stents enable one to treat aneurysms which were previously regarded as untreatable by this method. Availability to perform 3-D angiograms enables very precise evaluation of these disorders leading to accurate treatment (Fig.1).

## CEREBRAL ARTERIOVENOUS MALFORMATIONS (AVMs) :

AVMs can present with haemorrhage, seizures, focal neurological deficit or can be discovered incidentally. AVMs are usually apparent on CT/MR, but if hematoma is present or the AVM is small it can be missed on these imaging techniques. DSA is the "Gold Standard" investigation to diagnose AVM as well as for treatment planning. Brain AVMs can be treated by endovascular embolization, surgery or by radiation therapy (Gamma Knife). Endovascular treatment is performed by embolization with glue (NBCA, n-butyl 2-cyanoacrylate) through microcatheters placed in the nidus. Disadvantage of surgery is high complication rate in large or deep seated malformations. However superficial small AVMs situated in non-eloquent areas can be treated by surgical method. Gamma knife is useful in small size AVMs but the treatment effect takes almost two years to take place. Combined treatment by using more than one of the methods is done in many cases.

## DURAL ARTERIOVENOUS MALFORMATIONS

Dural fistulas are abnormal arteriovenous connections within the dura mater and especially within the walls of the sinus. They are usually acquired in nature many cases occur following thrombotic incidents in the dural sinuses. One should be aware of the fact that dural AVMs with cortical venous drainage have a high propensity to cause cerebral haemorrhage and should be treated as an emergency. They can be treated by transarterial and transvenous endovascular methods.

## ISCHAEMIC STROKE "BRAIN ATTACK"

CT is usually the first investigation to exclude the haemorrhage. MRI is more sensitive to detect infarcts, particularly in early stages. Diffusion-weighted imaging is most sensitive in early detection of infarcts. Doppler of neck vessels is usually done to evaluate for any carotid stenosis as the cause of the ischaemia. MR angiography (MRA) or CT angiography (CTA) can also be done to detect extra/intra cranial stenosis. Cardiac evaluation is also done to evaluate for possible source of embolus. DSA is done if stenosis found in non-invasive investigation and to evaluate for causes other than atherosclerosis (such as vasculitis, dissection, aneurysms etc.)

**Carotid artery angioplasty/stenting<sup>3</sup> (Fig.2) :** Carotid artery stenosis is cause of ischaemic stroke in many patients. Significant stenosis of carotid artery predisposes to repeat stroke in spite of medical treatment such as anti-platelet therapy. Carotid artery stenting can be done with limited risks and is an alternative to surgical endarterectomy. Protection devices are also available which have probably reduced the risk of this procedure. Significant stenosis in other arteries leading to brain such as vertebral artery and even the intracranial arteries such as basilar and middle cerebral artery can be treated by angioplasty/stenting procedures.

**Arterial Thrombolysis<sup>4</sup> (Fig.3) :** Ischaemic brain attack/stroke can be treated by giving thrombolytic drugs which can open up the blockade so as to save as much of the brain as possible. These drugs can be given by intravenous route if a patient comes to the

hospital within three hours of onset of brain attack. Intra-arterial thrombolysis can be performed by placing a microcatheter in to the blocked vessel followed by injection of thrombolytic drugs (urokinase or t-PA). This selective (intra-arterial) treatment can be given at least upto 6 hours after the stroke in anterior circulation and upto 24 hours in selected cases of posterior circulation stroke. However, to make use of these treatment modalities, patient should reach a stroke centre/hospital within the prescribed timeframe. The earlier the treatment is done, better are the outcomes. New techniques such CT/MR angiography and perfusion imaging can help to select cases most likely to benefit from Thrombolysis and to extend the time frame available from thrombolysis.

**Venous thrombolysis<sup>5</sup> :** Venous infarcts due to occlusion of the dural sinuses and the cortical veins are also common in our country. Most of the cases can be treated by heparin. However selected group of patients who are in bad clinical condition or who don't respond to heparin can be treated by endovascular transcatheter thrombolysis of dural venous sinus. The time window from occlusion to recanalization is much wider than in arterial thrombosis and patients can be treated many weeks after the sinus thrombosis.

## RECENT ADVANCES

**Intracranial Stenting<sup>6,7</sup> (Fig.4) :** Intracranial stenting is done for different purposes such as for stent assisted embolization of intracranial aneurysms, to treat intracranial stenosis and some time even for dural sinuses occlusion/stenosis.

Although extracranial stenting such as for carotid artery bifurcation stenosis have been treated by stent placement, intracranial stenting has gained popularity only recently. This is because of technical difficulty in placing the stents through the tortuous anatomy as well as possibility of devastating complications as the intracranial arteries are different from extra cranial vessels such as coronary arteries. Dedicated intracranial stents have become available which facilitate this procedure to a great degree and one is likely to observe significant growth of these procedures in near future.

In fact, recent data shows that intracranial stenosis is responsible for stroke in a significant number of patients and these patients have high risk of stroke in spite of aggressive medical treatment. Intracranial angioplast/stenting is fast becoming an option of treatment in these cases. In the past, wide-neck intracranial aneurysms were difficult to treat by endovascular method. However, with availability of intracranial stents, stent-assisted coiling is possible in these cases.

## Endovascular(Cath/Dsa) Lab

Dedicated angiography laboratories are needed to perform these procedures which should have all the facilities including high quality imaging as well as neuroanaesthesia facilities. There have been advances in technology which makes intracranial endovascular procedures safe and effective.

\* **The 3-D technology** allows construction of images in 3-D format, which can be post-processed and evaluated on a separate dedicated workstation. This results in accurate assessment of diseases affecting blood vessels such as

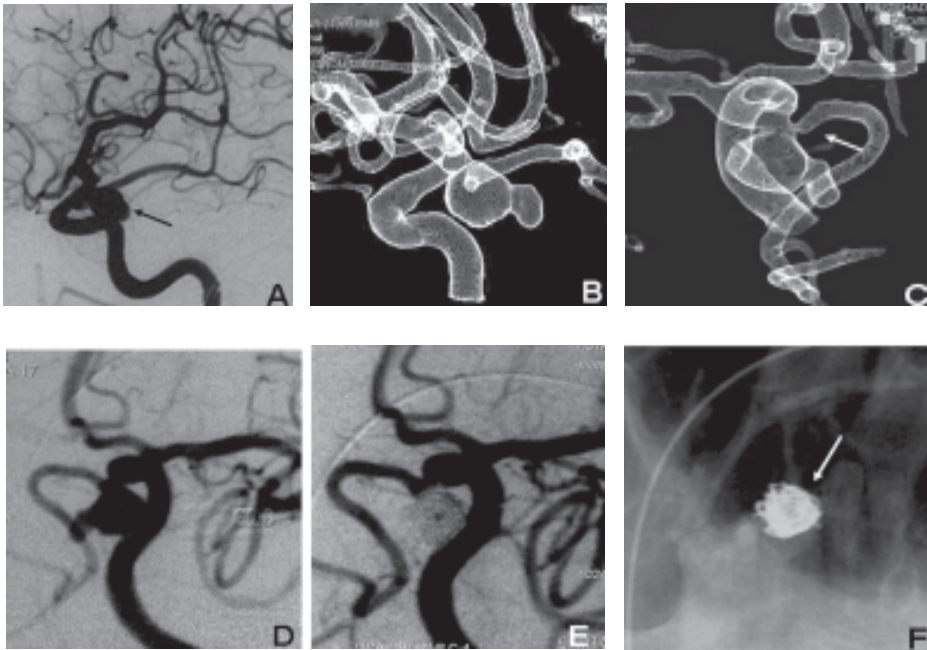


Fig.1 : A 65 year old female presented with subarachnoid haemorrhage due to an aneurysm on posterior communicating artery. The relationship of the aneurysm with the parent artery was not clear in routine DSA (Fig.A) 3-D angiogram was performed (Fig.B) which was then manipulated (rotated) to profile the aneurysm neck and the parent artery (Arrow, Fig.C). After obtaining this information, DSA was performed in the same angulation (Fig.D) followed by embolization with complete occlusion of the aneurysm (Fig.E). Fig. F shows the coil mass



Fig.2: Significant carotid stenosis (Fig.A) in a 60 year old patient with recurrent transient ischaemic attacks was treated by stent placement with complete recanalization (Fig.B)

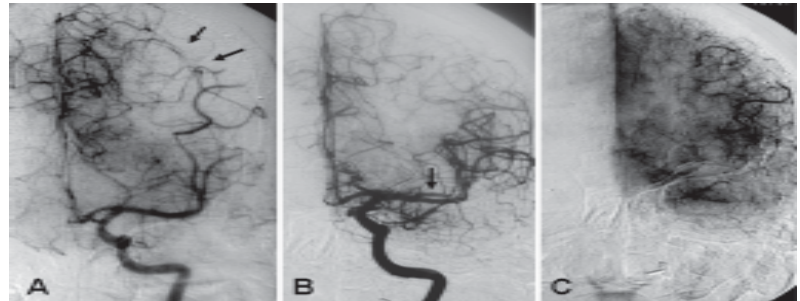


Fig.3 : A 62 year old patient presented with acute hemiparesis. Angiogram showed decreased filling of cortical branches of middle cerebral artery (MCA) with hypoperfusion in the left cerebral hemisphere (arrow, Fig.A). Thrombolysis was performed with microcatheter placed in MCA. Final angiogram revealed recanalization of upper division of MCA (Arrow fig.B) with reperfusion of cerebral parenchyma (Fig.C)



Fig.4 : A 60 year old female presented with syncopal attacks due to B/L intracranial ICA stenosis. The stenosis in right ICA (Arrow, Fig.A) was treated by stent-assisted angioplasty (Arrow, Fig.B) with complete resolution of the symptoms

aneurysms and stenosis, resulting in better treatment planning.

- \* **The flat panel DSA technology** helps in having high-resolution images with decreased radiation exposure. This is achieved by using a digital system rather than the older optical systems.

**Mechanical Recanalization Techniques in Acute Ischaemic Stroke**<sup>8</sup>: One of the problems associated with chemical thrombolysis has been the increased possibility of haemorrhage which increases the complication rate and limits the time period available for recanalization. One of the options is endovascular mechanical removal of clots which can avoid these problems. Result of the Mechanical Embolus Removal in Cerebral Ischemia (MERC1) 1 study, a phase 1 trial to evaluate the safety and efficacy of mechanical embolectomy in the cerebral vasculature have been reported which showed that cerebral embolectomy with the Merci Retriever was safe and that successful recanalization could benefit a significant number of patients, even when performed in an extended 8-hour time window. In future we are likely to use more and more mechanical devices in acute stroke patients.

**Stroke centre**<sup>9</sup>: Studies have shown that treatment of the stroke patients in dedicated centres result in significantly improved outcomes. Neurosurgical and neurology units should work as a team with the interventional neuroradiology (endovascular) group. Acute Stroke Unit and, if possible, stroke ICU also result in improved outcomes. Advanced neuroimaging facilities should be available with MRI and CT facilities. Care in stroke units decrease the number of deaths and increase the number of independent survivors. Treatment strategies must be developed in collaboration with other neurological sciences and experienced multidisciplinary teams must be responsible for the handling of patients with vascular CNS lesions.

## CONCLUSIONS

- \* Neurointerventional radiology plays a major role in management of intracranial vascular disorders.
- \* Improvements in imaging, hardware, expertise are occurring and likely to result in rapid growth of this speciality in coming years
- \* Endovascular intracranial procedures are potentially risky and therefore proper training, co-ordination with clinical branches and availability of specialized equipment is essential for good outcomes.
- \* Dedicated stroke centres with neurologist, neurosurgeons, interventional neuroradiologists and diagnostic radiologists working as a team result in better outcomes.

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## Imaging in Acute Ischemic Stroke

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**Abstract :** With recent advances in imaging and efficacious treatment of cerebral ischemia, the role of imaging and neuroradiologist has become central from peripheral. CT scan can be done as an initial imaging of clinically suspected patient of stroke mainly to rule out hemorrhage and stroke mimickers like mass lesion. CT angioplasty and perfusion imaging can be performed to look for major vessel occlusion and tissue at risk. MR imaging is better imaging modality to diagnose acute ischemic stroke with use of diffusion weighted imaging. Perfusion and diffusion mismatch are very much suggestive of salvageable brain parenchyma. MRA and MRS can be further supportive in strengthening the diagnosis of ischemic stroke. DSA and intravenous and intraarterial thrombolysis are established ways of treatment of acute ischemic stroke patients when performed within 6 hours of onset of symptoms (window period).

### INTRODUCTION

Stroke is an injury to the central nervous system that is characteristically abrupt in onset and due to a vascular insult. The term is reflective of damage to the brain secondary to ischemia or hemorrhage. It is the number three cause of mortality and the number one cause of disability in adults in the United States. Strokes are ischemic approximately 80% of the time, and until recently, there was no available beneficial intervention<sup>1</sup>. In 1995, the published results of the National Institute for Neurological Diseases and Stroke (NINDS) recombinant tissue plasminogen activator (rt-PA) trial represented the first demonstration of efficacious treatment for acute cerebral ischemia<sup>2</sup>. This has redefined the role of the radiologist and neuroimaging from peripheral to central in the management of acute cerebral ischemia.

### COMPUTED TOMOGRAPHY

Computed tomography (CT) is an established basic and most important tool for the diagnosis of ischemic or hemorrhagic stroke. CT imaging protocol for ischemic stroke includes - Non Enhanced Scan, CT perfusion and CT angiography on multislice scanner.

**Nonenhanced CT** can help exclude hemorrhage and detect "early signs" of infarction but cannot reliably demonstrate irreversibly damaged brain tissue in the hyperacute stage of ischemic stroke.

**Dynamic contrast enhanced CT scan or Perfusion CT** provides information about brain perfusion, which permits differentiation of irreversibly damaged brain tissue from reversibly impaired "tissue at risk".

**CT angiography** can help detect stenosis or occlusion of extra and intracranial arteries. Use of these three imaging techniques - nonenhanced CT, perfusion CT and CT angiography - assist in rapidly obtaining comprehensive information regarding the extent of ischemic damage in acute stroke patients.

### NONENHANCED COMPUTED TOMOGRAPHY (CT)

Used until the late 1980s primarily to exclude hemorrhage in patients with acute stroke. Requirements for diagnostic imaging in patients with ischemic stroke changed as a result of the 1995 study by the

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National Institute of Neurological Disorders and Stroke (NINDS)<sup>2</sup>. With the interruption of blood flow, the energy needs are no longer met, resulting in cytotoxic edema, which is defined as cellular injury with influx of fluid in the intracellular space without an increase in vascular permeability<sup>3</sup>.

Neurons, located in gray matter are the most sensitive cell to ischemia. Initially these are more dense than the white matter, later becomes increasingly less dense with an increase in water content.

The CT signs of acute cerebral infarction (Fig.1) :



Fig.1 : CT scan brain showing a well defined hypodense wedge shape area of infarct involving head of left caudate nucleus

- blurring of the clarity of the internal capsule,
- loss of distinctness of the insular ribbon cortex,
- loss of differentiation between the cortical gray matter and the subjacent white matter<sup>4,5</sup> and
- Due to the accumulation of intracellular fluid causing swelling of the Gray matter. This results in effacement of the spaces demarcated by the gyral infoldings (sulci) known as "sulcal effacement"<sup>6</sup>.

The “*hyperdense MCA sign*” is secondary to an embolus lodged in the MCA. This results in increased attenuation in the first segment of the MCA<sup>7</sup>. Angiographic correlation has demonstrated a corresponding thrombus. This sign is associated with worse patient outcomes. A similar “hyperdense” vessel sign has been described for the basilar artery. Whereas prominence of the parenchymal changes associated with vascular occlusion are a contraindication to thrombolysis, the “hyperdense MCA sign” signifies a vascular occlusion and a need for intervention when detected within the treatment window. However false positive hyperdense MCA sign can be seen in polycythemic, vessel calcification, post contrast scans and dehydrated patients and false negative in anemic patients. Administration of contrast material may be helpful in delineating infarcts in the subacute period when there may be obscuration of the infarct by “*fogging*”<sup>8</sup>. Fogging is described as the phenomenon of an area of previously hypoattenuating infarction evolving to a state of isoattenuation between days 14 and 21 after infarction; this occurrence was believed to be secondary to small potechial hemorrhages or infiltration of the infarcted tissue with macrophages<sup>9</sup>. Although difficult to see on a nonenhanced study, the area of infarction intensely enhances at the periphery.

In summary, nonenhanced head CT has a clearly defined role in the current management of acute stroke. A CT scan for the exclusion of hemorrhage. CT is appealing as an imaging study in that it is widely available, can be performed quickly and safely on critically ill patients, and is relatively inexpensive. Further, its utility has been proved in large-scale clinical trials.

**Limitation of NCCT in stroke :** (1) Up to 60% of CT scans are normal in the first few hours after ischemic insult. (2) Another 10%-20% had arterial dissections, occlusions sites not readily susceptible to thrombolysis, or minor branch occlusions that without intervention have a favorable natural outcome<sup>10</sup>. The lack of sensitivity and specificity in the diagnosis of stroke limits the attainable benefit.

## CT PERFUSION

Viability of the cerebral parenchyma is dependent on cerebral blood flow (CBF). The assessment of cerebral perfusion in patients with acute stroke, in a clinically relevant time frame, is of utmost importance for patient selection before thrombolytic therapy. Quantitative mapping of CBF to indicate the severity and potential reversibility of neuronal damage can be used to predict which brain tissue will be salvaged with reperfusion or die without it (pneumbra), as well as which brain tissue is already infarcted. Perfusion CT offers a number of practical advantages like it can be performed immediately after unenhanced CT and used in general to exclude cerebral haemorrhage. It is fast (typical procedure time < 5 min) and does not require specialized computer hardware<sup>11</sup>.

**Limitations of CT perfusion :** (1) Limited sample volume. Whole brain cannot be studied even with newer 64 slice CT scan. (2) Patient motion causes false registration of perfusion values and hence incorrect results. (3) Beam hardening due to any reason causes interpretation of perfusion study fallacious<sup>12</sup>.

## CT ANGIOGRAPHY

Computed tomographic (CT) angiography is a new method for evaluating vascular anatomy. Making use of slip-ring technology

and multi slice CT scan, visualization of vascular anatomy after intravenously administered iodinated contrast medium has been recently shown to be reliable alternative to MR angiography in the detection of arterial anatomy in the circle of Willis. It has shown promise in the evaluation of carotid bifurcation disease as well as for intracranial aneurysms and vascular malformations<sup>13</sup>.

## MRI

The diagnosis of intracerebral hemorrhage (ICH) is still a domain of CT rather than MRI, especially in acute stroke. The key substrate for MRI visualization of hemorrhage is deoxyhemoglobin, which causes a signal loss in T2-weighted imaging (T2-W1) because of paramagnetic susceptibility effects, although usually not within the first 12 to 24 hours. MRI has proved superior to CT scan in diagnosis of ischemic stroke with recent introduction of new multimodal MRI (mMRI) techniques such as diffusion and perfusion-weighted imaging (DWI and PWI) has improved diagnostic imaging in hyperacute ischemic stroke<sup>14</sup>. **Diffusion weighted MRI (DWI)** can render ischemic fields visible within minutes of ischemia onset and extent of ischemia.

**Magnetic resonance angiography (MRA)** allows rapid characterization of the cervical and cephalic large vessels. MRA detects and grades cervical internal carotid stenosis with an accuracy of 85% to 96% compared with digital subtraction angiography. With the use of MRS, stenosis and occlusions of intracranial vessels are identified with 80% to 100% sensitivity and specificity compared with catheter angiography<sup>15</sup>.

Together, DWI and cervical and cephalic MRA have the potential to identify the site of brain ischemia and the site of large vessel disease within the first hours after stroke onset and hospital admission, providing detailed pathophysiological information.

## CONVENTIONAL MR IMAGING

**Acute infarcts** are better and more visible on MR images than on CT scans, with over 80% of MR images positive in the 1st day compared to 60% of CT scans. MR imaging is particularly superior in the detection of stroke in the posterior fossa where CT is limited due to beam-hardening artifact from the adjacent skull base. **Lacunar infarcts** and **small cortical strokes** are also seen with higher conspicuity<sup>16</sup>.

The earliest MR changes are loss of normal intravascular flow voids, morphologic swelling of the gray matter and increased signal intensity on the T2 weighted and intermedate-weighted images. There is normally a loss of intraarterial signal with standard spin-echo (SE) sequences, referred to as a “*flow void*” in low-or-no flow states, there is a loss of the “flow void” such that signal intensity is demonstrated in the involved vessel. Similar to the “hyperdense MCA sign” in CT, absence of flow in involved vessels can be seen immediately after occlusion. The earliest signal intensity changes usually involve the gray matter, with the white matter typically appearing normal in the first 24 hours. Intermediate-weighted images enable differentiation of lacunar infarcts from perivascular spaces; the former hyperintense and the latter isointense to CSF<sup>1</sup>.

Intravenous contrast material can provide additional information. Vascular enhancement can be seen in cortical infarcts up to 75%

of the time. This is believed to be due to slow flow in the region of the infarction. Meningeal enhancement can also be seen acutely in approximately 33% of patients, possibly due to meningeal inflammation. Both types of enhancement resolve toward the end of the 1st week. Administration of contrast material is now typically reserved for those instances in which MR perfusion imaging is performed<sup>17</sup>. A fast SE sequence enables the acquisition of T2-weighted images in a fraction of the time (roughly four to 16 times faster). Modified fast FLAIR and fast SE FLAIR can reduce imaging time to 2-5 minutes. Acute infarct appears as hyperintense on T2 weighted and intermediate (FLAIR or PD) images and iso to hypointense on T1 weighted images (Fig.2).

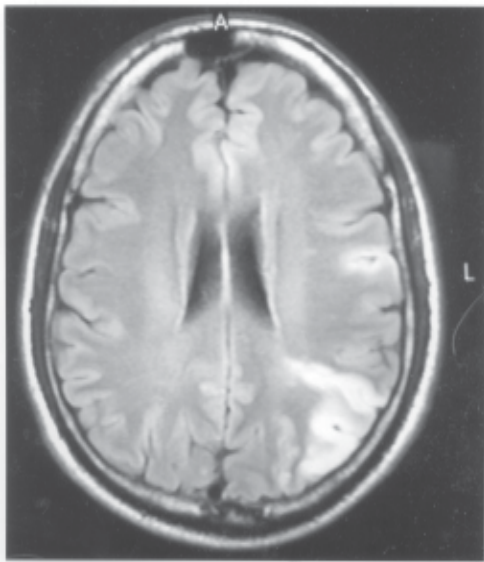


Fig.2 : MRI brain T2 FLAIR image showing areas of hyperintensity involving left parietal and few areas of frontal cortical and sub cortical white matter suggesting acute ischemic infarct

### MR DIFFUSION IMAGING

Cytotoxic oedema which is due to accumulation of intracellular water minutes after onset of acute cerebral ischemia, causes restriction (decrease in) of microscopic diffusion of protons. In diffusion weighted MRI, this is reflected as decrease of the apparent diffusion coefficient (ADC). It appears hyperintense on diffusion weighted images (DWI) (Fig.3).

The apparent diffusion coefficient (ADC) decreased by approximately 30-50% within 30 minutes after onset of focal ischemia. This change occurs while other MR image types such as T2 or intermediate weighted images remain normal. It is generally believed that the most likely cause of the decrease in ADC values is the redistribution of water from the interstitial to the (diffusion-restricted) intracellular space, as the energy-dependent  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase pumps fail (i.e. the initiation of cytotoxic edema<sup>1</sup>).

### MR PERFUSION IMAGING

Perfusion imaging can detect hypoperfused regions of brain either by monitoring the transit of a rapidly injected contrast agent<sup>6</sup> or

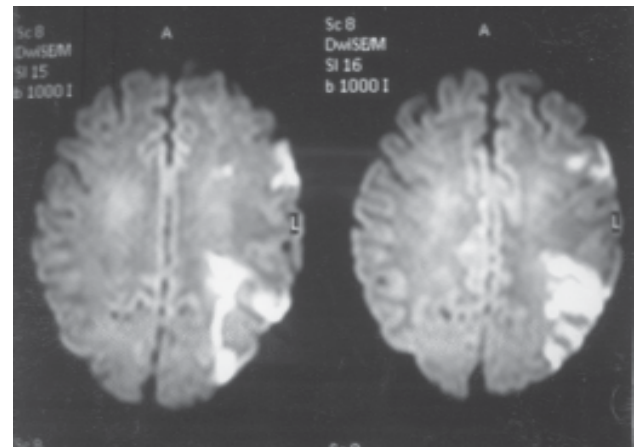


Fig.3 : Diffusion weighted image of same patient in Fig.2 showing hyperintensity on B1001 suggesting restricted diffusion in areas of acute ischemic infarct

magnetically tagged water molecules in arterial blood through the brain<sup>7</sup>. In region distal to arterial occlusion the arrival of contrast may be delayed and less in amount. The resulting signal - time curve can be converted into concentration - time curve, from which several functions like CBV, rCBF, TTP, MTT that describe regional perfusion can be determined and compared from normal side. A variety of perfusion abnormality has been described like reduced rCBF in the region of ischemia.

Varying pattern of "mismatch" between lesion extent on DWI and PI can occur.

- \* PI lesion > DWI lesion - larger area of brain is under threat of ischemia than shown by DWI alone.
- \* PI lesion = DWI lesion - the brain parenchyma at risk is minimum and final infarct may be of the size shown by either of image.
- \* PI lesion < DWI lesion - suggest that reperfusion has occurred in the infarcted tissue.
- \* Only PI abnormality - acute arterial occlusion but no infarct (keir - 84)

### MR ANGIOGRAPHY

MR angiography enables the noninvasive evaluation of vascular patency. Images can be generated on which flow within the vessel is increased in signal intensity (bright blood) or on which the lumen is depicted as decreased in signal intensity (black blood); the former is the more commonly used technique. Time of flight is the most frequently used bright-blood MR angiographic technique. For evaluation the intracranial circulation, a volumetric (three-dimensional) acquisition is optimal.

An image similar to a conventional arteriogram can be reconstructed from the intravascular signals that is sensitive to large vessel occlusion or narrowing in the internal carotid, vertebral, basilar and first and second segments of the anterior, middle and posterior cerebral arteries. Although the value of MR angiography has yet to be shown in a large-scale clinical trial, the need for differentiating

which patients have lesions amenable to thrombolysis seems clear given the potential risks of treatment.

### MR SPECTROSCOPY

In the evaluation of patients with cerebral ischemia the relevant metabolites are lactate at 1.33 parts per million (ppm) and N-acetylaspartate (NAA) at 2.02 ppm. Lactate is not present in sufficiently high concentrations to measure in the brain under normal conditions. NAA is normally present and is found only in neurons or axons in mature brain<sup>1</sup>.

MR spectroscopy depicts acute cerebral ischemia on the basis of increased levels of lactate. NAA decreases after the onset of either global or focal ischemia. NAA is either dramatically reduced or completely absent. It is postulated that in acute stroke, tissue that has high lactate, no conventional MR imaging abnormalities and normal or only slightly reduced NAA levels in the first few hours after stroke onset may represent ischemic tissue at risk of infarction. This issue could represent the "penumbra". It has been hypothesized that identification of such regions may, in the future, may be one of the criteria for initiating thrombolytic therapy<sup>1</sup>.

**Limitations of MRS :** (1) Proton MR spectroscopic imaging is not able to detect lacunar or small infarcts (<1 cm<sup>3</sup>). The higher spatial resolution of diffusion and perfusion MR imaging is definitely an advantage in this regard. (2) The implementation of MR spectroscopic imaging is hampered by the limited coverage and lengthy imaging times.

### DSA AND THROMBOLYSIS

DSA (Digital Subtraction Angiography) is the gold standard for delineation of arterial architecture and site of occlusion of artery. With improvement in technique it is now safer and effective in treating the selected patients with stroke with intra arterial thrombolysis in window period of 6 hours. Prompt reestablishment of flow with lysis of an occlusive thrombus is the goal of thrombolysis. It can be done either by intra venous route or direct intra arterial injection of thrombolytic agent. This is in contrast to anticoagulation, in which new clot formation is minimized. These agents convert the proenzyme plasminogen to the active enzyme in thrombin lysis, plasmin. Thrombolysis can be performed by using streptokinase, urokinase or rt-PA, rt-PA is the most specific of the three agents. It is fibrin specific, activating only thrombin-bound plasminogen. For this reason, it has the most favourable therapeutic index of the three thrombolytic agents.

Thrombolysis was introduced for the treatment of ischemic lesions of the middle cerebral artery (MCA) territory. Thrombolytic agents were used to treat acute ischemia within 3-6 hours after the acute event. This risk increased as the time interval between the onset of symptoms and thrombolytic therapy increased. Thus, patients are more likely to have a good outcome when treated within 3 hours than between 3 and 6 hours after the acute event. Therefore, the primary purpose of diagnostic imaging is to ensure selection of the appropriate patients for thrombolytic therapy to reduce severe complications<sup>1</sup>.

For this purpose, diagnostic imaging of acute stroke should reliably help (a) exclude intracranial hemorrhage; (b) differentiate between irreversible affected brain tissue ("dead brain") and reversibly impaired tissue ("tissue at risk"), which might benefit from early

treatment and (c) identify stenosis or occlusion of major extra and intracranial arteries.

Tissue at risk, or "penumbra," is defined as an area of markedly reduced perfusion with loss of function of still viable neurons<sup>1</sup>. Timely reperfusion of this tissue may prevent cell death and help reestablish normal function. Because thrombolysis of large areas of irreversibly affected brain tissue carries a high risk of hemorrhage, patients with infarction that affects more than one-third of the MCA territory should not undergo thrombolysis.

*The NINDS (National Institute for Neurological Diseases and Stroke) trial* was the first trial to demonstrate efficacy in the use of the thrombolytics for the treatment of cerebral ischemia<sup>2</sup>. The protocol was based on a 3-hour treatment window from the time of iclus to the administration of rt-PA. A CT scan was obtained and the detection of intracerebral thrombosis was an exclusion criterion. Although no short-term benefits were demonstrated, patients in the treatment group achieved improved stroke scale ratings as compared with those in the placebo group at 3 months. *The ECASS (European Cooperative Acute Stroke Study) is another trial* which allowed a longer treatment window of 6 hours<sup>18</sup>. This time-window prolongation increased the likelihood of manifest infarction at the time of reestablishing flow and thus the risk of reperfusion hemorrhage. In an attempt to avoid reperfusion hemorrhage, a CT scan was obtained to exclude patients with extensive infarction. Patients were excluded if on site interpretation detected infarction in greater than 33% of the middle cerebral artery (MCA) distribution. Unfortunately, the ECASS group failed to demonstrate efficacy in the intention to treat group.

Recent advances in techniques of intracranial vascular catheterisation have made it possible to deliver thrombolytic agents intraarterially directly proximal to the thrombus with much less systemic side effects<sup>19</sup>.

**Limitations of DSA and Thrombolytic Therapy :** The major disadvantage of intraarterial thrombolytic therapy is that it can only be undertaken in centers where neurointerventional specialists and infrastructure required for this intervention are available. Furthermore, the administration of a potentially toxic drug by a highly specialized technique to an acutely ill and vulnerable patient within a short time frame demand an expert decision making process after a thorough consideration of the risks and benefits. Because of these reasons, it is unlikely that selective intraarterial thrombolytic therapy will ever produce a significant impact in the treatment of acute ischaemic stroke in a developing country<sup>19</sup>.

**In summary,** acute ischemic stroke is prominent cause of death and morbidity. It needs to be identified by the clinician and the radiologist at the earliest, so as to start appropriate treatment immediately. The main role of CT scan is to rule out hemorrhagic stroke, however can be clubbed with CTA and CT perfusion study for better characterization of the site and extent of lesion. MR imaging proves to be a better modality as can detect changes as early as 3 hours with advent of newer imaging techniques like diffusion and perfusion imaging and supportive role of MRA and MRS. With appropriate patient selection, intra venous thrombolysis can be done within 3 hours of onset of symptoms and with help of DSA, intra-arterial thrombolytic agents can be used in window period of 6 hours in anterior circulation. Experience and expertise is required to carry out such procedure.

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## Future Special Issues/ Symposia

## Special Issues :

- Cosmetic Surgery: New Horizons
- Interventional Radiology: Current Trends
- Challenges of Diabetes in the Developing World
- Organ Transplantation: Current Scenario
- Advances in Neuro Surgery

## Symposia :

- Endovascular Surgery: Current Perspective
- Sexually Transmitted Diseases Current Scenario
- Prevention of Chronic Kidney Disease
- Metabolic Bone Disease : An update
- Advances in surgical Oncology
- Advances in Endourology

## DRUG PROFILE

## CILOSTAZOL

Cilostazol is quinolin derivative; - its metabolites are cyclic AMP (cAMP) phosphodiesterase 111 inhibitors (PDE III inhibitors). Inhibition of phosphodiesterase activity suppresses cAMP degradation with a resultant increase in cAMP in platelets and blood vessels leading to inhibition of platelet aggregation and vasodilatation, respectively. It reversibly inhibits platelet aggregation induced by a variety of stimuli, including thrombin, ADP, collagen, arachidonic acid, epinephrine and stress. It produces non-homogenous dilatation of vascular beds with greater dilatation in femoral beds than in vertebral, carotid or superior mesenteric arteries.

**Pharmacokinetics :** It is absorbed after oral administration; it is 95-98% protein bound, and extensively metabolized by hepatic cytochrome P-450 enzymes. The primary route of elimination of cilostazol is via the urine (74%) with the remainder excreted in the feces (20%). The total pharmacologic

activity of drug and its metabolites is similar with mild renal and hepatic impairment and also in normal subjects.

**Indications :** Cilostazol is indicated for the *reduction of symptoms of intermittent claudication*; improves pain free and maximal walking distance, has favourable effects on lipids.

**Dosage and administration :** Recommended dosage of drug is 100 mg BD, to be taken half an hour before meals or two hours after food.

**Contra-indication :** a) Contraindications are hypersensitivity to the drug; b) congestive heart failure of any severity; c) pregnancy and d) nursing mothers and children.

**Adverse reactions :** Commonly observed side effects include headache, diarrhoea, dizziness and palpitations, overdosage may cause headache, diarrhoea, hypotension, tachycardia, arrhythmia, not removed by dialysis.

**Cardiovascular effects :** Increased heart rate, ventricular premature complexes, non sustained VT is reported.

Compiled by Dr. .P.Chattree

## Management of Acute Ischemic Stroke

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**Abstract:** Treatment of stroke has undergone rapid evolution in last decade with establishment of thrombolysis in acute stroke. In coming years, there is likely to be further change in protocols in treatment of stroke, particularly with the emerging evidence that the ischemic penumbra may persist for up to 48-hrs after stroke onset. For optimum outcome it is essential that stroke teams are formed in hospitals and strict protocols are followed for stroke recognition, investigation and treatment. There is strong evidence that outcomes after stroke can be improved and that death or disability from stroke can be reduced with appropriate treatment.

The range of treatments available for acute ischemic stroke has expanded considerably in recent years. In general the timing of various therapeutic interventions is limited to the evolution of the ischemic process. There is a great deal of emerging evidence that may suggest that the duration of the ischemic penumbra varies considerably from patient to patient. This may depend upon factors such as the underlying mechanism of ischemia and the rate of recanalization. There is evidence that the ischemic penumbra may persist for upto 48 hrs after stroke onset, but in some cases, it may be as short as 3 hours or less. The concept of "time is brain" is generally a good one, regardless of the intervention planned.

### EMERGENCY ROOM

**I. Recognition :** Prompt and accurate diagnosis of stroke in the emergency is of paramount importance. The questions that need to be answered immediately are :1.Is it a stroke?; 2. Where is the lesion?; 3.What is the likely underlying pathogenic mechanism? It has been demonstrated by a number of authors that the sensitivity, specificity and accuracy for early stroke diagnosis using clinical criteria only are low. This can be improved considerably with the assistance of neuroimaging, particularly CT to identify cerebral hemorrhage and MRI using diffusion – weighted imaging (DWI) to identify the site of infarction. Stroke patients usually present with a history of sudden or rapid onset of focal neurological impairments common patterns of focal neurological impairments amongst patients with acute ischemic stroke are given in Table –1.

**Table - 1 Common patterns of neurological impairments among patients with AIS**

#### Left (dominant) hemisphere – major or branch cortical infarction :

- Aphasia, · Right Hemiparesis, · Right – sided sensory loss,
- Right – sided spatial neglect, · Right homonymous hemianopia ,
- Impaired right conjugate gaze,

#### Right (nondominant) hemisphere – major or branch cortical infarction :

- Left hemiparesis, · Left – sided sensory loss, ·Left – sided spatial neglect,
- Left homonymous hemianopia, · Impaired left conjugate gaze,

#### Deep (subcortical) hemisphere or brain stem

- Hemiparesis (pure motor stroke) or sensory loss (pure sensory stroke), · Dysarthria, including dysarthria – clumsy hand , · Ataxic – hemiparesis, · No abnormalities of cognition, language or vision,

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#### Brain stem

- Motor or sensory loss in all 4 limbs, · Crossed signs (signs on same side of face and other side of body) ·Dysconjugate gaze, · Nystagmus, · Ataxia
- Dysarthria, · Dysphasia,

**Cerebellum** · Ipsilateral limb ataxia, ·Gait ataxia,

**Investigations :** The recommended set of investigations is listed in Table – 2.

Table - 2 **Investigations for acute ischemic stroke**

#### Minimum set

- Computed tomography (non contrast); · Electrocardiography;
- Full blood examination; · Electrolytes; · Coagulation profile;
- Blood glucose; · Chest x – ray;

#### Patient – specific tests

- Magnetic resonance imaging/ angiography; · Extracranial Doppler ultrasound; · Transcranial Doppler ultrasound;
- Transthoracic or transesophageal echocardiography; · Lipids;
- Cardiac enzymes; · Blood gases; · Screen for arteritis;
- Genetic tests; · Electroencephalography;

These investigations should be performed as quickly as possible in the emergency department so that baseline, information about the patient can be obtained. A noncontrast CT needs to be performed as soon as possible to exclude cerebral hemorrhage. In many centers, MRI will be performed on all pts, although CT remains the imaging "work – horse" of stroke investigation. Further imaging using ultrasound of extracranial carotid arteries when artery to artery embolism is suspected as a mechanism and Transcranial Doppler ultrasound may be useful as a screen in the posterior circulation for large vessel disease or to confirm the hemodynamic status of the carotid system by demonstrating the presence or absence of cross – flow from one hemisphere to the other. Using MRA or CTA if available, occlusion of the main vessels can be reliably detected within a few minutes. Similarly, if embolism is a suspected mechanism, and carotid arteries are essentially normal transesophageal echocardiography may be indicated to determine the presence or absence of aortic arch atheroma as a potential embolic source. Cardiac enzymes and blood gases may provide useful information if a cardiac source of embolism is suspected or respiratory compromise is observed. An EEG may be indicated if the nature of the event, particularly in the presence of a pre existing ischemic stroke, is unclear.

**Specific Treatments :** The current status of specific treatments for acute ischemic stroke is given in Table - 3.

**Table - 3 Specific treatment of acute ischemic stroke**

*Yes<sup>a</sup>*

1. Tissue plasminogen activator within 3h; 2. Aspirin within 48h;
3. Management in stroke care unit;

*May be*

1. Neuroprotectants ;

*No?*

1. Heparin, heparanoids; 2. Hemodilution ; 3. Steroids ;

<sup>a</sup> Level 1 evidence of efficacy in improving outcomes

There is Level evidence for use of tissue plasminogen activator (rtPA) if it is given within 3 hours of onset of acute ischemic stroke in carefully selected patients; administration of oral aspirin within 48 hours of ischemic stroke onset and management with in a stroke unit. Neuro protectants are still being evaluated, although a large number of trials have reported negative results. Approaches that have been subjected to clinical trials in an adequate manner without any evidence of efficacy include the use of heparin or heparinoids; hemodilution and steroids.

## **HYPER ACUTE THROMBOLYSIS WITH RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR**

Because rtPA must be administered within 3 hours of stroke onset, based on current evidence, this usually is done more often in the emergency department. The evidence for efficacy is strong and fulfills the level I criteria. The hyperacute thrombolysis regimen must follow the NINDS – rtPA protocol, given in Table – 4 & 5.

**Table - 4 Characteristics of patients with ischemic stroke who could be treated with RT-PA**

- Diagnosis of Ischemic stroke causing neurological deficit
- The neurological signs should not be clearing spontaneously
- The neurological signs should not be minor and isolated
- Caution should be exercised in treating major deficits
- The symptoms of stroke should not be suggestive of subarachnoid hemorrhage
- Onset of symptoms < 3 hours before beginning treatment
- No head trauma or prior stroke in previous 3 months
- No myocardial infarction in the previous 3 months
- No GI. or urinary tract hemorrhage in previous 21 days
- No major surgery in the previous 14 days
- No arterial puncture at a noncompressible site in previous 7 days
- No history of previous intracranial hemorrhage
- Blood pressure not elevated (systolic < 185 mmHg and diastolic < 110mmHg)
- No active bleeding or acute trauma (fracture) on examination
- No anti coagulant if INR is > 1.5
- If receiving heparin in previous 48 hours, aPTT must be in normal range Platelet Count <sup>3</sup> 100 000 mm<sup>3</sup>
- Blood glucose concentration <sup>3</sup> 50 mg/ dL (2.7 mmol/L)
- No seizure with postictal residual neurological impairments
- CT does not show a multilobar infarction (hypodensity > 1/3 cerebral hemisphere)
- The patient or family understand the potential risks and benefits from treatment

**Table - 5 The Regimen for treatment of acute ischemic stroke with IVRTPA is given below**

1. Infuse 0.9 mg/ kg (maximum of 90 mg) over 60 minutes with 10% of the dose given as a bolus dose over 1 minute).
2. Admit to an intensive care unit or stroke unit for monitoring.
3. Perform neurological assessments every 15 minutes during the infusion of rt PA and every 30 minutes for the next 6 hours and then every hour until 24 hours from treatment.
4. If the patient develops severe headache, acute hypertension, nausea or vomitings, discontinue the infusion (if agent is still being administered) and obtain a CT scan of brain on an emergent basis.
5. Measure blood pressure every 15 minutes for the first 2 hours, every 30 mins for the next 6 hrs & then every hour until 24 hour from treatment.
6. Increase the frequency of blood pressure measurements if a systolic blood pressure <sup>3</sup> 180 mmHg or diastolic pressure of <sup>3</sup> 105 mm Hg is recorded. Administer antihypertensive medications to maintain blood pressure at or below these levels.
7. If diastolic BP 105 – 120 mmHg or systolic BP is 180 – 230 mmHg. Intravenously administer 10mg labetalol over 1–2 minutes. May repeat or double the dosage of labetalol every 10 to 20 minutes to a maximum dose of 300 mg. As an alternative, can start with the initial bolus dose of labetalol and then follow with a continuous labetalol infusion given at a rate of 2 – 8 mg/min.
8. If diastolic BP 121-140 mm Hg or systolic blood pressure > 230mm Hg. Intravenously administer 10 mg labetalol over 1-2 minutes. May repeat or double labetalol every 10 minutes to a maximum dose of 300 mg. As an alternative, can start with the initial bolus dose of labetalol and then follow with a continuous labetalol infusion given at a rate of 2 – 8 mg/ min. if the blood pressure is not controlled, consider starting infusion of sodium nitroprusside.
9. If diastolic blood pressure > 140 mmHg, start infusion of sodium nitroprusside at a rate of 0.5 mg/kg/min.
10. Delay placement of Nasogastric tubes, indwelling bladder catheters, or intra – arterial pressure catheters.

Intravenous rtPA (0.9 mg/kg, maximum dose of 90 mg) is strongly recommended for carefully selected patients who can be treated within 3 hours of onset of ischemic stroke and carries a Grade A recommendation. Intravenous administration of rtPA is currently the only FDA – approved therapy for treatment of patients with acute ischemic stroke. Earlier treatment (i.e; within 90 minutes) may be more likely to result in a favorable outcome. Treatment with rtPA is associated with symptomatic intracranial hemorrhage, which can be fatal (Level I). Management of intracranial hemorrhage following treatment with rtPA is problematic. The best methods for preventing bleeding complications are careful selection of patients and scrupulous ancillary care. Close observation and monitoring of the patient and early management of arterial hypertension are critical. The use of anticoagulants and antiplatelet agents should be delayed for 24 hours after treatment. The decision for treatment with rtPA is based on several features. The physician should review each of the criteria to determine the patient's eligibility. The safety and efficacy of rtPA for treatment

of pediatric patients are not established. Patients with major stroke (NIHSS score > 22) have a very poor prognosis whether or not they are treated with rtPA. Because of this, and because of the risk of hemorrhage is considerable among this population, caution should be exercised. However, they may still benefit from treatment. A patient with a seizure at the time of onset of stroke might be eligible for treatment as long as the clinician is convinced that the residual impairments are due to stroke and not the seizure. To date no other thrombolytic agent has been established as a safe and effective alternative to rtPA. Currently available data do not support the clinical use of either streptokinase or ancroed (Grade A).

### Aspirin

There is equally strong evidence that the administration of aspirin within 48 hours of onset of acute ischemic stroke improves outcome. Again, the general principle that "time is brain" should be adhered to and aspirin administered in the emergency department rather than waiting until the patient is transferred to the stroke unit. Overall, the benefit is somewhat small; for every 1000 patients treated only about 9 or 10 are saved from death or disability. Where as, for every 7 or 8 patients treated with i.v rtPA, one is saved from death or major disability. However, because, it is widely available, and is associated with modest risk (an increase of two intracranial hemorrhages per 1000 patients treated), the approach is worthwhile and now is a part of standard stroke management practice.

### MANAGEMENT IN A STROKE UNIT

Stroke units vary in type ranging from high – dependency/ intensive care models that are common in Germany and the USA to a lower – impact ward – based model. Evidence from accumulated trails suggest that the overall risk reduction in mortality is about 20% compared to management on a general medical ward. There is some evidence that a geographically discrete unit within one ward is associated with better outcomes than either management at home or by a mobile stroke service team visiting general wards. The reasons for this improved outcome are not clear but probably are related to better and more aggressive management of general medical complication.

Better management of blood pressure and earlier mobilization may be important. Because establishing a stroke unit in many instances involves merely reorganizing existing resources, more countries should be encouraged to increase the availability of these facilities.

### GENERAL TREATMENT RECOMMENDATIONS

There is general agreement to strongly recommend airway support and ventilatory assistance in the treatment of patients with acute stroke who have depressed levels of consciousness or airway compromise.

Supplemental oxygen to hypoxic patients is also recommended. Non hypoxic patients with acute ischemic stroke do not need supplemental oxygen therapy. There are insufficient data about the utility of hyperbaric oxygen to recommend this therapy for most patients with stroke. Treatment of sources of fever and the use of antipyretics to control elevated temperatures in the setting of acute stroke are recommended. Induced hypothermia in acute

ischemic stroke is being investigated. Cardiac monitoring during the initial evaluation of patients with acute ischemic stroke is also recommended to detect atrial fibrillation and potentially life – threatening cardiac arrhythmias.

A cautious approach is recommended towards the treatment of arterial hypertension in the acute setting. Although the level of arterial hypertension that mandates treatment is not known, there is consensus that antihypertensive agents should be avoided unless the systolic blood pressure is >220 mm Hg or the diastolic blood pressure is >120 mm Hg. Agents that have a short duration of action and little effect on cerebral blood vessels are preferred. Because some patients can have neurological worsening with rapid lowering of the blood pressure, the use of sublingual nifedipine and other antihypertensive agents causing precipitous reductions in blood pressure should be avoided. Patients with elevated blood pressure and who are otherwise eligible for treatment with rt PA can have their blood pressure lowered cautiously so that their systolic blood pressure is £ 185 mmHg and their diastolic blood pressure is £ 110 mmHg. Because the maximum interval from stroke onset until treatment of stroke is short, most patients with sustained hypertension above recommended levels cannot be treated with intravenous rt PA. Hyperglycemia or hypoglycemia following stroke need to treated. Until further data becomes available, a judicious approach to management of hyperglycemia is recommended. By consensus, a reasonable goal would be to lower markedly elevated glucose levels to < 300 mg/ dL. Management of an elevated blood glucose level following stroke should be similar to that given to treatment of other acutely ill patients, who have hyperglycemia. Blood glucose concentrations should be monitored. Intravenous administration of glucose – containing solutions be avoided. However, fluids and insulin should be administered if the blood glucose concentrations are markedly elevated. Overly aggressive therapy should be avoided because it can result in fluid shifts, electrolyte abnormalities, and hypoglycemia, all of which can be detrimental to the brain.

### TREATMENT OF BRAIN EDEMA & INCREASED INTRACARNIAL PRESSURE

Brain edema and increased intracranial pressure largely occur with occlusions of major intracranial arteries. Brain edema usually peaks at 3 to 5 days after stroke. It usually is not a problem within the first 24 hours of the ictus except among patients with large cerebellar infarctions. Less than 10 % to 20 % patients develop clinically significant edema that could warrant medical intervention. Increased intracranial pressure also can result from acute hydrocephalus secondary to obstruction of cerebrospinal fluid pathways by a large cerebellar lesion.

*The goals of management of brain edema are to :*

1. reduce intra cranial pressure
2. maintain adequate cerebral perfusion to avoid worsening of the brain ischemia, and
3. prevent secondary brain injury from herniation.

Initial care includes mild restriction of fluids. Hypo – osmolar fluids, such as 5 % dextrose in water, may worsen edema. Factors that exacerbate raised intracranial pressure (eg, hypoxia, hypercarbia,

and hyperthermia) should be treated. The head of the bed can be elevated by 20 to 30 degrees in an attempt to help venous drainage. An elevation of the arterial blood pressure may be a compensatory response to maintain adequate cerebral perfusion pressure in a patient with a markedly elevated intracranial pressure. Antihypertensive agents, particularly, should be avoided in this setting. Patients with raised intracranial pressure whose neurological condition is deteriorating can be treated with hyperventilation, osmotic diuretics, drainage of CSF, or surgery. The value of continuous intra cranial pressure monitoring in this population has not been established.

Hyperventilation is an emergency measure that acts almost immediately: a reduction of the  $PCO_2$  by 5 to 10 mm Hg can lower intra cranial pressure by 25 % to 30 %. Hyper ventilation is a temporizing measure and should be supplemented by another intervention to definitely control brain edema. Conventional or large doses of corticosteroids have been tested in clinical trials, but no improvement of outcomes after stroke was found. Although furosemide or mannitol often are prescribed to treat cerebral edema after stroke, no trials of these agents prove their value in improving outcomes after stroke. An acute intravenous bolus of 40 mg of furosemide has been used as an adjunct in the care of patients whose condition is rapidly deteriorating, but it is not used in long – term care. Mannitol (0.25 to 0.5 g/kg) intravenously administered over 20 minutes lowers intracranial pressure and can be given every 6 hours.

Hemicraniectomy has been advocated for malignant MCA infarction. Ventriculostomy and suboccipital craniectomy especially in concert with aggressive medical therapies, appear to be effective in relieving hydrocephalus and brain stem compression caused by large cerebellar infarctions.

The management of patients with acute ischemic stroke is multifaceted and indications for specific therapies vary among patients. There is strong evidence that outcomes after stroke can be improved and that death or disability from stroke can be reduced with appropriate treatment.

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## Next Issue Highlights

Special Issue : **COSMETIC SURGERY : NEW HORIZENS**

Guest Editor : **Dr. Rajiv B. Ahuja**

- Liposuction- Lakshyajit Dhami
- Hair Restoration Surgery - Manoj Khanna
- Non Surgical facial rejuvenation - KuldeepSingh
- Cosmetic Surgery of Breast - Rakesh Kr.Khazanchi
- Lasers in plastic surgery- S.S.Sethi, Kuldeep Singh
- Surgical facial rejuvenation - Kulwant S.Bhargav
- Abdominoplasty- Arun Goel
- Rhinoplasty- Rajiv B. Ahuja

## Acute ischemic Stroke - Is Thrombolysis need of the hour? A Clinical debate

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**Abstract :** *Thrombolytic treatment of stroke patients remains a controversial topic in clinical medicine .Contemporary acute ischemic stroke therapy protocols opt for time and ignore specificity. Therapeutic decisions regarding whether to use thrombolytics are complex and depend on more than simply the time that has expired since stroke symptom onset and findings on CT scan. There is considerable current interest in new MRI techniques and vascular imaging studies like diffusion -perfusion MRI, MRA , CTA and Doppler .These are capable of identifying the ischemic penumbra representing the tissue that may be salvaged if perfusion can be restored quickly enough , a key concept in stroke physiology in a clinically relevant manner. A good radiological selection of patients for thrombolysis may increase the number of potential patients who are actually treated for acute ischemic stroke . A number which is currently disappointingly low.*

Interventions in acute ischemic stroke should aim to minimize mortality, impairment, and disability and reduce the complications of stroke such as deep vein thrombosis. Therapies to reduce brain damage may act by restoring blood flow thus reducing infarction within the penumbra (thrombolysis), preventing thrombus extension (by giving antiplatelets), and increasing cerebral resistance to ischemia. (neuroprotective drugs).

**Thrombolysis** aims at reducing the volume of infarcted brain by recanalizing the occluded vessel and restoring blood flow. Although this may seem of obvious benefit thrombolysis is not currently routinely used owing to the uncertainty of the risk-benefit ratio. It may, however, prove to be appropriate in certain selected patients. At present the criteria for such a selection are unclear but the overall aim would be to identify cases of major ischemic stroke in which little spontaneous recovery is likely and in which the hemorrhagic transformation of infarct with thrombolysis is low. In addition patients in whom spontaneous recanalization of occluded vessel had occurred would need to be excluded.

There are various **Thrombolytic agents** available including tissue plasminogen activator (tPA), urokinase, single chain urokinase plasminogen activator, streptokinase and acylated plasminogen streptokinase activator complex. These agents differ in half life, stability and fibrin selectivity. The relative effectiveness and the most effective doses of the different thrombolytic agents is unclear owing to the lack of data from randomized controlled trials.

**Intravenous Thrombolysis** by giving recombinant tissue plasminogen activator (tPA) to selected patients within three hours of ictus has become part of emergency care of patients with hyperacute ischemic stroke<sup>1</sup>. Unfortunately only 2-3% of the eligible population in a developed country like U.K, receives this treatment. Currently, intravenous thrombolysis appears to result in improved outcome in certain patients but it remains unclear how to select patients who will benefit from the total population of patients with acute ischemic stroke. Shortly after the NINDS trial<sup>1</sup> and ECASS trial<sup>2</sup> and other studies<sup>3,4</sup> the FDA approved use of tPA for stroke, and committees of the American heart Association, AHA<sup>5</sup> and the American academy of Neurology,

AAN<sup>6</sup> published guidelines endorsing its use. Intravenous thrombolysis is initiated with, a dose of 0.9 mg/kg body weight, tPA (upto a maximum of 90 mg). The dose is divided in to an initial bolus (10 % of total dose) followed by infusion of the rest. (90% of total dose.)

Appropriately, each organization emphasized the urgency of treatment. When it is effective, tPA forestalls irreversible brain infarction by lysing occlusive thrombi, thus facilitating the reperfusion of ischemic brain. Ischemic brain cells die within hours without perfusion. Unfortunately, thrombolytic drugs sometimes can cause fatal brain hemorrhages. AHA and AAN recommended the intravenous administration of tPA immediately after CT scanning to rule out the intracranial hemorrhage. Strict adherence to this time window and choosing not to suggest test to detect underlying occlusive vascular lesions precludes many patients who might benefit from thrombolytic treatment and includes those who are unlikely to benefit, for example, those with ICA and main trunk MCA (M1) occlusions and those in whom the embolus has already dissipated. Severe strokes (implying a large relatively proximal clot) with little or no collateralization usually do badly with intravenous tPA and risk ICH. (1, 7) Alternative treatment should be considered in these cases. One of the views is that Hyperacute ischemic stroke comprises a heterogeneous group of patients and the time window must vary on an individual basis. The time window and the opportunity for treatment depend upon the site and extent of clot and collaterals. Ideally, management should be individualized following investigation with CT, CT angiography (CTA), and CT perfusion (CTP) studies. (OR MRI, MRA, DWI/PWI studies) to optimize and rationalize therapy. CTA /MRA will demonstrate the site and extent of clot and CTP/DWI/PWI will help to differentiate the already infarcted from ischemic "at risk" but potentially viable tissue i.e. ischemic penumbra. With a more distal branch occlusion and good collaterals, the time window is obviously longer. Conversely, if there is total occlusion of the M1 segment or proximal M2 which include the lenticulostriate arteries the time window may be less. Lenticulostriate are true end arteries, without collateral circulation, supplying the basal ganglia which have a high metabolic rate. Reperfusion after delay is associated with an increased risk of hemorrhage.

**Intra-arterial thrombolysis** has been proposed as a treatment of acute ischemic stroke since the 1980s, PROACT I 1988<sup>8,9</sup>.

Follow up clinical efficacy trial was reported in February 1999<sup>10</sup>. Intra-arterial thrombolysis involves the direct infusion of thrombolytic agent into the occluding thrombus achieving higher local concentration of drug, lower systemic concentration and fewer hemorrhagic complications<sup>11</sup>. It allows thrombolysis to be given to only those patients in whom vessel occlusion has been demonstrated. Further the exact site of occlusion can be seen. Recanalization rates appear to be higher than intravenous thrombolysis<sup>12</sup>. Additionally, mechanical means may be applied to disrupt the clot using the microguidewire and this may facilitate the action of the thrombolytic agent. Clot retrieval devices are now available (Merci, Bos sci, approved by FDA). Mechanical thrombolysis is obviously invaluable if clot is resistant to intra-arterial tPA. If thrombus is superimposed upon a stenosis, it may be necessary to undertake angioplasty or stent the lesion. Mechanical thrombolysis may also be considered if pharmacological thrombolysis is contraindicated.

Although intra-arterial techniques have distinct advantages there are logistical problems. Intravenous thrombolysis has obvious advantage of ease and rapidity of administration and avoids the disadvantage of intra-arterial treatment which includes the inevitable additional time delays, risk of procedure. In additional intra-arterial treatment requires specialist Neurointerventional training. There are a few small randomized trials<sup>9,10,13</sup> comparing intra-arterial thrombolysis with placebo, within six hours of the ictus and combined intra-arterial and intravenous treatment<sup>14-16</sup> reporting encouraging results. But there are no randomized trials comparing intravenous and intra-arterial treatment. Current opinion suggests that intra-arterial treatment may be useful for large vessel occlusions and in those presenting after 3 hours window period where DWI/PWI/CTP are favorable.

Vertebrobasilar occlusion is usually associated with a poor prognosis with overall mortality rates of 70-80% there are no randomized studies but many cases of thrombolysis are reported in literature using local intra-arterial infusions of urokinase or tPA<sup>17</sup>. The precise time window is uncertain and therapeutic windows of up to 72 hours have been reported. Signs of brain stem infarction on imaging are not always indicative of poor outcome. However, coma or tetraparesis for several hours is indicative of poor prognosis despite recanalization.

The current opinion suggests that immediate intravenous tPA opts for time and ignores specificity. To achieve specificity now requires resources but very little time. We will all agree that

patients are better served by accurate diagnosis and appropriate specific therapy. Intravenous tPA is an important therapeutic option that is appropriate for some occlusive lesions. However, it is not appropriate treatment for some other patients with acute ischemic strokes which might be better treated by other methods.

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## Announcement

### International Medical Educator Program Fellowships of CMCL-FAIMER Regional Institute 2007

The CMCL-FAIMER regional Institute's Fellowship is a One-year Fellowship program designed for Indian medical school faculties who have the potential to play a key role in improving medical education. The first session consists of five days of intensive course at Chirstan Medical College, Ludhiana, India during January 2007 followed by an inter session curriculam innovation project at the participant's home institution through internet discussion group; the second will be in January 2008. The program is uniquely designed to teach education methods and leadership skills, as well as to develop strong professional bonds with other medical educators. The CMCL-FAIMER Regional Institute, running in its second year, is sponsored by the Foundation For Advanced of International Medical Education and Research (FAIMER), which is a nonprofit foundation of the Educational Commission for Foreign Medical Graduates (ECFMG), USA. Limited funding is available to support Fellows' travel, local expenses and course fee. The cost of carrying out the project, however, is not included. Fifteen fellowships are on offer this year.

**For details visit our site. : <http://cmcl.faimer.googlepages.com/home> or contact Dr Tejinder Singh , Director of the Program and Vice Principal at Christian Medical College, Ludhiana 141008 Tel :01612608617, Mobile 09815400048, e-mail : [cmcl.faimer@gmail.com](mailto:cmcl.faimer@gmail.com)**

## Carotid Stenting in Stroke Prevention : Present Status

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**Abstract** : Stroke, one of the leading causes of disability and a major cause of loss of vocational ability, remains a major health problem. Large vessel disease accounts for about 30%-40% of all strokes. Atherosclerosis is the most common cause of extracranial cerebral arterial stenosis and carotid artery stenosis accounts for 20%-30% of ischaemic strokes. Studies show that carotid endarterectomy and carotid angioplasty and stenting can decrease the risk of stroke.

### INTRODUCTION

Stroke continues to remain a major health problem. In the West, it is the third most common cause of death after heart disease and all cancers. It is also one of the leading causes of disability and a major cause of loss of vocational ability. Each year, more than 600,000 men<sup>1</sup>. The average annual incidence of stroke in Japan is 3.94 for males and 2.52 for females per 1000 population, with cases of cerebral infarction outnumbering those of cerebral haemorrhage<sup>2</sup>. Fourteen per cent of people who have a stroke or transient ischaemic attack (TIA) will have another within a year. Approximately 30% of stroke survivors require assistance for the activities of daily living and about 70% have impaired vocational ability. Large vessel disease accounts for about 30%-40% of all strokes. Carotid artery (CA) stenosis, particularly involving the CA bifurcation region, alone accounts for 20%-30% of ischaemic strokes<sup>3-5</sup>. In this group of patients, the disease can be modified and the risk of stroke minimized by intervention.

### CAROTID ENDARERECTOMY

The benefit of carotid endarterectomy (CE) for the prevention of stroke in patients with extracranial CA stenosis has been well established in randomized trials. The landmark studies of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Asymptomatic Carotid Atherosclerosis Study (ACAS), have proved that CE is beneficial in reducing the risk of stroke for symptomatic and asymptomatic patients with significant CA stenosis<sup>6-9</sup>. For patients with recently symptomatic CA stenosis, the NASRT<sup>6</sup> demonstrated the efficacy of CE in preventing stroke in patients with 70%. 99% angiographic stenosis with a 2 year absolute risk reduction of 17%. In those with 50%-69% stenosis, there was a modest benefit with an absolute risk reduction of 6.5% at 5 years<sup>10</sup>. In the moderate category, only certain subgroups of patients experienced benefit, such as men and patients with hemispheric ischaemia. There was no demonstrable benefit of CE in patients with <50% stenosis<sup>10</sup>. Asymptomatic patients with extracranial CA stenosis have a lower risk of developing a stroke.

The ACAS<sup>7</sup> evaluated patients with > 60% stenosis. The 5-year natural history risk of ipsilateral stroke was shown to be 11% (annual rate 2.2%). CE reduced the 5- year risk of stroke to 5.1% (annual rate 1.0%). This benefit was achieved with a perioperative risk of stroke and death of 2.3%. For asymptomatic CA lesions, men lead a 66% reduction in the incidence of stroke over 5 years, whereas for women, there was a reduction of only 17%. The threshold of perioperative mortality and morbidity for achieving benefit either by surgical or interventional methods in

symptomatic patients is approximately 6% and that for asymptomatic patients is 3%.

There is controversy regarding the risk of CA surgery in day to day practice, which may not be reflected in the highly selected population of patients and surgeons represented by randomized trials. Wennberg et al<sup>11</sup> analyzed the mortality results for all Medicare patients (n=113,300) undergoing CE during the same period that the NASCET was being conducted (Table-1). They found that the 30-day mortality rate (1.75%) in the Medicare population was three times higher than that reported in randomized trials (0.6%). The 30 day mortality rate for Medicare patients at the trial hospitals was 1.44% compared with 0.6% reported in the NASCET study. The perioperative mortality in the non-trial hospitals was 1.77%. Given the higher mortality results in the Medicare population, which represents the majority of patients undergoing CA surgery, the authors argue that the results of CA surgery in highly selected patients and performed by highly selected surgeons are not representative of everyday practice.

### CAROTID ANGIOPLASTY AND STENTING

Early studies on carotid angioplasty and stenting (CAS) have shown promising results and CAS is emerging as a popular alternative to endarterectomy for the treatment of stenotic diseases of the CA. Endovascular stenting of the CA provides an alternative therapeutic option for patients with atherosclerotic CA stenosis, but poses a high surgical risk because of significant coexisting morbidity. It can also be offered to those with surgically inaccessible or tandem CA lesions, contralateral CA occlusion and post-endarterectomy restenosis. Non-atherosclerotic occlusive disease of the CA due to radiation therapy, fibromuscular dysplasia, spontaneous or traumatic intimal dissection of the cervical and intracranial CA can also be treated effectively using CAS.

There are many non-randomized CAS case series, which involve several hundred patients. At present, a larger overview of the performance of CAS can be obtained from a recent global survey of interventionists<sup>12</sup>. In this multicentre survey with self-reported data, 5210 vessels were stented (Tables-1 and 2). The overall rate of stroke and death was 5.07% and the rate of major stroke was 1.5%. The authors found a higher complication rate in symptomatic patients, with a stroke and death rate of 5.8% compared with 3.4% in asymptomatic patients. If these figures reflect the performance capability of CAS in the real world, then CAS would seem a viable alternative to CE. However, it should be stressed that for asymptomatic patients any procedure that carries a stroke risk >3% is likely to be worse than medical treatment alone. For this reason, we would at present recommend avoidance of intervention in asymptomatic patients.

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**Table - 1** Results of carotid stenting : 30 day complications

Study	Arteries (n)	Success rate(%)	All stroke death (%)	Major stroke rate(%)	Death (%)
Wholey et al <sup>12</sup>	5210	98.4	5.07	2.15	0.79
Yadav <sup>13</sup>	25	100	4.0	0	0
Hussain et al <sup>24</sup>	96	99	1	0	0
Bergeron et al <sup>48</sup>	99	NA	1	0	0
Gupta et al <sup>49</sup>	100	100	5	1	0
Meriole <sup>51</sup>	26	100	0	0	0

## CAROTID ENDARTERECTOMY VERSUS CAROTID ANGIOPLASTY AND STENTING

The results of a few clinical trials comparing CE and CAS are available. These are the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS)<sup>13</sup> and Stent and Angioplasty Protection in Patients at High Risk of Endarterectomy (SAPPHIRE)<sup>14</sup>.

In the CAVATAS trial, 504 patients with proximal internal carotid artery (ICA) atherosclerosis were randomly assigned to treatment with either CE or carotid angioplasty. Stenting was not mandatory and stents were used in only 26% of the patients. A vast majority of the patients (96.5%) were symptomatic and had severe stenosis (mean : 86.5% by the common carotid method). The patients had a greater prevalence of baseline coronary artery disease (36%) than the European Carotid Surgery Trial Population (24%)<sup>13</sup>.

There was no difference at all in the occurrence of periprocedural stroke or death between the CE (9.9%) and the angioplasty (9.9%) groups. In terms of major stroke and death rate, again there was no significant difference, the rates being 6.4% in the angioplasty group and 5.9% in the CE cohort. It is worth noting that the complications rates reached such high levels in both the CE (10%) and the angioplasty (9.9%) groups that it is likely no benefit would have been conferred beyond medical treatment alone.

With regard to other minor complications, some of the inherent benefits of angioplasty were borne out. Because there is no need for a neck incision, there was a lower incidence of cranial nerve palsies (none in the angioplasty group, 8.7% in the CE group) and would haematomas (1.2% in the angioplasty group, 6.7% in the CE group). With regard to cranial nerve palsies, many surgical series have shown that in the majority of instances, cranial nerve dysfunction after CE is transient. In the NASCET, for example, only 10 of 122 cranial nerve palsies (8%) were moderate in severity, which was defined as requiring a delay in discharge, readmission, or the absence of recovery<sup>6</sup>. The SAPPHIRE randomized trial compared CE with carotid stenting using embolic protection devices<sup>15</sup>. This study randomized high-risk patients to CE or carotid stenting using the PRECISE stent and the Angioguard embolic protection filter (both from Cordis, Miami Lakes, FL). In this small study there were fewer events in the stent arm as compared with the CE arm. The composite end point of death, stroke and MI at 30 days fell from 12.6% in the CE arm to 5.8% in the stent arm (p=0.047). Each individual end-point was in favour of stenting. The benefit of stenting was seen in both symptomatic and asymptomatic patients. The incidence of cranial nerve injury was 5.3% in

the CE arm and none in the stent arm (p<0.01).

## SAFETY AND EFFICACY COMPARISON

A randomized clinical trial, the Carotid Revascularization Endarterectomy Versus Stent Trial (CREST)<sup>16</sup> has standardized definitions of outcome events and re-stenosis, and will help to determine the safety and efficacy of stenting in a controlled fashion. Though it is relatively difficult to compare CA stenting with endarterectomy without a randomized trial, some early comparisons can be made. If all causes of death within a 30 day period of CAS are included, the stroke and death rate for carotid stent placement is 6.29%. Hence, the risk of carotid stent placement is at par with the American Heart Association's (AHA) guidelines for CE : <6% for patients with TIA and <7% for patients with symptomatic stroke<sup>17</sup>. Safety and Efficacy of Endovascular Treatment of Carotid Artery Stenosis versus Carotid Endarterectomy was compared in a recent review<sup>18</sup>. Five trials involving 1269 patients were included. No significant difference in the major risks of treatment (treatment related death or any stroke) was found at 30 days and 1 year while minor complication rates favoured endovascular treatment.

## RESTENOSIS AFTER REVASCULARISATION

The incidence of recurrent carotid stenosis after CAS is important in judging the benefits of CAS apart from the periprocedural complications. In a systematic review of the literature, the cumulative incidence of recurrent stenosis (for 50% stenosis) after CEA was about 10% in the first year<sup>19</sup>. Similarly, an early restenosis rate of 7.6% to 11.4% was found within 18 months of CEA in the ACAS<sup>20</sup>.

Much lower restenosis rates for >50% after CAS (2.70% after 12 months, 2.60% after 24 months, and 2.40% after 36 months) have been reported in the largest multicenter survey to date<sup>21</sup>. In another recently published review on early recurrent stenosis after CAS<sup>22</sup>, it was found that, the cumulative restenosis rates after 1 and 2 years were 6% and 7.5% in those studies, which used a lower restenosis threshold >50% to 70% and 4% in the first 2 years after CAS in those studies, which used a lower restenosis threshold > 70% to 80%.

To date, the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS)<sup>13</sup> is the only published prospective multicenter trial that directly compared early carotid restenosis rates after endovascular versus surgical treatment. However, in CAVATAS most patients were treated with angioplasty alone without use of stent, so that these results do not reflect the risk of recurrent stenosis after CAS. Thus the available literature shows a comparable or better early restenosis rates for CAS and CEA<sup>22</sup>.

## CLINICAL AND COST COMPARISON OF REVASCULARIZATION

The cost of treatment is another factor of concern when different treatment modalities are compared. In a study, William A. Gray et al<sup>23</sup> compared the clinical outcome and cost of treatment in 136 endarterectomies Vs 136 carotid stent procedures. The primary clinical outcome measures were in hospital major ipsilateral stroke and death, while primary economic measures were in hospital direct variable costs and length of stay. These nonrandomized groups were similar, but the endarterectomy group had more symptomatic patients (42% versus 31%; p=0.0004), and the stent group had more NASCET excluded patients (68% versus 35%; p<0.0001). In hospital major ipsilateral stroke and death occurred more frequently in the surgical group, but the difference was not significant (2.9% versus 0%;

$p=0.1$ ). Minor ipsilateral strokes were similar. Cost (\$5409 versus \$3417;  $p<0.0001$ ) and length of stay (3.0 versus 1.4 days;  $p<0.0001$ ) were significantly greater for the surgical group.

Cost and resource utilization with stenting appear to be substantially less than those with endarterectomy. They also found that, at 2 years, carotid stenting appeared not only durable but also effective in stroke prevention with a zero percent 2 year ipsilateral major stroke rate. Thus there is enough evidence for equivalent clinical efficacy of CAS compared with CEA, achieved at a lower cost.

There are numerous clinical situations in which the endovascular approach of carotid stent placement could benefit patients by causing less risk, trauma and discomfort. The *ideal patients for endovascular stent placement* have classically been the following :

- \* Patients with an isolated, high ICA lesion near the angle of the mandible, which is inaccessible for surgery
- \* Patients with post-radiation CA stenosis
- \* Patients with post-endarterectomy recurrent CA stenosis
- \* Patients with contralateral CA occlusion and an incomplete circle of Willis
- \* Patients with multiple medical problems
- \* Patients with tandem lesions
- \* Patients with non-atherosclerotic extracranial cerebrovascular diseases such as fibromuscular dysplasia, Takayasu arteritis, carotid dissection, etc.

#### Protocol for carotid stenting, Sir Ganga Ram Hospital

All patients qualifying for the procedure undergo a thorough neurological history and examination before the procedure. Baseline investigations include CBC, PT, aPTT, blood sugar, BUN, serum creatinine, ECG and chest X-ray. A baseline CT or MRI scan of the brain is obtained to document any pre-existing infarction and exclude other non-vascular pathologies that may resemble TIA. The patient is started on oral aspirin 325 mg/day and clopidogrel 75 mg/day at least 3 days before the procedure. After the procedure, the patient is maintained on oral aspirin at the same dose lifelong and on clopidogrel at the same dose for 12 weeks.

The procedure is performed under local anaesthesia, and conscious sedation is used only if required. The right femoral approach is preferred and a 7F sheath is placed. A complete four vessel cerebral DSA is performed in a minimum of two planes to analyse the intracranial circulation and formation of the circle of Willis. A 7F guiding catheter is advanced into the common carotid artery (CCA) and the catheter tip is positioned about 2.5 cm proximal to the stenosis. A baseline activated clotting time (ACT) is performed. A bolus of heparin (70-90 units/kg) is given to achieve an ACT 2-2.5 times the baseline and / or 250-300 seconds. Prophylactic atropine is not used; however, a syringe loaded with atropine is kept attached to the i.v. line to be injected only if the patient develops bradycardia during balloon dilatation or stent placement.

The stenosis is crossed with a 0.014 inch guidewire under roadmap imaging. Predilatation is performed only if the stenosis is of a high grade. Cerebral protection devices are seldom used. A self-expanding PRECISE stent or carotid Wallstent is used. After deployment of the self-expanding stent, it is dilated with a 5 or 6 mm balloon for lesions of the ICA. Self-expanding stents have an element of rebound to external compression and can be sized to conform to both the ICA and CCA. Stents are usually oversized by 1-2 mm and if deployed within both the ICA and CCA, they are sized to the larger vessel. Many stents being developed are better suited for carotid use; for example, the PRECISE stent (Cordis) has a 5.5 F deployment system, is quite flexible and produces less friction during

deployment, thus facilitating precision of placement. Heparin is not given after placement of the stent and the effect of the heparin already given is allowed to dissipate naturally. Protamine is not used to reverse the effect. At the end of the procedure, a complete angiographic evaluation is performed to ensure that there has not been any thromboembolism. The femoral sheath is removed when the ACT returns to the baseline level. The patient is kept under close observation for the day and is discharged the following day. Post procedure neurological evaluation is performed and NIH stroke scale is utilized at 24 hours, 1 month and 6 months. Fig.1 shows successful stenting of the origin of the ICA with a SMART stent (Cordis).

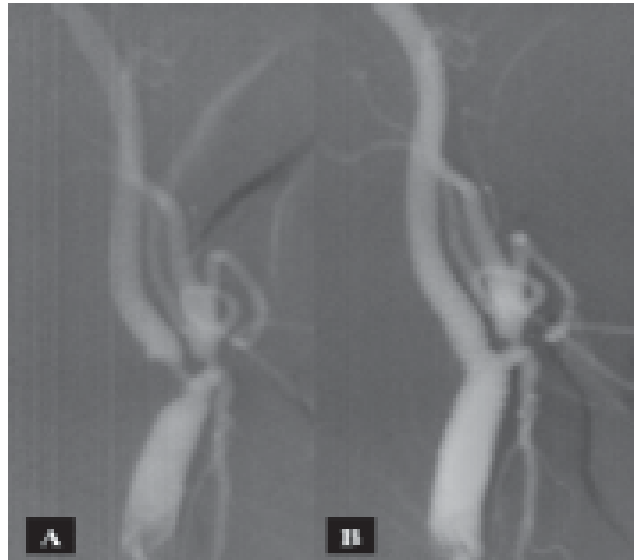


Fig. showing results of CAS in a 90% stenosed left carotid artery before (A) and (B) Stenting

At Sir Ganga Ram Hospital, between May, 1999 and December, 2004, CAS was performed in 96 symptomatic NASCET-ineligible patients (e.g. those with multiple medical problems, atherosclerotic disease beyond the bifurcation, recurrent carotid stenosis, post-radiation stenosis, etc.)<sup>24</sup>. Twenty eight patients (29.1%) had complete occlusion of the contralateral ICA. The mean lesion length was 22±7.9 mm and mean percent stenosis was 85±8.0% (reference diameter 5.8±0.3mm). Self expanding SMART stents (Cordis), PRECISE monorail carotid stents (Cordis), carotid Wallstents (Boston Scientific Inc) and Sinus carotid stent (Optimed, GmbH) were deployed (80% were deployed without predilatation). On an intention to treat basis, the overall technical success rate for carotid angioplasty was 99%. One patient had minor stroke 8 hours after the completion of the procedure, and an immediate CT scan of head performed suggested hyperperfusion injury. There were no major strokes. There was no mortality. Six patients (6.2%) had an uneventful transient focal seizure during balloon inflation, which reversed immediately following balloon deflation. All these patients had complete occlusion of the opposite ICA. Ten patients (10.4%) had transient bradycardia during balloon inflation, which did not require pacing.

Follow-up consisted of serial duplex ultrasonography and clinical assessment in 76 patients at a median of 16 months. 2.6% of the patients (2 out of 76) had TIA involving the same arterial territory in the 16 month median follow up period<sup>24</sup>.

## CEREBRAL PROTECTION DEVICES

There has been concern that balloon angioplasty in the proximal ICA would send emboli intracranially to the brain. Although emboli do occur from carotid angioplasty, early case series suggested that emboli do not invariably cause clinical stroke and in fact, the occurrence of post procedure stroke was roughly comparable with the stroke rate seen after CE. However, there has been a recent surge in the development of cerebral protection devices that trap the embolic particles during the procedure<sup>25</sup>. Various devices have been used for thromboembolic protection during stenting<sup>26-28</sup>. Henry et al<sup>26</sup> report the results of CA stenting with cerebral protection using Percusurge, a guide wire device, in 48 high-risk patients with 53 ICA stenoses. Their 30-day periprocedural risk has been minor stroke in 1 patient (2.08%) and death in 1 (2.08%).

The drawback of occlusive devices is that they cause prolonged occlusion of the ICA till the procedure is complete. The average time calculated from the beginning of the set-up to complete removal was 46 minutes<sup>27</sup>. Patients with an incomplete circle of Willis or inadequate collateral flow may not tolerate prolonged occlusion. Moreover, prolonged occlusion carries a risk of vasospasm, circumscribed dilatation at the site where the protective balloon is inflated and perioperative CA occlusion<sup>27,28</sup>.

Recently, Kastrup et al<sup>29</sup> systematically reviewed single-center CAS studies and concluded that protection devices appear to reduce thromboembolic complications during CAS. This review included a variety of single-center studies from 1990 to 2002. The combined stroke and death rate within 30 days was 1.8% in CAS with protection and 5.5% in CAS without protection.

In another study, Cremonesi et al<sup>30</sup> studied in hospital and 30 day adverse events in 442 patients treated percutaneously for CA disease with embolic protection devices. The percutaneous procedure was successful in 440 patients (99.5%). There was no periprocedural death with any embolic protection device. The in-hospital stroke and death rate and 30 day ipsilateral stroke and death rate was 1.1%. The overall complication rate was 3.4%. Major adverse events included 1 major stroke (0.2%), 4 intracranial hemorrhages (0.9%), ICA wall fissuring (0.2%) and 1 diffuse cardio embolism (0.2%). Minor adverse events included 4 minor strokes (0.9%) and 4 TIAs (0.9%). There were 4 complications (0.9%) related to the use of cerebral protection devices: 1 case of abrupt closure of the ICA because of spiral dissection (0.2%), 1 case of trapped guide wire (0.2%) and 2 cases of intimal dissection (0.5%). Transient loss of consciousness, tremors and fasciculations were present in 6 of the 40 patients (15%) in whom occlusive protection devices were used.

Neither Cremonesi et al nor Kastrup et al reported on the failure rate on application of protection systems, which can be upto 20% according to literature<sup>31</sup>. The observation of EVA-3S Trial committee<sup>32</sup>, favoring protected stenting has been rejected<sup>33</sup> as the higher incidence of strokes in the first 30 days in patients treated without protection could not be related to the non-use of a protection device.

### IS A CEREBRAL PROTECTION DEVICE USE FOR EMBOLIC CAPTURE NEEDED?

The appearance of debris during CAS and CE is a common event<sup>34-36</sup> the first glance, it seems reasonable to apply protection systems to catch the particles by means of occlusive balloon systems or filtration baskets if the ICA. The beneficial use of such devices seems to be supported by a growing number of publications, mostly from the field of cardiology,

which report declining rates of neurological complication. Despite the lack of further controlled studies, the use of protection devices has even become obligatory in the CREST (United States)<sup>16</sup> and EVA3S (France) trial testing for the equivalence of CAS and CE<sup>36</sup>. Paradoxically, some neurologists and neuroradiologists continue to successfully perform CAS without protection devices and hesitate to apply these as they demand an increase in both catheter time and technical complexity.

In centres in which experience with unprotected CAS has been gathered, skepticism about the the assumed self-evident improvement in implementation of protection devices is based not only on the low neurological complication rate without them but also on the technical complications associated with their use<sup>37</sup> such as dissection of the ICA (0.7%) or trapped guide wire needing surgical intervention (0.2%)<sup>30</sup>. Haemodynamic intolerance in occlusive balloon systems (5-15% of patients)<sup>31,35</sup> and congested nets are other typical problems encountered with the use of protection devices. Such experiences have apparently been poorly reported until now<sup>38</sup>. Furthermore, predilatation, which is often necessary in protected stenting and the removal of the protection devices may result in embolization<sup>38</sup>. From a neurological perspective, concentrating on the 10 studies appearing since 2002<sup>35,38-40</sup>, a strong recommendation for the use of protection devices can not be made.

Carotid artery stenting without protection devices appears to be safe. Of late, in a series of 245 consecutive patients<sup>41</sup> (260 hemispheres) underwent carotid artery stenting without protection devices, the technical success rate was 98.8%. Neurological complications (inclusive of transient ischemic attacks) were observed in 5.4%. The rate of major complications (death, major stroke and myocardial infarction) was 1.6% among the symptomatic and 1.5% among the asymptomatic cases. The rate of minor strokes was 3.2% in the symptomatic and 1.5% in the asymptomatic group. Neurological and other complications (death, major stroke and myocardial infarction) occurred only in comparable frequency as with protection devices. Majority of the neurological complications (64.3%) occurred post procedurally which could not have been prevented with protection devices.

The recent dramatic technical progress (e.g. less traumatic, self expandable stent devices, more friction-resistant introducer catheters and better guide wire systems leading to marked improvement of CAS), the associated learning curve of active interventionalists and the improved periprocedural antiplatelet and anticoagulation regimens may have been important factors in preventing cerebral embolism in the recent protected CAS studies<sup>33</sup>.

The use of cerebral protection devices remains a controversial issue. The real purpose of distal protection is to prevent embolization sufficient to cause stroke. Reports in the literature reveal that the use of protection devices does not completely prevent embolization. Moreover, the use of these devices may inherently add to the risk of the procedure. However, cerebral protection with the filter device is technically feasible in most cases. A much larger investigation will be required to determine whether stroke is less likely with distal protection than without it. Could stroke develop even if these devices successfully trap all macroscopic material? Hypothetically, yes. However, a shower of small particulate matter could cause microvascular obstruction. Of the various devices available, is there one that is superior? These critical questions still need to be answered by a head to head comparison in the form of a randomized clinical trial. We believe that protection devices not only complicate the entire procedure of CAS but also impose a significant cost concern. We propose to undertake a double blind randomized trial to clarify this controversy.

## GUIDELINES

In patients with severe symptomatic CA stenosis, the evidence in favour of intervention (CE/CAS) is strong. The merits and demerits of both CE and CAS should be discussed with the patients and their families and the final choice should be left to them. For patients in whom surgery carries a high risk, i.e. NASCET excluded patients, we consider CAS, especially if medical therapy has failed. Intervention is not indicated for patients with mild symptomatic CA stenosis (<50%). Some patients with 50%-69% symptomatic stenosis will benefit from surgery or stenting, but the decision should be individualized on the basis of several factors, including the presence or absence of vascular risk factors for stroke and technical expertise. For patients with asymptomatic 60% CA stenosis, the decisions are difficult. Clinicians should consider intervention (CE/CAS) for patients without apparent contraindications at a centre where they know that the surgeon/interventionist performing the procedure has a perioperative risk of stroke or death rate of <3%. Preoperative cardiac or haemodynamic evaluation may help in risk stratification. After the risks and benefits are explained to the patient, the ultimate decision depends on whether the patient is willing to accept the early risk and discomfort of surgery in the hope of long term benefit. In all cases, risk-factor control should be emphasized. We often recommend angiotensin-converting enzyme inhibitors to patients with hypertension and prescribe statins even for patients with normal to borderline cholesterol levels. Antiplatelet therapy (we prefer a combination of ASA and slow-release dipyridamole) is appropriate for all patients who do not have a contraindication and changes in lifestyle (smoking cessation, weight control, exercise and avoidance of excessive alcohol consumption) should be routinely encouraged.

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## IMSA News

### IMSA CHAPTER ACTIVITIES - April to June 2006

#### Tamil Nadu Chapter

09-04-2006 : Dr. Arjun Rajagopalan, "Finding, Filtering, Evaluating Rheumatology and Adopting Medical Evidence in Clinical Practice"  
 14-05-2006 : Dr. Abraham Thomas, "Face Transplantation"  
 11.06.2006 : Dr. Noordeen, "Elimination of Leprosy"

#### Delhi Chapter

01.04.2006 : "Clinical Meeting" in collaboration with Delhi Association at AIIMS, New Delhi  
 17.06.2006 : "Scientific Programme" organised in collaboration with Delhi Rheumatology Association at Seminar room, Indian Spinal Injuries Centre, Vasant Kunj, New Delhi.

#### T.N. Chapter Venue : Ranipet (Vellore)

18.06.2006 : Dr. B. Sumathi, "Recent Advances in Management of Diarrhoeal Disorders in Pediatrics"  
 Dr. M. Rajkumar, "Diabetic Foot Syndrome"

#### Rural CME

### HONOR

Dr. Tarun Gupta, Addl. Secretary General, IMSA has been installed the Hony. Secretary of the Rotary Club of Delhi Chanakyapuri, R.I. Dist. 3010 for the year 2006 -2007.

### World Congress on Clinical & Preventive Cardiology (WCCPC 2006)

Organised By

*Cardiological Society of India, Delhi Branch (CSI Delhi Branch),  
 Asian Pacific Society of Cardiology (APSC),  
 Healthy Heart Education and Research Foundation (HHERF),  
 International Medical Sciences Academy (IMSA)*

In association with

*J.W. Global Hospital & Research Centre (J.GHRC),  
 Defence Research & Development Organisation, Govt. of India (DRDO)  
 Indian Academy of Echocardiography (IAE) &  
 World Academy of Spiritual Science (WASS)*

On September 22 to 24, 2006

At The Academy for a Better World Gyan Sarovar, **Mount Abu, Rajasthan, India**

### ANNOUNCEMENT

**SPECIAL HIGHLIGHTS** : Recent advances in clinical cardiology, Preventive cardiology, hypertension, congestive heart failure, dyslipidemia, coronary artery disease, medical angioplasty, coronary imaging, cardiometabolic syndrome, echocardiography, electrophysiology and cardiac arrhythmia, interventional cardiology, cardiovascular surgery and cardiac anaesthesia. **REGISTRATION** : "Registration is free" for all Registered Delegates on "First cum First Serve Basis" upto 800 only upto July 15, 2006.; fee of Rs. 2500/- will be charged from 16 th July, 2006 **For Registration Contact: Dr. H.K. Chopra**, Organising Chairman, IMSA World HQ, 2nd Floor National Medical Library, Ansari Nagar, New Delhi 110029 E-mail: drhkchopra@yahoo.com, drhkchopra@gmail.com Fax: 011-26444242; M: +91-9811090204 Ph: 011-26444242, 25658826, 26656990 **Dr. Satish Kr. Gupta**, Organising Secretary, J.W. Global Hospital & Research Centre, Shantivan, 307510 (Abu Road, Rajasthan) E-mail: wccpc2006@bkindia.com, smbhmhealth@gmail.com, Fax : 02974 - 228116, M: +91-9829479888, +91-9414154041, Ph: 02974-228577, 228101...106, 228340

### IMSACOM 2006 ANNOUNCEMENT

Organising Secretary IMSACOM 2006 at Lahore has desired that all delegates/ participants who have already sent their passport papers to Dr. Shaheena Asif, should apply for **Visa** to the Pakistan High Commission in India urgent. **For Details see Page 74.**

### Dr. Pinnamanani Narasimha Rao International Award

*Recommendations for "Dr. Pinnamanani Narasimha Rao International Award" are invited from Fellows and Members as also the Board of Trustees of IMSA. The recommendations should be sent along with biodata, colour passport size photograph and abstract of the paper, to IMSA Headquarter, New Delhi by 31st August 2006. The Selected awardees will be required to deliver an oration at IMSACOM 2006 at Lahore.*

**Secretary General, IMSA**

## Stroke: An Indian Perspective

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**Abstract :** Stroke is a very common disorder affecting older people. Community surveys of different parts of the country indicate a crude prevalence of stroke of 203/1, 00,000 populations above 20 years which is much lower than that reported from the west. The causes of low prevalence of stroke in India are predominance of young population in India in which stroke is less prevalent and high early mortality leaving behind fewer survivors. The mortality rate due to stroke in India is 7.3/ 1, 00,000. Thus, deaths due to stroke are 22 times higher than malaria, 1.4 times that due to tuberculosis and 4 times that due to rheumatic heart disease. About 10-15 % of stroke occurs in population < 40 year old. Certain risk factors evaluated in Indian centers are hyperhomocystinemia, elevated anticardiolipin antibody, and elevated lipoprotein, in addition to hypertension, smoking and diabetes mellitus. Most centers show the ratio of ischemic to hemorrhagic stroke as 10-15% to 90- 85 %. As regards the vascular involvement both intracranial and extra-cranial involvement occurs in Indian patients. On the other hand in west <5% have intracranial disease and in the Far East <5% have extra-cranial disease.

### INTRODUCTION

Stroke is a very common disorder affecting older people. However a small sub group of stroke in young has been identified. Until recently stroke used to be the 4<sup>th</sup> most common cause of death world wide, but over the years it has the dubious distinction of becoming the 3<sup>rd</sup> common cause of death. In India there are certain differences as compared to other western countries among the stroke population. In this review we shall highlight these.

### INCIDENCE AND PREVALENCE

Stroke epidemiological data of 9 Asian countries (2000) that there is good data available from Hong Kong, Taiwan, South Korea and Singapore; moderate data from Philippines, Malaysia, Thailand and Indonesia and only fair data was available from India<sup>1</sup>. Problems in epidemiological studies from India are large population size, poor income and limited health care resources. Another problem with proper epidemiological study is lack of knowledge about stroke. Pandian et al<sup>2</sup> studied awareness about stroke among Indian population in Punjab, India, the study revealed that 45% did not know which organ is affected in stroke 23% did not know a single warning symptoms of stroke, 21% could not identify a single risk factor, 7% believed oil massage would improve symptoms (Pandian et al 2005)

Epidemiologic data with regard to incidence and prevalence for the whole population of stroke is not available. Community surveys of different parts of the country indicate a crude prevalence of stroke of 203/1, 00,000 populations above 20 years. This means about 1 million cases are affected at any given time. This is less as compared to the prevalence reported worldwide which ranges between 400-800/ 1,00,000 population.

Various community based prevalence studies from India are tabulated below (Table 1)

The Rotterdam Study (population based Cohort study) had showed that the prevalence of stroke differs in different age groups. In the Rohtak study where overall prevalence rate was low; it was found to be significantly more in persons >70 (356/

1,00,000). No separate age wise studies are available from India. The reasons which may explain the low prevalence of stroke in India are :

1. Predominance of young population in India in which stroke is less prevalent, which dilutes the overall stroke prevalence figures.
2. By definition, prevalence includes the number of patients who are alive at the given time; mortality due to stroke is high in India, so it reduces the numbers.

**Table1: Crude prevalence rate by survey of hemiplegia :**

Zone	City	Subjects	Prevalence/1,00,000
North	Kashmir	63645	145
	Rohtak	79046	44
	Ballabgarh	4786	125
West	Mumbai (Parsi)	14010	843
	Mumbai	318552	222
	Mumbai	14546	220
South	Vellore	258576	57
	Gowribadunur	57600	52
East	Malda	37286	126
	Kolkata	50291	147
	Kolkata	14200	270

The first population based study for stroke incidence in India was conducted in Vellore in 1967-71 and it revealed an incidence of 1/ 1,00,000/year. Incidence over a similar period from Rohtak in 1971-74 was 33/ 1,00,000/ year. Incidence in a recent study in 1998-99 (Kolkata) was 105/ 1,00,000/year.

As compared to western countries, stroke incidence in India is lesser but it is registering an upward trend in the last few decades. On the other hand incidence in western countries is showing a striking decline.

### BURDEN OF STROKE

Worldwide, about 20 million people suffer from stroke each year, 5 million die of it, 5 million of the remaining 15 million survivors are disabled due to stroke. The Global Burden of Disease Study

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Paper presented at the Annual Conference of IMA-NDB 2006 at India Habitat Centre, New Delhi

in 1990 reported 9.4 million deaths in India of which 61,900 were due to stroke and the Disability Adjusted Life Years (DALY) loss amounted to 28.5 million, nearly 6 times that due to malaria<sup>2</sup>. India faces an enormous socio-economic burden to meet the cost of rehabilitation of stroke victims. Hence *stroke prevention planning* is a necessity now, but it requires reliable epidemiologic information of pattern of disease, exposure to risk factors and morbidity and mortality trends for the disease in specified well defined populations which are not available at present<sup>2,3</sup>.

## STROKE IN YOUNG

Stroke in you is another common phenomenon in the Indian scene. Most studies in India show that 10-15 % of stroke occurs in population < 40 year old. Stroke in young in India much higher than that reported from other countries. These figures are higher as compared to other countries. This could be due to many local etiologic factors. The common risk factors of stroke in young, especially pertaining to India are :

- Puerperal cortical venous thrombosis.
- Rheumatic heart disease associated cardioembolic strokes.
- Coagulation disorders (hypercoagulable states)
- Atherosclerosis
- Subacute tuberculous meningitis with vasculitis.
- Meningovascular syphillitis (rare now).

Another study by Mehndirata et al (2004) has shown stroke in young accounts for 13.5% all strokes admitted under Neurology care. Major risk factors for stroke in young among their cohort were hypertension, elevated serum cholesterol and low triglyceride levels. Smoking, use of oral contraceptive pills, alcohol and drugs were not so common.

## STROKE RISK FACTORS IN INDIA

Risk factors considered for stroke are largely parallel to those for other vascular diseases such as coronary artery disease and peripheral vascular disease. These may be modifiable and non modifiable (table 2).

**Table 2: Stroke Risk Factors**

Modifiable	Non modifiable
Hypertension	Age
Smoking	Sex
Cardiac disease	Race
Altered lipid profile	Family history
Alcohol	

Diabetes mellitus is an intermediate risk factor which can be treated effectively but there is no evidence that its treatment reduces the risk of stroke. In an ICMR conducted study (1989) hypertension, Diabetes mellitus, tobacco use, low hemoglobin were important risk factors in both sexes. Another study by WHO Task force on stroke (1989) also identified similar risk factors in India. A Chennai study (1984) identified hypertension, heart disease, diabetes mellitus, smoking, and low HDL cholesterol as important risk factors.

Certain *specific risk factors* for stroke have been evaluated in some centers in India.

- Recently various studies published from India have looked into the following other risk factors associated with stroke: (a.) *Hyperhomocystienemia*<sup>4</sup>. (b.) *Elevated Anticardiolipin antibody*<sup>5</sup>. (c.) *Elevated lipoprotein (a)*.  
In a study by *Prabhakar et al*<sup>5</sup>, serum. homocystiene levels were significantly higher in stroke patients compared to controls. A strong correlation was observed between hypertension, smoking and high homocystiene levels<sup>5</sup>. In another study by *Nagaraja et al*, anticardiolipin antibody was present in 23 % of patients with stroke in young as compared to 3.2 % in controls. The anticardiolipin antibody positive patients had more frequency of prior TIAs, ischemic retinopathy and asymptomatic infection<sup>4</sup>.
- In a selective study of stroke cases occurring at high altitude areas, long term stay at high altitude was associated with higher risk of stroke. Although all types of stroke are seen, ischemic stroke was the commonest. Massive infarcts were common and polycythemia was an important risk factor<sup>6</sup>.
- For cardioembolic ischemic strokes, rheumatic heart disease and ischemic heart disease seem to be the dominant risk factors in India.
- Nagaraja et al<sup>7</sup> had sought to evaluate preceding infection as a risk factor of stroke. Evidence of infection was noted in 43.3 % of stroke patients compared to 6 healthy controls.
- In a study from Wardha, India, squatting position during toilet was incriminated as an important triggering factor for stroke in India by causing increase in the blood pressure<sup>8</sup>.
- There have been few case reports of acute strokes triggered by snake viper envenomation<sup>9</sup>.

## STROKE SUBTYPES IN INDIA

There is not enough information on the proportion of ischemic and hemorrhagic strokes from India. *Table 3* gives the hospital based data of two common subtypes.

**Table 3 : Hospital based data of Stroke types : (1)**

Reference	Place	Number	Infarct( %)	Bleed (%)
Dubey1943-62	Agra	480	82.7	15.2
Padmavaty1954-59	Delhi	453	57.3	22.7
Gupta1957-60	Patiala	260	79.2	9.6
Bharucha1961-63	Mumbai	926	70.5	17.2
Naik 1961-65	Hyderabad	866	75.5	18.2
Misra 1961-65	Lucknow	454	82.5	13.6
Wadia 1974-75	Mumbai	216	25.7	26.3
Dalal 1963	Mumbai	127	72.5	17.3
Abraham 1967-72	Vellore	850	77.0	5.9
Nagaraja 1979-83	Bangalore	2279	77.0	7.5

Clinical bed side examination is not foolproof in identifying stroke subtype, there may be an error of 15-20% on bedside clinical diagnosis of stroke type. In the Stroke registry of Nizam's institute , Hyderabad<sup>10</sup> in which more than 1000 stroke patients were recruited, 85 % patients had ischemic stroke<sup>3</sup>. There are not many studies on this aspect. However, a few reports available show that 70-85 % stroke cases are of ischemic stroke. In the stroke registry of Nizam's 2000-01, all ischemic stroke patients were further classified as : (a) *large artery atherosclerosis* 41 %, (b) *cardioembolic* 44 %, (c) *lacunar* 15 %, (d) *cryptogenic* 10 %.

(b) lacunar infarcts 18 %, (c) cardioembolic 10%, (d) other determined 4 %, (e) undetermined 27 %<sup>3</sup>.

### INTRACRANIAL VS. EXTRACRANIAL DISEASE

The most notable difference from Western registries was the predominance of intracranial rather than extracranial location of large artery atherosclerosis. Among atherosclerotic ischemic strokes, many studies have shown that there are significant racial ethnic differences in the distribution of the atherosclerotic lesions. Chinese, Japanese, Hispanics and blacks have greater preponderance of intracranial atherosclerosis while whites have more cases of extracranial carotid disease. Both vascular involvement patterns are seen in India and this has been referred to many as "the Indian pattern". Whereas in the west <5% have intracranial disease, in Far East <5% have extracranial disease. On the other hand both types are seen in Indian patients.

In a study using MR angiography done prospectively in acute stroke patients Padma et al observed operable lesions (significant extracranial carotid stenosis) in only 11 % patients.

In a study of lacunar infarcts by Kaul et al<sup>12</sup> common risk factor included hypertension, Diabetes mellitus, smoking, cardioembolism and cryptogenic. However patients with lacunar infarcts have higher frequency of diabetes mellitus and absence of significant extracranial carotid disease. The presenting syndrome included : (a) Pure motor hemiparesis (45%), (b) Ataxic hemiparesis (18 %), (c) sensorimotor stroke (18%), (d) dysarthria, clumsy hand syndrome (14%)

This study suggests that the clinical spectrum of lacunar stroke in India is similar to that in western countries<sup>12</sup>.

### STROKE MORTALITY

According to WHO Survey in 1990, out of 9.4 million deaths in India 6,19,000 were due to stroke. Thus, mortality rate in India due stroke is 7.3/ 1,00,000. Thus, deaths due to stroke were 22 times higher than malaria, 1.4 times that due to tuberculosis, 4 times that due to rheumatic heart disease and almost equal to that of ischemic heart disease. In India, delayed hospital arrival is important factor<sup>13</sup> of all deaths 1-2 % is due to stroke<sup>14</sup>. These figures suggest that stroke mortality in India is 2-3 times higher compared to Caucasians lipoprotein ( ) in particularly important risk factor in young<sup>15</sup>. Indians have higher risk of dying from stroke than Caucasians. A study has shown that among Indian immigrants to UK and Wales men have 53% more and women have 25% higher risk of dying from stroke (Balgan, 1991). There is a need to initiate steps to collect data on stroke mortality and morbidity as a first step towards control measures.

### LONG TERM OUTCOME

No major studies are available from India to address the issues like post stroke disability, stroke recurrence, functional outcome, due to lack of rehabilitation care facilities.

### ROLE OF THROMBOLYTIC THERAPY IN ACUTE ISCHEMIC STROKE AND ITS FEASIBILITY IN INDIA

Not many trails have been reported from India about use of thrombolytic treatment in India. The reasons cited for the relatively

minimal use of thrombolytic therapy in India are its unaffordability and late arrival of patients in hospital. Prasad et al studied factors delaying hospital arrival of stroke patients. The median time from symptom onset to reaching casualty was 7.66 hours, with 25 % cases arriving in 3 hours and 49 % in 6 hours. Distance from the hospital, contact with local doctor and low threat perception of symptoms were independent factors associated with delay in arrival<sup>10</sup>. In a study by Nandigam et al<sup>16</sup>, a significant number of patients' who reached casualty within the therapeutic window and who were eligible for thrombolytic treatment, did not receive thrombolytic therapy. Hence measures are also required to increase awareness of the extent of the therapeutic window of stroke and the efficacy of thrombolytic treatment in primary care doctors as well<sup>8</sup>.

In a hospital based study by Pandian et al, relatives of patients with a history of stroke were interviewed to assess awareness of symptoms, risk factors and treatment of stroke. The knowledge regarding organ involved, etiology and treatment was lacking. Considerable education is needed to increase public awareness in modern concept of stroke treatment<sup>16</sup>.

### CONCLUSION

Stroke in India has certain specific problems. Stroke in young and venous infarct form an important subgroup. Apart from the usual risk factors, anaemia, rheumatic heart disease and habit of squatting are unique risk factors. As compared to western countries, outcome is poorer among Indian patients. More commonly intracranial block of the arteries and long segment involvement is unique to Indian patients.

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