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# JOURNAL OF BANGLADESH COLLEGE OF PHYSICIANS AND SURGEONS

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# **FIBROMYALGIA SYNDROME: QUEST FOR A TREATMENT OPTION**

Fibromyalgia syndrome (FMS) is a chronic musculoskeletal disorder and is currently defined as the presence of both chronic widespread pain (CWP) and tenderness at multiple anatomical sites. Additional characteristics of the disorder include, among others, fatigue, insomnia or nonrefreshing sleep, diffuse stiffness, and other organic and psychological features. Confirmation of clinical diagnosis emphasizes on the presence of tenderness in 11 out of 18 anatomical points. About 20% of individuals with CWP suffer from FMS and they are likely to have higher levels of psychological distress<sup>1</sup>. It occurs predominantly in women and affects approximately 2-4% of people in industrialized societies<sup>2</sup>. There is no clear clinical diagnosis for the other 80% of individuals with less than 11/18 tender points, but it is likely that both FMS patients and the latter people have pain that is not due to inflammation or damage of peripheral structures, although both the central hypothesis like sleep disturbance, psychological affection, hypothalamushypophysis-adrenal axis disorder, neuromediator dysregulation, and the peripheral theory like anatomical and/or functional muscle disturbance have been the issues to explain the aetiopathogenesis of FMS<sup>3</sup>. Therefore, it may be said that FMS still represents an enigma to modern medicine and the aetiopathogenesis is yet to be firmly established<sup>4</sup>. But current day research into FMS led the present day medical fraternity to assume that neurobiological, psychological and behavioural factors can equally cause chronic pain like FMS<sup>1</sup>.

Recent evidences from neuroscience research suggest that the adult brain is capable of substantial plastic change in areas like primary somatosensory cortex that were formerly thought to be modifiable only during early experience. These findings have implications for our understanding of chronic pain. Functional reorganization in both the somatosensory and the motor system was observed in neuropathic and musculoskeletal pain. In the case of fibromyalgia

the reorganizational changes are thought to be increased with the development of chronicity. These central alterations may be viewed as pain memories that influence the processing of both painful and nonpainful input to the somatosensory system as well as its effects on the motor system. Cortical plasticity related to chronic pain and consequent maladaptive memory formation can be modified by behavioural interventions that provide feedback to the brain areas that were altered by somatosensory pain memories<sup>5</sup>. Pain amplification that occurs in FMS may be due to increased sensitivity of the pain system<sup>2</sup>.

The most accepted hypothesis regarding its aetiology takes multiple factors like genetic, neurological, muscular and psychological components into consideration. However, about psychogenic aetiology there is yet to be a consensus and therefore diverging hypotheses are proposed. Specific personality traits, traumatic life events, psychodynamic interpretation of depressive conflict are among important psychogenic propositions. Many suggested its inclusion under somatoform disorders<sup>6</sup>. Evidence suggests that psychological factors definitely influence the course of treatment. Behavioural aspects like avoidance behaviour with subsequent physical impairment, attitudes towards subjective theories of illness and therapeutic options play an important role in developing chronicity. Similarly, social factors like effects on work, interpersonal conditioning, and coping strategies may have equal effects in the process<sup>6</sup>.

A randomized intervention study to identify the prognostic factors in the course of fibromyalgia syndrome found that depressed mood at baseline was a significant predictor of sustainability of pain. Therefore, it was suggested that depressed mood should be considered a predictive factor in treatment response<sup>7</sup>. An investigation to determine whether individuals with fibromyalgia who are more physically active differ in various psychosocial characteristics from those who are less active, and



whether those who function better on a daily basis also differ in these characteristics from their less able counterparts demonstrated the importance of physical activity efficacy, pain efficacy, perceived control and health related quality of life to be important predictors of disability due to FMS<sup>8</sup>.

It is evident from previous discussion that actual aetiopathogenesis of FMS are still not very clearly understood and consequently the treatment principally aims at relieving symptoms. Therapeutic options therefore comprise drugs, exercise, educational and psycho-behavioural treatment. An integrated treatment plan combining these options, a sustainable doctor-patient relationship, and a continuous supportive maneuver are likely to be beneficial<sup>6</sup>. The condition responds best to a combination of symptom-based pharmacological therapies, and non-pharmacological therapies such as exercise, education and cognitive behaviour therapy (CBT). In contrast to drugs that work for peripheral pain due to damage or inflammation, neuroactive compounds, especially those that raise central levels of noradrenaline or serotonin are most effective for treating central pain<sup>1</sup>. Among pharmacological treatment tricycles antidepressants like amitriptyline and some muscle relaxants like ciclobenzaprime have demonstrated some beneficial effect contrary to the classical antirheumatic drugs like NSAID, corticosteroids<sup>3</sup>. Such therapy should be initiated only after careful patient information and delineation of therapeutic goals<sup>4</sup>.

Psychological and behavioural treatments are used more frequently now a days to treat patients with fibromyalgia. The rationale for including psychological therapies is not to treat the co-existing mood states, but rather to manage the many non-psychiatric psychosocial factors that comprise pain perception and its maintenance. In biopsychosocial models of illness the commonly used psychological therapy in the management of chronic pain conditions is CBT. The empirical literature supports the use of CBT in FMS and demonstrates a modest outcome across multiple symptom complex including pain, fatigue, physical functioning and mood. More benefits appear to occur when CBT is used adjunctively with exercise. Although the benefits are not curative or universally obtained by all patients, these are considerably accountable to encourage future improvement and development of newer CBT modules for this patient population<sup>9</sup>.

There are pragmatic and theoretical arguments about the application of psychological and behavioural therapies in FMS. It is pragmatic to target obvious and treatable factors including inactivity and depression. A theoretical model in which psychological, physiological and social factors interact offers a plausible rationale for such treatment. Cognitive behaviour therapy indeed offers a pragmatic and rational therapy for patients with FMS. There is evidence for the efficacy of cognitive behaviour therapy and most patients receiving cognitive behaviour therapy improve, especially in terms of functional impairment<sup>10</sup>. Controlled trials of various strategies including cognitive behavioural techniques have been reported over the years. Most of the studies showed significant benefits to patients with fibromyalgia<sup>11</sup>. The results of self-management programme enhancing the self-efficacy and life quality were positive. Patients who are treated intensively for even a short time can continue to improve as they practice non-drug treatment strategies<sup>11</sup>.

A recent study evaluating the association between treatment process variables and treatment outcome at the end of a 4-week multi-disciplinary treatment programme and also after 3- and 6- month follow ups by multiple regression analysis indicated that the outcomes were most closely related to therapeutic targets consistent with cognitive behavioural model of fibromyalgia. The factors that showed overt relationship to therapeutic outcome were an increased sense of control over pain, belief of not being disabled and the pain is not a sign of damage, decreased guarding, increased use of exercise, seeking support from others, activity pacing and use of coping self statements<sup>12</sup>. Another prospective randomized controlled clinical trial to see the effectiveness of an attention distracting and attention focusing guided imagery on fibromyalgic pain showed pleasant imagery has a significant therapeutic effect on fibromyalgic pain<sup>13</sup>.

There is high rates of complementary and alternative medicine use in fibromyalgia, but empirical research data support the use of only three: mind-body, acupuncture, and manipulative therapies. The strongest data exist for the use of mind-body techniques like CBT, biofeedback, hypnosis, particularly when utilized as part of a multi-disciplinary treatment approach. Although there are evidence that acupuncture may at times exacerbate



the symptoms, the data supporting the use of acupuncture for fibromyalgia are moderately strong and only very weak evidence is available in favour of manipulative therapies like massage<sup>14</sup>.

A firm theoretical basis for patient education in chronic pain disorders has been built up over the past 25 years. Education in self-management has enabled patients to control symptoms and contribute in their own care along with their health providers. Education for fibromyalgia patients in particular has come to the foreground during the last 15 years as health professionals have come to understand the syndrome better and recognized the role of psychological stresses in the exacerbation of symptoms. Management of simple fibromyalgia involves education regarding the nature of the problem, an exercise programme and advice on stress management. However, management needs to be flexible and holistic, and may involve relaxation programmes and physical therapies<sup>2</sup>.

The functional prognosis of FMS is usually favourable with a comprehensive supportive programme although some degree symptoms tends to persist and may only inadequately respond to treatment. FMS patients' work capacity cannot be established by mere diagnosis; individual impairments have to be taken into account: Clinical, psychosocial and behavioural dimensions have to be considered<sup>15</sup>.

In conclusion, it may be said that the importance of approaching the patients of FMS from a holistic and multidisciplinary viewpoint paying attention to the physical, emotional, spiritual and behavioural components of the syndrome is necessary. It is important that pain, tissue dysfunction and disability from pain are all separate issues and should be approached as such. Treatment in all cases should be individualized and comprehensive. Drug therapy, if chosen, should be administered in combination with physical treatment and CBT. Because of the appearing contours of pathogenic mechanisms, hopefully a number of new drugs will be available to the patients with this complex pain syndrome in the near future<sup>4</sup>. However, in any case the treatment programmes should not be geared to pain relief alone but rather to restore individuals to functional lifestyles and to promote both physical and emotional flexibility, balance and 'wellness'. It is often necessary to involve the family unit as an inherent and critical part of the treatment team, particularly with the patient who continues to be dysfunctional despite apparently appropriate treatment<sup>16</sup>. Although treatment always

starts at the tissue level, a good treatment programme must always be holistic in nature and should treat the patient as a whole, and her or his environment.

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### Syed Kamaluddin Ahmed

Member, Editorial Board, Journal of Bangladesh College of Physicians and Surgeons.

*(J Bangladesh Coll Phys Surg 2004; 22 : 1-3)*

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## ORIGINAL ARTICLES

# Effect of Calcium Supplementation on Serum Lipid Concentration in Normal Older Women : A Randomized Controlled Trial

AKM M RAHMAN<sup>a</sup>, S RAHMAN<sup>b</sup>, S AKHTER<sup>c</sup>, F BEGUM<sup>d</sup>, K NAHAR<sup>e</sup>, A BISWAS<sup>f</sup>

### Summary:

*The study was done to determine the effect of calcium supplementation on circulating lipid concentration in normal older women. One hundred and ten postmenopausal women were randomly assigned to receive calcium supplementation. Sixty of them received calcium carbonate 1 gm per day and fifty of them received no calcium for six months. None of them were receiving therapy for hyperlipidaemia and osteoporosis. Fasting total cholesterol, low density lipoprotein, high density lipoprotein and triglyceride were obtained at base line serum*

*lipid concentrations and at sixth month. After six months HDL cholesterol increased by 5% and LDL cholesterol decreased by 7% in the calcium group in comparison to the group without calcium. Total cholesterol and triglyceride level revealed non-significant decline. In conclusion calcium supplementation causes a beneficial changes in circulating lipids in postmenopausal women. This suggests that a reappraisal of the indications for calcium supplementation is necessary.*

(*J Bangladesh Coll Phys Surg 2004; 22 : 5-7*)

### Introduction:

Calcium supplementation is recommended and used widely among postmenopausal women for prevention of osteoporosis. There is consistent evidence from randomized controlled trials that calcium supplementation slows postmenopausal bone loss and there is some evidence that it prevents fracture in postmenopausal women<sup>1</sup>. Other benefits from the use of calcium supplements have been suggested. These include favourable effect on colon cancer, blood pressure and serum lipids<sup>2</sup>.

The suggestion that calcium intake might affect serum lipid concentrations has arisen from human and animal studies demonstrating that calcium binds to fatty acids and bile acids in the gut, leading to malabsorption of fat<sup>3,4</sup>. These observations are consistent with suggestions that calcium supplementation has beneficial effect on circulating lipid concentrations. However, the studies were small and short-term and most have not assessed effects on the levels of high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol separately<sup>4</sup>.

It is possible that changes in serum lipids resulting from the use of calcium supplements could be as important for

postmenopausal women as are its effects on osteoporosis. The present study was done to determine the effect of calcium supplementation (in the usual dose used to prevent osteoporosis) on lipid levels in older women<sup>5</sup>.

### Methods:

This randomized controlled trial of calcium supplementation was done on postmenopausal and older ladies attending Medicine Department, Shaheed Suhrawardy Hospital for a period of 4 years from January 1999 to December 2002. Women having menopause for more than five years and older than 55 years were included in this study. Subjects having significant renal, liver and kidney disease were excluded from the study. None of the subjects were using hormone replacement therapy (HRT) for hyperlipidaemia, anabolic steroids, glucocorticoids or bisphosphonates during the previous six months. One hundred and ten patients were included in the study, sixty of them received calcium 1 gm per day, and fifty received no calcium. Diet and physical activity were assessed by using validated questionnaires. Compliance were assessed by tablet counts.

Fasting serum levels of total cholesterol, High-density lipoprotein cholesterol and triglyceride were measured at baseline and at six month, using a Roche-Hitachi 747 autoanalyzer (Mannheim, Germany). Low-density lipoprotein levels were calculated using the Friedewald's formula.

The prespecified hypothesis that the changes in each of the lipid parameters over six months would be different in those treated with calcium and in those without calcium. This was tested by comparing the available data between groups using student 't' test

### Results :

Baseline clinical and lipid data were similar in the calcium and without calcium group. None of the subjects were

- Dr. AKM Mujibur Rahman, FCPS, MD, Senior Consultant, Department of Medicine, Shaheed Suhrawardy Hospital, Dhaka
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**Address for Correspondence :** Dr. AKM Mijibur Rahman, Senior Consultant, Department of Medicine, Shaheed Suhrawardy Hospital, Dhaka

**Table I**

<i>Clinical characteristics of the study subjects.</i>			
Characteristics.	Calcium group(n=60)	Without calcium group (n=50)	P value
	Mean $\pm$ SD		
Age (years)	62 $\pm$ 4	62 $\pm$ 5	0.99
Years since menopause,	16 $\pm$ 3	17 $\pm$ 3	0.99
Weight (Kg)	58 $\pm$ 11	57 $\pm$ 10	0.15
Height (centimeter)	158 $\pm$ 6	159 $\pm$ 6	0.99
Compliance (%)	95%	97%	0.99
Physical activity.	Moderate	Moderate	

**Table II**

<i>Effects of calcium supplementation on serum lipid level.</i>					
Measurement (mg/dl)	Group	Baseline	6 months	Percentage change (Baseline to 6 months)	P Value
HDL Cholesterol	With Calcium.	45.34 $\pm$ 9.4	42.50 $\pm$ 8.6	+5%	0.01
	Without Calcium	44.25 $\pm$ 9.1	43.46 $\pm$ 8.2	+2%	
LDL Cholesterol	With calcium	154 $\pm$ 28	142 $\pm$ 25	-7.26%	0.04
	Without Calcium.	148 $\pm$ 27	149 $\pm$ 24	-1.2%	
Total Cholesterol	With Calcium	196 $\pm$ 56	194 $\pm$ 52	-5%	0.52
	Without calcium	192 $\pm$ 58	200 $\pm$ 35	-3%	
Triglyceride	With Calcium	227 $\pm$ 67	217 $\pm$ 85	-4%	0.48
	Without Calcium	270 $\pm$ 106	265 $\pm$ 95	-3%	

alcoholic or smoker. Lipid profile were almost similar in both groups at the beginning of the study.

In the calcium group, mean HDL cholesterol level increased about 5% above baseline at six months, whereas LDL cholesterol level declined about 7%. Total cholesterol level showed a nonsignificant decrease of 5%. Triglyceride level also showed a nonsignificant decrease of 4% at the end of the study. Mean body weight did not show any significant change in any of the groups at the end of the study

#### **Discussion :**

The study findings indicate that the use of calcium carbonate in a daily dose containing 1 gm elemental

calcium increases serum HDL cholesterol level with reciprocal changes in LDL cholesterol level. Increase in HDL cholesterol of this magnitude may be associated with 20-30% reduction in the rates of cardiovascular events. Since atherosclerosis is the most common cause of death in postmenopausal women, the hypolipidemic effects of calcium could have greater effects on morbidity and mortality in these women than on osteoporosis.

The hypolipidemic effects of calcium was observed in earlier reports. Two substantial studies have been reported in adults. Bell et al<sup>7</sup> randomly assigned 56 hypercholesterolemic patients to placebo or calcium 1.2 gm/day (as carbonate) for six weeks, followed by

a crossover. Low density lipoprotein cholesterol level decreased by 4% and those of HDL cholesterol increased by 4%, consistent with this study. The smaller sizes of the changes they found may be related to shorter duration of their study or to the lower bioavailability of calcium.

There is also observational evidence that calcium intake is inversely associated with cardiovascular disease. In the Iowa Women's Health study, for example cardiovascular mortality was one-third lower among women whose calcium intake (diet or supplements) were in the highest quartile in comparison with those in the lowest quartile<sup>8</sup>. This reduction in event rate is very similar to that predicted from lipid changes that was observed in this study. Knox reported a strong inverse relationship between calcium intake and standardized mortality ratios for ischaemic heart disease in patients in the United Kingdom<sup>10</sup>.

The effects of calcium supplementation on lipid concentration are likely to result from calcium binding to fatty acids and bile acids in the gut, thus interfering with lipid absorption<sup>4</sup>. However, other mechanisms may also be involved. There is evidence that parathyroid hormone and 1, 25 dihydroxycholecalciferol (active form of vit. D) regulate adipocyte activity. Calcium supplementation suppresses circulating concentration of parathyroid hormone, thereby possibly promoting lipolysis<sup>12</sup>. Studies have shown that calcium supplementation can increase lipolysis and body temperature as well as reduce fatty acid synthesis and body weight. These direct effects on adipocyte may contributed to the weight loss that has been reported with the use of calcium supplements<sup>12</sup>.

#### **Conclusion :**

In conclusion, results of this study, together with those of previous studies, suggest that calcium intake has effect on intermediary metabolism that results in beneficial changes in serum lipid level. This study

provide reasons to encourage more wide use of calcium supplementation in postmenopausal women.

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# Role of Operative Choledochoscopy in Choledocholithiasis

ABMB HOSSAIN<sup>a</sup>, T ALAM<sup>b</sup>, ZR KHAN<sup>c</sup>, M CHOWDHURY<sup>d</sup>

## Summary :

*Operative choledochoscopy is a simpler procedure that can be easily learned and practiced by many surgeons at the time of common bile duct exploration. It is now well established in biliary tract surgery and is considered as an integral part of common bile duct exploration. It provides a better evaluation of intracholedochal pathology. It also provides an effective, safe & easy method of dealing with problem of stones in the intrahepatic branches of the bile duct which results in an almost negligible incidence of retained ductal calculi. Choledochoscopy was done in 25 patients through choledochotomy incision. The*

*choledochoscope was used after conventional common bile duct exploration. Complete stone clearance was confirmed by choledochoscopy in 21 patients and additional stones were found in remaining four patients. Dormia basket was used to extract those stones. Impacted common bile duct stones were found in two of the four patients in ampullary region and two in intrahepatic third generation duct. Post operative T-tube cholangiography done in twelve patients and no retained stone was found.*

*(J Bangladesh Coll Phys Surg 2004; 22 : 8-11)*

## Introduction :

Residual stone in common bile duct after choledocholithotomy is a difficult situation for surgeons and patients alike. Although techniques such as desolution<sup>1,2</sup>, basket extraction<sup>3</sup> and endoscopic sphincterotomy<sup>4</sup> are available to deal with these stones. It is obviously desirable to ensure that the ducts are free of stones at the time of operation. Two techniques are available to examine the bile ducts after exploration: T-tube cholangiography and choledochoscopy. Post exploratory T-tube cholangiography can be unreliable because air bubble may be introduced into the ducts and sometimes spasm of the sphincter of Oddi may prevent flow of contrast media into the duodenum. Examination of the bile ducts under direct vision with a choledochoscope seems a certain method of ensuring that there are no residual stone. Choledochoscopy has been performed for over 70 years<sup>2</sup>. Subsequently flexible fibre-optic instruments

have become available and experience with it has been reported<sup>5</sup>. Although satisfactory instruments have been available for almost 40 years, biliary endoscopy has not been widely used. Most surgeons probably underestimate the incidence of retained stones and may feel that there is no need for such an instrument. The cost of the instrument, particularly flexible scopes, is high and this has restricted the wide adoption of the technique. The common bile duct is explored in approximately 15% of all cholecystectomies and stones are removed in approximately 65% of these explorations. The incidence of concomitant choledocholithiasis with cholecystolithiasis varies between 8 and 10%<sup>6</sup>. The morbidity caused by the presence and removal of retained stones after cholecystectomy warrants the use of the most effective available means of common bile duct exploration. The use of choledochoscope offers many advantages during common duct explorations. This includes localization of impacted calculi, interpretation of cholangiogram abnormalities and extraction of intrahepatic calculi. In addition, it also delineates ductal anatomy and may assist in the diagnosis and biopsy of other ductal lesions<sup>7</sup>.

## Materials and method :

A prospective study was done to determine the value of operative choledochoscopy using a flexible choledochoscope. Twenty five patients were included in the study between June 2002 to November, 2003 in

a. Dr. ABM Bayezid Hossain FCPS, Junior Consultant, Surgery BSMMU, Dhaka.

b. Dr. Towhidul Alam FCPS, Associate Professor of Surgery, BSMMU, Dhaka.,

c. Dr. Z.R. Khan FCPS, FRCS, Associate Professor of Surgery, BSMMU, Dhaka.

d. Dr. Mohshen Chowdhury FCPS, Assistant Professor of Surgery, BSMMU, Dhaka.

Address for correspondence to : Dr. ABM Bayezid Hossain, Junior Consultant Surgery, BSMMU, Dhaka



the department of surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka. Preoperative investigations included routine examination like full blood count, blood glucose, urea, electrolytes; liver function tests (LFTs) and ultrasonogram of biliary system. Operative cholangiography was not routinely done prior to common bile duct exploration, Post operative T-tube cholangiography when carried out the contrast material used was 50% meglumine iohalamate solution or 50% sodium diatrizoate. The first film was taken after injection of 5 ml of contrast and second film after injecting another 15 ml. The decision to explore the common bile duct was based on clinical findings, ultrasound imaging and operative finding. Common bile duct was explored by a supraduodenal choledochotomy, although access through a transduodenal sphincterotomy or a combination of these was occasionally used. Conventional exploration was done with Desjardin's forceps to remove calculi. This was followed by flexible choledochoscopy (Pentax FCB-15H) to explore the biliary tract. Choledochoscope was introduced into the common bile duct and the proximal extra and intrahepatic ducts were examined first. Ducts were sequentially seen starting from right ductal system towards the left. The scope was advanced proximally until the secondary/tertiary biliary radicals were seen. The common bile duct was examined for stones, inflammatory signs of cholangitis, strictures or growth. Distally the common bile duct was visualized & the ampulla of Vater was identified. The sphincter of ampulla has a typical fish mouth appearance. A variety of accessories are available which can be inserted through the working channel of the scope for the removal of stones or biopsy of any suspicious lesion in the biliary tract. If stones were found, they were removed either by routine methods or by choledochoscopic instrumentation with a dormia basket. Biopsy of any growth in the biliary tract was carried out using biopsy forceps. The common bile duct was closed over a T-tube or a biliary enteric bypass was done according to the operative and choledochoscopic findings. The scope is introduced into the biliary tract by way of a standard choledochotomy incision. The stay sutures are crossed over to reduce leakage of saline solution around the instrument. A continuous

flow of sterile normal saline solution from a drip set through the instrumentation channel of the scope under a pressure of some 30 mm of Hg allows adequate distension of the duct and permits clear vision. The tip of the scope is first directed towards the liver, and the proximal part of the common bile duct, common hepatic duct and bifurcations are visualized. Both the right and the left ducts can be entered and in instances of dilated ducts, secondary and tertiary branches can be seen. The position at the entrance of the irrigation channel of the scope indicates the position (right / left) of the tip of the scope. This is usually slightly flexed upward while performing the examination. After completion of the hepatic endoscopic examination, the scope is reinserted into the distal part of the common bile duct and advanced towards the papilla under direct vision. Inspection is continued during withdrawal of the instrument when the best views may be obtained. By inspecting the distal part of the common bile duct, better visualization of the whole length can be achieved by placing two fingers of the left hand in the foramen of Winslow and by applying slight traction in the direction of the liver, which will thus straighten the common bile duct. Mobilization of the duodenum using Kocher's maneuver was not used routinely.

It is advisable to repeat the inspection of the distal portion of the common bile duct twice. The choledochoscopy is complete only when both main intrahepatic ducts, the bifurcation of the common hepatic duct, the common bile duct throughout its length and duodenal mucosa through ampullary or papillary orifice have been visualized and inspected.

#### **Result :**

All twenty five patients had undergone conventional common bile duct exploration with a Desjardin's forceps prior to scope. Complete removal of all stones (blind clearance) were confirmed by choledochoscopy in twenty one patients (Fig- 1). The scope was passed proximally up to the tertiary intrahepatic biliary radicals and distally beyond the ampulla in all these twenty one patients. During choledochoscopy associated stricture of the lower end of common bile duct was found in two patients. Closure of choledochotomy with a T-tube drainage was carried out in twenty three patients and choledochoduodenostomy done in the remaining two

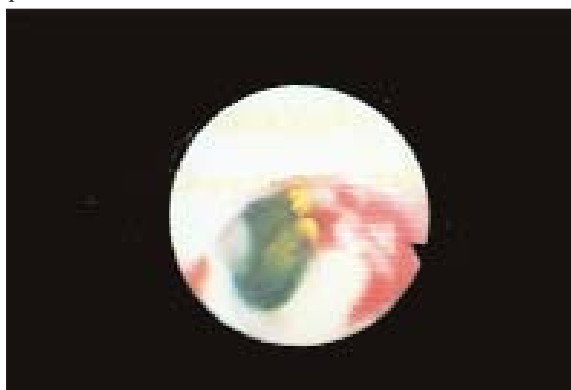




**Fig.-1 :** Normal choledochoscopic view of biliary tree

patients having stricture. Additional stones were detected in the four patients. Impacted stone in the lower end of common bile duct were seen in two of them. Complete extraction with dormia basket was possible only in one and other needed transduodenal sphincterotomy. In other two patients, impacted stones were seen in the third generation intrahepatic ducts

(Fig-2). These intrahepatic stones were extracted with the dormia basket. Post operative T-tube cholangiogram was done in twelve patients on the 10<sup>th</sup> post operative day to look for retained stone in the biliary system. No residual stone was found in these patients.



**Fig.-1 :** Choledochoscopic view of biliary tree showing retained stone after traditional removal (blind clearance) of stone

**Table – I**

*Findings of different studies showing frequency of additional stones overlooked by instrumental exploration.*

Reference	Year	Total Number of choledochoscopy	Additional stone recovered in patients	% of stones overlooked by instrumental exploration
Shore and Shore <sup>9</sup>	1970	100	22	22
Ottinger and Warshaw <sup>12</sup>	1974	30	9	30
Schein <sup>13</sup>	1975	117	6	5
Finnis and Rowntree <sup>5</sup>	1977	88	24	-27
Kappas et al <sup>14</sup>	1979	73	12	17
Yap et al <sup>15</sup>	1980	112	16	14
Escat et al <sup>16</sup>	1984	380	46	12
Present study	2003	25	4	16

**Discussion:**

Choledochoscopy is an indispensable tool in common bile duct surgery<sup>8</sup>. The choledochoscope is easy to sterilize and to use. The common duct is perfectly visualized and only basic endoscopic orientation is needed and no specific training is required. The length of the surgery is not increased and no complication related to its use has been reported. Choledochoscopy presents three major advantages:

1. It provides a reliable way to discover stones overlooked by classical methods (four cases in this series, 16%). The findings reported in different studies are shown in Table-I.
2. It visualizes common bile duct, the ampulla of Vater and the hepatic channels. This visualization decreases the rate of retained stone to 0% compared to (blind clearance) instrument exploration alone in which retained stone have been estimated to be 20%<sup>9</sup>.
3. It improves operative technique because it gives direct visualization of the biliary tree confirming its patency. This eliminates the necessity for sphincterotomy and biliary digestive anastomosis, which are reserved for impacted common duct stones. Therefore, endoscopy reduces operative morbidity and mortality.

It is reported that 96% of patients with overlooked stones required surgery within five years of cholecystectomy<sup>10</sup>. It is therefore, important to eliminate the problem of retained stone at the time of primary common bile duct exploration. Recent review of a large series of operative flexible choledochoscopy highlighted the benefits of this method over other methods of common bile duct exploration<sup>11</sup>.

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# Haemoglobin Level of Apparently Healthy Children

MA WAHED<sup>a</sup>, MH RAHMAN<sup>b</sup>

## Summary :

*A prospective and cross-sectional study was conducted in the department of Paediatrics of Rangpur Medical College Hospital to estimate the level of Haemoglobin (Hb) in the healthy and well nourished children. The total number of samples was 1500 with male : female ratio 1:1. Samples were collected from newborn babies to children upto 14 years of age from Children Out-Patient Department (COPD) and from a Baby Friendly Clinic of Rangpur Town. Haemoglobin level was estimated from all*

*the children by Methhaemoglobin method. Possible causes of anaemia were excluded from all the samples. Mean Hb level of both sexes was 10.03±1.16 gm/dl, with 10.41±1.09gm/dl in the male children and 10.17 ± 1.23 gm/dl in the females. Mean values were compared with the 50th centile of percentile (NCHS) charts of both sexes. The mean value of Bangladeshi children was lower than that of the developed countries.*

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## Introduction :

Haemoglobin is a complex protein consisting of iron containing haem and the protein moiety globin. In children the haemoglobin level is 23gm/dl at birth, falling to 10.5gm/dl at the end of the third month. The concentration then gradually rises to reach 12gm/dl at one year. In adult male, the mean blood haemoglobin level is 15.5gm/dl; the range is 14-18 gm/dl. In adult female, the mean haemoglobin concentration is 14.0 gm/dl with a range of 12-15.5gm/dl<sup>1,2,3</sup>. These are the findings from the studies carried out in developed countries. These values may differ in a country like Bangladesh due to racial, genetic and dietary variations. Amino acids, iron, copper, manganese, cobalt, nitrogen, vit-B12 and folic acid, which are necessary for haemoglobin synthesis, may have different bio-availability. Thyroxin, pituitary and adrenal hormones, and erythropoietin which are also necessary for haemoglobin synthesis, may vary in bio-activity<sup>4,5</sup>.

Iron deficiency anaemia is a common problem of children of Bangladesh. Seventy three percent of children and women suffer from iron deficiency anaemia<sup>6,7</sup>. It causes difficulty in maintaining attention and poor school performance, lowering IQ by about 9 points<sup>8,9</sup>. Few studies have been done on this subject, which are mainly related to iron metabolism and iron deficiency anaemia. Only one nation wide survey was carried out about 20 years

back<sup>6,7,8</sup>. The present situation is not known. So this study was designed to know the present status of Hb level and rate of anaemia among the children of this country.

## Materials and method :

A cross-sectional study was done to estimate the level of haemoglobin in healthy children. The objective of the study was to know the normal haemoglobin level of healthy children of Bangladesh and to compare this level with that of developed countries. The study was conducted in the department of Paediatrics of Rangpur Medical College Hospital (RMCH) for a period of two years from first July 1998 to 30th June 2000. Samples were collected from two places - a Baby Friendly Private Clinic in Rangpur town and the Children Out-Patient Department (COPD) of RMCH. Children from birth to 14 years of age were the study population. Children from birth to seven days of age were selected from the clinic. These babies were born in the clinic and had a birth weight of >2.5 kg. The mothers of these babies were healthy and had no intra-partum complication and Hb level was more than 60% during pregnancy. Children from the second week of age up to 14 years were selected from the COPD. These children first attended at COPD for treatment of different diseases. They were then asked to attend the COPD during their disease-free period for study purpose.

In the clinic, cord blood was collected from the babies delivered by LUCS and from heel prick from the babies delivered vaginally. In COPD, the samples

a. Dr. MA Wahed, FCPS, Assistant Professor (Paed.), Rangpur Medical College

b. Dr. Md. Hamidur Rahman, FCPS, Professor of Paediatrics, Rangpur Medical College

**Address of correspondence :** Dr M. A. Wahed, Assitt. Professor (Pead.), Rangpur Medical College

were weighed along with physical examination. Children having body weight of >80% of the expected weight in NCHS weight chart were considered. In these samples blood was collected from finger prick. In all cases haemoglobin was estimated by Cynmethhaemoglobin method from two selected private laboratories. Haemoglobin level of 16.0 gm/dl of blood was regarded as 100.0% and <11 gm/dl as anaemia. In children having mild splenomegally, blood film and reticulocyte count was done to exclude haemolytic anaemia. Routine examination of stool was done in children having history of taking anti-helminthic drugs more than four months back. Children having haemolytic anaemia, helminthiasis, giardiasis, any chronic systemic disease, chromosomal disease, rickets or gross bony abnormality and convalescent period of a disease were excluded from the study. Children having no biological mother and taking iron supplements were also excluded from the study. At first the children were divided into 15 groups. Newborn infants in one group and from one year to 14 years another 14 groups. In each group, there were 100 children, 50 male and 50 female. In this way, 1500 samples (750 male, 750 female) were selected for analysis. Finally the children were grouped into five groups for ease of analysis. In each case, consent from parents was taken to avoid any ethical obligation.

Before data collection, an "Interview schedule" was prepared to use as research instrument. Variables used were age, sex, religion, address, weight, splenomegally and Hb%. After data collection, each interview schedule was checked for consistency. Then the data were entered into a computer for analysis. Hb level was arranged according to age groups from birth to 14 years of age. Results were presented as tables. A frequency distribution curve was also constructed.

### Results :

The total number of children was 1500 among which 750 (50%) male and 750 (50%) female. In newborn babies, the average level of Hb was highest and in infancy it was lowest (Table I). In both the sexes, about 80% of children were anaemic (Table II). In all age groups, the level of Hb was lower in females (Fig. 1). The level of Hb was lower in

Bangladeshi children compared to NCHS standard (Fig. 2 and 3).

**Table I**

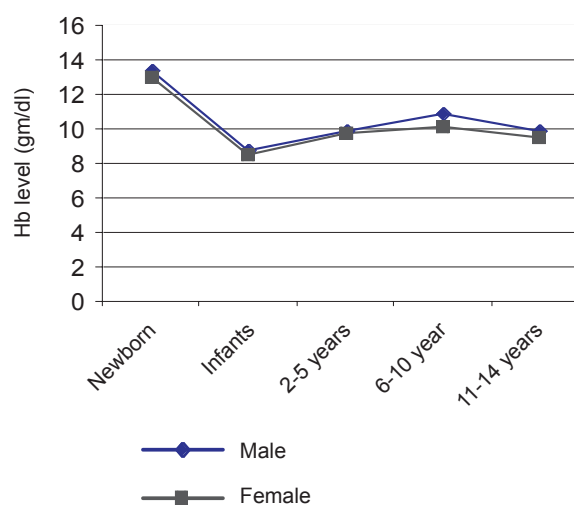
*Haemoglobin level in different age groups of studied children*

Age	Number		Mean Hb level (gm/dl)	
	Male	Female	Male	Female
Newborn	50	50	13.35	13.03
Infants	50	50	08.77	08.55
2-5 years	200	200	09.84	09.69
6-10 years	250	250	10.90	10.14
11-14 years	200	200	09.93	09.44
Total	750	750	10.41	10.17

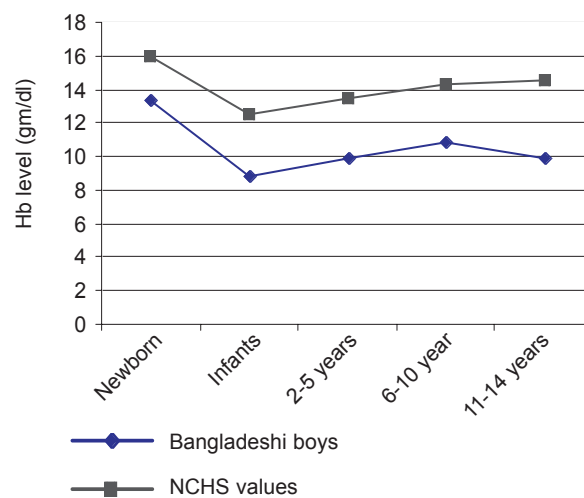
**Table II**

*Rate of anaemia (Hb < 11 gm/dl) among studied children*

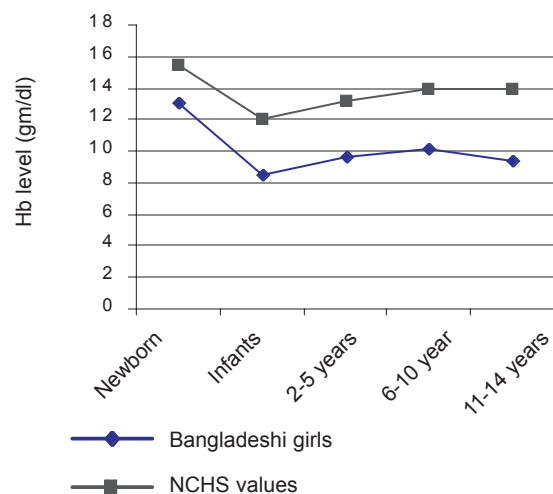
Sex	No of children	No of anaemic children (%)
Male	750	600 (80.00)
Female	750	604 (80.50)
Total	1500	1204 (80.25)



**Fig.-1 : Haemoglobin level according to sex**



**Fig.-2 :** Haemoglobin level of boys compared with NCHS median



**Fig.-3 :** Haemoglobin level of girls compared with NCHS median

### Discussion :

The study was carried out to estimate the level of Hb in healthy children of Bangladesh. Children up to 14 years of age were included in the study for ease of collection of samples as the Hospital Authority of RMCH regards 15 years as paediatric age instead of 12 years in other hospitals. In each age group, 50 children were included from both sexes to increase the number of samples and to decrease the variation or error. The average Hb level was  $10.03 \pm 1.16$  gm/dl in both sexes,  $10.41 \pm 1.09$  gm/dl in boys and  $10.17 \pm 1.23$

gm/dl in girls. The average level of Hb in both sexes is lower in this study than the figures shown in percentile charts. This may be the average level of Hb of Bangladeshi children. A study conducted in Dhaka city<sup>10</sup> showed Hb level of better nourished children as 9.6 gm/dl (60%) which is consistent with the present study. It may also be due to iron deficiency as low Hb level and iron deficiency has been a perennial problem in children age group and it is the most common single nutrient deficiency in the world<sup>8,10,11</sup>. There are some studies and surveys on healthy and hospitalized infants and toddlers in France<sup>12</sup>, Spain<sup>13</sup>, and United Kingdom<sup>14,15</sup> which have shown low Hb level in this age group. But as the children were healthy and non-hospitalized, this is not applicable on these children. The slightly higher level of Hb in boys, but this is not significant in statistical analysis. This may be due to improved nutritional status in girls as there is little difference in nutritional status between boys and girls due to gradual decline in intra-familial food discrimination between sexes<sup>16</sup>.

The result shows that the average level of Hb is lower in both sexes than that of percentile chart from birth throughout childhood. The lower level in newborn babies may be due to maternal malnutrition as 74% of non-pregnant and 47% of pregnant mothers have low Hb level in Bangladesh<sup>6</sup> and though the pregnant mothers in this study had Hb level above 60% during pregnancy, they were still mildly anaemic. Low Hb level in infancy and childhood may be due either to rapid growth or low content of iron in the foods of Bangladesh. Because infants have a high iron requirement for growth but frequently consume iron intakes below dietary recommended levels<sup>17</sup>. The combination of larger body size and rapid growth creates an increased demand upon dietary iron to fulfill the needs for haemoglobin synthesis and tissue growth<sup>18</sup>. During infancy, mother's milk or formula milk is usually the major part of the diet and frequently there is delayed or improper weaning. Both human milk and cow's milk provide relatively small quantities of iron (0.2-0.4 mg/l). Though the bioavailability of iron from human milk is considerably higher than cow's milk, it cannot maintain adequate iron level beyond six months of age<sup>19</sup>.

Dietary intake of iron during childhood is often low or marginal in most developing countries. Cereals and legumes, which are the most common staple foods, only provide modest amount of iron. In addition, iron bioavailability from cereals and legumes is low due to



the presence of phytates which inhibits iron absorption<sup>20</sup>. Meat which is a good source of iron with high bioavailability is rarely consumed or a minor part of the diet. Ascorbic acid provided by the fruits or vegetables can also has a pronounced positive effect on iron absorption, but it is taken in very small quantities by the children in developing countries<sup>21</sup>. Similar dietary patterns responsible for inadequate iron intake in developing countries has been described among toddlers aged 18-30 month living in villages in Egypt, Kenya and Mexico, the proportion judged to consume less than basal iron requirement was 35%, 13% and 43% respectively<sup>22</sup>. The cut-off point for anaemia by the World Health Organization (WHO) is 11 gm (69%) for the children from 6 months to 14 years<sup>23</sup>. According to this value, around 80% of the children in this study are anaemic. The survey conducted in this country<sup>6</sup> has shown that 73% of children are anaemic. The higher level in this study may be due to the fact that micronutrient deficiency has been worse in this country over the years though nutritional status as a whole has improved over the past few years<sup>24,25</sup>.

### Conclusion :

There are several limitations of the study. Serum iron level, serum ferritin level and malarial parasite could not be investigated due to lack of facilities. In spite of these limitations, this study shows the trend of Hb level in Bangladeshi children. Further study is needed to establish this finding.

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# Clinical, Biochemical, Serological, Ultrasonographic and Histological Evaluation of 300 Asymptomatic HbsAg Positive Individuals

MM RAHMAN<sup>a</sup>, MAM SIDDIQUI<sup>b</sup>, ZU AHMED<sup>c</sup>, SMB HOSSAIN<sup>d</sup>, MEA MONDOL<sup>e</sup>  
MN UDDIN<sup>f</sup>, A HUDA<sup>g</sup>

## Summary:

*The aim of this study is to know replicative markers of Hepatitis B virus (HBV) as well as evidence of chronic liver disease among asymptomatic HBV carriers. Three hundred consecutive asymptomatic HBsAg positive individuals were evaluated clinically, biochemically, serologically, ultrasonographically and histologically at Combined Military Hospital, Dhaka from January 2001 to June 2002. HBsAg was detected incidentally during routine screening test done for blood donation, foreign mission and courses abroad. They were evaluated after six months of initial detection of HBsAg. Age of the patient ranged from 16 years to 50 years (mean  $\pm$ SD = 32.44 $\pm$ 6.35 years). Two hundred*

*and ninety seven patients (99%) were male and three (1%) were female. HBsAg was found positive in 28 (9.3 %) cases, anti HBe was positive in 257 (85.7%) cases, raised ALT (>45 i.u./L) in 52 (17.33%) cases, prothrombin time more than three seconds of control in 54 (18.0 %) cases. Ultrasonography showed coarse hepatic echotexture in 20 (7.62%) cases. Hepatic histology revealed chronic hepatitis in 25 (10.41%) cases and cirrhosis of liver in 4 (1.66%) cases. Hepatocellular carcinoma was not found in any of the cases. Lamivudine therapy was given in 10 (3.33%) patients who had positive HBeAg and ALT more than two times the upper limit of normal.*

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## Introduction :

Chronic hepatitis B is a common problem in Bangladesh<sup>1</sup>. About 10% of adult and 90% of neonatal or early childhood HBV infection leads to chronicity<sup>2</sup>. Chronic HBV infection may cause chronic hepatitis, cirrhosis of liver and hepatocellular carcinoma<sup>3-5</sup>. Rate of progression to cirrhosis and hepatocellular carcinoma

vary according to the immune status and age of the host, stage of infection, geographic and genetic factors. Active viral replication may be found in some of the asymptomatic HBV carriers who may require antiviral or immunomodulatory treatment<sup>6-8</sup>. Reactivation and acute flares may develop during the course of the disease.<sup>9</sup> YMDD motif mutations are also detected in some lamivudine untreated HBV carriers<sup>10</sup>. The aim of this study was to know the clinical, biochemical, serological, ultrasonographic and histological status of asymptomatic HBsAg carriers and evaluate these cases for treatment.

## Materials and Method :

Three hundred consecutive asymptomatic HBsAg carriers were evaluated clinically, biochemically, serologically, ultrasonographically and histologically at Gastroenterology Department of Combined Military Hospital, Dhaka, in collaboration with Armed Forces Institute of Pathology and Department of Radiology. Patients were Armed Forces persons and their family members. All of them were asymptomatic. They were detected to have positive HBsAg incidentally during routine screening test for going abroad and blood donation. All the patients were observed for more than six months after initial detection of HBsAg. Detail

- Lt Col Md Mokhlesur Rahman FCPS, Classified Specialist in Medicine & Gastroenterologist, CMH, Dhaka.
- Maj Gen Md Abdul Moyeed Siddiqui FCPS, FRCP, Consultant Physician, Bangladesh Armed Forces, Dte Gen Med Svcs, Dhaka.
- Maj Gen Zia Uddin Ahmed MRCP, FRCPI, FCPS, Former Consultant Physician, Bangladesh Armed Forces, Dte Gen Med Svcs, Dhaka.
- Col Sk Md Bahar Hossain FCPS, Classified specialist in Medicine & Gastroenterologist, CMH, Dhaka.
- Lt Col Md Eunus Ali Mondol FCPS, Classified Specialist in Pathology, AFIP, Dhaka
- Lt Col Md Nabir Uddin FCPS, Classified Specialist in Pathology, AFIP, Dhaka.
- Maj Atiya Huda FCPS, Graded Specialist in Radiology, CMH, Dhaka.

**Address of Correspondence:** Lt Col Md Mokhlesur Rahman, Classified Specialist in Medicine & Gastroenterologist, Gastroenterology Department Combined Military Hospital, Chittagong, Bangladesh

history and clinical examination were done at the entry. Hepatitis B viral profile, serum alanine aminotransferase (ALT), prothrombin time (PT), albumin, alpha-fetoprotein (AFP) were done in all cases at the entry and during follow up. Polymerase chain reaction (PCR) for HBV DNA was not done due to lack of facility in the above laboratory. Ultrasonography of liver was done in the majority of the patients. Ultrasonography assisted liver biopsy was done at Radiology department. Upper gastrointestinal endoscopy was done in selected cases to see oesophageal and gastric varices. All clinical and laboratory data were recorded in a questionnaire and checklist and then analyzed in computer. Patients were followed up for one year. During follow up two patients showed reactivation of the disease with reversion to positive HBeAg from negative HBeAg. One of the cases with cirrhosis died of bleeding from duodenal ulcer and hepatic encephalopathy during follow up. One patient developed intraperitoneal haematoma during liver biopsy. Haemostasis was secured at laparotomy and he recovered well.

All the results were expressed as mean or percentage where indicated. Statistical significance of data was determined by using Pearson's  $X^2$  test. P value of  $<0.05$  was taken as statistically significant. All statistical analyses were done by using the SPSS package (version 10).

#### Results :

Age of the patients ranged from 16 years to 50 years (mean  $\pm$  SD=32.44 $\pm$ 6.35 years). Two hundred and ninety seven (99%) cases were male and three (1%) were female. Only small number of patients had previous history of jaundice (10#3.33%), hospital admission (12#4.0%), injection (5#1.66%), or transfusion (2#0.66%). Ten patients (3.33%) were health care workers of which four were doctors working in different hospitals. Among the doctors one was surgeon, one anesthetist and remaining two were internists. Hepatomegaly was found in two (0.66%) cases, splenomegaly in three (1.0%) cases and oesophageal varices in 1 (0.33%) case. Spider angioma, gynaecomastia, palmar erythema, testicular atrophy and ascites were not found in any of the cases (Table-I).

**Table -I**

Base line characteristics of HBV carriers (N=300)		
Characteristics	Number	Percentage
Age (Years)		
Range	16-50	
Mean $\pm$ SD	32.44 $\pm$ 6.35	
Sex		
Male	297	99.00
Female	03	01.00
Previous history of injection	05	01.66
Previous history of blood transfusion	02	00.66
Previous history of jaundice	10	03.33
Previous hospital admission	12	04.00
Contact with jaundice cases	01	00.33
Health care workers	10	03.33
Affected family members of index cases	12	04.00
I.V drug abuse	Nil	Nil
Sexual promiscuity	Nil	Nil
Asymptomatic	300	100.00
Hepatomegaly	02	00.66
Splenomegaly	03	01.0.0
Oesophageal varices	01	00.33

HBeAg was positive in 28 (9.3%) cases which signified replicating stage of the disease. Anti-HBe was positive in 257 (85.7%) cases. Serum ALT level ranged from 13 i.u/L to 379 i.u/L (mean±SD = 39.59 ±41.14 i.u/L). Fifty two (17.33%) cases had ALT above the upper limit of normal (>45 i.u/L). Serum albumin was moderately decreased (30-35 gm/L) in 15 (5.0%) cases. PT was more than three seconds of control in 54 (18.0%) cases. Abnormally coarse echotexture of liver was found in 20 (8.13%) cases. Abnormal hepatic histology was found in 29 (12.07%) cases (Table -II). Abnormally raised serum ALT, PT, decreased serum albumin, coarse hepatic echotexture and abnormal hepatic histology were found more commonly in HBeAg negative cases than HBeAg positive cases. They were statistically

significant in cases of raised ALT ( $P<0.0001$ ), hepatic histology ( $p <0.0001$ ) and hepatic echotexture ( $P<0.001$ ). Increased PT ( $p=0.988$ ) and decreased serum albumin ( $p=0.184$ ) were not statistically significant between HBeAg positive and HBeAg negative cases. HBeAg and anti HBe both were positive in 5 (1.66%) cases and both were negative in 20 (6.66%) cases. This was statistically significant ( $P <0.0001$ ). (Table-III). Ultrasonographic echotexture of liver and hepatic histology correlated well and was statistically significant ( $P<0.0001$ ) (Table - IV) Chronic hepatitis and cirrhosis were found in 22 (9.16%) cases in anti HBe positive patients in comparison to 7 (2.90%) cases in anti HBe negative patients. This was also statistically significant ( $P <0.05$ ) (Table V).

**Table-II**

Serological, biochemical, ultrasonographic and histological characteristics of Asymptomatic HBV Carrier (n=300)

Characteristics	Number	Percentage
HBsAg Positive	300	100.00
HBeAg Positive	28	009.30
HBeAg Negative	272	090.70
Anti HBe Positive	257	085.70
Anti HBe Negative	43	014.30
ALT: (I.U./L)		
Range	13-379	
Mean ± SD	39.59±41.14	
S. Albumin: (gm /L)		
Range	30-56	
Mean ± SD	46.34±4.16	
PT : (Sec)		
Range	12-28	
Mean ± SD	14.53±1.78	
AFP (<12.5ng /ml)	300	100.00
USG (N=246)		
Normal echotexture	226	091.86
Coarse echotexture	20	008.13
Hepatic histology (N=240):		
Normal histology	211	087.91
Abnormal histology:	29	012.08
Chronic hepatitis with mild activity	15	006.25
Chronic hepatitis with moderate activity	09	003.75
Chronic hepatitis with severe activity	01	000.41
Cirrhosis of liver	04	01.66

**Table-III**

Relationship Between HBeAg positivity and serum ALT, Anti-HBe, hepatic ultrasonography and histology (N=300)			
Characteristics	HBeAg +VE (N=28) no %	HBeAg -VE (N=272) no %	P value
ALT: (i. u/L)			<.0001
≤ 45	13 (4.33)	235 (78.33)	
≥ 45	15(5.0)	37(12.33)	
PT: (Control =12 sec)			0.988
≤ 15	22(7.33)	224 (74.66)	
≥ 15	06(2.0)	48 (16.0)	
Serum Albumin: (gm/L)			0.184
>35	25(8.33)	260(86.66)	
30-35	03(1.0)	12(4.0)	
< 30	Nil	Nil	
Anti HBe +VE	05(1.66)	252(84.0)	<.0001
Anti HBe -VE	23 (7.66)	20(6.66)	
Hepatic Histology (N=240)			<.0001
Normal Histology	08 (3.33)	203(84.58)	
Abnormal histology:	06 (2.5)	23(9.58)	
Chronic hepatitis with mild activity	01(0.41)	14(5.83)	
Chronic hepatitis with moderate activity	03(1.25)	06(2.50)	
Chronic hepatitis with severe activity	01(0.41)	-	
Cirrhosis of liver	01 (0.41)	03(1.25)	
USG (N= 246)			<.001
Normal hepatic echotexture	14 (5.69)	212(88.33)	
Coarse hepatic echotexture	01(0.40)	19 (7.72)	

**Table-IV**

Relationship Between Hepatic Histology and Ultrasonographic Findings (N=240)			
Hepatic Histology	Normal echotexture number (%)	Coarse echotexture number (%)	P value
Normal	200(83.33)	11(4.58)	
Chronic hepatitis with mild activity	13(5.41)	02(0.82)	
Chronic hepatitis with moderate activity	06(2.5)	03(1.25)	<.0001
Chronic hepatitis with severe activity	01(0.41)	-	
Cirrhosis of liver	01(0.41)	03(1.25)	

**Table-V**

Relationship Between Hepatic Histology and anti-HBe (N=240)			
Hepatic Histology	Anti HBe +VE Number (%)	Anti HBe -VE Number (%)	P value
Normal	188(78.33)	23(9.58)	
Abnormal histology (Chronic hepatitis and cirrhosis)	22(9.16)	07(2.90)	<0.05

### Discussion :

Chronic hepatitis B is the leading cause of chronic liver disease throughout the world. Its prevalence is highest in Asia-pacific region, China and Africa. HBsAg positive carriers are also very high in these areas. It is not clearly known about the status of hepatic inflammation and replication of the virus among the chronic HBV carriers.

In this study active viral replication (HBeAg positive) was found in 28 (9.3 %) cases, anti HBe positive in 257(85.7%) cases, chronic hepatitis in 25 (10.41%) cases and cirrhosis in four (1.66%) cases. Mukhopadhyaya A et al showed HBeAg positive in 6.5% and anti HBe in 75% of HBV carriers. Mean age of patients was 29.5±8.0 years and mean ALT was 34.9±23.3 U/L in his series<sup>11</sup>. In this series mean age of patients was 32.44±6.35 and mean ALT was 39.59±41.14 i.u./L. These findings were comparable in both these studies. Evidence of chronic hepatitis and replicating viral markers were found in 53.8% and 44% of cases in a study done by Puri P et al<sup>12</sup>. These findings were not comparable to the findings (10.42% and 9.3% respectively) of this study. Chaudhuri S et al revealed that both HBeAg and HBV DNA were positive in 32.9% of subjects (wild type) and HBeAg negative with positive anti HBe and positive HBV DNA was found in 34.2% of cases (precore mutant) which was also very high in comparison to this study<sup>13</sup>. Hepatocellular carcinoma was not found in any of the cases in this study. Thirty seven (12.33%) cases were found to have elevated ALT with negative HBeAg in this study. They might be the cases of precore mutant viral infection. However, HBV DNA analysis by PCR is required for its confirmation. Raised ALT, PT and decreased serum albumin were more commonly found in HBeAg negative than HBeAg positive cases. Chronic hepatitis and cirrhosis of liver were found more in anti-HBe positive than anti-HBe negative cases. Agarwal et al showed raised ALT in HBeAg positive cases which is contradictory to this findings<sup>14</sup>. Normal and coarse hepatic echotexture correlated well with normal and abnormal hepatic histology. This is statistically significant. Simonovsky showed that sensitivity of ultrasonography in diagnosing cirrhosis was 91.1% and specificity was 93.5%<sup>15</sup>.

In conclusion it may be said that chronic asymptomatic HBsAg positive carriers suffer from chronic hepatitis and cirrhosis in 12% of cases. They require treatment with antiviral drugs if active hepatic inflammation and replicating markers are present. Abnormal biochemical,

and ultrasonography findings are more common in HBeAg negative individuals than HBeAg positive individuals which signifies the later stage of the disease. Histological abnormality is more common in anti HBe positive cases than anti HBe negative cases. Risk factors for HBV infection are not identified in most of the cases. Reactivation of infection may occur and they should be followed up at least every year.

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## REVIEW ARTICLE

# Prevention of Variceal Bleeding: Current Concepts

S PERVEEN<sup>a</sup>, SMB HOSSAIN<sup>b</sup>, MA AHMED<sup>c</sup>, AM SIDDIQUE<sup>d</sup>, MG RABBANI<sup>e</sup>, M NAZIMUDDIN<sup>f</sup>

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### Introduction :

Bleeding from varices is a very serious complication in cirrhotic patients, with a mean mortality rate around 30%<sup>1</sup>. If the portal vein pressure is decreased by pharmacological therapy the varices will not bleed and progressively decrease in size. The portal hypertension in cirrhotic patients develops as a consequence of two mechanisms: the increase of portal inflow and the increase of intrahepatic resistance. Variceal haemorrhage accounts for one third of all deaths related to cirrhosis. Patients surviving a variceal bleed are at high risk of rebleeding over 60% at one year and mortality from each rebleeding is about 20%<sup>1-3</sup>.

Portal hypertension can be attenuated by decreasing intrahepatic resistance, reducing portal blood flow or both. Non-selective beta-blockers (propranolol and nadolol) effectively prevent variceal bleeding by reducing portal pressure and blood flow within the portal system<sup>4,5</sup>. Since increased vascular tone, partly due to reduced release of nitric oxide in the hepatic circulation, contributes significantly to increase hepatic resistance to portal flow in cirrhosis, it is rational to use vasodilators in the treatment of portal hypertension. Isosorbide-5-mononitrate (ISMN) is the only drug that has been tested in the randomized trials<sup>6,7</sup>. Losartan, an angiotensin II receptor blocker, has portal hypotensive effect. Losartan is as effective as propranolol in reducing portal pressure in cirrhotic patients who are not receiving diuretics<sup>8</sup>.

Local treatments act at the variceal bleeding site, without modifying the underlying pathophysiological abnormalities leading to haemorrhage. The best examples are endoscopic procedures like endoscopic injection sclerotherapy (EIS), endoscopic band ligation (EBL), variceal obturation with bucrylate and surgical techniques such as oesophageal transection or devascularization<sup>9-12</sup>. These procedures are often effective only for a short time, since portal pressure and blood flow remain unchanged, and varices frequently recur (about 50% at two years)<sup>9</sup>. Shunt surgery has been used for almost 50 years and is based on the simple concept of bypassing the site of increased resistance. It is effective at decreasing the risk of variceal rebleeding but has the disadvantage of enhancing encephalopathy and worsening liver failure. Selective shunts such as the distal splenorenal shunt (DSRS) or calibrated shunts aim to reduce this problem<sup>9,13-15</sup>.

### Target hepatic venous pressure-gradient (HVPG) to prevent variceal bleeding:

Clinically significant portal hypertension is defined by a portal pressure gradient measured as hepatic venous pressure gradient (HVPG) above 12 mm of Hg<sup>1</sup>. Variceal bleeding rarely, if ever, occurs below this threshold pressure. Haemodynamic studies have shown that if HVPG is decreased below this threshold, the patient has a lower risk of variceal bleeding. Moreover many studies show that if drug therapy achieves a reduction in HVPG of at least 20% of the baseline value, even without reaching values below 12 mm of Hg, the residual risk of variceal bleeding is low, about 10% at 2 years. The risk appears similar to that reported for patients treated with surgical shunts or with transjugular intrahepatic portosystemic shunt (TIPS)<sup>3,11,16,17</sup>.

### Primary prophylaxis of variceal haemorrhage:

Pharmacologic therapy is the current standard of treatment for primary prophylaxis of esophageal variceal bleeding. Patients with medium or large varices should be treated with a non selective beta

a. Major Shaila Perveen, FCPS, Classified Specialist in Medicine, CMH, Dhaka

b. Col. Sk. Md. Bahar Hossain, FCPS, DCP, Classified Specialist in Medicine, CMH, Dhaka

c. Major Mir Azimuddin Ahmed, MCPS, DCP, Graded Specialist in Pathology, Armed Forces Institute of Pathology, Dhaka.

d. Major Gen. Abdul Moyeed Siddique, FCPS, FRCP, Consultant Physician, Bangladesh Armed Forces

e. Brig. Gen. MG Rabbani, FCPS, Chief Physician, CMH, Dhaka

f. Col. Md. Nazimuddin, Personal Physician to the Honourable Prime Minister, Prime Minister's Office, Tejgaon, Dhaka

**Address of correspondence :** Dr (Major) Shaila Perveen, Classified Medical Specialist, CMH, Dhaka, Asst. Personal Physician to the Honourable Prime Minister, Prime Minister's Office, Tejgaon, Dhaka.



**Table -I**

<i>Reported rebleeding and mortality in randomised trials:</i>			
Treatment	Number of studies	Rebleeding rate	Mortality rate
Untreated	19	55-67%	23-54%
Beta blockers	26	37-57%	13-39%
EIS	54	34-53%	18-36%
EIS + Beta blockers	13	19-49%	7-26%
EBL	18	20-43%	19-34%
Beta blockers + ISMN	6	30-42%	12-32%
TIPS	14	12-22%	18-35%
DSRS	9	11-31%	22-55%

**Table-II**

<i>Risk of rebleeding in responders versus Non-responders on drug therapy:</i>				
Series	Drug	Non-responders	Rebleeding rate in responders	Rebleeding rate
In non-responders				
Feu et al	Propranolol	64%	54%	8%
Escorsell et al	Propranolol	62%	44. 8%	6%
Villanueva et al	Nadolol + ISMN	55%	47%	7%
Bureau et al	Propranolol + ISMN	41%	64%	10%

**Table-III**

<i>Endoscopic sclerotherapy compared with no specific treatment for the primary prevention of bleeding from the varices: (n-166, Followup period -32 months)</i>					
Treatment	n	At one year		At 3 year	
		Bleeding	Survival	Bleeding	Survival
Endoscopic Sclerotherapy :	84	16%	87%	33%	62%
No specific treatment:	82	16%	84%	29%	62%

blocker with the dose titrated to achieve a 25% decrement in resting heart rate or a heart rate of 55 to 60 bpm<sup>18</sup>. The development of symptoms will, of course, limit the dose used. The therapeutic end points are not well correlated with decreases in portal

pressure. Measurement of the HVPG before therapy and after 3 months of therapy provides a rational approach to drug dosing. If the HVPG decreases by 20% or to less than 12 mm of Hg, the medication dose will be effective in preventing haemorrhage. If,

however, the HVPG is not appropriately lowered, a long-acting nitrate may be added. Patients with small varices should be observed, with endoscopic examinations every 2 years to assess progression of variceal size. Endoscopic therapy is not indicated for the primary prevention of variceal bleeding<sup>18,19</sup>.

Reducing the portal pressure by at least 20% or to a HVPG of less than 12 mm of Hg is associated with significant protection against bleeding. In the absence of a determination of the HVPG, the dose of beta-blockers is titrated on the basis of clinical assessment. In addition to their side effects, an important problem with beta-blockers is their variable effects on portal pressure and the consequent difficulty in predicting a clinical response. The effectiveness of beta-blockers for primary prophylaxis against variceal bleeding has been demonstrated in several controlled trials. In addition, meta analysis have revealed a 40 to 50% reduction in the risk of bleeding and a trend toward improved survival. An analysis comparing propranolol with sclerotherapy and shunt surgery found propranolol to be the only cost effective form of primary prophylaxis<sup>9,20-22</sup>. In addition to beta-blockers, a number of vasodilators have been investigated in patients with portal hypertension. Isosorbide mononitrate (ISMN) has received the greatest attention. The mechanism of action of ISMN is unclear but they may reduce intrahepatic resistance, reduce portal pressure by means of reflux splanchnic arterial vasoconstriction in response to vasodilatation in other vascular beds or both<sup>23,24</sup>. Unfortunately ISMN can not currently be recommended as monotherapy even for those with an intolerance of beta-blockers because of their potential to accentuate vasodilative hemodynamics typical of cirrhosis<sup>25</sup>. But the addition of ISMN to propranolol results in an enhanced reduction in portal pressure and may improve protection against variceal bleeding<sup>24</sup>.

Endoscopic therapies have assumed a prominent role in the treatment of esophageal varices. Endoscopic sclerotherapy, most often with ethanol, morrhuate sodium, polidocanol or sodium tetradecyl sulfate has been used extensively. Most of the trials have shown no advantage of sclerotherapy in primary prophylaxis<sup>9,25,26</sup>. A recent trial comparing propranolol with endoscopic variceal ligation for primary prevention of

variceal bleeding revealed that the actuarial rate of bleeding was 43% with propranolol and 15% with ligation. Ligation is an acceptable option for patients at high risk of variceal bleeding who have an intolerance of or contraindication to medical therapy<sup>9</sup>.

#### **Prevention of variceal rebleeding:**

After an episode of acute variceal bleeding, patients are at high risk for recurrent bleeding and death. Thus therapy to prevent recurrent bleeding is essential. Variceal haemorrhage recurs in approximately two thirds of patients, most commonly within the first six weeks after the initial episode<sup>1, 9</sup>. Clinical predictors of early recurrence include the severity of the initial hemorrhage, the degree of liver decompensation and the presence of encephalopathy and impaired renal function. Endoscopic features predictive of early recurrence include active bleeding at the time of the initial endoscopy, stigmata of recent bleeding and large varices. In addition, the severity of portal hypertension, measured by the HVPG, correlates closely with the risk of recurrent bleeding as well as with the actuarial survival rate after an initial variceal hemorrhage<sup>9</sup>.

Given the risk of recurrent hemorrhage and its associated morbidity and mortality, secondary prophylaxis should be instituted after the initial episode. Treatment modalities to prevent variceal bleeding include (i) pharmacological treatment with non selective beta blocker (propranolol and nadolol), Isosorbide mono nitrate (ISMN), losartan or combination pharmacotherapy (beta blocker with ISMN). (ii) Endoscopic techniques which include a. Endoscopic injection sclerotherapy (EIS) b. Endoscopic band ligation (EBL). (iii) Transjugular in trahepatic portosystemic shunt (TIPS), (iv). Portacaval shunt operations. (v). Oesophageal transection or devascularization and (vi). Liver transplantation<sup>9</sup>.

#### *Pharmacotherapy:*

A number of pharmacological agents that reduce portal pressure have been proposed for use in secondary prophylaxis but the only ones for which there is sufficient evidence of efficacy are beta-blockers<sup>27-30</sup>. Several randomized placebo controlled trials, including a meta analysis, have demonstrated

that non-selective beta-blockers decrease the risk of recurrent bleeding and prolong survival. It has been customary to adjust the dose of beta-blockers to achieve a 25% fall in the resting heart rate. But this reduction by no means guarantees an effective fall in HVPG, and there is no correlation between changes in heart rate and changes in HVPG. The most rational approach is to titrate up the dose of beta-blockers to the maximum tolerated dose with dose escalation every two days<sup>1</sup>.

Until recently, drug therapy was based on the use of vasoconstrictors that reduce portal pressure and blood flow within the portal system. Non-selective beta-blockers eg. propranolol, nadolol act by this mechanism. It is rational to use vasodilators along with beta-blockers in the treatment of portal hypertension. ISMN is an important drug that has been tested in randomized trials. ISMN releases nitric oxide and reduces intrahepatic resistance<sup>24,31-33</sup>. The addition of ISMN to beta-blockers appears to enhance the protective effect of beta-blockers alone for the prevention of recurrent variceal bleeding but offers no survival advantage and reduces the tolerability of therapy. Some non responders will respond with the addition of a second drug. The addition of ISMN to a beta-blocker enhances the fall in portal pressure achieved by beta-blockers alone. About one-third of non-responders to beta-blockers become responders after addition of ISMN<sup>1,9</sup>.

Losartan is as effective as propranolol in reducing portal pressure in cirrhotic patients. Losartan is also superior to propranolol for achieving target level HVPG for prevention of variceal bleeding in non-cirrhotic cirrhotic patients<sup>8</sup>.

*ISMN alone in the prevention of variceal rebleeding:* Nonselective beta-blockers are very effective in preventing variceal bleeding in patients with cirrhosis of liver. However 15-25% of patients have contraindications or develop severe side effects precluding its use. One hundred thirty-three consecutive cirrhotic patients with esophageal varices and contraindications or intolerance to beta-blockers were included in a multicenter, prospective, double-blind randomized controlled trial. There were no significant differences in the one and two year actuarial probability of experiencing variceal

bleeding between the ISMN group and placebo group. Survival and adverse events were similar in the two groups<sup>25</sup>.

ISMN does not reduce the incidence of variceal bleeding in patients with cirrhosis of liver with varices who can not be treated with beta-blockers because of contraindications or intolerance to these drugs, suggesting that ISMN has no place in the prophylaxis of variceal bleeding<sup>25</sup>.

*Long term effects of propranolol on portal pressure in cirrhotic patients:*

Propranolol can prevent the bleeding from esophageal varices and act by reducing the portal inflow due to splanchnic vasodilatation. 53 patients with esophageal varices with portal hypertension were treated with propranolol and followed up for three years. Abdominal ultrasonography and Doppler of portal venous system were performed in all subjects. The ultrasonographic parameters were measured before and after a 3-year treatment with propranolol. The patients also underwent endoscopy for evaluation of esophageal varices at the beginning and at the end of the study. Propranolol reduced the portal blood inflow and size of the esophageal varices and the incidence of hemorrhages by variceal rupture was very low in these group of patients<sup>34</sup>.

*Adding ISMN to beta-blockers to all patients with varices: Is it rational ?*

In one randomized study the authors treated 34 patients with cirrhosis and portal hypertension with propranolol and measured HVPG after a median of 4 days. Target HVPG reductions were achieved in 13 responders. ISMN was added in the 21 non-responders and HVPG measured again. 7 more patients achieved target HVPG reduction. Rebleeding rates were lower in responders than in non-responders (10% versus 64%). The authors recommended adding ISMN to propranolol or nadolol in individual non-responders, but this requires measurement of the haemodynamic response in every patient. In another randomized study in China 76 cirrhotic patients with variceal bleeding were randomly assigned to treatment with propranolol plus ISMN (34 patients) and propranolol alone (32 patients). 7 patients in the propranolol and ISMN group and 13 patients in the propranolol group had rebleeding during the one year

after randomization. These results suggest that the addition of ISMN improves the efficacy of propranolol alone in the prevention of variceal rebleeding in cirrhotic patients<sup>35</sup>.

Assessment of HVPG response will provide strong prognostic information since responders on HVPG criteria do better than non-responders. This assessment should be done early preferably within 1-2 weeks of starting treatment because the risk of rebleeding is especially high during the first 6 weeks after the index haemorrhage. Others recommend adding ISMN in all patients thus obviating the need to assess HVPG response. This idea seems reasonable in a high risk situation, such as the prevention of recurrent bleeding<sup>1,36,37</sup>.

#### *Endoscopic injection sclerotherapy (EIS):*

Endoscopic injection sclerotherapy reduces the risk of recurrent esophageal variceal bleeding from approximately 65 percent to between 30-35 percent at one year but it does not appear to reduce overall mortality. Sclerotherapy is performed every 10 to 14 days until the varices are eradicated, which usually takes five or six sessions. A meta-analysis of nine trials found sclerotherapy and beta-blockers to be equivalent with respect to the risk of recurrent bleeding and the rate of survival. Moreover, combination of pharmacotherapy (beta-blockers and ISMN) is superior to sclerotherapy alone in patients with Child-Pugh class A or B cirrhosis<sup>9</sup>. Combined sclerotherapy and beta-blockers led to a lower incidence of recurrent bleeding than beta-blockers alone without any overall survival benefit<sup>9</sup>.

#### *Endoscopic Band Ligation (EBL):*

Endoscopic injection sclerotherapy (EIS) has been replaced by Endoscopic band ligation (EBL) which is safer and more effective. EBL is highly effective in obliterating varices. Ligation is associated with a lower risk of recurrent bleeding than sclerotherapy, approximately 25% versus 30% at one year, fewer complications, lower overall cost and higher rates of survival. Therefore, EBL should be considered as standard therapy for secondary prophylaxis. EBL combined with the pharmacological treatment may be more effective than either form of treatment alone. Although the addition of sclerotherapy to ligation

may theoretically offer greater protection against recurrent bleeding, this combination does not appear to be advantageous<sup>24,39,40</sup>.

Argon plasma coagulation has been used as supplemental treatment for eradication of varices and for prevention of variceal recurrence. Argon plasma coagulation along with EBL was compared with EBL in one recently published series. Mean follow up period was 16 months. No recurrence of varices or variceal hemorrhage was observed in the argon plasma coagulation group, whereas varices recurred in 42.8% of the patients treated with EBL alone. Argon plasma coagulation of the distal esophageal mucosa after EBL is safe and effective for reducing the rate of variceal recurrence<sup>41</sup>.

#### *Transjugular intrahepatic portosystemic shunt (TIPS):*

Transjugular intrahepatic portosystemic shunt (TIPS) has become widely accepted worldwide as a percutaneous interventional procedure for treating complications of portal hypertension. An experienced skillful team, however, is necessary to ensure the high technical success of TIPS and to avoid its potential procedural complications. Presently, TIPS is used mainly for treatment of acute or recurrent hemorrhage from gastroesophageal varices refractory to endoscopic therapy. Randomized trials have shown that it is more effective than endoscopic treatment for preventing rebleeding; however, it is associated with a higher incidence of encephalopathy. Both treatments produce comparable survival rates. The cumulative risk of recurrence of bleeding after TIPS is 8 to 18% at one year<sup>9,42,43</sup>.

In comparison with surgical shunts, TIPS is a significantly less invasive procedure that can be done in poor surgical candidates with advanced cirrhosis. The high rate of shunt obstructions seen with TIPS mandates close surveillance and maintenance, rendering TIPS a multistage procedure. This is a major disadvantage of TIPS compared to surgery. Stenosis and dysfunction of the shunt after TIPS represent an important complication; the reported rates are 31% at one year and 47% at two years. Presently, both TIPS and surgical shunts have their place in the treatment of gastroesophageal variceal hemorrhage unresponsive to endoscopic therapy.

TIPS is most suited for class B and C patients, particularly who are candidates for liver transplantation<sup>1,9,44,45</sup>.

#### *Surgical treatment:*

Decompressive surgical shunts, including nonselective and selective shunts are preferred for patients who are noncompliant with medical or endoscopic therapy and for those who are not candidates for liver transplantation. Although shunts are effective in eradicating varices and preventing recurrent bleeding, they are associated with important operative and post operative complications. Selective shunts are slightly less effective in achieving portal decompression but typically preserve liver function more effectively than nonselective shunts and do not adversely affect the potential for future liver transplantation. Elective surgical therapy is largely reserved for patient with Child-Pugh class A or B cirrhosis<sup>1,42</sup>.

Commonly used shunts include the distal splenorenal shunt (DSRS) and the low-diameter mesocaval or portocaval interposition shunt. Rates of recurrent bleeding range from 10 to 20%, with the highest risk occurring during the first month after surgery. Devascularization procedures eg. esophageal transection and devascularization are usually considered in patients who can not receive shunts because of splanchnic venous thrombosis and should be performed by experienced surgeons<sup>9</sup>.

Assuming that appropriate surgical expertise is available, the choice of surgical therapy should be individualized and must take into account the severity of the liver disease, patient's compliance and the likelihood of progressive liver dysfunction.

#### *Pharmacotherapy versus EBL:*

David Patch and colleagues randomized 102 patients surviving a variceal bleeding to EBL or drug therapy with propranolol with the addition of ISMN if target reductions in portal pressure (evaluated by the HVPG) were not achieved at three months. Overall, results of drug therapy were similar to those of EBL, 44% versus 54% rebleeding rate at one year. There was no differences in survival or non-bleeding complications<sup>46</sup>. Villanueva and colleagues randomly assigned 144 patients with cirrhosis who

were hospitalized with esophageal bleeding to receive treatment with EBL (72 patients) or the combined medical therapy with nadolol and ISMN (72 patients). The median follow-up period was 21 months. Thirty patients in the EBL group died, as did 23 patients in medical group. The probability of recurrent bleeding was lower in the medically treated group. Combined therapy with nadolol and ISMN is more effective than EBL for the prevention of recurrent bleeding and associated with a lower rate of major complications. Overall survival rate is also higher in the medically treated group<sup>47</sup>. Lui and colleagues recruited 172 patients with cirrhosis with grade II or III esophageal varices that had never bled. Forty four patients were treated with EBL, 66 were treated with propranolol and 62 patients were assigned to ISMN therapy. All the patients were followed up for six years. Variceal bleeding occurred in 7% of patients in EBL group, 14% in propranolol group and 23% in ISMN group. There was no statistically significant differences in mortality rates in the three groups. EBL was equivalent to propranolol and superior to ISMN in preventing variceal bleeding<sup>24</sup>.

In one randomized trial 121 patients with cirrhosis with portal hypertension were enrolled to undergo EBL (60 patients) or drug therapy by using nadolol plus ISMN (61 patients). After a median follow up period of 25 months, recurrent variceal bleeding developed in 23 patients in the EBL group and 35 patients in medically treated group. Complications occurred in 17% of the EBL group and in 19% of the medically treated group. Fifteen patients in EBL group and eight patients of the nadolol plus ISMN group died. This trial showed that EBL was more effective than nadolol plus ISMN in the prevention of variceal bleeding, with similar complications in both treatment modalities. However, EBL failed to improve overall survival<sup>48</sup>.

#### *EIS versus no treatment for the prevention of variceal bleeding:*

Since esophageal variceal bleeding is associated with a high mortality rate, prevention of bleeding, might be expected to result in improved survival. Few trials to evaluate prophylactic sclerotherapy found a marked beneficial effect of prophylactic



treatment. These results, however, were not generally accepted because of methodological aspects and because of the reported incidence of bleeding in control group was considered unusually high. In a recently conducted trial 166 patients with esophageal varices were randomized to groups receiving EIS (84 patients) or no specific treatment (82 patients). Primary end points were incidence of bleeding and mortality. During the 32 months of follow up variceal bleeding occurred in 25% of the patients of the EIS group and in 28% of the control group. The one year survival was 87% for the EIS group and 84% for the control group. The three year survival rate was 62% for each group. Complications were comparable for the two groups. In this trial, prophylactic EIS did not reduce the incidence of bleeding from varices in patients with cirrhosis and overall survival was not affected. Meta analysis of a large number of trials showed that the effect of prophylactic EIS is significantly related to the baseline bleeding risk. The effect of prophylactic EIS seems dependent on the underlying bleeding risk. A beneficial effect can only be expected for patients with a high risk of bleeding<sup>49</sup>.

*Combined EBL and EIS versus EBL alone- a meta analysis:*

EBL has been shown to be superior to EIS in prevention of rebleeding and improving survival in patients with cirrhosis. However 25% of patients will rebleed before completion of treatment. A number of trials have compared the combination treatment to EBL alone in achieving rapid and complete eradication of esophageal varices with conflicting results. Meta analysis of seven randomized controlled trials that compared EBL plus EIS with EBL alone showed no overall benefit of combined treatment over EBL alone. No significant difference was seen in cessation of actively bleeding varices, variceal rebleeding and mortality. A significantly higher incidence of esophageal stricture was seen in combination therapy. The combination of EBL and EIS offer no advantage over EBL alone in prevention of rebleeding and in reduction of mortality. It is also associated with a higher complication rate of esophageal stricture<sup>50,51</sup>.

*EBL plus propranolol versus TIPS:*

After a first variceal bleeding episode in patients with cirrhosis of liver, treatment with TIPS and EBL plus propranolol were compared with regard to prevention of variceal rebleeding, complications and mortality. Eighty five patients were randomly allocated to receive TIPS or EBL. The mean observation period was 4.1 years in the TIPS group and 3.6 years in the EBL group. Rebleeding rate was higher in the EBL group (29.9%) than in the TIPS group (19.4%), but the difference was not statistically significant. The probability of survival was similar in both groups (TIPS group 75.9%, EBL group 82.2%). Hepatic encephalopathy was observed more often in the TIPS group (40.5%) than in the EBL group (20.5%)<sup>52</sup>.

In view of its good efficacy and the lower cost of treatment, EBL plus propranolol may be recommended as initial procedure for prevention of recurrent variceal hemorrhage, whereas TIPS seems to be the preferable procedure in patients with recurrent bleeding in spite of getting treatment with EBL plus propranolol.

*TIPS as first-line therapy:*

Cirrhotic patients who survive an episode of acute variceal hemorrhage are at high risk of recurrent bleeding. Many treatments have been found to be effective in preventing rebleeding. Jalan et al compared three cohorts of patients with cirrhosis after index variceal bleeding and found a lower rebleeding rate in patients receiving TIPS (16.2%) compared to either EBL (39.3%) or EIS (74.6%). Despite the efficacy of TIPS in preventing variceal rebleeding, there was no significant difference in survival between the three groups<sup>53</sup>.

In another study, TIPS was compared with EBL in the prophylaxis of variceal rebleeding in patients with cirrhosis of the liver. Mean follow up was two years. Mortality risk at two years of follow up was 19.9% in the TIPS group and 16.5% in the EBL group respectively. Probability of remaining free from rebleeding was 83.7% in the TIPS group and 83.9% in the EBL group. Hepatic encephalopathy was more common in the TIPS group than in the EBL group<sup>16</sup>.

TIPS is not superior to EBL in the prevention of variceal rebleeding. Furthermore, similar mortality

rates in patients treated with TIPS or EBL negate TIPS as the preferred strategy for prevention of variceal rebleeding.

*Prevention of variceal bleeding; Current concepts:*

Variceal bleeding is the result of portal hypertension, which is a major complication of liver cirrhosis and carries a high mortality rate. Because of the mortality associated with variceal bleeding, strategies for prevention of the first bleed is important. Risk stratification is important in determining those at risk of bleeding from varices and current data suggest that patients with large varices with red signs, severe underlying liver disease and those who have a HVPG of greater than 12 mm of Hg are at high risk of bleeding. Surveillance for varices in patients with cirrhosis is therefore important. The current first choice treatment is non-selective beta-blockers; which is cheap, easy to administer and reduces the risk of variceal bleeding significantly. Combination of beta-blockers and nitrates looks promising but needs further evaluation. EBL compares favourably with non-selective beta-blockers in preventing the first bleeding episodes in cirrhotic patients and may be an alternative for patients who can not tolerate or have contraindications to beta-blockers. EBL is showed to be superior to EIS in preventing variceal rebleeding.

EIS, EBL or drugs are the standard treatments for the prevention of variceal rebleeding. Failure of this treatment indicates the need for rescue TIPS implantation. The current practice to use EBL as first line and TIPS as second line of treatment is however, not based on evidence since in unselected patients, both treatments have a comparable survival<sup>54</sup>.

The role of monitoring HVPG in those being treated with pharmacological agents, the role of newer drugs such as non-selective beta-blockers with intrinsic alpha-adrenergic activity and angiotensin receptor blockers require further evaluation.

Variceal bleeding: much to learn, much to explore:

The newer diagnostic and therapeutic options continue to evolve and important developments have been made in the field of variceal bleeding and portal hypertension. A meeting was held at Baveno to update consensus on different terminologies in

relation to portal hypertension. Beta-blockers continue to be the mainstay for primary prophylaxis of variceal bleeding and EBL is fast emerging as a strong contender. EBL is superior to EIS for obliteration of esophageal varices. For gastric varices cyanoacrylate glue continues to be the first line treatment and band ligation is being assessed further. Endosonography has developed strongly in the assessment of variceal eradication and prediction of variceal recurrence. TIPS significantly reduces rebleeding compared to EBL<sup>55</sup>. TIPS and surgical shunts have their place in the treatment of gastroesophageal variceal hemorrhage unresponsive to endoscopic therapy. TIPS is most suited for class B and C patients, particularly those who are candidates for liver transplantation. Surgical shunts should be considered for patients with well preserved liver function.

**Conclusion :**

Variceal hemorrhage is a common and devastating complication of portal hypertension and is a leading cause of disability and death in patients with cirrhosis. Although the role of endoscopic band ligation in primary prophylaxis is well established, treatment with beta-blockers is well accepted. Because there is a high risk of recurrence after an initial hemorrhage, preventive strategies are required and should be tailored to the patient's clinical condition, surgical risk and prognosis. Drug therapy is a safe and simple way to prevent variceal rebleeding, provided target reductions in HVPG are achieved. Future steps forward include the development of non-invasive ways to assess the hemodynamic response so that therapy can be tailored not only in research studies but also in clinical practice. Unless HVPG measurement is available, physicians will have to make decisions based on published results with a given treatment or combination. In the long term, it is hoped that more effective drugs or drug combinations will be available and that measuring the haemodynamic response will become unnecessary.

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## CASE REPORTS

# Premature Ovarian Failure in A 24 Years Old Young Lady - A Case Report and Review of Literature

S ROUF<sup>a</sup>, K BEGUM<sup>b</sup>

### Summary :

*Premature ovarian failure in a 24 years old young lady is reported. The patient had irregular cycles from menses proceeded to oligomenorrhoea, secondary amenorrhoea and ultimately diagnosed as a case of premature*

*menopause. Premature ovarian failure is not a very common feature and its occurrence in such a young patient is extremely unusual.*

*(J Bangladesh Coll Phys Surg 2004; 22 : 31-33)*

### Introduction :

Spontaneous ceseasation of menses before the age 40 is called premature menopause or premature ovarian failure<sup>1</sup>. Menopause is the final ceseasation of menstruation which occurs during the climacteric. Little is known about the frequency and cause of preterm ovarian failure<sup>2-5</sup>. Exact incidence is not known. It appears that approximately 0.9% of women in the USA may experience this early ceseasation of ovarian function<sup>1</sup>. As illustrated in the case below, a 24 years old young lady presented with secondary amenorrhoea and ultimately encountered as a case of premature ovarian failure. Review of the literature revealed that there had been very few case reports and studies on preterm ovarian failure. The case reported highlighting its clinical presentation and diagnosis, the aetiology and risk factors are discussed in the light of published literature.

### Case report:

A 24 years old young unmarried university student coming from an upper middle class family reported to a gynaecologist with the complain of ceseasation of menstruation for one year (secondary amenorrhoea). Careful history taking suggested that she had her menses at the age of 14 years. From the onset of menses, she had irregular menstrual cycles occurring at an interval of two to three months. Initially the flow was average but gradually the cycles

occurred at less frequent intervals. Eventually the duration of menses and amount of blood loss was also decreased gradually. She did not take these events into any consideration. Finally, for the last one year she developed amenorrhoea. She did not give any history of suffering from chronic illness (Tuberculosis), metabolic disorders, crash dieting or sudden weight loss. She was the only daughter of her parents and her mother was still menstruating and had no family history of preterm ovarian failure. She did not give any relevant drug history. On examination she was healthy looking, intelligent, cooperative with average built and nutrition. She was 150 cm tall and was weighing 55 kg. General gynaecological examination revealed no abnormality, with normal thyroid gland, well developed breasts and female distribution of hair lines. External genitalia were well developed.

Investigations revealed normal complete blood picture. Plasma glucose, fasting and two hours after breakfast were 5.39 mmol/L and 6.02 mmol/L respectively. Thyroid stimulating hormone (TSH) and prolactin levels were normal. Ultrasonogram of pelvic organs showed normal size uterus with thin endometrium. Both the ovaries were of normal size and volume but both the ovaries were quiescent without any visualized follicle.

Progesterone challenge test failed to have withdrawal bleeding. After that combined oestrogen and progesterone was given and withdrawal bleeding occurred. Subsequently serum follicle stimulating hormone (FSH), leutinizing hormone (LH), testosterone and oestradiol (E<sub>2</sub>) levels were measured. FSH and LH levels were remarkably high and were within the menopausal level.

a. Dr. Salma Rouf, FCPS, Assistant Professor Dept of Obs & Gynae, Dhaka Medical College & Hospital, Dhaka

b. Dr. Kohinoor Begum, FCPS, FICS, Prof. of Obs & Gynae, Dhaka Medical College & Hospital, Dhaka

Address for correspondence to : Dr. Salma Rouf, Assistant Professor, Dept. of Obs. & Gynae Dhaka Medical College & Hospital, Dhaka.



*Testosterone level was within normal limit and oestradiol level was within the menopausal range. All the hormone levels were summarized in the table below:*

Hormone	Level	Range
TSH	4.77 $\mu$ iu/ml	0.47 - 5.01 $\mu$ iu/ml
Prolactin	280.8 miu/L	45.6 - 621.6 miu/L.
FSH	109.9 miu/ml	3-20 miu/ml Follicular 9-26 miu/ml Midcycle 1-12 miu/ml Luteal 18-153 miu/ml Post menopausal
LH	44 miu/ml	2-15 miu/ml Follicular 22-105 miu/ml Midcycle 0.6-19 miu/ml Luteal 16-64 miu/ml Menopausal
Testosterone	0.56 nmol/L	0.35-3.3 nmol/L
Oestradiol	25 pg/ml	10-16 pgm/ml Follicular 34-400 pgm/ml Midcycle 27-246 pgmml Luteal <30 pgm/ml Menopausal

Serum FSH and LH levels were repeated on two occasions and thereafter at reasonable interval to verify the findings and all the values were found raised upto menopausal levels.

On the basis of the clinical findings and hormone levels the cause of secondary amenorrhoea was established as premature ovarian failure. The case was reviewed by senior gynaecologists and endocrinologists and the diagnosis was confirmed. Both the parents were properly counselled regarding the pathophysiology and consequences. She was advised to take hormone replacement therapy (cyclical oestrogen and medroxy progesterone withdrawal bleeding regime) along with calcium supplements and regular follow up. Karyo typing and chromosomal analysis showed normal profile (XX).

#### **Discussion :**

Age at menopause varies in different countries from 45 to 55 years with an average of 51.4 years in the United States.<sup>1</sup> Menopause apparently occurs in the human female because of two phenomena. First, oocytes responsive to gonadotrophins disappear from the ovary and second, the few remaining oocytes do

not respond to gonadotrophins. There does not appear to be any consistent relationship between age at menarche and age at menopause. Marriage, childbearing, height, weight and prolonged use of oral contraceptives do not appear to influence the age of menopause. Disease process, specially severe infections or tumours of the reproductive tract can occasionally damage the ovarian follicular structure so severely as to precipitate the menopause.

The menopause can also be hastened by excessive exposure to ionizing radiation, chemotherapeutic drugs and surgical procedures that impair ovarian blood supply. The associated endocrine abnormalities could also be a cause.

Spontaneous menopause at age <40 years is known as premature ovarian failure or premature menopause. Ceseasation of menstruation and the development of climacteric symptoms and complaints can occur as early as a few years after menarche. The reasons for premature ovarian failure are unknown.

A family history increases the risk of early menopause<sup>4</sup>. Several chromosomal abnormalities have been linked with preterm ovarian failure<sup>6,7,8</sup>. So genetic factors may

influence the onset of menopause. The association of environmental factors and their interactions with genetic ones are of interest to study<sup>5</sup>.

Early age at menarche, use of oral contraceptives, nulliparity and smoking are all factors associated with age at spontaneous menopause as reported in the literature<sup>9,10</sup>. Whether these factors also influence in risk of premature menopause is not known and are of subject of interest.

A large epidemiological study in Italy find out the risk factors for premature ovarian failure and suggested that nulliparity and life long irregular menstrual cycles were associated with an increased risk of preterm ovarian failure<sup>11</sup>. The study population was 15,253 women of which 1.8% reported preterm ovarian failure. Nulliparous women were at greater risk of preterm ovarian failure<sup>11</sup>. A recent case control study of 100 women with preterm ovarian failure confirmed that women with premature ovarian failure had fewer pregnancies than the control group<sup>5</sup>. However literature suggests that this association was limited to women without a family history of preterm ovarian failure and disappeared within patients with familial preterm ovarian failure. A possible explanation is that patients with a positive familial history may pay more attention to their reproductive patterns and tend to conceive earlier as they are aware of the earlier age at menopause of their relatives. Lower parity may be an effect rather than a cause of early menopause.

The association between life long history of irregular menstrual pattern and the premature ovarian failure has been well established in the literature<sup>5,10,11</sup>. Explanation is that irregular menstrual cycles are an effect of impaired ovarian functions of women who subsequently develop preterm ovarian failure.

Studies have failed to find out any relationship with age at menarche, oral contraceptive use, smoking, education and risk of preterm ovarian failure<sup>5,12</sup>. However, another study suggests that smoking is associated with early menopause. Women who smoke are more likely to have severe menopausal symptoms than who do not and such women may be more likely to go to a menopausal clinic than nonsmokers. Moreover one study suggested that smoking, no oral contraceptive use and late age of menarche were associated with later age of menopause<sup>5,11, 12</sup>.

As life expectancy of women has increased, women has to spend one third of their life span in the post menopausal state. The duration is more for preterm ovarian failure. Management is controversial but these women definitely need hormone replacement therapy to counter act the effect of oestrogen deficiency along with proper counselling.

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# Isolated Giant Primary Renal Hydatidosis A Rare Entity

TIMA FARUQ<sup>a</sup>, SN FERDOUS<sup>b</sup>, AKMA ISLAM<sup>c</sup>, A HANIF<sup>d</sup>

## Summary :

*A case of giant renal hydatid cyst in an elderly rural dwelling lady having no contact with dog, sheep or cattle is reported. No other hydatid cyst was demonstrable in any other organ. Diagnosis was suspected on ultrasonography and strongly supported by surgery. Final*

*diagnosis was based on histological examination of the surgical specimen. Complementary medical treatment (mabendazole/albendazole therapy) could be an effective prophylaxis.*

*(J Bangladesh Coll Phys Surg 2004; 22 : 34-38)*

## Introduction :

Hydatidosis is a parasitic condition of global distribution, known to the ancient physicians<sup>1</sup>. The biologic behaviour of the parasite responsible, *Echinococcus granulosus* greatly favour its survival in the nature. In pastural setting the parasite continuously repeats its life cycle between dog and sheep or cattle. Human happens to be an accidental or incidental host by ingesting eggs of adult worms which have been passed in dog's faeces. The eggs hatch in the small gut, penetrate the gut mucosa, enter the circulation to be distributed to various sites of the body<sup>1,2</sup>.

No organ system of the body is immune of the disease and the disease presents as a chronic localized affection being unaffected by age and sex or any intercurrent disorders. As the cystic parasite enlarges slowly the infected patient suffers no serious constitutional symptoms and the disease continues as a serious combat between host and parasite and in the end one or other die<sup>1</sup>.

Presentation may be affected by the site & size of the lesion. Physicians could promptly recognise the

disease and the surgeons generally know how to deal with it. The disease usually presents as a surprise in the western hospitals and often overlooked<sup>1</sup>.

The disease can be brought under control by simple public health measures but the management is still mysterious. The parasitology is easy to grasp and pathology is straightforward. It is one of the rare parasitic infestation that can be treated by surgery. Despite the improvement of surgical techniques the result is often incomplete with frequent local recurrence or secondary dissemination. Repeated interventions are often mutilating and do not always guarantee a definite cure<sup>3</sup>.

## Case Report :

A 52 years old rural dwelling housewife presented with painless slowly enlarging lump in the right hypochondriac and lumbar region along with irregular low grade fever for more than three years. She had history of jaundice seven years back which was cured with medical treatment. She is hypertensive, controlled with drugs. She is in menopausal state for last five years.

She is mildly anaemic. A big non-tender lump occupying right hypochondrium and loin was palpable measuring approximately 15 cm x 11 cm with smooth surface, firm consistency, restricted side to side mobility but moved above downwards with respiration. Rest of the abdomen was normal.

Haematological profile and blood chemistries were unremarkable except moderate eosinophilia and very high ESR. Liver function tests were within normal limit. Casoni's intradermal test was negative. Repeated ultrasonography of the abdomen revealed normal liver, gall bladder, biliary tree, pancreas,

a. Dr. T.I.M. Abdullah-Al-Faruq, MBBS (Dhaka), FCPS (Surgery), FICS, Associate Professor of surgery, Dhaka Medical College, Dhaka

b. Dr. Sultana Nasreen Ferdous, MBBS (Dhaka), MS (Surgery) Junior Consultant, Surgery Shaheed Suhrawardy Hospital, Dhaka

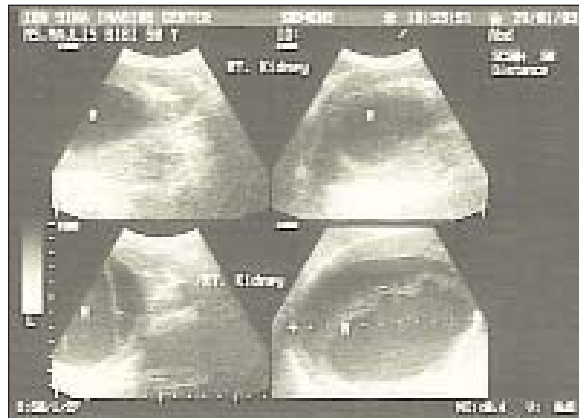
c. Dr. A.K.M. Anwarul Islam, MBBS (Dhaka), FCPS (Surgery) FRCS (Edin), FICS, Associate Professor of Urology, Bangabandhu Sheikh Mujib Medical University, Dhaka

d. Dr. Abdul Hanif, MBBS (Dhaka), MS (Paed. Surgery), Assistant Registrar, Paediatric Surgery, Dhaka Medical College Hospital, Dhaka.

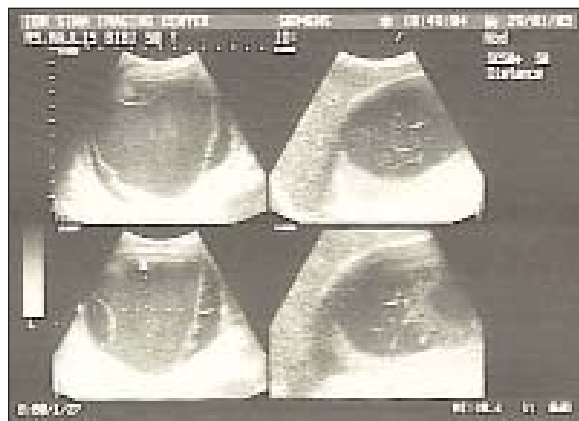
**Address of correspondence :** Dr. T.I.M. Abdullah-Al-Faruq, Associate Professor of Surgery, Dhaka Medical College, Dhaka

spleen and left kidney. But the right kidney was compressed from its postero-lateral aspect and sub-hepatic region by a huge, well defined, thick walled, complex, cystic mass lesion measuring 14.7cm x 11.2 cm x 9.6 cm. with floating membranes separated at places from parenchymal capsule with daughter cysts of varying sizes with low echo, consistent with the hydatid cyst (Fig. 1). IVU Impression was SOL in the right kidney (Fig-2) but the CT scan was inconclusive. FNAC was not tried for fear of dissemination of the disease and anaphylactic reaction.

Preoperative diagnosis was made as hydatid cyst of the right kidney. Prior to exploration the patient was treated with albendazole for more than four weeks. With all safety precaution exploration was done with right lumbar incision. A giant tense cystic mass was protruded through the incision (Fig. 3). Surrounding



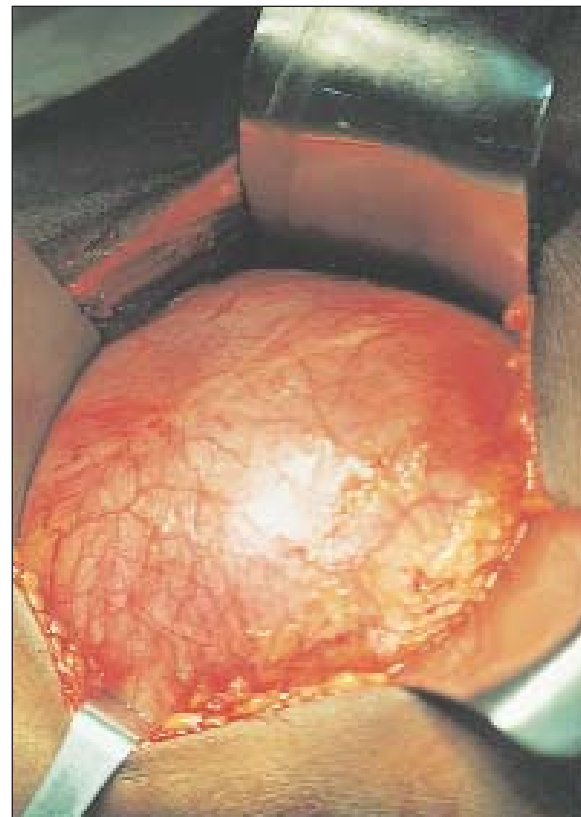
**Fig.-1 (a) :** Big Cystic lesion with daughter cysts



**Fig.-1 (b) :** Big Cystic lesion with daughter cysts



**Fig.-2 :** IVU reveals space occupying lesion in right kidney



**Fig.-3 :** Mass protruding through the incision

tissues were protected with sterile black towels soaked with scolicidal agents. The cyst was extremely tense. It was decompressed by aspiration as much as possible with caution (Fig. 4). Scolicidal agent was



**Fig.-4 (a) :** *Decompression of the cyst & injection of scolicidal agent is going on.*

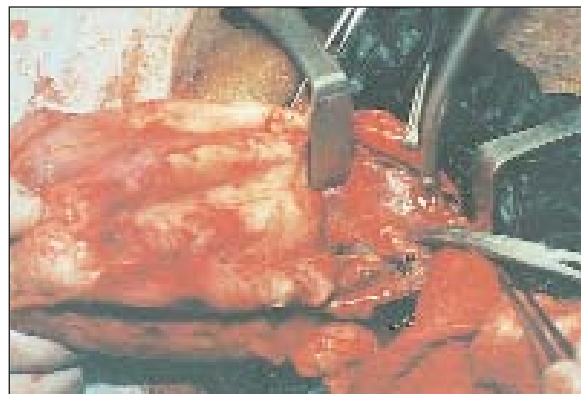


**Fig.-4 (b) :** *Decompression of the cyst is going on with suction.*



**Fig.-4 (c) :** *Decompression of the cyst is completed.*

injected inside the cyst with the same needle to destroy the scolices. As the cyst negotiation was very difficult a small opening was made on the cyst wall through the puncture point of aspiration with extra caution and the contents was sucked out very carefully (Fig. 5) with extra caution then closed with



**Fig.-5 :** *Dissection of the cyst is almost completed*



perse string suture. The cyst was then dissected entirely with a rim of pericystic tissue by sharp dissection. Haemostasis was secured, dead space was reduced as far as possible & wound closed with a drain inside. The patient recovered uneventfully. Histopathology of the resected specimen provided the final diagnosis of the sections as cyst wall made of laminated layers of hyalinized material containing hyalinized scolices.

She was then treated with albendazole for six months postoperatively. No recurrence could be detected during follow-up with history, physical examination & ultrasonographic examination at one month, six months & one year after operation.

### Discussion :

Cystic hydatid disease was known to Hippocrates and Galen but the parasitic nature of the disease was strongly suspected in the seventeenth century. However significant advances in diagnosis and treatment were made only during the last century<sup>3</sup>

The disease is endemic in many areas of Asia, Europe, South America, Near East, Australia & New Zealand where sheep and cattle are raised<sup>4</sup>. Approximately two third of the human hydatid cyst occur in the liver of which three quarters of them are solitary. When found outside the liver it is a good policy to suspect that they are also present in the liver until and unless proved otherwise<sup>3</sup>. Among the remaining, roughly 20% cyst is found in the lungs which is followed by cerebral hydatidosis. Renal hydatid disease is usually associated with hydatid disease in other organs. Isolated primary renal hydatid disease without any involvement of other organ is extremely rare, usually an incidental finding and responsible for 1 – 2 % of all the hydatid disease<sup>4,5,6</sup>. A pre-operative diagnosis is often not usually considered because of the extreme rarity of the disease and the infrequent occurrence of an isolated disease of the kidney<sup>6</sup>.

Non-specific flank pain is usually the common complaint. Some patient may present with very slowly enlarging lump in the lumbar region. There may be associated low grade fever. Hydatiduria may result from rupture of the cyst into the collecting system. Rupture of the cyst might cause severe anaphylactic reaction which attracts suspicion of the disease in most of the cases<sup>4,7</sup>.

Casoni's intradermal test does not provide specific results. Its diagnostic value is doubtful. Eosinophilia is non-specific. Complement fixation test is positive in 70% patients where as indirect haemagglutination test is positive in 90% patients. Fine needle aspiration could provide a presumptive cytopathologic diagnosis but considering the high risk of anaphylactic reaction and dissemination of the daughter cysts the use of FNA for the diagnosis has to be limited to the unexpected cases with unusual primary localization. Imaging studies including scout films of the kidneys may show calcification of the main cyst wall or daughter cysts. Intravenous urography usually reveals either a space occupying lesion or a large calcified cyst often with a non-functioning kidney<sup>7,8,9</sup>.

Ultrasonography offers a highest possibility of a confident pre-operative diagnosis including the measurement of the static dimension of the cyst<sup>8</sup>. Computerised Tomography (CT) is the most useful and specific diagnostic investigation<sup>5</sup>. Magnetic resonance image visualizes cyst location better than CT.

Simple public health measures with prevention of access to infected carcasses by dogs and the registration and regular treatment of dogs with anthelmintics is effective.

Medical treatment is not yet worth rewarding. The contribution of chemotherapy with protocoicidal agents in the management of hydatid disease is not well established until now. High dose of albendazole or mebendazole is claimed to provide some benefit including preoperative sterilization of the cyst and prevention of postoperative cyst recurrence. This concept requires large scale controlled clinical trial. Anti-hydatid drugs are also used on trial with percutaneous image guided drainage of the cysts in many centres. Medical treatment can be used alone where surgery is contraindicated or refused and also during preoperative period with the hope of cyst sterilization and for a prolonged period after surgery to prevent recurrence<sup>8,9</sup>.

Principle of hydatid surgery is removal of the cyst without contaminating the patient. Various procedure

may be adopted depending on the location of the cyst on the kidney and the size of the cyst. Protection of the operation field against the cysts using multiple coloured towel soaked with scolicedal agent is essential for prevention of spillage of infected particles which may produce disseminated disease or anaphylactic reaction during surgery. Since the hydatid fluid remains under high pressure the cyst is decompressed as far as possible and scolicedal agent is injected through the same needle. kept for five to ten minutes and then definitive surgery is attempted 8,9,10.

Parenchyma sparing surgery like excision of the cyst along with it's adventitia is the treatment of choice. Nephrectomy must be reserved for completely destroyed kidney <sup>10</sup>.

#### Conclusion :

Echinococcosis is a global disease, endemic in many areas. Hepatic & pulmonary cysts are most common followed by cerebral infestation. Renal hydatid cyst is an uncommon presentation of echinococcal disease. Isolated primary hydatid cyst of the kidney is extremely uncommon. Diagnosis is based mainly on ultrasonography & intravenous urography. Though the contribution of chemotherapy to the management of hydatid disease is growing gradually, open surgery is still the treatment of choice with excellent results.

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## **COLLEGE NEWS**

*(J Bangladesh Coll Phys Surg 2004; 22 : 39)*

### **Fellowship & Membership Examinations :**

The Fellowship Part -I & Part - II and Membership examinations of the College for January 2004 has commenced on scheduled from the 1st January 2004. As the previous years a number of senior and reputed academicians of Royal Colleges of United Kingdom, College of Physicians & Surgeons of Pakistan, Tribhuvan university teaching hospital, Kathmandu , Nepal have been invited to examine the students of the above mentioned examinations.

### **Annual General Meeting :**

The annual general meeting of the college for 2004 will be held on 27th February 2004 at 8.30 AM at the college auditorium. A number of agenda along with the annual budget will be placed before the meeting.

### **Publication :**

College council has decided to publish a year book for the first time to present the last one year's activity of the college. Different committees & faculties are requested to send their performance on or before 15th February latest.

### **Academics :**

#### *Courses -*

The weekend orientation course for the FCPS Part - I candidates will commence from first February. Intending candidates are requested to enroll. Seats are limited and will be filled up on first come first serve basis.

The orientation course for FCPS Part - II surgery & MCPS surgery will commence from April 2004. Interested Candidates are requested to enroll. Seats are limited and will be filled up on first come first serve basis.

#### *CPD programme:*

The fortnightly continuous, professional development programme scheduled to be held from September to December was commenced on time. A number of interesting topic were discussed A good number of fellows and postgraduate students attended and actively participated.

The CPD programme for 1st half of 2004 has been finalized and will be notified soon. Fellows are requested to attend and participate in the discussion