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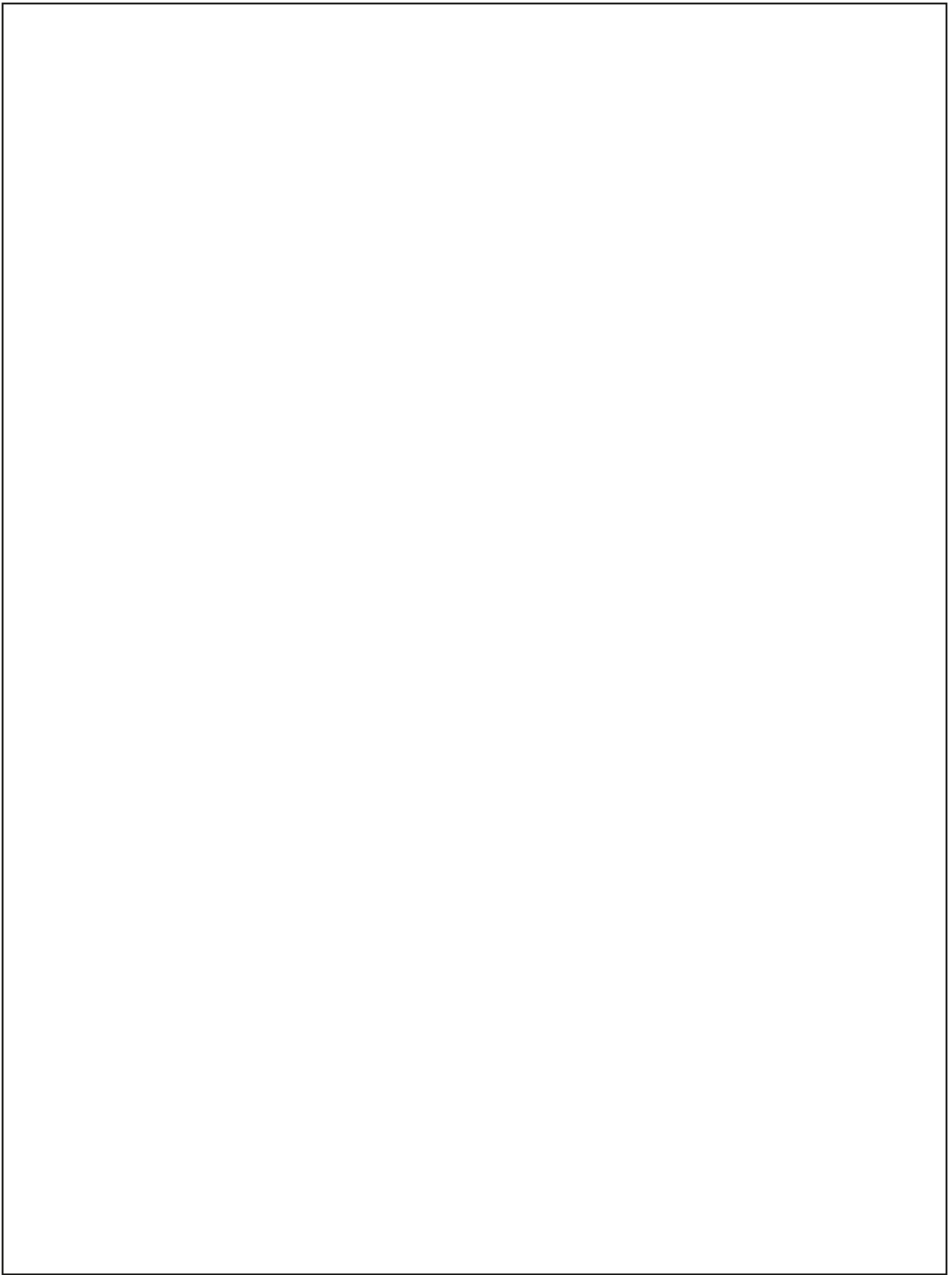
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CONTENTS

Page No.

INSTRUCTIONS TO AUTHORS

EDITORIAL

- Concepts of Physical Medicine & Rehabilitation (Physiatry) in Medical Science & Bangladesh Perspective* 47
Mamun KAA, Patwary MSR, Mansura F
-

ORIGINAL ARTICLE

- Tc-99m MDP Bone Scan Evaluation in Breast Cancer: A Study on 425 Patients* 49
Hosen MMA, Begum N, Hossain M, Ahmed P, Mutsuddy P, Chowdhury SA
- Efficacy and Safety of Pimecrolimus Cream (1%) in the Treatment of Discoid Lupus Erythematosus* 53
Hussain MA, Rahim MR, Alam MN, Haque MR, Hasan MR, Rahman MS, Ferdous M
- Evaluation of Serum Calcium Levels in Pre-eclampsia* 57
Roy HL, Nargis S, Rahman MM, Hossain MS, Amin MR, Majumder M, Begum H
- Antimicrobial Resistance Pattern of Uropathogenic Escherichia coli and Klebsiella species Isolated in a Tertiary Care Hospital of Sylhet* 61
Rahman MM, Chowdhury OA, Hoque MM, Hoque SA, Chowdhury SMR, Rahman MA
- Health Seeking Behavior of Women with Eclampsia Attending at Institute of Child and Mother Health in Dhaka City* 67
Jabeen M, Akhter D, Shimul S, Salma U
- Outcome of Laparoscopic Transperitoneal Ureterolithotomy for Proximal Ureteric Stones - Our Two Years Experiences* 71
Haque MN, Hossain MM, Islam MS, Mohammad A
- Correlation between Body Mass Index and Fasting Blood Glucose Level in a Selected Group of Teenagers in Bangladesh* 74
Howlader MH, Islam AKMM, Rahman MM, Mili US, Nur RS, Kibria MG
- Granulomatous Mastitis: Unusual Presentation and Management, Experience at Birdem General Hospital* 78
Narmeen T, Pervez MMM
-

REVIEW ARTICLE

- Arsenicosis: A Review of Its Diagnosis and Treatment.* 81
Hye MA
- Rheumatoid Arthritis: Monotherapy versus Combination Therapy* 89
Sarkar DN, Sarkar D, Alam SMR, Baset MA
-

CASE REPORT

- Management of Bile Duct Injury after Laparoscopic Cholecystectomy* 95
Islam MR, Ali MS, Azam SMG

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Concepts of Physical Medicine & Rehabilitation (Physiatry) in Medical Science & Bangladesh Perspective

Mamun KAA¹, Patwary MSR², Mansura F³

Physical Medicine and rehabilitation (PM & R) also known as physiatry or rehabilitation medicine is a branch of medicine that aim to enhance and restore functional ability and quality of life to those with physical impairments or disabilities¹. It deals with total care of medical illness by drugs, physical agents, exercises and assistive devices. A physician having completed training in this field is referred to as physiatrist or rehabilitation medicine specialist. Physiatrists specialize in restoring optimal function to people with disease, and injuries to the muscles, bones, tissues and nervous system (such as stroke patients)¹.

The term 'physiatry' was coined by Dr. Frank. H. krusen in 1938. The term was accepted by the American medical association in 1946. The field grew notably during and 2nd world war to accommodate the large number of injured soldiers². In Bangladesh physical medicine and rehabilitation is started as a post graduate course in Bangladesh College of Physicians & Surgeons (BCPS) in 1990. Up to July 2013, about 70 fellows from BCPS has come out and serving all over the country.

Common conditions that are treated by the physiatrists include amputation, spinal cord injury, sports injury, stroke, musculoskeletal pain syndrome such as low back pain, fibromyalgia and traumatic brain injury. Cardiopulmonary rehabilitation involves optimizing function in those affected with heart or lung disease. Chronic pain management is achieved through a multidisciplinary approach involving psychologist, physical therapist, occupational therapist, exercise therapist, anesthesiologist and interventional procedure

when indicated. In addition to previous methodology, stroke is often treated with help of a speech therapist and recreational therapist when possible³.

The major concern that PM & R deals with a medical field is the disability of a person to function optimally within the limitation placed upon them by a disabling impairment or disease process for which there is no known cure. The emphasis is not on the full restoration to the pre morbid level of function, but rather the optimization of the quality of life for those not able to achieve full restoration. Comprehensive rehabilitation is provided by specialists in this field, who act as a facilitator, team leader, and medical expert for rehabilitation⁴.

Rehabilitation must be started at the earliest possible time in order to ensure the best results. It is administered in conjunction with specific medical or surgical treatment of the precipitating disease⁵. The role of rehabilitation is to minimize disability and handicap, and a help of handicapped person lead a useful life within his limitation in order to make a disabled person in to a "differently abled" person⁵.

Rehabilitation Medicine is recognized today as a necessary and integral part of management of chronic diseases and disabilities. About 5 to 10 percent of total population are estimated to be in need of physical medicine and rehabilitation services at this time. At least three times as many physiatrist would be needed to provide those services⁶. There is also an increasing demand for rehabilitation services for all kinds of medical problems proportional to the increasing awareness among the general public that restoration of a satisfactorily high quality of life of the physically impaired patient⁷.

It is unfortunate for persons impaired by physical handicaps that as more and more hospital, skilled nursing facilities, and extended care facilities establish components of rehabilitation services, there are not enough qualified physiatrists available to provide the evaluation and supervision that result in best outcome⁷.

In Bangladesh, the demand of physical medicine & Rehabilitation service is extending day by day. As the awareness about this speciality and public interest rapidly growing up about non- pharmacological procedures of pain management, it is now emmence

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need to grow up this speciality for comprehensive management of musculoskeletal problems including sports injuries. For example, many people and also many healthcare personnels suffer from neck pain due to muscular spasm & joints stiffness which is not due to specific disease rather than posture related conditions. These patients have special treatment in physical medicine as soft tissue massage, Ultrasound therapy, specific neck muscles exercise, ADL (Activities of daily living instructions) advices other than pharmacological agents as NSAIDS (Non steroidal anti inflammatory drugs) and muscle relaxants.

There are about 85 tertiary level healthcare institutes in Bangladesh which include govt. and private medical college hospitals, specialized govt. and non govt. hospitals. But the number of physical medicine & Rehabilitation Specialist or Physiatrist are only about 100 in number. According to our total population, for about twenty lacs people there is only one physiatrist. The number of physiatrist should be at least three time more than the present number. There is also shortage of proper Rehabilitation centres and other personnels as physiotherapist and Rehab technician. So special attempts should be taken from govt. and non- govt. sectors to overcome the deficiency of all of these shortages for comprehensive management of musculoskeletal problems of our patients.

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Tc-99m MDP Bone Scan Evaluation in Breast Cancer: A Study on 425 Patients

Hosen MMA¹, Begum N², Hossain M³, Ahmed P⁴, Mutsuddy P⁵, Chowdhury SA⁶

Abstract

Breast cancer is the most frequent female cancer, especially in 'developed' countries. 30-85% of metastatic breast cancer patients will develop bone metastases during the course of the disease. The objective of this study was to evaluate the skeletal metastases in breast cancer patients by using Tc-99m MDP bone scan. A retrospective study was conducted on 425 consecutive female breast carcinoma patients referred for bone scan to Institute of Nuclear Medicine and Allied Sciences, Rajshahi from January 2015 to November 2017. Bone scan was performed by an intravenous bolus injection of 20 mCi Tc-99m-MDP (technetium 99m methylene-diphosphonate). Bone phase images were taken at three hours after injection of the radiotracer. Out of 425 patients, 290 patients (68.24%) had either normal bone scan or negative for skeletal secondaries and 135 patients (31.76%) were positive for skeletal metastases. Out of 135 positive bone scans 114 (84.44%) patients had multiple sites (two or more) and 21 (15.56%) patients had solitary site of bony involvement. Highest number of skeletal

metastases was noted in thoraco-lumbar spine (81.48%). Other sites of metastases were in cervical spine (22.96%), pelvic bones (54.81%), ribs (40.74%), sternum (16.30%), scapula (19.26%), upper extremities (28.15%), lower extremities (36.30%), skull bone (12.60%) and clavicle (13.33%). Tc-99m MDP bone scan is very cost effective in comparison to other imaging modalities (CT, MRI, and PET) and play a major role in early detection of skeletal metastasis in breast cancer patients.

Keywords: Breast Cancer, Tc-99m MDP Bone Scan, Skeletal Metastasis.

Number of Figures: 04

Number of References: 20

Number of Correspondences: 06

Introduction

Breast cancer is the most frequent female cancer, especially in 'developed' countries. Incidence of breast cancer varies geographically (20-30 cases per 100,000 women in South-Central Asia)¹. Women with breast cancer are vulnerable to develop metastatic diseases during the early stage. Bone is the most frequent site of distant metastasis from breast cancer. Between 30% and 85% of patients with metastatic breast cancer will develop bone metastases during the course of the disease. Bone also represents the first site of metastasis for 26% to 50% of patients with metastatic breast cancer. The rate of five-year survival will be significantly decreased and severe complications will present following bone metastases in breast cancer patients. In addition, bone metastases are predominant osteolytic in breast cancer. Osteolytic metastases can cause dramatic bone loss, which finally resulted in skeletal related events (SREs), such as pathological fractures, severe pain, bone instability, spinal cord compression and hypercalcemia. These will reduce the quality of patients' life. Therefore, early detection and diagnosis of bone metastasis in patients with breast cancer is helpful for the treatment²⁻⁴.

Bone scan is a traditionally sensitive and efficient method for initial evaluation and follow-up of bone metastases. Many radiopharmaceuticals (radionuclides) have been used in bone scan including technetium-99m bound to methylene diphosphonate. Published sensitivity and specificity rates of bone scan for diagnosis have varied, with sensitivity ranging from 62% to 100% and specificity from 78% to 100%. However, bone scan is generally

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considered sensitive for detecting bone metastases on whole-body images⁵⁻⁸.

The aim of this study was to evaluate the skeletal metastases in breast cancer patients by using Tc-99m MDP bone scan.

Materials and Methods

A retrospective study was conducted on 425 consecutive female breast carcinoma patients irrespective of clinical stage, menopausal status and pre-operative / post-mastectomy status, referred for bone scan to Institute of Nuclear Medicine and Allied Sciences, Rajshahi from January 2015 to November 2017. The mean age of the patients was 45.2 ± 11.7 years (mean $\pm$ SD) with range from 29 to 71 years. Patient's clinical records and bone scan reports were reviewed retrospectively. In our institute we used SPECT (single photon emission computed tomography) digital dual head gamma camera (e-cam series, Siemens from Germany) with a low-energy high resolution parallel-hole collimator. Bone scan was performed by an intravenous bolus injection of 20 mCi Tc-99m-MDP (technetium 99m methylene-diphosphonate). Bone phase images were taken at three hours after injection of the radiotracer and the scan time was about 15 minutes for a whole body scan. Whole body scan in anterior and posterior projections were obtained. All scans were interpreted for metastatic deposits by two nuclear medicine physicians.

Results

Out of 425 patients, 290 patients (68.24%) had either normal bone scan or negative for skeletal secondaries and 135 patients (31.76%) were positive for skeletal metastases (Figure-1).

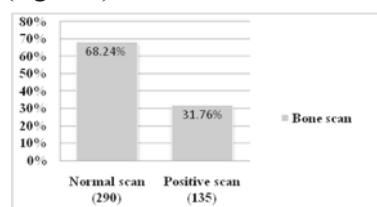


Figure-1: Distribution of bone scan findings in frequency and percentage in the study group (n= 425).

Out of 135 patients with positive skeletal metastases 109 (80.74%) patients were symptomatic or had bone related events and 26 (19.26%) patients were asymptomatic for any bony involvement (Figure-2).

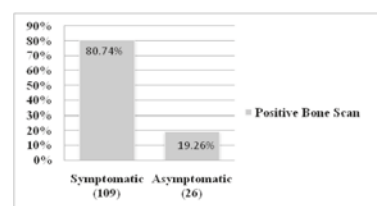


Figure-2: Distribution of bone scan in frequency and percentage by clinical symptoms in the study group (n= 135).

Out of 135 patients with positive bone scan 114 (84.44%) patients had multiple sites (two or more) and 21 (15.56%) patients had solitary site of bony involvement (Figure-3).

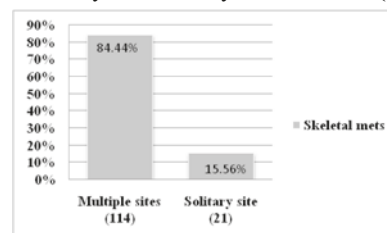


Figure-3: Distribution of skeletal metastases in frequency and percentage by number of site in the study group (n= 135).

Among 135 positive bone scan patients, highest number of skeletal metastases was noted in thoraco-lumbar spine (81.48%). Other sites of metastases were in cervical spine (22.96%), pelvic bones (54.81%), ribs (40.74%), sternum (16.30%), scapula (19.26%), upper extremities (28.15%), lower extremities (36.30%), skull bone (12.60%) and clavicle (13.33%) (Figure-4).

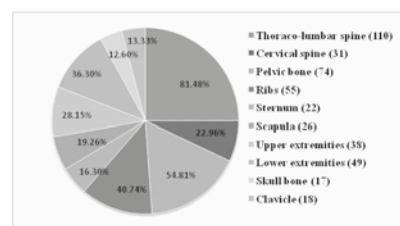


Figure-4: Distribution of skeletal metastases in frequency and percentage by anatomical sites (n= 135).

Discussion

Bone is known to be one of the most common sites of metastasis for breast cancer patients. Several imaging modalities, including plain radiography, computed tomography, magnetic resonance imaging, SPECT-bone scan and positron emission tomography are available to detect bone metastasis. Compared to other modalities, bone scan is characteristic by its high sensitivity, easy accessibility, and providing whole-body imaging of bone metabolism^{9,10}. The high sensitivity of this technique is based on physiological basis for preferential uptake of methyl diphosphonate, which identifies as little as 5-15% alteration in local bone turnover. Delineation of a lytic lesion by conventional radiology requires a minimum size of 1cm and a focal loss of at least 50% of bone mineral, while at least 30% increase in bone mineral content is essential to appreciate sclerotic lesion. That's why bone scan may pick up bone metastases up to 18 months earlier than conventional radiology, with an average lead of 4 months. The usual appearance of skeletal metastases on bone scan is focal hot spot; however, rarely focal cold defects are also noted. Therefore, it is more frequently used than the other modalities, and breast cancer patients can benefit from a routine baseline bone scan and a regular follow-up^{11,12}.

The routes of skeletal metastasis are direct extension or invasion, lymphatic spread, hematogenous dissemination and intraspinal spread. Skeletal metastases of breast cancer will mainly occur from hematogenous dissemination. The mechanism or a route of venous system dissemination to develop skeletal metastasis was proposed by Batson¹³. He insisted that owing to the extensive communications of this venous system and to the variability of the direction of this blood flow, tumors arising in many sites release cells that could be deposited anywhere along the course of vessels, including the skeleton, even in the absence of pulmonary and hepatic metastasis. Breast carcinoma cells can easily migrate to neighboring ribs and spinal vertebrae via Batson venous plexus, and spread to the sternum via the parasternal lymph nodes^{13,14}.

In our study, out of 425 patients, 290 patients (68.24%) had either normal bone scan or negative for skeletal secondaries and 135 patients (31.76%) were positive for skeletal metastases. MS Afzal et al.¹¹ found positive bone scan in 38% patients out of 465 breast cancer patients. Skeletal metastases were seen in 23.42% (241/1029) patients in a study by Doddala S et al.¹⁵. Kotb MH et al.¹⁶ found positive bone scan in 18.2% patients out of 450. Out of 135 patients with positive skeletal metastases 109 (80.74%) patients were symptomatic or had bone related events and 26 (19.26%) patients were asymptomatic for any bony involvement. I Kuchuk et al.¹⁷ found 26.8% patients was asymptomatic for skeletal metastases in breast cancer patients.

In present study, out of 135 patients with positive bone scan 114 (84.44%) patients had multiple sites (two or more) and 21 (15.56%) patients had solitary site of bony involvement. In a study of comparison between solitary and multiple skeletal metastatic lesions of breast cancer patients by M. Koizumi et al.¹⁸ found that out of 703 patients with metastatic bone lesions, 289 (41%) had a solitary bone lesions and 414 (59%) had multiple bone lesions at the time of diagnosis. Boxer et al.¹⁹ found that out of 160 consecutive studied breast cancer patients, 79% were having multiple metastatic lesions. He stated that solitary metastases are much more common in cases of breast cancer, than they are thought to be. Reported incidence of solitary skeletal metastases in breast cancer patients having skeletal metastases ranges from 11% to 21%.

Among 135 positive bone scan patients, highest number of skeletal metastases was noted in thoraco-lumbar spine (81.48%) in our study. Other sites of metastases were in cervical spine (22.96%), pelvic bones (54.81%), ribs (40.74%), sternum (16.30%), scapula (19.26%), upper extremities (28.15%), lower extremities (36.30%), skull bone (12.60%) and clavicle (13.33%). MS Afzal et al.¹¹ found highest number of bony lesions was in spine (84.5% -most common in thoracolumbar), followed by ribs (55.5%), pelvis (37.3% - most frequent in iliac bone),

skull (32%), scapula (27.3%), sternum (26.4%), femur (19.1%), humerus (14.5%), clavicle (3.6%) and tibia (0.9%). In another study of patients with breast cancer conducted by Musat E et al.²⁰, out of 23 subjects with skeletal metastases, 16 cases were having multiple secondaries; the most involved site was the ribs (18 cases), followed by the spine (in 17 cases), iliac bone (9 cases), the femur (7 cases), the skull (3 cases). In spine, the more frequently involved vertebrae were dorsal (49.23%), followed by lumbosacral (26.13%) and lastly cervical vertebrae (12.3%).

Conclusion

Skeletal metastases are much more common in multiple sites than solitary lesion in breast cancer patients. Thoraco-lumbar spine was the most common site of involvement in our study. Tc-99m MDP bone scan is very cost effective in comparison to other imaging modalities (CT, MRI, and PET) and play a major role in early detection of skeletal metastasis in breast cancer patients.

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Efficacy and Safety of Pimecrolimus Cream (1%) in the Treatment of Discoid Lupus Erythematosus

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Abstract

Discoid lupus erythematosus (DLE) is commonly treated with topical agents, the most important of which are glucocorticosteroids. However, prolonged use of these agents, especially on sensitive areas such as the face, may result in side-effects (e.g. atrophy and telangiectases) by altering collagen synthesis. This was a randomized double-blind pilot study, performed in Department of Dermatology & VD, Ibn-Sina Sina Medical College, Dhaka. Seventy four patients aged 20-53 years with moderate to severe DLE of the face were randomized 8 weeks of treatment and 8 weeks of follow-up after treatment.

In this double-blind study, one group applied pimecrolimus 1% cream twice daily to facial lesions. Efficacy end-points included a combined score based on evaluation of erythema, infiltration and presence of scale. This study was conducted to evaluate the efficacy and safety of topical pimecrolimus 1% cream in discoid lupus erythematosus. It was observed that before treatment, erythema was severe in 43.2% cases, moderate in 51.4% cases and mild type erythema was present in 5.4% cases. The post-treatment revealed, 29.7% severe type erythema, none evidenced moderate type erythema, only 43.2% had mild type and 27% cases no erythema at all. Before treatment, infiltration was severe in 27% cases, moderate in 54.1% cases and only 18.9% had mild type infiltration. But after treatment, 10.8% had severe type infiltration, 18.9% had moderate, 51.4% had mild and 18.9% had no infiltration at all. Similar response to treatment was noticed with squamation which exhibited a drop from 37.8% to 18.9% in severe cases and from 62.2% to 10.8% in moderate cases. There was a 45.9% mild case and 24.3% had no squamous. It was interpreted that score of patients of DLE, before treatment was 6.78 ± 1.36 and after treatment was 3.97 ± 1.21 . Improvement was shown in 70.3 cases and 29.73 cases shown no improvement at all. This study suggest that pimecrolimus cream for discoid lupus erythematosus seems to be a safe and clinically effective option. However, this was an open and uncontrolled study, and double-blind, placebo-controlled studies are needed.

Keywords: Discoid Lupus Erythematosus, Pimecrolimus, Infiltration, Erythema.

Number of Tables: 06

Number of References: 24

Number of Correspondences: 07

Introduction

Discoid lupus erythematosus (DLE) is one of the skin presentations of lupus erythematosus (LE), characterized by the presence of scaly red patches and plaques associated with atrophy¹. The main goal of treatment in this skin disorder is to improve the appearance of the skin, while preventing disfiguring scars, atrophy or pigmentary alterations². The customary treatment in most cases has been topical therapy, which to some extent can control and occasionally even clear lesions without the need for systemic therapy. Such treatment usually consists of a prolonged course of potent glucocorticosteroids.

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The use of glucocorticosteroids may affect collagen synthesis, resulting in various side-effects, including atrophy and telangiectases,^{2,3} thus a better therapeutic alternative is needed.

Topical calcineurin inhibitors (TCIs) are a new generation of immunomodulator therapies, which show promising results in treating inflammatory skin disorders such as atopic dermatitis^{4,7}. This family includes ciclosporin, tacrolimus and the newest member, pimecrolimus (Elidel; Novartis Pharmaceuticals, East Hanover, NJ, USA). Several studies have investigated and established the role of tacrolimus in treating DLE⁸⁻¹⁴. The efficacy of pimecrolimus in DLE has not undergone the same scrutiny, but the studies performed to date have shown encouraging results^{2,15,16}. This study performed a pilot study to further appraise the efficacy and safety of pimecrolimus as an alternative to more commonly used therapies in treating patients with DLE.

Materials and Methods

This study, a randomized controlled pilot trial, was designed to compare pimecrolimus 1% in the treatment of DLE. All patients were informed about the study procedures and gave their written informed consent. DLE was diagnosed if erythematous, well-defined, scaly plaques, which tended to heal with atrophy and scarring, were present together with histological epidermal atrophy. A precise medical history was obtained and all patients were carefully examined. Biopsy specimens were obtained for histology and direct immunofluorescence, and routine blood tests and complete blood cell count were performed. To ensure no traces of other therapeutic agents (oral and topical steroids, chloroquine, hydroxychloroquine) remained, patients were asked to stop using all topical and systemic treatments at least 4 weeks before the commencement of the trial. The study comprised an 8-week treatment plan plus an 8-week follow-up period. Before patient enrolment, all patients with odd numbers were allocated to patients. Patients were scheduled for follow-up visits at 2-week intervals. Clinical severity score was determined by assessing three factors including erythema, infiltration and presence of scale (0 = normal; 1 = mild; 2 = moderate; 3 = severe)^{2,16,19}. Therefore, by adding the scores given to these three independent criteria, the minimum and maximum clinical scores were 0 (normal skin) and 9 (maximum skin damage), respectively, with mild, moderate and severe disease severity defined as scores of 1-3, 4-6 and 7-9, respectively.

Results

Male and female percentage of cases were 21.6 and 78.4 respectively (Table I).

Table-I: Sex distribution of the study subjects (n=74).

Sex	Number	Percentage
Male	16	21.6
Female	58	78.4
Total	74	100.0

It was interpreted that score of patients of DLE, before treatment was 6.78 ± 1.36 and after treatment was 3.97 ± 1.21 (Table II).

Table-II: Mean distribution of before treatment and after treatment (n=74).

Treatment	Mean $\pm$ SD	P value
Before treatment	6.78 ± 1.36	0.001
After treatment	3.97 ± 1.21	

Erythema was severe in 43.2% cases, moderate in 51.4% cases and mild type erythema was present in 5.4% cases. The post-treatment scenario revealed- 29.7% severe type erythema, none evidenced moderate type erythema, only 43.2% had mild type and 27% cases no erythema at all (Table III).

Table-III : Grading of erythema before and after treatment (n=74).

	Before treatment		After treatment	
	No	%	No	%
Normal	0	00	20	27
Mild	4	5.4	32	43.2
Moderate	38	51.4	0	00
Severe	32	43.2	22	29.7

Before treatment, infiltration was severe in 27% cases, moderate in 54.1% cases and only 18.9% had mild type infiltration. But after treatment, 10.8% had severe type infiltration, 18.9% had moderate, 51.4% had mild and 18.9% had no infiltration at all (Table IV).

Table-IV: Grading of infiltration before and after treatment (n=74).

	Before treatment		After treatment	
	No	%	No	%
Normal	0	00	14	18.9
Mild	14	18.9	38	51.4
Moderate	40	54.1	14	18.9
Severe	20	27.0	8	10.8

Squamation exhibited a drop from 37.8% to 18.9% in severe cases and from 62.2% to 10.8% in moderate cases. There was a 45.9% mild case and 24.3% had no squamation (Table V).

Table-V: Grading of squamation before and after treatment (n=74).

	Before treatment		After treatment	
	No	%	No	%
Normal	0	00	18	24.3
Mild	0	00	34	45.9
Moderate	46	62.2	8	10.8
Severe	28	37.8	14	18.9

Improvement was shown in 70.3 cases and 29.73 cases shown no improvement at all (Table VI).

Table-VI: Percentage of improvement of the study subjects (n=74).

	Number	Percentage	P value
Improved	52	70.3	0.001
Not improved	22	29.7	
Total	74	100.0	

Discussion

In recent years, treatment of DLE worldwide has been mainly restricted to the use of mid-potency to high-potency topical glucocorticosteroids. Prolonged use of these drugs can lead to a number of side-effects, including atrophy or thinning of the skin, telangiectasia, or rarely, systemic adrenal suppression^{2,3}. Calcineurin inhibitors, do not have these adverse effects, and the main side-effects reported with these drugs have been a local burning sensation and pruritus^{17,18}.

The present study trials the effects of pimecrolimus 1%. At the end of the 8-week treatment the clinical severity score showed a substantial improvement, which was confirmed by statistical analysis.

The main reason for developing new drugs as an alternative to topical steroids is to overcome side-effects, such as thinning of the skin and adrenal gland suppression, and recent studies have demonstrated that skin thinning is avoided with the use of pimecrolimus cream¹⁹. This pilot study demonstrates that pimecrolimus 1% cream as monotherapy was effective in the amelioration of the skin score of patients of DLE, before treatment was 6.78 ± 1.36 and after treatment was 3.97 ± 1.21 ($P = 0.001$). The safety profile in this open trial is similar to those reported in previous atopic dermatitis clinical trials²⁰. Zabawski²¹ was the first to describe, in a single case report, a moderate improvement of DLE lesions under pimecrolimus ointment; however, he did not mention the schema employed, the duration of treatment or the method of assessing improvement. More recently, Kreuter et al.²² reported on topical pimecrolimus in 11 patients with different forms of cutaneous lupus, including four patients with DLE, three with SLE, two with subacute cutaneous and two with lupus tumidus. The patients were treated with pimecrolimus twice daily, and the evening applications were followed by overnight occlusion with hydrocolloid dressings to increase the cutaneous uptake of the cream. Significant amelioration of the skin lesions was observed after therapy. Interestingly, the overall percentage of improvement was very similar 74% in this study, but without using overnight occlusion.

A few studies in DLE have included the analysis of QOL; this aims to measure objectively how the patient's life is affected by the disease²³. Skindex-29 is a generic and widely validated instrument to measure QOL in patients with skin diseases [17]. Therefore we employed the Spanish version of Skindex-29, which had demonstrated validity, reliability and sensitivity to change, which is an specially important issue for drug evaluation trials¹⁸. Systemic side-effects are absent with topical pimecrolimus, but topical side-affects include

burning sensation, tingling, flushing and folliculitis at the application site²⁴.

In our study 51.4% had moderate erythema in before treatment and after treatment shows had no moderate erythema. 43.2% were severe erythema in before treatment and 29.7% were severe in after treatment. Therefore, the findings of the study are in well agreement with the findings of the other research works^{2,3}.

Our data suggest that pimecrolimus 1% cream for DLE seems to be a safe and clinically effective option, especially for resistant DLE at sensitive sites such as the face, where the use of potent topical steroids carries a high risk of thinning of the skin and telangiectasia. However, the place of pimecrolimus in the treatment of cutaneous lupus will depend on its efficacy when compared with established topical treatments, such as corticosteroids. The present study had an open-label design and involved only a small number of patients and no control group, therefore double-blind, placebo controlled studies are needed in order to confirm our data. This work was supported in various other studies conducted across India^{13,14}.

There were few side-effects in the pimecrolimus this could be due to the limited exposure time to these medications. In addition, despite the improvement lasting for 8 weeks observed in our patients, we cannot draw any conclusions on the efficacy of pulsed topical treatments because of the limited number of patients and followup period. Our trial, moreover, did not include a placebo control group.

Conclusion

It was observed that pimecrolimus is a good alternative for corticosteroids in dealing with the scaly and atrophic patches found in discoid lupus erythematosus. Further studies on larger groups of patients are needed.

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Evaluation of Serum Calcium Levels in Pre-eclampsia

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Abstract

Pre-eclampsia is the most common medical complication of pregnancy associated with increased maternal and infant mortality and morbidity. Reduced serum calcium level are found associated with elevated blood pressure in preeclampsia. To evaluate serum calcium level in pre-eclamptic women. This cross sectional study was carried out in among 50 pre-eclamptic patients, aged 20 to 40 years, and gestational age ranges from 20 to 40 weeks and 50 age and gestational age matched normotensive pregnant women having no proteinuria. Serum calcium was measured by Colorimetric method. The mean age and mean gestational age of pre-eclampsia was not significantly different from those of normotensive pregnant women ($p=0.203$ and $p=0.251$ respectively). The mean body mass indexes of the test patients were significantly

different from those of normotensive pregnant women ($p<0.001$). The mean serum calcium level was 7.27 ± 3.01 mg/dl in pre-eclampsia and 7.25 ± 2.59 mg/dl in normal pregnant women; did not differ significantly between the subjects of pre-eclampsia and normal pregnant women ($p=0.963$). Serum calcium has no association in occurrence of pre-eclampsia.

Keywords: Pre-eclampsia, Calcium.

Number of Figures: 02

Number of References: 26

Number of Correspondences: 07

Introduction

Pre-eclampsia is idiopathic multisystem disorder specific to human pregnancy¹. It is defined as the onset of hypertension and the presence of proteinuria during pregnancy, usually occurring after the 20th week of gestation in a previously normotensive woman and resolving completely by the sixth week after delivery of fetus².

Pre-eclampsia is transient but potentially dangerous complication of pregnancy. Generally, the incidence of pre-eclampsia is in the range of 4 - 8% of all pregnancies³. The incidence of pre-eclampsia has fallen in developed countries due to improved antenatal care, but it's incidence is still high in the developing countries⁴, and pre-eclampsia accounts for about 20-80% of the maternal mortality in developing countries⁵. Pre-eclampsia and eclampsia cause about 16 % of maternal death in Bangladesh⁴.

Despite of pre-eclampsia's prevalence and severity, the pathophysiology of this multisystem disorder is still poorly understood and it's etiology has not yet been fully elucidated. Environmental and nutritional factors may play a role in the development of pre-eclampsia⁶. The epidemiology of pre-eclampsia, being more common in poor women, long ago suggested that nutrients might be involved in the disorder⁷. It is assumed that deficiency of several essential micronutrients may be a predisposing factor in the development of pre-eclampsia because nutrients can modulate oxidative stress by increasing or decreasing free

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radicals or antioxidant and providing substrates for formation of free radicals⁴. Nutritional deficiencies are commonly found in pregnant women and it is well established that the pregnant women from developing countries usually consume diets that are low in minerals and vitamins⁸.

Calcium plays an important role in muscle contraction and regulation of water balance in cells. Modification of plasma calcium concentration leads to the alteration of blood pressure. The lowering of serum calcium and the increase of intracellular calcium can cause an elevation of blood pressure in pre-eclamptic mothers⁹. So the modification of calcium metabolism during pregnancy could be one of the causes of pre-eclampsia¹⁰⁻¹¹. Several studies showed that significantly low serum calcium level in pre-eclamptic women as compare to normal pregnant ($p < 0.05$)¹²⁻¹⁶. But in other studies serum levels of calcium did not differ significantly between pre-eclampsia and comparative group^{17,18}.

Serum calcium level was significantly lower in pre-eclamptic women compare to normal pregnant women in a study in Dhaka Bangladesh. This is not enough to reach valid conclusion. So, this study was conducted to estimate the serum calcium level in pre-eclampsia and normal pregnancy and find out any association between calcium and pre-eclampsia.

Materials and Methods

This cross-sectional study carried out in the Department of Biochemistry, Sylhet MAG Osmani Medical College in collaboration with the Department of Obstetrics and Gynaecology, Sylhet MAG Osmani Medical College Hospital during the period from January 2016 to December 2016. Fifty pre-eclamptic patients, aged 20 to 40 years, and gestational age ranges from 20 to 40 weeks and 50 age and gestational age matched normotensive pregnant women having no proteinuria were included in group-A and Group-B respectively. All subjects were primi. Pregnant women having essential hypertension, systemic or endocrine disorders, malabsorption syndrome, and patients on calcium supplementation were excluded.

Detailed history about present pregnancy regarding pre-eclampsia and exclusion criteria was asked. Gestational age was based on menstrual date and confirmed through ultrasound.

Data were collected from the selected subjects on variables of interest using a semi structured questionnaire by interview, observation, clinical examination, investigation and from the history.

Blood pressure was measured in supine position or sitting position. Urine was tested for gross proteinuria (heat coagulation test). The pre-eclamptic patients were diagnosed by the presence of persistent hypertension (more than 140/90 mm of Hg), gross proteinuria (tested by heat coagulation test of urine), and pathological oedema.

Maternal weight was recorded in kilograms with the subject standing on the weight machine without shoes and minimum clothing. Maternal height was recorded with the subject barefoot, feet together, back against the upright bar of the height scale, head upright in Frankfort horizontal plane - look straight ahead. The height measuring equipment consists of a vertical bar with a horizontal bar of wood which was brought down on examinee's head. Body mass index (BMI) was calculated by the formula ($BMI = \text{Weight in kilogram} / \text{Height in meter}^2$).

Five ml of venous blood was collected from ante-cubital vein under aseptic precaution in a metal-free sterile tube without any anticoagulant. Test tube was coded for identification of sample. The sample was kept at room temperature for about 20-25 minutes to allow it to clot and was sent to the Department of Biochemistry, Sylhet MAG Osmani Medical College, Sylhet where serum calcium was measured by Colorimetric method. Data were analysed with the help of Statistical Package for Social Science (SPSS) Version 21. Quantitative data were expressed as mean $\pm$ SD (standard deviation) and unpaired test was done to see the significance. Qualitative data were expressed as frequency and percentage. The p-value of < 0.05 was considered statistically significant.

Informed written consent was taken from each of the patient or legal guardian and an approval of study protocol was obtained from the ethical committee of Sylhet MAG Osmani Medical College prior to the commencement of the study.

Results

The mean age was 26.70 ± 5.59 years in pre-eclampsia and 25.32 ± 5.17 years in normotensive pregnant women; difference was not significant ($t=1.281$; $p=0.203$) (Figure-1). The mean gestational age was 32.14 ± 3.19 weeks in pre-eclampsia and 32.84 ± 2.86 weeks in normotensive pregnant women; difference was not significant ($t=-1.154$; $p=0.251$) (Figure-1). The mean body mass index was 25.98 ± 2.58 Kg/M² in pre-eclampsia and 22.49 ± 2.72 Kg/M² in normotensive pregnant women. The mean body mass index in pre-eclampsia was significantly higher compared to normotensive pregnant women ($t=6.601$; $p<0.001$) (Figure-1).

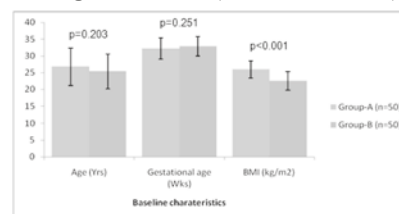


Figure-1: Distribution of the study groups according to baseline characteristics. *unpaired 't' test were used to reach a level of significance. A $p < 0.05$ was the level of significance.

The mean serum calcium level was 7.27 ± 3.01 mg/dl in pre-eclampsia and 7.25 ± 2.59 mg/dl in normal pregnant women. The mean serum calcium level did not differ significantly between the subjects of pre-eclampsia and normal pregnant women ($t=0.046$; $p=0.963$) (Figure-2).

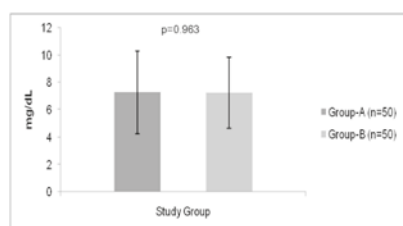


Figure-2: Serum calcium in study groups.

*unpaired 't' test were used to reach a level of significance. A $p < 0.05$ was the level of significance.

Discussion

Serum concentrations of various macrominerals are altered during pregnancy with changes in the mother's physiology and the requirements of growing fetus. Changes on serum level of Calcium (Ca) during pregnancy were estimated. In addition, it has been reported that reduction in serum level of Ca during pregnancy might be possible contributors in etiology of pre-eclampsia (PE), and supplementation of these minerals to diet may be of value to prevent PE¹⁸.

In this study the mean age in pre-eclampsia and normal pregnant women. There was no significant difference of the mean age between two groups ($p = 0.203$). This result was consistent with the study of Golmohammad lou et al.¹⁷ that the mean age of the pre-eclamptic women was 25.70 ± 1.20 years. This result was also supported by Akhtar et al.¹⁹ that the mean age of the pre-eclamptic mother was 25.20 ± 4.85 years.

In this study the mean gestational age was 32.14 ± 3.19 weeks in the subjects with pre-eclampsia and was 32.84 ± 2.86 weeks in normal pregnant women. There was no significant difference of mean gestational age between two groups ($p = 0.251$). This result was similar to the study of Akhtar et al.¹⁹ that gestational age was 31.53 ± 3.90 weeks in pre-eclampsia group and 32.35 ± 3.53 weeks in normal pregnancy group; the difference was not significant ($p = 0.321$). Ephraim et al.²⁰ also reported that the gestational age was 30.72 ± 2.84 weeks in pre-eclampsia and 31.92 ± 4.69 in normal pregnancy; the difference was not significant ($p = 0.2518$).

This study showed that the mean body mass index was 22.97 ± 2.62 Kg/M² of the subjects with pre-eclampsia and was 22.49 ± 2.72 Kg/M² of the normal pregnant women. The mean body mass index of the subjects did not differ significantly between the two groups ($p = 0.362$). This result was correlated with the study of Lambe et al.¹⁴ that the mean body mass index was 22.75 ± 1.99 Kg/M² in pre-eclampsia and was 23.01 ± 2.02 Kg/M² in normal pregnant women. The mean body mass index of the subjects did not differ significantly between the two groups ($p = 0.4854$). Several other studies did not show significant difference of body mass index between the two groups ($p > 0.05$)^{8,17}. But Akhtar et al.¹⁹ found that the

mean body mass index of the subjects with pre-eclampsia was 25.30 (SEM 0.36) Kg/M² and normal pregnant women was 23.48 (SEM 0.28) Kg/M². There was a significant difference of body mass index between the two groups ($p < 0.001$).

In this study the mean serum calcium was 7.27 ± 3.01 mg/dl in mg/L in pre-eclampsia and was 7.25 ± 2.59 mg/L in normal pregnant women. The mean serum calcium did not differ significantly between the subjects of pre-eclampsia and normal pregnant women ($p = 0.963$). This was in contrast with several studies,^{5,6,13-15} suggesting hypocalcemia as a possible cause for preeclampsia. All theses study reported significantly lower calcium in pre-eclamptic patients than normal pregnancy. However, in corroboration with our study finding, other studies,^{17,19-21} have refuted the suggestion of the involvement of low calcium in the pathogenesis of preeclampsia. On the basis of the physiological role of dietary calcium,²² epidemiologic studies have shown that restricted dietary calcium is associated with increased blood pressure. Such finding led to dietary calcium supplementation trials in normotensive and hypertensive populations. For example, Levine et al.²³ in a prospective study in American population showed that calcium supplementation during pregnancy did not prevent preeclampsia in healthy nulliparous women. Recently Alzate et al.²⁴ reported that calcium supplementation during pregnancy did not have preventive effects on preeclampsia. But calcium plus conjugated linoleic acid provided to adolescents was observed to have preventive effect on pre-eclampsia. Although Herrera et al.²⁵ and Hofmeyr et al.²⁶ reported otherwise.

Conclusion

Macro minerals are very essential during pregnancy. This study showed that serum calcium level did not differ significantly between pre-eclamptic and normal pregnant women. It may be concluded that serum calcium have no association in occurrence of pre-eclampsia. However further multicentre study involving large sample needed should be carried out to find the association between pre-eclampsia and serum calcium.

Acknowledgement

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Antimicrobial Resistance Pattern of Uropathogenic *Escherichia coli* and *Klebsiella* species Isolated in a Tertiary Care Hospital of Sylhet

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Abstract

The rapid emergence of antimicrobial resistance in major uropathogens has created a global threat especially in the developing countries. In Bangladesh, prescribers of different regions generally diagnose microbial infection on clinical judgment and select antimicrobial on empirical basis, which unfavorably affects the sensitivity pattern of microbes. The present study was designed to determine the prevalence of antimicrobial resistance of *Escherichia coli* and *Klebsiella* species isolated from patients with UTI in a tertiary care hospital. This was a cross sectional study conducted at Sylhet MAG Osmani Medical College Hospital, Sylhet from 1st January to 31st December 2016. A total of 200 clinically suspected urinary tract infection patients aged 16-85 years were included in this study. The isolated *Escherichia coli* and *Klebsiella* species were tested for antimicrobial susceptibility according to the guideline of Clinical and Laboratory

Standards Institute (CLSI) 2011 using the modified Kirby-Bauer disc diffusion technique. Out of 107 pus cell positive ($\geq 05/\text{HPF}$) urine samples, 75 (70.1%) yielded significant bacteriuria of which 49 (65.3%) were *Escherichia coli* and 9 (12%) were *Klebsiella* species. The isolated *Escherichia coli* showed absolutely high resistance to ampicillin and cefuroxime (100%), moderately high resistance to ceftazidime (81.6%), ciprofloxacin (77.6%), cotrimoxazole (75.5%), cefotaxime (67.4%) and ceftriaxone (59.2%), moderate rate of resistance to amikacin 48.9% and imipenem 46.9% and least rate of resistance to gentamicin (22.5%), nitrofurantoin (22.5%) and netilmicin (6.1%). In addition, *Klebsiella* species revealed completely resistance to ampicillin, cotrimoxazole, cefuroxime, cefotaxime, ceftriaxone, ceftazidime (100%), moderately high resistance to imipenem (88.9%), nitrofurantoin (77.8%), moderate resistance to ciprofloxacin (44.4%), amikacin (33.3%) and gentamicin (33.3%) and least resistance to netilmicin (11.1%). Hence very high resistance rates of 1st line drugs found in uropathogenic *Escherichia coli* & *Klebsiella* species, it is necessary to diagnose clinically followed by culture and sensitivity testing. Regular antibiotic surveillance of a particular geographical area is required to establish reliable information regarding susceptibility pattern of uropathogens in order to preserve the continued usefulness of most antimicrobial agents.

Keywords: Antimicrobial resistance, UTI, *Escherichia coli*, *Klebsiella* species.

Number of Tables: 03

Number of Figures: 02

Number of References: 31

Number of Correspondences: 06

Introduction

Urinary Tract Infections (UTIs) are the second most common bacterial infections after respiratory tract infections that lead patients to seek medical attention. Approximately 10% of humans will have a UTI at some time during their lives. UTIs are also the most common hospital-acquired infection, accounting for as many as 35% of nosocomial infections¹. In Bangladesh, 20-35% females experience at least one episode of UTI in their lives. The prevalence increases among patients from lower socio-economic group^{2,3}.

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Acute infections of the lower urinary tract (urethritis and cystitis) are often considered superficial (or mucosal) infections, while upper tract (acute pyelonephritis, prostatitis, and intrarenal and perinephric abscesses) signify tissue invasion. In microbiological point of view, UTI exists when pathogenic microorganisms are detected in the urine, urethra, bladder, kidney, or prostate. In most cases, growth of $\geq 10^5$ organisms per milliliter from a properly collected midstream "clean-catch" urine sample indicates infection⁴. Typical organisms causing UTI in the community include *Escherichia coli* derived from the gastrointestinal tract (about 75% of infections), *Proteus species*, *Pseudomonas species*, *Streptococci* and *Staphylococcus epidermidis*. In hospital, *Escherichia coli* still predominates, but *Klebsiella* or *Streptococci* are more common⁵.

In present scenario, the rapid emergence of antimicrobial resistance in major uropathogens has created a global threat especially in the developing countries. Moreover, Irrational and indiscriminate use of antibiotics as well as fake and substandard drugs is common in these countries^{6,7,8}. The link between inappropriate use of antimicrobials and development of antimicrobial resistance has been acknowledged in different scientific studies and global proceedings. In Bangladesh, prescribers of different regions generally diagnose microbial infection on clinical judgment and select antimicrobial on empirical basis, which unfavorably affects the sensitivity pattern of microbes. In addition, reluctance of the law makers and regulators to enact law to overcome inadequacy in rules and regulation to control antimicrobial prescribing and dispensing led to worsening of the situation⁹. Thus, updated knowledge of antimicrobial resistance patterns in specific geographical location may aid clinician in choosing the appropriate antimicrobial empirical treatment and development of appropriate drug policies. Therefore, the present study was designed to determine the prevalence of antimicrobial resistance of *Escherichia coli* and *Klebsiella species* isolated from patients with UTI in a tertiary care hospital.

Materials and Methods

Study population

This prospective cross sectional study was carried out in the Department of Microbiology, Sylhet MAG Osmani Medical College, Sylhet from 1st January to 31st December, 2016. A total 200 consecutive urine samples were collected from clinically suspected patients of UTI of different age and sex attending either at the outpatient department (OPD) or admitted in this tertiary care hospital. An informed written consent was taken from patients before collection of their sample. Those with clinical manifestations of UTI but on antibiotics within seven days were excluded.

Collection of specimens

Patients were advised to collect clean-catch midstream urine (CCMU) into a sterile wide mouth container with all aseptic measures (information on how to collect proper sample in sterile container aseptically was given prior to collection). In case of catheterized patients, urine was collected from the catheter by sterile disposable syringe after proper cleaning of the catheter. After proper labeling with patient's name, ID number, collection date and time, the specimens were transported to the laboratory as soon as possible¹⁰.

Direct microscopy

Urine was transferred into a clean and dry 15 ml centrifuge tube and was centrifuged at 1000 rpm for 5 minutes. The supernatant was discarded and one drop of sediment was taken into a clean glass slide, a cover slip was placed over it and then examined for pus cells under light microscope using 10x and 40x objectives. Microscopic demonstration of pus cells ≥ 5 /HPF (high power field) was included as study cases^{10,11}.

Culture and identification of isolates

The well-mixed and noncentrifuged urine samples were inoculated by a wire loop that can deliver 0.004 mL of urine specimen into 5% sheep blood agar and MacConkey agar plates (Himedia, Mumbai, India) by using streak plate method following the standard microbiological procedures. Then, the plates were aerobically incubated at 37°C for 24 hours and examined for the presence or absence of the bacterial growth. Colonies were counted and checked for significant bacteriuria on blood agar. A culture that grew $\geq 10^5$ colony-forming unit (CFU/mL) was considered significant bacteriuria¹¹.

All positive urine cultures showing significant bacteriuria were further tested for their physical characteristics such as colony morphology, odor, swarming, and the presence of hemolysis on their respective media. Then, it was confirmed by the pattern of biochemical reactions using the standard procedures. Thus, Gram-negative rods were identified with the help of a series of biochemical tests such as triple sugar iron agar, indole, simmons citrate agar, oxidase, urease, and motility^{10,11}.

Antimicrobial susceptibility test

Samples which showed significant colony count were taken into consideration and antimicrobial susceptibility pattern of the isolated *Escherichia coli* and *Klebsiella species* was tested using Mueller Hinton agar media by the modified Kirby-Bauer disc diffusion technique¹⁰ as described by Clinical and Laboratory Standards Institute 2011 (CLSI, former NCCLS). As per CLSI guidelines susceptibility was noted as sensitive (S), intermediate sensitive (I) and resistant (R) based on the diameter of

zone of inhibition. The following first and second line antibiotic discs (Himedia, Mumbai, India) were used in the testing: cotrimoxazole (25µg), ampicillin (10µg), gentamicin (15 µg), amikacin (30 µg), ceftazidime (30 µg), cefotaxime (30 µg), ceftriaxone (30 µg), cefuroxime (30 µg), imipenem (10 µg), ciprofloxacin (5 µg), netilmicin (30 µg) and nitrofurantoin (300µg)¹².

Quality control

As per manufacturer's instruction, the discs were stored in refrigerator between temperatures 2-8°C up to date of expiry. Discs from each batch was standardized first by testing against reference strain of *Escherichia coli* ATCC 25922 and *Klebsiella pneumoniae* ATCC 700603 collected from BSMMU, Shahbag, Dhaka.

Data analysis

All Data were processed and analyzed with the help of SPSS (Statistical Package for Social Sciences) Version 23.0. Qualitative data were analyzed by frequency and percentage and comparisons were performed by Pearson's Chi square (χ^2) test. A probability value ($p < 0.05$) was considered statistically significant.

Results

A total 200 cases of clinically suspected UTI patients of different age and sex fulfilling the inclusion criteria either visited the outpatient department (OPD) or admitted in inpatient department (IPD) of Sylhet MAG Osmani Medical College Hospital, Sylhet were studied. Majority of patients belonged to the age group of 16-40 years and most of them were females (Table I).

Table -I: Prevalence of UTI in different age group and gender (n=200).

Age Group	Sex of the Patients			
	Male		Female	
	Number	Percentage	Number	Percentage
16yr-40yr	51	50.5	68	68.7
41yr-65yr	31	30.7	24	24.2
66yr-90yr	19	18.8	7	7.1
Total	101	50.5	99	49.5

In this study, samples with pus cells ≥ 05 /HPF were included as study cases. Out of 107 pus cell positive (≥ 05 /HPF) urine samples, 75 (70.1%) showed significant growth of bacteria of which 36 (78.3%) isolates were from IPD and 39 (63.9%) were from OPD. This result was statistically significant ($p < 0.05$) as shown in the Table II.

Table-II: Distribution of urine samples with or without significant growth.

Urine Culture	IPD	OPD	Total	P-value*
Significant growth	36 (78.3%)	39 (63.9%)	75 (70.1%)	
No growth	10 (21.7%)	22 (36.1%)	32 (29.9%)	.022
Total	46 (100%)	61 (100%)	107 (100%)	

*Pearson's Chi-square test was applied to see the association. Here "P" value < 0.05 was taken as significant.

Among the isolated Gram-negative urinary pathogens *Escherichia coli* was the predominant (65.3%) followed by *Klebsiella species* (12%), *Enterobacter species* (9.3%), *Pseudomonas species* (9.3%) and *Proteus species* (4%) as depicted in the Table III.

Table-III: Frequency of Gram negative bacteria (GNB) isolated in UTI.

GNB isolated	Number of isolates	Percentage
<i>Escherichia coli</i>	49	65.3
<i>Klebsiella species</i>	9	12.0
<i>Enterobacter species</i>	7	9.3
<i>Pseudomonas species</i>	7	9.3
<i>Proteus species</i>	3	4.0
Total	75	100.0

Analysis of the antimicrobial susceptibility test in this study revealed that *Escherichia coli* showed very high rate of resistance to ampicillin and cefuroxime (100%), followed by high resistance to ceftazidime (81.6%), ciprofloxacin (77.6%), cotrimoxazole (75.5%), cefotaxime (67.4%) and ceftriaxone (59.2%). Moderate rate of resistance to amikacin and imipenem was found 48.9% and 46.9% respectively. *Escherichia coli* also showed least rate of resistance to gentamicin (22.5%), nitrofurantoin (22.5%) and netilmicin (6.1%) as shown in Figure 1.

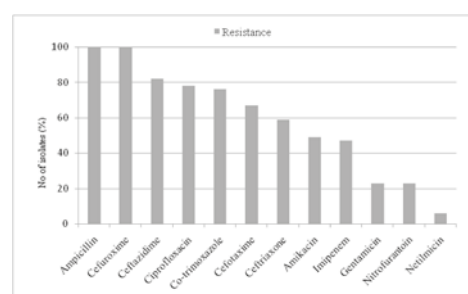


Figure-1: Antimicrobial resistance pattern of *Escherichia coli*.

In addition, the antimicrobial resistance patterns of *Klebsiella species* are shown in figure 2. Very high resistance to ampicillin, cotrimoxazole, cefuroxime, cefotaxime, ceftriaxone, ceftazidime (100%) followed by high resistance to imipenem (88.9%), nitrofurantoin (77.8%) were shown by *Klebsiella species*. Moderate resistance was found to ciprofloxacin (44.4%), amikacin (33.3%) and gentamicin (33.3%) and least resistance to netilmicin (11.1%).

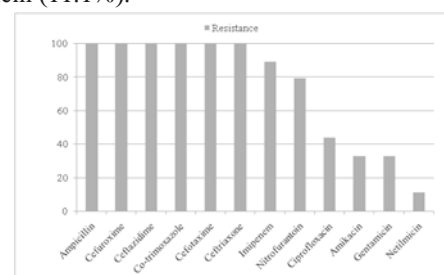


Figure-2: Antimicrobial resistance pattern of *Klebsiella species*.

Discussion

Adequate knowledge by continuous antibiotic surveillance on local antimicrobial resistance pattern of uropathogens is very important for clinicians to select and use the best effective antimicrobial agent for the treatment of UTI patients. The current study described the antimicrobial resistance rates of urinary pathogens especially *Escherichia coli* and *Klebsiella species* which are the predominant microbial agents in community and hospital acquired urinary tract infections respectively.

The age and gender wise data was analyzed in order to assess the frequency of UTI in different age groups. This study showed that females in the reproductive age group of 16-40 years (68.7%) were more prone to UTI than any other groups. This result is in comprehension with other studies^{13,14}. In this study, majority of isolated bacteria were *Escherichia coli* (65.3%) and the second most common was *Klebsiella species* (12%) among the Gram negative bacteria. Similar finding was reported by the other researchers^{15,16}.

The pattern of antimicrobial resistance to microorganism causing UTI varies with time and between geographical areas¹⁷. In the current study, the antimicrobial resistance rate of isolated *Escherichia coli* and *Klebsiella species* was very high to ampicillin, cefuroxime, cotrimoxazole and ciprofloxacin. High resistance to first line drugs found in this study is similar to other studies in developing countries^{13,18}. The observation may be due to wide empirical use, excessive and injudicious use of these drugs because they are relatively cheap and being oral antibiotics easy to administer.

Surprisingly, it was observed that rate of resistance towards cefuroxime in both isolated *Escherichia coli* and *Klebsiella species* was absolutely high. In the year 2015, another study by Haque et al.¹⁹ recorded 78.8% & 63.6% respectively of these urinary isolates resistant to cefuroxime whereas, present study yielded that value about 100% in both isolates. This finding is supported by the study of Davi and Rajkumar²⁰ who showed 94% and 100% of urinary isolates were resistant to cefuroxime respectively. Carelessness misuse of this drug for a long period in our country especially this region would have been thought as the cause of this rapid emergence of absolute cefuroxime resistance.

The prevalence of ciprofloxacin resistance in Bangladesh was 26 per cent²¹. In this study, *Escherichia coli* and *Klebsiella species* showed significantly high resistance to ciprofloxacin (77.6% & 44.4% respectively). These findings are similar to the result of Sarkar et al.²², who found similar resistance pattern (78.9% & 64% respectively). Besides, there are more studies^{23, 24} with similar results indicating high level resistance to ciprofloxacin. This increased resistance might be due to widespread indiscriminate use, their oral route of

administration, easy availability and affordability of ciprofloxacin over the country. So, physicians should prescribe this drug with caution to preserve its effectiveness.

In our setting, we found imipenem had lost its sensitivity (40.7% & 14.3% respectively) in both *Escherichia coli* and *Klebsiella species*. Our result is similar with the works done in Saudi Arabia, India and Iran^{25,26,27} where incidences of carbapenem-hydrolyzing enzymes amongst *Enterobacteriaceae* has been reported. Carbapenems are used to treat life threatening infections caused by MDR bacterial pathogens and antibiotics in this class represent the last line of therapy in treatment options against very serious infections such as those caused by extended spectrum beta-lactamases.

Urinary isolates of *Escherichia coli* of the present study showed low resistance (22.5%) against nitrofurantoin. Although the value was slightly higher compared to Haque et al.¹⁹ (16.1%) but still it remains as most sensitive drug and similar results were also reported from others studies^{28,29,30}. The reason behind this might be due to low use of this drug for long period considering its toxicity and side effects. With sensitivity rate of 74.1% for nitrofurantoin might be the only useful oral antibiotic in the treatment of uncomplicated UTI and prophylaxis in the context of gradually decreasing susceptibility of the most of the comparatively cheaper anti-UTI drugs.

In our setting, netilmicin was the most sensitive antibiotic (resistant rate 6.1% & 11.1% respectively) for both *Escherichia coli* and *Klebsiella species* to treat the UTI patients. As increased amikacin resistance to both the isolates showed in this study by 49% & 33.3% respectively, netilmicin may be an alternative parental drug for the treatment of complicated UTI in the local setting, at least in a tertiary health facility³¹.

Conclusion

Hence very high resistance rates of 1st line drugs found in uropathogenic *Escherichia coli* & *Klebsiella species*, it is necessary to diagnose clinically followed by culture and sensitivity testing; otherwise direct empirical treatment might lead to treatment failure. Regular antibiotic surveillance of a particular geographical area is required to establish reliable information regarding susceptibility pattern of uropathogens in order to preserve the continued usefulness of most antimicrobial agents. However, nitrofurantoin and netilmicin are more sensitive compared to the other antibiotics tested in this study and therefore, these might be the drugs of choice for the treatment of uncomplicated community acquired and complicated hospital-acquired UTIs respectively after culture and sensitivity report available.

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Health Seeking Behavior of Women with Eclampsia Attending at Institute of Child and Mother Health in Dhaka City

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Abstract

Eclampsia constitutes a leading cause of maternal and perinatal mortality and morbidity worldwide. To assess health seeking behaviour of the family members and the patient with eclampsia. This cross sectional study was carried out on 100 eclampsia patients in the Institute of Child and Mother Health (ICMH), Dhaka from December' 2004 to November' 2005. In this study it was found that more vulnerable age group was 19-27 (49.0%) and primae-gravida was 52.0%. This study revealed that knowledge about preconceptional health checkup was 3.0%, antenatal checkup was 52.0%, causes of preeclampsia & eclampsia in pregnancy was 20.0%, plan of delivery was 16.0%, safe hospital delivery was 20.0%, savings of money for delivery was 32.0%, transportation to hospital was 26.0%, consequences of severe preeclampsia & eclampsia was 9.0% of the study population. This study also showed that 82.0% and 77.0% of the patients had negative attitude towards antenatal check up and hospital delivery respectively. Only 58.0% of the patients had antenatal checkup. In this study 58.0% and 42.0% of the patients were referred to hospital by trained birth attendant (TBA) and relatives respectively. Half of the patients were referred by relatives. The present study showed that the maternal death was 4.0% and perinatal death was

27.0%. Lack of proper knowledge about consequences of eclampsia and severe preeclampsia and poor knowledge about proper antenatal care and negative attitude towards hospital delivery affects the outcome of both maternal and fetal condition.

Keywords: Eclampsia, Health Seeking Behavior.

Number of Tables: 05

Number of References: 11

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Introduction

Preeclampsia/Eclampsia is associated with raised blood pressure and proteinuria whereas eclampsia is defined as the occurrence of convulsions usually superimposed on preeclampsia. Geographic, social, economic and racial differences are thought to be responsible for incidence rates up higher in some population^{1,2}.

Preeclampsia/Eclampsia probably accounts for more than 60,000 maternal death worldwide each year^{2,3}. Besides it is associated with fivefold increase in perinatal mortality. The rate of eclampsia is higher in developing countries with the highest rate reported from Colombia as 8.1/1,000 deliveries and the lowest in UK as 4.9/10,000 deliveries. These results imply that preeclampsia and eclampsia constitute a wide public health problem to be dealt with especially in developing countries¹. Eclampsia is a relatively common and serious complication of pregnancy and is the major cause of maternal and perinatal mortality. In Bangladesh eclampsia contributes to 16.0% of maternal mortality and about 4,500 women die due to eclampsia in each year^{4,5}.

Lack of knowledge, regarding preconceptional health check up, antenatal care and proper intrapartum care had a significant impact on maternal morbidity and mortality. There is still no positive attitude of the family members and woman herself towards the proper care and appropriate management during delivery and also postnatal follow-up. Mothers are also victimized during convulsion in pregnancy, labour or postnatal period. All mothers are not properly under adequate antenatal and postnatal health check up. Some of them were treated by 'jharphuk' and 'panipara' also during the time of convulsion. These harassment increase the morbidity and mortality of both mother and fetus also.

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The above aspects of eclampsia patients are not focused with importance in any of the previous studies in Bangladesh. Bad communication, absence of nearly hospital facilities, delay in decision making, various superstition are also adding to the problems and deterioration of maternal condition and hypoxia and acidosis of fetus. The result is high maternal and perinatal mortality and morbidity.

The aim of this study was to assess health seeking behaviour of the family members and patient herself suffering from eclampsia.

Materials and Methods

This cross sectional descriptive study was carried out in the Institute of Child and Mother Health (ICMH) at Dhaka City over a period of 12 months from 1st December' 2004 to 30th November' 2005. Consecutive 100 eclampsia cases were selected purposively after fulfillment of selection criteria. All antenatal, intranatal and postnatal eclampsia cases were included in this study. Hysteria, epilepsy and tetanus cases were excluded.

Results

In this study it was found that more vulnerable age group was 19-27 (49.0%) and 35.0% of the study population had age between 14 and 18 years. More than half of the patients were illiterate and 89.0% of the patients were housewife (Table I).

Table-I: Demographic profile of the patients (n=100).

	Frequency	Percentage (%)
Age (years)		
14-18	35	35
19-27	49	49
28-36	12	12
37-45	4	4
Level of education		
Illiterate	56	56
Primary	22	22
Secondary	18	18
Higher secondary	3	3
Graduate	1	1
Occupation		
House wife	89	89
Domestic helper	4	4
Service holder	5	5
Others	2	2
Monthly family income		
< 3000	88	88
3001-5000	8	8
> 5000	4	4

In this study primae gravida was 52.0%, multipara was 34.0% and grand multipara was 14.0% (Table II).

Table-II: Distribution of the patients by parity.

Parity	Frequency	Percentage (%)
Primi	52	52%
Gravida 2-4	34	34%
Gravida 5-8	14	14%

This study showed that only 3.0% of the study population had knowledge about pre conceptional health check up, 52.0% had antenatal check up, 20.0% had knowledge about preeclampsia and eclampsia in pregnancy, 16.0% had knowledge about plan of delivery, 20.0% had knowledge about safe hospital delivery, 32.0% had knowledge about savings of money for delivery, 16.0% had knowledge about transportation to hospital and only 9.0% had knowledge about consequences of severe preeclampsia and eclampsia (Table III).

Table-III: Distribution of the patients by knowledge about the pre-conceptional health check up.

Knowledge about	Frequency	Percentage (%)
Pre-conceptional health check up	3	3.0
Antenatal check up	52	52.0
Causes of eclampsia and preeclampsia	20	20.0
Plan of delivery	16	16.0
Safety of hospital delivery	20	20.0
Savings of some money for delivery	32	32.0
Transportation to hospital	26	26.0
Consequences of eclampsia and severe pre-eclampsia	9	9.0

This study also showed that 82.0% and 77.0% of the patients had negative attitude towards antenatal check up and hospital delivery respectively (Table IV).

Table-IV: Distribution of the patients by attitude towards regular antenatal check up.

Attitude towards	Frequency	Percentage (%)
Antenatal check up		
Yes	18	18.0
No/irregular	82	82.0
Hospital delivery		
Positive	23	23.0
Negative	77	77.0

Only 58.0% of the patients were under antenatal checkup in this study and 58% & 42% of the patients were referred to hospital by trained birth attendant (TBA) and relatives respectively. Forty eight percent of study population took drugs, 12.0% had done jhar phuk and 40.0% took panipara as anticonvulsant at home. Various prejudices still prevail in our population which affects their health status adversely. Half of the patients were referred by relatives and others were by other health workers to transfer hospital. Thirty eight percent of the patients reached to the hospital within ½-2 hours of convulsion and 47.0% within 2-4 hours of convulsion. The present study showed that the maternal death was 4.0% and perinatal death was 27.0% (Table V).

Table-V: Distribution of patients by practice of family members and patient herself.

	Frequency	Percentage (%)
Antenatal care		
No check up	42	42
Irregular/regular checkup	58	58
Decision taken by for proper management		
TBA	58	58
Mother in law	24	24
Mother	6	6
Husband	12	12
Types of measure to control convulsion		
Drug	48	48
Jharphuk	12	12
Pani pora/other measure	40	40
Decision maker for referral to hospital		
Relatives	49	49
TBA	40	40
FWV	5	5
Nurse	4	4
Doctor	2	2
Time Interval onset of convulsion and arrival to hospital		
Within ½ - 2 hrs.	38	38
Within 2-4 hrs.	47	47
Within 4-8 hrs.	7	7
Within 8-12 hrs.	8	8

Discussion

Eclampsia constitutes a leading cause of maternal and perinatal mortality and morbidity worldwide. In this study, It was found that more vulnerable age group was 19-27 (49%) and 35% of study population had the age group of 14-18 years. Sultana et al.⁶ revealed 25-34 years age group as the most vulnerable. In Khanom's study 55.8% of eclamptic patients were below the age of 20 years and 63.7% of the patients were primigravidae⁷.

Generally eclampsia is seen in primipara. This statement is consistent with the present study where primae-gravida were 52%, 34% were multipara and 14% were grand multipara. Maximum cases were seen in primigravida and multi gravida in the study of Sultana et al.⁶. In Khanom's study 63.7% of the patients were primigravidae⁷.

Similar to Khanam et al. study most of the patients were either illiterate or got primary education⁷. Level of education has a significant influence on the antenatal care. In present study 89% of the patients were housewife. But in a study Chowdhury et al. showed 97.8% of study population were housewife⁸. This is why women cannot enable to take decision to seek care of her own health and also due to low status of her family.

This study showed that only 3.0% of the study population had knowledge about pre conceptional health check up, 52.0% had antenatal check up, 20.0% had knowledge about preeclampsia and eclampsia in pregnancy, 16.0% had knowledge about plan of delivery, 20.0% had knowledge about safe hospital delivery, 32.0% had knowledge about savings of money for delivery, 16.0% had knowledge about transportation to hospital and only

9.0% had knowledge about consequences of severe preeclampsia and eclampsia. This study also showed that 82% and 77% of the patients had negative attitude towards antenatal check up and hospital delivery respectively.

Only 58% of the patients were under antenatal checkup which was revealed in this study. Whereas in Khanam's study only 24.0% patients had regular antenatal check up, while 75.95% patients had no or infrequent check up⁷. So the present study reflected a little change of attitude and awareness in general population.

In this study 58% and 42% of the patients were referred to hospital by taking decisions by trained birth attendant (TBA) and relatives respectively. 48% of study population took drugs, 12% had done jhar phuk and 40% took panipara as anticonvulsant at home. Various prejudices still prevail in our population which affects their health status adversely. 49% of the patients were referred by relatives and others were by other health workers. A study showed that decision makers in women during obstetrics emergency were husband 48.6% and husband wife together 38.5%⁹. 38% of study population came within ½-2 hours of convulsion and 47% came within 2-4 hours.

The present study showed that the maternal death was 4% and perinatal death was 27%. A study of Lee et al.⁹ showed no maternal death, but the rate of major maternal complication was 32%, perinatal mortality was 6.4% and the rate of severe perinatal complication (severe birth asphyxia, stillbirth etc) was 56%. Another study of Vigil-De Gracia showed maternal death rate 6.8%¹⁰. A study done at India (17 years of study period) showed maternal death rate due to eclampsia was 61 in 69 maternal death¹¹.

Conclusion

So this study shows that lack of proper knowledge about consequences of eclampsia and severe preeclampsia of the family members and patient herself and poor knowledge about proper antenatal care and negative attitude towards hospital delivery affects the outcome of both maternal and fetal condition of eclampsia patients.

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Outcome of Laparoscopic Transperitoneal Ureterolithotomy for Proximal Ureteric Stones - Our Two Years Experiences

Haque MN¹, Hossan MM², Islam MS³, Mohammad A⁴

Abstract

To evaluate the results of laparoscopic transperitoneal ureterolithotomy for management of large proximal ureteric stones. This study was performed on 24 patients having proximal ureteric stone greater than 1.5cm at the Department of Urology, Shahid Sheik Abu Naser Specialized Hospital, Khulna, Bangladesh from January 2016 to December 2017. Patients having stone size less than 1.5cm, previous abdominal surgery and sepsis were excluded from this study. Patients characteristics, stone characteristics, perioperative and follow-up data were studied. Twenty-four patients (mean age=52.9±12 years) with large upper ureteric stones (mean stone diameter=35±12) were included. Twenty-two patients had single stone and 2 patients had two stones. Mean operative time was 107±49.5 min with mean blood loss of 60.5±19.2 cc. Mean total pain score was 38.4±5.5 (100 point scale) and mean time resuming oral intake was 7.2±1 h. Mean duration of hospital stay was 2.6±1.4 days and mean time of stenting was 7.2±2 weeks. Throughout a mean duration of follow-up of 10.8±6.6 months 100% stone clearance rate was achieved with no recurrence. Laparoscopic transperitoneal ureterolithotomy is a safe and effective approach for selected patients with large

proximal ureteric stones with reduced postoperative pain short hospital stays and cost effective and should be considered as a choice of treatment option for such stones.

Keywords: Laparoscopy, Stone, Ureterolithotomy.

Number of Table: 01

Number of Correspondences: 04

Number of References: 14

Introduction

The treatment of urinary lithiasis has been revolutionized during the last three decades. Minimally invasive therapies in the form of endoscopic surgery in conjunction with the advent of shock wave lithotripsy have diminished the role of open stone surgery¹.

Laparoscopic surgery provides a higher degree of patient satisfaction than open surgery from a cosmetic perspective. It is also effective in reducing postoperative pain, operative wound complications, blood loss, and the length of hospital stay. Accordingly, it has been remarkably developed in the field of urology over the past 20 years. Laparoscopy as a minimally invasive treatment is continuously gaining place in the treatment of urinary stones, mainly replacing open surgery².

Skolarikos et al.³ have tried to identify the level of evidence and grade of recommendation supporting the laparoscopic approach of stone extraction. The highest level of evidence was found for laparoscopic ureterolithotomy. It is technically feasible and having lower postoperative morbidity compared to open ureterolithotomy. It is mostly recommended for large impacted stones or when endoscopic ureterolithotripsy or shock wave lithotripsy have failed.

The present prospective study aimed to evaluate the results of laparoscopic transperitoneal ureterolithotomy for management of large proximal ureteric stones.

Materials and Methods

This study was carried out at the Department of Urology, Shahid Sheik Abu Naser Specialized Hospital, Khulna, Bangladesh from January 2016 to December 2017 on patients having large (≥ 1.5 cm) proximal ureteral stones. Patients with stones < 1.5 cm in size, previous transperitoneal surgical procedure or follow-up duration < 3 months were excluded from the study.

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The studied characteristics included patient's age, sex, stone (size and number) and past history of stone surgeries. Collected operative data included type of anesthesia applied, operative time, mean amount of intra operative blood loss and the frequency of conversion to open surgery. Postoperative data included postoperative pain severity judged using 100-point pain visual analogue scale (VAS) with 0 = no pain and 100 = the worst intolerable pain, time till resumption of oral intake and duration of hospital stay. Follow-up data included duration of follow-up, stone recurrence, ureteral stricture formation and other complications.

After induction of anesthesia, patients were in flank position with no flexion of the operating table. The procedure was performed through 3 ports, a 10 mm camera trocar inserted 2 finger breadth lateral and superior to the umbilicus and 2 additional 5 mm working ports inserted a handbreadth superior and inferior to the camera port. A fourth 5 mm trocar is occasionally used for liver retraction in right-sided cases. After reflection of the colon, the ureter was identified and stone was located and extracted through a vertical ureterotomy. A 6F DJ stent was then inserted and the ureterotomy is closed with 4/0 Vicryl sutures. Using a 5 mm scope, the stone is extracted in a sac through the 10 mm port and then a small drain is inserted via the other 5 mm port.

Results

Twenty-four patients fulfilled the inclusion criteria (16 males and 8 females) with mean age of 52.9 ± 12 (range 26-64) years. The mean stone largest diameter was 35 ± 12 (range 18-62) mm. Fifteen patients had left-sided and 9 had right-sided ureteral stones. Twenty-two patients had solitary stone and 2 patients had two stones. Stone clearance was achieved in 100% of patients.

Operative data are shown in Table-I. All procedures were completed uneventfully without any intraoperative complications or the need for open conversion.

Table-I: The characteristics before, during and after treatment of laparoscopic transperitoneal ureterolithomy

Data	Findings
No of patients	24
Sex (M:F)	16:8
Age (year)	52.9 ± 12 (26-64)
Stone size (mm)	35 ± 12 (18-62)
Anesthesia (General)	24(100%)
Open conversion rate	0
Operative time (min)	107 ± 49.5 (70-250)
Intra operative blood loss (ml)	60.5 ± 19.2 (35-90)
Pain VAS Score	38.4 ± 5.5 (30-45)
Hospital stay (day)	2.6 ± 1.4 (2-5)

Mean total pain VAS score at the time of first request of postoperative analgesia was 38.4 ± 5.5 ; range: 30-45 and was significantly ($P < 0.05$) lower Table I.

Only two patients had paralytic ileus, while the other 22 patients resumed oral intake after a mean duration of 7.2 ± 1 (range: 6-8 h). Mean duration of hospital stay was 2.6 ± 1.4 ; range: 2-5 days and duration of stenting was 7.3 ± 2 ; range: 4-10 weeks. Throughout a mean duration of follow-up of 10.8 ± 6.6 ; range: 3-24 months and all patients remained stone free.

Discussion

All enrolled patients had laparoscopic ureterolithotomy through the transperitoneal approach, a finding that confirms the established experience of the working team with this approach rather than retroperitoneal approach, which is more familiar to the urologists throughout their experience in open surgery. The transperitoneal approach offers more working space and better identification of anatomical landmarks Henkel et al.⁴ However, previous abdominal surgery with the possibility of intraperitoneal adhesions could be a limiting factor; such a limitation was avoided in the current study, where patients with past history of abdominal or pelvic surgeries were excluded.

The favorable surgical outcome depends on combined proper patient selection and surgical experience. In line with this, the mean operative time was about 107 min within a range of 70-250 min. Our operative time was superior to that reported by Huri et al.⁵ who reported a mean operative time of 124 min; this extended operative time could be attributed to the larger number of cases operated using the retroperitoneal approach. In support of this assumption, Simforoosh et al.⁶ compared extraperitoneal versus intraperitoneal approach for laparoscopic proximal ureterolithotomy and reported that operative time was different significantly in favor of the intraperitoneal approach.

Moreover, the procedure was associated with minimal intraoperative bleeding with a mean blood loss of 60 ml and this goes in hand with El-Feel et al.⁷ and Kongcharonsombath et al.⁸ who reported that estimated blood loss during intraperitoneal laparoscopic ureterolithotomy was 62 and 51 cc, respectively.

All patients had low pain VAS scores and this could be attributed to minimal dissection and minimization of wound-related pain. The lower pain scores and the decreased consumption of postoperative narcotics allowed early ambulation and resumption of oral intake and spared the narcotic-related side effects, especially nausea and vomiting. These data go in hand with the conclusion provided by Almeida et al.⁹ who documented that comparison of laparoscopic and open ureterolithotomy proved that laparoscopy offered significant advantages over traditional open ureterolithotomy, resulting in improved analgesia and shorter hospital stays, but with similar complication rates.

All patients were discharged stone-free without stone recurrence throughout follow-up period. These data indicate the efficacy and safety of laparoscopic transperitoneal approach. In support of that, Basiri et al.¹⁰ compared three surgical options for the management of urinary stones in the upper ureter, namely, retrograde ureteroscopic lithotripsy using a semirigid ureteroscope, transperitoneal laparoscopic ureterolithotomy and percutaneous nephrolithotripsy and reported stone-free rates at discharge and 3 weeks later of 56%, 88%, and 64% and 76%, 90%, and 86%, for the three procedures, respectively. El-Moula et al.¹¹ indicated that laparoscopic ureterolithotomy was successful in 94.6% of cases and Matias et al.¹² reported the global rate of stone free was 91%. Khaladkar et al.¹³ reported stone clearance rate of 39.1% with ESWL, 79.2% with ureteroscopic pneumatic lithotripsy and 100% with the laparoscopic method, with a statistically significant difference in favor of laparoscopic methods.

Our reported mean duration of hospital stay of 2.6 ± 1.4 days was superior to that previously reported by El-Feel et al.⁷ and Abolyoser¹⁴ who reported a mean hospital stay of 4.1 and 3.8 days, respectively, despite the absence of intraoperative or postoperative complication, but was in line with Matias et al.¹² who reported a mean hospital stay duration of 3.3 days.

Conclusion

Laparoscopic transperitoneal ureterolithotomy is safe and effective approach for selected patients with large proximal ureteric stones with reduced postoperative pain, short hospital stay and maximum stone clearance rate and should be considered as a choice of treatment option for such stones.

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Correlation between Body Mass Index and Fasting Blood Glucose Level in a Selected Group of Teenagers in Bangladesh

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Abstract

The trend of increasing overweight and obesity is not related to genetic factors only; rather majority of this burden is attributable to the environmental factors. The aim of the study was to observe the correlation between body mass index (BMI) and fasting blood glucose (FBG) level in a selected group of teenagers of Bangladesh. A cross sectional study was conducted involving 39 male and 41 female MBBS students of Faridpur Medical College during 06-04-2014 to 22-05-2014 by purposive sampling. Data were collected using a questionnaire & check list. Out of 80 students 48.8% male, 51.2% female, 12.5% underweight, 67.5% normal, 16.2% overweight & 3.8% was obese. Mean age of the students was 18.99, BMI 21.99, SBP 121.12, DBP 79.19 and FBG 4.53. Most of students were normotensive (SBP 88.8%; DBP 96.2%) & a few students (SBP 8.8% & DBP 3.8%) were hypertensive.

Majority of students (66.2%) were normoglycemic and rest of the students were hypoglycemic. Correlation between BMI and FBG ($P=0.65$) was not significant but correlation between BMI and systolic blood pressure (SBP) ($p<0.0001$); BMI & diastolic blood pressure (DBP) ($p<0.05$) was significant. Comparison of SBP between male and female students showed ($p<0.001$) was significant. BP and family history of hypertension showed ($\chi^2=5.85$), $p=0.05$ level of significance. BMI and FBG showed no significant correlation. BMI and BP showed positive correlation. Male has higher BP than female. Students with family history of hypertension are prone to develop hypertension.

Keywords: Body Mass Index, Fasting Blood Glucose, Teenagers, Bangladesh.

Number of Tables: 06

Number of References: 14

Number of Correspondences: 06

Introduction

The world health organization (WHO) regards a BMI of less than 18.5 as underweight and may indicate malnutrition, an eating disorder, or other health problems, while a BMI greater than 25 is considered over weight and more than 30 is considered as obese¹. The trend of increasing overweight and obesity cannot be attributed to the genetic factors only; rather majority of this burden is attributable to the environmental factors, the "Obesogenic environment"². This implies a massive chronic disease burden, resulting in an economic burden in the next 10 to 20 years if nothing is done to prevent it. In low income countries the people from the high socioeconomic status and urban areas are more likely to be obese³.

In recent times, there have been a lot of critical biochemical investigations into the inter-relationship between body mass index (BMI) and blood pressure⁴. It is not unexpected for increase in blood glucose to induce increase in BMI; as increase in blood glucose level have associated with increase in lipid biosynthesis (lipogenesis) and hence, an increase in weight⁵. A strong correlation has been established between a high BMI and the

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development of type-2 diabetes mellitus from a study of more than 7000 British men (mean follow up of 12 years)⁶. It is therefore, expected that BMI should correlate with blood glucose levels but this is not however always the case because a Scottish study has shown no significant statistical correlation between the random blood sugar level and Body Mass Index (BMI)⁷.

Rasul et. al. found the prevalence of overweight and obesity among the medical students was 27.16% (Male 39% and female 22%). 58% of the respondents had positive family history of overweight/obesity and around 70% of them had positive family history of Type 2 Diabetes and Hypertension⁸. Gopalakrishnan et. al. found that overweight was encountered for 15.9% of the total (18.3% in male and 13.8%) study subjects and they also showed that 5.2% of study subjects were obese, 14.8% were found to be underweight (12.2% in male and 17.0% in female)⁹. Chaudhry et. al. found that the prevalence of overweight was 8.2% and that of obesity was 2.4%. Overall 18.6% of males and 7.4% of females were found to be overweight or obese¹⁰. It is expected that BMI should correlate with blood glucose levels but this is not always proved because Lohitashwa et. al. & Erasmus et. al. has shown no significant statistical correlation between the blood sugar level and body mass index (BMI)^{11,12}.

There is no sufficient data about overweight and obesity and its correlation with blood glucose level among teenage population especially medical students in public medical colleges of Bangladesh. So far our knowledge goes there is no such study showing correlation between overweight, obesity and Fasting blood glucose level in a selected teenage population like medical students of Bangladesh. So assessment of correlation between BMI and FBG in young generation of our country especially medical students will provide valuable information's about health status of future health service providers of Bangladesh.

Materials and Methods

A descriptive cross sectional observational study was conducted from 06-04-2014 to 22-05-2014 in the Department of Biochemistry, Faridpur Medical College, Faridpur. To obtain the selected group of teen agers, 1st year (F-23, session 2013- 2014) MBBS students of Faridpur Medical College, Faridpur was taken as sample. Calculated sample size was 233. Number of 1st year MBBS student in Faridpur Medical College was 113. Due to limited time, 80 students (male 39, female 41) were taken as sample purposively. All students of 1st year (F-23, session 2013- 2014) MBBS students of Faridpur Medical College, Faridpur willing to be volunteers of the study was included. Students taking steroid and seriously ill students due to any disease were excluded.

BMI 18.5-24.99 was considered as normal, 25.00 - 29.99 was considered as overweight, 30 - 39.99 was considered as obese. SBP <100 mm of Hg was considered as low, 100 - 139 mm

of Hg was considered as normal & >139 mm of Hg was considered as hypertensive. DBP <60 mm of Hg was considered as low, 60 - 89 mm of Hg was considered as normal & >89 mm of Hg was considered as hypertensive. FBG <4.4 mmol/L was considered as low, 4.4-6.0 mmol/L was considered as normal & >6.1 was considered as high Data were collected in a questionnaire & check list. FBG was estimated by semi-automated analyzer- Evolution 3000.

The questionnaire was pre-tested before finalization. Data were collected after giving ethical clearance from the ethical review committee of Faridpur Medical College, Faridpur. Data was checked and edited, if needed. Statistical analysis was done by using SPSS (version 16.0 for windows). Mean value of the findings were compared between sexes by unpaired students, t test. Categorical variables were analyzed by χ^2 test. Correlation between variables was determined by Pearson's correlation coefficient test. For all the statistical analysis, 2- tailed p value < 0.05 was considered as level of significant.

Results

Mean age of the students was 18.99 ± 0.75 , BMI was 21.99 ± 3.55 , SBP was 121.12 ± 9.74 , DBP was 79.19 ± 7.79 , and FBG was 4.53 ± 0.54 . Out of 80 students 48.8% was male, 51.2% was female, 12.5% was under weight, 67.5% was normal, 16.2% was overweight & 3.8% was obese. Majority of students were normotensive (SBP 88.8%, DBP 96.2%) & few students (SBP 8.8% & DBP 3.8%) were hypertensive. Majority of students (66.2%) were normoglycemic and rest of the students were hypoglycemic, no students were hyperglycemic. Distribution of students showed no significant difference between sex & BMI; between sex & FBG. Distribution of students showed significant difference between sex & BP (SBP; $p = 0.001$ & DBP; $p = 0.06$). Significant difference ($\chi^2 = 5.85$; $p = 0.05$) between BP and family history of hypertension. Showed highly significant positive correlation ($p = 0.000$) between BMI and SBP of students. Showed significant positive correlation ($p = 0.04$) between BMI and DBP of students showed no significant correlation between BMI and FBG of students.

Table-I: Characteristics of the students by sex and category.

Variables	Mean $\pm$ SD	Category	No. of student	Frequency
Sex		Male	39	(48.8)
		Female	41	(51.2)
Age	Male			
	19.08 $\pm$ 0.77			
	Female			
	18.90 $\pm$ 0.73			
	Total			
	18.99 $\pm$ 0.75			
BMI	Male	Under wt.	10	(12.5)
	22.12 $\pm$ 3.22	Normal	54	(67.5)
	Female	Over wt.	13	(16.2)
	21.88 $\pm$ 3.88	Obese	3	(3.8)
	Total			
	21.99 $\pm$ 3.55			

SBP	Male	Low	1	(1.2)
	124.74±9.59	Normal	72	(88.8)
	Female	High	7	(8.8)
	117.68±8.66			
	Total			
DBP	Male	Low	1	(1.2)
	80.90±8.02	Normal	76	(96.2)
	Female	High	3	(3.8)
	7.56±7.67			
	Total			
FBG	Male	Low	27	(33.8)
	4.61±0.47	Normal	53	(66.2)
	Female			
	4.46±0.60			
	Total			
	4.53±0.54			
	Total		80	(100)

Table-II: Distribution of students by sex.

Variables	Sex	Frequency	Mean±SD	T value	P value
BMI	Male	39(48.8%)	22.12±3.22	0.304	
	Female	41(51.2)	21.88±3.88		0.76 ^{ns}
FBG	Male	39(48.8%)	4.61±0.47		
	Female	41(51.2)	4.46±0.60	1.23	0.22 ^{ns}
SBP	Male	39(48.8%)	80.90±8.02		0.001 ^{**}
	Female	41(51.2)	77.56±7.67	3.45	
DBP	Male	39(48.8%)	80.90±8.02		
	Female	41(51.2)	77.56±7.67	1.87	0.06 ^{ns}

ns = Not significant. **= significant

Table-III: Comparison of BP of students with and without a Family History of hypertension.

BP category				Total Frequency	X ² value	P value
Family H/O						
HTN	Low:(SBP<100 or DBP<60)	Normal(SBP: 100-139 or DBP: 60-89)	High:(SBP: 140 or above or DBP:90 or above)	Frequency		
	Present	0(0%)	33(41.2%)	7(8.8%)	40(50%)	
	Absent	1(1.2%)	38(47.5%)	1(1.2%)	40(50%)	5.85
Total				1(1.2%)	71(88.8%)	8(10.0%)

ns = Not significant

Table-IV: Correlation between BMI and SBP of students.

Variables	N	R	P
BMI	80		
SBP	80	0.382	0.000 ^{***}

***=significant at 0.0001 level

Table-V: Correlation between BMI and DBP of students.

Variables	N	r value	P
BMI	80		
DBP	80	0.227	0.04 [*]

*=significant at 0.05 level

Table-VI: Correlation between BMI & FBG of the students.

Variables	N	r- value	p value
BMI	80		
FBG	80	-0.18	0.65 ^{ns}

ns = Not significant

Discussion

Obesity is a global problem affecting both the developed and developing countries. It is a leading preventable cause of morbidity and mortality associated with non-communicable disease. World health organization (WHO) showed mean BMI 20.32, male 21.00 and female 19.63 in 2011 in Bangladesh.

In the present study, age (Mean±SD) of the students was 18.99±0.75 (years), BMI (Mean±SD) was 21.99±3.55 (Kg/m²), SBP (Mean±SD) was 121.12±9.74 (mm of Hg), DBP (Mean±SD) was 79.19±7.79 (mm of Hg), and FBG (Mean±SD) was 4.53±0.54 (mmol/L). Out of 80 students, 48.8% was male, 51.2% was female, 12.5% was under weight, 67.5% was normal weight, 16.2% was overweight & 3.8% was obese. Most of the students were normotensive (SBP 88.8%; DBP 96.2%) & few students (SBP 8.8% & DBP 3.8%) were hypertensive. Majority of students (66.2%) were normoglycemic and rest of the students were hypoglycemic. None students were hyperglycemic.

Comparison ($\chi^2=0.23$; $p=0.97$) and correlation ($r=-0.18$, $p=0.65$) between BMI & FBG showed no significant difference or correlation. No significant difference was found in BMI between sexes ($\chi^2=1.06$; $p=0.79$). No significant difference was found between BMI & BP ($\chi^2=4.42$; $p=0.62$) of the students. There was no statistical significant difference between BP and family history of hypertension ($\chi^2=5.85$; $p=0.05$) but may be significant in near future. Distribution of SBP shows significant difference between male & female ($t=3.45$; $p=0.001$). Though DBP did not show significant difference between male & female ($t=1.87$; $p=0.06$) which may be significant in future. Significant positive correlation ($p=0.000$) between BMI and SBP of students was found. Also significant positive correlation was found between BMI and DBP of students ($p=0.04$).

World Health Organization (2011) showed mean (total) BMI 20.32, male 21.00 and female 19.63 in Bangladesh. In this study mean BMI was 21.99, male 22.12 and female was 21.88 which is near to WHO finding.

Study conducted by Rasul et. al. found 27. 16% (Male 39% and female 22%) was overweight & obese, 58% of the respondents had positive family history of overweight/obesity and around 70% of them had positive family history of Type 2 Diabetes and Hypertension. Similar type of study conducted by Gopalakrishnan et. al. found 14.8% respondent were underweight (12.2% in male and 17.0% in female), 15.9% (18.3% in male and 13.8%) was overweight and 5.2% of study subjects were obese. Chaudhry et. al. found 8.2% medical students were overweight and that of obesity was 2.4%. Overall 18.6% of males and 7.4% of females were found to be overweight or obese and Lohitashwa et. al. found obese I in 17.7% of subjects and obese II was in 6.7% of subjects. The present study showed 12.5% of students was under weight, 67.5% was normal, 16.2% was overweight & 3.8% was obese. This study also showed 50% students have positive family

history of hypertension & 38.8% students have positive family history of DM. So the findings of this study are somewhat similar to other study mentioned above.

No significant difference ($\chi^2=0.23$; $p=0.97$) was found between BMI and FBG of the students. It is expected that BMI should correlate with blood glucose levels but this is not always proved because Lohitashwa et. al. & Erasmus et. al. has shown no significant statistical correlation between the blood sugar level and body mass index (BMI). So this study is in the line of other study.

Distribution SBP shows significant difference between male & female ($t= 3.45$; $p =0.001$). Highly significant positive correlation ($p=0.000$) between BMI and SBP of students. Significant positive correlation ($p=0.04$) between BMI and DBP of students was found which is agreed with Ravisankar et. al. & Adediran et. al.^{13,14}.

Conclusion

BMI and FBG of students showed no significant correlation. BMI and BP showed positive correlation. Male has higher BP than female. Students with family history of hypertension are prone to develop hypertension.

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Granulomatous Mastitis: Unusual Presentation and Management, Experience at Birdem General Hospital

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Abstract

Tuberculosis of breast is an unusual presentation of extrapulmonary tuberculosis. It occurs mostly in women who are of reproductive age group, multiparous and lactating. Common presentation is tumor like but patients of our study group mostly presented with abscess and mastitis. This study was carried out at BIRDEM GENERAL HOSPITAL, ShegunBagicha, Dhaka. Retrospective data of 9 patients with breast tuberculosis was analyzed. Information about demographic details, clinical presentation, cytology, histopathology, comorbidity and management was taken into account. Out of 1202 patients who presented with breast problem during the study period only 9 (0.75%) suffered from tuberculosis of breast. Their age ranged from 20 to 55 years. All patients except 2 presented with abscess formation, 1 with lump and 1 with multiple sinuses. All patients were subjected to histopathology. Their pathological examination showed chronic granulomatous inflammation with caseous necrosis and langerhans giant cells suggestive of tuberculosis. All 9 patients were treated with Anti TB drug therapy after adequate surgical intervention when required. The rare entity tubercular mastitis is a disease of relatively younger age group. Though the usual presentation is tumor like, the patients of the study group mainly presented with abscess formation. Diabetes might be a contributing factor for the unusual presentation among the patients of my study group.

Number of Table: 01

Number of References: 13

Number of Correspondences: 02

Keywords: Breast Abscess, Granulomatous Mastitis, Breast Tuberculosis.

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Introduction

Tuberculosis is an age old disease but continues to be a major health hazard along with new diseases like AIDS. It is among top 10 infectious causes of global mortality¹. Despite high prevalence of tuberculosis breast tuberculosis is a rare form of tuberculosis. Mammary cells offer great resistance to survival and multiplication of mycobacterium tuberculosis². This is due to the fact that, like skeletal muscle and spleen, it provides infertile environment for the survival and multiplication of tubercular bacilli³. Thus tuberculosis of breast is an extremely rare disease even in countries where the incidence of pulmonary tuberculosis is high³. Sir Astley Cooper was the one who reported the first case of mammary tuberculosis in 1829 and named it "scrofulous swelling of bosom", since then there are off and on few cases reported in the literatures⁴. The incidence of breast tuberculosis varies from 0.1%-3% of all breast diseases⁵. The significance of breast tuberculosis lies in its rarity of occurrence and conflict in diagnosis with breast cancer, acute granulomatous mastitis or pyogenic abscess. Diagnosis is based on typical histological features or the finding of tubercular bacilli under microscope. Antitubercular treatment with or without surgical intervention is the mainstay of treatment.

Matirials and Methods

The study was done at BIRDEM GENERAL HOSPITAL-2, Shegunbagicha, Dhaka, Bangladesh. It is a retrospective analysis of data of 1202 diabetic patients attending the breast clinic with various breast problems namely (1) benign or malignant breast lump, (2) abscess formation (3) mastitis. Study period was from March 2015 till March 2018. Of all cases presenting to the breast clinic only cases with tuberculosis of breast were taken into account. The source of information was the record sheets of the selected patients. From the record sheet clinical sign symptoms, method of diagnosis and treatment and outcome were noted.

Results

Nine breast TB cases were treated at BIRDEM 2 Hospital in the period of 3 years. All 9 (100%) patients were confirmed histopathologically as tubercular mastitis. All 9 (100%) patients were non-lactating diabetic females. Thier age were from 20 to 55. Among them 6 (66.67%) were between the age group of 20-40 years. 3 (33.33%) of them

were of age between 45-55 years. Of all patients 7 (77.78%) presented with abscess and mastitis except 1 (11.11%) patient who presented with lump formation and 1 (11.11%) presented with lump formation with multiple sinuses. All patients had unilateral presentation. 3 (33.33%) were right sided and 6 (66.66%) were left sided. 7 (77.78%) patients were treated with incision and drainage of abscess and excision biopsy. Surgery was followed by four drug antitubercular therapy for 6-9 months. In All patients' tuberculosis of other sites were excluded. Only one patient who presented with lump formation had suffered from intestinal tuberculosis 4 years prior which was treated accordingly and adequately. All patients were followed up clinically and ultrasonologically and with CRP and CBC monthly.

All patients completed the medical treatment without complications. All patients improved clinically and ultrasonographic evidence showed absence of inflammatory lesion after successful antitubercular drug therapy. Patients had undergone long time dressing. 3 (33.33%) patients required incision drainage of abscess more than once. Antitubercular drug was continued for 6 to 9 months.

Table I: Type of breast tuberculosis, clinical presentations, side, site and investigations.

Variables		Number	%
Side	Right	3	33.33
	Left	6	66.67
Type	Primary	9	100
	Secondary	0	0
Clinical presentation	Mastitis with abscess	7	77.78
	Lump alone	1	11.11
	Swelling and sinus formation	1	11.11
Investigation			
X-ray chest lesion	No	9	100
	Positive	3	33.33
Mantoux test	Negative	6	66.67
	Positive	6	66.67
FNAC	Negative	3	33.33
	Tubercular	9	100
Biopsy & Histopathology			
Treatment	I/D or excision followed by anti TB therapy	7	77.78
	Anti TB therapy alone	2	22.22
Outcome (cured)			100

Discussion

Breast, skeletal muscle and spleen is remarkably resistant to tuberculosis. Tuberculosis of breast is a disease of younger age group. Sometimes it can present in older age group as lump mimicking carcinoma of the breast. In younger age group the presentation is of pyogenic breast abscess⁷.

In our study tubercular mastitis comprised 0.75% of breast diseases and was approximately 37 times less common than breast carcinoma. Mammary tuberculosis is said to be primary if no other focus of tuberculosis exists and secondary in the presence of a demonstrable focus. This primary focus could be in lungs or lymph nodes including axillary, para tracheal and internal mammary lymph nodes⁸.

In my series of 9 patients only primary tuberculosis of the breast was evident. In all cases bacilli infect the ducts and then spread to the lobules. Dilated ducts of pregnant and lactating women appear to be especially susceptible to infection. Retrograde spread of infection from lymphnode to the breast was observed in none of our patients. 4(44.44%) patients had clinically non-significant axillary lymph node enlargement.

Tuberculosis of breast has been classified into 5 different types. Acute milliary tubercular mastitis, Nodular tuberculosis mastitis, disseminated tuberculosis mastitis, Sclerosing tuberculosis mastitis and Tuberculosis obliterans⁹. There are three recognized modes of spread of the tubercle bacilli to the breast: direct, lymphatic and haematogenous⁹. It is seen that lactating females are more susceptible to develop breast tuberculosis. This could be due to vascularity of breast during lactation which facilitates infection and dissemination of bacilli. Shinde et al and Banerjee et al reported 7% and 33% of their patients to be lactating at the time of initial presentation^{3,10}. All my patients were nonlactating but diabetic. Breast tuberculosis predominantly affects young multiparous women with most patients between the age of 20-40 years^{11, 12, 13}. All my patients except 3 were between the age group of 20-40 years. 3 (33.33%) of them were of age between 45-55 years. Early diagnosis is difficult as the characteristic sinuses occur late in course. In addition appearance of sinuses is not the distinctive feature of tuberculosis. Several cases of non-tubercular granulomatous mastitis also present with sinuses. However tuberculosis should be suspected in a patient whoever has recurrent breast abscess after proper drainage on previous occasions. Biopsy and detection caseous necrosis confirmed final diagnosis in all my cases. The patients who present with lump are clinically indistinguishable from breast cancer. All my cases except 2(22.22%) presented with mastitis and abscess formation. One of my patients, a 20 year old girl presented with a firm lump mimicking breast neoplasm. Another patient presented with lump and multiple sinuses involving almost whole of her breast. Diabetes is a chronic disease and patients with diabetes are immunodepressed and florid infection is very common among diabetic patients. Diabetes can be a cause as to why most of my patients with tubercular mastitis presented with abscess and mastitis clinically mimicking pyogenic abscess.

Conclusion

Extra pulmonary tuberculosis occurring in breast tissue is extremely rare even in countries where tuberculosis is a prevalent disease. In the absence of well-defined clinical features the disease remains obscure and often is mistaken for carcinoma of breast or pyogenic abscess. Chronic debilitating diseases like diabetes probably can play a role in the clinical presentation of tubercular mastitis. Caseating granuloma in histopathology is diagnostic of tuberculosis. The disease is curable with antitubercular chemotherapeutic drugs needing surgical intervention occasionally.

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Arsenicosis: A Review of Its Diagnosis and Treatment

Hye MA¹

Abstract

Prolong ingestion of arsenic contaminated water affects human health severely. More than 67 million people in Bangladesh are exposed to 0.05 mg/ liter or above of arsenic in their drinking water and it is now considering a biggest crisis in health and social sector in the modern world. Arsenicosis affects almost all the vital system of the body. Skin involvement is the earliest and commonest feature. Diagnosis is usually done by history, clinical feature and laboratory analysis. Still there is no international consensus on its diagnosis and treatment. Antioxidant and food supplements are tried with different range of success.

In this article, author describes the extent of arsenicosis and elaborates its diagnosis and treatment.

Keywords: Arsenicosis, Arsenic Contamination, Melanosis, Keratosis, Diagnosis, Treatment, Bangladesh.

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Introduction

WHO working group defined Arsenicosis as "a chronic condition arising from prolonged ingestion of arsenic above safe dose for at least six months, usually manifested by characteristic skin lesions of melanosis and or keratosis with or without involvement of internal organs"¹.

The WHO Guideline value for arsenic in drinking water is set at 10 ppb. This is the drinking water standard adopted in many industrialized countries. However, many developing countries have kept the limit at 50 ppb for practical reasons².

Arsenicosis has become a major health problem in Bangladesh and West Bengal of India. It is also identified in many countries, irrespective of geographical or economic situation.

The symptoms and signs of arseniosis differ in individuals, population groups and geographical areas. There are no internationally recognized criteria for the diagnosis and management of arsenicosis². The purpose of this paper is to review pathogenesis, diagnosis and treatment of this disorder.

Arsenic: Fact Sheet

Basic

Arsenic(As) is a natural component. Concentrations of arsenic in environment are following:

- i) Rock- 1.5-2.0 mg.
- ii) Contaminated soil up to 500 mg/kg.
- iii) Natural water - 0.1-0.4 microgram/L.

Arsenic is also emitted into the atmosphere by high-temperature processes such as coal-fired power generation plants, burning vegetation and volcanic action.

Arsenic combine with both metals and non-metal elements to form mainly following 2 types of compounds:

- i) Inorganic Arsenic (Trivalent, e.g. arsenates, and Pentavalent, e.g. arsenates).
- ii) Organic Arsenic{Mono- methyl arsonic acid (MMA), and Di-methyl arsinic acid (DMA)}.

The organic forms are comparatively non-toxic and mostly present in sea foods. Inorganic forms are toxic to human health and present in almost everywhere including air, water, soil and food.

Historical Background

Arsenic is known to human since from prehistoric era. Hippocrates recommended arsenic for treatment of skin ulcer & boil. In Indian sub-continent during the period of Buddha, it had been used for the treatment of many diseases. Alchemiste Geber-discovered arsenic oxide in 9th century. The poison was transformed into a medicine in the 1700s, when Thomas Fowler developed a solution of arsenic trioxide in potassium bicarbonate (1%w/v) for the treatment of asthma, chorea, eczema, pemphigus, and psoriasis³. It was also used empirically for the treatment of a variety of diseases, including leprosy, syphilis, and yaws⁴. In 1822 arsenic was identified as possible carcinogen. Interestingly enough, the dilemma of its effects and side effects is still going on; in spite of health

crisis due to arsenic poisoning, in many countries, arsenic trioxide (trisenox) has been used in the treatment of patients with acute promyelocytic leukemia⁵ in modern time and has even obtained the FDA approval in September 2000³ for use in the condition.

It is colorless, odourless, and tasteless and these characteristics contributed much to use it as a poison of choice. Arsenic poisoning, accidental or deliberate has been implicated in the illness or death of number of people throughout the history. Recent forensic evidence uncovered the evidences of arsenic poisoning as a cause of death of following prominent people: Francesco I de Medici, Grand duke of Tuscany (1541-1587), Eric VII of Sweden (1533-1577), George III of Great Britain (1738-1820), Theodor Ursinus (1749-1800), Napoleon Bonaparte (1769-1821)^{6,2}.

Arsenicosis: Bangladesh Perspective

"Bangladesh is in the midst of a mass poisoning in history, dangerous level of arsenic have been found in the ground water, entering millions of people sip by sip as they drink from over 4 million tube wells."(7)

Prior to the 1970s, Bangladesh had one of the highest infant mortality rates due to ineffective water purification sewage system. Millions of wells were constructed then to provide drinking water. In result, infant mortality and diarrheal diseases were reduced by 50%. But among 8.4 million wells, approximately 1 in 4 of these wells is now contaminated with arsenic. So far ground water contamination by arsenic is detected in 62 districts out of 64 and about 38200 arsenicosis patients were identified across the country⁸.

Arsenicosis was first reported in Chapai Nawabgonj district in year 1993. Now, it is estimated that between 35 to 77 million Bangladeshi or 28 to 62% of the total population of 125 million are now at risk of chronic arsenic poisoning⁹. It is described in world media as the largest known mass poisoning in history⁷.

Global Scenario:

Arsenic contamination of ground water is widespread and there are a number of regions where arsenic contamination of drinking-water is significant. It is now recognized that at least 140 million people in 50 countries have been drinking water containing arsenic at levels above the WHO provisional guideline value of 10 µg/L⁹.

In 1917, arsenicosis through ground water was first identified in Cordoba of Argentina (Bell Ville Disease). High concentrations of arsenic in drinking-water are found in various parts of the world including Argentina, Bangladesh, Chile, China, Hungary, India (West Bengal), Mexico, Nepal, Pakistan, Thailand, USA, and Viet Nam. It may be mentioned that in USA, and many other countries safe level of arsenic is below 0.01mg/l¹⁰.

Pathogenesis

After ingestion, arsenic is absorbed from the gastrointestinal tract; following absorption, arsenic undergoes metabolism through repeated reduction and oxidative methylation. It is widely accepted that methylated metabolites of inorganic arsenic are less reactive and less genotoxic; metabolism is regarded as a bio-inactivation mechanism.

Following metabolism, arsenic is rapidly cleared from blood, and only 0.1% of the arsenic remains in the plasma 24 hours after dosing. Urine is the most common route of elimination. As much as 45% to 75% of the dose is excreted in the urine within a few days to a week^{11,12}. The trivalent state of arsenic (As³⁺), is widely distributed by virtue of its binding with sulfhydryl groups in keratin filament and has a tendency to accumulate in the skin, hair, nails, and mucosae of the oral cavity, esophagus, stomach, and the small intestine¹³. On the other hand, arsenate (As⁵⁺) is the predominant form deposited in the skeleton because of its ability to replace phosphate in the apatite crystal in bones; as a result of this it is retained there for a longer time¹³. Within 30 hours of ingestion, arsenic deposits in the hair.

Daily consumption of water with greater than 50 micrograms per liter of arsenics, usually lead to health problems¹⁴.

Some people may be affected by lower levels of arsenic than others. Young children, the elderly, people with long-term illnesses, and unborn babies are at greatest risk of being affected.

If the exposure is of a large concentration then the progression of the arsenic poisoning event would lead to seizures, electrolyte disturbances and systemic shock and even death.

Trivalent arsenic is believed to be a carcinogen that induces chromosomal abnormalities. However, the exact molecular mechanism of arsenic induced carcinogenesis is less understood¹⁵.

It has been shown to induce sister chromatid exchanges, chromosomal aberrations, and also DNA-protein crosslinks in lymphocytes and in fibroblasts^{8,16} to explain this genotoxicity. Several mechanisms have been put forward, one of which emphasizes the role of reactive oxygen species in inducing the chromatid exchange¹⁷. The other theory highlights the role of arsenic in impairing the DNA repair process. DNA excision repair of thymine dimer in human fibroblast is inhibited by inorganic arsenic¹⁸. As⁺³ is found to inhibit DNA ligase¹⁹ and tubulin polymerization²⁰. It has also been shown that arsenic alters the activity of tumor suppressor gene p53 by DNA methylation.

Dermatological Manifestations

Arsenicosis is a multisystem disorder. Its common features are dermal lesions, peripheral neuropathy, skin cancer, bladder and lung cancers and peripheral vascular disease^{21,22,23,24,25,26}. Usually dermatological manifestations start to appear after minimum exposure periods of approximately 5 years. It may be 80% of them with urinary excretion of arsenic value between 1-3 mg/l²⁷. In one large-scale study, 3695 (20.6%) of 18,000 persons in Bangladesh and 8500 (9.8%) of 86,000 persons in West Bengal living in arsenic-affected districts were found to show dermatological features of arsenicosis²⁷. Pigmentary changes (melanosis) and hyperkeratosis are the predominant cutaneous effects; though at times, Bowen's disease or skin cancers may arise too.

Epidemiological studies in different regions of the world have consistently demonstrated a strong association between long-term inorganic arsenic ingestion and skin lesions, typically in the form of hyperkeratosis, hyperpigmentation or hypopigmentation. Observations of skin lesions following low chronic exposure have suggested that these characteristic dermal changes are sensitive indications of the toxic effects of inorganic arsenic²⁸. These effects have been demonstrated in many studies using different study designs. Exposure-response relationships and high risks have been observed for each of these end-points. The effects have been most thoroughly studied in Taiwan²⁹. In this large study a population of 40 421 was divided into three groups based on the arsenic content of their well water (high, >0.60 mg/l; medium, 0.30-0.59 mg/l; and low, <0.29 mg/l³⁰).

A similar exposure-response pattern was observed in a study in Bangladesh, where prevalence of keratosis was used as a surrogate for arsenic exposure^{31,32}. Dermatological lesions are classified or described different ways in different studies. GuhaMazumdar et al.³³ described skin lesions of arsenic in Table-I:

Table-I: Classification of skin lesions in arsenicosis

Grade-I	Mild	a. Diffuse melanosis.
		b. Suspicious spotty depigmentation/ pigmentation over trunk/limbs
		c. Mild diffuse thickening of soles and palms.
Grade-II	Moderate	a. Definite spotty pigmentation /depigmentation on the trunk and limbs, bilaterally distributed.
		b. Severe diffuse thickening (with/without wart like nodules of the palms and soles).
Grade-III	Severe	a. Definite spotty pigmentation/ depigmentation as above with few blotchy pigmented/ depigmented macular patches over trunks or limbs
		b. Pigmentation involving the undersurface of tongue and/or buccal mucosa.
		c. Larger nodules over thickened palms and soles.
		Diffuse verrucous lesions of the soles with cracks and fissures and keratotic horns over palms/soles.

Followings are the major dermatological manifestations:

1. **Melanosis:** The earliest and the commonest cutaneous sign is melanosis^{34,35} [Fig-1].



Figure-1: Melanosis.

In a study, conducted in the arsenic-prevalent area of Bangladesh, 100% of the patients of arsenic was showed pigmentary changes³⁵. Prolonged ingestion of arsenic results in pigmentation, most intense on the trunk, which can be diffused^{36,37} or localized, particularly affecting skin folds^{15,36}. Fine freckles of spotted pigmentary changes are also seen, known as 'rain-drop pigmentation'^{15,36} [Fig-2].

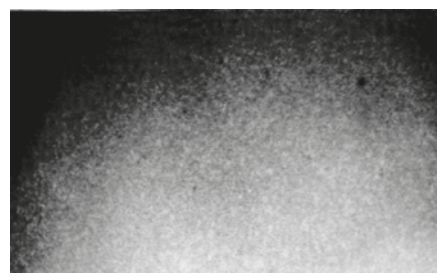


Figure-2: Rain drop pigmentation.

Sometimes macular areas of depigmentation may appear on normal skin or hyperpigmented background producing the distinctive appearance of 'leucomelanosis'^{15,37} [Fig-3].



Figure-3: Leucomelanosis.

Blotchy pigmentation may also involve mucous membranes such as the under surface of the tongue or buccal mucosa^{15,36,37}.

2. **Keratosis:** Arsenical hyperkeratosis appears predominantly on the palms and soles, and it has been found that keratosis on the soles is the most sensitive marker for the detection of arsenicosis at an early stage³⁸. Keratoses are graded as mild, [Fig-4] moderate, or severe

depending on the extent and severity¹⁵. In the mild variety of keratosis, the involved skin has a hardened texture with papules less than 2 mm in size [Fig-4] that can be best felt by palpation. In the moderate variety, the lesions usually advance to form raised, punctate, keratosis, 2-5 mm in diameter [Fig-5]. When the keratosis becomes severe, it may form keratotic elevations more than 5 mm in size and sometimes become confluent and diffuse and sometimes result in cracks and fissures too^{34,39} [Fig-6].



Figure-4: Mild Keratosis.



Figure-5: Moderate Keratosis.



Figure-6: Severe Keratosis with crack and fissure.

Though palms and soles are primarily affected by hyperkeratosis, dorsa of the extremities and trunk may also be affected by it. It is interesting that palmar keratosis usually appears earlier than arsenic-related cancers of bladder and lung; thus it can act as an early marker of carcinogenicity⁴⁰.

3. Skin Cancers: Usually three types of skin cancers are observed: Bowen's disease; basal cell carcinoma and squamous cell carcinoma. In Japan, a study showed that Bowen's disease develop after 10 years, invasive squamous cell carcinoma develop after 20 years and internal malignancy particularly pulmonary malignancy develop after 30 years of arsenic exposure⁴¹.

It has been suggested that human papilloma virus (HPV) infection could constitute an additional risk factor for the development of non-melanoma skin cancer in humans chronically exposed to arsenic⁴². It is also reported that Merkel cell carcinoma⁴³ sometimes co-exist with Bowen's disease^{44,45} in patients with arsenicosis. There is also a study which has demonstrated an increased risk of melanoma in persons with elevated toenail arsenic concentrations⁴⁶, raising the issue relating to the role of arsenic in the development of melanoma. Skin cancer in arsenicosis can arise in the hyperkeratotic areas, as well as on non-keratotic areas of the trunk, extremities, or head^{47,48}.

Skin is thought to be perhaps the most sensitive site for arsenic-induced malignancies⁴⁹. The lesions are frequently multiple and involve covered areas of the body; unlike non-arsenical skin cancer, which usually presents as a single lesion and which occurs frequently on the exposed parts of the body^{29,50}.

Diagnosis:

The diagnosis relies on both laboratory and clinical criteria. A dermatologist or a clinical expert should differentiate the findings with other mimicking findings. A reliable history of consuming drinking water with an elevated concentration of arsenic for at least six months is sufficient to establish exposure. In the absence of adequate information regarding a subject's exposure history, the finding of elevated levels of arsenic in a subject's hair or nails could offer presumptive evidence of elevated arsenic exposure.

A diagnostic algorithm is formulated by WHO to provide a simplified scheme for implementing the case definition and classifying patients under field conditions and in various levels of health care facilities.

The present algorithmic approach for the diagnosis of arsenicosis highlights that the condition can be diagnosed as 'clinically confirmed' by an arsenic expert even without laboratory confirmation of raised arsenic content in drinking water, hair, or nail¹⁵. This algorithmic approach allows for further arsenic estimation if resources permit and a clinically confirmed case is further classified as clinical and laboratory confirmed, if laboratory results favor the diagnosis.

Histopathological Feature

Only few numbers of studies are found in literature regarding the types and patterns of histopathological

changes in skin lesions of arsenicosis. A study from Bangladesh⁵¹ showed that hyperkeratosis, parakeratosis, acanthosis, papillomatosis, hypergranulosis, and dysplastic changes to be the most important and constant findings. However, basal pigmentation and dermal changes were found to be inconstant features.

In another study, hyperkeratotic lesions of 70 patients with arsenicosis were compared with 20 controls⁵². Significant findings included hyperkeratosis (100%), parakeratosis (97%), acanthosis (95.7%), and papillomatosis (74%). The results were found to be significantly more ($P < 0.001$) in the patients than in controls. Basal cell pigmentation was found in 42.8% ($P > 0.05$) and dysplasia and malignant changes in 7% ($P > 0.1$). There is no study about the histopathology of arsenic related pigmentary lesions.

A study on the severe keratotic lesions of arsenicosis revealed that pre-cancerous skin lesions were in 6.6% and cancerous lesions in 0.8% of the patients⁵³.

Laboratory Criteria

1. Water: Consumption of drinking water with an arsenic concentration more than the prevailing national standard for at least 6 months is essential for the establishment of elevated exposure to arsenic. The maximum permissible limit of arsenic in drinking water as per the recent guideline of WHO is 0.01 mg/L. In India and Bangladesh, maximum permissible limit is 0.05 mg/L.

2. Nails and hairs: Both nails and hairs provide circumstantial evidence of arsenic exposure within the preceding 9 months. A hair arsenic concentration of 1 mg/kg is a marker of significant exposure; however, a concentration of 1.5 mg/kg in nail is required to correlate with a diagnosis of chronic arsenicosis. Hair analysis for arsenic is a semi-reliable method for confirming chronic toxicity. It does not discriminate between externally deposited arsenic and arsenic found within the hair shaft. Arsenic levels in hair sections may provide an indication of the time of exposure based on length from growth site. The hair of an individual who died 6 to 8 hours after ingestion of an arsenic overdose generally does not contain arsenic.

The current standard for arsenic analysis is atomic absorption spectroscopy,⁵⁴ which measures total arsenic, does not distinguish between pentavalent, trivalent, or organic arsenic⁵⁵.

Blood arsenic level is less useful than urine level unless exposure occurred on the same day. Serum (or blood) arsenic levels are detectable only during the first 2 to 4 hours after ingestion. The half-life of inorganic arsenic in blood is 2 hours and that of the methylated metabolites is 5 to 20 hours.

Urinary AS^{+3} and AS^{+5} levels present about 10 hours and return to normal in 20 hours. Urinary monomethylarsine and dimethylarsine levels peak at 40 to 60 hours and return to baseline in 6 to 20 days after ingestion. Urine (in absence of intake of seafood) - Level $> 50 \mu\text{g As/L}$ is indicative of continuing Exposure⁵⁵.

Treatment

Until now, there is no internationally recognized module to treat patients of arsenicosis. Following guidelines of WHO are now followed in Bangladesh:

Cessation of exposure to drinking water or other items with elevated concentration of arsenic;

- i. Administration of drugs or nutrients directed at hastening recovery or averting disease progression;
- ii. Provision of non-specific supportive care to improve physical symptoms or treat selected complications;
- iii. Secondary prevention of latent effects through medical surveillance, and
- iv. Counseling and education to address psychosocial sequelae of the illness and provision of appropriate rehabilitation.

Administration of non-specific nutritional supplements or anti-oxidants is practicing on many countries. It may hasten recovery or avert the disease progression. Some commonly used anti-oxidants include beta carotene, vitamin E and vitamin C. Still there is lacking of large-scale, randomized-controlled double-blinded trial to evaluate the efficacy of these treatment regimens. Their use depends on the national policy and the recommendations of the concerned medical bodies in respective countries.

In Bangladesh, a small number of clinical trial are done to ascertain the efficacy of mentioned drugs. Momin et al. found Selenium is very effective in a recent double blind study⁵⁶.

In another double blind randomized trial, Dr. Hasina Mamataz et al. found Spirulina as a very effective remedy in treatment of Arsenicosis⁵⁷. Following antioxidants or food supplements are commonly prescribed in Bangladesh:

- i. Retinol
- ii. Beta-carotene
- iii. Ascorbic acid
- iv. Alpha-tocopherol
- v. Selenium
- vi. Spirulina
- vii. Zinc

Symptomatic treatment for patients with keratosis or keratosis and melanosis includes the application of keratolytic agents. Presently, 5-10% of salicylic acid and 10-20% of urea-based ointment for the treatment of keratotic lesions is the most common prevailing practice in Bangladesh.

Counseling and education to combat the psychosocial sequelae of the illness is important. Programs should be implemented on educating patients and other community members about basic public health aspects of arsenicosis and to dispel misconceptions that may lead to stigmatization. It is also needed to provide appropriate rehabilitation.

The patient should be evaluated for the presence of other medical conditions, potentially related to arsenic exposure. Patients should be referred, as appropriate, for further treatment.

Conclusion

Arsenicosis is a public health crisis in Bangladesh and also in a part of India. However, the prevalence of this disease is not confined in this region only but it is prevailing in others countries also.

Still, knowledge an regarding arsenic contamination and its health hazards is less understood. A multidisciplinary approach is urgently needed to combat this high magnitude of health catastrophe.

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Rheumatoid Arthritis: Monotherapy versus Combination Therapy

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Abstract

Rheumatoid arthritis is an autoimmune disease characterized by joint destruction, disability and disability adjusted life years of a patient. Early diagnosis and appropriate treatment may improve outcome. Disease-modifying anti-rheumatic drugs suppress the disease progression. Recent guidelines advise early and sustained use of disease-modifying anti-rheumatic drugs of which methotrexate (MTX) and sulfasalazine (SSZ) are the most frequently used. Both drugs are effective, cheap, available and well tolerable. Now days MTX and SSZ are used as monotherapy and in combination. Basically the outcomes of two combinations of drugs are multiplicative. One drug promotes the action of the other. In daily practice interactions are often not well studied when using combinations of Disease Modifying Anti-Rheumatic Drugs (DMARDs). The aim of this study is the use of combination of MTX and SSZ is frequently used in the therapy for RA and has been tested in several clinical trials globally.

Keywords: Rheumatoid Arthritis(RA), Disease Modifying Anti-Rheumatic Drugs (DMARDs), Methotrexate (MTX), Sulfasalazine (SSZ). Non Steroidal Anti-Inflammatory Drugs (NSAIDs).

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Introduction

Rheumatoid arthritis is a chronic, autoimmune, inflammatory disorder of unknown etiology that is characterized by symmetric synovitis and the propensity to cause joint destruction, disability and premature death¹. Optimal treatment in early disease may provide a window of opportunity leading to improved outcome². Disease-modifying anti-rheumatic drugs (DMARDs) slow the natural course of the disease, reduce joint damage and pain, and retard loss of function and disability³. Disease modifying agents should be started as early as possible.

Current guidelines advise early and sustained use of disease-modifying anti-rheumatic drugs (DMARDs) of which methotrexate (MTX) and sulfasalazine (SSZ) are the most frequently used⁴. Both drugs are effective, have an acceptable toxicity and their cost is low. MTX and SSZ are used as monotherapy and in combination⁵. Although their mechanism of action remains unclear, several reports suggest that these drugs may differ in their effects on circulating cytokines and cytokine production⁶.

Two studies using the combination of drugs used in this study⁷. In the first, a controlled open step-up study in 40 patients "resistant" to SSZ, the combination was significantly better than MTX alone. In the second⁸, the individual drugs were compared with the combination in a parallel design from the outset. A modest trend favoring the combination of SSZ and MTX was seen, with comparable results from the two individual drugs. Nausea was documented as an adverse event more often in the combination group.

Epidemiology:

RA affects approximately 0.5-1% of the adult population worldwide. There is evidence that the overall incidence of RA has been decreasing in recent decades, whereas the prevalence has remained the same because individuals with RA are living longer. Both genetic and environmental factors appear to be involved in the pathogenesis of RA. The concordance rate of RA is higher in monozygotic (12-15%) than in dizygotic twins (3%), and there is an increased frequency of disease in first-degree relatives of patients. Up to 50% of the genetic susceptibility is due to genes in the HLA region. HLA-DR4 is the major susceptibility haplotype in most ethnic groups. Susceptibility is increased post-partum and by breastfeeding. Cigarette smoking is a strong risk factor for developing RA and also associates with greater severity.

Pathophysiology:

Whatever the initiating stimulus, RA is characterised by infiltration of the synovial membrane with lymphocytes, plasma cells and macrophages. CD4⁺ T cells play a central role by interacting with other cells in the synovium. Activated T cells stimulate B cells to produce immunoglobulins including RF, and macrophages to produce pro-inflammatory cytokines. These act on endothelium, synovial fibroblasts, bone cells and chondrocytes to promote swelling and congestion of the synovial membrane and destruction of bone, cartilage and soft tissues.

The pro-inflammatory cytokine TNF- α plays an important role in this process by regulating production of other cytokines, whose actions are shown in. The B cells release immunoglobulins, including RF, which can form immune complexes within the joint and in extra-articular tissues, leading to vasculitis. Lymphoid follicles form within the synovial membrane. Inflammatory granulation tissue (pannus) spreads over and under the articular cartilage, which is progressively eroded and destroyed. Later, fibrous or bony ankylosis may occur. Muscles adjacent to inflamed joints atrophy and may be infiltrated with lymphocytes⁹.

Criteria for diagnosis of rheumatoid arthritis (According to ARA 1987 revision)⁹

- Diagnosis of RA is made with four or more of the following:
- Morning stiffness (> 1 hr)
- Arthritis of three or more joint areas
- Symmetrical arthritis
- Rheumatoid nodules
- Rheumatoid factor
- Radiological changes
- Duration ≥ 6 wks

In 2010, a collaborative effort between the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) revised the 1987 ACR classification criteria for RA in an effort to improve early diagnosis with the goal of identifying patients who would benefit from early introduction of disease-modifying therapy. Application of the newly revised criteria yields a score of 0-10, with a score of ≥ 6 fulfilling the requirements for definite RA. The new classification criteria differ in several ways from the older criteria set.

Classification Criteria for Rheumatoid Arthritis (According to 2010 ACR/EULAR collaborative initiative)¹⁰

Joint involvement	1 large joint (shoulder, elbow, hip, knee, ankle)	0
	2-10 large joints	1
	1-3 small joints (MCP, PIP, Thumb IP, MTP, wrists)	2
	4-10 small joints	3
	>10 joints (at least 1 small joint)	5
Serology	Negative RF and negative ACPA	0
	Low-positive RF or low-positive anti-CCP antibodies (3 times ULN)	2
	High-positive RF or high-positive anti-CCP antibodies (>3 times ULN)	3
Acute-phase reactants	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
Duration of symptoms	<6 weeks	0
	>6 weeks	1

Note: These criteria are aimed at classification of newly presenting patients who have at least 1 joint with definite clinical synovitis that is not better explained by another disease.

Extra-articular manifestations of rheumatoid disease

Systemic

- Fever
- Weight loss
- Fatigue
- Susceptibility to infection

Musculoskeletal

- Muscle-wasting
- Tenosynovitis
- Bursitis
- Osteoporosis

Haematological

- Anaemia
- Thrombocytosis
- Eosinophilia

Lymphatic

- Felty's syndrome
- Splenomegaly

Nodules

- Sinuses
- Fistulae

Ocular

- Episcleritis
- Scleritis
- Scleromalacia
- Keratoconjunctivitis sicca

Vasculitis

- Digital arteritis
- Ulcers
- Pyoderma gangrenosum
- Mononeuritis multiplex
- Visceral arteritis

Cardiac

- Pericarditis
- Myocarditis
- Endocarditis
- Conduction defects
- Coronary vasculitis
- Granulomatous aortitis

Pulmonary

- Nodules
- Pleural effusions
- Fibrosing alveolitis
- Bronchiolitis
- Caplan's syndrome

Neurological

- Cervical cord compression
- Compression neuropathies
- Peripheral neuropathy
- Mononeuritis multiplex

Amyloidosis**Investigations and monitoring of rheumatoid arthritis:****To establish diagnosis:**

Clinical criteria

Acute phase response (APR)

Serological tests (anti-CCP antibodies & RA factor)

To monitor disease activity and drug efficacy

Pain (visual analogue scale)

Early morning stiffness (minutes)

Joint tenderness

Joint swelling

DAS 28 score

APR

To monitor drug safety

- Urinalysis
- Biochemistry (Serum Creatinine, SGPT)
- Haematology (CBC)

Management:

Physical rest, targeted anti-inflammatory therapy and passive exercises are the mainstays, with the aim of relieving symptoms, suppressing inflammation, and conserving and restoring function in affected joints. A multidisciplinary approach is required, including doctors, nurses, physiotherapists and occupational therapists, and patient education and counselling play a key role. During treatment, periodic assessment of disease activity, progression and disability is essential. In the vast majority, management is outpatient-based, but hospital admission can be helpful in patients with very active disease for a period of bed rest, multiple joint injections, splinting, regular hydrotherapy, physiotherapy and education.

Drug Therapy: The medications used for the treatment of RA may be divided into broad categories:

- Nonsteroidal anti-inflammatory drugs (**NSAIDs**);
- Glucocorticoids**, such as prednisone and methylprednisolone;
- Conventional disease-modifying anti-rheumatic drugs (**DMARDs**); and
- Biologic DMARDs**

NSAIDs: NSAIDs were formally viewed as the core of all other RA therapy, but they are now considered to be adjunctive therapy for management of symptoms uncontrolled by other measures. Chronic use should be minimized due to the possibility of side effects, including gastritis and peptic ulcer disease as well as impairment of renal function.

Glucocorticoids: Glucocorticoids may serve in several ways to control disease activity in RA. First, they may be administered in low-to-moderate doses to achieve rapid disease control before the onset of fully effective DMARD therapy, which often takes several weeks or even months. Second, a 1-2 week burst of glucocorticoids may be prescribed for the management of acute disease flares, with dose and duration guided by the severity of the exacerbation. Chronic administration of low doses (5-10 mg/d) of prednisone (or its equivalent) may also be warranted to control disease activity in patients with an inadequate response to DMARD therapy.

DMARDs: DMARDs are so named because of their ability to slow or prevent structural progression of RA. The conventional DMARDs include hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide; they exhibit a delayed onset of action of approximately 6-12 weeks. Methotrexate is the DMARD of choice for the treatment of RA and is the anchor drug for most combination therapies. Short description of MTX & SSZ is given below.

Sulfasalazine:

Dosage: Initially 500 mg orally twice daily. Maintenance: 1000-1500 mg twice daily.

Serious Toxicities: Granulocytopenia & Hemolytic anemia (with G6PD deficiency)

Other Common Side Effects: Nausea, Diarrhea & Headache.

Initial Evaluation: CBC, LFTs & G6PD level.

Monitoring: CBC every 2-4 weeks for first 3 months, then every 3 months.

Methotrexate:

Dosage: 10-25 mg/week orally. Folic acid 1 mg/d to reduce toxicities.

Serious Toxicities: Hepatotoxicity, Myelosuppression, Infection, Interstitial pneumonitis, Pregnancy category X.

Other Common Side Effects: Nausea, Diarrhea, Stomatitis/mouth ulcers, Alopecia, Fatigue.

Initial Evaluation: CBC, LFTs, hepatitis B surface antigen, hepatitis C viral antibody & Chest X-ray.

Monitoring: CBC, creatinine, LFTs every 2-3 months.

Discussion

The level of activity was assessed in 334 out-patients who visited the Clinic of Physical Medicine at the Hanusch-Krankenhaus¹¹. The self-administered Health Assessment Questionnaire (HAQ) was used for that purpose by the authors. The mean HAQ-Score was low (>6 (25 percentile=0)) indicating only slight restrictions of personal activity. Older subjects presented with higher scores than younger people. The mean HAQ score was 0.3 in third decades, reached a plateau about 0.55 to 0.57 between 40 to 70 years and rises to 0.69 in the 8th decade and to 0.73 in subjects older than 80 years. Subjects with disease of the central nervous system such as hemiparesis after stroke or M. Par-kinson, and patients after amputation ranked highest. Patients after joint surgery, after fractures or contusion and also patients with tendovaginitis followed them in the score rank. The majority of out-patients was not highly restricted in activity.

Several new drugs for rheumatoid arthritis are available including leflunomide. Comparative studies of treatment with leflunomide (against methotrexate) report a better

quality of life. In a study designed to evaluate the efficacy of combination of methotrexate and hydroxychloroquine with leflunomide, a new disease modifying antirheumatoid drug¹². Analysis was of intent to treat group. Their study was an open labeled, randomized, comparative clinical trial in the department of rheumatology and immunology, at a tertiary care center in Bangalore. Patients who have diagnosed with rheumatoid arthritis as per American College of Rheumatology aged between 18 and 60 years were recruited and randomized to receive leflunomide (10mg/day p.o.) or a combination of methotrexate and folate supplementation for 12 weeks. The European League Against Rheumatism criteria of improvement according to disease activity score 28 was considered as the primary efficacy variable. Baseline and end of study values were evaluated. The duration of the study period was 1 year. After 12 weeks, improvement noted in patients treated with leflunomide was similar to those treated with a combination of methotrexate and hydroxychloroquine. There was no statistical significance in improvement in disease activity between the two groups ($P=0.377$). Combination of methotrexate and hydroxychloroquine is equivalent to leflunomide in terms of efficacy in reducing disease activity in the initial treatment of severe rheumatoid arthritis.

To compare efficacy, toxicity, and the pharmacokinetics of the combination of SSZ and MTX vs MTX alone in the treatment of SSZ-resistant RA, conducted a controlled open clinical trial¹³. Forty RA patients with active arthritis despite adequate SSZ therapy were allocated randomly to regimes of either SSZ+MTX or MTX alone. The patients were evaluated openly by a single observer for 24 weeks. In the first 115 patients using the combination, pharmacokinetics of MTX without and with SSZ were studied. Thirty-eight patients completed the trial. The mean decrease in the disease activity score in the group of patients receiving the combination was significantly greater than in the MTX group (-2.6vs-1.3 respectively). The same pattern was seen concerning the other efficacy variables. There was no difference in the occurrence of toxicity. SSZ had no influence on the pharmacokinetics of MTX. This open study the efficacy of combination of MTX and SSZ seems to be superior to MTX alone, the toxicity of both therapies was similar. This effect was not explained by the pharmacokinetics of MTX which were not altered by concomitant SSZ administration.

Early aggressive treatment of rheumatoid arthritis is associated with improved disease control, slower radiological progression and improved functional outcomes¹⁴.

The results of randomized controlled trials (RCTs) on the combination of MTX and SSZ in naive patients and in patients with an insufficient response to SSZ¹⁵.

The diagnosis of rheumatoid arthritis was concluded on diagnostic criteria of American Rheumatism Association (ARA)¹⁶ compared medical results between group I (with tablets Methotrexate), as simple therapy and group II (with MTX, SSZ and HCQ), as combined therapy of drugs that modify rheumatic diseases (DMARDs), according to laboratory analysis, subjective and objective parameters, as well as side effects of drugs that were used. During application of DMARDs the investigators were based on principals of drug applications. To the investigated patients of group I and II that were of ages (23-72 years old vs, 21-69 years old) with average (46 vs. 45), Most of the patients of group 1 and 2 belong in 1st and 2nd functional stage according to Steinbrocker. Average value of morning stiffness for group 1 and 2 was (69.5 vs. 73 minutes) in the beginning of treatment, while in the end of the treatment was (26 vs. 21 minutes, $p < 0.01$). Average value of hands grip before the medication was (67 vs. 62 mm), while after medication (85 vs. 92 mm, $p < 0.01$). Pain to all patients of group I and II before the medication was present, but after the medication changed intensively, had no pain (5 vs. 9 patients), had light pain (13 vs. 10 patients), while remained patients with strong pain (2 vs. 1 patients). Average value of swelling on proximal interphalangeal joints in group I and II in the beginning of medication was (70 vs. 67 mm), while after the medication was (68 vs. 62 mm). Average value of erythrocytes sedimentation before the medication was (33 vs. 38) while after the medication was 09 vs. 14). The positive rheumatoid factor was found to (55 vs. 17 patients).

Therefore, at some stage during the lengthy course of RA, institution of traditional DMARDs that have previously been applied may have to be reconsidered. In a investigation the effectiveness of re-employed methotrexate in patients with a history of previous methotrexate failure (original course)¹⁷. A total of 1,490 RA patients (80% female, 59% rheumatoid factor positive) were followed from their first presentation, yielding a total of 6,470 patient-years of observation. The investigators identified patients in whom methotrexate was re-employed after at least one intermittent course of a different DMARD. The investigators compared reasons for discontinuation, improvement in acute phase reactants, and cumulative retention rates of methotrexate therapy between the original course of methotrexate and its re-employment. Similar analyses were performed for other DMARDs. Methotrexate was re-employed in 86 patients. Compared with the original courses, re-employment was associated with a reduced risk for treatment termination because of ineffectiveness ($P = 0.02$, by McNemar test), especially if the maximum methotrexate dose of the original course had been low (< 12.5 mg/week; $P = 0.02$, by logistic regression). In a Cox regression model, re-employed MTX was associated with a significantly reduced hazard of treatment termination compared with the original course of methotrexate, adjusting for dose and year of employment (hazard ratio 0.64, 95% confidence interval 0.42-0.97; $P = 0.04$).

In a assessment the impact of these therapies on the cytokine cascade, the in vitro production and circulating concentrations of several cytokines and endogenous cytokine antagonists were measured in 30 healthy controls and longitudinally in a subset of 26 patients enrolled in this study¹⁸. Compared to controls, RA patients had significantly higher circulating concentrations of interleukin-6 (IL-6), soluble receptors for tumour necrosis factor (sTNFR), soluble receptors for interleukin-2 (sIL-2R) and interleukin-1 receptor antagonists (IL-1RA), and their peripheral blood mononuclear cells (PBMC) showed a higher spontaneous production of interleukin-1 beta (IL-1 beta), tumour necrosis factor alpha (TNF alpha) and IL-1RA (both secreted and cell-associated) and a higher stimulated production of cell-associated TNF alpha, IL-1RA and (to a lesser extent) IL-1 beta. Treatment with MTX alone ($n = 12$) or combined with SSZ ($n = 14$), resulted in significant reductions of circulating IL-6 and sIL-2R but did not alter IL-1 beta, TNF alpha or IL-1 RA concentrations. Decreases in circulating levels of sTNFR and in the in vitro production of cell-associated IL-1 beta and IL-1RA after stimulation were only observed in patients treated with MTX + SSZ. The concentrations of IL-1 RA and sTNFR in the circulation exceeded moderately those of IL-1 beta and TNF alpha but this is probably insufficient to block IL-1 and TNF alpha activity.

For pharmacological reasons, the effect of the combination of MTX and SSZ may be different in RA patients who are naive to these drugs compared to patients with an insufficient response to one of them. Therefore, compared the results of randomized controlled trials (RCTs) on the combination of MTX and SSZ in naive patients and in patients with an insufficient response to SSZ¹⁹. A systematic literature search was performed to identify RCTs that compared the MTX-SSZ combination to either drug alone. The databases MEDLINE and the Cochrane Clinical Trials registry were searched from 1966 up to April 2007. The efficacy of the single therapeutic agents or their combination was assessed using the mean change in the disease activity score (DAS) and the ACR improvement criteria. Four RCTs were identified to compare the efficacy of the combination MTX-SSZ to the efficacy of either drug alone. Two parallel trials were performed with patient's naive to both drugs and two add-on trials were performed in SSZ failures. In the trials with naive patients, the mean DAS changes for the combination MTX and SSZ pointed to a sub-additive efficacy. In the trials with patients who previously failed to SSZ, the mean DAS changes for the combination MTX and SSZ indicated additive efficacy. In RA, addition of MTX to SSZ is a therapeutic option in SSZ failures, whereas combination of MTX and SSZ in DMARD-naïve patients has no added value.

Conclusion

This suggests that the mean changes in the DAS28 score significantly lower in those who received combination

therapy compared with those who received either MTX or SSZ alone. Combination showed no drug toxicity or had not been stopped in any patients due to side effects. The combination of MTX and SSZ, is relatively inexpensive. Combination of MTX & SSZ proved more effective than monotherapy in patients of Rheumatoid arthritis.

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Case Report

Management of Bile Duct Injury after Laparoscopic Cholecystectomy

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Abstract

Bile duct injury is one of a life threatening complication of laparoscopic cholecystectomy. It is a disaster for both patient and surgeon because of the associated morbidity, prolonged hospitalization and mortality. The complication can be minimized by early diagnosis and treatment. Minor injury can be managed by conservative treatment. Bile in drainage tube is diagnostic. Minimum bile leakage automatically sealed provided the natural passage remain patent. Further bile leakage can be reduced by stenting the common bile duct by ERCP. Major bile duct injury needs early diagnosis, categorization of level of injury, control of sepsis and some form of surgical intervention. Early referral to tertiary level hospital under experienced hepatobiliary surgeon will give the good result.

Keywords: Bile Duct Injury, Laparoscopic Cholecystectomy.

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Introduction

Gall stone disease is one of the most common digestive health problems. Laparoscopic Cholecystectomy is now the most commonly performed surgical procedures and since its introduction in the late 1980s has been the

standard procedure for the management of symptomatic gall bladder stones or acute cholecystitis¹. Although there are major benefits related to the procedure, such as reduced pain and shorter hospital stay, laparoscopic cholecystectomy also has a downside, it is associated with higher incidence of bile leaks and injuries to common bile duct than was observed in the open cholecystectomy².

The consequences of bile duct injuries might have some severe consequences for some of the patients. Apart from early post-operative complications there is also a risk of long term sequel as stricture of the common bile duct and repeated attack to cholangitis. In addition such injuries represent a vast economic burden to the society and also represent high rate of medico legal claims².

The management of patients following major bile duct injury is a surgical challenge often requiring the skills of experienced hepatobiliary surgeons at tertiary referral centers. Collaboration among surgeons, gastroenterologist and interventional radiologist is imperative in the care of such injuries.

The aim of the study is to analyze the presentation, characteristic, relevant investigations and treatment results of 3 cases with bile duct injury after laparoscopic cholecystectomy.

Case presentation

Case no 1:

Mrs. Salma aged about 40 years from Fakirhat, Bagerhat was admitted in a private clinic as a diagnosed case of cholelithiasis. After pre-operative checkup she was decided for Laparoscopic cholecystectomy. Operative procedure was clean, no abnormal situation was there. On 3rd post-operative period (POD), patient developed abdominal pain, distention and there was collection of bile about 200 ml indrainage bag (Fig. no 01). The amount of bile was increased between 200 ml to 500 ml. Ultrasonography of whole abdomen shows some amount of collection of fluid at sub hepatic region. From 7th POD the amount of bile gradually decreased. On 14th POD it was almost nil. Ultrasonography shows no collection of fluid at sub-hepatic region. The drain tube was removed and patient was discharged. On final follow up patient was good.

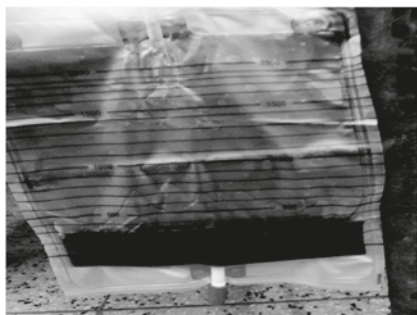


Figure-1: Showing bile in the drainage bag.

Case no 2:

Mrs. Sufia Begum aged about 37 years from Kaligang, Satkhira presents with asymptomatic cholelithiasis. After pre-operative checkup she was decided for Laparoscopic cholecystectomy. Operation was done as a routine case. There was no per-operative complication, operative procedure was clean. On 3rd post-operative period (POD), patient complaints of pain at right hypochondrium (RHC) with jaundice (Fig. no 02).



Figure-2: Showing jaundice.

On conservative treatment no improvement were there. Ultrasonography shows collection at right hypochondriac region. On 7th POD decision of laparotomy was taken, after laparotomy collection of bile found at RHC about 300 ml. Bile was removed. Abdomen was closed with a T-tube at CBD and a drain tube at hepatorenal angle. T-tube was managed accordingly. Post-operative T-tube cholangiogram was done. Normal patency of biliary tree was found. T-tube was removed and patient was discharged. Patient is good even after one year of operation.

Case No 3:

Mrs. Aleya Khatun aged about 35 years from Shaikhpara, Khulna presents with cholelithiasis. It was asymptomatic and was diagnosed incidentally during Ultrasonography of whole abdomen due to pain at the lower abdomen. She was decided for Laparoscopic cholecystectomy. She was non-diabetic, non-hypertension and all other investigations were found within normal limit. Laparoscopic cholecystectomy was started under General Anesthesia with endotracheal intubation, cystic duct, cystic artery with all structure were identified clearly. During the procedure slipping of cystic artery causes sprouting. Attempt of arrest of bleeding was done, several clips were applied. Procedure was completed with a drain at operation site. On 3rd POD, patient developed mild

jaundice, fluctuation of level of bilirubin between 4-6 mg/dl. Pain at operation site gradually become aggravated. Patient was referred to higher center for further management. Laparotomy was done on 14th POD, collection of bile at sub hepatic region was found which was drained and abdomen was closed in layers keeping a drain at hepatorenal angle and a T-tube at porta-hepatis. After 3 months MRCP followed by T-tube cholangiogram was done.

There was no continuity between the biliary channel and duodenum. Intra hepatic biliary channel were visualized up to the confluent of the right and left hepatic duct. Patient gradually become non-icteric. Further laparotomy followed by hepaticojejunostomy with roux-en-y anastomosis was done. Abdomen was closed with a drain. The patient was discharge after 7th POD without any postoperative complication. On follow up after one year, patient was completely all right.

Discussion

Biliary injuries include biliary leakage, hemobilia, and biliary fistula. It usually occurs due to slipping of clip or ligature, diathermy injury or improper identification of biliary tree in the presence of acute inflammation or chronic fibrosis³. The treatment of patients with major bile duct injury (MBDI) after laparoscopic cholecystectomy (LC) is a difficult problem and depends on the time of diagnosis after the initial injury and the type, extent and level of the injury. There have been a few proposals to classify postoperative strictures and bile duct injuries. The Corlette-Bismuth classification (Table-I) is based on the length of the proximal biliary stump but not on the nature and length of the lesion. Another classification is by Strasberg (Table-II), and this is the most detailed classification as all types of injury, including leaks can be classified. The aim of the treatment is immediate management of the associated sepsis, fistula, and obstruction of the biliary system.

The reported incidence of MBDI after laparoscopic cholecystectomy has been shown to be higher (0.6%) than that after open cholecystectomy (0.1%)⁴. Several risk factors have been identified, mainly dangerous pathology, dangerous anatomy, and dangerous surgery⁵. A good practice is that the cystic duct should not be separated until the junction of the common hepatic and cystic ducts is positively identified.

Proper diagnosis and appropriate treatment of MBDI, are paramount in preventing life- threatening complications of cholangitis, biliary cirrhosis, portal hypertension, end-stage liver disease, and death. The problem is not recognized at the time of the initial procedure, particularly in the presence of acute inflammation or chronic fibrosis. Usually diagnosed post operatively due to presence of bile in the drainage tube, abdominal pain and distention, jaundice.

Table-I: Corlette -Bismuth classification

Type 1 Low common hepatic duct stricture, with a length of the common hepatic duct stump of > 2cm

Type 2 Middle stricture; length of common hepatic duct < 2 cm

Type 3 Hilar stricture, no remaining common hepatic duct, but the confluence is preserved

Type 4 Hilar stricture, with involvement of confluence and loss of communication between right and left hepatic duct

Type 5 Combined common hepatic and aberrant right hepatic duct injury, separating from the distal common bile duct

Table-II: Strasberg classification

Type A Bile leak from cystic duct or liver bed without further injury.

Type B Partial occlusion of the biliary tree, most frequently of an aberrant right hepatic duct.

Type C Bile leak from duct (aberrant right hepatic duct) that is not communicating with the common bile-duct.

Type D Lateral injury of biliary system, without loss of continuity.

Type E Circumferential injury of biliary tree with loss of continuity.

Post-operative imaging studies such as ultrasonography (US), magnetic resonance cholangiography (MRC), ERCP, and PTC correctly delineate the location and nature of MBDI^{6,7}. Once the sepsis and leaks have been controlled and the MBDI is classified, a hepaticojejunostomy should be constructed to a roux-en-y jejunal limb, or less commonly an end to side roux-en-Y choledochojejunostomy. This data support the concept of early referral to a tertiary care center with experienced hepatobiliary surgeons and skilled interventional radiologists to assure optimal short-term and long-term outcomes.

Conclusion

The case of biliary injury is usually not detected at the time of operation. They present postoperatively as abdominal pain, distension, fever with jaundice, and collection of bile at drainage bag. Diagnosis of biliary injury depends on clinical findings and some relevant investigations. Bile in the drainage tube is diagnostic. Supportive investigation includes ultrasonography (us) shows collection of fluid at gall bladder fossa. In severe case bile may occupy whole peritoneal cavity, computed tomography (CT) shows dilatation of biliary tree with collection of fluid. Others investigations are MRCP, ERCP, PTC in order to delineate the biliary anatomy. In a few cases conservative treatment is sufficient provided a drain is kept at the site of operation during the operative procedure (case no.1). Slipping of ligature or minimum

injury of CBD can be managed if the natural passage is remain patent. In some cases endoscopic stenting of CBD is sufficient. Majority of cases some form of surgical interventions are required. Initially drainage of bile and control of sepsis either by open or laparoscopic procedure can be done, then planning for permanent procedure should be done in the form of choledochojejunostomy or hepaticojejunostomy (case no. 3).

These data support the concept of early referral to a tertiary care center with experienced hepatobiliary surgeons and skilled interventional radiologists to assure optimal short-term and long-term outcomes.

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All photographs are taken from the reporting cases with the prior permission of patient parties.

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