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JOURNAL OF BANGLADESH COLLEGE OF PHYSICIANS AND SURGEONS

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EDITORIAL

Artimisinin in the Treatment of Falciparum Malaria

Malaria remained as one of the most important infections causing huge health burden in the tropical world to the extent of more then one million deaths per year. The strategies for its control were changed by the World Health Organization (WHO) on several occasions with limited success each time. Present strategy of malaria control has important elements of early diagnosis and effective treatment by drugs coupled with promotion of use of insecticide impregnated mosquito nets. Using the available technology WHO has targeted to reduce the burden and mortality by 50% by the year 2010[1].

Until recently, diagnosis of malaria in most cases in endemic countries including Bangladesh was clinical and malaria including dreadful falciparum malaria was being treated with drugs like chloroquine or sulfadoxine pyremethamine against which the parasite has already developed resistance[2]. Many cases, even up to 60-70%, treated as malaria on clinical diagnosis were not really malaria at all[3]. Present day treatment of choice in falciparum malaria is artemisinin based combination treatment either artemether lumefantrine or artesunate mefloquine which has high degree of efficacy with relative safety but at the same time very expensive for the countries most in need. Bangladesh has already changed the regimen for treatment of uncomplicated falciparum malaria and recommended for using six dose artemether lumefantrine but yet to use and implement it widely[4]. The drug has been found to be effective to the extent of more then 97% and is equivalent to artesunate mefloquine in areas of multi-drug resistance[5]. Due to availability of easy method of rapid diagnostic test based on HRPII of falciparum antigen, diagnosis of malaria can be done at patient's home and a new challenge of providing effective treatment has been suggested. The spread and increase of malaria were contributed by the development of resistance of the parasite to the commonly used antimalarials. It has been found that use of effective combination treatment in infectious diseases could prevent development of resistance. Rediscovery of artemisinin, a very potent antimalarial, now gives a hope of containment of malaria. Artemisinin is a plant derived (*Artemisia annua*) sesquiterpine lactone containing antimalarial discovered by Chinese scientists and now available in most malaria endemic countries. Delay in development of resistance to this class of antimalarial could be made possible by combination with other slow acting effective drugs. Currently, WHO has recommended such of combinations for effective treatment of falciparum malaria by using artemisinin with lumefantrine, mefloquine, amodiaquine, or S-P. Based on the available local evidence of increasing chloroquine and S-P failure, and also as per WHO recommendations the antimalarial regimen recommend in Bangladesh for treatment of falciparum malaria was adopted in 2004, and it recommends using an artimisinin based combination antimalarial, artemether-lumefantrine. The drug also has potentiality of reducing transmission due to gametocytocidal effects. It is essential to use the artemisinin based antimalarial treatment in confirmed falciparum cases in complete dose only, thus not to abuse the drug which is expected to delay the development of resistance. Considering the cost of the drug and RDT the poor countries and people in malaria endemic region need subsistence in order to provide the community with optimal benefit of the strategy. We cannot afford to use the artemisinin-based drug on clinical diagnosis alone. It is expected that the malaria control programme will carefully deploy and extend the access to rapid diagnosis and ACT based treatment for the treatment of uncomplicated malaria (UM) down to the periphery involving different types of health care providers from government and non-government sectors.

The antimalarial drug used for the management of severe malaria was evaluated by a number of trials

before without finding any significant superiority of artemether over quinine[6,7]. The exception was some indication of better outcome in adult patients of severe malaria particularly with multiple organ involvement in Asia. This finding along with availability of better artemisinin with water soluble formulation artesunate prompted the scientists to compare artesunate with quinine in an open-label randomised control trial among 1461 adults and children with severe malaria in four countries of Asia including Bangladesh. The findings show a reduction of mortality by 34.7% compared to quinine[8]. Artesunate has been found to be well tolerated and was not associated with hypoglycaemia as has been found in quinine group. The new WHO guideline for management of severe malaria promptly accepted the results and recommended artesunate over quinine in the treatment of severe malaria in adults in Asia and travelers world wide[9]. Such a study involving children is in progress in Africa. Many cases of severe malaria used to die before arrival or in early period of treatment in hospital. The treatment delay includes arrival delay for parenteral treatment in the hospital. Intramuscular quinine was recommended as a pre referral treatment, which was not really in practice in remote rural areas. Per rectal formulations of artesunate has been found to be effective as good as parentral quinine in severe malaria in hospital setting[10]. This could be an alternative to parenteral quinine in remote areas. How far it is effective in community setting while using as a pre-referral treatment in preventing death in malaria is yet to be seen.

The present day treatment of falciparum malaria is thus based on artimisinin compounds both for uncomplicated and severe malaria. For the treatment of UM combination ACT is recommended, for the treatment of SM artesunate is the preferred drug. The availability of antigen based rapid diagnostic test for the diagnosis of falciparum malaria along with highly potent ACT based therapy is expected to contribute significantly in achieving the target of 50% reduction of mortality due to malaria. At the same time insecticide impregnated mosquito net or long lasting nets would be used as an important element of integrated vector control. It is high time to act now for using this knowledge base in malaria diagnosis, treatment and prevention for achieving the target before it is too late.

M A Faiz[a], Emran Bin Yunus[b]
M Ridwanur Rahman[a]

[a]Department of Medicine, Dhaka Medical College, Dhaka; [b]Department of Nephrology, Chittagong Medical College, Chittagong.

(J Bangladesh Coll Phys Surg 2005; 23 : 99-100)

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ORIGINAL ARTICLES

Plasma and CSF Aluminium in Sporadic Motor Neuron Disease (MND)

MA HAYEE[a], M NUSRATULLAH [b]

Summary:

Study of aluminium in plasma and cerebrospinal fluid in motor neuron disease (MND) was carried out in the Neurology department of Sir Salimullah Medical College and Mitford Hospital, Dhaka, Bangladesh. The duration of study was from January 2002 to June 2004. Seventy MND subjects between 16 to 65 years were selected. Among them 42 were male and 28 female. Same number of controls matched for age, sex, occupation and habitation (rural or urban) were also selected. Plasma and CSF were collected from the subjects and controls. Aluminium was estimated both from plasma and CSF. Cerebrospinal fluid aluminium level (18.09 ± 2.02 μg/dl) was significantly higher (p<0.001) in subjects as compared to the controls (12.22 ± 2.42 μg/dl). Plasma aluminium level of subjects and controls did not show any significant difference. Aluminium level in cerebrospinal fluid varied in different subtypes of MND and controls. The p-values were <0.01, <0.02 and <0.001 respectively in amyotrophic lateral sclerosis, progressive muscular atrophy and progressive bulbar palsy when compared with controls.

(J Bangladesh Coll Phys Surg 2005; 23 : 101-106)

Introduction:

Motor neuron disease is used to designate a progressive degenerative disorder of motor neurons in the spinal cord, brain stem and motor cortex, and manifest clinically by muscular weakness, atrophy and corticospinal tract signs in varying combinations[1].

The disease predominantly affects middle aged and elderly people and mean age of onset is 55 years, although middle-aged people are occasionally affected. There are three types of MND: (I) sporadic-which is the commonest form(90%), (II) familial, a small number of cases usually with an autosomal dominant mode of inheritance[2] and (III) Guamanian, a high number of cases of MND found in Guam and the Trusrt Territories of the Pacific.

The aetiology and pathogenesis of sporadic MND are not known. Numerous hypotheses about the pathogenesis/aetiology of MND have been proposed including environmental hypothesis, free radical hypothesis, immunological hypothesis, neurotropic factor deficiency hypothesis, altered neurofilament metabolism hypothesis, excitatory amino acid toxicity hypothesis, deficiency or toxicity of trace element hypothesis. Trace elements neurotoxicity has been implicated in the pathogenesis of MND. Several trace elements have been reported to be increased in the spinal cord of MND patients including lead[3], copper[4], iron[4], manganese[5] and selenium[5]. Epidemiological studies show that long term exposure to toxic trace elements are present in some MND patients[6-8]. Possible involvement of aluminium, calcium and manganese in ALS/Parkinsonism/dementia complex of Guam[9-11] and reports of MND-like syndromes in chronic intoxication with mercury[12] and lead also support the hypothesis[13].

Recently, many researchers found relationship of aluminium to sporadic MND. Aluminium is a widely dispersed metal being found in igneous rocks, shales, clays and moist soils. Aluminium is absorbed by many plants and occurs in plant products in diet. The daily ingestion of Al by humans is estimated to be 30 to 50 mg[14]. The general population is also exposed to Al from its widespread use in water treatment, as a food additive, from various Al-based pharmaceuticals, from occupational dusts, and from Al containers and cooking utensils[15]. The leaching of Al from the soils by acid rain increases free Al in the environment and in the surface waters. The increase exposure of the general population to Al has become

a. Dr. MA Hayee FCPS, MD, PhD, FRCP, Fellow (Interventional Neurology), Associate Professor and Head, Department of Neuromedicine, SSMC, Dhaka, Bangladesh.

b. Dr. M Nusratullah, Consultant, Department of Cardiology, University Hospital, Lausanne, Switzerland

Address of correspondence: MA Hayee FCPS, MD, PhD, FRCP, Fellow (Interventional Neurology), Associate Professor and Head, Department of Neuromedicine, SSMC, Dhaka, Bangladesh.

an increasing concern with publications that suggest possible association between exposure and neurological diseases[15-18].

Toxicity of Al in human is known to occur in at least two specific situations. Dementia in dialysis patient is related to Al exposure[16,19]. The Al intoxication in patients can be controlled by control of Al levels in dialysis fluids[20]. Chronic renal failure may lead to decreased Al excretion and enhances Al toxicity[21]. The pathogenesis of Al toxicity is complex and may be related to other factors such as impaired parathyroid function which affects Al absorption/or distribution[14]. A second prominent Al toxicity found in dialysis patients is osteomalacia or metabolic bone diseases[22,23].

Pre-term infants with parenteral administration of nutritional solutions are also at risk for Al-induced neurotoxicity[24,25]. Aluminium inhalation, especially in workers, may be associated with increased incidence of asthma[26,27]. Pre-term infants are also at risk for Al-induced metabolic bone diseases[28,29].

Aluminium is clearly neurotoxic causing degeneration of astrocytes[19] and interferes with the metabolism of the neuronal cytoskeleton[30]. It causes encephalopathy in patients undergoing renal dialysis[16,31,32]. Cerebral dysfunction was reported in people exposed to drinking water that had been contaminated with Al-sulphate[17]. Aluminium has been implicated in a series of neurological diseases including amyotropic lateral sclerosis, dementia associated with Parkinson's disease, and suggested for Alzheimer's disease although this link is quite tenuous[30]. Animal studies indicate that oral exposure to Al leads to accumulation in the brain, bone, muscle, kidney and other organs.

No study on this issue has so far been done in Bangladesh and literature survey revealed very few works throughout the world. This study was done to find out whether deficiency or excess of alumimium is present in MND. The study may give a clue about the role of it in the causation of a disease and this may help planning further studies.

Materials and methods:

This was a prospective study. The study was carried out at the Neurology Department of Sir Salimullah Medical College and Mitford Hospital, Dhaka. The duration of the study was from January 2002 to June 2004. Seventy sporadic motor neuron disease subjects aged between 16 and 65 years were included in this study. Same number of controls matched for age, sex, occupation and habitation (rural or urban) were selected. The diagnosis of MND was done according to the E L Escorial World Federation of Neurology Criteria: (1) signs of lower motor neuron degeneration by clinical, electrophysiological or neuropathological examination, (2) signs of upper motor neuron degeneration by clinical examination and (3) progressive spread of signs within a region or to other regions. Together with the absence of: (1) electrophysiological evidence of other disease processes that might explain the signs of lower motor neuron and/or upper motor neuron degeneration and (2) neuroimaging evidence of other disease process that might explain the observed clinical and electrophysiological signs.

For confirmation of clinically detected motor neuron disease electrophysiological study was done and MND was confirmed by doing EMG and NCV. CT scan and MRI were also done to exclude other pathology. The controls were free from any major neurological diseases and were not suffering from functional disorders, tension headache, lumbar disc prolapse etc. None of the patients or controls had a history of exposure to heavy metals. Informed consent was taken before the individuals were included in the study. The patients of MND were grouped according to various clinical subtypes such as progressive bulbar palsy (PBP), progressive muscular atrophy (PMA), amyotrophic lateral sclerosis (ALS) and primary lateral sclerosis (PLS) [34].

Blood (15 ml) was obtained through antecubital venepuncture by metal-free plastic syringes. It was collected in metal-free heparinised glass vials. Ten milliliters of the sample was centrifuged at 5000 rmp for 10 minutes and plasma was collected in a separate vial. Cerebrospinal fluid was collected by lumbar puncture done with steel needles which were previously washed with deionized water and sterilized. Samples were stored at –4° C for a variable period before estimation. To remove the organic

matrix, a measured amount of the sample was digested with 3 ml of digestion mixture containing metal free concentrated nitric acid and perchloric acid in a ratio of 6: 1. More digestion mixture was added if the sample did not digest completely with 3 ml of mixture. Samples were cooled and made up to 5 ml with deionized distilled water.

The estimations were done by direct current plasma emission spcectrophotometer (Beckman, USA) in which an electric arc was generated between two carbon anodes and one tungsten cathode. Pure argon gas was sustained as plasma between the electrodes which acted as a source of vapourisation, automization and excitation. The system first generated a straight line calibration curve by setting two standard solutions (a high and a low) of the element concerned which was used to convert subsequent signal measurements into concentration values. A blank sample of digestion mixture was run with each batch of samples. The method has been standardized in the laboratory; its accuracy being checked periodically by analyzing unknown samples. Aluminium was estimated in plasma and CSF. All the samples in the study group and controls were analyzed. Results were reported as mean ± standard error. Statistical significance was assessed by Student's *t*- test between patients and controls.

Results:

Seventy patients were evaluated in this study. After clinical assessment, all patients were investigated. Same number of healthy age and sex-matched controls were selected and their serum and CSF aluminium were estimated. In this study, the mean age of the patients was 41.60 (± 4.12) years. Age of onset of disease was 41.8 (± 3.7) years. There was slight difference of age of onset of disease between males (40.2 ± 3.38 years) and females (43.40 ± 4.02 years). Sex distribution showed male/female ratio 3: 2. None of the patients had a positive family history of MND and there was no evidence of geographic clustering of the disease. All of the patients were classed into clinical subtypes. Twenty seven (38.57%) patients presented as amyotrophic lateral sclerosis, 21(29.99%) as progressive bulbar palsy, 20 (28.57%) as progressive muscular atrophy and two (2.87%) as progressive lateral sclerosis. Cerebrospinal fluid aluminium level was estimated both in the patients and the controls. Aluminium concentration in patients was 18.09 (± 2.02) μg/dl and that in controls was 12.22 (± 2.42) μg/dl. Therefore, CSF aluminium concentration level of patients was significantly higher than that in controls i.e. $p<0.001$ (Table-I). CSF aluminium level among different subtypes was compared with their controls (Table – I). Statistical analysis revealed that CSF aluminium level was significantly higher in the patients than controls in each subtype. Plasma aluminium level of patients and controls were also estimated. Aluminium concentration in patients was 35.70 (± 3.71) μg/dl and that was 34.02 (± 4.21) μg/dl in controls. The difference was not statistically significant ($p>0.10$) (Table-II). Serum aluminium level in different subtypes was also compared with controls (Table – II). Statistical analysis revealed no difference between patients and controls.

Table-I

CSF aluminium level in patients with different types of MND and in controls

MND types	Patient Mean with SE(μg/dl)	Control Mean with SE(μg/dl)	t-value	p-value
All MND (n=70)	18.09 ± 2.02	12.22 ± 2.42	3.41	<0.001
ALS (n=27)	17.01 ± 2.98	11.98 ± 3.01	2.82	<0.01.
PBP (n=21)	20.12 ± 1.78	12.01 ± 2.12	5.12	<0.001
PMA (n=20)	17.15 ± 1.30	12.67 ± 2.13	2.48	<0.02

Table-II

Plasma aluminium level in patients of different types of MND and controls

MND types	Patient Mean with SE(μg/dl)	Control Mean with SE(μg/dl)	t-value	p-value
All MND (n=70)	35.70 ± 3.71	34.02 ± 4.21	1.51	>0.10 (Not sig.)
ALS (n=27)	36.01 ± 2.98	34.99 ± 3.99	1.71	>0.05 (Not sig.)
PBP (n=21)	34.96 ± 4.01	34.05 ± 4.29	1.71	>0.05 (Not sig.)
PMA (n=20)	36.13 ± 4.14	33.02 ± 4.35	1.96	>0.05 (Not sig.)

Discussion:

Majority of the subjects in this study were of age between 26 and 55 years. This findings correlate with the findings of a study in Bangladesh[34] but does not corroborates with the other Europian studies. This finding may be due to regional variation of MND.

The mean age of the patients was 41.6 (± 4.12) years which was similar to the findings of an Indian study[35] and also to that of a Bangladeshi study[34].

In this study the age of onset of disease was 41.8 (± 3.7) years which correlates with a Mexican study[36]. The distribution by gender (60% males and 40% females) concurred with the world pattern[37-39].

The distribution of the different types of MND in this study was similar to the Indian studies[35,40] but differed from other studies[38,41]. This dissimilarity is probably due to geographical variation of the disease. This can also be supported by similarity with the Indian study i.e. people of Bangladesh and India are in the same geographical area and expose to same risk factors which is different from that of European population.

The finding of higher CSF aluminium than controls correlates with the study of Sood[35]. Cerebrospinal fluid aluminium estimation in different subtypes of MND was also higher than controls. Each subtype showed significant difference and this finding is similar to that of other studies[35,36].

No study on this issue has so far been done in Bangladesh. In this field very few works had been done in the world. First study was carried out in India[35]. The other studies of muscle metals in MND did not show any difference in aluminium levels from a control popultion. The finding of high CSF aluminium in MND is important as aluminium is a potential neurotoxin. It has been proved that aluminium has been associated with some other degenerative neurological disorders like Alzheimer's disease[42] and dialysis dementia[43].

The neurotoxicity of Aluminium has already been established. Studies from Japan and Guam have reported a high content of aluminium in the spinal cord[44] and hippocampal cortex[48] of MND patients. Aluminium has also been seen to accumulate in significant amounts within the nucleoli of lumbar anterior horn cells of MND patients[44] and it has a positive correlation with the number of neurons showing neurofibrillary tangles and granulovacular degeneration[44].

Aluminium has been linked with the formation of neurofibrillary tangles in the cortical neurons in patients of Alzheimer's disease[42] and spinal cord of patients dying of Guamanian MND[33]. Intraventricular[45], subcutaneous[46] and intracellular[47] injection of aluminium in rabbits, cats and ferrets causes neurofibrillary degeneration which resembles neurofibrillary tangles seen in the disease states except for some morphological differences[48]. The studies on Guamanian MND patients have shown intraneuronal deposition of aluminium with calcium as a hydroxyapatite[11], which interferes with slow axonal transport by altering normal neurofilament production leading to excessive neurofilament accumulation and formation of neurofibrillary tangles[49].

High CSF aluminium in MND may be of relevance keeping in view the dynamics of this element in the body[50]. Aluminium is known to accumulate very slowly in cell nuclei and chromatin and large long-

lived cells e.g. neurons are most liable to this accumulation. This uptake is very slow (1mg in 36 years) and the amount once taken up by the brain, cannot be eliminated and therefore gets accumulated. The normal and lethally toxic brain levels of aluminium are narrow. When the aluminium concentration of brain neurons become three to 10 times the normal then it becomes toxic.

The exact role of high CSF aluminium in MND seen in this study is not clear. It is not certain if it indicates neurofibrillary pathology in patients and their resemblance with MND seen in the Western Pacific as no data are available on neuropathological changes in MND in Bangladesh or any reports of trace metal eliminations in brain tissue in MND.

Therefore, results of the present study provide some evidence of a causal relationship between aluminium and MND particularly to progressive bulbar palsy.

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A Controlled Trial on the Efficacy of Mefloquine in an Area with Reported Prevalence of Multi-drug Including Mefloquine Resistant Falciparum Malaria in Bangladesh

MR RAHMAN[a], MA FAIZ[b], R SAMAD[c], EB YUNUS[d], A HUSSAIN[e]
DC PAUL[f], S NAHAR[g], MS ALAM[h]

Summary:

An open controlled chemotherapeutic trial to describe the efficacy of mefloquine in an area with reported mefloquine resistance in a multi-drug resistant falciparum area of Bangladesh was done. Subjects were symptomatic patients, 12 years or older, with parasite density between 500-250,000/cmm and no history of taking antimalarials during the previous week. The regimens used were mefloquine 25 mg/Kg, divided into two doses six hours apart in 70 cases, and oral quinine sulphate tablets (10 mg/Kg eight hourly) for seven days in seven cases. Five healthy controls were recruited. Subjects were kept in a reasonably reinfection free environment in a makeshift hospital for 28 days. Drug administration was supervised and subjects were followed up clinically and with blood films in the hospital. Blood films were examined daily on days 1-8, then on days 14, 21 and 28, and on unscheduled days in case of relapse of symptoms. A total of 83 (71+ 7+ 5) cases were enrolled and one patient failed to complete the follow up. The drugs were well tolerated in all cases (except reversible cinchonism in two cases on quinine) and there was no clinical failure in the mefloquine group. One patient in the quinine group had late clinical failure. Five patients in the mefloquine group showed R III type of parasitological response (D2 parasitaemia more than 25% of D0), and in all of them radical cure was achieved. The study area can be considered to have preserved sensitivity to mefloquine in 25 mg/Kg dosage.

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Introduction:

Malaria constitutes a significant public health problem in Bangladesh and situation has slowly deteriorated since 1988[1]. Out of a total population of about 125 million, 10 million people living in south-eastern region are at the highest risk, with *P. falciparum,* the predominant species. In 1997, there were about 889,000 clinical malaria cases, about 69,000 laboratory confirmed cases (*P. falciparum* rate was about 62%) and 457 confirmed malaria deaths, reported through the primary healthcare set up (PHC) of the country[2]. This represents a gross underestimate of the total burden as many people do not attend the government health care facilities for various reasons, mostly due to lack of transportation facilities and shortage of medicines. A revised National Malaria Control Policy was adopted in 1995, which included the anti-malaria drug policy[3]. Three clinical case definitions and their respective treatment guidelines were adopted[4]. Objective information on drug sensitivity pattern of *P. falciparum* to various antimalarials are not available from most of the areas of the country, but resistance to chloroquine (CQ) and sulfadoxin/pyremethamine (SP) is known to be present for long[5,6,7].

In the recent years, multi-drug resistant falciparum malaria emerged as a major public health problem in

a. Dr. Md. Ridwanur Rahman, Associate Professor, Medicine, Dhaka Medical College, Dhaka.
b. Dr. Md. Abul Faiz, Professor of Medicine, Dhaka Medical College, Dhaka
c. Dr. Rasheda Samad, Assistant Professor, Paediatrics, Chittagong Medical College, Chittagong
d. Dr. Emran Bin Yunus, Associate Professor, Nephrology, Chittagong Medical College, Chittagong
e. Dr. Amir Hossain, Associate Professor, Medicine, Faridpur Medical College, Faridpur
f. Dr. D C Paul, UH&FPO, Cox'sBazar Sadar Upazilla, Cox'sBazar
g. Dr. Shamsun Nahar, Ex-Professor of Pharmacology, Chittagong Medical College, Chittagong
h. Dr. M Sultanul Alam, Ex-Professor of Community Medicine, Chittagong Medical College, Chittagong

Address of correspondence : Dr. Md. Ridwanur Rahman, Associate Professor, Medicine, Dhaka Medical College, Dhaka.

Bangladesh, with both the first and second line drugs showing unacceptable proportions of treatment failures[8]. In one study, the respective rates of clinical failures to first line agent CQ, second line agent three days oral quinine followed by single-dose fansidar (Q3+SP), proposed second line agent mefloquine (Mef) and third line agent oral quinine for seven days (Q7) were 77%, 28%, 27% and 18% in 1996-1997 in the present study area[8]. The group recommended Q3+SP regimen for slide-positive falciparum malaria cases as first line agent in the area. Mefloquine was proposed as the second line drug for treatment failure cases in the same area.

Mefloquine was registered and introduced in the country market in late 1997. The National Malaria Control Programme is not using the drug and the drug is not widely available in the local medicine shops because of the cost, and the area could be considered an area without any selection pressure for development of resistance to the drug. A clinical failure rate of 11% and parasitological failure rate of 27% (95% CI, 17-49) observed with mefloquine in 20 mg/Kg single dose was alarming for the National Control Programme, which was already in problem with multi-drug resistance. However, there is no data on the resistance to mefloquine when used with an increased dose of 25 mg/Kg in two divided doses, which is well tolerated[8]. The study was therefore carried out to check whether there is resistance to high dose mefloquine within 28 days following treatment in the area where multi-drug resistance is present.

Materials and methods:

*Study design***:** The study was designed as an unblinded, controlled trial to describe the cure rate for the high dose of mefloquine. A few concurrent positive (blood slide confirmed falciparum malaria treated with seven days oral quinine) and negative controls (blood slide negative for *P. falciparum* and were not treated) were included primarily to see the re-infection rate. However, in the positive controls, clinical and parasitological cure as outcome were also recorded.

*Study site***:** The study was conducted in a primary care hospital [Ramu Upazila Health Complex (RUHC)] situated in a high-risk malarious area of the country, between January and August 1998. The RUHC is the only in-patient facility for about 200,000 population over an area of about 191 square kilometers. The area consisted mostly of forested, deforested and forest-fringe areas and some plain areas with valleys. The transmission is considered intense and perennial, with a largely stable population with malaria accounting for about half of the in- and out- patient load in the study hospital.

*Study population***:** The patients, screened at the outpatient department, presented with fever or history of fever over the previous 48 hours, suspected of having uncomplicated malaria, and were subjected to blood film examination. Positive cases were checked for exclusion criteria. A trained laboratory technician measured parasite density immediately. Male patients aged between 12 and 60 years with asexual *P. falciparum* parasite density between 500-200,000/cmm were initially selected. Those agreeing with written informed consent to take part in the investigation, to choose the treatment regimen by lottery and to remain in hospital for 28 days were enrolled, admitted and assigned to treatment regimen. Pregnant and lactating women, and patients with a history of taking antimalarials over the previous one week, presence of any of the severe manifestations, co-existence of other infections, co-infection with *P. vivax*, and known hypersensitivity to quinine or mefloquine, and patients with history of psychiatric illness were excluded.

*Study size and allocation of treatment***:** Patients fulfilling the eligibility checklist were enrolled, admitted and assigned to treatment regimens by lottery. The sample size chosen was 70 for mefloquine. In the same setting it was decided to recruit five negative (healthy) controls, who got no treatment but monitored with blood film throughout the study, to ensure that there was no transmission in the ward. In addition, there was a control group of seven patients who were given Q7 regimen just to monitor the efficacy of quinine. Codes for treatment were prepared, kept in a jar with 10 codes for mefloquine and one code for Q7. Each time a patient drew his own treatment regimen, and the jar was re-filled in the same manner after being exhausted.

*Hospital arrangements***:** Patients were accommodated in a dormitory in the immediate neighborhood of the hospital, used earlier for accommodating hospital nurses. The whole dormitory was mosquito protected by wire-netting with smallest hole nets for all doors, windows and exhaust holes. The doors were provided with automatic door closers. The dormitory and

adjacent areas were insecticide-sprayed twice daily. The enrolled patients were allowed to go out of room after 7 AM and had to enter the dormitory by 4 PM. In addition to compensation for the work loss, the enrolled patients were provided with entertainment arrangements like TV, VCP, newspapers, news magazines and other indoor games facilities (carom, ludu, chess and playing cards), popular in the area.

Drug regimens: The treatment groups were group I (mefloquine, 25 mg/Kg, in two divided doses, six hours apart) and group II [oral quinine sulfate tablets 10 mg/Kg/dose eight hourly for seven days (21 doses)]. Single dose primaquine 45 mg base, was used in all cases on the last day of treatment according to the national guidelines. The drugs used were Larium® from F. Hoffman-la-Roche, Basel, Switzerland and Quinine tablets from Jayson Pharmaceuticals Ltd., Bangladesh. Patients were weighed and doses were rounded to the nearest half tablet. The maximum dosage of drugs used were 1800 mg/day for quinine and 1500 mg for mefloquine. Each treatment dose was administered by a team nurse and observed for one hour thereafter for vomiting. The total dose was replaced in case of vomiting within one hour of ingestion and again observed in the same manner. The patients had daily clinical follow-up and blood slide examination during days 0 to 7 and thereafter on days 14, 21 and 28.

Recrudescent treatment: Patients who had fever (more than 100^0F) and parasitaemia (clinical treatment failure) from day 3 through day 28, were given alternative antimalarial treatment regimens, i.e., seven days oral quinine for the mefloquine and Q7 failures with seven days of oral quinine plus seven days of oral oxytetracycline. Voluntary withdrawal, development of severe manifestations and overt toxicity (hypersensitivity) to drugs were considered reasons for dropping patients from the study.

Definitions (WHO, 1995) used in outcome measurement:

Clinical response was categorized as –

1) Early treatment failure (ETF): Study subjects with parasitaemia and persistent fever from day 3 onwards, as well as those whose condition has worsened before day 3;
2) Late treatment failures (LTF): Study subjects with initial clearance of fever (body temperature less than 100^0F) by Day 3 but with persistent/recurrent parasitaemia and fever (body temperature more than 100^0F or history of fever) at a later time over the observation period; and
3) Adequate clinical response (ACR): The remainder (excepting those withdrawn because of a change of diagnosis or lost to follow-up).

Parasitological response was categorized as –

1) R III: Density of parasite on day 2 more than 25% of density on day 0, or alternative antimalarial therapy was required on or before day 2;
2) R II: Positive on day 2, with a density less than 25% of density on day 0, and either positive on day 7 or alternative antimalarial therapy was required on any of days 2 to 7;
3) R I: Negative or positive (less than 25% of day 0) on day 2, negative on day 7 and positive anytime thereafter (within 28 days); and
4) S: The remainder including those positive on day 2 (with density less than 25% of density on day 0) and negative thereafter.

Fever clearance time (FCT) was defined as the time from admission to the start of at least 48 hours when the temperature remained below 100^0F. Parasite clearance time (PCT) was defined as the time between admission and the first of the two consecutive negative blood slides. FCT and PCT were calculated from the initial responders (those who failed to clear fever and parasitaemia and received alternative treatment were not followed). Haemoglobin level was estimated by colour matching technique and done on days 0, 14 and 28 to observe the haematological response.

Statistical analysis: Data analysis was done using EPI INFO 6.04 statistical package. Statistical tests used were *chi-square* for frequency, ANOVA (*t-test*) for continuous variables and Kruskal Wallis as non-parametric test. Confidence intervals were determined by exact binomial distributions. Means ($\pm$ standard error of the mean), median (range) and percentages (with 95% CI) were used to describe the parameters.

Results:

Completed data from 77 cases and five healthy controls were available for analysis. One case was

lost to follow up in the mefloquine group; it was excluded and an additional case was recruited. The baseline percentiles of the study population characteristics and actual drug dosage per kilogram received after breaking down the tablets to the next half pill are shown in Table-I. The socio-demographic characteristics of the populations (positive and negative controls) in the control group were similar to the study population (data not shown).

Table-II describes the outcome parameters. No clinical failure was observed in the mefloquine group. One patient in the quinine group had clinical failure on day 27. None of the healthy controls developed any clinical illness. Mean PCT and FCT were significantly shorter with mefloquine compared to quinine. RIII type of parasitological response was observed in four cases with mefloquine and one case with quinine, however all of them showed radical cure up to 28 days of follow up without alternative antimalarial treatment.

Both the drug regimens were well tolerated. Two patients on Q7 had reversible cinchonism from day 5 onwards. Twenty two patients complained of nausea, nine had vomiting, four had loose motion and in none of them additional treatment was required to relieve the symptoms.

Table-I

Description of study population and actual drug-doses received in baseline percentiles (n=70)

Variables	Minimum	25%ile	50%ile	75%ile	Maximum
Age of subjects (years)	12.0	18.0	20.0	26.0	60.0
Body weight (Kg)	27.0	40.0	46.5	50.0	60.0
Duration of fever at inclusion (days)	1.0	3.0	4.0	7.0	45.0
Initial parasite count (n/cmm)	960	4260	12000	24624	150,400
Haemoglobin at inclusion (g/dl)	7.0	9.5	10.6	11.7	14.5
Actual total drug-dose received (mg/kg)- Mefloquine	23.1	24.0	25.0	25.0	26.5
Actual total drug-dose received (mg/kg/day)- Quinine	25.0	27.0	27.6	32.7	33.7

Table-II

Response to therapy in the four groups (n=77)

Type of response to therapy	Group I	Group II	P-value
	N (%) (95% CI)	N (%) (95% CI)	
Adequate clinical response (ACR)	70/70 (100) (95-100%)	6/7 (86) (42-100%)	
Early treatment failure (ETF)	0/70	0/7	
Late treatment failure (LTF)	0/70	1/7 (14) (.4-58%)	
S (Radical cure)	66/70 (94) (86-98%)	06/07 (86) (42-100%)	
R I	0/70	0/07	
R II	0/70	0/07	
R III	04/70 (06) (1-14%)	01/07 (14) (.4-58%)	
PCT* (days, mean+SD)	2.49 + .76	2.57+ .79 (n=7)	<.001
FCT** (hours, means+SD)	27.17+21.05	33.43+ 32.65	< .005

Discussion:

The study showed a 100% (95% CI, 95-100) in-vivo cure rate for mefloquine high-dose in uncomplicated falciparum malaria in malaria endemic study area in Bangladesh. In the previous study using mefloquine, the rate of clinical failure was 11% and that of parasitological failure was 27% (R III, R II and R I failures were 10%, 4% and 13% respectively)[8]. The reasons for clinical and parasitological failures found in the earlier study could be due to the lower dosage used of mefloquine and/or due to re-infections acquired in the community. However, with mefloquine observed R III failures (6%) were still observed, which could suggest onset of *P. falciparum* resistance, and should be kept under continued monitoring over time.

It is alarming to find even one clinical failure out of seven patients on Q7, in a situation free from re-infections. The recrudescence during the earlier study in Q7 group was considered re-infections, but they could be recrudescence as well. R III response was also observed in another case on Q7, which ultimately showed radical cure during follow up.

In the earlier study, the PCT was significantly ($p < .02$) lower with Q7 regimen compared to mefloquine and the FCT was not significantly different. But now, a significant prolongation of the PCT and FCT was observed in the Q7 group. Though, the number of cases in the Q7 group was very small, clinical failure, R III response and prolonged PCT and FCT, all could suggest beginning of resistance to Q7 in the study area.

Resistance to mefloquine appeared in regions at border between Thailand and Cambodia within a few years, perhaps owing to widespread use of quinine, to which it is structurally related[9]. Resistance in that border region remains high[10]. However, in nearby regions resistance to mefloquine remains relatively low[11]. Smithius et al reported more than 90% sensitivity to mefloquine (at a dose of 15 mg/Kg) from the western border region of Myanmar[12]. In Bangkok 86% of cases treated with mefloquine (at a dose of 25 mg/Kg) was sensitive[12]. The findings of failure to mefloquine 15 mg/Kg in an earlier study and also finding of failure to quinine could represent beginning of failure to both these drugs, and demands a continued monitoring of efficacy of these drugs over time. The present recommendations of WHO encourages not to use single antimalarials alone in order to preserve efficacy of the new drugs, instead combination of antimalarials preferably artemisinin based one is now recommended[13]. The high efficacy of large dose mefloquine in the present study suggests that mefloquine plus artesunate may be an alternative option for such a regimen for uncomplicated falciparum malaria instead of artemether lumefantrine. Both the regimens have been found to be highly effective in another high endemic area of malaria in Bangladesh[14].

It is apprehended that results of this study could be skewed, since the study population represent only those seeking treatment at a government facility, an estimated 20% of total malaria cases. A pre-condition for 28 day hospitalization could also impose a selection bias. However, since the majority of cases attend private drug vendors prior to reporting to health centres, the patients here may be selected for high levels of drug resistance.

The two consecutive studies with eight days hospitalization versus 28 days hospitalization, suggest that a higher failure rate could be detected by the 8-day trial. Thus, on a programme basis, and for a rapid assessment of drug efficacy situation, much simplified tests like 14-day in-vivo test on an outpatient basis[11] may be sufficient. But for new drugs (like mefloquine in the study area), a 28-day test with prevention of re-infection is required as an optimal test of efficacy of antimalarials.

The recommendation for use of mefloquine in the earlier study as the second line agent in the area appears justified. However, the drug should not be used alone in order to conform to the WHO policy. The efficacy trials should be continued in the area to specially document the possible declining sensitivity to Q7 regimen and the status of Q3+SP regimen should be re-evaluated in the area, including the sensitivity of the component parts.

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Immediate Problems and Clinical Outcome of Preterm Infants

S BEGUM[a], MD. SHAHIDULLAH[b], NA BEGUM[c], SA RAHMAN[d]

Summary:

This prospective study was done to understand the immediate problems and clinical outcome of preterm infants. A total of 50 consecutively hospitalized preterm infants were enrolled into this study, 56% of them were male and 44% were female. Among them 40% and 2% were very low birth weight (VLBW) and extreme low birth weight (ELBW) respectively and 58% were low birth weight (LBW) infants. Eighty percent of study population survived, 18% died and 2% were discharged against medical advice. Each baby had one or a combination of problems like infection (32%), perinatal asphyxia (20%), jaundice (24%), poor feeding (24%), apnoea (14%) and convulsion (10%). Perinatal asphyxia (45%) and septicaemia (22%) were the major causes of death. Mortality rate was highest (75%) among babies having gestational age 28 weeks or less and lowest (8.40%) in those having gestational age 35 weeks and above. In addition to prematurity, birth weight was the important factor influencing the mortality. The study concludes that neonatal infection, perinatal asphyxia, poor feeding, jaundice, apnoea and convulsion are the major problems of preterm newborns. High case fatality rates among preterm infants were due to perinatal asphyxia, neonatal infection and ELBW.

(J Bangladesh Coll Phys Surg 2005; 23 : 113-117)

Introduction:

A liveborn infant delivered before 37 weeks from the first day of the last menstrual period is termed preterm by the World Health Organization[1]. Preterm infants account for the majority of high-risk newborns[2]. The preterm infants faced a variety of physiological problems like apnoea, infection and poor feeding. A preterm infant may be appropriate for gestational age or small for gastational age, depending on birth weight above or below 10th centile for gestational age respectively. In Bangladesh, the incidence of low birth weight (LBW) is about 30%[3]. In one hospital-based study, it was shown that incidence of preterm was 16.3%[4]. Among them preterm weighing more than 2.5 kg was 32% and preterm LBW was 68%. In another study, it was found that 9.57% babies were preterm[5].

Prematurity is related to difficulty in extra-uterine adaptation due to immaturity of organ system. Apnoea of preterm babies occurs in 25% of preterm low birth weight babies[6]. Incidence of respiratory distress syndrome (RDS) in preterms is 6.56%[7]. Twenty percent of premature infants develop necrotizing enterocolitis (NEC)[2]. Preterm infants are vulnerable to infection as compared to term neonate. Preterm babies have a highest risk of death during the neonatal period[8]. Preterm LBW infants are five times as likely to die as term low birth weight infants[9]. So far it is known, no study has been done regarding the problems and outcome of preterm infants in this country. The present study was conducted with the aim to find out the immediate problems and clinical outcome of preterm infants.

Materials and methods:

This prospective study was done in neonatal unit of Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University during September 2003 to February 2004. The neonatal department of this hospital has intensive care unit facilities having incubators, radiant warmer and ventilator support system. A total of 50 consecutively admitted infants were included in the study. The inclusion criterion was inborn and outborn neonates with gestational period less than 37 completed weeks and the exclusion criterion was inborn and out born neonates with gestational period 37 completed weeks and more. After taking the verbal consent from the attendent, the relevant information from the history and physical

a. Dr. Suraiya Begum, FCPS. Paediatrician.
b. Dr. Md. Shahidullah, FCPS. Professor and Head of The Division of Neonatology, Bangabandhu Sheikh Mujib Medical University, Dhaka.
c. Dr. Nargis A Begum, FCPS, MD (Neonatology). Paediatrician.
d. Dr. Shahana A Rahman, FCPS. Professor of Paediatrics, Bangabandhu Sheikh Mujib Medical University, Dhaka.

Address of correspondence: Dr. Suraiya Begum, 197, Water works road, Chawkbazar, Dhaka-1211, E-mail: drsuraiyabegum@yahoo.com, Phone: 7317312, Cell Phone: 0175131535.

findings were recorded within 24 hours of admission in a purposely prepared questionnaire. Elaborate antenatal, natal and postnatal histories were taken. New Ballard Scoring system was used for assessment of gestational age[10]. Birth weight was taken by using standard scale with 50 grams sensitivity. The necessary laboratory investigations e.g. haemoglobin estimation, complete blood count, blood culture, blood glucose estimation, CRP, urine analysis, CSF study, X-ray and ultrasonography were done as indicated by clinical evaluation. The standard management of the preterm infants was then offered according to the individual need. Each infant was reassessed daily till discharge or death to assess the problems and outcome. Data were recorded in a pretested questionnaire and analysed using relevant software.

Results:

A total of 50 preterm infants were included in this study, 28 (56%) of them were male and 22 (44%) were female. Ten babies (20%) had gestational age of 30 weeks or below and 40 (80%) had gestational age of 31-37 weeks. Irrespective of sex one (2%) had normal birth weight, 28 (56%) were of LBW, 20 (40.0%) were VLBW and one (2%) was of ELBW.

Infection was found in 32% babies and found to be the major problem in preterm babies (Table-I). Other problems that were found included perinatal asphyxia (20%), poor feeding (24%), jaundice (24%), apnoea (14%), convulsion (10%), NEC (4%), temperature instability (6%), hypoglycaemia (8%), hyperglycaemia (6%), hypocalcaemia (6%), RDS (6%), patent ductus arteriosus (4%), intraventricular haemorrhage (2%), acute renal failure (2%) and congenital malformation (4%). Majority of infants had more than one problem.

Table-II shows the outcome of 50 preterm babies of different gestational age groups. It is evident from the table that as the gestational age increased the rate of survival increased. Out of total 50 preterms, 80% survived, 18% died and 2% was discharge against medical advice. Among four babies at gestational age of 28 weeks and below, three died and rest was taken away by the parents against medical advice. Out of 12 infants of 35 - 37 weeks of gestational age group, 91.60% survived and 8.47% died.

Table III shows the mortality in different birth weight categories. The single neonate in the less than 1000 gm group died, causing the mortality rate to be 100%. An increased birth weight caused increased survival. In 1500 - <2500 gm weight group babies, mortality rate was 17.8% and there was no mortality in the 2500 grams or more weight group.

Table IV shows the causes of death in preterm babies. Perinatal asphyxia was the commonest cause of death (45%). Other causes were septicaemia (22%), apnoea (11%), RDS (11%) and intraventricular haemorrhage (11%).

Table-I

Distribution of preterm babies by immediate major problems. (n=50)

Problems	Number	Percentage
Infection	16	32.00
Perinatal asphyxia	10	20.00
Poor feeding	12	24.00
Jaundice	12	24.00
Apnoea	07	14.00
Convulsion	05	10.00
Necrotizing enterocolits	02	4.00
Temp. instability	03	6.00
Hypoglycaemia	04	8.00
Hyperglycaemia	03	6.00
Hypocalcaemia	03	6.00
Respiratory distress syndrome	03	6.00
Patent ductus arteriosus	02	4.00
Intraventricular haemorrhage	01	2.00
Acute renal failure	01	2.00
Congenital malformation	02	4.00

Table-II

Outcome of preterm babies by gestational age (n=50).

Gestational age (weeks)	Total Number	Survived		Died		Discharged against medical advice	
		Number	Percentage	Number	Percentage	Number	Percentage
28 and below	04	00	0.0	03	75.00	01	25.00
29-30	06	05	84.0	01	16.00	00	0.00
31-32	12	10	83.0	02	17.00	00	0.00
33-34	16	14	87.5	02	12.50	00	0.00
35-37	12	11	91.6	01	8.40	00	0.00
Total	50	40	80.0	09	18.00	01	2.00

Table-III

Outcome of preterm babies by birth weight (n=50).

Weight in grams	Total number	Survived		Died		Discharged against medical advice	
		Number	Percentage	Number	Percentage	Number	Percentage
<1000	01	00	00	01	100	00	00
1000-<1500	20	16	80	03	15	01	05
1500-<2500	28	23	82	05	18	00	00
2500	01	01	100	00	00	00	00
Total	50	40	80	09	18	01	02

Table IV

Mortality of preterm babies by cause of death (n=9).

Causes of death	Number of death	Percentage
Perinatal asphyxia	04	45.00
Septicaemia	02	22.00
Apnoea	01	11.00
RDS	01	11.00
IVH	01	11.00
Total	09	100.0

Discussion:

Preterm infants account for a high morbidity, disability and mortality all over the world[10]. In this study, infection was found to be the commonest problem (32%) in preterm babies. A recent study from Malaysia reported neonatal sepsis as common as 5-10% in preterm babies[11]. Prematurity increases the risk of infection by 20-fold[12]. Higher incidence of infection in this study is probably due to improper antenatal care regarding maternal infection screening and treatment, inadequate aseptic precaution during delivery and inadequate infection control programme including hand washing, lack of visitor control during hospital care etc.

In this study, perinatal asphyxia was found in 20% cases, which is much higher than other observations. The incidence of perinatal asphyxia is about 1-1.5% in most centers of developed countries[13]. The incidence of perinatal asphyxia is usually related to gestational age and birth weight. It occurs in 9% of infants less than 36 weeks gestational age and in 0.5% of infants more than 36 weeks gestational age[12]. High incidence of perinatal asphyxia in this study could be due to inadequate antenatal and perinatal care. Poor feeding was observed among 24% cases in this study in contrast to another study that found 14.81% cases with this problem[14]. High incidence of feeding

problems could be due to the fact that more sick infants like asphyxiated and septicaemic preterm babies were included in this study.

Jaundice is another common problem in preterm newborns. In this study, 24% cases of preterm babies developed jaundice which is higher than what was observed by other workers[14,15]. Greater incidence of jaundice in this study could be explained by the fact that asphyxia and infection were found more in this study population. No infant developed kernicterus due to early treatment with phototherapy and exchange transfusion as and when needed.

Apnoea was found in 14% cases in this study. Tabib et al in their study found that 8.33% preterm infants had apnoea[14]. James et al found apnoea of prematurity occurring in at least 25% of preterm low birth weight babies[6]. Panja et al found apnoeic spell as one of the major causes of death in preterm babies[16]. Low incidence in the present study may be due to the fact that less number of VLBW and ELBW babies were included. Another factor may be that, cases of apnoea were missed due to lack of continuous monitoring by apnoea alarms.

Ten percent cases had convulsion which is consistent with the study done by Hosne ara et al (11.5%)[7]. Higher result (20%) was found by another observation[16]. Convulsion in this study population was associated with asphyxia, septicaemia, hypoglycaemia and hypocalcaemia.

Three (6%) preterm babies presented with RDS in this study which is consistent with findings of Tabib et al who found RDS in 5.55% preterm babies[14]. Another study found incidence of RDS to be as high as 13.43%[17]. Panja et al in their study found RDS in as high as 10.0-15.0% of study subjects[18]. Occurence of RDS is inversely proportional to gestational age and occurs in all parts of the world. The incidence is 1.0-3.0% of all births irrespective of birth weight and gestational age but it is important as it is responsible for the deaths of many preterm infants[12].

In the present study, necrotizing enterocolitis (NEC) and patent ductus arteriosus (PDA) was found in 4% cases each and hypothermia in 6% preterm babies. Another study observed much higher incidence of NEC, PDA and hypothermia which were as high as 30%, 47% and 54% respectively[19]. Lower incidence of NEC, PDA and hypothermia in this study probably reflects inclusion of less number of VLBW and ELBW babies in this study.

While analyzing the immediate outcome, 80% preterm babies survived, 18% expired and 2% was discharged against medical advice. Seventy five percent died at gestational age of 28 weeks or below and 8.4% died with gestational age 35 - 37 weeks. It was found that as gestational age increased, mortality rate decreased and happened at statistically significant level. Other studies also showed similar findings[14,15,17,]. Two studies done earlier by Manajjir et al and Tabib et al in the same institute showed 20% and 28.12% mortality among babies with gestational age of 33 - 37 weeks which were much higher than the observations of similar age group in the present study[14,15]. The lower rate of mortality in this study may be explained by the recent improvement in the management of very sick and preterm infants in this institute.

The major cause of death in the present study was perinatal asphyxia (45%). Death due to perinatal asphyxia might be related to lack of proper antenatal care, obstetric complications, late referral for admission to neonatal unit and overall lack of appropriate nursing care. In this study 22% deaths were due to possible septicaemia alone or in combination with other problems. Different studies in this country have found 42.67%, 42.0% and 14.82% of deaths due to perinatal asphyxia and 21.87%, 25.0% and 22.2% due to septicaemia respectively[14,16,17]. Eleven percent of deaths due to RDS in this study is consistent with the findings of other studies[16].

In this study, perinatal asphyxia, neonatal infection, poor feeding, apnoea and convulsion were the major problems of preterm newborns. High case fatality rates among preterm infants were mostly due to perinatal asphyxia and neonatal infection. Eighteen percent of the preterm newborns died in the present series.

The study recommends further study covering large sample size including urban and rural population to assess the health status of preterm infants in our country. This study also recommends strengthening of antenatal and perinatal care in the country.

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A Comparative Study of Root Canal Shaping by Automated Rotary Ni-Ti and Conventional Hand Instruments

MS ALAM[a], AKM BASHAR[b]

Summary:

A total 30 root canals, curvature ranging between 0 and 35 degree, were divided into three groups, A, B and C, consisting of 10 canals in each. Five canals from each group were prepared with FlexMaster using crown-down technique and the others with hand instrument K-Felxofile using conventional and step-back technique. Irrigation was done with sodium hypochlorite (NaOCl) solution and ethylene di-amine tetra-acetic acid (EDTA) after canal preparation by each instrument size. All the prepared roots were then cut longitudinally using diamond burs in turbine handpiece. Canal preparation was examined separately with scanning electron microscope (SEM). The preparation time was also recorded. Data were analyzed statistically using the non-parametric test (Mann-Whitney U test). Completely cleaned root canals were not found with any of the two instruments. FlexMaster instruments maintained the original canal shape and curvature with uniform and regular dentine surface. The time taken to prepare root canal by FlexMaster was significantly better (p< 0.01) than hand instruments.

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Introduction:

Primary goal of root canal treatment is to completely clean and shape the root canal system, maintaining the original path of root canal. Over the years, a variety of instruments and techniques have been proposed to reach the goal. Optimal shaping and cleaning of root canals is one of the difficult aspects of root canal procedure. Manual instrumentation, to reach the goal, is generally believed to be more effective than mechanical instrumentation[1-4]. But several studies have concluded that none of the instrumentation techniques or devices is able to produce completely cleaned root canals, maintaining the original curvature, especially when the canal is curved[1, 5, 6]. It is, therefore, important to develop an instrumentation technique that will prepare the root canal maintaining the original curvature in a minimum time. However, some investigators have recently claimed that automated devices using rotary Nickel-Titanium instruments with various tapers led to good instrumentation results, even in severely curved root canals[7, 8]. But a little is known about the effectiveness of these systems. Rotary FlexMaster instruments (VDW, Antaeos, Munich, Germany) have recently been introduced with varying tapers and designs. According to the manufacturer, the FlexMaster instruments, available in 2, 4, 6 and 11% taper K-type blades with their unique cross section similar to a triangle having convex sides offer increase stability, high cutting efficiency, good debris removal and tortional resistance. Three different tapers made the system best suited for each canal portion and reduced stress on instruments. Instrument with 11% taper is used as an introfile for coronal enlargement; 4% and 6% taper instruments are used for radicular canal preparation using crown-down technique whereas 2% taper is used for safe apical enlargement (Fig-1). The non cutting tip prevents canal transportation and ledge formation while the unique depth marking, being X-ray visible, facilitates clear identification of the file position in the canal thus determines correct working length. With all these benefits, FlexMaster system is claimed to be an efficient, reliable, simple, clear and safe system for easy and faster preparation of all types (more or less straight, moderately curved & curved) of root canals. So far, there are only a very few experimental studies have been carried out on the efficiency of FlexMaster system[9-12]. This experimental study was designed to compare rotary Ni-Ti FlexMaster instruments with K-Flexofile hand instruments in shaping root canals. Time needed for completion of root canal preparation were also evaluated.

a. Dr. MS Alam, BDS,DCD, Professor, Dept of Conservative Dentistry and Endodontics, Dental faculty, BSM Medical University, Dhaka

b. Dr. AKM. Bashar, BDS, MS, Consultant Endodontist, New Oro-Dental Clinic, 106/A, Green road, Farmgate, Dhaka

Address of correspondence : Dr. Md. Shamsul Alam, BDS, DCD, Professor, Dept of Conservative Dentistry and Endodontics, Dental faculty, BSM Medical University, Dhaka, Bangladesh
Tel: 8614545-9, ext. 458, 0171-031755

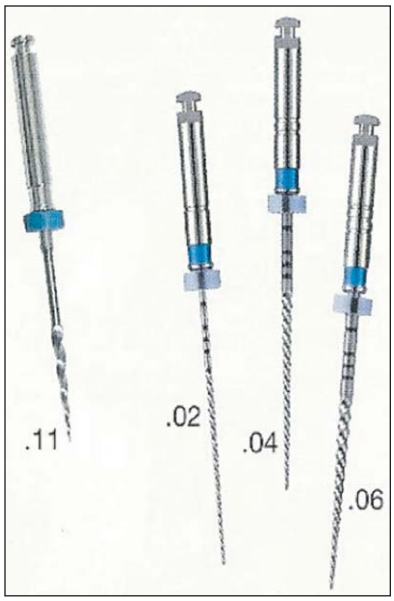


Fig.-1: *Showing Flexmaster instruments with different tapers.*

Legends to Figure 1: FlexMaster instruments, available in 2, 4, 6 and 11% taper K-type blades. Instrument with 11% taper is used as an introfile for coronal enlargement; 4% and 6% taper instruments are used for radicular canal preparation using crown-down technique whereas 2% taper is used for safe apical enlargement.

Materials and methods:

A total number of 47 extracted human maxillary and mandibular molars were collected. Coronal access cavities were prepared using diamond burs on a high speed handpiece according to the standard extension for optimal inspection of all root canal openings. Radiographs were taken with ISO number. 10 or 15 files, using paralleling technique, to determine the canal curvatures according to the method described by Weine in 1968[13]. Finally 30 root canals out of 119 that met the criteria for acceptance (Table-I) were selected. The selected specimens were divided into three groups and prepared with either FlexMaster rotary Ni-Ti instruments or with stainless steel hand K-Flexofiles as described in Table-II. Irrespective of the system applied, after each instrument, the canal was flushed with 5.25% NaOCl and 15% EDTA alternatively[14]. Selected 15 canals for control (five canals randomly selected from each group) were prepared with stainless steal hand K-Flexofile instruments. Specimens in group A were prepared by conventional method whereas specimens in group B and C were prepared by Step-back technique. Residual 15 canals (five canals from each group) with different curvatures were prepared with rotary Ni-Ti FlexMaster instruments using Crown-down pressureless technique in a low torque motor (E Master, VDW, Munich, Germany) at 150-300 rpm contra angle 4: 1 handpiece (W & H, Burmos, Austria) according to the manufacturer's instructions (Table-II and Fig.-2)

Table-I

Criteria for acceptance of the root canals

Inclusion criteria	Exclusion criteria
1. Canal curvature ranging 0° to 35° according to method described by Weine in 1968	1. Wisdom teeth
2. Previously untreated root canals	2. Teeth with open apices
3. Canals that could be negotiated to the apical foramen with a file size ISO 10 without any resistance	3. Teeth with filling
4. Initial binding file that did not exceed size ISO 20	

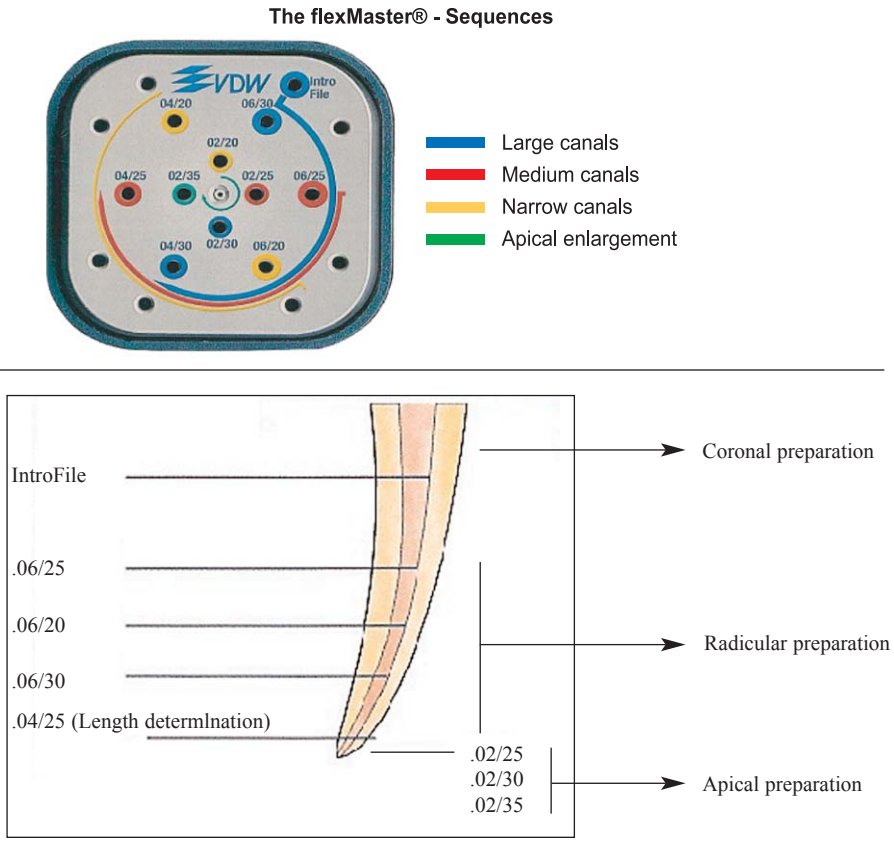
Table-II

Distribution of specimens and corresponding preparation system

Group	Number of specimen (root canals)	Degree of canal curvature	Number of canals prepared	
			FlexMaster (Crown-down technique)	K-Flexofile (conventional and step-back technique)
A	10	0-15 (more or less straight)	05	05
B	10	16-30 (moderately curved)	05	05
C	10	>30 (curved canals)	05	05

Sequence of FlexMaster Instrumentation:

- Estimation of working length by X-ray
- Determination of the size of the canal (large, medium, narrow) and selection of the instrumentation sequence as guided by the manufacturer.
- Creation of straight coronal access and coronal enlargement by Introfile
- Preparation of the radicular canal short of working length (WL-1mm) with sequential series of FlexMaster files of varying tapers (4% and 6%) using crown-down technique as guided by the manufacturer for any specific size (large, medium or narrow) of canals



- Determination of exact working length
- Apical enlargement by using FlexMaster 2% files in increasing sizes as guided by canal anatomy

Fig-2: *Diagrammatic representation of root canal preparation with different taper FlexMaster instruments*

Following examinations were done:

Time required for canal preparation:

Mean working time includes the time for canal shaping, time needed for instrument change and irrigation. Time required for canal preparation was determined for each preparation and the difference in the times required were analyzed statistically using Mann-Whitney's U test; a value of $P<0.01$ was considered significant.

Shaping of the prepared canal:

After preparation, all the roots were separated from crown with a diamond disc, then the root canals were flushed with 5.25% NaOCl and dried with absorbent paper point. All the canals were split longitudinally into two halves with diamond fissure burs in a turbine handpiece, polished and prepared for SEM evaluation. Evaluation was carried out by a second examiner who was blind with all respect of all to the

experimental groups. A SEM (JEOL JSM-T220A scanning microscope, Tokyo, Japan) which produced a 15 kV alteration voltage, at the Department of Operative Dentistry, Showa University, Japan was used to examine and take micrographs of every specimen at 35-1000X magnifications. Canal walls were qualitatively evaluated using the same set of reference photograph as in previous investigations[1,15,16].

Results:

Time required for canal preparation:

Mean working time taken to prepare the canals with FlexMaster system and stainless steel hand K-flexofile is shown in Table-III. Assessments of canal preparation revealed that the FlexMaster instruments have taken almost half of time in comparison to hand instruments irrespective of canal curvature. The mean working time was 4.7±0.76, 5.1±0.74 and 5.6±0.65 minutes for FlexMaster instrumentation and 9.7±0.57, 10.4±1.19 and 12.6±0.65 minutes for the stainless steel hand instruments. The difference was statistically significant ($P < 0.01$) for two different instruments in all groups but the mean time taken by different groups of the same type instrument was not significant.

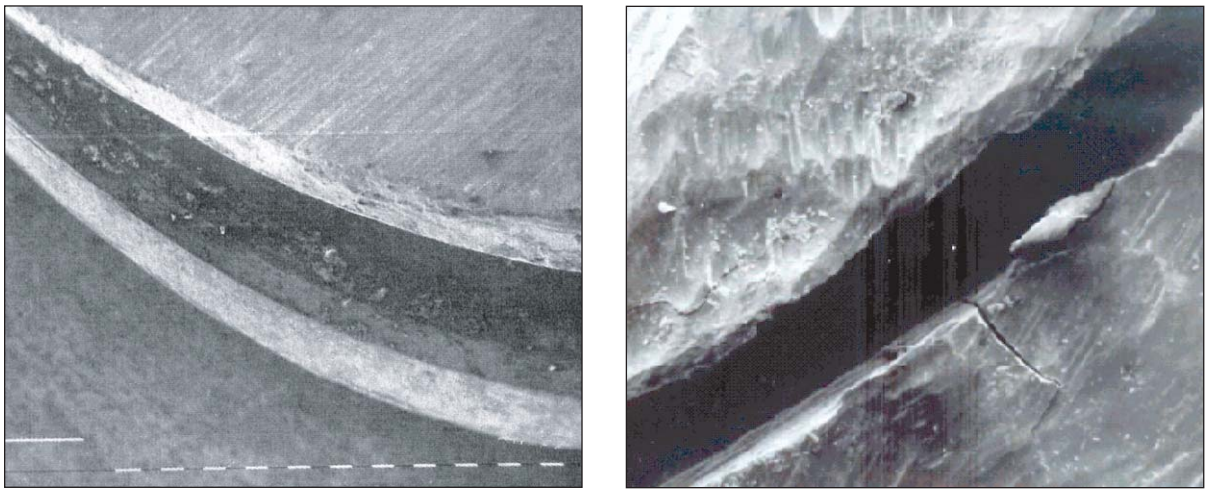
Root canal shaping:

The FlexMaster instruments maintained the original canal shape without any deformity in the canal walls whereas the manual technique, in which hand instrument is used, did not maintain their original shape leaving behind irregular deformed surfaces (Fig.-3).

Table III

Mean working time required by different technique

Group	Degree of canal curvature	Mean working time required in minute	
		FlexMaster (Crown-down technique)	K-Flexofile (conventional and step-back technique)
A	0-15 (more or less straight)	4.7 ± 0.76	9.7 ± 0.57
B	16-30 (moderately curved)	5.1 ± 0.74	10.4 ± 1.19
C	>30 (curved canals)	5.6 ± 0.65	12.6 ± 0.65



(A) (B)

(A) Canal prepared by FlexMaster, curvature of root canal is maintained (No irregular deformed surface) (B) Canal prepared by K-Flexofile, curvature of root canal is not maintained FlexMaster with irregular deformed surface (original magnification x 35).

Fig.- 3: *Canal prepared by FlexMaster and by hand instrument K-Flexofile in apical region.*

Discussion:

In the present study, the root canal preparation efficiency of two instrumentation methods were studied qualitatively by means of a SEM evaluation in the apical and middle portions of the canals. It has been evaluated that only the FlexMaster instruments maintained the original shape without any deformity in the canal wall. In both Ni-Ti and hand instrumentation techniques, partially un-instrumented areas with remaining debris were also found. Similar finding has also been described by other authors, [1, 4, 5, 9] and it is consistent with two other investigations using micro-computer tomography assessment of the canal shapes[17,18]. Peters reported that approximately 35% of the canal surface area was not prepared when different nickel-titanium preparation techniques were used[18]. Although it is recommended to use antibacterial irrigants in combination with chelating agents in order to remove debris as well as the inorganic/organic smear layer[1,19,20] some investigators used sodium hypochlorite alone due to its antibacterial and organic tissue-dissolving properties[10, 21, 22], but Yamada reported that it is not possible to remove the smear layer with sodium hypochlorite[23]. In the present study, 5.25% sodium hypochlorite and 14% EDTA was used as chelating agent but they failed to remove the loose debris and smear layer from both experimental and control groups. Further study may be carried out to evaluate the strength and volume of different root canal irrigants in removing the debris and smear layer during preparation of root canal in the same procedures.

FlexMaster instrumentation was significantly ($p<0.01$) faster than the hand instrumentation. This finding corroborates with the results of several others, that the instrumentation times or other performance outcomes with rotary Ni-Ti instruments are substantially better than those of hand instruments[9, 11, 24,25].

Within the parameters of this study, the FlexMaster maintained original canal curvature in shorter time better than hand instruments. Because of not maintaining the original curvature of the root canal and leaving behind irregular deformed surface, it can be hypothesized that the stainless steel hand instrumentation left the possibility of canal space being inadequately debrided of vital or necrotic pulp tissue, subsequently an inadequate obturation of the root canal space.

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A Review on Osteoarthritis

MR CHOUDHURY[a], MM ZAMAN[b], SM HUQ[c], F ALAM[d], F HAKIM[e], PR SAHA[f], SA HAQ[g]

Summary:

Osteoarthritis (OA) is a common musculoskeletal condition worldwide. In Bangladesh, it is also the most prevalent rheumatological disease. Recent research on the disease pathogenesis and treatment has stimulated new interest in OA. The previous "degenerative" and "wear and tear" concept of OA has been discarded. Diagnosis of difficult cases has already improved with new imaging techniques and improving further. Studies have emphasized the positive role of patient education and the multidisciplinary approach to the disease. Numerous new studies on the pharmacological modality of therapy of OA have shown paracetamol to be the most appropriate first line drug. Emphasis is also on the cautious use of NSAIDs, especially in at-risk patients. The cyclooxygenase-2 specific inhibitors also show less gastrointestinal toxicity in OA but there are warnings. Short-term benefit is found with intra-articular steroids and longer term with hyaluronic acid. Glucosamine is shown to be a safe drug in OA. Further studies are going on for the development of a disease modifying osteoarthritis drug but are not yet approved for prescribing. This review summarizes the current evidences on OA.

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Introduction:

Osteoarthritis (OA), a common, chronic, degenerative, musculoskeletal disorder of unknown etiology represents failure of the diarthroidal (movable, synovial lined) joint[1]. It is one of the most prevalent disease in our society, with a worldwide distribution. It ranks fourth in health impact in women and eighth in men in the western world[2]. The recently concluded Community Oriented Programme for Control of Rheumatic Diseases (COPCORD) study has determined the prevalence of OA in Bangladeshi population. According to this study, OA prevalence in rural, slum and affluent areas are 7.4%, 9.0% and 11.3% respectively and tops all other rheumatological diseases in Bangladesh.

The name "osteoarthritis" emerged from the observation of the striking overgrowth of marginal and subchondral bone by the pathologists and radiologists at the turn of the century[3]. It has been regarded as an age related "wear and tear" phenomenon for many years until now. There are claims that this attitude led to the negative approach to research and treatment in OA. Some authors have also argued that the descriptor "degenerative" for OA is erroneous[4]. Recent research on the disease have led to newer concepts in pathogenesis and non-pharmacological and pharmacological modalities of management of the disease.

Classification:

Osteoarthritis is grossly classified into primary and secondary groups. The primary is again divided into localized and generalized forms. The latter is more prevalent in post-menopausal women with development of Heberden's nodes. Secondary OA is pathologically identical to the primary variety and here an underlying cause, such as trauma, obesity, Paget's disease or inflammatory arthritis, is present. Table-I gives a detailed description of the classification of the disease.

a. Dr. Minhaj Rahim Choudhury, FCPS (Medicine) MD (Internal Medicine) DTCD, Fellow Rheumatology (UK), Associate Professor (Medicine-Rheumatology), Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

b. Dr. M Mostafa Zaman MPH PhD, Assistant Professor (Epidemiology).

c. Dr. Syed Mahfuzul Huq MBBS, Emergency Medical Officer, National Center for Control of Rheumatic Fever and Heart Diseases, Sher-e-Bangla Nagar, Dhaka-1207, Bangladesh.

d. Dr. Faizunnesa Alam MBBS, Research Associate, National Institute of Cardiovascular Diseases and Hospital, Sher-e-Bangla Nagar, Dhaka-1207, Bangladesh (SMH).

e. Dr. Ferdous Hakim MBBS, Research Associate, ICDDR,B, Dhaka, Bangladesh .

f. Dr. Pradip Ranjan Saha FCPS, Consultant Physician, Labaid Cardiac Hospital, Dhaka, Bangladesh.

g. Prof. Syed Atiqul Haq FCPS (Medicine), MD, Professor, Department of Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

Address of correspondence: Dr. Minhaj Rahim Choudhury: 19, Sukrabad, Dhaka-1207, Bangladesh. Tel: 9666995(off) Mobile: 0189221095 Email: drminhaz@dhaka.net

Table-I

Classification of osteoarthritis[5]

I. Idiopathic/ Primary:
- A. Localized OA:
  1. Hands: Heberden's and Bouchard's nodes (nodal), erosive interphalangeal arthritis (nonnodal), first carpometacarpal joint
  2. Feet: hallux valgus, hallux rigidus, contracted toes (hammer/cock-up toes), talonavicular
  3. Knee:
     - a. Medial compartment
     - b. Lateral compartment
     - c. Patellofemoral compartment
  4. Hip:
     - a. Eccentric (superior)
     - b. Concentric (axial, medial)
     - c. Diffuse (coxae senilis)
  5. Spine:
     - a. Apophyseal joints
     - b. Intervertebral joints (discs)
     - c. Spondylosis (osteophytes)
     - d. Ligamentous (hyperostosis, Forestier's disease, diffuse idiopathic skeletal hyperostosis)
  6. Other single sites, e.g., glenohumoral, acromioclavicular, tibiotalar, sacroiliac, temporomandibular
- B. Generalized OA includes 3 or more of the areas listed above (Kellgren-Moore)

II. Secondary:
- A. Trauma:
  1. Acute
  2. Chronic (occupational, sports)
- B. Congenital or developmental:
  1. Localized diseases: Legg-Calve-Perthes, congenital hip dislocation, slipped epiphysis
  2. Mechanical factors: unequal lower extremity length, valgus/varus deformity, hypermobility syndromes
  3. Bone dysplasias: epiphyseal dysplasia, spondyloepiphyseal dysplasia, osteonychondystrophy
- C. Metabolic:
  1. Ochronosis (alkaptonuria)
  2. Hemochromatosis
  3. Wilson's disease
  4. Gaucher's disease
- D. Endocrine:
  1. Acromegaly
  2. Hyperparathyroidism
  3. Diabetes mellitus
  4. Obesity
  5. Hypothyroidism
- E. Calcium deposition diseases:
  1. Calcium pyrophosphate dihydrate deposition
  2. Apatite arthropathy
- F. Other bone and joint diseases:
  1. Localized: fracture, avascular necrosis, infection, gout
  2. Diffuse: rheumatoid (inflammatory) arthritis, Paget's disease, osteopetrosis, osteochondritis
- G. Neuropathic (Charcot joints)
- H. Endemic:
  1. Kashin-Beck
  2. Mseleni
- I. Miscellaneous:
  1. Frostbite
  2. Caisson's disease
  3. Hemoglobinopathies

Clinical Features:
Typical feature is pain that worsens on weight bearing and activity, which improves with rest. Morning stiffness of less than 20-30 minutes and gelling of the involved joints after periods of inactivity may also be present. Physical examination may reveal localized tenderness and bony or soft tissue swelling. Bony crepitus is a characteristic feature. Synovial effusion, if present, is not large. On palpation, presence of some warmth is not unusual. Periarticular muscle atrophy due to prolonged disuse, gross joint deformity, bony hypertrophy, subluxation and marked loss of range of movement may be the features of advanced cases. Systemic symptoms are absent in OA and erythrocyte sedimentation rate is usually normal. The American College of Rheumatology has produced a criterion for diagnosis of OA (Tables-II, IV-VI). But as it was developed for epidemiological purpose, its use in routine clinical practice is not recommended. A comprehensive list of differential diagnosis is shown in Table-III.

Table-II

Clinical features of osteoarthritis

Symptoms:
- Joint pain
- Morning stiffness lasting less than 30 minutes
- Joint instability or buckling
- Loss of function

Signs:
- Bony enlargement at affected joints
- Limitation of range of motion
- Crepitus on motion
- Pain with motion
- Malalignment and/or joint deformity

Pattern of joint involvement*:
- Axial: cervical and lumbar spine
- Peripheral: distal interphalangeal joint, proximal interphalangeal joint, first carpometacarpal joints, knees, hips

*Disease with multiple joint involvement is a subtype of osteoarthritis; most commonly, osteoarthritis affects the hands, hips, knees and/or spine.

Table-III

Clinical findings differentiating osteoarthritis from other causes of painful joints

Condition	History	Physical findings
Bursitis/ Tendonitis;	Pain increased with movement Pain worse at night No systemic symptoms Pain on some maneuvers, not others	No joint abnormality or swelling Certain passive maneuvers produce pain Pain on resisted active range of motion of affected muscles
Mechanical intra-articular Conditions;	Recurrent joint swelling Joint locks Joint “gives way” Intermittent pain with pain-free intervals	Pain and limitation at certain points of flexion or extension Pain on combined rotation and extension of the knee
Rheumatoid arthritis	Often insidious onset Morning stiffness of 1 hour Systemic symptoms Associated symptoms (e.g., Raynaud’s syndrome, skin rash)	Involvement of MCP, wrist, elbows, ankles Synovial thickening Classical deformities: Swan neck Boutonniere Ulnar deviation Loss of range of motion of wrist, elbows

MCP denotes metacarpophalangeal joint
Adapted from: E, Bjelle A, Eden S, Svanberg A. A longitudinal study of the occurrence of joint complaints in elderly people. Age Ageing 1992; 21: 160-7.

Table-IV

Combined clinical (history, physical examination, laboratory) and radiographic classification criteria for osteoarthritis of the Hip [6]*

Hip pain and at least 2 of the following 3 features:
ESR<20 mm/hour
Radiographic femoral or acetabular osteophytes
Radiographic joint space narrowing (superior, axial, and/or medial)

ESR denotes erythrocyte sedimentation rate (Westergren)
*This classification method yields a sensitivity of 89% and a specificity of 91%

Table-V

Classification criteria for osteoarthritis of the Hand[7]*

Hand pain, aching, or stiffness and 3 or 4 of the following features:
Hard tissue enlargement of 2 or more of 10 selected joints
Hard tissue enlargement of 2 or more DIP joints
Fewer than 3 swollen MCP joints
Deformity of at least 1 of 10 selected joints

DIP denotes distal interphalangeal; MCP, metacarpophalangeal
*The 10 selected joints are the 2nd and 3rd DIP, the 2nd and 3rd proximal interphalangeal and the 1st carpometacarpal joints of both hands. This classification method yields a sensitivity of 94% and a specificity of 87%.

Table-VI

Criteria for classification of idiopathic osteoarthritis of the Knee[8]

Clinical and laboratory	Clinical and radiographic	Clinical†
At least 5 of following 9: Age > 50 years Stiffness < 30 minutes Crepitus Bony Tenderness Bony enlargement No palpable warmth ESR <40 mm/hour RF <1: 40 SF OA	Knee pain and at least 1 of following 3: Age > 50 years Stiffness < 30 minutes Crepitus and Osteophytes	At least 3 of following 6: Age > 50 years Stiffness < 30 minutes Crepitus Bony tenderness Bony enlargement No palpable warmth
92% sensitive 75% specific	91% sensitive 86% specific	95% sensitive 69% specific

ESR denotes erythrocyte sedimentation rate (Westergren); RF, rheumatoid factor; SF OA, synovial fluid signs of OA (clear, viscous, or white blood cell count <2,000/mm3).
† Alternative for the clinical category would be 4 of 6, which is 84% sensitive and 89% specific.

Natural history:

The natural history of OA is a slow process. In the knee, progression may take many years. Once established however, the joint may remain in a stable condition for many years. Spector *et al* found that in a cohort of 63 patients, radiographic deterioration occurred in approximately one third[9]. In another study of 31 patients with established knee OA followed up for eight years, 20 patients got worse and seven remained the same. Changes in symptoms, disability, and radiographs do not correlate[10]. In the hip, natural history is variable. In a Danish study, two thirds of hips studied deteriorated radiographically over 10 years, however symptomatic improvement was common[11]. Other studies have shown clinical deterioration to be more common. Unlike knee OA, symptomatic and radiological recovery is possible. Avascular necrosis of the femoral head occurs late in disease and is a major problem. In the hand, it is initially a relapsing and remitting disease with episodic inflammatory phases associated with joint redness and swelling. Bony swellings form at this time. The frequency of disease flares then reduces and the joint swellings become hard and fixed. This is associated with a reduction in pain.[11]

Pathogenesis:

Traditionally, OA was viewed as an inexorably progressive degenerative disease. The notion may be incorrect as many OA patients the disease stabilizes. Recent research suggests that it is a dynamic process and may progress in an episodic manner.

Cartilage is made of water (70%) and a type II collagen framework with proteoglycans and glyco-saminoglycans (consisting mainly of aggrecan and also chondroitin), produced by chondrocytes. Proteoglycans in turn bind to hyaluronate which stabilizes the macromolecule. Chondrocytes receive nutrition from the synovium by diffusion and the synovial fluid is circulated by joint movement. It has been postulated that if the joint stops moving (as a result of a fracture or immobility) and chondrocytes lose their source of nutrition, they go into shock and cartilage repair ceases. Metalloproteinases are produced, which catalyse collagen and proteoglycan degradation. The synovium has been shown to be variably inflamed in OA producing increased levels of interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF-α), cytokines that induce nitric oxide and metalloproteinase production. Interleukin-6 (IL-6) and mechanical loading of the joint also induce catabolic cytokine receptors. These bind IL-1 and TNF-α within cartilage causing more destruction.

It is thought that the osteophytes and subchondral sclerosis seen in OA may be the body's way of trying to compensate for lack of cartilage, although some researchers have found bony changes before cartilage changes in animal models[12]. This sort of abnormal bone is also thought to lead to further degradation of the cartilage surrounding it. Poor synthesis of cartilage building blocks may be caused by dysfunctional forms of insulin-like growth factor-1 and transforming growth factor-beta, agents that normally promote new cartilage formation[12].

Pathology:

Macroscopically, the osteoarthritic process results in cystic degeneration of the bone surrounding the joint, with loss of cartilage and irregular, abnormal bone formation at the edges of the joint (osteophytes) and narrowing of the joint space. Microscopically, there is flaking and fibrillation of the articular cartilage surface and destruction of the cartilage microarchitecture with formation of holes within it, as well as bony cysts[13].

Variations in the cellularity and vascularity of subchondral bone leads to sclerosis in some areas and new bone and callous formation where the synovium is continuous with the periosteum. The cartilage itself has three discrete zones within it: a surface layer adjacent to the synovium consisting of collagen aligned parallel to the surface; a middle zone consisting of thicker, wider spaced collagen molecules arranged randomly; and an inner zone adjacent to bone, consisting of collagen arranged perpendicular to the surface[13].

Risk factors:

Several risk factors may predispose to the development of OA. Table-VII summarizes some of the factors. Among these, age is the most powerful unmodifiable risk factor. The Framingham Study found that 27% of those aged 63-70 years had radiographic evidence of knee OA, increasing to 44%

Table-VII

Risk factors for osteoarthritis

Age
Female sex
Race
Genetic factors
Major joint traumaa
Repetitive stress, e.g., vocational
Obesitya
Congenital/developmental defects
Prior inflammatory joint disease
Metabolic/ endocrine disorders

[a] Potentially modifiable

SOURCE: Adapted from M Hochberg: J Rheumatol 18: 1438, 1991.

in the over 80 years age group.[14] Studies of proprioception in OA have found that it is reduced in an elderly patient group with knee OA[15]. Obesity is the strongest modifiable risk factor. Three to six times the body weight is transferred across the knee joint during walking. Any increase in weight should be multiplied by this factor to estimate the excess force across the knee joint when an overweight patient walks. The Chingford Study showed that for every two unit increase in body mass index (approximately 5 kg), the odds ratio for developing radiographic knee OA increased by 1.36[16]. Increasing weight increases the risk of contralateral OA of the knee in women with established OA of one knee. Being overweight at an average age of 36–37 years is a risk factor for developing knee OA in later life (>70 years of age). Losing 5 kg of weight reduced the risk of symptomatic knee OA in women of average height by 50%[12]. Also, increased risk of developing progressive OA seems to be apparent in overweight people with localized disease[17]. Bone density has an inverse relationship with OA. Increasing subchondral bone density may lead to increased loading through weight bearing joint cartilage[18].

Laboratory findings:

Table-VIII shows a summary of the laboratory methods proposed for diagnosis of OA. Radiographs

Table-VIII

Laboratory investigations suggested for diagnosis of osteoarthritis

Imaging:
Plain radiographs
Magnetic resonance imaging
Computed tomography
Radionucleotide imaging
Ultrasound
Arthroscopy
Biochemical markers
Marker of Cartilage Destruction
Cartilage Ologometric Matrix (COMP)
Markers of synovial inflammation
C Reactive Protein
Hayaluronan
YKL-40
Metalloproteases
Markers of bone turnover
Pyridinoline
Bone Sialoprotein

though cheap, provide a permanent record and are easily available, are not a precise measure of disease progression. Disease progression is measured by joint space narrowing which occurs at the rate of <0.1 mm per year and so it is difficult to measure accurately. Plain radiograph shows the following changes in OA:

- Joint space narrowing
- Osteophytes
- Bony cysts
- Subchondral sclerosis

Table-IX shows the radiographic differentiating features of OA and other causes of painful joints. The relationship between symptoms and radiographic findings has always been under debate and results are conflicting in different studies, partly due to the differences in population studied and radiographic and clinical criteria used. The presence of osteophytes has a very strong association with knee pain. However, absence or presence of joint space narrowing was not associated[19]. Knee pain severity was a more important determinant of functional impairment than radiographic severity of OA.[20, 21] There was no correlation between joint space narrowing and a disability score (Western Ontario and McMaster Universities Osteoarthritis index, WOMAC) at a single time point[21].

Magnetic resonance imaging (MRI) is already established for assessment for ligament and meniscal tears of the knee. It has no role in routine clinical practice. However, it is sensitive in quantifying cartilage loss (change in surface morphology and full thickness cartilage defects). It is not yet sensitive enough to detect preclinical OA, as it cannot evaluate cartilage fibrillation[22, 23]. Ultrasound is also good for assessing cartilage integrity and destruction but cartilage is not easily accessible in most weight bearing joints.

Current diagnosis of OA relies on a clinical history and radiography. Radiographic changes occur late in the disease and are largely irreversible. Molecular markers may theoretically be able to detect osteoarthritic changes at an early stage. Ideally, these markers would be sensitive to change, reliable, and quantitative[24]. Table-VIII outlines some of the proposed markers of OA.

Management:

The aims of management of patients with OA are:

- Patient education
- Pain control
- Improve function
- Alter the disease process

Table-IX

*Radiographic findings differentiating osteoarthritis from other causes of painful joints**

Condition	Bone density	Erosions	Cysts	Joint Space loss	Distribution	Bone production
OA	Normal overall	No, unless erosive OA	Yes, subchondral	Nonuniform	Unilateral and/or bilateral; asymmetric	Yes; osteophytes; subchondral sclerosis
RA	Decreased	Yes	Yes, synovial	Uniform	Bilateral; symmetric	No
Psoriatic arthritis	Normal	Yes	No	Yes	Bilateral; asymmetric	Yes
CPPD	Normal	No	Yes	Uniform	Bilateral	Yes; osteophytes; chondrocalcinosis; subchondral
AS	Early-normal Late-decreased	Yes	No	Yes	Bilateral; symmetric	Yes
DISH	Normal	No	No	No	Sporadic	Flowing osteophytes; ossification of tendon, ligaments

OA denotes osteoarthritis; RA, rheumatoid arthritis; CPPD, calcium pyrophosphate deposition disease; AS, ankylosing spondylitis; DISH, diffuse idiopathic skeletal hyperostosis

*Adapted from: Brower AC. Arthritis in black and white. Philadelphia: Saunders, 1998: 23-57.

The management strategies are:

- Education
- Exercise
- Weight Loss
- Physiotherapy
- Appliances
- Drugs
- Surgery

These recommendations are not meant to be rigid but should be flexible and customized according to the individual patient's needs and expectations. Comorbid conditions, such as cardiac disease, hypertension, peptic ulcer disease, renal disease, which are very likely to be present in the elderly age group, must be of prime importance.

Non-pharmacological modalities:

Non-pharmacological therapy is the mainstay of intervention. Table-X outlines the nonpharmacological therapies for patients with OA. Formal education should be an initial part of management of OA. A meta-analysis showed that patient education has a significant effect on pain and function, but that it was only 20% as effective as NSAIDs[25]. Exercise is the single most important intervention. There have been many studies showing the benefit of exercise in OA[26, 27]. Evidence suggests that while advice regarding exercise is important, being given a specific programme to do with "follow up" is probably more effective than advice alone. Table-XI shows the American Geriatrics Society protocol for an exercise programme[28]. A study of 21 obese elderly men and women with knee OA randomised to either a diet and exercise group or diet alone group found that the former group lost more weight but both groups had similar improvements in self reported disability, knee pain intensity, and frequency after six months[29]. In knee OA, shock absorbing footwear reduces the impact of a load on the knee. Heel wedging improves proprioception and reduces pain in OA of the knee. The occupational therapist can provide assessment for walking aids, for example, sticks and for providing a safe and functional environment at home and work. There is historical and anecdotal evidence for their benefit rather than from controlled trials. Therapeutic knee taping has also been effective in knee OA. A recently published study by Rana et al concluded that significant greater improvement in pain and disability was observed with knee taping[30].

Pharmacological therapies

Several modalities of pharmacological therapies exist. They are:

- Analgesics
- NSAIDs

Table-X

Nonpharmacological therapy for patients with osteoarthritis

Patient education
Self-management programs (e.g., Arthritis Foundation Self-Management Programme)
Personalized social support through telephone contact
Weight loss (if overweight)
Aerobic exercise programmes
Physical therapy range-of-motion exercises
Muscle-strengthening exercises
Assistive devices for ambulation
Patellar taping
Appropriate footwear
Lateral-wedged insoles (for genu varum) bracing
Occupational therapy
Joint protection and energy conservation
Assistive devices for activities of daily living

Table-XI

American Geriatrics Society recommendations for exercise[28]

Warm up: 5 min
Exercises:
Isometric strength training: daily
Isotonic strength training: 2-3 times/week
Flexibility training: daily
§Aerobic training (endurance): 3-5 times/week
Cool down: 5 min

Many patients need to concentrate on strength and flexibility training first before considering aerobic training. The exercise programme should be adapted to the patient's age and functional ability.

- Corticosteroids
- Hyaluronic acid derivatives
- Topical treatments
- Glucosamine Sulfate

Possible DMOADs Pharmacologic therapy is considered as additional to the non-pharmacological modalities as drug therapy is most effective when combined with non-pharmacologic therapies.[31]

Table-XII

Risk factors for gastrointestinal complications occurring with NSAIDs

Patient related factors:
Age > 60 years
History of ulcer disease
Drug related factors:
Use of relatively toxic NSAID
High dose of NSAID (or two NSAIDs used concurrently)
Concurrent use of anticoagulant
Concurrent use of corticosteroids
Uncertain or possible risk factors:
Duration of NSAID treatment
Female sex
Underlying rheumatic disease
Cardiovascular disease
Helicobacter pylori infection
Smoking
Alcohol consumption

Analgesics and non-steroidal anti-inflammatory drugs.

Relief of mild to moderate joint pain can be achieved by simple analgesic like acetaminophen and it is comparable to non steroidal anti-inflammatory drugs (NSAIDs)[32-36]. Bradley and his colleagues failed to demonstrate differences in responses to acetaminophen and ibuprofen in knee OA patients with clinical features of joint inflammation[37]. However, Eccles and colleagues, in a metaanalysis of trials comparing simple analgesics with NSAIDs in patients with knee OA, did note that NSAID-treated patients had significantly greater improvement in both pain at rest and pain on motion[36]. In another study, acetaminophen and ibuprofen were comparably effective in patients with mild-to-moderate pain, but ibuprofen was statistically superior to acetaminophen in patients with severe pain[38] and in another study diclofenac was statistically superior to acetaminophen for both pain and function measured with several validated outcome measures[39]. Although a number of patients may fail to obtain adequate relief even with full doses of acetaminophen, this drug merits a trial as initial therapy, based on its overall cost, efficacy, and toxicity profile[36,40]. American College of Rheumatology (ACR) and European League Against Rheumatism guidelines recommend this as initial therapy[41, 42]. The daily dose of acetaminophen should not exceed 4 gm. Although it is one of the safest analgesics, acetaminophen can be associated with clinically important adverse events. Recent reports have highlighted long-recognized conditions in which increased awareness of potential toxicity is important. For example, because acetaminophen can prolong the half-life of warfarin sodium, careful monitoring of the prothrombin time is recommended in patients taking warfarin sodium who subsequently begin high-dose acetaminophen treatment[43, 44]. Hepatic toxicity with acetaminophen is rare with doses of ? 4 gm/day. Nonetheless, the drug should be used cautiously in patients with existing liver disease and avoided in patients with chronic alcohol abuse because of known increased risk in these settings[45-47]. Even though acetaminophen was reported to be weakly associated with end-stage renal disease, the Scientific Advisory Committee of the National Kidney Foundation

recommends it as the drug of choice for analgesia in patients with impaired renal function[48].

If acetaminophen fails to control symptoms adequately, alternative or additional pharmacological agents should be considered. The choice will depend on the presence of relevant risk factors. Table-XII shows some of the important risk factors that should be looked for. All NSAIDs are thought to have similar pain relieving effects, with a reduction in pain of around 30% and an improvement in function of around 15%[49,50]. If used, the dose should be titrated depending on response and side effect profile. Renal and gastrointestinal side effects are a major source of mortality and morbidity, especially in the elderly. If a patient is at risk of peptic ulceration, gastroprotection in the form of misoprostol or proton pump inhibitors should be prescribed. The new cyclo-oxygenase-2 (COX-2) specific inhibitors are increasingly used. They have equal efficacy to standard NSAIDs and thought to pose less gastrointestinal toxicity. However, they can still cause upper gastrointestinal adverse events along with increased predisposition to myocardial events[51] and renal toxicity. An increasing number of evidences also exist showing interaction of various NSAIDs and aspirin. It has been argued that aspirin loses its cardioprotective effect when given concomitantly with different NSAIDs[52, 53].

Intra-articular modalities[54]:
Corticosteroids (tiamcinolone hexacetonide and methyl prednisolone) show significant short-term benefit of 2-4 weeks in comparison to placebo in knee joints. Data on hip, thumb base and finger injections are lacking. Side effects of skin atrophy, dermal pigmentation, specially with long acting preparations and if soft tissues are injected, are reported. Infection is rarely reported. Though early studies suggested cartilage damage with excessive intra-articular injection use, now the damage is thought to be mostly due to the progression of the disease itself. However, intra-articular injection should be reserved for flare-ups only. Some studies describe a greater benefit in OA with knee effusions. American College of Rheumatology guidelines suggest no more than 3–4 knee joint injections per year. In patients needing more than this number, other therapeutic maneuvers should be considered.

Hyaluronic acid (HA) is a high molecular weight polysaccharide, and is a major component of synovial fluid and cartilage. The molecular weight and amount of HA decrease OA. It was postulated that supplementation with intra-articular HA could help to improve synovial fluid viscosity. Both high and low molecular weight HA have been studied. They have been shown to be superior to placebo in reducing pain and number of intra-articular corticosteroid injections needed for 12 months. Symptomatic effect started at week 3–5 and persisted up to 12 months. In comparison with intra-articular steroid, a double blind study found that hyaluronic acid and intra-articular corticosteroids had similar efficacy up to week 5, followed by superior efficacy of hyaluronic acid until the end of the six-month study. There is also evidence that hyaluronic acid injections have similar efficacy to NSAIDs for between 3–6 months.

Topical treatments:
Topical capsaicin (a derivative of hot chilli peppers) cream is often used on hands and knees in patients with moderate pain. Topically applied capsaicin is proposed to exert its action by stimulating a subpopulation of nociceptive pain neurons. Exposure to capsaicin depletes substance P that matter the neurons insensitive to all other exposures including the capsaicin itself. However, redness and burning is reported at the site of application[55]. There are trials showing the efficacy of capsaicin in OA[56, 57]. There is little evidence of efficacy of topical NSAIDs.

Glucosamine sulphate:
Glucosamine sulphate is a nutrient supplement available as over the counter in Europe and USA, and is used to relieve musculoskeletal symptoms. Many preparations are available, some of which also contain chondroitin sulphate. Both glucosamine sulphate and chondroitin sulphate are derivatives of glycosaminoglycans found in articular cartilage. Their mechanism of action is unclear, especially as they cannot be absorbed from the gut intact. Reginster *et al* studied 212 patients with primary knee OA and found that there was a 20%-25% improvement in symptoms and a reduction in knee medial compartment changes over three years in those taking glucosamine.[58] A meta-analysis has also shown that glucosamine sulphate has some analgesic efficacy[59].

Interestingly, a recent double blind placebo controlled trial found no clinical or statistical analgesic effect, and only a large placebo response (33%)[60]. This trial included patients with a wider spectrum of disease severity and higher pain and disability scores than the Reginster trial. Glucosamine sulphate has probably an analgesic effect in mild to moderate knee OA. There is little evidence for its use in OA at other sites.

In Search for disease modifying osteoarthritis drug (DMOAD):

DMOADs are drugs whose action is not aimed principally at the control of symptoms, but instead at the prevention of structural damage in normal joints at risk for development of OA, or at the progression of structural damage in joints already affected by OA. For the most part, such approaches have been aimed at inhibiting the breakdown of articular cartilage by matrix metalloproteinases, or at stimulating repair activity by chondrocytes. Although a number of agents are under study, including matrix metalloproteinase inhibitors and growth factors, no agent has been shown to have a DMOAD effect in humans, and none are available for this indication. The new interest in OA will hopefully allow the development of true DMOAD.

Diacerein is a drug that inhibits production and activity of metalloproteinases and interleukins and may have an effect in delaying progression of hip osteoarthritis as measured by minimum joint space measured visually[62]. There is also interest in the use of bisphosphonates and specific leukotriene antagonists as disease modifiers.

Local delivery of anti-inflammatory cytokines (for example, IL-1-Ra) or gene induction using gene transfer methods may provide a novel treatment regimen.

Further work on cartilage culture and transplantation for other joints is needed.

Large clinical trials to assess the efficacy of interventions are also necessary, using validated and reliable outcome measures that reflect disease activity, damage, and quality of life.

Surgery:

Surgery is used where medical therapy has reached its limits. Arthroscopic debridement and lavage can improve symptoms in degenerative meniscal tears, but does not halt progression. Autologous cartilage transplantation, where grafts of normal cartilage are taken from the edge of the diseased joint, cultured in-vitro and reimplanted into areas where the cartilage is denuded may be an effective technique, but it is expensive and is not currently recommended for first line treatment of knee joint articular cartilage defects[61].

Conclusion:

OA is a potentially treatable condition with positive patient benefit if the application of modalities of therapy is judicious and current evidence based. New insight into the disease process and advent of new drugs hold great promises for the OA patients and the treating physician. Though there are no DMOAD is available for therapeutic use presently, studies are going on for development of such a drug. Till then patients can rip the benefits of the current treatment.

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Management of High Output Intestinal Fistulae

MAW KHAN

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Introduction:

Management of high output intestinal fistula is a challenging task. When a fistula develops there is rapid development of hypovolumia and electrolyte imbalance. Also there is a tendency to do nothing at first and see how bad it is going to be. By the time the patient is septic, anaemic, nutritionally depleted and having extensive breakdown of skin[1]. Early surgical closure almost always fails and mortality rate further increases[2]. To prevent this entire catastrophe and thus to reduce mortality and morbidity, the problems should be defined and classified, and a planned approach to the management of the patients with fistula must be followed[3].

Definitions:

A fistula is an abnormal communication between two epithelial surfaces lined by unhealthy granulation tissues, epithelium or endothelium[4] and the discharge should be continued for more than 24 hours[3,5]. It is said to be high output when the discharge is more than 500[3]-1000[6] ml/d.

Classifications:

Fistulae can be classified according to communicating surfaces as internal, external and mixed. The communicating tract may be straight and single when it is said simple and multiple /horseshoe tract or tract abscess making it complicated[2].

According to the continuity of the viscous wall, fistulae again can be designated as lateral fistula and end fistula[3].

The term proximal and distal was used according to the part of the viscera involved[2]. Enterocutaneous fistulae are also classified into type I fistula like esophageal, gastric and duodenal, type II fistula involving small intestine, type III fistula involving large intestine and type IV fistula where any of the above drains through a major abdominal wound defect[7].

Address of correspondence : Dr. M A Wohab Khan, Associate Professor, Department of Surgery, BSMMU, Shahabag, Dhaka

Most important for management is the fistula output and it is considered as high output when the discharge is more than 500 ml in 24 hour, when it is less than 500 ml/d it is said to be a low output fistula[3].

Causes:

About 80% of all fistulae results from surgical intervention and is due to unrecognized injury and anastomotic disruption[2]. Momen and Siddiqui have shown that emergency surgery for typhoid perforation (45%) and intestinal tuberculosis (30%) were the commonest causes of postoperative enterocutaneuous fistula[8], 2% of the fistulae may be spontaneous due to underlying disease[6]. The other causes of fistulae are developmental, accidental injury, malignancy, inflammatory bowel disease, diverticular diseases, anastomotic ulcer, radiation enteritis and erosion by drain tube or suction catheter [2, 6].

Pathology:

High output fistula usually is complicated with three major systemic problems[2] with 15-20% overall mortality[9]:

1. Nutritional disturbances:
   It is the major cause of death in intestinal fistula even if the fluid and electrolytes are replaced[10]. There is fewer intakes and more demand. About 30-70% of this increased demand is due to the fistula and 10% is due to abscess and wound dehiscence. So, there will be muscle wasting, hypoproteinaemia, vitamin and trace element deficiency resulting the decreases in resistance to infection and impaired wound healing[2, 3].
2. Water, electrolyte and acid base imbalance:
   This is due to loss of proximal gastrointestinal content and partial or complete failure of absorption from the distal part as it is bypassed[2, 3].
3. Sepsis:
   It is a consequent effect of leakage of contents into peritoneal/ pleural cavity and remains the major factor in determining mortality[6].

In addition, there may be skin excoriation and associated urinary and respiratory tract infection[11]. Septicaemia may be the final blow leading to SIRS and MODS[12].

Management outline:

A patient having a high output fistula needs skill nutritional support, parenteral nutrition and maintenance of fluid and electrolyte balance. Adequate and careful stoma therapy for protection of skin is also mandatory. Elimination of sepsis by free external drainage of the effluent and septic focus is the key steps for successful outcome. A carefully timed, well judged and well carried out surgery is needed if it does not heal spontaneously[2, 3].

Sheldon and his coworkers' four phase approach[13] has given a basis for a logical management and if adopted with minor modifications, will give the best result[2].

In phase I, resuscitation and skin protection is the main concern. Nutritional support in phase II is essential for the patient to have a spontaneous closure or to make the patient fit for surgery. The next step or phase III is to do necessary investigations for anatomical delineation of the tract and to asses the condition of the proximal and distal gut. The definitive treatment is planned and done in phase IV.

Pase I (resuscitation and skin protection):

Resuscitation by correcting hypovolumia and electrolyte imbalance should be done with blood transfusion and intravenous fluid containing electrolytes[10].

For protection of skin the opening of the fistulae are classified into four categories and their management is according to the situation[14].

Category 1

A single orifice passing through intact skin is easily manageable by barrier skin gel[2] (ZnO^2 /Stomhasive paste/ Orabase/ Karaya gum) and intubations of the fistula tract with a drain tube[6] or with the application of a flat adhesive drainage bag to prevent soiling[2].

Category 2

In this category a single or multiple orifices are close to bony prominence, umbilicus, surgical scar or other stoma, where flat bags can not be used effectively. These can be managed by frequent change of dressings, multiple small bags can be used or a large sheet of adhesive dressing with multiple holes can be applied over the whole area with the patient nursing in a face down position[2].

Category 3

If the fistula is through a small wound dehiscence, low pressure suction (sump drain) can be used to prevent spread of the discharge. Stomhasive wafers with fashioned hole and repeated wound dressing will minimize the skin excoriation[2].

Category 4

Here the opening is through a major wound dehiscence and can be managed by low pressure suction, postural drainage and frequent dressing. Proximal diversion with enterostomy is most effective method[2] or if possible, recycling of the effluents with controlled collection from proximal stoma of the intestinal secretion by any suitable technique and reinfusion of these into the distal part may be the alternative and effective method[15]. The use of octreotide is highly recommended by Memon and his colleagues as it definitely converts high output fistula to a low output one[8].

A semi permeable barrier method to keep the intestinal content into the lumen and continuing enteral feeding is shown very effective in reducing output immediately without the need for octreoide or parenteral nutrition in selected cases.[16]

Phase II (*Nutrition and electrolyte balance*):

Daily calorie requirements for a patient having high output fistula is suggested as 2000 C and very rarely they may need up to 4000 C. The nitrogen requirement is 3 to 4 gm plus daily loss in urine (1 gm nitrogen is for 150-200 C).The fluid balance is assessed and maintained by usual rule. Electrolytes, vitamins, trace elements should be replaced as required[2]. A patient with hypercatabolic state will not be benefited by excess nitrogen, in that case 15-18 gm is the highest amount to be replaced[3].

The patient will need regular monitoring for change of body weight, urinary volume and nitrogen loss in urine daily[2]. Serum electrolytes and blood urea should be checked, at least twice weekly[3]. Monitoring of Hb%, plasma albumin, liver enzymes

and WBC total count should be done weekly[17]. Accordingly blood transfusion, plasma or albumin infusion, amino acids, intralipose supplements should be given. Sodium, potassium and vitamin replacement is to be given as daily requirement and to replace ongoing loss. Trace element should also be monitored and replaced twice weekly[2,3]. Dextrose as 40% solution can be given throws central vein and will provide 1600 C .The remaining need will be better fulfilled by 10-20 percent fat emulsion. [18]

Phase III

Once the patient is settled, thorough investigations should be done to ascertain the origin of the fistula and the condition of the gut *i.e.* continuity, active disease, any distal obstruction and the length of the proximal or distal segment. Intraabdominal abscess or a fistula abscess should be searched, and the general health status should be assessed[2].

Assessment is done clinically and with some tests like contrast X-ray of the fistula tract and small/large gut enema, endoscopic examination of upper/lower GIT. Cystoscopy is done if indicated. Ultrasonography, CT scan and isotope studies may be needed in some cases. For overall evaluation biochemical, hematological, bacteriological examination are to be done[2,3].

Phase IV (Definitive treatment):

Spontaneous closure is expected if there is decrease in fistula output, increase in plasma albumin, increase in body weight and increase in Hb%[2, 3]. A flow chart is maintained and with the above criteria, conservative treatment can be continued for at least 4-6 weeks[6, 10]. Treatment with somatostatin analog may be useful to reduce fistula/stoma output[12].

Urgent laparotomy:

Urgent exploration is indicated if the fistula is interno-external and if there is spreading or generalized peritonitis and/or distended silent abdomen with uncontrolled sepsis. All these cases need intervention for peritoneal lavage and to exteriorise the ends to have an effective sepsis control[2].

Early operation:

The indications for early operation are: if the fistula is associated with intra-peritoneal abscess cavity or if the fistula is unusually complicated by the presence of intra-peritoneal abscess or the stoma is in a difficult anatomical location[2].

The definitive elective operation:

Elective operation should be done in the situations like total discontinuity or more than 50% of bowel circumference disruption[6], distal obstruction[2,3], mucocutaneous continuity or epithelialization of the tract[6], complicated fistula with multiple serpentine tract[3], tract less than 2.5cm in length[6], tract drains throw an abscess[2], presence of foreign body[3], presence of active diseases like malignancy, inflammatory bowel diseases or TB, any internal fistula producing symptoms or nutritional problem and radiation enteritis[6] which will prevent the fistula to heal spontaneously[2]. If there is no sign of healing within 4-6 weeks, elective operation is suggested in that case also[2,3,6].

Management of complications of fistula infection:

Infection is the common complication in these patients, the types of infections are intraabdominal abscess[2], wound infection, sepsis, spreading cellulites[2], UTI[3], RTI[3] and septicemia[2,3]. These should be treated with appropriate antibiotics, drainage of the abscess by percutaneuos method with wide bore drain or open free drainage may be needed if there is recurrent, multiple or pancreatic abscess[2, 3, 6].

Hemorrhage:

The causes of bleeding are erosion of blood vessels at the site of fistula due to infection, stress ulceration, hematemesis and malena due to sepsis, and strain of fistula[2,3]. Bleeding can occur due to the underlying disease[6]. Treatment should be started immediately by blood transfusion if the bleeding is alarming. Antibiotics and drainage of abscess with debridement and packing of the cavity as early as possible and H_2 receptor or proton chanel blocker should be given to treat or prevent stress ulcer[2].

Pulmonary complications like pneumonia, embolism from deep vein thrombosis and urinary tract infection should be prevented or treated[3, 11].

Principles of surgical intervention for management of fistula:

It has become the classical surgical teaching “no suture in pus” because intestinal hyperaemia, oedema, friability and bacterial enzymatic protein lysis caused by enteric fistula associated peritonitis

cause the leakage of the intestinal anastomosis or suture of early operative closure of enteric fistula[19], but with the recent advancement in infection control, nutritional repletion and enhancement of tissue healing, and definitive early operation in enterocutaneous fistula may be viewed as the first choice of treatment for certain cases[20].

Patients can be divided into two major groups for surgical intervention[2]. The first group includes those patients who need operations to improve general condition for definitive management and the procedure includes drainage of abscesses, insertion of central venues line and creation of feeding enterostomy or proximal diversion (controlled fistula)[2, 3]. The other group of patients need definitive operation for fistula closure[2].

Principles of definitive operation:
The incision should be made through the previous wound, should be extensive and should commence in a virgin area[2]. A good exposure is mandatory and to avoid injury to the underlying adherent structures, entry should be through the residual peritoneal cavity[2, 3, 6].

The total procedure can also be done with a small incision around the granulation bed after laparoscopic adhesionolysis from the anterior abdominal wall[21]. Regan and Salky have concluded that laparoscopic management of enteric fistula diseases is safe and effective[22].

Surgical treatment entails complete mobilization of the bowel[2], resection of the involved segment along with the fistula tract and re-anastomosis; if there is no sepsis, there is no hypoalbuminaemia, and no malnutrition[2].

Primary reanastomosis and proximal diversion should be done if there is sepsis, anaemia, malnutrition, hypoalbuminaemia and associated abscess cavity[2, 3]. If it is not possible, exteriorization of the gut may be done to do a reanastomosis later on[2, 3]. If the fistula is not resectable, proximal diversion or a bypass operation are the alternatives[2, 3, 18].

Discussion:
The high out put gastrointestinal fistula was a surgical catastrophe of the first order of magnitude[23] and although the management of these cases is still troublesome, with proper management in the form of effective fluid and electrolyte replacement and nutritional support[24,25], good local care and appropriate antibiotics[23], a survival rate up to 80-95% can be achieved[24,25]. The only factor that remains in determining mortality is uncontrolled sepsis[26]. About 92% of death of fistula patient is due to sepsis, and poor drainage at early stage is the principle reason for development of tertiary peritonitis[27]. Surgical wound infection was almost 100% in patient with partial or complete wound dehiscence and routine use of ileostomy for diverting the faecal stream was effective in bringing down the mortality rates[28]. In general, early surgical attempt at closure almost invariably follows recurrence and high death rate (43%)[2,13]. About 80% of early operation fails due to severe intra-abdominal infection in which intestinal loops are oedematous and healing process was impaired[27]. Near about 70-80% of intestinal fistula closes spontaneously with modern conservative management[25]. Among them, more than 90% of small intestinal fistula close within one month, less than 10% fistula close within two months and none closes spontaneously after three months[29]. Lavy and Yasin[30] have shown that treating with somatostatin in fistula resulting from Crohn's disease have some role for spontaneous closure. Failure to eliminate sepsis is almost always fatal[2]. Failure to maintain adequate nutrition is the major cause of death in intestinal fistula even if the fluid and electrolytes are replaced[31]. The single most important factor to a successful outcome in the management of intestinal fistula is adequate and sustained nutritional support[3]. The aim is to improve the general condition of the patient till the fistula closes spontaneously or the patient is fit for surgery[2,3]. Jieshou and co-worker achieved 98% success with definitive surgery in non-healing fistula[27]. Chapman and coworkers have shown that mortality rate was 57-65% if only fluid and electrolytes are replaced without nutritional support and if at least 1600 C is added daily the mortality dropped to only 18%[1]. Bazaev and his colleagues adopted a differential approach to choice of treatment method, intraaortic therapy before and after surgery, use of developed devices for treatment of non-formed fistulas permitted to improve results of treatment and to reduce lethality from 10.3% to 3.3%

in different groups[32]. Taryk and his colleagues also have shown that nutritional status and well timed surgery influence the healing of enterocutaneous fistula[33]. In high output fistula parenteral nutrition should be started within 48 hours via central venus catheter[29]. If total parenteral nutrition is given, 37% of fistula heals spontaneously, 24% need intervention for sepsis for spontaneous closure and others need definitive surgery[34]. Enteral feeding can be substituted if there is more than 100 cm of healthy gut present proximal or distal to fistula through oral or enterostomy[29]. The most important and serious prognostic sign is low serum albumin and if it continues to fall, which is a good indication of the presence of coexistence active infection, one is almost certainly losing the battle for the patient's life[3]. In an acutely ill patient, body weight is an indicator for body water rather than body mass[5]. For the assessment of long term progress, anthropometric measurements like mid arm circumference and triceps skin fold thickness should be made at weekly interval[2,6].

Although the outcome has been substantially improved but still there are many factors that need further study because the overall mortality is still high, spontaneous closure is still low and treatment duration is long[27] specially in high output fistula. The best management for fistula is prevention, because most of the fistulae are iatrogenic. So, we should be very cautious not to invite surgical misadventure[13] like anastomotic leakage, injury of the bowel or blood supply and laceration of bowel wall during or after surgery with surgical instruments or appliances.[6]

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CASE REPORTS

Myotonia Congenita in a Bangladeshi Family

S DAISY, QD MOHAMMAD, A HOQUE, B ALAM, S HOSSAIN, M HABIB, B HAQUE, T SAHA

Summary:

Myotonia congenita, a rarely found hereditary disease has been reported recently in the Department of Neurology, Dhaka Medical College Hospital. A family of a brother and sister with myotonia congenita is reported. Both of them presented with identical features i.e. myotonia and muscular hypertrophy . To the best of our knowledge no account of a family has earlier been reported from Bangladesh with myotonia congenita.

(J Bangladesh Coll Phys Surg 2005; 23 : 143-145)

Introduction:

Congenital myotonia is a rare hereditary disease of skeletal muscles that starts in early life and is characterized by myotonia and muscular hypertrophy. It may be of autosomal dominant (Thomsen's disease) and autosomal recessive form (Becker's disease)[1]. Both are due to chanellopathies, where the transport of chloride ion is faulty and the genetic locus is at 7q35 chromosome[2].

A family has reported of a brother and a sister with myotonia congenita. Both of them presented with identical features i.e. myotonia and muscular hypertrophy.

Case report:

A 20 year young male came to Neurology OPD Dhaka Medical College Hospital with complaints of difficulty in daily movements, which was more at initiation and lessened gradually with activity. This started at the age of 10-12 years as he can remember. He felt tightened/frozen initially for any attempted movement, which gradually lessened with activity.

In addition to this, he complained of very muscular body even he never did any exercises. He also got occasional generalized pains and cramps.

His symptoms did not exacerbate in cold. The patient had no history of any other medical problem. He also had no history of any routine medication use or substance abuse.

Dr. Selina Daisy, MD (USA), Prof. Dr. Quazi Deen Mohammad, FCPS, MD, Dr. Azharul Hoque, FCPS, MD, Dr. Badrul Alam, MD, Dr. Sakhawat Hossain, FCPS, Dr. Mansur Habib, FCPS, MRCP, Dr. Badrul Haque, Dip in Neurology, Dr. Tapash Saha, MBBS.

Department of Neurology, Dhaka Medical College and Hospital, Dhaka, Bangladesh.

Address of correspondence: Dr. Selina Daisy, MD (USA), Department of Neurology, Dhaka Medical College and Hospital, Dhaka, Bangladesh, e-mail: daisyselina@yahoo.com / nrc@agni.com

His parents have a history of consanguinity of marriage. His older sister (26 years of age) had exactly same complaints.

Patient had physical therapy for long time, which failed to ameliorate his symptoms.

Physical examination was essentially unremarkable except one characteristic finding of pronounced muscle development despite a lack of exercise.

Percussion myotonia was mildly positive and he had slight difficulty in releasing his grip or opening his eyes after forcefully closing them. He had no temporal wasting, cataracts, testicular atrophy or alopecia. Needle EMG examination was significant for myotonic discharges with characteristic "Dive bomber" sound in the palm (abductor pollicis brevis) and all other muscles. It was more marked in proximal muscles.

The diagnosis was myotonia congenita based on the young age of onset, muscular hypertrophy rather than dystrophy and EMG findings. The characteristic EMG findings confirmed the diagnosis of myotonia, which was more marked proximally than distally. Lack of typical findings of dystrophic features (e.g. muscle wasting, myopathic facies, cataracts and frontal balding) along with myotonic potentials more marked proximally than distally support the diagnosis of myotonia congenita. Distinction of the type of myotonia congenita is based on inheritance. Since he has one more member in his family with same findings, onset of symtoms for both of them was at the age of 10-12 years, and both of his parents were unaffected, Becker type (autosomal recessive form) was most likely.

We started our patient on carbamazepine (100 mg BID). He came for follow up and his symtoms

improved by 50%. His sister is also on same medication, her symptoms also improved.

Discussion:

The myotonias encompass several neuromascular disorders characterized by sustained involuntary contraction of a group of muscles. Myotonias are traditionaly classified into dystrophic and nondystrophic types. Dystrophic myotonias are characterized by the prominence of muscle weakness and wasting, both of which were absent in our patient. Thus, he had a nondystrophic form of myotonia. These disorders include the paramyotonias and myotonia congenita.

Paramyotonia is a rare hereditary (autosomal dominant) nonprogressive muscular disorder. It is characterized by cold-induced myotonic stiffness that is increased with sustained muscle activity (paradoxical myotonia) and may be followed by a variable degree of weakness[3]. There is no wasting (atrophy) or increase in bulk (hypertrophy).These characteristics arise from a sodium channel abnormality, and our patients' clinical picture was not consistent with paramyotonia.

Myotonia congenita is nonprogressive and nondystrophic. Myotonia congeneta exists in two forms. Becker type, sometime called generalized myotonia, is more common version of the disease. It is autosomal recessive, meaning that it requires two copies of the defective CLCNI gene. The second form, Thomsen's disease, is relatively rare and is inherited as an autosomal dominant manner, meaning that it require only one copy of the defective CLCNI gene. Both diseases are caused by mutations in the chloride channel gene (CLCN1) and the criterion of differentiating Thomsen's from Becker's myotonia congenita lies in the mode of inheritance. However, more than 60 mutations have been identified in families with the disorders.[4]

The clinical feature usually begins during the first decade but in rare cases, onset may occur as late as approximately 18 years of age[5]. Worldwide prevalence is 0.2 to 7.3 per 100,000. Finland has unusually high occurrence, at 7.3 per 100,000[6]. The incidence of the disease among Asians is not well established. A literature search produced only two cases reports[7,8] of the disease in two Chinese families in Singapore and few cases reported in India[9, 10, 11]. Both dominant and recessive forms are associated with muscle hypertrophy and produce patients' extremely muscular appearance, classically described in the literature as "Herculean". The myotonia creates a higher level of resistance and movement against resistance which is a stimulus for muscle growth[12].

Myotonia congenita is due to a chloride channel abnormality (channelopathy) in skeletal muscle. Both forms of myotonia congenita are channelopathies caused by several nonsense and missense mutations in the skeletal muscle *CLCN1* gene[3] that has been localized to human chromosome 7q35. [13, 14]

A tale of two ions[12]: Normally, in a relaxed muscle cell, chloride channels in the cell membrane are open, allowing a current of negatively charged chloride ions to pass into the cell. Chloride channel account for most (70% to 80%) of skeletal muscle resting membrane conductance [15]. This creates a negative membrane potential relative to the outside. A nerve cell triggers contraction of the muscle cell by turning the membrane potential from negative to positive. Chemicals from the nerve cells stimulate the opening of sodium channels in the muscles cell, causing an inward current of positively charged sodium ions. When the positive current overcomes the negative (chloride) current, the muscle cell contracts. In muscle cell affected by myotonia congenita, defective chloride channels reduce the entry of chloride into the muscle cell or allow excess sodium to enter. Therefore, just a small amount of sodium influx is enough to change the membrane potential and cause contraction. The contraction is sustained by a buildup of positively charged ions at the muscle cell membrane, and relaxation is delayed[11], so the hyperexitability and repetitive firing of action potentials in myotonia congenita are caused by a low chloride conductance of the sarcolemma [16]. The abnormal chloride conductance maps to a region that contains the skeletal muscle voltage –gated chloride channel gene *CLCN1*[16].

Because myotonia congenita is rare and the underlying CLCN1 mutations are diverse, testing of the disease is limited.

For most people the diagnosis of myotonia congenita is a clinical diagnosis (based on symptoms) with

supportive evidence from the EMG and family history. Another important part of this diagnosis is exclusion of the most common disease, myotonic muscular dystrophy which is caused by a genetic defect on chromosome 19 that is detectable by a commercially available test.

When the chloride channels in the muscles are not working enough, muscles become hyperexcitable because of sodium channels opening. So, a drug that blocks the sodium channels when they are open will counteract the myotonia. Therefore, the therapy target is electrical stabilization of the muscle membrane. Successful therapies include anticonvulsants (such as carbamazepine and phenytoin), acetazolamide, and drugs such as, tocainide hydrochloride, thiazides, anti-arrhythmic mexiletine hydrochloride, quinine, procainamide hydrochloride and beta-adrenergic agents [17].

In comparison to myotonic dystrophy, myotonic congeneta carries better prognosis and the subject may live up to adult life.

Genetic counseling is advised.

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Juvenile Chronic Myeloid Leukaemia (JCML): Report of Two Cases

MM SAHA[a], DK MONDAL[b], MA BAKAR[c], MQ ZAMAN[d]

Summary:

A baby of four months was admitted into Khulna Shishu Hospital with the complaints of intermittent dyspnoea, fever and cough of one month duration. Systemic examination revealed mild hepatosplenomegaly, superficial cervical lymph node enlargement, facial rash and pallor of conjunctiva. Another two years old male child was admitted into a Private Clinic in Khulna with the history of fever, joint pain, general weakness and gum bleeding of six months duration. Physical examination revealed moderate hepatosplenomegaly, cervical lymph node enlargement and conjunctival pallor. During haematological investigations, both of these patients showed the feature of juvenile chronic myeloid leukaemia.

(J Bangladesh Coll Phys Surg 2005; 23 : 146-149)

Introduction:

Juvenile chronic myeloid leukaemia (JCML) is a clonal expansion of haematopoietic stem cells that typically affects the children younger than two years of age.[1] Patients with this disease do not have philadelphia chromosome, a characteristic finding of juvenile chronic myeloid leukaemia. Leukaemia in infant and children generally is acute. Fewer than 5% of patients with chronic myeloid leukaemia are children.[2] Children and infants may have ph1(+) CML in which case the clinical features of the disease, including the response to therapy are indistinguishable from those in adults.[3] Most patients with JCML present with facial rash, anaemia, breathlessness, mild to moderate hepatosplenomegaly and lymphadenopathy. Analysis of peripheral blood film often shows a considerable elevation of blood leukocyte count and an accumulation of all forms of mature and immature granulocytes.

Chronic myeloid leukaemia is a disorder with considerable historical significance. In 1960, Nowell and Hungerfold working in Philadelphia reported that myeloid cells from patient with chronic myeloid leukaemia showed a deletion of portions of long arm of one member of the G group of chromosome.[4] Subsequently, this chromosome was found to be an almost constant feature of the disease indicating that it was an acquired chromosomal abnormality that could be linked to specific malignant process. The Ph1 chromosome and its relationship to CML provided an exemplary model for studying the effects of genomic changes in the causation of cancer.[5]

In 1973, results of studies showed that the Ph1 chromosome is the result of a reciprocal translocation of genetic material between chromosome 9 and 22. (t9; 22) (q34.1; q11.21).[6] In a small proportion of patients (4-5%), anomalous and complex translocation occur, usually chromosome 9 and 22 are involved and 9 is involved universally.[7]

Details of JCML perhaps has not yet been reported in our country. Here, a rare malignant disorder of children, JCML, diagnosed clinically in two children as bronchopneumonia or pyrexia of unknown origin is reported.

Case report-1: A female baby of four months was admitted into Khulna Shishu Hospital on 22nd January, 2004 with the complaints of intermittent dyspnoea, fever and cough of one month duration. The patient came of an average socio-economic background and her general condition was poor. Systemic examination revealed mild hepatosplenomegaly, superficial cervical lymph node enlargement, facial rash and pallor of conjunctiva.

a. Dr. Moni Mohan Saha, MBBS (Dhaka), M. Phil (Path), Associate Professor, Department of Pathology, Khulna Medical College, Khulna

b. Dr. Dulal Krishna Mondal, MBBS(Dhaka), M. Phil(Anatomy), Assistant Professor, Department of Anatomy, Khulna Medical College, Khulna

c. Dr. Md. Abu Bakar, MBBS (Dhaka), FCPS (Medicine), Associate Professor, Department of Medicine, Khulna Medical College & Hospital, Khulna

d. Dr. Md. Quamruzzaman, MBBS, DCH (Dublin), Senior Consultant, Khulna Shishu Hospital, Khulna.

Address of correspondence : Dr. Moni Mohan Saha, MBBS (Dhaka), M. Phil (Path), Associate Professor, Department of Pathology, Khulna Medical College, Khulna

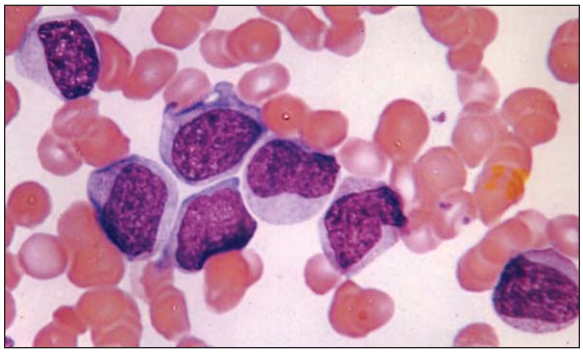

Fig.-1: *Blood film of JCML showing primitive cells of myeloid series promyelocyte, myelocyte and myeloblast and also promonocyte and monocyte (Giemsa stain x 1200)*

Chest X-ray of posterio-anterior and lateral view showed soft opacity involving middle lobe of right lung. Ultrasonography showed that the liver and spleen were mildly enlarged (bipolar length of spleen was about 15 cm) but tissue appearance was uniform with no focal lesion. Fine needle aspiration cytology of enlarged cervical lymph node showed the features of reactive lymphadenitis. Haematological investigations showed the followings: haemoglobin level : 6.6 gm/dl; ESR: 75mm after first hour (Westergren method); total leukocyte count : $120x10^9$/L; differential count: neutrophil 16%, lymphocyte 15%, promonocyte 10%, monocyte 14%, eosinophil 2%, basophil 1%, segmented band form 6%, promyelocyte 17%, myelocyte 9%, metamyelocyte 6%, and myeloblast 4%; and platelet count: $80x10^9$/L. Alkaline denaturation technique showed that foetal haemoglobin (Hb-F) was present in increased proportion. Peripheral blood film analysis showed the followings: red blood cells showed anisochromasia with anisocytosis; a good number of erythroblasts were also seen; white blood cells showed shift to the left with the prominence of promyelocyte, myelocyte and monocyte; and platelets were reduced. Bone marrow study findings were as follows: hypercellular marrow with partial replacement of fat spaces, myeloid and erythroid ratio increased (M: E = 36: 1), granulopoiesis was hyperplastic and showed maturation arrest with the predominance of myelocyte (> 40%), myeloblast (<30%), promyelocyte and metamyelocyte; erythropoiesis was active and dyserythropoietic including asynchrony between maturation of cytoplasm and nucleus, megaloblastoid changes, multinuclearity, nuclear fragmentation and cytoplasmic vacuolation; and megakaryocytes were normal but many of them were morphologically abnormal, micromegakaryocytes and large monolobular megakaryocytes were common findings.

Case report-2: A two years old male child was admitted into a private clinic in Khulna on 14th March, 2004 with history of fever, joint pain, general weakness and gum bleeding of six months duration. Physical examination revealed moderate splenomegaly, cervical lymph node enlargement and conjunctival pallor. Chest x-ray of posterio-anterior and lateral view showed prominent bronchovascular markings with patchy soft opacity in the middle lobe of right lung. Ultrasonography showed that the liver and spleen were moderately enlarged (bipolar length of spleen was about 18 cm) but the tissue appearance was uniform with no focal lesion. The splenic vein at the hilar region was dilated. Fine needle aspiration cytology of the affected lymph node showed the features of reactive lymphadenitis.

Haematological investigations showed the followings: haemoglobin level: 7.5gm/dl; ESR: 32mm after 1st hour (Westergren method); total leukocyte count: $80x\ 10^9$/L; differential count: neutrophil 13%, lymphocyte 18%, promonocyte 8%, monocyte 12%, eosinophil 1%, basophil 2%,

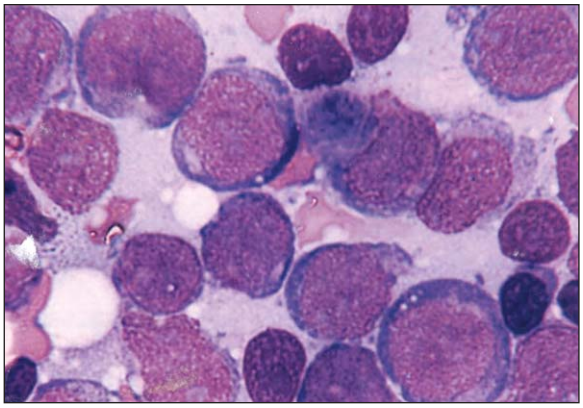

Fig.-2: *Marrow film of JCML showing primitive cells of the myeloid and monocyte series. Myeloblasts bottom right and monoblast top left (Giemsa stain x 1200).*

segmented band form 8%, promyelocyte 19%, myelocyte 10%, metamyelocyte 5%, myeloblast 4%; and platelet count: $100x10^9$/L. Alkaline denaturation technique showed that foetal haemoglobin (Hb-F) was present in increased amount. Peripheral blood film analysis showed the followings: red blood cells showed anisochromia with anisocytosis, some erythroblast were also seen; white blood cells showed marked shift to the left with the predominance of promyelocyte, myelocyte, promonocyte and monocyte; and platelets were mildly reduced. Bone marrow study findings were as follows: hypercellular marrow with increased myeloid and erythroid ratio (M: E = 48: 1); granulopoiesis was hyperplastic with maturation arrest and the predominance of myelocyte (>30%), myeloblast (upto 20%), promyelocyte and metamyelocyte; erythropoiesis was active and dyserythropoietic including megaloblastoid changes, multinuclearity, nuclear fragmentation and cytoplasmic vacuolation; and megakaryocytes were increased and many micromegakaryocytes and large monolobular megakaryocytes were seen.

Discussion:

Juvenile chronic myeloid leukaemia (JCML) is found at an average age ranging from one to two years and there is no sex predominance.[8] Age of the reported patients were four months and two years respectively which agree with the findings of Reisman and Trurjillo.[9]

Both patients presented with mild to moderate hepatosplenomegaly, cervical lymph node enlargement, conjunctival pallor and facial rash. These features agree with the findings of Shapira and Ota.[10] The patients reported here also had intermittent dyspnoea, cough, fever, joint pain and gum bleeding. These seem to be an atypical presentation of patients, with juvenile chronic myeloid leukaemia. Philadelphia chromosomal study was not done in these cases because of lack of availability of the test in Khulna. Moreover, one patient died before doing this investigation and another left the clinic without notification and finally not being followed up. Haematological investigations of both cases showed thrombocytopenia and total leukocyte count lower than in patients, with typical chronic myeloid leukaemia. These haematological investigations agree with the finding of Takanashi.[11]

Cytogenetic and molecular studies showed that approximately 90% of patients with chronic myeloid leukaemia have a chromosomal abnormality known as the Philadelphia chromosome (Ph). This is a shortened chromosome 22 and is the result of reciprocal translocation of material with chromosome 9.

Two major subtypes of CML are recognized on the basis of the presence, Ph1(+), or absence, ph1(-), of Philadelphia chromosome, clinical manifestation, course and survival rate. In a small minority of patients, eosinophilia, basophilia or monocytosis predominantes, but such cases are unusual and are considered variants of "typical" CML.

All patients studied to date had an increase in the proportion of foetal haemoglobin, ranging as high as 85% of the total haemoglobin concentration.[12] The persistence of elevated levels of foetal haemoglobin and the early age of onset of CML infants, as well as it's development in infant siblings, have lead to speculation that the disease may be a variant of congenital leukaemia.[13]

On the basis of the course and the frequent involvement of the monocytic as well as neutrophilic series, certain authors have suggested that the disease is more akin to acute myelomonocytic leukaemia than to CML.[14]

Patients with neurofibromatosis have a predilection for this type of leukaemia.[15] Therapeutic reports are largely anecdotal. Survival rate from the time of diagnosis is usually less than one year, and response to therapy has been poor.[16]

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COLLEGE NEWS

(J Bangladesh Coll Phys Surg 2005; 23 : 150-152)

EXAMINATION NEWS:

Result of FCPS Part-I, FCPS-II and MCPS Examination held in July, 2005 are given below.

4451 candidates appeared in FCPS Part - I Examination held in July 2005, of which 874 candidates came out successful. Subject-wise results are as follows:

FCPS Part I Examination

Subject	No. of Candidates appeared	Passed
Medicine	1420	134
Surgery	822	393
Paediatrics	489	69
Obst. & gynae	1026	181
Ophthalmology	105	24
Otolaryngology	102	02
Psychiatry	32	03
Anaesthesiology	67	04
Radiology	74	03
Radiotherapy	14	03
Dermatology & venereology	106	15
Physical medicine	20	07
Dental surgery	90	20
Family medicine	08	02
Haematology	34	03
Biochemistry	06	02
Histopathology	17	07
Microbiology	19	02
	4451	874

502 Candidates appeared FCPS Part-II Examination in different subjects. List of candidates who satisfied the board of examiners is as follows:

Roll Nos.	Name of the candidates	Graduated from	Speciality
17.	Dr. Abul Bashar Mohammad Nurul Alam	Mymensingh Medical College, Mymensingh	Medicine
19.	Dr. Mohammed Rashed Mirjada	Sher-e-Bangla Medical College, Barisal	Medicine
23.	Dr. Aniruddha Ghose	Dhaka Medical College, Dhaka	Medicine
25.	Dr. Mohammad Mahbub Alam Mazumder	Dhaka Medical College, Dhaka	Medicine
35.	Dr. Mohammad Abu Naser Siddique	MAG Osmani Medical College, Sylhet	Medicine
39.	Dr. Indrajit Kumar Datta	Dhaka Medical College, Dhaka	Medicine
42.	Dr. Muhammad Khaled Hasan	Dhaka Medical College, Dhaka	Medicine
51.	Dr. Shamim Ahmed	Dhaka Medical College, Dhaka	Medicine
57.	Dr. A.K.M. Mijanur Rahman	Sir Salimullah Medical College, Dhaka	Medicine
63.	Dr. Md. Mahbubur Rahman	Dhaka Medical College, Dhaka	Medicine
86.	Dr. Md. Sirajul Islam	Dhaka Medical College, Dhaka	Medicine
92.	Dr. Mohammad Abul Kalam Azad	Chittagong Medical College, Chittagong	Medicine
114.	Dr. Muhammad Habib Hassan	MAG Osmani Medical College, Sylhet	Medicine
117.	Dr. Syed Mohammad Monowar Ali	Rajshahi Medical College, Rajshahi	Medicine

Roll Nos.	Name of the candidates	Graduated from	Speciality
124.	Dr. Md. Shafiquzzaman Siddiqui	Rajshahi Medical College, Rajshahi	Medicine
132.	Dr. Abu Shahed Muhammed Zahed	Chittagong Medical College, Chittagong	Medicine
144.	Dr. Md. Nowshad Ali	Rajshahi Medical College, Rajshahi	Surgery
157.	Dr. Md. Azizul Islam Khan	Mymensingh Medical College, Mymensingh	Surgery
161.	Dr. Md. Kamal Pasha	Sir Salimullah Medical College, Dhaka	Surgery
163.	Dr. Khaja Masum Kabir	Mymensingh Medical College, Mymensingh	Surgery
175.	Dr. N.A.M. Golam Mahbub	DIPLOMA	Surgery
196.	Dr. Md. Abdul Hannan	MAG Osmani Medical College, Sylhet	Surgery
203.	Dr. Md. Al Amin Salek	Dhaka Medical College, Dhaka	Surgery
204.	Dr. Shamima Jahan	Sir Salimullah Medical College, Dhaka	Surgery
224.	Dr. Abul Khair Muhammad Kawsar Habib	Dhaka Medical College, Dhaka	Surgery
256.	Dr. Md. Belal Uddin	Dhaka Medical College, Dhaka	Paediatrics
261.	Dr. Lutfun Nessa	Dhaka Medical College, Dhaka	Paediatrics
304.	Dr. Major Taslima Ferdous	MAG Osmani Medical College, Sylhet	Paediatrics
322.	Dr. Md. Rakibul Haque Khan	Rajshahi Medical College, Rajshahi	Paediatrics
331.	Dr. Md. Hasanuzzaman	Rangpur Medical College, Rangpur	Obstetric & Gynaecology
334.	Dr. Kakali Saha	Dhaka Medical College, Dhaka	Obstetric & Gynaecology
339.	Dr. Sultana Afroj	Sher-e-Bangla Medical College, Barisal	Obstetric & Gynaecology
344.	Dr. Laxmi Saha	Chittagong Medical College, Chittagong	Obstetric & Gynaecology
345.	Dr. Suchanda Das	MAG Osmani Medical College, Sylhet	Obstetric & Gynaecology
349.	Dr. Lutfun Naher	Sher-e-Bangla Medical College, Barisal	Obstetric & Gynaecology
360.	Dr. Farzana Deeba	Dhaka Medical College, Dhaka	Obstetric & Gynaecology
369.	Dr. Begum Rokeya Anwar	Dhaka Medical College, Dhaka	Obstetric & Gynaecology
381.	Dr. S. M. Shahida	Sir Salimullah Medical College, Dhaka	Obstetric & Gynaecology
382.	Dr. Fatema Siddiqua	Rajshahi Medical College, Rajshahi	Obstetric & Gynaecology
383.	Dr. Sumana Rahman	Dhaka Medical College, Dhaka	Obstetric & Gynaecology
386.	Dr. Jesmin Akter	MAG Osmani Medical College, Sylhet	Obstetric & Gynaecology
387.	Dr. Suraiya Sultana	MAG Osmani Medical College, Sylhet	Obstetric & Gynaecology
388.	Dr. Mst. Khurshida Jahan	Mymensingh Medical College, Mymensingh	Obstetric & Gynaecology
390.	Dr. Rhea Homaira	Sir Salimullah Medical College, Dhaka	Obstetric & Gynaecology
394.	Dr. Husne Ara Khatun	Dhaka Medical College, Dhaka	Obstetric & Gynaecology
401.	Dr. Jahanara Rahman	Sher-e-Bangla Medical College, Barisal	Obstetric & Gynaecology
403.	Dr. Nusrat Fatima	Dhaka Medical College, Dhaka	Obstetric & Gynaecology
404.	Dr. Muhammad Rezaul Karim	Rajshahi Medical College, Rajshahi	Obstetric & Gynaecology
408.	Dr. Sharmina Yeasmin	Dhaka Medical College, Dhaka	Obstetric & Gynaecology
412.	Dr. Rowshan Hosne Jahan	Rangpur Medical College, Rangpur	Obstetric & Gynaecology
417.	Dr. Nurul Alam	Mymensingh Medical College, Mymensingh	Ophthalmology
420.	Dr. Shah-Noor Hassan	Sir Salimullah Medical College, Dhaka	Ophthalmology
421.	Dr. Ferdous Akhter Jolly	Sir Salimullah Medical College, Dhaka	Ophthalmology
422.	Dr. Ishtiaque Anwar	Bangladesh Medical College, Dhaka.	Ophthalmology
436.	Dr. Sabir Ahmed Bhuiya	Mymensingh Medical College, Mymensingh	Ophthalmology
437.	Dr. Md. Harisur Rahman	Rajshahi Medical College, Rajshahi	Ophthalmology
444.	Dr. Md. Manjur Rahim	Sir Salimullah Medical College, Dhaka	Otolaryngology
446.	Dr. Sheikh Shawkat Kamal	IAHS, Chittagong.	Otolaryngology
455.	Dr. Tapas Chakraborty	Chittagong Medical College, Chittagong	Otolaryngology

Roll Nos.	Name of Candidates	Graduated from	Speciality
464.	Dr. Skanta Kumar Mazumder	Rajshahi Medical College, Rajshahi	Anaesthesiology
465.	Dr. (Lt. Col.) MHM Delwar Hossain	Mymensingh Medical College, Mymensingh	Anaesthesiology
469.	Dr. Md. Shahadat Hossain	Sir Salimullah Medical College, Dhaka	Anaesthesiology
470.	Dr. Masud Ahmed	MAG Osmani Medical College, Sylhet	Anaesthesiology
471.	Dr. Sajjad Ahmed	Chittagong Medical College, Chittagong	Anaesthesiology
474.	Dr. Nadeem Parvez Ali	Sir Salimullah Medical College, Dhaka	Anaesthesiology
475.	Dr. Montosh Kumar Mondal	Mymensingh Medical College, Mymensingh	Anaesthesiology
476.	Dr. Tauhid-UI-Mulk	Dhaka Medical College, Dhaka	Anaesthesiology
480.	Dr. Nibedita Nargis	Mymensingh Medical College, Mymensingh	Anaesthesiology
483.	Dr. Maksuda Mannan	Mymensingh Medical College, Mymensingh	Radiology
485.	Dr. Aysha Khatun	Dhaka Medical College, Dhaka	Radiology
500.	Dr. Maj. Md. Abdur Rab	D. Dental College, Dhaka.	Oral & Maxillofacial Surgery
506.	Dr. A. B.M. Abdul Wadud	Dhaka Medical College, Dhaka	Microbiology

203 candidates appeared in MCPS Examinations in different subjects. List of candidates who satisfied the board of examiners is as follows:

Roll Nos.	Name of the candidates	Speciality
025.	Dr. Nisith Kumar Majumder	Medicine
067.	Dr. Mohammad Rafiz Imtiaz	Surgery
070.	Dr. G.M. Morshed	Surgery
074.	Dr. Md. Abdur Rahim	Surgery
097.	Dr. Forrukh Ahammad	Paediatrics
103.	Dr. Nasrin Fardous	Obst. & Gynae
104.	Dr. Nasreen Sultana	Obst. & Gynae
109.	Dr. Jaharatul Ferdous	Obst. & Gynae
119.	Dr. Nargis Nahar	Obst. & Gynae
128.	Dr. Md. Shahadat Hossain	Obst. & Gynae
134.	Dr. Sabrina Siddiqui	Obst. & Gynae
137.	Dr. Ayinur Nahar Hamid	Obst. & Gynae
142.	Dr. Asma Khatun	Obst. & Gynae
143.	Dr. Mst. Rebeka Khanam	Obst. & Gynae
148.	Dr. Naznin Akhter Jahan	Obst. & Gynae
162.	Dr. Md. Abdullah Al Masum	Ophthalmology
177.	Dr. Ahmed Minhaz Shumon	Otolaryngology
178.	Dr. Mohammad Ali Azad	Otolaryngology
186.	Dr. Sheikh Firoj Kabir	Anaesthesiology
187.	Dr. Mohammad Nurul Amin	Anaesthesiology
188.	Dr. Abul Kalam Md. Zillul Haque	Anaesthesiology
190.	Dr. Atiqur Rahman	Anaesthesiology
200.	Dr. Mamunur Rahman	Anaesthesiology
206.	Dr. Osmanur Rashid	Radiology
212.	Dr. Mohammad Nasir Uddin	Dermatology & VD
224.	Dr. Mansur Khalil	Forensic Medicine
241.	Dr. Md. Nowfel Islam	Clinical Pathology
242.	Dr. Amina Bashir	Clinical Pathology