EDITORIAL

Risk Factors for Coronary Artery Disease for Bangladeshis : Do They Differ from Western Population

South Asians particularly Bangladeshis, Indians and Pakistanis have the highest rate of coronary artery disease (CAD) compared to any ethnic group studied in different western countries[1,2]. Standardized mortality rate per 100,000 for CAD in these South Asian countries are alarming[3]. The CAD mortality is higher in south Asian men, by a factor of 1.4 in comparison to whites in England by 1.2 compared to whites and 3.3 compared to Chinese in Canada, 3.8 compared to Chinese in Singapore and 22.9 compared to blacks[3]. In Singapore CAD mortality in south Asians is almost four times higher compared to Chinese[4].

In England and Wales, coronary mortality was 36% higher in men and 46% higher in women born in south Asia aged 20-29 years than in the general population[5]. The relative risk of CAD in south Asian men is highest at early ages. In England, coronary mortality in men aged less than 40 years born in south Asia was more than twice the national average. The high coronary mortality is common in Gujarati hindus, Punjabi sikhs and muslims from Pakistan and Bangladesh[6]. The prevalence of silent ischaemic electrocardiographic abnormalities was higher in south Asians than in Europeans, 17% versus 12%[7]. In a recent comparative study of south Asian and white patients in UK, south Asians had a two-fold higher risk of admission with myocardial infarction and they had a two-fold higher risk of death over the ensuing six months[2]. So, it is clear that there is a disparity of CAD mortality between south Asians and whites in the UK. The excess risk of CAD in south Asians appears to be greater at younger ages. Compared to whites in the UK, the relative risk of CAD mortality in south Asians is 3.13 between the ages of 20 and 29 as opposed to 1.36 in all age groups[1]. In Singapore, the relative risk of CAD mortality in south Asians compared to Chinese is 12.5 in men aged 30-39 years compared to 3.0 in men aged 60-69. In an angiographic study of CAD in Malaysia, south Asians under 40 years of age had a 15-fold higher rate of CAD compared to Chinese and a 10-fold higher rate compared to Malays[8]. In patients referred for coronary angiography, the anatomical distribution of disease does not differ between south Asians and Europeans although the extent and severity of lesions are greater in south Asians. CAD among south Asians is known to be more severe and extensive and follows a malignant course[1].

The consistency of the high risk of CAD in south Asian populations around the world, affecting both sexes and with early onset, suggests a common underlying explanation, but the conventional risk factors, however, do not fully account for the excess of CAD among Bangladeshis, Indians and Pakistanis, suggesting that other risk factors may be more important[9]. The prevalence of high blood pressure, high cholesterol and cigarette smoking among the south Asians are similar to or lower than that in other populations[2]. Average serum cholesterol level among the south Asians is lower than those in whites, prevalence of hypertension is not higher than that in white Caucasians and smoking in south Asian patients is generally less common. Only one observational study showed higher smoking rate in Bangladeshi

men[9]. In population surveys, differences between south Asians and Europeans in smoking, blood pressure, serum cholesterol or haemostatic activity do not explain the high risk of CAD in south Asians[9-11]. Insulin resistance hypothesis provides a unifying explanation for the high rates of CAD in South Asians. Non-insulin dependent diabetes is present in about 20% of south Asian men and women aged over 40 years in UK, compared to about 5% of Europeans[9]. Most south Asian patients with CAD are not diabetic and glucose intolerance cannot alone explain more than a small proportion of excess CAD in south Asian people. It is now clear that the high prevalence of diabetes in south Asians is but one manifestation of a pattern of physiological disturbances related to insulin resistance in this group. On the basis of a study comparing Bangladeshi migrants to United Kingdom with native Europeans, it was suggested that a pattern of metabolic disturbances related to insulin resistance might underlie the high rates of CAD in South Asian people[5]. These physiological disturbances include hypertriglyceridaemia (TG), low concentration of high density lipoprotein cholesterol (HDL) and hyperinsulinaemia. The mechanisms underlying these associations even in non-diabetic patients are poorly understood[1,9]. The Southhall study concluded that average fasting and postload serum insulin, plasma triglycerides and waist-hip girth ratio were higher and high density lipoprotein cholesterol was lower in south Asian than in European men[10]. Association of high TG and low HDL as an independent predictor of CAD in non-diabetic patients have been reported in Bangladesh[12]. This form of dyslipidaemia is associated with a three-fold higher risk of CAD, irrespective of the level of low density lipoprotein (LDL)[1]. Abdominal obesity appears to be an independent and strong risk factor for CAD among south Asians indicating that even modest increases in body fat with central distribution may be potentially harmful from cardiac point of view. Most studies have shown reduced level of physical activity among south Asian population[1,11].

It is certain that individuals of south Asian descent (India, Pakistan and Bangladesh) have an increased risk of ischaemic heart disease compared to most other ethnic groups[13]. It is also established that conventional coronary risk factors like hypertension, smoking and high cholesterol level do not explain the very high prevalence of CAD among the South Asians[13,14].

A reduction in the risk of coronary artery disease in south Asians is likely to require different strategies from those recommended for the western population. Control of diabetes and treatment of hypertriglyceridaemia may have a real positive impact in prevention of CAD among the Bangladeshis. Control of abdominal obesity and increased physical activity are likely to be the most effective means of reducing the risk of CAD in South Asians if the insulin hypothesis is correct. The efficacy of weight reduction and physical training in reversing insulin resistance may be beneficial in prevention of CAD among the south Asians. Prevention of diabetes and coronary artery disease may require control of obesity and regular exercise to be maintained throughout life.

BAREN CHAKRABORTY
Associate Professor, Department of Cardiology
Bangladesh Medical College, Dhaka.

(J Bangladesh Coll Phys Surg 2000; 18 : 44-46)

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ORIGINAL ARTICLES

Progressive Muscular Dystrophies – A Study of 60 Cases

MM RAHMAN, FCPS[a], BA MONDOL, MD[b], AKMA HAQUE, FCPS[c]

Summary :

Sixty-two cases of progressive muscular dystrophies are reported here. They attended the Bangabandhu Sheikh Mujib Medical University (BSMMU) neurology outdoor during March 1997 to December 1998. Total number of patients attending the neurology outdoor during this period was 7909, i.e., 0.78% of the total outdoor patients were of progressive muscular dystrophy.

Of the 62 cases, limb girdle muscular dystrophy (LGMD) topped the list with 32 (51.62%) patients. Duchenne muscular dystrophy (DMD) was second with 19 (30.54%) cases. The age range of muscular dystrophy cases was six to 61 years. The mean (±SD) age of onset of first symptoms was 4.63 (±1.3) years in DMD patients and 20.05 (±6.48) in LGMD patients. Most of the patients belonged to Dhaka division (74%). Predominantly males (81.25%) suffered from LGMD diseases.

The predominant symptoms included difficulty in walking, delayed milestone, frequent falls, difficulty in standing from sitting and climbing stairs, muscle wasting and pseudohypertrophy in DMD patients. Common symptoms in LGMD patients were difficulty in walking, difficulty in standing and muscle wasting. Pelvic pectoral girdle muscles were commonly affected in most cases of DMD patients, while only pelvic girdle muscles were most frequently involved in LGMD patients.

(J Bangladesh Coll Phys Surg 2000; 18 : 48-54)

Introduction :

The muscular dystrophies are progressive hereditary degenerative diseases of skeletal muscles. The innervation of the affected muscle is sound[1]. Each type of muscular dystrophy has unique phenotypic and genetic features[2]. The clinical characteristics of muscular dystrophy began to be clearly defined during the last century. The patient with muscular dystrophy may present in various ways, but the weakness of gradual onset starting either in childhood or in adolescence is the commonest feature[3]. The study reported herein attempts to define the demographic and clinical characteristics of the disease. The information thus gathered may provide useful guide for further study.

Materials and method :

This study was carried out in the department of neurology, BSMMU, Dhaka, during the period of March 1997 to December 1998. As this neurology center is the only well organized center in Bangladesh, it is expected that patients from all over Bangladesh attend this center. So, picture of this study represents more or less that of the whole country. Patients attending the neurology outdoor were the subjects. Patients suspected of having progressive muscular dystrophies were selected for the study. After selection, partiuclars of each patient, detailed history and physical examinations were noted in a predesigned data collection sheet. At the same time, serum CPK, serum aldolase, nerve conduction velocity (NCV), electromyography (EMG) and muscle biopsy were done. Other laboratory tests, such as, complete blood count, Hb%, blood glucose, plain x-ray chest

a. Dr. Md. Matiur Rahman, Assistant Professor, Department of Neuromedicine, Sylhet MAG Osmani Medical College, Sylhet.

b. Dr. Badrul Alam Mondol, MD, Assistant Professor, Department of Neuromedicine, Mymensingh Medical College, Mymensingh.

c. Prof. Anisul Haque, FCPS, FRCP, PhD, Professor and Head, Department of Neuromedicine, Bangabandhu Sheikh Mujib Medical University, Dhaka.

Address correspondence to : Dr. Badrul Alam Mondol, 19/6 Sobhanbag Govt. Quarter, Sobhanbag, Dhaka

Received : Oct. 25, 1999 Accepted : April 29, 2000

P/A view, electrocardiography and echocardiography were done. A total of 68 patients are collected and after confirmation of diagnosis, six patients were excluded from the study.

Criteria for patient selection :

For Duchenne muscular dystrophy[4] the inclusion criteria were :

a) The patient must be male;

b) The patient must have the onset of weakness before the age of five years. If the boy had not been examined before the age of five, a history of the disease starting before that age was accepted, permitting the inclusion of patients seen for the first time in the latter stages of the illness;

c) The patient must have proximal weakness;

d) The patient must have increased serum creatinine kinase activity of at least 10 times the upper limit of normal at some stage of the disease.

Exclusion criteria were :

a) Patients with ptosis or weakness of extra ocular muscles;

b) Patients with skin rash suggestive of dermatomyositis,

c) Patients with normal muscle biopsy or muscle biopsy evident of denervation, glycogen storage disease, lipid storage disease or inflammatory myopathy;

d) Patients with normal electromyogram or with major evidence of denervation;

e) If there was any girl in the family who fulfilled the criteria for diagnosis (with obvious exception of criteria 'a').

For Becker muscular dystrophy[5] :

Patients must fulfill all the inclusion and exclusion criteria for DMD with exception of criteria 'b'. A patient was classified as having BMD if he was diagnosed later than age seven years, wheel chair dependent for past 15 years and still living without life support systems in his late 20's to mid 30's.

For limb girdle muscular dystrophy[6] :

Inclusion criteria :

a) Person of either gender with progressive, more or less symmetric, limb girdle weakness;

b) Anciliary investigations, including serum creatine kinase, EMG and muscle biopsy were compatible with primary myogenic disorder.

Exclusion criteria :

a) Congenital onset;

b) Ptosis or external ocular muscles;

c) Skin rash compatible with dermatomyositis;

d) Sensory abnormalities;

e) Severe facial weakness;

f) Distal weakness more than proximal; and

g) Signs of denervation, extensive cellular infiltration in muscle biopsy.

Clinical, serum enzymes, EMG and biopsy findings were used for diagnosis of other types.

Results :

Total number of patients from March 1997 to December 1998 attending the neurology outpatient department, BSMMU, was 7909. During this period, a total of 62 cases of progressive muscular dystrophy were found i.e., 0.78% of the total outdoor patients.

The most common form of muscular dystrophy was LGMD. Next common type was DMD. This is shown in Tale-I.

Age of the muscular dystrophy patients ranged from six to 61 years. The mean (±SD) age of onset of the first symptoms in DMD patients was 4.63 (±1.3) and in LGMD patients it was 20.05 ± (6.48) years.

Sex distribution showed male preponderance. All the DMD patients were male. Among the

LGMD patients, 26 (81.25%) were male and six (18.75%) female.

Maximum number of patients were from Dhaka division (Table-IV).

Out of 19 DMD patients, 12 showed X-linked recessive pattern of inheritance. No family history was found in seven patients. Out of 32 LGMD patients, 18 showed autosomal recessive pattern of inheritance. Fourteen patients had no family history of the disease.

The common manifestations of DMD were delayed milestone, frequent falls, and difficulty in walking and standing. LGMD patients presented with difficulty in walking and difficulty in climbing stairs. The common symptoms of muscular dystrophy patients are shown in Table-VI.

In DMD patients, both pelvic and pectoral girdle muscles were affected during presentation in the majority of cases. On the other hand, in case of LGMD, pelvic group of muscles were affected in most cases. The pattern of muscle involvement during presentation is shown in Table-VII.

Table-I

Different varieties of muscular dystrophies (n=62)

Type of muscular dystrophy	Number of patients	Percentage
Limb-girdle muscular dystrophy	32	51.62
Duchenne muscular dystrophy	19	30.54
Fascioscapulohumeral muscular dystrophy	04	06.55
Becker muscular dystrophy	03	04.84
Ocular myopathy	02	03.23
Myotonia dystropica	01	01.61
Congenital muscular dystrophy	01	01.61

Table-II

Age distribution of the patients of muscular dystrophy

Age groups (years)	Number of patients	Percentage
05-10	16	25.81
11-15	10	16.13
16-20	07	11.90
21-25	12	19.35
26-30	07	11.90
31-35	05	08.06
>35	05	08.06

Table-III

Sex distribution of muscular dystrophy patients

Type of muscular dystrophy	Male (%)	Female (%)	Total (%)
Limb girdle muscular dystrophy	26 (81.25)	06 (18.75)	32 (51.62)
Duchene muscular dystrophy	19 (100.0)	00 (00.00)	19 (30.54)
Fascioscapulohumeral muscular dystrophy	03 (75.00)	01 (25.00)	04 (06.55)
Becker muscular dystrophy	03 (100.00)	00 (00.00)	03 (04.84)
Ocular myopathy	01 (50.00)	01 (50.00)	02 (03.23)
Myotonia dystrophica	01 (100.00)	00 (00.00)	01 (01.61)
Congenital Muscular dystrophy	01 (100.00)	00 (00.00)	01 (01.61)
Total	54 (87.10)	08 (12.90)	62 (100.00)

Table-IV

Distribution of muscular dystrophy patients according to place of residence in different divisions (n=62)

Division	Number of patients	Percentage
Dhaka	46	74.19
Rajshahi	07	11.29
Chittagong	03	04.84
Sylhet	03	04.48
Barisal	02	03.23
Khulna	01	01.61

Table-V

The pattern of inheritance of muscular dystrophy patients

Type of muscular dystrophy	Autosomal dominant	Autosomal recessive	X-lined recessive	? New mutation
Limb girdle muscular dystrophy	00	18	00	14
Duchene muscular dystrophy	00	00	12	07
Fascioscapulohumeral muscular dystrophy	00	00	00	04
Becker muscular dystrophy	00	00	02	01
Ocular myopathy	00	00	00	02
Myotonia dystrophica	00	00	00	01
Congenital muscular dystrophy	01	00	00	00

Table-VI

Common presenting symptoms of muscular dystrophy patients (n=62)

Symptoms	DMD n=19	LGMD n=32	FSHD n=4	BMD n=3	OM n=2	MD n=1	CMD n=1
Difficulty in walking	18	32	00	03	00	00	01
Delayed milestone	19	00	00	00	00	00	10
Frequent falls	18	03	00	02	00	00	01
Difficulty in standing from lying position	18	30	00	03	00	00	01
Difficulty in climbing stairs	18	32	00	03	00	00	01
Mental retardation	04	00	00	00	00	00	00
Drooping of eyelid	00	00	00	00	02	00	00
Myotonia	00	00	00	00	00	01	00
Chair bound	01	00	00	00	00	00	00
Difficulty in combing hair	06	13	04	00	00	00	00
Muscle wasting	19	30	04	03	00	01	00
Swelling of muscles	15	00	00	03	00	00	00

Table-VII

Pattern of muscle involvement during presentation in muscular dystrophy patients (n=62)

Muscle group affected	DMD n=19	LGMD n=32	FSHD n=4	BMD n=3	OM n=2	MD n=1	CMD n=1
Only pectoral girdle	00	02	03	0	00	01	0
Only pelvic girdle	04	15	0	01	00	00	01
Distal muscles	00	00	00	00	00	00	00
Pelvic and pectoral girdle	15	11	00	02	00	00	00
Pelvic, pectoral and distal muscles	00	00	01	00	00	00	00
Focal muscles group	00	00	00	00	00	00	00
Facial muscle	00	00	04	00	00	01	00
Eye lid and extraocular muscles	00	00	00	00	02	00	00

Discussion :

DMD is the most frequent childhood muscular dystrophy[7]. The mean incidence is 1:4451 livebirths[8]. The estimated prevalence of LGMD in Netherlands is at least 0.81/100,000 population[6]. The prevalence of LGMD in Japan is 1.55 / 100.000 population[9]. These suggests that LGMD is a less common disease than DMD. On the other hand, this series shows that 32 of 62 cases were of LGMD, constituting about 51.62% of cases. It is due to the fact that neurology department mainly deals with adult patients and many cases of DMD do not even come to the notice of physicians. There were three cases of BMD, so the findings of the present study correlate well with observation of Mendel et al[10] that the BMD is approximately ten times less frequent than DMD. Myotonic dystrophy has an incidence of 13.5 per 100,000 livebirths[11]. But in the present series, there was only one myotonic dystrophy patient. Probably

myotonic dystrophy is an uncommon disease in this community. The mean (±SD) age of onset is 4.63±1.3. Similar findings was observed in Austrian DMD patients. Mean age of onset of their study children was 3.1±1.1 years[8]. Sex distribution in this study showed male predominance in LGMD patients, 26 of 32 patients. Just an opposite finding was reported in the study of Van der Kooi et al[6] and in a Duch study[12]. Most of the patients presented here were inhabitants of Dhaka division (74%). Dhaka division is the most populous and its district and Thana towns are well communicated with capital City.

In the present series, 18 out of 32 LGMD patients conform the pattern of autosomal recessive inheritance. Fourteen cases did not have any family history. Probably they represent new mutation. In the series of 105 cases of Van der Kooi et al, 42 were autosomal recessive, 34 sporadic and 29 autosomal dominant[6]. In the study of Skyring and Mckushick[13], out of 27 DMD patients, 23 belonged to X-linked recessive form and four non-X-linked. In this study, 12 (63.16%) cases were X-linked recessive and seven (36.84%) were probably due to new mutation. This findings correlate with the other studies. Approximately one third cases of DMD result from new mutation[14].

The common presenting symptoms in the present study were difficulty in walking, frequent fall, difficulty in standing from lying position, difficulty in climbing stairs and calf hypertrophy. This agrees with the findings of Vignos et al[15]. In the present study, 18 of 19 DMD patients had pseudohypertrophy of the calf muscles, which conforms to the findings of Mannan et al[16]. In the present series, out of 32 LGMD patients, 15 had only pelvic girdle involvement whereas 11 patients had both pectoral and pelvic gridle muscle involvement. On the other hand, majority of the patients had both pelvic and pectoral girdle involvement in the series of van der Kooi et al[6].

It may therefore be concluded that demographic and clinical pattern of progressive muscular dystrophy in this country is more or less similar to western countries.

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Journal of Bangladesh College of Physicians and Surgeons
Vol. 18, No. 2, May 2000

Clinical Presentation and Outcome of Hepatocellular Carcinoma

JC DAS, MD[a], AK AZAD, FCPS[a], SAA MAMUN, MBBS[a], MA FAIZ, FCPS[b], MR RAHMAN, FCPS[b], A GHOSH, MBBS[b], SR FARUQUE, MBBS[c], ZJ KHAN, DCH[b], M RAHMAN, MBBS[b]

Summary :

Forty biopsy proven cases of hepatocellular carcinoma (HCC) were included in this study to see their clinical presentation and outcome after the diagnosis. Patients were selected at random irrespective of age, sex, race and socio-economic condition. Detail history and physical findings were noted and patients were kept in follow up monthly for one year. The mean age was 49.15 years. The male-female ratio was 4:1. Common symptoms were anorexia in 38 (95%), malaise in 34 (85%), abdominal pain in 33 (82.50%) abdominal lump in 25 (62.50%) and weight loss in 23 (57.50%) patients. Common physical findings were hepatomegaly in 39 (97.50%), wasting in 30 (75%), ascites in 17 (42.50%), splenomegaly and jaundice each in 15 (37.50%) patients. Nine (22.50%) patients were dropped out from the follow up. All of remaining 31 (77.50%) patients died within six months of discharge from the hospital. Median survival period was 88 days (range : eight to 179 days). No significant difference was observed in terms of median survival in patients who received Tamoxifen (93 days) and in patients who did not (83 days).

(J Bangladesh Coll Phys Surg 2000; 18 : 55-60)

Introduction :

Hepatocellular carcinoma (HCC) is the most common primary malignant tumour of the liver[1,2]. It is one of the common cancers all over the world with an estimated annual incidence of 1,000,000[3]. Pockets of high, intermediate and low risk areas have been identified. HCC is very common is south Asia, China, Japan and Western Pacific regions and is believed to be the most common of all cancers in Sub-Saharan Africa. Though no epidemiological study on HCC has yet been conducted in Bangladesh, it can be presumed that the incidence of HCC should be high here.

The clinical manifestation of HCC varies from country to country. There is a considerable disparity of clinical manifestations in different geographical regions. Many putative factors e.g. age, sex, nutrition, aetiology of HCC, environmental cofactors, genetic predisposition, associated comorbid disease and availability of diagnostic and screening procedures can modify the clinical features of HCC in various geographical areas[4,5,6].

HCC occurs in particularly high risk populations like patients with cirrhosis, and HBV and HCV infections. Many of these patients can be screened by at least periodic ultrasonographic follow up so that patients can be detected at an earlier stage to offer the surgical resection as well as other practicable approach of therapy to prolong survival of the patients[7]. The facilities for screening high risk patients are absent in this country. Also there are little information about how patients of HCC present to the physicians and what is the outcome of HCC patients after the diagnosis. It is very important to know the clinical presentation and outcome of patients of HCC in a given population. This is particularly useful for the clinical diagnosis and for making a plan to manage the patients of HCC.

The aim of this study was to identify the common clinical presentation and to determine the outcome of patients of HCC after the diagnosis.

a. JC Das, MD, AK Azad, FCPS , SAA Mamun MBBS, Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka.

b. MA Faiz, FCPS, MR Rahman, FCPS, A Ghosh, MBBS, ZJ Khan, DCH, M Rahman, MBBS, Department of Medicine, Chittagong Medical College Hospital, Chittagong.

c. SR Faruque, MBBS, Department of Surgery, Sher-e-Bangla Medical College Hospital, Barisal

Address correspondence to : Jiban Chandra Das, MD, Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University, Dhaka

Received : Oct. 02, 1999 Accepted : April 29, 2000

Materials and method :

The study was conducted in Chittagong Medical College Hospital. The period of case selection was July 1994 to July 1996. Patients were selected at random irrespective of age, sex and socio-economic condition.

Initially, sixty cases of clinically suspected HCC were taken for the study. All of these cases were investigated by ultrasonography, measurements of α-fetoprotein and percutaneous needle biopsy. Finally, forty biopsy proven cases were included in the study. Detail history including major complaints, mode of onset, duration of illness and physical findings were recorded. Investigations done were complete blood count, PBF, BT, CT, liver function tests e.g. AST, ALT, serum bilirubin, alkaline phosphatase, serum total protein, albumin-globulin ratio, prothrombin time; blood urea, serum creatinine; viral markers-HBsAg; α-fetroprotein; x-ray chest P/A view, ultrasonography; and finally liver biopsy. The liver biopsy was done by tru-cut needle and histopathological slides were stained by H and E stain.

Majority of the patients were already at an advanced stage where surgical resection was impossible. Tamoxifen at a dose of 20 mg twice daily was prescribed in 20 patient. Remaining patients were managed symptomatically. Informed consents were obtained before putting the patients in each of the groups.

All patients were advised to attend the follow up clinic. Follow up schedule was monthly for 12 months for each patient. Communication was done by letters inquiring the condition of the patients in those who could not attend the follow-up clinic after three months of discharge from the hospital.

Results :

The age distribution is shown in Table-I. The peak age group was between 40 and 50 years which comprised of 20 (50%) patients. Most of the patients were between 31 and 70 years. The mean age was 49.15 years. The male-female ratio was 4:1. Twenty five (62.50%) patients presented between one and three months of illness (Table-II). Among them, 15 (37.50%) had duration of illness of one to two months. The commonest symptom was anorexia and was found in 38 (95%) patients, which was followed by malaise in 34 (85%), abdominal pain in 33 (82.5%), abdominal mass in 25 (62.50%), weight loss in 23 (57.50%), jaundice in 15 (37.50%), vomiting in 10 (25%) and fever in four (10%) patients (Table-III). Hepatomegaly was the commonest sign and was found in 39 (97.50%) patients (Table-IV). Other signs were weight loss in 30 (75%), ascites in 17 (42.50%), splenomegaly in 15 (37.50%) and jaundice in 15 (37.50%) cases. In 50% of cases liver was hard and tender.

Results of routine liver function is shown in Table-V. Serum bilirubin was raised in 14 (35%) patients. Ultrasonography revealed signs of mass lesion in 30 (75%) and multiple masses in 10 (25%) of the cases. AFP was raised (>20 ng/ml) in 23 (57.50%) patients. More than 500 ng/ml was found in 12 (20%) cases. HBsAg was positive in 14 (35%) patients.

Outcome of patients with or without therapy is shown is Table-VI. Nine (22.50%) patients were dropped out from the study because they did not attend the follow up schedule. Remaining 31 (77.50%) patients were reported dead within six months of discharge from the hospital. Five (16.13%) deaths occurred in the first month. Twenty seven (87.08%) died within four months. Median survival period was 88 days (range : eight to 179 days). No significant difference was observed between patients who received Tamoxifen and who did not in terms of survivability. Median survival period in patients who received Tamoxifen and who did not was 93 days (range : 16 to 179 days) and 83 days (range : eight to 179 days) respectively (p=0.26).

Table-I

Age distribution of patients with hepatocellular carcinoma (n=40)

Age in years	Number of patients	Percentage	Mean age (years)
11-20	01	02.50	
21-30	02	05.00	
31-40	05	12.50	49.15
41-50	20	50.00	
51-60	05	12.50	
61-70	05	12.50	
71-80	02	05.00	

Table-II

Duration of Illness of patients with hepatocellular carcinoma (n=40)

Duration in months	Number of patients	Percentage
0 to 1	02	05.00
1 to 2	05	12.50
2 to 3	10	25.00
3 to 4	04	10.00
4 to 5	03	07.50
5 to 6	05	12.50
6 to 12	01	02.50

Table-III

Symptoms of hepatocellular carcinoma (n-40)

Symptoms	Number of patients	Percentage
1. Anorexia	38	95.00
2. Malaise	34	85.00
3. Abdominal pain	33	82.50
4. Abdominal fullness	29	72.50
5. Abdominal mass	25	62.50
6. Weight loss	23	57.50
7. Constipation	20	50.00
8. Jaundice	15	37.50
9. Leg swelling	12	30.00
10. Vomiting	10	25.00
11. Fever	04	10.00
12. Dyspnoea	04	10.00
13. Haematemesis	01	02.50

Table-IV

Physical signs of patients with hepatocellular carcinoma (n=40)

Signs	Number of patients	Percentage
Hepatomegaly	39	97.50
Weight loss	30	75.00
Ascites	17	42.50
Splenomegaly	15	37.50
Jaundice	15	37.50
Palmar erythaema	10	25.50
Clubbing	07	17.50
Oedema of legs	05	12.50
Spider angioma	03	07.50
Testicular atrophy	03	07.50
Signs of metastasis	08	20.00

Table-V

Result of liver function tests (n=40)

Name of the test	Normal (%)	Abnormal (%)
Serum bilirubin	26 (65.00)	14 (35.00)
A.L.T. (S.G.P.T.)	32 (80.00)	08 (20.00)
A.S.T. (S.G.O.T.)	30 (75.00)	10 (25.00)
Serum alkaline phosphatase	32 (80.00)	08 (20.00)
Serum albumin	26 (65.00)	14 (35.00)
Prothrombin time	31 (77.50)	09 (22.50)
α-fetoprotein (>20 ng/dl)	17 (42.50)	23 (57.50)

Table-VI

Survival of patients of hepatocellular carcinoma after diagnosis (n=31)

Death of patients	Number of patients	Percentage
In first month	05	16.15
In second month	08	25.80
In third month	10	32.25
In fourth month	04	12.90
In fifth month	02	06.45
In sixth month	02	06.45

Discussion :

In this study, the mean age was 49.15 years. Majority of the patients (50%) presented between 40 and 50 years of age. Age of onset in this study is consistent with other studies conducted in this country and in India[8,9]. Age of onset varies in different parts of the world. Patients of south Asian and African countries present in an earlier age with peak incidence in third to fifth decades of life[9-11]. Patients from low prevalence area like northern Europe and USA present in relatively older age. The findings that majority of patients here presented between 30 and 50 years is consistent with other studies conducted in high prevalence area reflecting that people of this area are affected at much earlier age.

The male to female ratio in this study was 4:1. Previous studies reflected a similar male-to female ratio in Bangladesh and India[8,9]. The male-female ratio ranges from 4:1 to 8:1 in high prevalence areas[8] suggesting that HCC in high prevalence area is a male predominating carcinoma. It is not clear whether male preponderance of HCC reflects increased susceptibility of men to the tumour or their greater exposure to the environmental risk factors (e.g. HBV infection) for HCC[12,13]. It is also true that male population in this country have more access to medical care in comparison to females.

The duration of illness in patients of HCC varies from 15 days to 12 months. In this study, most patients (62.50%) had the duration of illness between one and three months at presentation. Only one patient presented with more than six months duration. Vague complaints were not considered in this regard. There are very few reports from Bangladesh regarding the duration of illness in HCC. Most series from other countries reported a three to six months median survival after the onset of symptoms[14-17]. In some patients, the duration of illness is usually longer. This may be due to associated cirrhosis in those patients.

The most common presenting symptoms were anorexia, general malaise, abdominal pain, fullness of abdomen, abdominal mass, weight loss and constipation. Physical signs in this study were palpable liver, 50% of them were tender and hard and 40% had irregular surface, bruit was present in 25% of cases. Other physical signs were wasting, jaundice and splenomegaly. Ascites detected clinically and in addition by ultrasonography in 42.50% of cases. Surprisingly, peripheral signs of chronic liver disorder were less. With little variations, these are consistent with findings of other studies conducted in this country[8,9]. The features are also similar in African countries. In Japan, major clinical symptoms were malaise and other vague symptoms rather than abdominal pain and lump.

There is a considerable variation of clinical picture in different geographical regions[4]. In this study, most of the patients had abdominal pain and hepatomegaly with nodular surface and hard consistency. This is far advanced stage of the disease which is beyond the scope of surgical resection. In developed countries like USA, Japan and Hong Kong, most patients present with vague symptoms rather than abdominal pain and hepatomegtaly. This difference depends on the availability of very effective screening procedures like ultrasongraphy and α-fetoprotein estimation in high risk groups e.g. in patients with cirrhosis.

Upto the end of this study, 31 (77.50%) cases were reported dead, 29 (93.55%) within four months of discharge from the hospital (majority of death occurred in second and third months, 29.03% and 35.48% respectively). Median survival period was 88 days. Nine (22.50%) patients dropped out from the follow up. Though the course of HCC varies from case to case[18,19], according to therapeutic modalities, it usually runs a rapidly fatal course[20-23]. In 83.50% of patients, death occurred within six months of the onset of symptoms. Almost all patients with fully evolved presentation die within one

year[18]. This down hill course is mostly due to the fact that most of the patients with HCC present to physician in an far advanced stage and this is when the patient presents with recognizable symptoms and signs like abdominal pain and mass. This is particularly true for the developing countries. No significant differences was observed in terms of survivability between patients who received Tamoxifen and who did not. In this study, therefore, the therapy with Tamoxifen failed to show increased survivability.

In conclusion, it can be stated that pateints of this common male predominating malignancy in this country present in an advanced stage which is beyond the scope of any definitive therapy and most of them die within a few months of diagnosis of HCC. Information gathered from this study may be utilized for the clinical suspicion of HCC. It also can be realized from this study that the main option regarding the therapeutic utility resides in the prevention of the disease.

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Journal of Bangladesh College of Physicians and Surgeons
Vol. 18, No. 2, May 2000

Fine Needle Aspiration Cytology in the Diagnosis of Breast Lump

MG MOSTAFA, MPHIL[a], S CHIEMCHANYA, MD[b]

Summary :

An audit of the breast lump aspirates received from January 1996 to December 1996 from patients sent to the Cytology Division, Department of Pathology, Ramathibodi Hospital by their physician was done. The aim of this retrospective study was to determine the pattern of diseases that commonly present with breast lump and to evaluate the accuracy of fine needle aspiration cytology (FNAC) in the diagnosis of breast lumps. An excision biopsy was available in 86 cases for comparison of the cytological findings with the histopathology. The predominant lesions were benign : fibrocystic disease (70%) and fibroadenoma (25%). The predominant malignant lesion was duct cell adenocarcinoma (90%). The sensitivity and specificity of FNAC were 92.6% and 100%.

(J Bangladesh Coll Phys Surg 2000; 18 : 61-65)

Introduction :

Fine needle aspiration cytology (FNAC) has gained popularity as a procedure for diagnosing breast lesions. Numerous authors have reported their experience in applying diagnostic FNAC[1-4]. In the western literature, it has already been established that FNAC of the breast is an easily performed outpatient diagnostic method for determining the nature of breast masses. The advantages of FNAC are many while the disadvantages are few[3]. In Bangladesh, FNAC of breast is gaining popularity too because of its simplicity, good tolerance by the patients, rapidity, cost-effectiveness and safety. Its acceptance and success will stand or fall, firstly on its diagnostic efficacy and secondly on its cost effectiveness in relation to the standard methods of management of a breast mass. In a study in USA conducted by Kaminsky, it was found that the use of FNAC may reduce the cost of diagnosis by as much as 90% compared to hospitalization and excision biopsy[5]. The quality of FNAC depends on many factors, including the performance of the aspirator, the microscopic examination and the patient population[6]. Reliability depends on the availability of well-equipped and well-trained department of cytopathology and varies from one place to another. Training and experience are important in performing and interpreting FNA specimens. Every centre should have their own evaluation of reliability and limitations on performing FNA of breast lump.

This paper reports a series of 239 FNAC of breast lumps that were evaluated over a period of one year at Ramathibodi Hospital of Mahidol University. The aims were 1) to determine the pattern of breast diseases and 2) to evaluate the accuracy of FNAC in the diagnosis of breast lump.

Materials and method :

This is a retrospective study with 239 consecutive FNAC of palpable breast lesions. These specimens were received in the cytology division of the department of pathology of Ramathibodi Hospital, Mahidol University, Bangkok, Thailand during a one-year period (January to December 1996). Subsequent H and E stained slides of tissue sections of standard surgical specimens of breast lesions were obtained in 96 cases.

a. Mohammad Golam Mostafa, M.Phil, Associate Professor, Department of Pathology, Institute of Child and Mother Health, Matuail, Dhaka

b. Dr. Suetrong Chiemchanya, MD, Cytopathology Division, Department of Pathology, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Address correspondence to : Mohammad Golam Mostafa, M.Phil, Associate Professor, Department of Pathology, Institute of Child and Mother Health, Matuail, Dhaka

Received : Oct. 26, 1999 Accepted : March 02, 2000.

The results of cytological examinations of the aspirated specimens were compared to histopathological examinations of tissue sections of 86 standard surgical biopsies. In the remaining 10 cases the cytological material was unsatisfactory. These were not included in this study.

FNAC was performed in an outpatient setting for general surgical and gynaecological services. Several physicians performed aspirations. The FNAC specimens were interpreted by two trained cytopathologists.

The technique of aspiration was straightforward. The area of suspicion was identified and fixed with the fingers of the aspirator's nondominant hand. The skin was then cleansed with an alcohol swab. Using a 5 ml disposable syringe with a 23-gauge 1.25 inch needle, the skin was pierced. Continuous suction was achieved by withdrawing the plunger of the syringe and maintaining this suction throughout the procedure. Several passages into the lesions were made while maintaining continuous suction. The needle was withdrawn after the suction pressure was released and the aspirated material was then expressed into a glass slide. The material was spread between two glass slides. The slides were stained by Papanicolaou's stain

The authors reviewed the Papanicolaou stained cytology slides and the available histopathology slides before consensus diagnosis was made for every case. The outcomes were compared.

The satisfactory smears were classified into benign, malignant and atypical groups. In the benign group, there were six pathological patterns i.e. fibrocystic disease, chronic abscess, fibroadenoma, fat necrosis, duct ectasia and duct papilloma.

In the malignant group, the majority of cases was ductal adenocarcinoma NOS; there were a few medullary carcinoma and melano-carcinoma.

Duct cell adenocarcinoma was diagnosed when a very cellular smear contained an abundance of single population cells, arranged in poorly cohesive groups. Many of the single lying cells showed cellular and nuclear pleomorphism. Cellular pleomorphism meant that the cells showed variation in cell and nuclear size and shape, enlarged nuclei, coarse irregular chromatin, prominent or macronucleoli, single cell necrosis and mitotic figures including atypical forms. Irregular nuclear membranes and cytoplasmic secretory vacuoles were seen in some of the cases.

Medullary carcinoma was diagnosed when a cellular smear contained an abundance of markedly pleomorphic cells. The cells were arranged in a diffuse syncytial pattern without gland formation or secretory vacuoles. A prominent lymphoplasmacytic infiltration was seen.

Fibrocystic disease was diagnosed when the cellularity was less abundant with smaller sheets of cells and a few naked nuclei. A stromal component was seen in some and was absent in others. Histiocytes were usually present, sometimes only a few.

Fibroadenoma was diagnosed when abundant cellular material with larger antler shaped sheets of cells and many naked nuclei in the background were present. Myxoid appearing background with a stromal component was present. A dual population of epithelial cells was noted, ductal cells and myoepithelial cells.

Chronic abscess was diagnosed when numerous polymorphs mixed with many degenerated macrophages were seen.

In fat necrosis, cellular material containing "ghost adipocytes", large foamy macrophages, some of which were be multinucleated, were found in a background of inflammation and sheet like cholesterol crystals depending upon the duration of the lesion.

Duct ectasia showed poorly cellular material containing a few small, cohesive sheets or crowded groups of ductal cells, perhaps with slight reactive or degenerative changes with "foamy" macrophages. Granular debris was

seen in the background. Mixed acute and chronic inflammatory exudate was present.

In duct papilloma, moderate cellular material containing three dimensional papillary clusters with fibrovascular core was seen. There was good intercellular cohesion. A few myoepithelial cells with naked bioplar nuclei were seen.

Extremely hypocellular material with regard to epithelial cells or blood stain to an extent that all other elements were obscured were grouped as unsatisfactory.

Hypercellular specimen with an admixture of regular cells and others with abnormal nuclear and cytoplasmic features failling short of a firm diagnosis of malignancy were grouped as atypical.

Results :

A total 239 aspirates were included in this study. Of those, 29 (12%) were unsatisfactory. The age of the patients ranged from 20 to 73 years, with a mean of 44 years.

The results of FNA of breast are summarized in Table-I. Thirty one specimens were diagnosed as showing malignant disease. Of these, 29 were duct cell adenocarcinoma, one medullary carcinoma and one metastatic melanocarcinoma.

One hundred seventy six specimens were diagnosed as benign disease of which 154 were of fibrocystic disease (Table-II). One case was diagnosed as fat necrosis, which was subsequently proved to be malignant. One case diagnosed cytologically as fibroadenoma was proved by histology to be a malignant phylloides tumour. These two cases constituted the false negative cases.

A cytohistological correlation was possible in 86 cases (Table-IV).

Statistical analysis of the results was done using a binary 2 x 2 table (Table-IV). Sensitivity is defined as the probability that the test will be positive when malignancy is absent. In this study there was no false positive result. The positive predictive value is defined as the probability that the disease is present when the test is positive. Negative predictive value is defined as the probability that the disease will be absent when the test is negative. Accuracy is calculated from sum of true positive and true negative cases out of the total number of cases.

Table-I

Cytodiagnosis of 239 aspirates of breast lump

Diagnosis	Number	Percentage
Benign	176	73.64
Malignant	31	12.97
Unsatisfactory	29	12.13
Atypical	03	01.26
Total	239	100.00

Table-II

Cytodiagnosis of the benign breast lumps

Diagnosis	Number	Percentage
Fibrocystic disease	154	87.50
Chronic abscess	10	05.68
Fibroadenoma	08	04.54
Duct papilloma	02	01.04
Fat necrosis	01	00.57
Duct ectasia	01	00.57
Total	176	100.00

Table-III

Cytodiagnosis of the malignant breast lesions

Tumour	Number	Percentage
Duct cell adenocarcinoma	29	93.54
Medullary carcinoma	01	03.23
Melanocarcinoma, metastatic	01	03.23
Total	31	100

Table-IV

Histocytological correlation of 86 cases

Cytodiagnosis	Histodiagnosis		Total
	Malignant	Benign	
Malignant	25	00	25
Benign	02	59	61
Total	27	59	86

Table-V

Evaluation of accuracy of FNAC

Parameter	Calculation	Percentage	95% CI
Sensitivity	25/25+2	92.60	74.2, 98.70
Specificity	59/59+0	100.00	32.4,100
Positive predictive value	25/25+0	100.00	33.4,100
Negative predictive value	59/59+2	96.70	87.6, 99.4
Efficiency	25+59/25+59+0+2	97.70	

Discussion :

Numerous indications for FNAC of breast could be listed even though some of the workers opined that there is essentially no contraindication, but in essence, they usually boiled down to one key question : is the lump benign or malignant ? The FNA report should give as clear and concise an answer to this question as possible.

In this study, out of 27 malignant breast lesions, 25 were correctly diagnosed as malignant. All the cytologically diagnosed benign lesions were proved to be benign on histology. Three patients were diagnosed cytologically as atypical smear. These patients were followed up for six months without any change of the lesion. The patients were then lost. False negative diagnosis was made in two patients. In one case the material was not actually adequate and the presence of necrosis with polymorphs and foamy macrophages was interpreted as fat necrosis. On histology section, this tumour was found to incorporate extensive areas of necrosis. The necortic area was most probably the area which was sampled. The other case was a malignant cystosarcoma phylloides. The smear was diagnosed as a fibroadenoma. The malignant stromal component was not

present in the smear. Stromal tissue can not usually be aspirated with ease.

There was no false positive diagnosis in this series of 239 breast FNA studies. This indicates that an experienced cytopathologist can indeed eliminate false positive (alpha error), thereby strengthening the clinician's trust in a positive breast cytology diagnosis.

Among the patients with unsatisfactory cytology (Table-I), nine of the 29 patients underwent surgical biopsy. Of these nine cases, six were negative for malignancy and three were positive for malignancy. The remaining 20 cases were lost to follow up. All three cases with suspicious cytological findings were proved to be atypical epithelial hyperplasia on subsequent histological findings.

Overall diagnosis efficiency of FNAC in this series was 97.67% (84 of 86). Girad[7] and Zarbo[8] calculated a statistics (sensitivity 92.5%, specificity 99.8%, positive predictive value 99.7%, negative predictive value 94.2% and accuracy 96.5%) from a summary of 18 reported studies of 988 pathologists from 294 institutions. This study results compared quite favourably with the diagnostic accuracy cited by Zarbo[8] and Grant[9].

In conclusion, FNAC is a very sensitive and specific diagnostic tool for the assessment of breast masses. The routine use of FNAC would greatly reduce the number of unnecessary biopsies and frozen sections for histopathological evaluation.

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Journal of Bangladesh College of Physicians and Surgeons
Vol. 18, No. 2, May 2000

Gluteus Maximus Myocutaneous Flap for Closure of Large Sacral Sores in Paraplegic Patients

SH KHUNDKER, FCPS[a], MA KALAM, FCPS[b]

Summary :

Sacral pressure sores in paraplegic patients due to trauma to the spinal cord is a difficult problem to deal with and more so in the developing countries where opportunities are very limited. Gluteus maximus myocutaneous flaps are of value in the surgical closure of large sacral sores. Eighteen cases were operated upon in plastic surgery unit of Rehabilitation Institute and Hospital for the Disabled (RIHD), Dhaka between September '89 and September '93. All the patients were kept under follow up for four years. Results were encouraging in terms of recurrence with an overall success rate of 100%. Complications in terms of infection, partial wound breakdown and flap loss were insignificant. Morbidity was significantly reduced.

(J Bangladesh Coll Phys Surg 2000; 18 : 66-69)

Introduction :

Many theories have been put forward between the period 1749 and 1940 on the aetiology of the pressure sores without much attention to its treatment[1]. Charcot in 1879 was of opinion that nerve injury caused the release of neurotrophic factors which resulted in tissue necrosis. Leyden in 1874 and Munro in 1940 stated that loss of both sensation and autonomic control resulted in a decrease in peripheral reflexes that predisposed to skin ulceration. But Brown Sequard in 1853 stated his belief that pressure and moisture played a key role in the aetiology of pressure sores. However, the assertions of Charcot and Munro overshadowed others, thinking during this period[2]. These various theories regarding aetiology of pressure sores dominated the general thinking during this period and gave little hope for any successful treatment.

a. Dr. Shafquat H. Khundkar, FCPS (Surgery), FICS (Plastic), Associate Professor, Plastic Surgery, Rehabilitation Institute and Hospital for Disabled (RIHD), Sher-e-Bangla Nagar, Dhaka-1207.

b. Dr. Md. Abul Kalam, FCPS, Medical Officer, Plastic Surgery unit, RIHD, Sher-e-Bangla Nagar, Dhaka-1207

Address correspondence to : Dr. Shafquat H. Khundkar, FCPS (Surgery), FICS (Plastic), Associate Professor, Plastic Surgery, RIHD, Sher-e-Bangla Nagar, Dhaka-1207

Received : Oct. 01, 1999 Accepted : Jan. 06, 2000

It has now become an axiom that in addition to neuropathic factor and shearings forces, the single most important factor in the aetiology of pressure sores is ischaemic necrosis resulting from sustained excessive pressure against bony prominences[3]. Pressure which is unrelieved for a period of one to twelve hours is the major aetiological factor. It is estimated that in supine position, sacrum is subjected to maximum pressure in the range of 40 to 60 mm of Hg. Poor nutritional status, infection, starvation and disturbed metabolic states were other contributing factors for the causation of pressure sores.

The surgical management of pressure sores found popularity during World War-II when large number of paraplegic patients were rehabilitated in an organized fashion[4,5]. Most surgeons gave credit to the concept of using flap coverage of pressure sores to provide bulky and well padded skin coverage over the bony prominences. First report of the surgical closure of pressure sores under antibiotic coverage came out in 1945.

Ger in 1971 introduced the principle of transposing adjacent muscle flaps into the defects of pressure sore followed by application of split thickness skin graft over the muscle[6]. Recently, myocutaneous flap have been used for coverage of the defects of pressure sores in which overlying skin is

supplied by perforating arteries through the muscle.

The present study used bilateral gluteus maximus myocutaneous flaps based on the superior and inferior gluteal vascular pedicles to slide horizontally to cover the defect over the sacrum in a V-Y advancement. The potential disadvantage of this flap is that the resultant suture line lies directly over the sacrum in lthe midline.

Materials and method :

Eighteen cases of large sacral pressure sores were treated with horizontal sliding of the gluteus maximus myocutaneous flaps in the plastic surgery unit of the Rehabilitation Institute and Hospital for Disabled (RIHD) between September '89 and September '93 with a four year follow up.

Excision of the ulcer was done in such a way so as to make the resultant defect into a broad vertical ellipse. It includes excision of all the scarred tissue, surrounding scar tissue bursae and calcified soft tissues well down to healthy looking tissue. The bony prominences along with osteophytes were osteotomised and the irregularities resulting from the ostectomy were smoothed with a rasp to have an evenly contoured sacrum. Proper haemostasis was ensured. The flap outline was planned as to size and orientation of the excised area.

Gluteus maximus muscle receives its blood supply from three sources, superior and inferior gluteal arteries and the first branch of the profunda femoris artery. There are a large number of intercommunications among these three arteries within the muscle and the overlying skin is capable of surviving on any one of these three sources alone. The superior and inferior gluteal arteries were identified using posterior superior iliac spine, greater trochanter of the femur, ischial tuberosity and the sacrum as surface landmarks.

The gluteus maximus muscles were freed from their attachments along the sacrum and from the gluteus medius, preserving the superior and inferior gluteal neurovascular bundles. The inferior portion of the muscle was freed along the sacrotuberous ligament. The distal attachment along the gluteal tuberosity of the femur may or may not be divided. Once the muscle was freed, it was advanced medially for upto 10 cm each side to allow coverage of the entire sacrum[7]. The overlying skin was designed as a V-Y advancement, with its base along the sacrum and its sides along the superior and inferior border of the gluteus maximus, converging on its insertion in the greater trochanter. The wound was closed primarily in layers with low negative suction drains. The drains were left in situ until drainage was less than 10 ml in 24 hours.

The age of the patients ranged from 25 years to 60 years with a mean age of 35.25 years. All were male paraplegic patients. The cause of paraplegia was traumatic injury to the spinal cord.

Of the 18 cases, in three cases the wounds were initially closed by split thickness skin graft which broke down with recurrence of the pressure sore, requiring coverage with a flap. The rest fifteen cases were infected open sores with exposed sacrum. All patients were prepared with nutritional support, anaemia was corrected by blood transfusion and wounds were freed from infection by antibiotics according to culture sensitivity tests and by daily dressings. Horizontal dimension of the defect after the surgical excision of the sores were 10 cm to 12 cm in two cases, 12 cm to 18 cm in twelve cases and more than 18 cm in four cases (Table-I).

Table-I

Horizontal dimension of the defect

Horizontal dimension	Number of cases (%)
10 cm to 12 cm	02 (11.11)
12 cm to 18 cm	12 (66.67)
12 cm to 18 cm	04 (22.22)

All flaps had minimum medial advancement of 5 cm, two of them had medial advancement between 5 cm and 6 cm and twelve between 6 cm and 9 cm. Four flaps had medial advancement between 9 cm and 10 cm (Table-II).

Table-II

Medial advancement of flaps

Medial advancement	Number of cases (%)
5 cm to 6 cm	02 (11.11)
6 cm to 9 cm	12 (66.67)
9 cm to 10 cm	04 (22.22)

Complications were measured in terms of flap loss and recurrence of the pressure sores. Underlying haematoma and mild to moderate infections were sporadic and of little significance. There was no flap loss in this series. Only two patients (11.11%) had suffered from medial marginal flap necrosis resulting from excessive tension in closure, underlying haematoma and florid infection. These two patients were salvaged by excising the necrosed margin and further advancement of the flap and closure of the wound with secondary sutures after control of infection. All patients were kept under follow up for four years and no recurrence was evident during this period (Table- III).

Table-III

Complications in terms of flap Loss

Flap loss	Number of cases (%)
No flap loss	16 (88.89)
Medial marginal necrosis	02 (11.11)

Results :

Sixteen patients (88.89%) had good results with excellent flap adhesion and no flap loss. Two cases (11.11%) had medial marginal flap necrosis which were salvaged subsequently and were taken to be acceptable (Table- IV).

Sustained pressure on skin and underlying tissues particularly against bony prominences produce significant compromise to their circulation which may lead to a vascular necrosis if left for prolonged periods.

Table-IV

Results of reconstruction

Results	Criteria	Number of cases (%)
Good	No flap loss Excellent flap adhesion	16 (88.89)
Acceptable	Marginal flap necrosis Salvageable	02 (11.11)
Poor	Major flap loss Not salvageable Alternate procedure required	Nil

Discussion :

Sacral pressure sores are the common acute "sores" seen in patients confined to bed during medical and surgical emergencies where the patient is comatose and particularly common in patients with paraplegia. Most of these patients are found to have been nursed in supine position without timely and adequate change of posture because of ignorance and callousness. The sacral and trochanteric areas are very prone to such pressure and are always at risk of developing pressure sores in the paraplegics.

The surgical principles in the treatment of sacral pressure sores include total excision of the ulcer, complete removal of all infected bones, careful haemostasis and closure of the wound with well vascularized flap[8-12]. Appropriate low negative suction drainage with obliteration of all potential "dead spaces" is mandatory.

Remirez et al described the sliding gluteus maximus myocutaneous flap to cover the sacral sore in ambulatory patients[13]. Out of his 30 cases, 25 cases (83.33%) were termed as good, three (10%) had medial marginal flap necrosis and two (6.67%) had recurrence with subsequent flap breakdown. Conway et al described the surgical closure of the pressure sores with various types of superiorly and

inferiorly based fascio-cutaneous flaps[14]. Out of their 50 cases, 35 cases (70%) were termed as good, ten (20%) had partial flap necrosis and five (10%) had recurreence. Griffith et al described the surgical closure of the sacral pressure sore with various techniques other than gluteus maximus myocutaneous flap e.g. superiorly or inferiorly based skin flaps. But they had a recurrence rate of 44% at four years after surgery[15].

In the present study of surgical closure of the sacral pressure sore with horizontal sliding of gluteus maximus myocutaneous flap, out of 18 cases 16 (88.89%) had good results and two cases (11.11%) had medial marginal flap necrosis which were satisfactorly salvaged. There was no recurrence at four years after the surgical closure. Thus an overall success rate of 100% was attained in this study as compared to Remirez et al (93.33%), Conway et al (90%) and Griffith et al (56%).

The problem of large sacral sore coverage particularly in young paraplegic patients can be safely overcome by using bilateral gluteus maximus myocutaneous flaps with significant reduction in morbidity. However, because the flap is asensate the ritual of postural change needs regular attention.

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REVIEW ARTICLE

(J Bangladesh Coll Phys Surg 2000; 18 : 70-78)

Applications of Medicinal Plants in the Treatment of Tropical (Particularly Protozoal) Diseases

MA FAIZ, FCPS[a], D MANTLE, PhD[b], AT PICKERING, PhD[c]

Introduction :

Parasitic protozoal diseases are widespread in developing countries and constitute a major cause of morbidity and mortality. A number of problems have become apparent in the use of synthetic drugs to treat these diseases, including the development of drug resistance and high cost, which has stimulated interest in the development of medicinal plant based treatments. In this paper, some of the recent research into the development of medicinal plant based treatment for the major protozoal diseases, malaria, trypanosomiasis, schistosomiasis, leishmaniasis, filariasis and amoebiasis, as well as medicinal plant based treatments for snake envenomation are reviewed.

Malaria :

Malaria is one of the most widespread and devastating parasitic diseases affecting man, with an estimated 300-500 million cases per annum worldwide (approximately 90% of which occur in the African continent), resulting in up to three million deaths per annum. Malaria is a vector born disease transmitted by the female Anophelid mosquito and results from infection by protozoal Plasmodium species, which localise in the host liver or erythrocytes (according to specific life cycle stages). *Plasmodium falciparum* is considered to be the most dangerous strain, because of the widespread and unpredictable clinical presentation and potential severity. Diagnosis in the field relies mainly on clinical assessment, with confirmation of *Plasmodium falciparum* by microscopic examination of blood films. New clinical definitions recognize three categories of malaria, namely uncomplicated malaria, treatment failure malaria and severe malaria; the severe form can account for up to 50% of cases in some geographical areas, and can result in rapid death (particularly cerebral malaria) from severe anaemia and multiple organ failure (especially renal/liver failure). For more than three hundred years, there has been reliance on the use of extracts from the bark of Cinchona species, or modern synthetic secondary derivatives, to treat malaria. The development of resistance to chloroquine (and more recently quinine), originally in *Plasmodium falciparum* and later in other species, together with the relative failure of malaria/vector eradication programmes, has stimulated a search for new anti-malarial chemotherapeutic agents. The high reliance traditionally placed on medicinal plants as a source of such agents in developing countries has led to a systematic search of native cultures[1]; anti-malarial activity has been reported in the flora from Madagascar (239 species)[2], the Roraima region of Brazil (90

a. Md. Abul Faiz, Department of Medicine, Chittagong Medical College, Chittagong.

b. David Mantle, Medicinal Plant Research Centre,University of Newcastle upon Tyne, Newcastle upon Tyne, NE1 7RU.

c. AT Pickering, Medicinal Plant Research Centre,University of Newcastle upon Tyne, Newcastle upon Tyne, NE1 7RU.

Address correspondence to : Dr. D. Mantle, Neurochemistry Department, Regional Neurosciences Centre, Newcastle General Hospital, Newcastle upon Tyne, NE4 6BE, UK.

Received : April 12, 2000 Accepted : May 07, 2000

species)[3], the Amazonian region of Brazil (41 species)[4] and Tanzania (five species)[5]. The mechanism of action of most of the above remains to be determined; however, further studies on one species identified from the Roraima region, *Bidens pilosa (Asteraceae)* have been carried out. Ethanol or chloroform extracts of whole plant, leaves or roots, at a concentration of 50 µg/ml inhibited *Plasmodium falciparum* growth by up to 90% in vitro, and a partial reduction of *Plasmodium bergei* parasitaemia loads in mice. Further HPLC analysis of the above extracts correlated anti-malarial activity with the presence of aliphatic acetylene compounds such a 1-phenyl-1, 3-diyn-5-en-7-ol-acetate[4]. Roemrefidine, an aporphine alkaloid isloated from the stem bark of the Bolivian vine *Sparattanthelium amazonum*, has recently been shown to have activity against both resistant and sensitive strains of *Plasmodium falciparum* in vitro, and *Plasmodium berghei* in mice. There was no evidence of cytotoxic activity of this compound in several cell lines, including Hela cells[6] . Aqueous extract of two Nigerian medicinal plants (*Cymbogus giganteus* and *Ethanti chlorantha)* were shown to have anti-malarial activity against chloroquine resistant *Plasmodium voelli nigeriensis* in infected mice; intraperitoneal treatment for three consecutive days with different doses of extracts cleared the infection in a dose dependent manner[7]. The anti-malarial activity of two bisbenzylisoquinolines (penduline and tetrandine) purified from *Isopyrum thalictroides* has been reported in synchronised cultures in vitro, with growth interference between the eight and 32nd hours of parasite infection[8]. Francois et al have described the isolation of quassinoid compounds from stem bark extracts of *Hannoa chlorantha* and *Hannoa klaineana*, traditionally used for the treatment of malaria in central African countries[9]. Chaparrinone was considered to have the most potent anti-malarial potential (in terms of anti-plasmodial versus cytotoxic activities), with good activity against *Plasmodium falciparum* in vitro (IC_{50} approximately 40ng/ml), and in mice in vivo (ED_{50} < 50 mg/Kg), without obvious adverse effects. Steele et al have reported the isolation of the lupanetype triterpene betulinic acid from an ethanolic extract of root bark of the Tanzanian tree *Llapaca nitida*[10]. In vitro antiplasmodial IC_{50} values for betulinic acid against chloroquine resistant and sensitive *Plasmodium falciparum* were 20 and 26 µg/ml respectively. However, when betulinic acid was tested for in vivo activity in a murine malaria (*Plasmodium berghei*) model, the highest dosage used (250 mg/Kg/day) was ineffective at reducing parasitaemia, and some toxicity was noted. Particular attention has focused on the anti-malarial activity of the Chinese medicinal plant *Artemisia annua*, which possesses a different anti-malarial principle to those of drugs in current use[11]. The active component is artemisinin, an endoperoxide sequiterpene lactone, present mainly in leaves and inflorescence. Artemisinin is thought to act as a prooxidant in the generation of reactive oxygen free radical species (in addition to generation of the latter by activated neutrophils in the host) as a defence against the parasite. Artemisinin binds to erythrocyte and parasite cell membranes; accumulated iron within the parasite (from digestion of host haemoglobin) reacts with the peroxide moeity to generate free radicals, leading to subsequent destruction of parasite cells[12]. Various pharmacological parameters, including mode of action, interaction with other drugs, pharmacokinetics, toxicological effects and clinical results have been described[13,14]. For example, extracts of *Artemisia annua* have been shown to inhibit *Plasmodium yoelli* growth in mice, with reproduction inhibited by 99% after five days treatment compared to controls (with ED_{50} of 29.2 mg/Kg and EM_{50} of 28.7)[15]. Biotechnological research is currently underway to identify or produce plant species or cell cultures with high artemisinin content, to allow the industrial scale production of this novel anti-malarial

compound. Semi-synthetic derivatives of artemisinin, such as β-artemether and artecther, typically show 2-3 fold increased anti-malarial activity, and the metabolite dihydroartemisinin up to 10-fold more activity. In monkeys infected with *Plasmodium cynomolgi*, clearance of the parasite was obtained with two days using β-artemether at a dose of 2mg/Kg/day, whilst artemisinin doses 10 times greater were required to obtain a similar result[9].

The treatment of patients with uncomplicated *Plasmodium falciparum* infection using various dihydroartemisinin formulations (600 mg total over five days) has been reported; most patients were blood smear negative for parasites after three days with no serious adverse effect[16]. Semi-synthetic drugs derived from artemisinin provide treatment of severe malaria, and even other drug resistant malaria[17]. β-artemether (Artenam) is commercially available in ampoule (intramuscular injection) or tablet (oral) forms, with a recommended loading dose of 300 mg on day 1, followed by 100 mg/day for four days. At this therapeutic dose there are virtually no adverse effects, although higher doses may result in transient abdominal pain and diarrhoea. The evaluation of Eucalyptus based repellents against Anopheles species of mosquito (the major malaria vector) has also been described,[18].

Trypanosomiasis :

The African trypanosomiases result from infection by *Trypanosoma gambiense*, *Trypansoma rhodesiense* and *Trypanosoma brucei*, the causative agents of sleeping sickness, a vectored disease spread by Glossina (tsetse) flies. The infective agents are found initially in the human lymphatic and peripheral blood systems, and later in CNS tissues. Conventional chemotherapy is based on administration of suramin (20 mg/Kg intravenous at three day intervals for three weeks) or pentamidine (3-4 mg/Kg intramuscular daily for 10 days). American trypanosomiasis (Chagas disease) results from infection by *Trypanasoma cruzi*; chemotherapy is based on administration of nitrofuran 5-15 mg/Kg daily for up to 120 days.

As noted above, problems associated with the use of these synthetic drugs have stimulated interest in the development of medicinal plant based treatments. Although a number of such natural products have been described, their potential use has been limited by requirements for high concentrations, unfavourable pharmokinetics and/or low solubility in blood[19]. There has therefore been considerable interest in the screening of African and south American flora to identify novel species/active compounds for treatment of the above disorders. Extracts (using a variety of solvents) from 24 African plant species (from 19 families) reported as traditional remedies for sleeping sickness were screened for activity in vitro against *Trypanosoma brucei*. Promising trypanocidal activity (IC_{50} <10 μg/ml) was found in 32 extracts from 13 species, with the most active extracts (IC_{50} < 1 μg/ml) derived from *Annona senegalensis*, *Bussea occidentalis* and *Physalis angulata*. These plant extracts showed a modest selectivity index however, in contrast to commercially available trypanocides with more selective toxicity against trypanosomes[20]. Nine plant species from Tanzania and Uganda, traditionally used for treatment of sleeping sickness were extracted and screened for activity in vitro against *Trypanosoma brucei*; eight extracts from five species revealed promising anti-trypanosomal activity with IC_{50} values < 1 μg/ml as follows: *Albizia gummifera*, *Ehretia amuena*, *Entada abyssinica*, *Securinega vitosa* and *Vernonia subuligera*. Activities with IC_{50} values between 1-10 μg/ml were determined for a further 15 extracts. The cytotoxicity of these active extracts, tested on a human fibroblast cell line was found to be high and therefore selectivity indices resulted in less favourable ranges than those for the few

commercially available drugs[21]. The effect of *Allium sativum (Liliacae)* on trypanosome infected mice has been reported, a dose of 5 mg/ml of pulp oil extract completely suppressed the ability of the parasite to be effective in the host. An acetic acid/methanol chromatographic fraction of this extract cured experimentally infected mice of trypanosomiasis in four days at a dose of 120 mg/Kg per day; the extract also inhibited the procyclic form of *Trypanosoma brucei* and phospholipases from *T. congolensa, T. brucei* and *T. vivax*. The extract appears to be a diallyl disulphide and interferes with the parasites synthesis of membrane lipids[22].

The trypanocidal activity of some Paraguayan Asteraceae species was evaluated against the bloodstream form of *Trypanosoma cruzi*. Ethanolic extracts from *Chromolaena christieana* (stem and bark), *Achyrocline satureoides* (leaves and flowers) and *Mikania cordifolia* (root and stem) at concentrations of 250 μg/ml showed the highest percentage lysis of the bloodstream form of *Trypanosoma cruzi*[23]. Screening programmes of Brazillan flora have led to the development of novel synthetic compounds derived from Tabebuia species (heterocyclic napthooxazole and napthoimidazole derivatives) and *Lausonia alba* (alyl guinone derivatives); ID_{50} values for the latter compounds were 300-400 μmol/L, and for the former compounds were less than for crystal violet. It is suggested that the napthooxazole/napthoimidazole compounds may act via intercalation of DNA, rather than generation of free radical species[24]. Analysis of essential oils from *Minthostachys andina* and *Hedomen mandonianum*, Bolivian plants traditionally used as pesticides, and their effectiveness as insecticides against *Rhodnius neglectus* and *Triatoma infestans* (vectors of Chagas disease) has been described by Fournet et al[25]. Bastos et al have reported the isolation of the lignan(-) methylpluviatolide from a hexane extract of leaves of *Zanthoxylum naranjillo*[26]. This compound was effective against several strains of *Trypanosoma cruzi* in both in vitro and in vivo assays. Healthy animals injected with blood samples containing (-) methylpluviatolide did not develop disease; however, whilst this compound was highly active against bloodstream forms of *Trypanosoma cruzi* strains, it was not active against tissue forms of the parasite.

The activities of crude plant extracts (or subsequent fractions) of five plants (*Neurolaena lobata, Petiveria alliacea, Tridax procumbens, Byrsonima crassifolia, Gliricidia sepium*) commonly used in Guatemala against protozoal infections, have been evaluated against the trypomastigote and epimastigote forms of *Trypanosoma cruzi* in vitro[27]. Only the hexane or ethanolic crude extracts of *Neurolaena lobata* were active against both forms of the parasite in vitro. A further fraction of the ethanol extract of *Neurolaena lobata* was also highly active against *Trypanosoma cruzi* in vivo.

Schistosomiasis :

Schistosomiasis (bilharzia) results from infection by the trematodes (blood flukes) *Schistosoma mansoni, Schistosoma haemobium* and *Schistosoma japoniuum*, with an estimated 200 million cases worldwide. Part of the development cycle occurs in snails, with adult worms living mainly in host blood vessels. Fever, the formation of characteristic lesions and renal damage are characteristic symptoms of the disease. The drugs most commonly used for treatment are niridazole (25 mg/Kg oral, daily for seven days) and stibocaptate (6-10 mg/Kg intramuscular as 10% solution, daily for five days). Serious limitations of conventional methods of controlling trematode infections such as schistosomiasis and fasciolasis have become apparent, and the potential importance of plant molluscicides in the future control of these infections recognised as a sustainable and environmentally acceptable altermative[28,29]. In the search for novel plant molluscicides for schistosomiasis control, the characteristics of new compounds

are evaluated against those of the synthetic molluscicide of choice, niclosamide[30]. Screening programmes of African medicinal plants, which provide a rich source of relevant biologically active compounds, have been described[31]. Several hundred plant extracts were screened for molluscicidal activity against the schistosomiasis trasmitting snail *Biomphalaria globrata*; a number of active compounds (particularly saponins) were identified[32]. Because of the prohibitive cost (time/financial) of random surveys, there is a need to develop objective selection procedures. One such system is based on the coincidence of endemic areas of plant, snail host and disease, ethno-medical value and molluscicidal activity (LD_{50} < 100 ppm); using the latter approach, a survey of some 60 candidate plant species was carried out, from which a number of potentially active species were identified [33].

The potential of molluscicidal Eucalyptus species as a self sustaining delivery system (via intermittent leaf fall) has been described[28]. Eucalyptus species containing so-called G-compound endoperoxides/ Mannich bases were shown to be effective in killing protozoa in vitro. Results with synthethic analogues derived from these compounds show a relationship between chemical structure and anthelminthic activity; aromatic ring side chain and long aliphatic side chain analogues were most active with LD_{50} < 0.1 mM in an in vitro assay using changes in larval motility as the end point. The mode of action of these compounds may involve generation of free radical species, to which helminthic parasites appear to be susceptible[34]. The molluscicidal activity of the leaf or bark of *Azadirachta indica* (neem) against *Lymnae acuminata* and *Indoplanorbis exuitus* has been shown to be both time and dose dependent; the toxic effect of purified azadirachtin against both snail species was greater than that of synthetic molluscicides[35]. Aqueous extracts of *Rheum palmatum* and *Rheum dentalis* showed molluscicidal activity against the snails *Oncomelania hupensis*, *Biomphalaria glabrata* and *Balinus globins*, vectors of *Schistosoma japonicum*, *Schistosoma mansoni* and *Schistosoma haematobium* respectively. Anthelminthic activity was correlated with antroquinone content (identified by HPLC); rhein and chrysophanol-anthron were most active (>50% dead snails after two days using 0.03% solution). Extracts of *Jatropha curcas* seeds also showed molluscoidal activity associated with the phorbol ester content of jatropha oil (purified 4-B-phorbol-13-decanoate killed snails at a concentration of 0.001%/10 ppm[36]. The potential anti-helminth activity of Pyrethum and Papaya species has also been described[29]. The possible use of extracts of *Phytolacca dodecandra* berries against schistosome larval stages in fresh water in schistosomiasis control programmes has also been suggested [37].

Leishmaniasis :

Visceral leishmaniasis (kala-azar) is an infection of endothelial cells throughout the body by the protozoan parasite *Leishmania donovani*. The disease is transmitted by sandfly vectors, principally Phiebotomus species. The disease is characterised by fever, enlargement of liver and spleen, progressive wasting, and leucopaenia, and has a high morbidity and mortality rate. Due to the relative failure of the anti-malarial eradication campaign and consequent proliferation of sandflies, kala-azar is prevalent in India (especially Bengal/Assam) and Bangladesh as well as parts of China, Africa and the Middle East. The parasite lives in the host macrophage cells, and infection is diagnosed via Giemsa stained smears of splenic or bone marrow biopsy tissue. Two types of drug are used for conventional treatment, antimonials or diamidine. Sodium antimony tartrate is inexpensive but toxic; less toxic antimony compounds such as sodium antimony gluconate are used (600 mg intravenous or intramuscular per day for 20 days). The diamidine pentamidine isothionate is given

intravenously or intramuscularly, 4 mg/Kg per day for 10 days. Extracts of *Annona haemantha* root have been used to isolate argentilactone (an α-β-unsaturated delta lactone). This compound exhibited in vitro activity against various strains of Leishmania species at 10 mg/ml; mice infected with *Leishmania amazonensis* were treated four weeks after infection with argentilactone (oral or subcutaneous) for 14 days using 25 mg/Kg daily. A reference drug, N-methyl glucoamine antimonate was administered by subcutaneous injection at 100 mg/Kg for 14 days. Under these conditions argertilactone showed the same efficacy as the reference drug, reducing by 96% the parasite load in the lesion and by 50% the parasite burden in the spleen[38]. DaSilva et al have demonstrated that oral treatment with a leaf extract of *Kalanchoe pinnata* significantly decreases the lesion size and parasite load in mice infected with *Leishmania amazonensis*[39]. The protective effect may not be due to a direct effect on the parasite, but rather to the activation of NO production in host macrophages.

Akendengue et al have recently reviewed in detail medicinal plants traditionally used world-wide for treatment of Leishmaniasis[40]. Active compounds identified include : quinoline (alkyl-2-quinoline), isoquinoline (isoguattouregidine) and indole (conodurine) alkaloids isolated from *Galipea longiflora*, *Guatteria foliosa* and *Pescheiera van heurkii* respectively, terpenes (jatrogrossidione) from *Annona senegalensis*, and lignans (nyasol) from *Asparagus africanus*. Other natural compounds with anti-leishmanial activity include coumarins, chalcones, lactones, tetralones and saponins.

Amoebiasis :

Amoebiasis resulting from *Entamoeba histolytica* infection is endemic in many regions worldwide. The organism lodges in the large intestine, with infection typically via swallowing of cysts in faecal contaminated drinking water, resulting in characteristic symptoms of amoebic dysentery. Confirmation of infection is via microscopic examination and conventional chemotherapy based on administration of metronidazole (400-800 mg three times daily for 5-7 days). A number of medicinal plants/natural constituents with amoebicidal activity or activity against dysentery have been described[41]. A formulation of crude dry herbal extracts used in the Indian traditional system of medicine with antiamoebic activity against *Enatamoeba histolytica* in vitro and in vivo has been described. The formulation of five herbs (*Bochavia diffusa*, *Berberis aristata*, *Tinospora cordifolia*. *Terminalia chebula* and *Zingiber officinale*) extracted in ethanol had a minimal inhibitor concentration (MIC) for in vitro amoebicidal activity of 1000 μg/ml, compared to 10 μg/ml for metronidazole. In experimental caecal amoebiasis in rats, the formulation had a curative rate of 89% with the average degree of infection (ADI) reduced to 0.14 in a group treated with 500 mg/Kg per day, compared with an ADI of 3.8 for sham treated control rats. Metronidazole had a cure rate of 89% (ADI 0.4) at a dose rate of 100 mg/Kg per day. Varying degrees of inhibition of a range of enzyme types was noted in axenically cultured amoebae using the above formulation[42]. The ability of *Entamoeba histolytica* trophozoites to destroy monolayers of baby hamster kidney cells was inhibited by allicin, one of the active principles of garlic. Cysteine proteinases, an important contributor to amoebic virulence, as well as alcohol dehydrogenase, were strongly inhibited by allicin[43]. In relation to the above, an ethno-botanical survey of the Luo people of the Lake Victoria basin in Kenya/Tanzania was carried out using an in vitro assay with *Giardia lamblia* (a flagellate intestinal parasite). Methanolic extracts of 21 of 31 taxa assayed were lethal or inhibited growth of *Giardia* trophozoites at 1000 ppm; seven species were lethal at 500 ppm[44].

Snake envenomation :

Many plants are recommended in traditional medicine as being active against various effects of snakebite. Experiments have been carried out in vitro and in vivo to investigate the basis of action of the above, using preparations according to traditional formulae. In some studies, extracts were administered to mice before or after treatment with different elapid or crotalid venoms. Other studies deal with selected compounds isolated from *Schumanniophyton magnificum*, *Eclipta prostrata* or *Aristolochia shimadai*, and their capacity to inhibit phospholipase A_2 or other enzymes (e.g. ATPase), or for physiological or biochemical properties (such as effects on uterine tone or the protection of mitochondrial membranes). Japanese workers have described the anti-haemorrhagic effect of persimmon tannin from *Diospyros kaki*. Atropine has been attributed a life-prolonging effect after black mamba venom treatment. Prolonged survival was also observed after pre-treatment with extracts of *Diodia scandens* and *Andrographis paniculata*, a potentially useful strategy to allow patient hospitalization and antivenom administration before the potentially dangerous effects of envenomation develop. To date, there has been little systematic investigation in this field[45]. A list of flowering plants used for treatment of snakebite has been compiled from a variety of literature sources, giving details of geographical areas, plant parts used and basis of reputed activity[46]. The adjuvant effect and antiserum potentiation of the compound 2-hydroxy-4-methoxybenzoic acid, isolated from a root extract of the Indian medicinal plant *Hemidesmus indicus* has been described[47]. This compound showed anti-snake venom activity in rabbits immunized with *Vipera russellii* venom, and potentiated the venom neutralizing action of commercial equine polyvalent snake venom antiserum in experimental models.

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CASE REPORTS

Papillary and Solid Epithelial Neoplasm of Pancreas (PSEN) : A Rare Case Report

MM SAHA, MPhil[a], RK MOLLICK[A], FCPS[b], K BISWAS, MPhil[c]

Summary :

A seventeen years old unmarried girl was admitted into the surgery department of Sher-e-Bangla Medical College and Hospital, Barisal with history of intermittent pain in the left hypochondrium radiating to the back. Systemic examination revealed a firm slightly tender left upper quadrant abdominal mass which moved minimally with respiration. Ultrasonography report revealed a solid and partly cystic mass arising from the tail of pancreas. At the time of surgical exploration, a large (12x10x9 cm) complex mass was found adherent to the tail of pancreas. The mass was partly solid and partly cystic filled with haemorrhagic fluid. The pancreatic mass on histopathological examination showed papillary and solid epithelial neoplasm. The patient was discharged on twelfth post-operative day and lost in follow up.

(J Bangladesh Coll Phys Surg 2000; 18 : 79-81)

Introduction :

Papillary and solid neoplasm is a relatively newly described epithelial neoplasm of pancreas. The incidence of such tumour is rare, although an increasing number of cases have been reported in recent years.

Papillary and solid epithelial neoplasm (PSEN) of pancreas is usually found in young women as enlarging abdominal masses[1]. The tumour can invade locally but rarely metastasizes.

Ultrastructural detail including eccentric nucleoli, numerous mitochondria, sparse endoplasmic reticulam and little evidence of secretory activity suggest a duct cell origin for this rare tumour[2]. Solid and papillary neoplasm of pancreas have only recently become well recognized as disease entities. Because of their rarity and uncertain histogenesis such neoplasms have been variously referred to as Frantz's tumour, papillary epithelial neoplasm, papillary cystic tumour/neoplasm, and solid and papillary neoplasm[3].

Grossly, the tumour appears well encapsulated with focal or extensive haemorrhage and necrotic change. PSEN of pancreas may occur anywhere in the pancreas but has a slight predilection for the tail of the pancreas[4]. Here a rare tumour, papillary and solid epithelial neoplasm of the pancreas, which was diagnosed clinically as a malignant neoplasm, is reported.

Case report :

A seventeen years old unmarried girl was admitted into the surgery department of Sher-e-Bangla Medical College and Hospital, Barisal on 8th September 1998, with the complaints of pain in left upper quadrant radiating to the back. The patient came of an average socio-economic background and her general condition was good. Abdominal examination revealed a well defined solid and partly cystic mass in the left upper quadrant.

a. Dr. Moni Mohan Saha, MPhil (Path), Senior Consultant, Pathology, 200-bedded Hospital, Narayangonj.

b. Dr. Ranjit Kumar Mollick, FCPS, Resident Surgeon (General), Sher-e-Bangla Medical College and Hospital, Barisal.

c. Dr. Kamalendu Biswas, MPhil (Path), Professor of Pathology, Sher-e-Bangla Medical College and Hospital, Barisal.

Address correspondence to : Dr. Moni Mohan Saha, Senior Consultant, Pathology, 200-bedded Hospital, Narayangonj.

Received : Nov. 29, 1999 Accepted : March 02, 2000

The mass was mobile, tender and adherent to pancreas. Haematological investigation showed the following : haemoglobin-10.3 gm/dl, total leucocyte count $9.0x10^9$/L, ESR-25 mm after first hour (Westerngren method).

Chest roentgenogram and intravenous pyelogram were normal. Coagulation studies, urinalysis, serum amylase level, liver function studies, serum electrolyte and fasting blood glucose were all within normal limits.

Ultrasonography of the abdomen showed a large complex mass having solid and partly cystic components in the left upper abdomen obscuring the tail of pancreas.

Laparatomy was done on 23rd September, 1998. With all aseptic precaution abdomen was opened under general anaesthesia by a left upper paramedian incision. A large encapsulated mass was found adherent to the tail of the pancreas. The mass was partly solid and partly cystic, and also loculated and filled with haemorhagic fluid. The tumour was removed by distal pancreatectomy with excision of the mass attached with it. Resected tumour mass was sent for histopathological examination.

Gross appearance : Specimen consisted of a well circumscribed, oval, brown pancreatic tumour measuring about 12x10x9 cm. The tumour was partly solid and partly cystic filled with haemorhagic fluid. The tumour was haemorrhagic on cut surface. Cross section of the mass revealed an intact firm white capsule of 0.4-1.0 cm thickness. The central portion of the mass was yellow, soft and spongy with several areas which were friable, purple and necrotic. Two blocks were made for paraffin embedding.

Microscopic appearance : Haematoxylene and eosin stained slides revealed an encapsulated pancreatic mass consisting of many pseudopapillae covered with multilayered ephithelial cells, areas of haemorrhage and foam cells. The tumour cells were monomorphic and showed mild pleomorphism. Mitotic figures were sparse. Bits of normal pancreatic tissue were included in this biopsy.

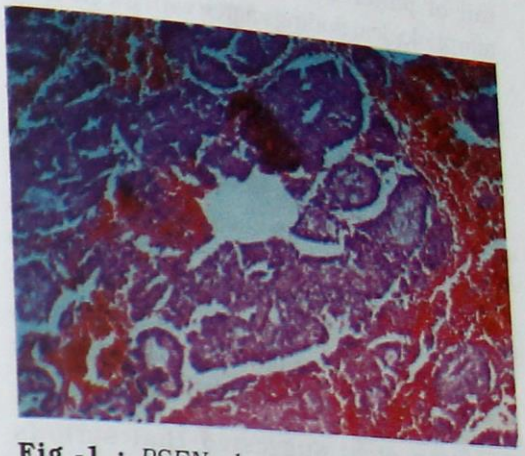

Fig.-1 : *PSEN showing multiple pseudo-papillae, area of haemorrhage, and foam cells (H & E x 150).*

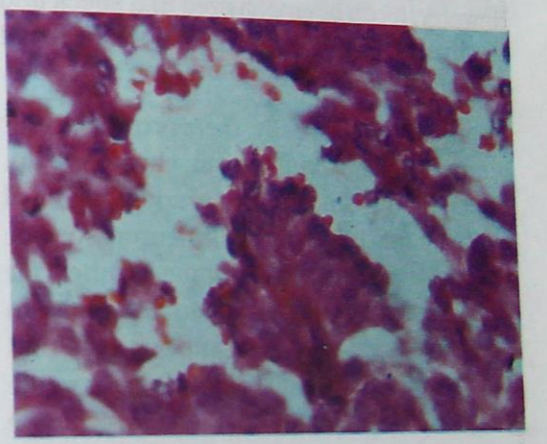

Fig.-2 : *PSEN showing distinct pseudopapillae lined with multilayered epithelial cells (H & E x 375).*

Discussion :

PSEN predominantly occurs in young female with an average age of about twenty six years[5]. Different workers have also reported that age incidence may vary from fifteen to forty seven years[6]. Age of this patient was seventeen years which agrees with the finding of Kuo et al[7]. The tumour appeared grossly well capsulated with focal or extensive haemorrhage and

necrotic change. This findings agree with the findings of Sanfey et al[8]. This neoplasm had solid and cystic components obscuring the tail of pancreas or arising from it. This morphological findings agree with the findings of Morrison et al[9]. The histogenesis of this peculiar neoplasm is debatable. However, ultrastructural observations support a ductal cell origin. Pathological classification of this neoplasm is difficult. PSEN does not form ducts and hence it would not be grouped with any of the adenocarcinomas which make up over 85% of primary nonendocrine pancreatic carcinomas[10]. It can not be classified as a pleomorphic carcinoma because of absence of bizzare multinucleated giant cells.

Kaufman et al suggested that serious complication of PSEN is shock and positive peritoneal sign secondary to rupture of tumour resulting in haemoperitoneum[11]. But this patient had no such complication. However, it can be emphasized that shock and positive peritoneal sign may be the atypical presentation of PSEN.

Immunohistochemically, there is reactivity for keratin, desmoplakin, trypsin, chymotrypsin, amylase and vimentin[12]. In addition, focal positivity has been found for neuron-specific enolase and at least in some studies for various islet cell hormones such as insulin and glucagon[13]. These result suggest, that PSEN is a tumour of primitive pancreatic epithelial cells with predominance of exocrine features but having the capacity for dual (exocrine and endocrine) differentiation[14]. Progesterone receptors have been detected both immunohistochemically and by the dextran-coated charcoal method[15]. These results, which are consistent with its well-known predilection for females, suggest that PSEN is a hormone dependant neoplasm and therefore potentially susceptible to hormonal therapeutic manipulation.

Acknowledgement :

We are thankful to Dr. Sabitri Sanyal, Professor and Head, Department of Pathology, Medical College, Calcutta for reviewing the histopathological slides.

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Journal of Bangladesh College of Physicians and Surgeons
Vol. 18, No. 2, May 2000

Balloon Atrial Septostomy in a Patient of D-Transposition of the Great Arteries : A Case Report

NNF BEGUM, FCPS[a], MH RAHMAN, FCPS[b], QS AHMED, FCPS[c]

Summary :
This is a report on a new born baby admitted to Neonatal Intensive Care Unit, Combined Military Hospital (CMH), Dhaka with perinatal asphyxia, on 12 January 1999, and was found to have D-transposition of great arteries (D-TGA) on subsequent work up. Balloon atrial septostomy (BAS) was performed on the fifth day of life and patient showed dramatic response after the procedure. This procedure is a life saving one for D-TGA cases until surgical facility is available. Paediatric cardiologists are practcing it widely in developed countries. This is the first balloon atrial septostomy in Bangladesh Armed Forces which led to this report.

(J Bangladesh Coll Phys Surg 2000; 18 : 82-86)

Introduction :

The term transposition describes an abnormal or discordant ventriculo-arterial connection in which the aorta arises from the morphological right ventricle and the pulmonary artery arises from the morphological left ventricle. Cynosis in the first day of life suggests the possibility of transposition and if the ventricular septum is intact, patients become severely cynanotic within hours of birth. When the transposition is associated with large ventricular septal defect (VSD), cyanosis is less and may not be noticed in the first few months. Diagnosis should be done rapidly from hyperoxia test, chest x-ray, ECG and echocardiography. Prostaglandin infusion should be started immediately and balloon atrial septostomy (BAS) should be performed to allow mixing between pulmonary and systemic circulation. Then, ideally, anatomical correction or arterial switch operation should be performed within one month of age.

a. Nurun Nahar Fatema Begum, FCPS, Paediatric Cardiologist, Combined Military Hospital, Dhaka.

b. Md. Hamidur Rahman, FCPS, Cardiac Anaesthesiologist, Combined Military Hospital, Dhaka.

c. Quazi Shaffiuddin Ahmed, FCPS, Cardiologist, Combined Military Hospital, Dhaka.

Address correspondence to : Major Nurun Nahar Fatema Begum, Paediatric Cardiologist, Combined Military Hospital, Dhaka.

Received : Nov. 07, 1999 Accepted : April 29, 2000

Case report :

A newborn term baby weighing 4 Kg had been admitted to the neonatal intensive care unit (ICU) immediately after caesarean section with the diagnosis of perinatal asphyxia and aspiration pneumonia. He had history of delayed cry after delivery and his APGAR score was six at first and fifth minutes of life. He was tachypnoic and cynosed on admission, his chest x-ray showed no evidence of lungs pathology. Hyperoxia test was positive in favour of cyanotic congenital heart disease. He had been suspected clinically as a case of TGA and confirmed later by colour doppler echocardiography. Echocardiography also showed a small perimembranous VSD of 2 mm size and a tiny PDA. In initial three days, he was stable inspite of desaturation and tachypnoea but from the fourth day he had started showing signs of haemodynamic instability with desaturation and severe respiratory distress. His condition was discussed with the parents and decision was taken for urgent balloon atrial septostomy as a life saving measure. A central femoral venous line was established and dopamine infusion started. He was taken to the cath laboratory on the fifth day of his life and balloon atrial septostomy was done with the aim to create a hole in the atrial septum.

Equipment used : 7Fr catheter introducer sheath, 20g leader catheter, Haemostatic

bleed back valve, 5Fr NIH catheter, Miller septostomy balloon, pressure tubing red line (line I) and blue line (line II), 20G x $1^1/_2$" needle and .021 x 100 cm guidewire.

Drugs used : Ini. Ketamine (1.5 mg/Kg) and Inj. Midazolam (0.1 mg/Kg I.V.)

Procedure : The patient was sedated initially with Inj. Ketamine and Midazolam and secured to the table. He was then connected to the ECG monitoring and pulse oximetry and base line readings taken. Cleaning and draping was done leaving both femoral area exposed. The groins were anaesthetised with 1% lignocaine. The left femoral vein was entered percutaneously and a 7Fr sheath was placed. A 5Fr NIH catheter was attached to line II and flushed whilst advancing the catheter through the sheath to inferior vena cava (IVC). A saturation and pressure run was performed in all chambers of the right side of the heart i.e. superior vena cava (SVC), innominate vein, right atrium, right ventricle (RV) etc. Also 1 ml of dye was injected to the innominate vein to rule out the presence or absence of left SVC. Cine angiogram was performed in the right ventricle which showed aorta arising from the RV. Then NIH catheter was taken out. Miller septostomy balloon was checked properly and introduced through IVC to right atrium and then to the left atrium through *foramen ovale*. The balloon was inflated initially with 2 ml contrast taking care about safety of the pulmonary veins and mitral valve. Balloon was then withdrawn gradually until it pressed against the atrial septum. Inflated and locked balloon was then pulled down with sudden jerk across the septum. Care was taken to prevent complication like avulsion of the IVC. The balloon was deflated immediately to avoid occlusion of the IVC. This procedure was repeated four times with increasing amount of contrast inside the balloon (upto 4 ml). The balloon was then removed on negative pressure. Again NIH catheter was used to run saturation and pressure on right as well as left side of the heart. A cine angiogram was obtained from left ventricle this time. On completion of the procedure, femoral venous line was preserved for giving medication. The whole procedure was performed under anaesthesia (Figs.-1,2,3).

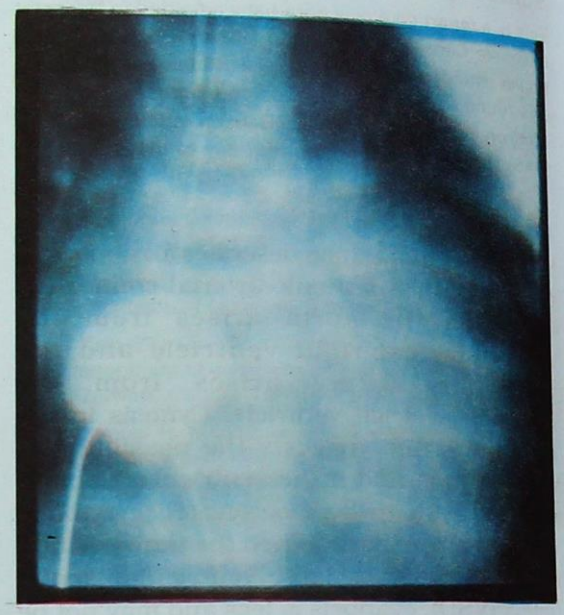

Fig.-1 : *Miler septostomy balloon against the interatrial septum, ready for septostomy.*

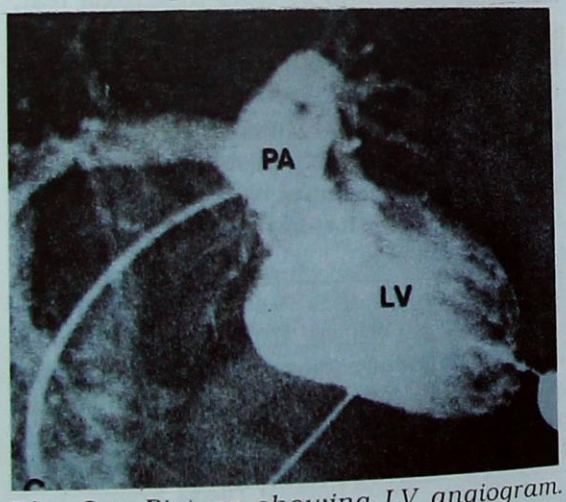

Fig.-2 : *Picture showing LV angiogram. Pulmonary artery is coming out from the left ventricle (TGA).*

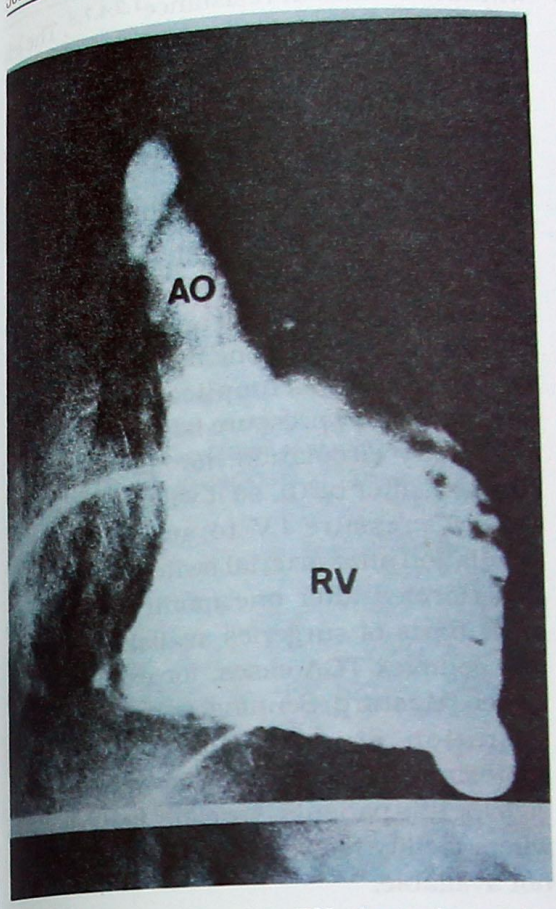

Fig.-3 : *Picture showing RV. Aorta is coming out from the right ventricle (TGA).*

Immediately after the procedure patient's saturation went up and left atrial pressure dropped down. Clinically, patient resumed pink colour with spo_2 of 95%. Respiratory rate went down to normal and body perfusion became better. Echocardiography (Fig.-4) showed 8 mm defect in the atrial septum. The patient was shifted to neonatal intensive care unit (ICU) with dopamine infusion at the rate of 10 microgram Kg/min with an aim to wean off in 24 hours. But the patient developed severe sepsis within 48 hours of the procedure and injections cetazidime, cloxacillin and dobutamine were added. His condition improved gradually and he was discharged from the CMH on the 14th day of the procedure with an advice for atrial switch operation within six months.

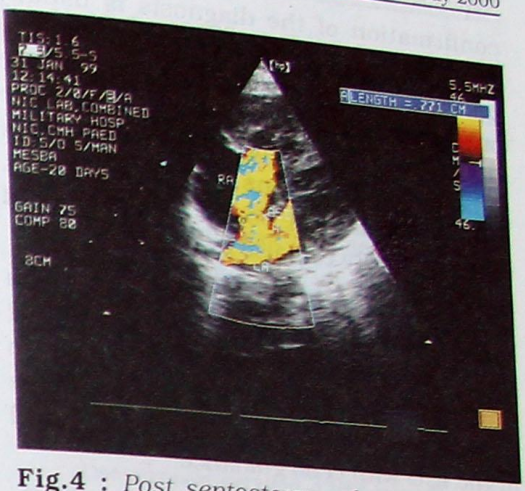

Fig.4 : *Post septostomy echocardiography showing 7.7 mm ASD with left to right shunt.*

Discussion :

Transposition of the great arteries is the second commonest cyanotic lesion. It describes reversal of the anatomical relation of the great arteries. Normally, the aorta is postero-medial and the pulmonary artery is anterior and left ward. In a transposition, each vessel assumes the position of the other. The physiological effect of this is to produce effectively two separate circulations rather than the normal figure of eight circulation. Mixing of two circulation is possible through patent *ductus arteriosus* and *foramen ovale* initially. As soon as ductus closes, severe cyanosis becomes apparent[1,2,3]. In simple transposition, without other complex association, baby looks apparently well at birth but becomes persistently cyanosed within the first day of life. If prompt action is not taken the baby becomes increasingly blue and develops a progressive metabolic acidosis. This happened in this case who was more or less stable for first three days when a tiny PDA was seen in echocardiography. But when his PDA closed on day three he became severely cyanosed and acidotic.

Cardiac catheterization is not usually necessary for diagnostic purpose but if the child needs to be treated by balloon septostomy, it should be performed and

confirmation of the diagnosis is usually carried out at the same time by giving contrast injection into both ventricles. The pressure and saturation in all the cardiac chambers and great arteries can be measured. Other associated lesions like ASD, VSD, PDA, left ventricular out flow obstruction, and coronary artery can also be evaluated[1,2,3,4].

Echocardiography can help not only in anatomical diagnosis but also in treatment modalities. In some very sick neonates who are severely acidotic and hypoxic, immediate balloon atrial septostomy can be performed in the ICU with echo guidance[5,6].

Successful management of infants with D-TGA requires the close coordination of the referring hospital, transport service and the receiving centre. If managed suboptimally, brain injury if not death, may be the result. For these babies, urgent transfer to paediatric cardiology unit is mandatory[1,2]. If the baby is severely cyanotic and acidotic the metabolic acidosis should be corrected with intravenous sodium bicarbonate and prostaglandin infusion should be sarted to keep the ductus patent. This in turn will increase the left artial pressure, thus help in opening the foramen ovale and allow mixing at the atrial level. The problem with prostaglandin infusion is that it may induce apnoea, so prophylactic intubation and ventilation is sometimes recommended. The subsequent management of uncomplicated transposition is uniform in most centres and consist of balloon atrial septostomy to provide adequate mixing of saturated and unsaturated blood[1,2].

For balloon atrial septostomy, the catheter is advanced under radiographic control untill the balloon at the tip is in the left atrium, taking care that it does not enter into the pulmonary veins or left ventricle. The balloon is then inflated with contrast media and pulled by sharp tug back into the right atrium and mouth of inferior venacava. The size of the hole produced can be estimated by seeing what volume in the ballloon can easily be withdrawn without resistance[1,2,4,7,8]. The left atrial pressure and systemic saturation will show dramatic improvement immediately. All this management are life saving and to stabilize the patient for surgery. So, corrective surgery should be performed as per protocol of the respective cardiac centre.

Now a days, arterial switch operation is the treatment of choice for patients with transposition of the great arteries. This should be performed before one month of age of the babies to avoid complications from left ventricular (LV) pressure fall. As LV supports pulmonary circulation, its pressure starts dropping after birth, so it will not be possible for low pressure LV to support systemic circulation after arterial switch operation if it is performed after one month[1,2]. There are other types of surgeries available for simple and complex TGA cases, for example, atrial switch (Musturd, Senning) or two stage switch operation etc.[4-14]. But balloon atrial septostomy (BAS) is the first and life saving step for this patients, specially in those places where facility for arterial switch operation is not available.

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