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ADDRESS OF CORRESPONDENCE

Dr. Bakhtiare Md. Shoeb Nomany
Executive Editor, Dhaka Central International Medical College Journal,
Associate Professor, Department of Medicine, Dhaka Central International Medical College
Tel: +88029124396, Cell No. +8801770008844, Fax: +88029118598
Web: www.dcimch.com, email: jdcimc@yahoo.com
2/1, Ring Road, Shyamoli, Dhaka-1207, Bangladesh.

From the Desk of Editor-in-Chief

We are delighted to inform that the Volume 7, Number 1 of the Dhaka Central International Medical College Journal (DCIMCJ) is going to be published very soon. In this issue we have added a new section, Medical Quiz: Images. We are grateful to Almighty Allah. We are sending the complimentary copies of the journal to the libraries of most of the medical college and other medical institutions in Bangladesh. Already our journal has been approved by Bangladesh Medical & Dental Council (BMDC). We invite the doctors of medical colleges and institutes to submit their research articles to the journal committee for publication. We accept both hard & soft copies of the articles. We go through the papers and if necessary, communicate the authors. We also thank all the authors for giving us opportunity to publish their research papers in this journal. We have tried our best to avoid erroneous information. We like to add here that DCIMC Journal and its editorial board accept no liability for any inaccurate and misleading information, opinion and statements. It is the responsibility of the individual author (s). We have mentioned the instruction for the authors in this issue. We request the contributing authors to follow the instructions for their manuscripts. We appreciate our chairman, editors, members and advisors for their encouragement and also appreciate the contributors and reviewers for their participation. Last of all we welcome valuable suggestion, opinion, advice and constructive criticisms for improvement of the quality of the journal.

Prof. Bidhu Bhushan Das
Editor-in- Chief

INFORMATION FOR AUTHORS

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A manuscript number will be mailed to the corresponding author within two working days. The cover letter should include the corresponding author`s full address and telephone / fax numbers and should be in an e-mail message sent to the editor, with the file, whose name should begin with the first author`s surname attachments or triplicate Hard copy with a soft copy.

Article types:

Five types of manuscripts may be submitted:

Editorials:

It will be preferably written invited only and usually covers a single topic of contemporary interest.

Original articles:

These should describe new and carefully confirmed findings, and experimental procedures should be given in sufficient detail for others to verify the work. The length of a full paper should be the minimum required to describe and interpret the work clearly.

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A Short Communication is suitable for recording the results of complete small investigations or giving details of new models or hypotheses, innovative methods, techniques, images in clinical practice, letter to editors, short reports or apparatus. The style of main sections need not conform to that of original article. Short communication are 2 to 4 printed pages (about 6 to 12 manuscript pages) in length.

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Submissions of reviews and perspectives covering topics of current interest are welcome and encouraged. Reviews should be up to date. Reviews are also peer-reviewed.

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This should cover uncommon and /or interesting cases with appropriate confirmation process.

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All manuscripts are initially screened by editor and sent to selective reviewer. Decisions will be made as rapidly as possible, and the journal strives to return reviewers comments to authors within 3 week. The editorial board will re-review manuscripts that are accepted pending revision. The DCIMCJ editorial board will try to publish the manuscript as early as possible fulfilling all the rigorous journal needs.

I. A. Preparing manuscript for submission to DCIMCJ Editors and reviewers spend many hours reading manuscripts that are easy to read and edit. Much of the information in this journal`s Instructions to Authors is designed to accomplish that goal in ways that meet each journal`s particular editorial needs. The following information provides guidance in preparing manuscripts for this journal.

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- Ethical aspect of the study will be very carefully considered at the time of assessment of the manuscript.
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Preparation:

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2. Margin should be 5 cm for the header and 2.5 cm for the remainder.
3. Style should be that of modified Vancouver.
4. Each of the following section should begin separate page :
    - Title page
    - Summary/abstract
    - Text
    - Acknowledgement
    - References
    - Tables and legends

Page should be numbered consecutively at the upper right hand corner of each page beginning from the title page

I. A. 1.a. General Principles:

- The text of observational and experimental articles is usually (but not necessarily) divided into the following section: Introduction, Methods, Results, and Discussion. This so-called "IMRAD" structure is a direct reflection of the process of scientific discovery.

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- Electronic formats have created opportunities for adding details or whole sections, layering information, cross linking of extracting portions of the articles.
- Authors need to work closely with editors in developing or using such new publication formats and should submit supplementary electronic material for peer review.
- Double-spacing all portions of the manuscript- including the title page, abstract, text, acknowledgments, references, individual tables, and legends- and generous margins make it possible for editors and reviewers to edit the textline by line and add coments and queries directly on the paper copy.
- If manuscripts are submitted electronically, the files should be double-spaced to facilitate reviewing and editing.
- Authors should number on right upper corner of all of the pages of the manuscript consecutively, beginning with the title page, to facilitate the editorial process.

I. A.1.b. Reporting guidelines for specific study designs:

Research reports frequently omit important information. Reporting guidelines have been developed for a number of study designs that DCIMC journals ask authors to follow. Authors should consult the information for Authors of this journal. The general requirements listed in the next section relate to reporting essential elements for all study designs. Authors are encouraged also to consult reporting guidelines relevant to their specific research design. A good source of reporting guidelines in the EQUATOR network (http: //www.equator-network.org/home/) or CONSORT network (http://www.consort-statement. org).

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1. Article title. Concise title is easier to read than long, convoluted ones. Titles that are too short may, however, lack important information, such as study design (which is particularly important in identifying type of trials). Authors should include all information in the title that will make electronic retrieval of the article both sensitive and specific.
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8. A short running head or foot line, of no more than 40 characters (including litters and spaces). Running heads are published and also used within the editorial office for filing and locating manuscript.
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- Structured abstracts are essential for original research and systematic reviews. Structured abstract means introduction, methods, results and conclusion in abstract
- Should be limited to 250 words
- The abstract should provide the introduction of the study and blinded state and should state the study's purpose, basic procedures (selection of study subjects or laboratory animals, observational and analytical methods), main findings (giving specific effect sizes and their statistical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations. Articles on clinical trials should contain abstracts that include the items that the CONSORT group has identified as essential (http: //www. consort-statement. org).
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- State the specific purpose or research objective of, or hypothesis tested by, the study or observation; the research objective is often more sharply focused when stated as a question.
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- Identify the methods, apparatus (give the manufacturer's name and address in parentheses), and procedures insufficient detail to allow others to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief description for methods that have been published but are not well-known; describe new or substantially modified methods, give the reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration.
- Authors submitting review article should include a section describing the methods used for locatin, selection, extracting, and synthesizing data. These methods should also be summarized in the abstract.

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- Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals).

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- Specify the computer software used.

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- Present results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Please keep the sequence of specific objective selected earlier.

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- Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables.

- Avoid nontechnical uses of technical terms in statistics, such as “random” (which implies a randomizing device), “normal,” “significant,” “correlations,” and “sample.” Where scientifically appropriate, analyses of the data by such variables as age and sex should be included.

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- For experimental studies, it is useful to begin the discussion by briefly summarizing the main findings, then explore possible mechanisms or explanations for these findings, compare and contrast the results with other relevant studies, state the limitations of the study, and explore the implications of the findings for future research and for clinical practice.

- Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been complete. State new hypotheses when warranted, but label them clearly as such.

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- Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source.

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- Tables capture information concisely and display it efficiently.

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- Type or print each table with double-spacing on a separate sheet of paper. Number tables consecutively in the order of their first citation in the text and supply a brief title for each.

- Do not use internal horizontal or vertical lines. Give each column a short or an abbreviated heading. Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviation in footnotes, and use the following symbols, in sequence:
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- Identify statistical measures of variations, such as standard deviation and standard error of the mean.

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- Authors should review the images of such files on a computer screen before submitting them to be sure they meet their own quality standards. For x-ray films, scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, send sharp, glossy, black-and-white or color photographic prints, usually 127 X 173 mm (5 X 7 inches)

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The editor reserves the right to style and if necessary, shorten the material accepted for publication and to determine the priority and time of publication

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Editorial

DCIMCJ

DCIMCJ 2020 January;7(1):14-16

Use of Loop Diuretics in Nephrotic Syndrome

Nomany BMS[1]

Introduction:

The treatment of generalized edema from nephrotic syndrome consists of four key interventions:

1. Dietary salt (sodium) restriction,
2. Measures to mobilize fluid from edematous tissues.
3. Diuretic drug therapy and
4. Treatment of the underlying disorder in kidney. Here we will focus on use of diuretic drugs for management of nephrotic syndrome.

Loop diuretics are the treatment of choice for nephrotic edema. Because among all the diuretics, this class is the most potent than theother diuretic classes to produce a clinically significant natriuretic and diueffects.

But m retic assive proteinuria, the hallmark of the nephrotic syndrome, reduces the efficacy of loop diuretics. These observations led Inoue and colleagues to evaluate the efficacy of combination therapy in analbuminemic rats and hypoalbuminemic patients[1].

1. Dr. Bakhtiare Md. Shoeb Nomany, Associate Professor of Medicine (Nephrology wing), Dhaka Central international Medical College.

These investigators demonstrated a significant increase in urine output in analbuminemic rats when furosemide and albumin were administered together, as compared with either furosemide or albumin alone. The fractional excretion of furosemide was significantly lower in analbuminemic rats compared to normal rats when furosemide was given alone, suggesting diffusion of furosemide into various tissues. This distribution into tissues was decreased when furosemide was combined with albumin, with resultant decrease in furosemide excretion.

Inoue et al. also reported similar results in human subjects with hypoalbuminemia due to different causes, like cirrhosis and chronic renal failure. The combination of albumin and furosemide produced an increase in urine output ranging from 31–245 mL/h when compared to furosemide or albumin alone[1].

Low albumin level in blood plays important role to reduce the effectiveness of loop diuretics. This observation may be due to the fact that, loop diuretics (egfursemide) are organic anions (A-) that can bind to albumin (Alb^+) tightly and this binding is more than 95%, thus their volume of distribution is small. In nephrotic syndrome, due to low albumin level in blood, most of the loop diuretics remain free and their volume of distribution becomes high. Therefore most of the diuretics go to the tissue and relatively little amount reach the kidneys.

Ultimately less amount of drugs will be secreted by the basolateral-to-apical proximal tubularorganic anion transport system into the tubular lumen for delivery to loop of Henle. The result is less diuresis.

The loop diuretics that reach the renal tubular lumen by secretion in proximal convoluted tubules remain bound to the albumin. In nephrotic syndrome, huge amount of albumin is present in the tubular fluid, so a large fraction of the furosemide remain in inactive form and unable to inhibit the Na-k-2Cl cotransport system in loop of Henle. Thus albuminuria contributes to less diuresis and diuretic resistance.
The above mentioned scenario provides the rationale for infusing albumin together with loop diuretics to the patients with profound hypoalbuminemia. This clinical practice is supported by many literatures like Brater. Brater and colleagues also showed that such an approach is less useful, if serum albumin level is more than 2 gram/dl[2].

Now, we shall discuss about diuretic resistance. Typically the brisk increase in urinary solute and water excretion that is seen just after diuretic therapy is reduced gradually over several days of treatment. This phenomenon occurs because certain renal and systemic adaptation takes place in response to diuretic therapy. When this occurs before the achievement of the desired recovery of edema, that is called diuretic resistance.

These adaptation and resistance are classified into:

i) Immediate

ii) Short-term and

iii) Chronic[3].

1. Immediate adaptation and resistance:

This is classically seen in acetazolamide use. When acetazolamide is used, it decrease sodium reabsorption in proximal convoluted tubules and increases sodium reabsorption along the loop of Henle and hence limits the natriuretic effectiveness. Co-administration of a loop diuretic with acetazolamide can limit the sodium reabsorption along the loop of Hanle and counteract the immediate diuretic resistance.

2. Short term adaptation and resistance:

Once the diuretic concentration declines, sodium reabsorption along the nephron is stimulated. This phenomenon is referred to post-diuretic Nace retention". This is due to oven activation of RAAS, sympathetic over activation and suppression of ANP. Moreover the number of thiazide-sensitive co-transporters in the distal convoluted tubules increase within 60 minutes of loop diuretic administration[4].

3. Chorine adaptation & retention:

It refers to the decline in natriuresis following each repeated dose of diuretic. It is due to RAAS over activation, a hypertrophy and hyperplasia of sodium chloride reabsorbing cells. For example, loop diuretic infusions of 7 days increase the number and size of a distal convoluted cells substantially and also increases the number of active thiazide-sensitive NaCl cotransporters[5,6,7]. This can reduce the therapeutic effectiveness of loop diuretics and contribute to diuretic resistance. As chronic loop diuretics increase the NaCl reabsorption in thiazide -sensitiveNaCl transporters in the DCT, combining a low dose thiazide with a loop diuretic can be a highly effective way to counteracting resistance.

In conclusion, gross edema in nephrotic syndrome with very low albumin level is a medical challenge. Management is sometimes difficult. Only furesemide, oral or intravenous, is not sufficient. Concomitant use of injectable loop diuretics and albumin infusion may provide satisfactory response.

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Original Article

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Response of Paclitaxel-Capecitabine versus Cisplatin-5F.U. Prior Radiotherapy in Locally Advanced Inoperable Oesophageal Carcinoma

Hossain MRZ[1], Alam S[2]

Abstract:

Objective: To compare efficacy profiles between paclitaxel- capecitabine and cisplatin-5-fluorouracil-based sequential chemo radiotherapy for advanced inoperable oesophageal cancer. Method: This prospective analytical study was conducted in the Department of Oncology, Bangabandhu Sheikh Mujib Medical University, Department of Radiation oncology, National Institute of Cancer Research and Hospital and Department of Radiotherapy, Dhaka from July 2016 to June 2017. Eighty patients with locally advanced carcinoma of the esophagus (stage IIB – stage IVA) treated with sequential chemo radiation were enrolled in this study. Patients were divided into two groups. Arm A treated with chemotherapy with Cisplatin and 5-Flurouracil followed by radiotherapy and Arm B treated with Paclitaxel and Capecitabine followed by radiotherapy. Result: In this study, mean age 49.9 ± 8.6 years in Arm A and 47.1 ± 12.0 years in Arm B. In Arm A, males were 31 (77.5%) and females were 9 (22.5%). In Arm B, males were 29 (72.5%) and females were 11 (27.5%). In Arm A, toxicity was significantly higher than Arm B (52.5% vs 25.0%). Completed response was 3 (7.5%) in Arm A and 7 (17.5%) in Arm B. Partial response was 14 (35.0%) in Arm A and 22 (55.0%) in Arm B. Stable disease was 9 (22.5%) in Arm A and 6 (15.0%) in Arm B. Progressive response was 14 (35.0%) in Arm A and 5 (12.5%) in Arm B. Conclusion: Sequential chemoradiation with Paclitaxel- Capecitabine is effective, tolerable, convenient and less toxic than Cisplatin-5 F.U. in the treatment of locally advanced carcinoma oesophagus.

Keywords: Paclitaxel- capecitabine, cisplatin-5F.U., radiotherapy, oesophageal carcinoma

Introduction:

Cancer is a great health problem all over the world. The incidence of oesophageal carcinoma is increasing in the world as well as in Bangladesh. Oesophageal cancer is the sixth most commonly diagnosed cancer, with over 480,000 new cases, and the fifth most common cause of cancer related death, with more than 400,000 deaths annually in the world[1]. Histologically, oesophageal cancer mainly divided into squamous cell carcinoma (SCC) and adenocarcinoma but other subtype may occur rarely[2].

Oesophageal cancer is frequently diagnosed at the advanced stages of disease, and despite recent progress in diagnosis and treatment, the 5-year survival rate of oesophageal cancer is still very low. Locally advanced cancer means that the cancer has spread into the tissues around the oesophagus. It hasn't spread to other organs. Locally advanced cancers are either stage 2 or stage 3. As a result, these patients are unable to undergo resection, the gold standard therapy for solid tumor[3].

Indeed, treatment of advanced inoperable locally advanced oesophageal cancer patients involves chemotherapy and radiotherapy. Systemic chemotherapy with local radiation therapy has been developed to control local disease and metastasis and to improve progression-free survival (PFS) in patients with inoperable oesophageal cancer. Chemotherapy has also been used as adjuvant and neoadjuvant therapies for patients with operable oesophageal cancer and has become the standard of care to reduce tumor lesions prior to resection.

1. Dr. Md. Rifat Zia Hossain, Resident, Phase-B, MD (Oncology), BSMMU.

2. Prof. Sarwar Alam, Professor and Chairman, Department of Oncology, BSMMU.

Correspondence: Dr. Md. Rifat Zia Hossain
E-mail: rzhossain@gmail.com

Overall; radiation therapy alone may effectively control local tumor growth, while chemotherapy can block progression of systemic disease[4].

Different combinations of chemotherapeutic drugs with radiation treatment greatly affect the efficacy and response. Current standard treatment involves cisplatin and 5-fluorouracil (PF) along with sequential radiation therapy.

Although such regimens show antitumor effects to control local and systemic tumors in esophageal cancer patients, the toxicity, especially gastrointestinal adverse effects, significantly limit their use[4]. Over the past decade, there have been advancements in drug development and many alternative chemotherapeutic drugs have been identified. For example, taxane has been successfully used to treat patients with different types of cancer in various settings[5]. In addition to its antitumor activity, taxane can sensitize tumor cells to radiation therapy. When used as a single agent in combination with radiation therapy in oesophageal cancer patients, taxane has similar effects as PF therapy with less toxicity[6]. Taxane in combination with cisplatin has also been used to treat esophageal cancer patients, with a response rate of over 50%. Furthermore, sequential chemo radiation with paclitaxel and platinum has improved the survival of patients with locally advanced oesophageal cancer[7]. Recently, capecitabine has demonstrated an extended spectrum of antitumor activity and does not have cross-resistance with cisplatin thus it can effectively treat cisplatin-resistant oesophageal cancer[8]. In addition, Honing et al. found that carboplatin and paclitaxel treatment improved the survival of inoperable oesophageal cancer when compared with Cisplatin-5F.U. treatment[9]. However, more studies are needed to provide medical evidence for the treatment of advanced inoperable esophageal cancer with Paclitaxel- Capecitabine based sequential chemoradiotherapy.

Materials & method:

Study design: It was a prospective analytical study.

Place of Study: This study was conducted in the Department of Oncology, Bangabandhu Sheikh Mujib Medical University, Department of Radiation oncology, National Institute of Cancer Research and Hospital and Department of Radiotherapy, Dhaka.

Duration of study: This study was conducted from July 2016 to June 2017.

Study population: Patients with locally advanced carcinoma of the esophagus (stage IIB – stage IVA) treated with sequential chemo radiation were enrolled in this study.

Sample size (n): A total of 80 patients with above mentioned criteria were selected as sample 40 in each arm from July 2016 to February 2017. These patients were assigned to in two arms containing 40 patients in each arm.

Sampling technique:

Diagnosed patients of locally advanced carcinoma of oesophagus were selected first. Initially patients were selected purposively who met the inclusion criteria for the study, then random sampling was done by randomized number generator which is a computational process that produces random numbers by using statistical algorithm.

Missing data imputation:

In the analysis of clinical trial results, dropouts need to be addressed during the trial. In this trial the Last Observation Carried Forward (LOCF) imputation method is used as the data are longitudinal. It is considered good practice not to ignore dropouts. Last observation carried forward (LOCF) is a commonly used way of imputing data with dropouts. LOCF uses the last value observed before dropout, regardless of when it occurred.

The FDA has traditionally viewed LOCF as the preferred method of analysis, considering it likely (but not certain) to be conservative and clearly a good method. The last observed value (non-missing value) is used to fill in missing values at a later point in the study.

Therefore one makes the assumption that the response remains constant at the last observed value.

Selection criteria:

Inclusion criteria:

- Histopathological diagnosed case of carcinoma of oesophagus (stage IIb to IV).

Exclusion criteria:

- History of prior chemotherapy, radiotherapy or surgery.
- Patients with ECOG performance status more than 2.
- Patients with obstructive feature.
- Serious concomitant medical illness including severe heart disease, uncontrolled diabetes mellitus or hypertension.
- Life expectancy <6 months
- Patients with uncontrolled infection
- Patient dropped out or lost to follow up
- Age more than 70 years

Criteria for discontinuation of treatment:

- Patient's refusal to continue study participation.
- Occurrence of unacceptable toxicity necessitating major modification of treatment.

Justification for inclusion and exclusion criteria:

A cut-off age of 70 year was selected as these patients have no co-morbidities with limited life expectancy. Patients with distant metastasis and obstructive feature were excluded because they are not treated radically. Patients with uncontrolled infection were excluded as radiotherapy may worsen the patient's general condition. Patients with history of prior chest and pelvic radiotherapy were excluded.

Research instrument:

Semi structured questionnaire was used as research instrument.

Study method:

Selected patients in each arm receive treatment as mentioned below.

Arm A- Chemotherapy with Cisplatin and 5 Flurouracil followed by radiotherapy.

Arm B- Chemotherapy with Paclitaxel and Capecitabine followed by radiotherapy.

All patients of this study will have radiation treatment with a total dose of 44 Gy in 22 daily fractions at 2 Gy per fraction after receiving the chemotherapy scheduled for each arm.

Data collection:

A questionnaire was prepared considering key variables like demographic data, clinical presentation, clinical findings and investigations were collected.

Statistical analysis:

Statistical analysis of the study was done by computer software devise. The result was presented in tables, figures and diagrams. Caterogorical data was presented as frequency & percentage and numerical data as mean & standard deviation. Confidence interval was considered at 95% level. P value of <0.05 will be considered statistically significant.

Variables:

1) Age of the patient
2) Gender
3) Socioeconomic condition
4) Tumour size
5) Histopathological type
6) Site of primary tumour
7) TNM staging of the disease
8) Performance status
9) Treatment response
10) Toxicity

Pretreatment evaluation:

Following procedures will be followed to evaluate the patient's condition before treatment.

General:

- Complete history, performance status and physical examination.
- Location and size of the tumor were recorded prior to treatment.

Laboratory studies:

- Complete blood count
- Kidney function tests (serum creatinine, creatinine clearance rate if needed).
- Liver function tests (serum bilirubin, SGPT, SGOT).
- ECG

Radiological studies:

- Endoscopy of upper GIT X-ray chest P/A view.
- X-ray chest P/A view.
- Ultrasonogram of whole abdomen.
- Other on need basis
- CT scan of chest and abdomen.
- Barium swallow

Registration procedures:

Patients were evaluated for registration into the study. Pretreatment assessment was done and patients who fulfilled all the criteria for enrollment into the study were included.

Treatment planning & procedures:

Patients were selected from the Department of Oncology, Bangabandhu Sheikh Mujib Medical University, and Department of Radiation oncology, National Institute of Cancer Research and Hospital, Dhaka as per inclusion and exclusion criteria.

Each patient was interviewed and history was documented according to prescribed datasheet. After selecting patients a written informed consent was taken from each patient before his/her participation in the study. After selection of the patient; aims, objectives and procedures of the study was explained with understandable language to the patient.

Risks and benefits were also made clear to the patient. The patients were encouraged for voluntary participation and they were allowed being free to withdraw themselves from the study. Then, informed written consent was taken from each patient.

Clinical examination and necessary investigations were done. Patients of arm A received chemotherapy with Cisplatin 80 mg/m2 I.V on day 1 and 5-Fluouracil 1000mg/m2 I.V. from day 1-4. They received this regime three weekly for a total of six cycles. Patients of arm B received chemotherapy with Paclitaxel 80 mg/m2 I.V on day 1and day 8 and Capecitabine 900mg/m2 orally from day 1-14.

They received this regime three weekly for a total of six cycles Proper hydration and premedication were maintained.

Treatment by radiotherapy:

Target volume:

This should include the primary tumour as defined by oesophagoscopy or barium swallow, with a margin of 5 cm above & below. The length of the volume should not exceed 18 cm. The lateral margin should be sufficient to encompass the soft tissues of oesophageal wall 6-8 cm , if the adjacent nodes liable to invasion are included.

Technique:

For treatment of the upper third of the oesophagus the patient lies supine with the cervical spine straight and parallel to the couch top and a perspex cast is made to immobilize the neck, jaw and upper thorax. For middle and lower third esophageal lesion, the patient lies supine with their arms above their head. `With the patient in the treatment position anterior-posterior simulator films are taken after the patient has shallowed barium in order to localize the length and width of the target volume. Anterior-posterior and lateral films are taken to determine the target volume. The position of the spinal cord should be marked at each level.

Conventional radiotherapy fields

Cervical esophagus RT:

Superior: 5 cm proximal to tumor+ Supra clavicular LN+ Upper Mediastinal

LN Inferior: 5 cm distal to tumor

Lateral: Tumor+ 2.5 cm+ Mediastinal LN+2/3rd of clavicle for SCF LN

Middle esophagus RT:

Superior: 5 cm proximal to tumor+ Upper Mediastinal LN

Inferior: 5 cm distal to tumor+ Upper Mediastinal LN

Lateral : Tumor+ 2.5 cm-3 cm+ Mediastinal LN

Lower esophageal RT:

Superior : 5 cm proximal to tumor+ Mediastinal LN

Inferior: 5 cm distal to tumor+ Mediastinal LN+ celiac LN (until L1-2 vertebrae)

Lateral: Tumor+ 2.5 cm-3 cm+ Mediastinal LN

Dose:

All patients of this study receive radiation treatment with a total dose of 44 Gy in 22 daily fractions at 2 Gy per fraction 3 weeks after receiving the chemotherapy scheduled for each arm with Telecobalt machine. Tumour response was evaluated after completion of 6th cycle of chemotherapy and at week 6 (1st follow up) and 12 (2nd follow up) after completion of radiotherapy but symptomatic responses and toxicities were assessed after completion of each cycle of chemotherapy and in every week during radiotherapy and at week 6 (1st follow up) and 12 (2nd follow up) after completion of treatment. Improvement of quality of life was assessed by ECOG performance scale.

Assessment of patients:

Tumour response

Tumour response was evaluated according to the WHO criteria issued in 1979 (WHO 1979). To assess the tumor response to the treatment WHO criteria was followed. Tumour responses were categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The final response was assessed after clinical examination including upper GIT endoscopy which was done at twelve weeks after completion of all therapy.

Quality of life:

Improvement of quality of life was assessed by ECOG performance scale.

Toxicity reporting:

To assess toxicity, the national cancer institute "Common terminology criteria for adverse events, v. 4.0 published on June 14, 2010" was used. Any development of toxicity during treatment was managed appropriately.

Ethical implication:

Prior to commencement of this study, the research protocol was approved by IRB of BSMMU, Dhaka. All the patients included in this study were informed about the nature, risk and benefit of the study. Proper permission was taken from the department and institution concerned for this study.

Results and observation:

A total of 80 patients were enrolled in this study to compare the effectiveness and toxicity of two different regimens of chemotherapy along with radiotherapy in locally advanced oesophageal cancer. Among 80 patients, 40 patients were treated with cisplatin-5 F.U. in Arm-A, and 40 patients were treated with Paclitaxel-Capecitabine Arm-B.

Table I: Distribution of patients according to age in Group (n=80)

	Group		P value
Age (years)	Arm A n (%)	Arm B n (%)	
≤31	3(7.5)	5 (12.5)	
31 - 40	3(7.5)	6 (15.0)	
41 - 50	9 (22.5)	4 (10.0)	
51 - 60	22(55.0)	24 (60.0)	
>60	3 (14.7)	1 (13.8)	
Mean ± SD	49.9 ± 8.6	47.1 ± 12.0	0.228

Unpaired t test was done to measure the level of significance

Table I shows distribution of patients according to age in Arm A and Arm B. Mean age 49.9 ± 8.6 years in Arm A and 47.1 ± 12.0 years in Arm B. There was no significant difference between Arm A and Arm B.

Table II: Distribution of patients according to gender in group (n=80)

Gender	Group		P value
	Arm A n (%)	Arm B n (%)	
Male	31 (77.5)	29 (72.5)	0.606
Female	9 (22.5)	11 (27.5)	

Chi-square test was done to measure the level of significance

Table II shows distribution of patients according to gender in Arm A and Arm B. In both groups males were predominant than female. There was no significant difference between Arm A and Arm B.

Distribution of patients according to economic condition:

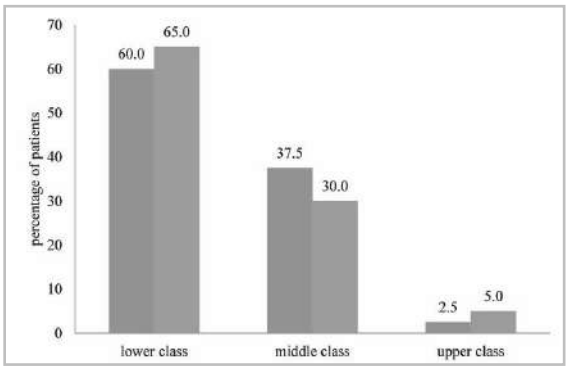

Figure 1: Bar diagram shows economic condition of patients in both arms

Majority of patients in this study belongs to low to middle class economic condition.

Table III: Distribution of patients according to TNM stages (n=80)

TNM stages	Group		P value
	Arm A n (%)	Arm B n (%)	
T1	0(0.0)	1(2.5)	0.082
T2	4 (10.0)	3(7.5)	
T3	24(60.0)	14(35.0)	
T4	12(30.0)	22(55.0)	
N1	33(82.5)	28(70.0)	0.189

Chi-square test was done to measure the level of significance.

Table III shows TNM stages of the patients. There was no significant difference between Arm A and Arm B in TNM stages.

Table IV: Distribution of patients according to tumour site (n=80)

Tumour site	Group		P value
	Arm A n (%)	Arm B n (%)	
Upper	6 (15.0)	11(27.5)	0.125
Mid	3(7.5)	5 (12.5)	
Distal	21(52.5)	21 (52.5)	
GEJ	10(25.0)	3(7.5)	

Chi-square test was done to measure the level of significance

Table IV shows tumour site of the patients. In both groups maximum tumours were in distal. There was no significant difference between Arm A and Arm B in TNM stages.

Table V: Distribution of patients according to tumour length (n=80)

Tumour length (cm)	Group		P value
	Arm A n (%)	Arm B n (%)	
≤ 5	12 (30.0)	10 (25.0)	0.617
> 5	28 (70.0)	30 (75.0)	

Chi-square test was done to measure the level of significance

Table V shows tumour length of the patients. In both groups maximum tumours were > 5cm long. There was no significant difference between Arm Aand Arm B in tumour size.

Table VI: Distribution of patients according to histology (n=80)

Histology	Group		P value
	Arm A n (%)	Arm B n (%)	
SCC	24 (60.0)	17 (42.5)	0.117
AC	16 (40.0)	23 (57.5)	

Chi-square test was done to measure the level of significance.

Table VI shows histology of the tumours. There was no significant difference between Arm A and Arm B.

In group A, SCC was 24 (60.0%) and AC was 16 (40.0%). In Arm B, SCC was 17 (42.5%) and AC was 23 (57.5%).

Table VII: Distribution of patients according to toxicity (n=80)

Toxicity	Group		P value
	Arm A n (%)	Arm B n (%)	
Toxicity	**21 (52.5)**	**10(25.0)**	**0.012**
Hematological	8 (20.0)	2(5.0)	
Febrile Leucopenia	6 (15.0)	2(5.0)	
Thrombocytopenia	1(2.5)	2(5.0)	
Bleeding	1(2.5)	2(5.0)	
Anaemia	3(7.5)	2(5.0)	
Non hematological	13(32.5)	8 (20.0)	
Nausea/vomiting	2(5.0)	0(0.0)	
Fatigue	1(2.5)	0(0.0)	
Diarrhea	0(0.0)	1(2.5)	
Mucositis	2(5.0)	2(5.0)	
Others	8 (20.0)	5 (12.5)	

Chi-square test was done to measure the level of significance

Table VII shows toxicity of the treatment. In Arm A toxicity was significantly higher than Arm B (52.5% vs 25.0%). Hematological toxicity was 8 (20.0%) in Arm A and 2 (5.0%) in Arm B. Non hematological toxicity was 13 (32.5%) in Arm A and 8 (20.0%) in Arm B.

Table VIII: Distribution of the patients by symptomatic response during 1st follow up

	Group A n (%)	Group B n (%)	Total n (%)	P value
Progressive dysphagia	20(50.0)	29(72.5)	49(61.3)	0.038
Painful swallowing	3(7.5)	5 (12.5)	8 (10.0)	0.711
Vomiting	6 (15.0)	10(25.0)	16(20.0)	0.263
Cough	5 (12.5)	7 (17.5)	12(15.0)	0.532
Loss of appetite	7 (17.5)	10(25.0)	17(21.3)	0.413
Hoarseness of voice	1(2.5)	1(2.5)	2(2.5)	1.000

Table IX: Assessment of treatment response (n=80):1st follow up

Treatment response	Group		P value
	Arm A n (%)	Arm B n (%)	
Completed response	3(7.5)	7 (17.5)	0.041
Partial response	14(35.0)	22 (55.0)	
Stable disease	9 (22.5)	6 (15.0)	
Progressive response	14(35.0)	5 (12.5)	

Chi-square test was done to measure the level of significance

Table IX shows treatment response. Completed response was 3 (7.5%) in Arm A and 7 (17.5%) in Arm B. Partial response was 14 (35.0%) in Arm A and 22 (55.0%) in Arm B. Stable disease was 9 (22.5%) in Arm A and 6 (15.0%) in Arm B. Progressive response was 14 (35.0%) in Arm A and 5 (12.5%) in Arm B.

Table X: Assessment of treatment response (n=80): 1st follow up

Treatment response	Group		P value
	Arm A n (%)	Arm B n (%)	
Yes	17 (42.5)	29 (72.5)	0.007
No	23 (57.5)	11 (27.5)	

Chi-square test was done to measure the level of significance

Table X shows treatment response. Response was significantly higher in Arm B than that of Arm A (72.5% vs 42.5%).

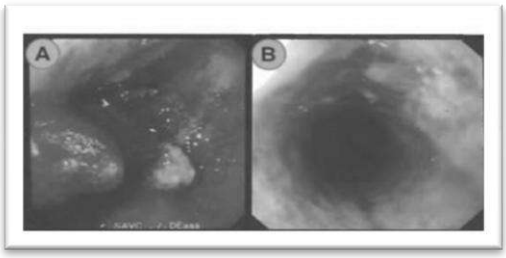

Figure 24: White-light endoscopic images of a 54 year old male with squamous cell carcinoma of the oesophagus (A) Pre-treatment diagnostic upper-gastrointestinal endoscopy; this demonstrates a 1cm tumour. (B) Post- chemoradiotherapy: This patient had a complete luminal and complete pathological response to chemoradiotherapy.

Table XI: Assessment of treatment response after 2nd follow up (n=80)

Treatment response	Group		P value
	Arm A n (%)	Arm B n (%)	
Yes	20 (50.0)	29 (72.5)	0.038
No	20 (50.0)	11 (27.5)	

Chi-square test was done to measure the level of significance

Table XI shows treatment response. Response was significantly higher in Arm B than that of Arm A (72.5% vs 50.0%).

Table XII: Assessment of treatment response after final follow up (24 weeks) (n=80)

Treatment response	Group		P value
	Arm -A n (%)	Arm- B n (%)	
Yes	20 (50)	29 (72.5)	0.038
No	20 (50)	11 (27.5)	

Chi-square test was used to determine p value.

Table XII shows treatment response. Response was significantly higher in Arm B than that of Arm A.

Final follow up was done at 6 month (24 weeks) after completion of treatment and it was observed that 50.0% of patients had complete response in group A. In group B 72.5% had complete response. Statistical analysis revealed there was significant difference that means Arm-B patients had better response than Arm-A.

Discussion:

This prospective analytical study was conducted in the Department of Oncology, Bangabandhu Sheikh Mujib Medical University, Dhaka from July 2016 to June 2017 over a period of one year to compare the efficacy profiles between paclitaxel- capecitabine and cisplatin- 5- fluorouracil-based sequential chemoradiotherapy for advanced inoperable oesophageal cancer. Eighty patients were included in this study and divided equally into two groups. Arm A had chemotherapy with Cisplatin 80 mg/m2 I.V. on day 1 and 5 F.U. 1000mg /m2 I.V. from day 1-4, three weekly, total six cycles. Arm B had chemotherapy with Paclitaxel 80 mg / m2 I.V. on day 1 & 8 and Capecitabine 900mg/ m2 orally from day 1-14, 3 weekly, total six cycles.

In this study, mean age 49.9 ± 8.6 years in Arm A and 47.1 ± 12.0 years in Arm B. There was no significant difference between Arm A and Arm B. Age was comparatively higher in the study of Honing et al. In both groups males were predominant than female.

In Arm A, males were 31 (77.5%) and females were 9 (22.5%). In Arm B, males were 29 (72.5%) and females were 11 (27.5%). There was no significant difference between Arm A and Arm B. Male predominance was also observed in the study of Honing et al[9]. In Arm A, T2 was 10.0%, T3 was 60.0% and T4 was 30.0%. In Arm A, T1 was 2.5%, T2 was 7.5%, T3 was 35.0% and T4 was 55.0%. N1 was 82.5% in Arm A and 70.0% in Arm B. Honing et al[9]. and found similar findings.

Regarding tumour site, 15.0% in upper, 7.5% in mid, 52.5% in distal and 25.0% in GEI in Arm A whereas 27.5% in upper, 12.5% in mid, 52.5% in distal and 7.5% GEI in Arm B. Honing et al[9]. observed similar findings. In both groups maximum tumours were > 5cm long (70.0% vas 75.0%). Similar findings also seen in the study of Honing et al[9].

In Arm A, AC was 24 (60.0%) and SCC was 16 (40.0%). In Arm B, AC was 17 (42.5%) and SCC was 23 (57.5%). There was no significant difference between Arm A and Arm B. Honing et al. found similar findings[9].

In Arm A, toxicity was significantly higher than Arm B (52.5% vs 25.0%). Hematological toxicity was 8 (20.0%) in Arm A and 2 (5.0%) in Arm B.

Non hematological toxicity was 13 (32.5%) in Arm A and 8 (20.0%) in Arm B. Febrile leucopenia was 6 (15.0%), thrombocytopenia was 1 (2.5%), bleeding was in 1 (2.5%) and anaemia was in 3 (7.5%) cases in Arm A. Febrile leucopenia was 2 (5.0%), thrombocytopenia was 2 (5.0%), bleeding was in 2 (5.0%) and anaemia was in 2 (5.0%) cases in Arm B. Similar toxicity also observed in the study of Honing et al[9].

Nausea was in 2 (5.0%), fatigue in 1 (2.5%), mucositis in 2 (5.0%) and other non hematological toxicity in 8 (20.0%) cases in Arm A. Diarrhoea in 1 (2.5%), mucositis in 2 (5.0%) and other non hematological toxicity in 5 (12.5%) cases in Arm B. Similar findings also observed in the study of Honing et al. 2014.

In this study, completed response was 3 (7.5%) in Arm A and 7 (17.5%) in Arm B. Partial response was 14 (35.0%) in Arm A and 22 (55.0%) in Arm B. Stable disease was 9 (22.5%) in Arm A and 6 (15.0%) in Arm B. Progressive response was 14 (35.0%) in Arm A and 5 (12.5%) in Arm B. Response was significantly higher in Arm B than that of Arm A (72.5% vs 42.5%).

Conclusion:

Sequential chemoradiation with Paclitaxel Capecitabine is effective, tolerable, convenient and less toxic than Cisplatin-5 F.U. in the treatment of locally advanced carcinoma oesophagus.

Limitations:

Although optimum care was given in every steps of the study, still there are some limitations:

1. Small sample size was a major limitation to have an accurate clinical outcome.

2. The study was analyzed among the patients who attended in different selected hospitals of Dhaka city only and therefore, the entire situation of the patients with carcinoma oesophagus in the country was not possible.

Recommendations:

1. Further study involving multiple centers with a larger sample size should be carried out
2. The study should be continued to see overall survival and late toxicities of treatment.

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Original Article

DCIMCJ

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A Comparative Study of the Effects of Low-Dose Topiramate-versus Sodium Valproate in the Prophylaxis of Migrainous Vertigo

Mamun KAA[1], Barua R[2], Nomany BMS[3]

Abstract:

Objective: The present study was performed to compare the efficacy of low-dose topiramate and sodium valproate in the prophylaxis of migrainous vertigo. Methods: This was a randomized clinical trial. 86 patients diagnosed as definite migrainous vertigo were recruited in the study. Topiramate and valproate were administered at 50 mg/day and 400 mg/day, respectively, during the follow-up period. Frequency, intensity, duration, associated symptoms with vertigo, as well as drugs' side effects were studied. Prophylaxisofmigrainous vertigo were studied in two groups ,first group comprising of 42 patients received topiramate and another 44 patients received sodium valproate . Collected data analyzed by statistical methods in SPSS version 25. P<0.05 was considered as significant. Results :The reduction of severity of vertigo in the topiramate group was significantly more than in the valproate group (p = .027). During the study, no statistically significant reduction of associated symptoms with vertigo were observed in both the groups. Conclusions: This study showed that topiramateis better than sodium valproate.

Keywords: Migrainous vertigo, topiramate, sodium valproate

Introduction:

Migrainous vertigo is defined as vertigo or dizziness caused by migraine[1]. Using strict criteria the prevalence is nearly 1% of the population[2].

Although there is no universally recognized definition for migrainous vertigo, several recent studies have employed criteria originally proposed by Neuhauser and Lempert[3].These criteria are extensions of the definition of migraine as proposed in the International Classification of Headache Disorders (2nd Edition) (ICHD-II)[4] and are as follows:

1. Recurrent vestibular vertigo.
2. Migraine according to the International Headache Society-migrainous symptoms during at least two vertiginous attacks (migrainousheadache, photophobia, phonophobia, or aura symptoms) and.
3. Vertigo not attributed to another disorder.

Headache is not required to make the diagnosis of migraine-associated vertigo[5,6]. There are only a few published randomized trials of medications specifically for migranousvertigo . In clinical practice it is managed similarly to migraine. Prophylactic strategies are favored when attacks are frequent (ie, more than once per week) or severe (eg, making driving dangerous)[7]. Prophylactic strategies are also necessary for long-duration symptoms[8]. There are two main groups of prophylactic medications that can be employed: anticonvulsants and antidepressants. Agents from each group can be combined in refractory situations[9]. It is justified to start with very low doses of any chosendrug. Treatment most commonly starts with the antidepressant, followed by the anticonvulsant, topiramate or sodium valproate .

1. Dr. Kazi Abdullah Al Mamun, Associate Professor Department of Neuromedicine, Dhaka Central International Medical College.
2. Dr. Raju Barua, Assistant Professor, Department of ENT, Dhaka Central International Medical College.
3. Dr. Bakhtiare Md Shoeb Nomany, Associate Professor, Department of Medicine, Dhaka Central International Medical College.

Correspondence: Dr. Kazi Abdullah Al Mamun
E-mail: abdalmamun39@gmail.com

Methods:

Study design and patients

We conducted a prospective, randomized clinical trial. A total of86 patients were randomized to receive topiramate 50mg/d (n= 42) and valproate 400mg/d (n= 44). The patients were evaluated for treatment efficacy after 3 months. Efficacy was assessed as a more than 50% decrease in vertigofrequency and duration.

Inclusion criteria:

1. Patients fulfilled the criteria of migrainousvertigo mentioned above.
2. More than 2 attacks of vertigo per month.
3. Age 19 to 50 years old .

Exclusion criteria:

1. Patients with a history of sodium valproate and topiramate use, breast feeding , had underlying illnesses such as liver failure, the use of sedative medications and pregnant women were excluded from the study.
2. Diagnosis of the following: benign paroxysmal positional vertigo, Meniere's disease, vestibular migraine with headache, intracranial mass, perilymphatic fistula, or multiple sclerosis
3. History of cholesteatoma
4. Prior ear surgery
5. Prior radiation to head or neck.
6. Pregnant or lactating females

Data collection:

This was a Randomized Clinical Trial carried out in Department of neurology DCIMC from March to August, 2018. Non-probability consecutive sampling technique was used. All patients were aged 19-50 were taken. Permission was sought from hospital Ethical Committee. 86were selected after detailed history and examination on 1st visit. Informed written consent was taken from all the patients.

Patients were randomly divided into two groups –one group was taking topiramate and other group was on Sodium Valproate. Patients visited monthly and the efficacy of treatment based on the frequency and duration of vertigo attacks per month was assessed.

Statistical analysis:

Collected data were analyzed by SPSS version 25 using descriptive and analytical statistical methods. The level of significance was less than 0.05.

Results:

There was no significant difference between two groups in terms of age, sex, diet, education level, history of headache, headache frequency, drug use and MIDAS (Table 1). Of the topiramategroup, 9 (21%) were male and 33 (79%) were female of sodium valproate group, 8 (18%) were male and 36 (82%) were female. The average age of group Sodium valproate was 35.14±7.3 and topiramate group was 36.33±6.6 and the mean age of the all patients was 35.91±6.9. This difference wasn't significant. The duration of vertigo was 9.95±5.93 years in group Sodium valproate and 10.95±5.43 years in group topiramate and 10.47±6.63 years in all group. This difference was not significant (Table 1).

The frequency of vertigo in group Sodium valproate was 4.6±1.75 and in group topiramate was 2.6±1.43 which was not statistically significant in the baseline. After 3 months the frequency of vertigo was 3.9±1.18 and 2.29±0.88 in groups Sodium valproate and topiramate, respectively which was statistically significant difference (P=0.0001) and indicates a better topiramate effect. The duration of vertigo attack was 16.63±6.8 in group Sodium valproate and 14.21±4.5 in group topiramate respectively that it was not statistically significant. After 3 months of treatment the duration of migraine attack was 11.4±6.09 and 10.5±2.5 in the Sodium valproate and topiramate groups respectively and the difference was statistically significant (P=0.0001).

Table 1: Comparison of frequency and duration in two groups before prescribing the drug (at baseline).

Variables	Group	Mean	SD	P value
Age	Sodium valproate	35.14	7.3	0.5
	Topiramate	36.33	6.6	
Frequency of vertigo	Sodium valproate	4.6	1.75	0.27
	Topiramate	2.6	1.43	
Duration of each attack of Vertigo (in hours)	Sodium valproate	16.63	6.8	0.36
	Topiramate	14.21	4.5	

Table 2: Comparison of frequency and duration of vertigo after the administration of the drug.

Variables	Group	Mean	SD	P value
Frequency of vertigo	Sodium valproate	3.9	1.18	0.001
	Topiramate	2.29	0.88	
Duration of each attack of Vertigo (in hours)	Sodium valproate	11.4	6.09	0.001
	Topiramate	10.5	2.5	

Discussion:

Although the efficacy of sodium valproate in preventing migraine has been confirmed in valid clinical studies and this drug is one of the approved drugs in the prevention of migraine. But long term side effects (depression, muscle weakness, tremor, ataxia, headache, insomnia, drowsiness, blurred vision, nausea, vomiting, indigestion, diarrhea, abdominal cramps, constipation, increased appetite, anorexia, hepatitis, weight gain, alopecia, multiple form erythema, flu like syndrome, itching, rash, Stevens Johnson syndrome) may limit its use in future[10].

This study is in line with previous studies that reported the efficacy of topiramate in preventing migrainousvertigo. Virgilio Gallai et al, in a study reported a reduction of 50% in the number of vertigo attacks after receiving topiramate and showed that the number of migraine attacks was significantly reduced, which was in line with the resul t of our study which showed high efficacy of topiramate[11]. In this study, the dosage of topiramate was 50 mg per day that few adverse drug effect was observed in any of the patients it may be due to low dose medication.

Sadeghian in a study in the Tehran showed that the topiramate had a 50% reduction in the number of vertigo attacks after receiving topiramate and has a comparable effect with other antiepileptic drugs such as sodium evaporate which was in line in this study results[12].

M. Homam et al, in a study in Mashhad showed that the side effects of topiramatewas lower than sodium valproate[13]. In the present study, both drugs had significant effects in reducing attacks and severity of vertigo attacks. In this study the effect of topiramate on the reduction of headache frequency was greater than that of sodium valproate. Verma et al reported a reduction 50% in the vertigo attacks after topiramate treatment which was in line with our study results[14].

Conclusion:

Results showed that both of topiramate and sodium valproate were effective in reducing the frequency and duration of migrainousvertigo. Of course, the reduction of headache frequency in topiramate group was significantly higher than sodium valproate group. It seems that the topiramatein preventing vertigo was better than sodium valproate.

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DCIMCJ

Original Article

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Awareness Regarding Health Hazards among the Garment Workers in a Selected Garment Factory

Begum N[1], Tarafdar MA[2], Das SR[3], Begum S[4], Afrin M[5], Rahman M[6], Begum R[7]

Abstract:

Background: Garment workers constitute a lion share of the total labour force in Bangladesh, which bring most of the country's foreign currency. The competitiveness of the garment industry in the world market is seriously affected by the ill health of the workers. Objective: The study analyzed the types of occupational health hazards and practice on preventive measures regarding health hazards among the garments workers in relation to knowledge and socio-demographic characteristics. Total sample was 129 and purposive sampling technique was followed for data collection, which was done by face to face interview by an interviewer. The data was collected on a structured questionnaire. Results: Out of 129 respondents, majority 93.8% were found in the age group of 18-35 years and the least 6.2 % were found in the age group of above 35 years. The mean age of the respondents was 26.05±5.549 years. Among all the respondents, 97.75% were female workers whereas, only 32.25% were male. Majority of the respondents (83.7%) received institutional educations. but still a few numbers (9.3%) of respondents were illiterate. length of working hour 8-10hours and their percentage was 48.8%. 26.4% had length of working hour 6-8hour. Only 7.8% had length of working hour less than 2 hours. maximum hazards related to headache (55.8%), musculoskeletal pain(31%) & eye strain(25.6%). Regarding the use of personal protective equipment only 35.7% of the garment workers had proper protective equipment's among them males that is 25 in number were use more than female 21 in number. There was a significant association between use of PPE and sex of the respondents. (P=0.032). Conclusion: More emphasis should be given to the workers to improve their health condition and working environment, so that they can increase their efficiency which can ultimately increase the production and add GDP to the country.

Keywords: Garment sector, health hazard, health status, safety measures

Introduction:

The Ready Made Garment (RMG) has been placed largest export earnings of Bangladesh. The first garment factory opened in 1976. The industry has grown dramatically over the past 35 years, which can be treated as a life blood of the Bangladesh economy. The industry deserves special connotation for at least three reasons: (a) it is the single largest earner about 77 % of the yearly foreign exchange earning of the country; (b) it has been the fastest growing industry in the recent years; (c) The industry

1. Dr. Nadia Begum, Associate Professor, Department of Community Medicine, Z.H Sikder Women's Medical College & Hospital.

2. Dr. Monowar Ahamad Tarafdar, Professor & Head, Department of Community Medicine, Z.H Sikder Women's Medical College & Hospital.

3. Dr. Shila Rani Das, Associate Professor, Department of Community Medicine, Z.H Sikder Women's Medical College & Hospital.

4. Dr. Sultana Begum, Assistant Professor, Department of Community Medicine, Z.H Sikder Women's Medical College & Hospital.

5. Dr. Meheruba Afrin, Assistant Professor, Department of Community Medicine, Z.H Sikder Women's Medical College & Hospital.

6. Dr. Md. Mahbubar Rahman, Professor, Department of Community Medicine, Dhaka Central International Medical College.

7. Dr. Rahana Begum, Assistant Professor, Department of Community Medicine, Dhaka Central International Medical College.

Correspondence: Dr. Nadia Begum
E-mail: nadiabegum.zhs@gmail.com

employees about 3.6 million people and the growth rate of RMG export was over 20% in the last two decades (BGMEA, Members' Directory 2010-2011)[1]. In a developing country like Bangladesh, it plays an important role in the overall economic development. At present, approximately 20 lakh workers (among which 80% is female) are working in this sector which is a great source of employment (EPB, 2006). It is also mentionable that about 76% of our foreign exchange is earned by this sector (BGMEA, 2008)[2].According to 2010-11 survey of BGME, Export Promotion Bureau, Bangladesh Bank, compiled by BGMEA, the number of garment factories are 5150, total number of workers is 3.6 million, products of about US $17914.46 million is exported from ready-made garment factories and total US $22924.38million worth of products are exported, 79.15% of RMG's is utilized for national export[3].Bangladesh's thriving RMG industry has grown from $12,000 in exports in 1978 to $21.5 billion in 2012-13, and now accounts for about 80 percent of total exports[4].

According to WHO (1948), "Health is a state of complete physical, mental and social wellbeing and not merely the absence of diseases or infirmity". But Bangladeshi garment workers are unable to maintain any of the health condition prescribed by the WHO[5].Occupational health hazard is concerned with health hazard in relation to work environment. The science of occupational health hazards covers a wide field, like work physiology, occupational hygiene, occupational psychology, occupational toxicologyetc[2]. The working environment in Bangladesh RMG sector is below standards. Health and Safety regulations, as prescribed in Factory Rules 1979 are routinely ignored by management and are hardly enforced by government.

Most factories do not have adequate ventilation and exhaust fans that leave the garments workers exposed to toxic substances and dust. As a result, many workers suffer from constant fatigue, headaches, anaemia, fever, chest, stomach, eye and ear pain, cough and cold, diarrhea, dysentery, urinary tract infection and reproductive health problems due to overwork, uncongenial working conditions, and wide-ranging labour law violations. In fact the Factories Act of 1965 sets the occupational safety and health standards in Bangladesh, but like every other aspect of the Labour Code, it is rarely enforced due to the lack of resources and corrupt practices in the system[6].

Social compliance has emerged as a major issue in the Bangladesh RMG sector. Despite the additional costs these compliance demands place on the sector, there are sound economic reasons why the Bangladesh garment industry should meet them. Alternatively ensuring social compliance is very important in Bangladesh's garments industry to both maintain quality of products. It ensures labour rights, labour standards, fair labour practices and a Code of Conduct[2].

Materials and methods:

Study Area: This cross sectional study was conducted among the garment workers of Savar in Dhaka city.

Sample Size: Total sample was 129 and purposive sampling technique was followed for data collection.

Data Collection and Analysis:

Data was collected through face-to-face interviews of the respondents with the help of a pretested semi structured interview schedule. Written informed consent was taken from the respondents.

Results:

Table1: Distribution of Garment Workers according to the Selected Characteristics:-

Characteristics	Categories	Respondent	
		No	Percent
Age group (years)	15-20	31	24.0
	21-25	37	28.6
	26-30	23	17.8
	31-35	19	14.7
	>35	19	14.7
	Mean = 26.05±5.549		
Education level	Illiterate	12	9.3
	Informal education	2	1.6
	Primary level	51	39.5
	Secondary level	55	42.6
	Graduate	2	1.6
	Others	7	5.5
Marital status	Unmarried	46	35.6
	Married	77	59.6
	Widow	2	1.5
	Separate	4	3.1
Religion	Muslim	125	96.8
	Hindu	4	3.1
Sex	Male	42	32.55
	Female	87	67.44

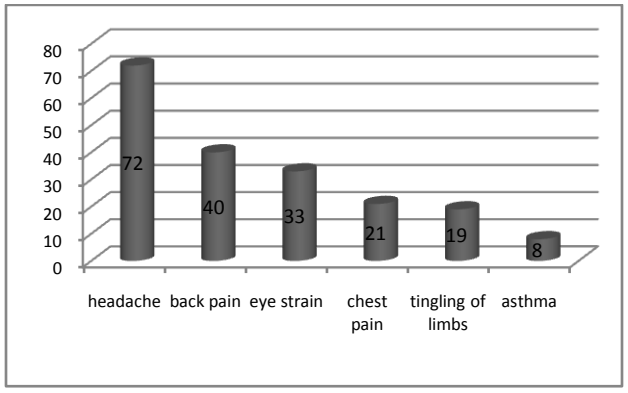

Figure 1: Distribution of the respondents by type of disease and illness

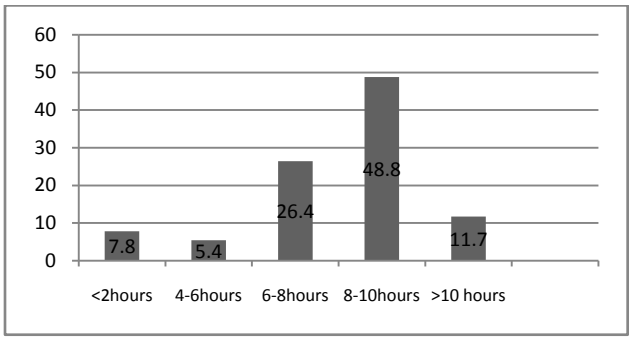

Figure 2: Distribution of respondents by length of working hours

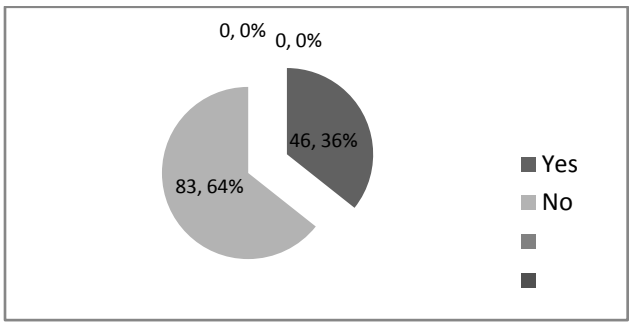

Figure 3: Distribution of respondents by use of protective device

Table 2: Distribution of the respondents by association between PPE use and sex of the respondents-

Sex of the respondents	Use of personal protective device		p-value*
	Yes	No	
Male	25	26	0.032
Female	21	56	
Total	46	83	

*p value is from Pearson's χ^2 test

Discussion:

This descriptive cross sectional study was aimed at finding out the safety measures among 129 garment workers of both sex and with age limitation above 18 years. In our study, among 129 respondents, the highest 93.8% were found in the age group of 18-35 years. Mean age was 26.05±5.549 years. A study by Haque A showed the mean age of the respondent was 20.4 ± 5.5 years, ranging between 12 to 42 years.[7]In present study about 97.75% were female workers whereas, only 32.25% were male. A reverse ratio of sex was observed in the study done by Gupta R.D found 754 (78.4%) males and 208 (22%) females with a sex ratio 3.7:1 respectively[3]. Our study revealed that majority of the respondents (83.7%) received institutional educations. but still a few number (9.3%) of respondents were illiterate. But a little bit different pictures was found by Sikder M H, that 2.50%were illiterate, 35% of the workers have primary education, and 48 % have secondary education, while only 2.50% have higher secondary education[1]. There was study done by Gupta R.D where, 8 (26.6%) workers had no formal education but could sign their names, 6 (20%) had education at primary level and up to class eight each[3].

There was one shift of work to be the norm in the garment industry. As in any other industry, the normal working hours in the garment factory is 9 hours a day, usually from 8 a.m. to 5 p.m. According to the Factory Act 1965, no person can be employed for more than 8 hours a day in a factory. Work in excess of these hours should be paid for at the overtime rates, which is twice the basic salary. Usually, the basic salary is considered to be 60 percent of the monthly pay[8]. In our study most of the workers had length of working hour 8-10hours and their percentage was 48.8%. 26.4% had length of working hour 6-8hourd. Only 7.8% had length of working hour less than 2 hours. Ahmed S showed in her study that the female workers have to work for long time without moving anywhere else and for this reason they feel pain in their arms, legs, and muscle as well[5].Gupta R. D also showed in her study that the longer duration of time during which a worker is exposed to a certain hazardous agent may greatly increased the health hazards of the workers involved in garments. On the other hand reduction of time during which a worker is exposed to a certain hazardous agent may reduce the health hazards. This can be achieved through work practices, rotation of worker or administrative control. Among the ninety respondents, 58.89 percent respondents implied that their extent of headache was severe[3]. Ali R. N. showed that maximum (70%) of the female workers was headache, musculoskeletal pain (37%). This also similar to our findings. In our study maximum hazards related to headache (55.8%), & eye strain(25.6%)[8].But a reverse findings showed by Ahmed S that the most important disease or health hazard of the female garment workers is the problems in their bones due to sitting for a long time[5].

Regarding the use of personal protective equipment only 35.7% of the garment workers had proper protective equipment's among them males that is 25 in number were use more than female 21 in number. There was a significant association between use of PPE and sex of the respondents.(P=0.032)More than one half of the workers were aware of the benefits of personal protective equipments (PPE), but only a few workers in the cutting section(42%) were using PPE. Similar findings were found in the study conducted by Gupta R.D in his study showed that all the worker 59% were aware of the benefits of the personal protective measures. Yet in cutting section only 4% and in stitching & finishing section none of them use these protective measures for improper fitting and other causes[3].In our study it is found that 100% of the garments had medical Centre facilities but only 62.8% had periodic health check-up. Study reaveled that 42.6% of the respondents source of information about training regarding health hazards from trainer and 28.7% from doctors and authority, 35.7% knew about training & education regarding operation of instruments from authority,17.1 % from supervisor, 12.4% from HR department and 43.9% from others. Ahmed. F suggested regulatory measures and its strict implementation and monitoring by the government agency that could overcome work place in security problem of garments workers in Bangladesh[6].

Conclusion:

Gupta R.D reported that occupational health hazard is concerned with health hazard in relation to work environment. The science of occupational health hazards covers a wide field, like work physiology, occupational hygiene, occupational psychology, occupational toxicology etc. Healthy people are productive people. There is no alternative but to keep the people sound physically and mentally to ensure efficient manpower for the country. The policy makers, authority and concern bodies should take special care to ensure healthy and productive workforce in our country to fulfill the dream of our Bangladesh[3].

Recommendations:

To improve working conditions the Bangladesh Government needs to conduct a thorough review of labour regulation. The government should protect workers' rights by creating a system for complaints concerning violations, adjudication, remedies, and punishments[6]. Based on our research findings, we offer some policy recommendations to improve efficiency at the factory level, including providing improved benefits to workers, and developing coalitions between the private sector and local and international NGOs, as well as among factories, to establish industry standards. We also suggest reforms of the business environment that could provide an overall boost, not only to the garment industry, but to the economy as a whole.

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DCIMCJ

Original Article

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Detection of Main Pathogens Causing Urinary Tract Infection in Children Admitted in Paediatric Nephrology Unit in a Tertiary Care Hospital.

Abdullah M[1], Afrin F[2], Subhan SS[3], Hossain SMR[4], Alam MM[5], Chowdhury FA[6], Fatema K[7], Nurunnobi ABM[8], Iqbal Asif[9], Kabir KM[10]

Abstract:

Urinary tract infection (UTI) is a common disease in paediatric practice and an important cause of morbidity and mortality. Early recognition and prompt treatment of UTI is important to prevent progression of infection to pyelonephrites or urosepsis and to avoid late sequelae such as renal scarring or renal failure. UTI in children is very common in our country and is most commonly found to be due to bacterial infection. This case control study was done to find out the main pathogen of urinary tract infection (UTI) in children admitted with UTI with different kidney diseases in paediatric nephrology unit, National Institute of Kidney Diseases and Urology (NIKDU), a tertiary level hospital in Dhaka, Bangladesh. This study was done on 30 cases of UTI patients admitted with different kidney diseases and Hypercalciuria and 40 ages –sex matched apparently healthy children as control. Urine Routine and Microscopic Examination (RME) and urine culture were done by traditional method in all study subjects. Ultrasonography of KUB was done to exclude any urinary tract abnormality of these study subjects. Blood samples of all subjects where analyses for serum total calcium concentration to exclude hyper or hypocalcaemia. Random urine sample were analyzed for urinary calcium-creatinine ratio to screen hypercalciuria. In this study urinary calcium-creatinine ratio>- 0.20 was conserdred as hypercalcaemia. The mean age of the study subjects were 6.87±.2.94 years. Among those, 76.7% had recurrent UTI and 23.3% had first time UTI. Along with UTI they had associated diseases, such as- Nephrotic Syndrom (NS), Renal Failure (RF), Complicated UTI, Glomarulo Nephrites (GN) in 17 (56.7%), 4 (13.3%), 5 (16.7%), and 4 (13.3%) study subjects respectively. Hypercalciuria were reported in 14 (46.7%) of cases. The pathogens isolated in urine culture of UTI patients were- Escherichia coli (76.7%) remains the predominant, followed by Pseudomonusaeruginosa (10%), staphylococcus saprophytic us (13.3%) (n=23/30, 3/30 and 4/30 respectively). It was therefore concluded that Escherichia coli is found as the main pathogen of UTI in children admitted with different kidney diseases and Hypercalciuria.

Keywords: UTI, pathogen, hypercalciuria, children

Introduction:

Urinary tract infection (UTI) is a common disease in paediatric practice and an important cause of morbidity and mortality, accounting for 4.6%-5.9%

1. Dr. Muhsina Abdullah, Associate Professor, Department of Biochemistry, National Institute of Cardiovascular Diseases.
2. Dr. Fahmida Afrin, Associate Professor, Department of Biochemistry, Ibn Sina Medical College.
3. Dr. Syeda Shahina Subhan, Professor, Department. of Clinical Biochemistry, National Institute of Cardiovascular Diseases.
4. Dr S M Rahat Hossain, Associate Professor, Department of Microbiology, Sheikh Hasina Medical College, Tangail.
5. Dr. Mohammed Morshed Alam, Assistant Professor, Department of Biochemistry, National Institute of Kidney Diseases & Urology.
6. Dr. Farzana Ahmed Chowdhury, Medical Officer, Department of Biochemistry, NICVD.
7. Dr Kaniz Fatema, Medical Officer, Department of Biochemistry, NICVD.
8. Dr ABM Nurunnobi, Assistant Professor, Department of Catrdiology, NICVD.
9. Dr Asif Iqbal, Medical Officer, Department of Cardiology, NICVD.
10. Dr Khaja Masum Kabir, Assistant Professor, Surgery Department, Mymensingh Medical College, Mymensingh.

Correspondence: Dr. Muhsina Abdullah
E-mail: drsdilshad72@gmail.com

offibrile episode[1,2]. UTI may be recurrent. Recurrence is frequent and occurs in approximately 40% in female and 32% in male which may cause renal scar formation leading to hypertension and renal failure[3,4,5].

Prevalence ratesof UTI varies by age, gender, race, and circumcision status[6]. Age-dependent variation is of considerable clinical significance, since it defines important risk factors for UTI. The incidence of febrile UTI is highest during infancy. In the age range from birth to 2 months, the diagnosis of acute pyelonephritis is usually made during evaluation for neonatal sepsis. The incidence of UTI is about 4% in both male and female infants during the first year. However, most of the infections in male infants occur during the first 3 months[7]. Infants and young children with UTI may present with few specific symptoms. Older pediatric patients are more likely to have symptoms and findings attributable to an infection of the urinary tract[8]. Numerous studies have shown that uncircumcised male infants have about 10 times as many UTIs as circumcised male infants, the infections occurring mainly during the first 3 months of life. The increased risk of a UTI in the uncircumcised male infant appears to be secondary to adherence of E coli to the unkeratinized squamous mucosal surface of the prepuce. The circumcised baby is much less likely to harbor these potential uropathogens.[7] UTI generally begins in the bladder due to ascending infection from perineal contaminants, usually from bowel flora such as Escherichia coli.

In neonates, infection of the urinary tract is assumed to be due to hematogenous rather than ascending infection and this etiology may explain the nonspecific symptoms associated with UTI in these patients. After the neonatal period, bacteremia generally is not the cause of UTI, and the bladder is the initial primary locus of infection with ascending disease of the upper tract (kidneys). Bacterial invasion of the bladder with UTI is more likely to occur if urinary stasis or low flow conditions exist[9]. Bacterial infection are the most common cause of UTI. Escherichia coli is the most common by far, causing 75-90% of UTIs.

Other causative organisoms are Klebsiella species, Proteus species, Enerococcus species and Staphylococcus saprophyticus[8]. The diagnosis of UTI was based on clinical signs/symptoms and laboratory findings: positive laboratory finding include- pyuria (more than 5 leucocytes per high-power field), and positive urine culture (>10^5 bacteria per milliliter of urine sample obtained by spontaneous urination from the midstream portion of urine)[10]. The association of hypercalciuria and UTI has been pointed out by several authors from different countries during last several years they found hypercalciuria as an important contributing factor in UTI[8]. In this study, the main pathogen of UTI in children admitted with different kidney diseases in paediatric nephrology unit, NIKDU, was evaluated by detecting the causative organism found in urine culture.

Materials and methods:

This case control study was conducted in paediatric nephrology unit of National Institute of Kidney Diseases and Urology (NIKDU), a tertiary level hospital in Dhaka, Bangladesh. The investigations were done in Microbiology department of National Institute of Kidney Diseases and Urology (NIKDU), Dhaka. The study period was one year. A total number of seventy children were included in the study. Among them thirty diagnosed UTI patients with different kidney diseases were selected as case and forty age sex matched apparently healthy children were selected as control. The age ranges of the study subjects were between 1and 12 years.

Routine and microscopic examination of urine (R/M/E) and urine culture were done to detect UTI in study subjects. Blood samples of all subjects where analyzed for serum total calcium concentration to exclude hyper or hypocalcaemia. Random urine sample were analyzed for urinary calcium-creatinine ratio to screen hypercalciuria. In this study urinary calcium-creatinine ratio>- 0.20 was conserdred as hypercalcaemia. The data were analyzed by computer using SPSS (version 12 for Windows). For all tests, p- values less than 0.05 ($p<0.05$) were considered statistically significant.

Results:

Mean age (±SD) of the study subjects was 6.87±2.94) years and of control was 7.73±1.41 years. Among the 30 UTI patients- nephritic syndrome (NS), renal failure (RF), complicated UTI, glomarulo nephrites (GN) were associated in 17 (56.7%), 4 (13.3%), 5 (16.7%), and 4 (13.3%) study subjects respectively, 76.7% had recurrent UTI and in 23.3%, UTI was diagnosed for the first time, 20 (66.7%) were presented with dysuria, voiding dysfunction (frequency) were found in 6 (20%) and haematuria was found in 4 (13.3%), hypercalciuria was present in 14 (46.7%) of cases.

Table: I Age distribution of study subjects

Parameter	Cases (n=30) Mean±SD	Control (n=40) Mean±SD
Age (in year)	6.87±2.94	7.73±1.41

Table-II: Distribution of study subjects according to associated diseases (n=30)

Name of disease	Frequency	Percent
Nephrotic Syndrom	17	56.7
Renal Failure	4	13.3
Complicated UTI	5	16.7
Glomarulo Nephrites	4	13.3

Table-III: Frequency and percentage of study subjects according to first time and recurrent UTI. (n=30)

UTI	Frequency	Percent
First time	7	23.3%
Recurrent	23	76.7%

Table-IV: Percentage of study subjects according to symptoms. (n=30)

Symptoms	Frequency	Percent
Dysuria	20	66.7%
Voiding dysfunction (frequency)	6	20%
Haematuria	4	13.3%

Table-V: Comparison of hypercalciuria among case and control. (n=70)

Subject	Hypercalciuria		Total	X^2 value	p value
	Yes	No			
Case	14(46.7%)	16	30		
Control	8(20.0%)	32	40	4.48	0.03 ($p<0.05$)
Total	22	48	70		

Table-VI: Percentage of study subjects according to causative organism found in urine culture. (n=30)

Name of organism	Frequency	Percent
Escherichia coli	23	76.6
Pseudomonas aeruginosa	3	10
Staphylococcus saprophytic us	4	13.3

Discussion:

Urinary tract infection (UTI) in childhood is a significant and common problem encountered by primary, secondary and tertiary healthcare professionals and is important cause of acute illness. UTI may be recurrent that causes considerable distress, anxiety and inconvenience to children and their families[5]. UTI occurs in approximately 1% of boys and up to 3% of girls in school age.[11] Early recognition and prompt treatment of UTIs are important to prevent progression of infection to pyelonephritis or urosepsis and to avoid late seqelae such as renal scarring or renal failure[8].

The present study was designed to find out the main pathogen of urinary tract infection (UTI) in children (aged 1-12 years) admitted in paediatric nephrology unit, NIKDU, Dhaka for different nephropathies with UTI. Along with hypercalciuria. Total 30 admitted patients with UTI selected as study subjects and 40 age sex match apparently healthy children as control. Mean age of study subjects was 6.87 years with

standard deviation of 2.94 years. Among the 30 studysubjects, 14 were male and 16 female. Children having uncomplicated UTI are rarely admitted in hospital and usually treated from the outpatient department, some are treated by the local physician, and some do not seek any medical advice. Many do not seek any medical treatment. In this study most of the study subjects had the following co morbidity like nephrotic syndrome (56.7%), glomerulonephritis (13.3%) and renal failure (13.3%) for which they admitted in the hospital. Only 5 patients (16.7%) with UTI not responding to conventional oral antibiotic also admitted. Hypercalciuia has been increasingly recognized as a cause of UTI in clinical paediatrics. The association of hypercalciuria with UTI has been pointed out by several authors during last several years[10].

Urinary tract infections are caused mainly by colonic bacteria. In females 70-90% of all infections are caused by Escherichia coli followed by klebsiella and proteus and Staphylococcus saprophyticus is a pathogen in both sexes[12].

There are few reports on urinary tract infections caused by Haemophilus influenzae or Haemophilus parainfluenzae in children[13]. Staphylococcus saprophyticus is a pathogen in both sexes. Adenovirus may also cause UTI, especially cystitis[14].

In this study, hypercalciuria were found in 46.7% cases and Escherichia coli was found as most common pathogen (76.7%), followed by Staphylococcus (13%) and Pseudomonus (10%) which was consistent with the findings of Ann et al[8] and Sobczyk et al[1] (Escherichia coli 75-90%, Staphylococcus saprophytic us 10% to 15% and Pseudomonas aeruginosa 9%).

Conclusion:

It can be concluded from the present study that event in children admitted with UTI due to different kidney diseases ,who also had hypercalciuria, Escherichia coli is the most common pathogen, followed by Staphylococcus and Pseudomonus in paediatric nephrology unit, in a tertiary care hospital.

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Original Article

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Ultrasound Elastography, Useful Tool in Discriminating Benign from Malignant Complex Breast Masses and Making the Biopsy Decision.

Parvin A[1], Haque R[2]

Abstract:

Objective To evaluate the additional effect of ultrasound elastography on the radiologist's ability for discriminating benign from malignant complex breast masses and to decide whether to perform biopsy by B-mode US. Materials and Methods: One hundred eighteen complex breast masses (15 malignant lesions, 103 benign lesions) were included. Five blinded readers independently assessed the likelihood of the malignancy score from 1 to 5 for two data sets (B-mode ultrasound alone and B-mode ultrasound with sonoelastography). Elasticity scores were categorized as 0, 1, or 2 based on the degree and distribution of strain of the echogenic component within complex masses. The readers were asked to downgrade the likelihood of the malignancy score when an elasticity score of 0 was assigned and to upgrade the likelihood of the malignancy score when an elasticity score of 2 was assigned. The likelihood of the malignancy score was maintained as it was for the lesions with an elasticity score of 1. The Az values, sensitivities, and specificities were compared. Results: The Az value of B-mode ultrasound with ultrasound elastography (mean, 0.863) was greater than that of B-mode ultrasound alone (mean, 0.731; p= 0.001-0.007) for all authors. The specificity of B-mode ultrasound with ultrasound elastography (mean, 37.1%) was greater than that of B-mode ultrasound alone (mean, 3.8%; $p < 0.001$) for all readers. The addition of ultrasound elastography led to changes in decisions. A mean of 33.6% of benign masses were recommended for follow-up instead of biopsy. Conclusion: For complex breast masses, ultrasound elastography allows increase in both the accuracy in discriminating benign from malignant lesions and the specificity in deciding whether to perform biopsy.

Keywords: Breast, Neoplasm, ultrasound elastography

Introduction:

Supplemental screening breast ultrasound (US) has been shown to increase the cancer detection rate to 2.3-4.6 cancers per 1000 women screened[1-9]. However, the main limitations of breast US are its low specificity and low positive predictive value (PPV). The PPV of screening breast US for suspicious lesions has been reported to be from 5.6-13.7%[8,9]. Cystic breast lesions have been reported to contribute to the low PPV of screening breast US for suspicious lesions[8,9]. Among the cystic breast lesions, complex breast masses containing both an echogenic solid component and a cystic component have been considered suspicious for malignancy based on an overall malignancy rate of 36% (97 of 270) (range, 18-62%)[8,9]. Therefore, better characterization of an echogenic solid component is necessary to distinguishing benign from malignant complex breast masses.

Ultrasound elastography is an imaging modality that quantifies the relative stiffness of the target tissue compared with the surrounding tissue using US[10,11]. Recent studies have reported that ultrasound elastography is helpful in discriminating benign from

4. Dr. Afroza Parvin, Assistant Professor, Department of Radiology & Imaging, Dhaka Central International Medical College.

5. Dr. Rushaida Haque, Consultant, Department of Radiology & Imaging, Ibn Sina Medical Imaging Centre.

Correspondence: Dr. Afroza Parvin
E-mail: afroza.rumpa@yahoo.com

malignant solid breast masses and shows better specificity (range, 41.0-98.5%) than that of B-mode U-S alone (range, 7.1-98.8%)[12-20]. In addition, the potential application of ultrasound elastography in discriminating solid masses from cystic lesions has been reported in several studies[21,22] .

To the best of our knowledge, however, the additional effect of ultrasound elastography in discriminating benign from malignant complex masses has not yet been reported. The cystic component tends to be softer than the solid component. Therefore, diagnostic criteria and the diagnostic performance of ultrasound elastography in cystic masses might be different compared to that in solid breast masses.

We hypothesized that the relative stiffness of the echogenic component of the complex breast mass could be used for the elasticity score of complex breast mass. The purpose of our study was to evaluate the additional effect of ultrasound elastography on the radiologists' ability to distinguish benign from malignant complex breast masses and to decide whether to perform biopsy by B-mode US.

Materials and methods:

Patients and Lesions: Our institutional review board approved this study, and informed consent was obtained from each female patient prior to biopsy. From October 2016 through October 2018, 2754 consecutive women underwent B-mode ultrasound, ultrasound elastography; and a subsequent ultrasound-guided needle biopsy was performed for 3089 breast masses that were classified as Breast Imaging-Reporting and Data System (BI-RADS) category 4, 5 or category 3. The images were saved as video clips in the avi format. Among these 3089 lesions, 2916 lesions were excluded because they were not complex masses, and 31 lesions were excluded due to poor image quality. Additionally, 24 lesions were excluded because they were followed up for less than 1 year after a benign biopsy. A complex breast mass was defined as a cystic lesion with an echogenic component such as a thick wall (> 0.5 mm), thick septations (> 0.5 mm), an intracystic mass or a solid mass with cystic areas[23]. Finally, 118 complex breast masses in 118 women (mean age, 45.1 years; range, 24-71 years) were included in this study. Of the 118 lesions, 103 (87.3%) were benign and 15 (12.7%) were malignant. Malignant lesions included invasive ductal carcinoma (n = 8), ductal carcinoma in situ (n = 5), mucinous carcinoma (n = 1) and lymphoma (n = 1) (Table- 1). Two intraductal papilloma lesions on core biopsy were proved to be ductal carcinoma in situ on subsequent excision. Benign lesions included fibrocystic changes (n = 50), fibroadenoma (n = 14), intraductal papilloma (n = 24), usual ductal epithelial hyperplasia (n = 3), atypical ductal hyperplasia (n = 2), duct ectasia (n = 4), adenosis (n = 2), phyllodes tumor (n = 1), fat necrosis (n = 2), and foreign body granuloma (n = 1). Three atypical ductal hyperplasia lesions on core biopsy were confirmed as one usual ductal epithelial hyperplasia lesion and two atypical ductal hyperplasia lesions on subsequent surgical excision. The mean duration of imaging follow-up for histologically benign lesions was 29.5 months (range, 12-75 months). No cases of breast cancer were detected during the follow-up period. The lesion type, based on a retrospective review of B-mode US images by two radiologists in consensus, was as follows: 67.8% (80 of 118) were intracystic or intraductal masses, 26.3% (31 of 118) were solid masses with a cystic component and 5.9% (7 of 118) were cysts with thick septations or thick walls. Lesion size was defined as the maximal diameter measured on B-mode US. The mean size of the malignant lesions was 15.6 ± 7.3 mm (range, 6-35 mm). The mean size of the benign lesions was 12.5 ± 7.3 mm (range, 4-47 mm). Among the 118 complex breast masses, 59.3% (70 of 118) showed a blue-green-red appearance on sonoelastography. The indications for US examination were as follows: in 50.0% (59 of 118) of complex breast masses, US examinations were performed for asymptomatic screening, in 22.9% (27 of 118) of complex breast masses, US examinations were performed due to palpability, in 10.2% (12 of 118) of complex breast

masses, US examinations were performed due to pain, and in 17.0% (20 of 118) of complex breast masses, US examinations were performed due to nipple discharge. Of the 118 patients, 113 underwent mammography. On mammography, 46 patients (40.7%, 46 of 113) showed normal findings, 41 patients (36.3%) showed a non-calcified mass or focal asymmetry, 19 patients (16.8%) showed calcifications, 5 patients (4.4%) showed a mass with microcalcifications, and 2 patients (1.8%) showed architectural distortion.

Table -1: Distribution of median elasticity scores for five readers according to histopathology

Histology	Median Elasticity Score		
	0	1	2
Benign			
Fibrocystic Changes	31 (62.0)	17 (34.0)	2 (4.0)
Fibroadenoma	6 (42.9)	7 (50.0)	1 (7.1)
Intraductal Papiloma	5 (20.8)	11 (45.8)	8 (33.3)
Usual ductal epithelial Hyperplasia	1 (33.3)	0 (0.0)	2 (66.7)
Atypical ductal Hyperplasia	1 (50.0)	1 (50.0)	0 (0.0)
Ductectasia	1 (25.0)	2 (50.0)	1 (25.0)
Adenosis	1 (50.0)	1 (50.0)	0 (0.0)
Phyllodes	0 (0.0)	1 (100.0)	0 (0.0)
Fat necrosis	0 (0.0)	2 (100.0)	0 (0.0)
Foreign body Granuloma	0 (0.0)	1 (100.0)	0 (0.0)
Malignant			
DCIS, Low grade	0 (0.0)	2 (50.0)	2 (50.2)
DCIS, high grade	0 (0.0)	0 (0.0)	1 (100.0)
IDC, low grade	0 (0.0)	0 (0.0)	0 (0.0)
IDC, high grade	0 (0.0)	3 (37.5)	5 (62.5)
Mucinous Carcinoma	0 (0.0)	0 (0.0)	1 (100.0)
Lymphoma	0 (0.0)	1 (100.0)	0 (0.0)

US Data acquisition:

B-mode US and ultrasound elastography data were acquired by 1 of the 5 radiologists with 2-10 years of experience in breast US, using GE Volusion E8 and E10 ultrasound systems with a 11MHz linear transducer. A target lesion was determined on a B-mode US image, and then real-time imaging with ultrasound elastography was separately saved as cine clips of at least 5 seconds per case in the audio-video interleave format on a hard drive for later review. The cine clip of ultrasound elastography was composed of simultaneously acquired split-screen images of B-mode US and ultrasound elastography. For elastography, a region-of-interest (ROI) box was placed to focus on the target lesion and to include the surrounding subcutaneous fat layer and the superficial portion of the pectoralis major muscle layer. The target lesion was vertically compressed by the transducer under light pressure. A color-coding system for the degree of displacement of all pixels within the ROI was used for real-time strain images with a scale from red (greatest strain, softest component) to green (average strain, intermediate component) to blue (no strain, hardest component). The pressure and speed of manual compression were adjusted to depict the subcutaneous fat layer as a mix of red and green and the pectoralis muscle layer as blue.

The data acquisition procedure took approximately 1-2 minutes per case. After data acquisition, a histologic diagnosis was established in all women by using US-guided 14-gauge automated gun biopsy (n = 93, Pro-Mag 2.2, Manan Medical Products, Northbrook, IL, USA) or an 11-gauge vacuum-assisted device (n = 25, Mammotome; Ethicon Endo-Surgery, Cincinnati, OH, USA).

Readers and reading procedures:

Five radiologists who had not performed the data acquisition participated as readers. They had undergone fellowship training in breast imaging and had a mean 4.6 years of experience (range, 2-10 years) interpreting mammograms and performing US examinations.

They also had a mean 3.5 years of experience (range, 2-5 years) with elastography imaging. Reviewers were advised against overestimating the elasticity score based on the stiffness of an echogenic component of the lesion, since the cystic component tends to be markedly softer than the solid component[21,22].

All readers were blinded to the mammographic, clinical, and histologic findings, as well as to the proportion of cases with benign and malignant histologic findings. A three-step reading was performed using the 3 data sets consisting of cine clips of B-mode US alone, those of elastography alone, and a combined set of B-mode US and elastography with a 4-week interval between each reading session. At the first reading session, readers assessed the likelihood of malignancy category with a score of 1 to 5. They were reminded that a likelihood of malignancy score of 2 or higher indicated that the lesion should undergo biopsy.

A score of 1 indicated a benign finding and a likelihood of malignancy of less than 2%, which is similar to the BIRADS final assessment category of 2 or 3[24]. As the scores increased from 2 to 5, the likelihood of malignancy increased from 3% to 100%. Readers were instructed that the likelihood of malignancy for scores of 2 to 5 was proportionally increased as follows: a score of 2 indicated a low suspicion for malignancy (ranging from 3% to 10%), a score of 3 indicated an intermediate suspicion (ranging from 11% to 50%), a score of 4 indicated a moderate suspicion (ranging from 51% to 94%), and a score of 5 indicated a high suspicion for malignancy (95% or higher). Specific imaging criteria for the likelihood of the malignancy score were not provided to the readers.

In the second session, 118 ultrasound elastographic images were reviewed. The readers scored the elasticity of the complex breast masses without information of the prior B-mode US score. The elasticity score was categorized as 0, 1, or 2 on the basis of the degree and distribution of strain in the echogenic component of the lesions as in previous studies[17]. A score of 0 indicated an even strain for the echogenic component (i.e., the echogenic component was evenly shaded green). A score of 1 indicated strain in most of the echogenic component with some areas of no strain (the echogenic component had a mosaic pattern of green and blue). A score of 2 indicated no strain in the entire echogenic component (i.e., the entire echogenic component was blue). The order of cases in each reading session was randomized to reduce bias.

In the third reading session, both the B-mode US and elastographic images were simultaneously reviewed. The readers scored the likelihood of malignancy with the information of their own scores from the prior B-mode US alone session and the prior elastography alone session. At this session, the readers were asked to downgrade the likelihood of the malignancy score when an elasticity score of 0 was assigned and to upgrade the likelihood of the malignancy score when an elasticity score of 2 was assigned. But, the change in the likelihood of the malignancy score was not mandatory. In addition, for the lesions with an elasticity score of 1, the likelihood of the malignancy score was not changed.

Data and statistical analysis:

The rate of malignancies was calculated according to the B-mode US and elastography scores. To evaluate the additional effect of elastography in distinguishing benign from malignant complex breast masses, a receiver operating characteristic curve analysis was performed for the B-mode US alone and the combined set of B-mode US and elastography, and the results were compared between readers. The sensitivity and specificity (based on the binary management decision of whether to perform biopsy) of the B-mode US alone and the combined set of B-mode US and elastography for each reader were also compared by using the Mc Nemar test. Reader agreement between the five radiologists in classifying the elasticity score was estimated by using multirater κ statistics[25]. The total number of changes in the biopsy decisions of each reader was calculated at each reading session.

P values of less than 0.05 were considered to indicate a significant difference. All statistical analyses were performed using statistical software.

Results:

Median Elasticity Scores of the Five Readers According to Histopathology.

The most common benign histologic finding was fibrocystic changes, and the most common malignant histologic finding was invasive ductal carcinoma (Table 1). An elasticity score of 0 (44.7%, 46 of 103) was the most common score for benign lesions, whereas an elasticity score of 2 (60%, 9 of 15) was the most common score for malignant lesions.

Rate of Malignancy According to the B-Mode US and Elasticity Scores.

The mean rate of malignancy according to the likelihood of the malignancy score with B-mode US alone was 0% for a score of 1, 5.1% (range; 0-8.2%) for a score of 2, 12.3% (range; 6.7-18.2%) for a score of 3, 35.0% (range; 21.4-50.0%) for a score of 4, and 70.6% (range; 55.6-100%) for a score of 5 (Table 2).The mean rate of malignancy according to the elasticity score was 0% for a score of 0, 13.3% (range; 8.6-17.8%) for a score of 1, and 37.8% (range; 30-47.1%) for a score of 2. All lesions with an elasticity score of 0 or a B-mode US score of 1 were confirmed to be benign regardless of the other modality scores.

Table 2: Rate of malignancy according to b-mode us and elasticity scores

	Reader	Elasticity Score of 0	Elasticity Score of 1	Elasticity Score of 2	Malignancy rate (%)
B-mode US score of 1	1	0(0/5)	NA	0(0/4)	0(0/9)
	2	0(0/1)	0/1	NA	0(0/2)
	3	0(0/6)	NA	NA	0(0/6)
	4	0(0/1)	NA	NA	0(0/1)
	5	0(0/2)	NA	NA	0(0/2)
B-mode US score of 2	1	0(0/23)	6.7(2/30)	37.5 (3/8)	8.2(5/61)
	2	0(0/34)	11.4(5/44)	28.6 (2/7)	8.2(7/85)
	3	0(0/13)	0(0/4)	16.7 (1/6)	4.3(1/23)
	4	0(0/39)	10.5(2/19)	20(1/5)	4.8(3/63)
	5	0(0/16)	0(0/1)	0(0/3)	0(0/20)
B-mode US score of 3	1	0(0/13)	11.1(2/18)	37.5 (3/8)	12.8(5/39)
	2	0(0/8)	12.5(1/8)	50 (3/6)	18.2(4/22)
	3	0(0/23)	10.7(3/28)	21.7 (5/23)	10.8(8/74)
	4	0(0/11)	13.3(2/15)	27.8 (2/5)	12.9 (4/31)
	5	0(0/28)	9.1(1/1)	20 (2/10)	6.7 (4/60)
B-mode US score of 4	1	NA	100 (2/10)	42.9 (3/7)	50 (4/8)
	2	NA	20 (2/5)	75 (3/4)	44.4 (4/9)

Table 2 (Continued)

	Reader	Elasticity Score of 0	Elasticity Score of 1	Elasticity Score of 2	Malignancy rate (%)
	4	0(0/1)	22.2 (2/9)	25 (1/4)	21.4 (3/14)
	5	0(0/13)	30 (3/10)	62.5 (5/8)	25.8 (8/31)
B-mode US score of 5	1	NA	NA	100 (1/1)	100 (1/1)
	2	NA	NA	NA	NA
	3	NA	NA	66.7 (2/3)	66.7 (2/3)
	4	0(0/3)	100 (2/2)	75 (3/4)	55.6 (5/9)
	5	0(0/1)	100 (1/1)	66.7 (2/3)	60 (3/5)
Malignancy Rate (%)	1	0(0/41)	10.2(5/49)	35.7(10/28)	12.7(15/118)
	2	0(0/43)	12.1(7/58)	47.1(8/7)	12.7(15/118)
	3	0(0/43)	8.6(3/35)	30 (12/40)	12.7(15/118)
	4	0(0/55)	17.8(8/45)	38.9 (7/18)	12.7(15/118)
	5	0(0/66)	17.6(6/35)	37.5 (9/24)	12.7(15/118)

Receiver Operating Characteristic Analysis, Sensitivity, Specificity, Management Decision Changes

Compared with B-mode US alone, the combined use of elastography and B-mode US improved the performance of all readers in distinguishing benign from malignant lesions (mean Az from 0.731 [range, 0.676-0.791] to 0.863 [range, 0.835-0.901]) (p = 0.007 for reader 1; p < 0.001 for readers 2 and 5; p = 0.002 for reader 3; p = 0.003 for reader 4) (Table 3).

Table 3: Az Values for Distinguishing Benign from Malignant Complex Breast Masses

Parameter	B-mode US Alone	B-mode US and Sonoelastography	P
Reader 1	0.713 (0.571, 0.856)	0.835 (0.745, 0.925)	0.007
Reader 2	0.676 (0.534, 0.819	0.842 (0.750, 0.935)	<0.001
Reader 3	0.713 (0.586, 0.840)	0.861 (0.776, 0.947)	0.002
Reader 4	0.761 (0.624, 0.899)	0.874 (0.796, 0.951)	0.003
Reader 5	0.791 (0.683, 0.899)	0.901 (0.841, 0.961)	<0.001
Mean ± standard Deviation	0.731 ± 0.045	0.863 ± 0.026	

The sensitivities and specificities based on the binary management decision of whether to perform a biopsy were obtained. The sensitivity (biopsy decisions for malignant masses) of B-mode US was 100% in all five readers. This result did not change after the addition of elastography (Fig. 1). However, the specificity (follow-up decisions for benign masses) of the combination of B-mode US and elastography (mean, 37.1%; range, 21.4-51.5%) was greater than that of B-mode US alone (mean, 3.8%; range, 1.0-8.7%) for all readers ($p < 0.001$ for all readers) (Table 4). With respect to the net effect of management decision changes, the combined use of B-mode US and elastography led to biopsy decisions being changed to follow-up decisions for a mean of 33.6% (34.6 of 103, range: 15.5-50.5%) of the benign masses (Table 5) (Fig. 2). For malignant masses, the management decision did not change in any of the cases after the addition of the ultrasound elastography findings.

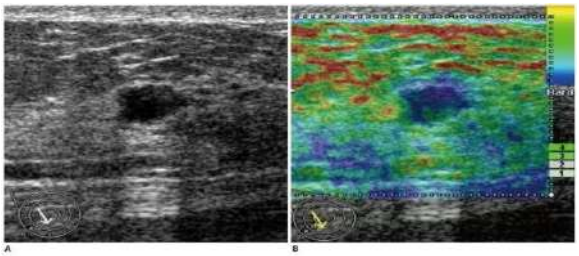

Fig: 1- 45 year old woman with ductal carcinoma in situ (DCIS)

B mode US image (A) shows microlobulated intracystic mass. Ultrasound elastographic image (B) shows solid component as blue, indicatind hard lesion with elasticity score of 2. At B mode US, 3-5 readers classified lesion as score of 2 (low suspicion for malignancy). Other 2 readers classified lesion as score of 3 (Intermediate suspicion for malignancy) and 4 (Moderate suspicion for malignancy). At elastography, all readers classified lesion as elasticity score of 2 (no strain in entire echogenic component). At B mode US and elastography, none of those readers changed their scores. US guided biopsy revealed the lesion to be Ductal carcinoma in situ (DCIS). US= ultrasound.

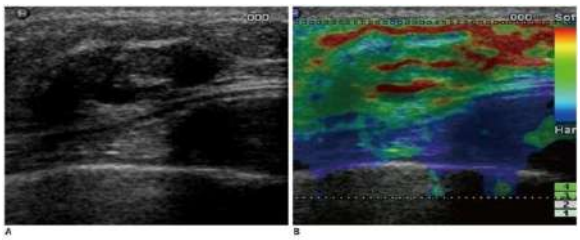

Fig: 2- 45 year old woman with fibrocystic changes.

B mode US image (A) shows oval, circumscribed intracystic mass. Ultrasound elastographic image (B) shows entire solid component of complex mass as red or green, indicating soft lesion with elasticity score of 0. At B mode US, 3-5 readers classified lesion as score of 2 (low suspicion for malignancy). Other 2 readers classified lesion as score of 3 (Intermediate suspicion for malignancy). At elastography, all readers classified lesion as elasticity score of 0 (even strain for echogenic component). At B mode US and elastography, all readers downgraded the lesion to likelihood of malignancy score of 1(follow up recommended). US guided core biopsy revealed fibrocystic changes. Lesion was stable during 2 year follow up period. US= ultrasound.

Table 4: Sensitivities and specificities for biopsy decision

Parameter	B-mode US Alone	B-mode US and Sonoelastography	P
Sensitivity (%)			
Reader 1	100 (15/15)	100 (15/15)	NA
Reader 2	100 (15/15)	100 (15/15)	NA
Reader 3	100 (15/15)	100 (15/15)	NA
Reader 4	100 (15/15)	100 (15/15)	NA
Reader 5	100 (15/15)	100 (15/15)	NA
Specificity (%)			
Reader 1	8.7 (9/103)	36.9 (38/103)	<0.001
Reader 2	1.9 (2/103)	39.8 (41/103)	<0.001
Reader 3	5.8 (6/103)	21.4 (22/103)	<0.001
Reader 4	1.0 (1/103)	51.5 (53/103)	<0.001
Reader 5	1.9 (2/103)	35.9 (37/103)	<0.001
Mean ± standard Deviation	3.8 ± 3.3	37.1 ± 10.8	

Table 5:Changes in Decision of Biopsy Recommendation in 103 Benign Masses

	Change from follow-up Decision to Biopsy Decision	Change from Biopsy Decision to Follow up decision
Reader 1	2	31
Reader 2	0	39
Reader 3	0	16
Reader 4	0	52
Reader 5	0	35
Mean ± standard Deviation	0.4 ± 0.9	34.6 ± 13.0

Reader agreement:

Interobserver agreement was moderate for the elasticity score of 0 ($\kappa = 0.541 \pm 0.094$), fair for the elasticity score of 1 ($\kappa = 0.313 \pm 0.090$), and moderate for the elasticity score of 2 ($\kappa = 0.574 \pm 0.074$). The overall agreement of the readers was moderate ($\kappa = 0.467 \pm 0.021$ [standard error]).

Discussion:

In this study, we found that the combined use of B-mode US and elastography improved the ability of all radiologists in distinguishing benign from malignant complex breast masses compared with B-mode US alone. The mean Az value increased from 0.731 to 0.863. Furthermore, the specificity of B-mode US significantly increased from 3.8% to 37.1% without sacrificing sensitivity. Our results are consistent with those of prior studies of solid breast masses, in which elastography showed a higher specificity (range, 41.0-98.5%) than B-mode US (range, 7.1-98.8%) for the differentiation between benign and malignant lesions, and its sensitivity (range, 70.1-100%) was similar to that of B-mode US (range, 71.2-100%)[12-20].

The most interesting point in our results was that the elastographic criteria, based on the stiffness of an echogenic component, were effective for characterizing complex breast masses. The diagnosis of complex breast masses showing internal echoes due to small particulate matter or reverberation artifacts has become increasingly common due to the advent of high resolution US and the increased usage of whole breast screening US[23]. The utility of elastography for the characterization of cystic breast lesions has not yet been established. Since ultrasound elastography has been developed to quantify the relative stiffness of the target tissue compared with the surrounding tissue; it is likely that the stiffness of the target tissue adjacent to the cystic component, which tends to be very soft, might be overestimated. There have been a few descriptive studies regarding its application in cystic breast lesions. In our study, the blue-green-red pattern that was observed in the cystic breast lesions can be explained by an aliasing artifact[28]. The target or bull's-eye appearance found with the use of other machines can be explained by the subtle motion of the fluid[23]. Another study suggested that correlation coefficients obtained by using the speckle-tracking algorithm were markedly lower in cystic lesions[21]. Although the elastographic features of the cystic component of breast lesions vary depending on the algorithm and display form of elastography, all of these features are suggestive of the extremely soft nature of the cystic component. However, the diagnostic uncertainty due to the echogenic component within cystic breast lesions remains the primary reason for performing biopsies and obtaining benign results. The visualized anechoic areas in high-grade malignant complex breast masses might represent areas of necrosis and this finding might explain why invasive cancers appear as complex masses[23]. Hence, we expected that sonoelastography could be helpful in distinguishing echogenic debris from necrotic malignancy in complex breast masses by demonstrating the inherent differences in their stiffness[10,11]. Indeed, we found that an elasticity score of 0 (44.7%, 46 of 103) was the most common score for benign lesions, whereas an elasticity score of 2 (60%, 9 of 15) was the most common score for malignant lesions. In addition, all 8 invasive ductal carcinoma masses in our study proved to be high grade malignancies with necrosis.

With respect to the decision to perform biopsy, the sensitivity for all five readers was already 100%

in the B-mode US alone session, and it did not change after the addition of elastography in our study. A previous study on the application of elastography in cystic breast lesions reported that because malignant complex cystic masses often show angular, indistinct or microlobulated margins or thick walls on B-mode US[23], they usually undergo biopsy without further characterization of the echogenic components. Indeed, in our study, there were no false negative results for the identification of malignant lesions based on B-mode US findings.

With respect to the specificity, the specificity of 3.8% without ultrasound elastography seems to be very low. This low specificity might partly be due to the overestimated categorization of B-mode US findings by the readers due to the nature of the study, which could have led to the overestimation of the additional role of elastography. Another possible reason for this low specificity is the method of case selection in our study. In our study, we included those patients who had been initially sent to the radiology department for US-guided biopsy, and hence the lesions tended to have some suspicious findings. We believe that the main role of elastography in distinguishing benign from malignant complex breast masses is for improving the specificity, which is similar to that in studies focusing on the characterization of solid masses[14,15]. Our study shows that a biopsy could be avoided in a mean of 33.6% (34.6 of 103) of the women with a benign complex breast mass.

With respect to the interobserver variability, the three point scale used in our study led to moderate overall agreement for the elasticity score ($\kappa = 0.467$), which means that this categorization is generally concordant. This result is similar to that in previous studies on lesion management using breast US[26] and breast MRI[27], in which a fair agreement (κ of 0.52) was reported.

Our study has some limitations. First, we only included cystic breast lesions that underwent US-guided core biopsy. Therefore, we cannot generalize our results to evaluate all types of cystic breast lesions that are commonly seen in clinical practice. Second, the sample size was also insufficient to arrive at a solid conclusion. However, our cases were selected from 3089 consecutive cases. Third, we performed the study using only one commercially available ultrasound elastographic machine, and the results might vary according to the type of the equipment.

In conclusion, there was an increase in the diagnostic performance with the combined use of B-mode US and elastography for discriminating benign from malignant complex breast masses. When complex breast masses with a low suspicion for malignancy show no stiffness in the echogenic component on ultrasound elastography, we suggest that follow-up can be recommended without missing the diagnosis of breast cancer, potentially leading to a reduction in the number of biopsies with benign results.

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Original Article

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A Study of Hospital Outcome of Liver Cirrhosis Patients Admitted in a Tertiary Level Hospital

Hossain MI[1], Islam MMS[2], Siddique MAB[3] Raha A[4], Talukder MSI[5]

Abstract:

Cirrhosis is a leading cause of morbidity and mortality. This cross-sectional study was carried out in the Department of Medicine of Faridpur Medical College Hospital from November 2018 to April 2019 to assess patterns of hospital outcome and associated factors among admitted liver cirrhosis patients. A total of 89 patients were included; most patients were male (69.7%) with a male female ratio of 1:0.44.The in-hospital case fatality rate was 11.2%. Age and sex was not significant factors of treatment outcome in this study. There is an impact of different clinical features of decomposition on survival .In this study, the patients presented with decreased urinary output, peripheral edema and encephalopathy had statistically significant death rate. Overall case fatality rate was compatible with other studies.

Keywords: Cirrhosis, decomposition, encephalopath

Introduction:

Cirrhosis refers to a progressive, diffuse, fibrosing, nodular condition that disrupts the entire normal architecture of the liver. It often is an indolent disease; most patients remain asymptomatic until the occurrence of decompensation[1]. At this stage, patients experience complications associated with portal hypertension, including ascites, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy (HE), hepatorenal syndrome, portopulmonary hypertension, or variceal bleeding[2]. The worldwide prevalence of cirrhosis is unknown; however, in the United States, it has been estimated to be between 0.15% and 0.27%[3]. The common causes of cirrhosis worldwide are alcohol abuse and viral hepatitis (B and C)[4].

Liver cirrhosis represents the end - stage of many chronic liver diseases and accounts for more than one million deaths each year worldwide[5]. It is a leading cause of death in Asia. In USA, cirrhosis ranks as the tenth most common cause of death[6].

The patients with cirrhosis showing signs of decompensation have a higher mortality. Several studies tried to define the impact of different clinical features of decompensation on survival. Vergara et al as cited by Horvath A et al identified factors associated with high mortality and found that hepatorenal syndrome carried the highest mortality rate, followed by spontaneous bacterial peritonitis, hepatic encephalopathy, pneumonia and malnutrition[7]. Schmidt ML et al revealed that hepatorenal syndrome, hepatocellular carcinoma, variceal bleeding, spontaneous bacterial peritonitis as well as sepsis were associated with a higher mortality rate[8]. In a study in Korea that included Korean cohort of 2,165 patients revealed that hospitalized patients with alcoholic cirrhosis died of acute cirrhotic

1. Dr. Mohammad Iqbal Hossain, Assistant Professor, Department of Medicine, Faridpur Medical College.
2. Dr. M. M. Shahin-Ul-Islam, Associate Professor (c.c), Department of Gastroenterology, Faridpur Medical College.
3. Dr. Mohammad Abu Bakar Siddique, Assistant Professor, Department of Medicine, Faridpur Medical College.
4. Dr. Arunangshu Raha, Assistant Professor, Sheikh Russel Gastroliver Institute & Hospital, Dhaka.
5. Dr. Md. Shahidul Islam Talukder, Assistant Professor, Department of Medicine, Shaheed M Monsur Ali Medical College, Sirajgonj.

Correspondence: Dr. Mohammad Iqbal Hossain
E-mail: hossain9596@gmail.com

complications such as variceal bleeding, HE, or SBP in 2002; however, hepatic failure or HRS were major causes of in-hospital death in 2011.Among patients with nonalcoholic cirrhosis, hepatic failure and HRS remained the principal causes of in-hospital death from 2002 through 2011. 9 Despite a steady increase in the number of cirrhosis hospitalizations, in-hospital mortality in patients with cirrhosis decreased from 9.1% in 2002 to 5.4% in 2010, representing a 40% decline over time in a study[8].

The clinical course of cirrhosis in Bangladesh is unknown. There is a paucity of data regarding demographic characteristics, hospital outcome and other factors in cirrhotic patients which highlights the importance of the present study.

Methods:

This cross-sectional study was carried out in the Department of Medicine of Faridpur Medical College Hospital from November 2018 to April 2019 with prior approval of ethical committee. Patients having evidence of cirrhosis of the liver on clinical and diagnostic evaluation were included in this study. All those patients who (1) were not confirmed to be cirrhotic (2) were transferred to another acute care facility; (3) left against medical advice or if the discharge status was unknown; or (4) did not give consent, excluded from this study. Data were collected by detailed history (from patients or their relatives) thorough physical examination and necessary investigations; patients were followed up to discharge or expiry; then collected data were checked, verified for consistency and edited for result. After editing and coding, the coded data were analyzed by using the SPSS\PC software package.

Results:

A total of 89 cirrhosis patients were included in the study; 62 (69.7%) were male and 27(30.3%) were female with a male female ratio of 1:0.44. Age of patients ranged between 22-106 years with mean age of 52.33 year. Maximum patients (44.9%) lie in the 41-60 year age group.

The substantial number of patients (61.8%) had significant past history; of them 27% had a history of surgery or other invasive procedures, followed by blood transfusion in 15.7%, history of exposure in 10.1%, positive family history in 7.9% and alcohol abuse in 1.1% of cases. Regarding mode of presentation, most patients presented with ascites (49.4%) followed by gastrointestinal bleeding (27%), peripheral edema (24.7%), and encephalopathy (21.3%).

The rest of the patients presented as follows, decreased urinary output (6.7%), hepatocellular carcinoma (4.5%), jaundice (3.4%) and incidental or others (6.7%). Considering outcome, 79 (88.8%) patients out of 89 were discharged uneventfully and 10 (11.2%) patients expired (table 1); of them 3 patients expired due to variceal bleeding,4 due to hepatic encephalopathy,2 due to hepatorenal syndrome, and 1 due to sepsis (table 2).

Table 1: Distribution of patients according to hospital Outcome (n=89)

Hospital outcome	Frequency (%)
Discharged	79 (88.8)
Death	10 (11.2)

Table 2: Distribution of patients according to cause of death (n=10)

Cause of death	Frequency
Variceal bleeding	3
Encephalopathy	4
Hepatorenal syndrome	2
Others (Sepsis)	1

There is no significant difference in outcome regarding age and sex (table 3). According to age group, 9.09 % patient of below 40 year, 15% of 41-60 year age, 9.09 % of 61-80 year and, 00% of 80 or above age group expired in the hospital settings. The mortality rate in male is 14.52 % and in female 3.70 %.

Table 3: Distribution of patients' outcome in relation to age (n=89)

Age group in year	Discharged	Death (%)	Total	P value*
40 or less	20	02 (09.09)	22	
41-60	34	06 (15.00)	40	
61-80	20	02 (09.09)	22	0.705
80 or more	5	00 (00.00)	05	

*Test was carried out by $\chi 2$ test. df =3

Table 4: Distribution of patients' outcome in relation to Stroke Event (n=390)

Gender	Discharged	Death (%)	Tota	P value*
Male	53	09 (14.52)	62	0.138
Female	26	01 (03.70)	27	

*Test was carried out by $\chi 2$ test.df =1

The patients presented with decreased urinary output, peripheral edema and encephalopathy (table 5, 6, 7) had a statistically significant death rate of 50%, 27.27% and 26.32% respectively. The patients presented with ascites, gastrointestinal bleeding (table 8), abdominal pain, Jaundice, hepatocellular carcinoma had death rate of 13.64%, 12.5%, 11.11% 00% 00%, respectively

Table 5: Distribution of outcome of patients according to the presence of decreased urinary output (n=89)

Decreased urinary output	Discharged	Death Frequency (%)	Total	p value*
Present	3	3 (50)	6	0.002
Absent	76	7 (8.43)	83	

*Test was carried out by $\chi 2$ test. df=1

Table 6: Distribution of outcome of patients according to the presence of peripheral edema (n=89)

Peripheral edema	Discharged	Death Frequency (%)	Total	p value*
Present	16	6(27.27)	22	0.006
Absent	63	4(5.97)	67	

*Test was carried out by $\chi 2$ test. df=1

Table 7: Distribution of outcome of patients according to the presence of encephalopathy (n=89)

Encephalopathy	Discharged	Death (Frequency %)	Total	p value*
Present	14	5(26.32)	19	
Absent	65	5(7.14)	70	0.019

*Test was carried out by $\chi 2$ test. df=1

Table 8: Distribution of outcome of patients according to the presence of gastrointestinal bleeding (n=89)

Gastrointestinal bleeding	Discharged	Death (Frequenc%)	Total	p value*
Present	21	3(12.5)	24	0.819
Absent	58	7(10.77)	65	

*Test was carried out by $\chi 2$ test. df=1

Discussion:

In this study a total of 89 patients were included and demographic as well as pertinent data regarding cirrhosis including their hospital outcome were collected. Most patients were male 69.7% with a male female ratio of 1:0.44.

The in-hospital case fatality rate was 11.2%. This result is much better than a cohort of hospitalized

patients in Riyadh, Saudi Arabia (the case fatality rate was 35%)and a cohort of Bucaramanga, Colombia (in-hospital mortality was 23.5%)[6,10]. The result was fairly worse than hospitalized patients of United States where the inpatient mortality was 5.4% [8].

Age and sex were not significant factors of treatment outcome in this study. In a retrospective cohort study as cited by Chen CY et al revealed that for patients with compensated cirrhosis age showed no significant correlation with mortality or clinical outcomes and for patients with decompensated cirrhosis, age ≥ 75 years was significantly correlated with in-hospital mortality[11]. In patients hospitalized with cirrhosis as cited by Rubin J et.al, women have lower rates of hepatic decompensating events resulting in lower in-hospital mortality[12].

In this study, the patients presented with decreased urinary output, peripheral edema and encephalopathy had statistically significant death rate of 50%, 27.27%, and 26.32% respectively. As cited by Heidemann J et a, Type I HRS patients have a mortality of 50% two weeks after diagnosis[13]. Bajaj JS et al revealed in an analysis of more than 1500 patients hospitalized for cirrhosis, HE of grade 3 or 4 was associated with higher in-hospital and 30-day mortality, independently of failure of other organs[14]. These are mostly coherent with the designed study. In our settings, overall in-hospital mortality due to variceal was 12.5%; this is fairly better than a hospital based study conducted by Dy SM, et al (in-hospital mortality due to variceal bleeding was 15%)[15].

Limitations:

The first limitation of this study is the relatively small number of patients included. The second limitation was the generalizability of the results; the number of cirrhosis-related deaths in the community may be limited because the sample in this study was chosen from a tertiary level hospital.

Conclusion:

Liver cirrhosis is a leading cause of disability and death worldwide. Most of the patients present with features of decompensation in the hospital.

The percentage of Liver cirrhosis hospitalizations resulting in death is compatible with other mentioned study which reflects overall improvement in cirrhosis care.

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Review Article

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Hypomagnesemia – An Overlooked but Important Clinical Condition

Nomany BMS[1], Akter Z[2], Begum N[3]

Introduction:

Magnesium (Mg) in the fourth most common electrolyte or cation in the body after sodium, potassium and calcium. It is stored in the bones and muscles and largely found in the intracellular compartment. It is the second most abundant intracellular cation. The total body magnesium of an adult male is approximately 1 mol (24 g). Approximately 66% is distributed in bone, 33% in muscle and soft tissues, and less than 1% in blood. In blood 55% of the magnesium is free (ionised) and physiologically active, 30% is bound to proteins (primarily albumin), and 15% is complexed to anions[1].

In ATP - requiring reactions in the body, magnesium acts as a key player. It is mainly necessary for protein synthesis, glycolysis, DNA transcription, ion currents and membrane voltage stabilization in the body.

Like calcium, magnesium also regulates parathyroid hormone secretion from parathyroid glands. Therefore low magnesium level in blood leads to less parathyroid hormone release as well as less parathyroid hormone release leads to low magnesium level in blood.

1. Dr. Bakhtiare Md. Shoeb Nomany, Associate Professor, Department of Medicine (Nephrology wing), Dhaka Central international Medical College.

2. Dr. Zakia Akhter, Professor & Head, Department of Anatomy, Dhaka Central International Medical College.

3. Dr. Nurjahan Begum, Assistant Professor, Department of Microbiology, Dhaka Central International Medical College.

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Correspondence: Dr. Bakhtiare Md. Shoeb Nomany
E-mail: shoebnomany@googlemail.com

Role of magnesium in the body:

The overall effect of magnesium in the body is to stabilize the cell membranes of excitable tissue, eg. muscle & neurons.

1. Magnesium is important to the function of many enzymes, including Na, K-ATPase.
2. Magnesium can regulate both potassium and calcium channels.
3. Magnesium also regulate parathyroid hormone secretion and it's function on parathyroid hormone receptors in tissue.

Normal range of magnesium

Normal range of magnesium in plasma is 0.75 – 1.0 mmol/L or 1.5 – 2.0mEq/L or 1.8–2.4 mg/dl. About70-80% magnesium remains as free form and 20-30% as bound form with protein, bicarbonate, phosphate and citrate.

Magnesium homeostasis:

Predominantly the kidneys control the magnesium level in the body. Magnesium is absorbed from the gut and freely filtered across the glomeruli. In healthy individual, about 70 % is reabsorbed in the thick ascending loop of Henle (TALH). Here strongly negative paracellular protein, paracellin-1 allows efficient absorption of magnesium & calcium under control of both parathyroid hormone and calcium sensing receptor. Fine control in achieved in distal convoluted tubules. Here a transmembrane protein TRPM6 allows further uptake. Therefore, loss of function of either paracellin-1 or TRPM6 leads to renal loss of magnesium.

Determinants of renal tubular Mg^{2+} transport:

1. **Parathyroid hormone (PTH)** increases **magnesium absorption** both in the loop of Henle (LOH) and in the distal convoluted tubules (DCT)[2] .

2. Chronic aldostenone administration results in renal Mg^{2+} wasting, because mineralocorticoid receptors are present in DCT cells[3]. Therefore, **aldosterone antagonist (eg. Spironolactone)** causes **magnesium retention,** in addition to potassium retention.

3. **Insulin** increases Mg^{2+} absorption, at least in the loop of Henle. So, **insulin causes magnesium retention** in the body.

4. Prostaglandin E_2 (PGE_2), synthesized in the mammalian kidneys, inhibits magnesium absorption in the renal tubules and increases Mg^{2+} excretion in urine[4]. **NSAIDs** can inhibit PGE_2 synthesis and hence minimize the urinary loss of Mg^{2+}. Therefore NSAIDs can cause **retention of fluid (edema), magnesium and also potassium.**

5. **Proton pump inhibits (PPI)** increase renal loss of magnesium, resulting in **hypomagnesemia.**

6. **Systemic metabolic acidosis** is associated with **renal Mg^{2+} wasting**[5]. which may lead to cardiac arrhythmias. Correction of metabolic acidosis with bicarbonate infusion deceases renal Mg^{2+}loss and hence reduces the chance of cardiac arrhythmias[6].

Magnesium-rich diet:

The twenty highest magnesium-rich foods are:

1. Almonds
2. Coconut milk
3. Cashew nuts
4. Pumpkin seeds.
5. Cocoa
6. Spinach
7. Tamarind
8. Lady's finger
9. Sea snail
10. Oysters
11. Sunflower seeds
12. Watermelon seeds
13. Peanuts
14. Banana
15. Beans
16. Fatty fish
17. Dark chocolate
18. Avocado
19. Yogurt

Magnesium absorption in gut:

Typically daily absorption of magnesium in gut is 120mg. Magnesium is absorbed in small & large intestines. The proportion of magnesium absorption in gut is - in duodenum 11%, jejunum 22%, ileum 55% and colon 11%.

There are two types of types of absorption

1. Paracellular: paracellular absorption of Mg is conducted by tight junction between intestinal cells.
2. Transcellular: transcellular absorption of Mg is conducted by TRPM 6 and 7 channels in intestinal epithelium.Mutations in transcellular channel lead to hypomagnesmia.

Magnesium absorption in human intestines starts about 1 hour after intake and after 5 hours, absorption declines. After 6 hours, magnesium absorption is completed by about 80%.

Physical factors that influence the magnesium absorption are:

1. The amount of magnesium in diet
2. P^H in gut
3. Volume & viscosity of the meal
4. Gastrointestinal transit time: Fast transit time (eg. diarrhea) and damaged mucosal tissue reduce the time of interaction between diet and the mucosa and impair the magnesium absorption.
5. Medicine that alters the gastric P^H (eg. proton-pump inhibitors increase gastric P^H and decrease magnesium absorption in gut).

Daily dietary intake of magnesium is 360 mg and fecal loss is 260 mg. Therefore a daily net uptake is about 100mg in the intestine. Daily renal filtration of magnesium is 2400 mg and reabsorption is 2300 mg. Therefore a daily net renal loss is 100 mg. So there is a good equilibrium or balance between daily net intake and loss of magnesium in the body. In magnesium deficiency gut, bones, muscle and other soft tissues provide magnesium to restore blood level metticulously.

Physiology of renal tubular magnesium reabsorption:

1. Segmental magnesium reabsorption along the nephron

- In adults, the proximal convoluted tubule (PCT) contributes to 15% of filtered Mg^{2+} reabsorption which is less than the fractional reabsorption of $Na^+$and Ca^{++} . Rest of the Mg^{2+} is delivered to LOH[7].
- About 70% & 10% of filtered Mg^{2+} are reabsorbedin ascending limb of LOH & DCT, respectively.
- 5% of filtered Mg^{2+} is lost in urine daily.
- The DCT regulates selectively the Mg^{2+} reabsorption and plays an important rolein determining final urinary excretion of Mg^{2+}[8].

2. Magnesium reabsorption in PCT:

- In adult, about 15% of filtered Mg^{2+} is reabsorped in PCT[7].
- On the other hand, in neonates, about 70% of filtered $Mg^{2+}$is reabsorpedhere[9].
- Any drug that limits salt & water reabsorption in the proximal convoluted tubule, also limits Mg^{2+} reabsorption and ultimately results in greater Mg^{2+} delivery to LOH, DCT and urinary loss.
- This may lead to hypomagnesaemia[10].

3. Magnesium reabsorption in LOH:

- Cortical thick ascending limb of LOH (cTALH) contributes to 70% reabsorption of Mg^{2+} in blood. Here Mg^{2+} reabsorption is passive, moving from lumen to the interstitial space through the paracellular pathway. The driving force is the positive luminal voltage, generated by K^+ recycling into the lumen. Any drug that alters luminal voltage or permeability of paracellular pathway will also alter Mg^{2+} reabsorption in the cTALH[7].
- Defective reabsorption in cTALH results in massive Ca^{2+}& Mg^{2+} wasting in urine. Loop diuretics may lead to this picture[11].
- Low serum Mg^{+2} > Low Mg^{2+} in lumen > Less positivity in lumen > More K^+ comes out in lumen (ē ROMK) & less Ca^{+2} drivesto blood > more K with proton& Ca^{+2} in leman---- More K^+ (& proton) & calcium are lost in urine leading to hypomagnesaemia, hypokalemia, hypocalcaemia with metabolic alkalosis (hypoprotonemia)[12].

4. Magnesium reabsorption in Distal convoluted tubules (DCT):

- About 10% Mg^{2+} is reabsorped in DCT & it determines the final urinary Mg^{2+}exenetion[8].
- Here Mg^{2+}reabsorption is transcellular and active through TRPM6 ion channels, driven by transmembrane negative electrical potential[13].

- The driving force for Mg^{2+} entry is likely to be the cytoplasmic negative charge in cells. The potassium channel determines the transmembrane voltage that allows Mg^{2+} entry through TRPM6[13].

- The reabsorption of NaCl by DCT cells is necessary to sustain Mg^{2+} reabsorption. Defects in NaClreabsorption in DCT is associated with renal loss of Mg^{2+}.

7. PTH, insulin and calcitonin increase Mg^{2+} reabsorption in the cortical TALH and DCT (like Ca^{+2}) resulting in high serum Mg^{2+} (like serum$Ca^{+2).}$)[14].

- Aldosterone receptoris present in DCT cells and chronic hyperaldosteronism results in renal Mg^{2+} wasting (like K^{+})[15].

- Aldosterone antagonist (eg. Spironolactone) causes Mg^{+2}, K^{+}& H^{+} retention leading to hypermagnesemia, hyperkalemia & metabolic acidosis.

Hypomagnesemia:

Definition:

Low magnesium level in blood below normal level (0.75mmol/L or 1.5 mEq/L or 1.8 mg/dl) is called hypomagnesemia.

Hypomagnesemia occur in up to 12% of hospitalized patients. The diabetic patients are more prone to develop hypomagnesemia.

The most important causes of hypomagnesaemia are

A. Gut:

i) Castro-intestinal losses due to chronic diarrhoea, prolonged vomiting, nasogastric suction, small intestinal bypass surgery, malabsorptionsyndrome, fistulae.

ii) Pancreatitis (due to fat saponification in peripancreatic necrosed tissue followed by deposition of Mg^{2+}& also Ca^{2+}).

iii) Alcohol abuse causes more GI loss of magnesium.

Prolonged use of proton-pump inhibitors (PPI).

B. Renal:

Inherited disorders of magnesium handling:

1. Primary salt wasting disorders like:

   i) Bartters syndrome

   ü) Gitelmans syndrome

   iii) EAST syndrome (Epilepsy, ataxia, sensoryneuraldeafness ,tubulopathy leading to loss of $Na^{+}Ca^{2+,}$ Mg^{2+}in urine)

2. Familial hypomagnesaemia with hypercalciuria andnephrocalcinosis[11].

3. Isolated dominant hypomagnesaemia[16].

4. Isolated recessive hypomagnesaemia[17].

5. Hypomagnesaemia with secondary hypocalcaemia[18].

6. Mitochondrial hypomagnesaemia[19].

Acquired renal Mg^{2+} wasting disorders:

1. Drugs -Aminoglycosides, Amphoterecin B, Cisplatin, Carboplatin, Ciclosporin, Tacrolimus Proton-pump inhibitor (PPI).

2. DM and diabetic ketoacidosis (DKA).

3. Prolonged use of diuretics, eg. loop and DCT (thiazide) diuretics.

4. Recovery phase of acute tubular necrosis (ATN) & post renal type of acutekidney injury (AKI).

5. Metabolic acidosis (increase in urinary Mg^{2+} excretion).

6. Phosphate depletion & phosphate restriction (Urinary calcium and magnesium excretion).

7. Alcohol abuse causes renal loss of magnesium.

How doaminoglycosides cause hypomagnesaemia?
Aminoglycosides cause hypermagnesaemia and hypomagnesaemia in 25% patients[20]. Aminoglycosides may have effects on the calcium sensing receptor (CaSR). Activation of this receptor inhibits the passive reabsorption of magnesium and calcium in the thick ascending limb of loop of Henle (TALH) & also inhibits the active transportin the DCT, leading to renal wasting of magnesium & calcium[21].

How do calcineurin inhibitors (CNI) cause hypomagnesaemia?
CNI is associated with in inappropriately high fractional excretion of magnesium, suggesting impaired passive reabsorption in TALH or active Mg^{2+} transport in the DCT[22].

How do antibiotics, anti-tuberculosis therapy and antiviral drugs result in hypomagnesaemia?
These groups of medicine result in renal magnesium wasting due to cytotoxicity in tubular cells (acute tubular injury, ATI)[20]. Amphotericin B may cause acquired distal renal tubular acidosis, leading to reducemagnesium reabsorption in kidneys. Pamidronate used in the treatment of tumor-associated hyperkalcemia has been reported to cause transient hypomagnesaemia[23].

How does DM and its complications cause hypomagnesaemia?
Diabetic patients frequently present with hypomagnesaemia and also magnesium deficiency in cellular level[24,25]. This is due to urinary magnesium wasting. Insulin deficiency and diabetic ketoacidosis (DKA) diminish magnesium transport in the TALH[26] and DCT, resulting in more renal loss of magnesium[13].

How does phosphate depletion cause hypomagnesaemia?
Hypophosphatemia and cellular phosphate depletion cause renal excretion of magnesium leading to overt hypomagesemia[27].

Three mechanisms have been proposed:
1. Mobilization of calcium & magnesium from bone.

2. Suppressed PTH secretion.

3. Disturbed tubular transport.

How doacute and chronic metabolic acidosis cause hypomagnesaemia?
- Acute and chronic metabolic acidosis of any actiology lead to diminished magnesium reabsorption in distal tubules resulting in hypomagnesaemia[8].

How do proton pump inhibitors cause low Mg^{2+} level in blood?
Proton pump inhibitors is one of the most widely prescribed class of drug worldwide. Due to the large number of patients, even rare side effects could become apparent. Hypomagnesaemia, clinically apparent as muscle cramps, tetany, nausea, vomiting, convulsion have been observed in a small, but significant number of patients receiving PPIs. Following prolong treatment with PPI, hyporparathyroidism, hypocalcaemia and hypomagnesemia have been described[28]. PPI treatment is also associated with TRPM6 channel inhibition in intestine and renal tubules, leading to less absorption of Mg^{2+} from intestine and more renal loss of Mg^{2+} in urine[29]. (.Therefore, it is recommended to monitor serum Mg^{2+} levels in patients receiving PPIs, particularly those with concomitant cardiac disease, arrhythmia and getting diuretics.

Association of low magnesium in blood:

Low magnesium in blood is associated with low potassium (upto50% of cases), low calcium and low H^+ (metabolic alkalosis) in blood.

ROMK channel activity in increased to in DCT by low magnesium in blood. This ROMK channel opening leads to more renal excretion of potassium. The result is hypokalemia. It is accompanied with more renal loss of H^+ leading to metabolic alkalosis.

Magnesium depletion has important effects on Ca^{2+} homeostasis. Low magnesium in blood causes less secretion of parathyroid hormone and more parathyroid receptor resistance. This hyperparathyroidism & PTH receptor resistance cause hypocalcaemia.

Hypophosphatemia and cellular phosphate depletion cause renal excretion of magnesium leading to overt hypomagesemia[27].

So, low Mg^{2+} =low Ca^{2+}=low K^+ =low H^+= low PO4

Hypomagnesaemia is also associated with hyponatremia through uncertain mechanism which may contribute to some clinical manifestations.

Clinical features of hypomagnesaemia:

Hypomagnesaemia leads to abnormalities in many systems:

1. **Loss of appetite, nausea and vomiting:** These the nonspecific magnesium deficiency symptoms.

2. Musculo-skeletal system:

i) Generalized weakness: Since this mineral plays a crucial role in proper muscle functioning, an inadequate magnesium intake is likely to be associated with myasthenia (muscle weakness)[30]. This happens because magnesium deficiency is also associated with a drop in potassium levels in muscle cells[31]. Scientists believe that low magnesium and potassium contribute to muscle weakness.

ii) **Fatigue:** Everyone feels fatigued from time to time. But feeling persistent fatigue that doesn't get better with adequate rest and quality sleep, it's time to take notes and see a professional thinking should come forward, like low blood magnesium levels.

iii) **Muscle cramp:** Magnesium plays a crucial role in helping muscles relax and regulating muscle contractions[32]. Magnesium deficiency can also cause a secondary deficiency, hypocalcemia, which also causes muscle spasm and cramps. So getting rid of them requires the correction of both conditions.

iv) Carpopedal spam (Tetany)

v) Positive Chvostek's sign and

vi) Positive Trousseau's sign.

vii) **Osteoporosis:** Magnesium-deficient people are also at a higher risk of developing osteoporosis with a higher risk of fractures. Adequate magnesium intake is associated with higher bone mineral density and can prevent hypocalcemia[33]**.** Though magnesium or lack thereof can act directly on bones, it also affects their strength by causing a lack of calcium[34.]

2. Cardiovascular system:

i) **Hypertension (due to vasoconstriction):** Observational studies of humans have found that lack of magnesium through dietary intake ups the odds of high blood pressure[35,36]. A meta-analysis of studies on magnesium found that supplements of this mineral can successfully lower blood pressure[37].

ii) Supraventricular tachycardia (SVT)

iii) Ventricular tachycardia (VT)

iv) Ventricular ectopics (VEs)

v) Ventricular fibrillation (VF)

They are more common and dangerous with underlying acute coronary syndrome and congestive cardiac failure. Cardiac arrhythmia caused by low levels of magnesium is a medical emergency. It can cause chest pain, lightheadedness, shortness of breath, or even fainting[38].

3. Nervous system:

i) Delirium, depression: Personality changes like apathy, marked by numbness and lack of emotion, can occur and with a very low blood magnesium level, even delirium, and coma may happen[39]. A meta-analysis found an association between low magnesium levels and an increased risk of depression[40].

ii) Movement disorders, liketremors

iii) Vertigo, nystagmus.

iv) Convulsion / seizures:It is believed that a low blood magnesium irritates the neurons through the way it affects calcium in cells[41].

4. Others:

i) Electrolytes imbalance, like hypokalemia, hypocalcaemia, metabolic alkalosis (hypoprotonemia).

ii) Inappropriately low or normal parathyroid hormone level in blood.

Investigation for hypomagnesaemia:

1. **Serum magnesium level:**

More than 99% of whole body Mg^{2+} is located intracellularly or in the skeleton. Less than 1% of total $Mg^{2+}$is present in the body fluid which is the most assessable for clinical testing. Total serum Mg^{2+} is the most widely used to measure Mg^{2+}states.

2. Serum electrolytes:

Low Potassium level (below 3 mmol/L) may be present in more than 50% cases. Hypokalaemia is often resistant to potassium supplementation until Mg^{2+} is normalized. After normalization of Mg^{2+} renal excretion of K^{+} is reduced & hypokalemia is corrected.

3. Serum calcium (Ca^{2+}):

If serum Mg^{2+} is low (below 0.5 mmol/L), hypocalcaemia may be present with inappropriately low or normal parathyroid hormone level. Hypomagnesaemia decreases secretion of parathyroid hormone and also function of parathyroid hormone on tissue receptors leading to hypocalcaemia.

4. ECG:

Hypomagnesaemia is associated with many ECG changes, like:

i) Prolonged PR interval.

ii) Widening of the QRS complex.

iii) Flattening of the T waves.

iv) Polymorphic ventricular tachycardia.

v) Ventricular arrhythmia (which is fatal).

5. 24 hours urinaryMg^{2+}or fractional excretion of Mg^{2+}:

These 2 tests can distinguish renal losses of Mg^{2+} from other causes of low Mg^{2+} level in blood. Normal range of 24 hours urinary Mg^{2+} is <10-30 mg/ day. These tests are less practiced now.

Treatment of hypomagnesaemia:

1. Asymptomatic hypomagnesaemia (>0.4 mmol/L): Oral correction with low release Mg^{2+}:6-18 mmol/day in 4 divided doses.

The preparations are:

Magnesium glycerophosphate, Magnesium oxide

Diarrhea may limit the use of magnesium orally.

2. Symptomatic hypomagnesaemia or hypomagnesaemia with hypocalcemia or hypokalemia:

10 mmol magnesium sulfate (MgSO4) (4%) intravenous infusion bolus over 5 minutes.

Then 20mmolmagnesium sulfate in 100 ml 0.9% saline intravenous infusion over 4 hours. It may be repeated as required. Intramuscular injection is painful

Magnesium sulfate decreases the level of acetylcholine in motor nerve terminals. It also acts on SA node by decreasing the impulse generation and also prolongs the conduction time.

If there is cardiac arrhythmia (eg, torsade de pointes): Intravenous infusion of magnesium sulfate 8 mmol stat, then 20 mmol 12 hourly. Aim for serum Mg^{2+} level is >0.4 mmol/L.

If we consider locally available brand, Injection Magnesium sulfate infusion$\frac{1}{2}$unit over 5 minutes and then, 1 unit 12 hourly @ 20 drops/minute. 50% of administered magnesium is lost in urine. So prolonged administration may be necessary.

In magnesium deficiency, 0.5-1 mmol/kg/day on the first day, followed by 25 mmol daily, upto 160 mmol oven upto 5 days.

If total body weight of the patient is 60kg, magnesium requirement on the first day is 30-60 mmol i.e. 8 gram (200 ml = 2 units) to 16 mmol (400 ml = 4 units).

On the next day to 5th day, daily reauireant of magnesium is 25 mmol i.e. 6 gram (150 ml = $1\frac{1}{2}$ units). Maximum recommended daily dose is 40 gram i.e. 160 mmol = 1000 ml =10 units.

In diuretic-induced chronic hypomagnesemia, diuretic replacement with Spironolactone or eplerenone on amiloride 5mg daily ore helpful. Because they limits loss of K+ as well as Mg2+ in urine. They are potassium, proton and magnesium retaining diuretics.

Spironolactone &eplerenone are aldosterone antagonists, therefore they can cause painfulgynaecomastia. At that situation, they can be replaced by amiloride which does not cause gynaecomastia.

Management of other drug induced hypamagnesemia is obvious. The culprit drugs should be replaced by alternate medicine.

Side effects of magnesium (Mg^{2+}):

Side effects of intravenous magnesium are features of hypermagnesaemia, like nausea, vomiting, flushing, thirst, hypotension, drowsiness, confusion, stunned speech, double vision, bradycardia, muscle weakness.

Magnesium in dialysis patients:

The portion of total plasma Mg that can be removed during a dialysis treatment is called ultrafiltrable Mg^{2+}.A small amount of Mg^{2+} is removed by ultrafiltration[42]. Use of low dialysate Mg^{2+} has been shown to be a risk factor for hypomagnesemia in patients both on HD & PD (Alhosainis M. et al., Am J Nephol and 2014)[43].

In the past, dialysate Mg^{2+} concentrations of 1.5 mEn/L were used, and more recently, the standard of care in the USA in 0.75-1.0 mEn/L. When a 1.5 mEn/L dialysate Mg^{2+} is prescribed most patients will have normal or a slightly higher serum Mg^{2+}[44].

When using of 1 mEq/L dialysate Mg^{2+} concentration, a small number of patients will have pre-dialysis hypomagnesemia[45]. Moreover, hypomagnesemia in more common (Upto 33%) when a 0.5 mEn/L dialysate Mg^{2+} is used. When using a dialysate Mg of 1.5 mEq/L, episodes of hypotension during HD were less common when comparedwith a 0.5 mEq/L.

It should be kept in mind that, dialysis prescription may affect Mg flux across the dialyzer and then plasma Mg^{2+}concentrations.

Dialysate pH (bicarbonate concentration) will have an effect on the number of anionic sites on albumin and may increase or decrease the Mg^{2+} binding to albumin in plasma. Use of dialysate - citrate might affect Mg^{2+} concentration because citrate may forma complex with Mg^{2+}, which is dialyzable and increase intradialytic Mg^{2+} removal.

Administrating glucose in dialysate will stimulate insulin, which may increase the cellular uptake of magnesium into insulin sensitive tissues.

A study showed that when using dialysate calcium of 2.5 mEn/L in combination with Mg^{2+} of 0.5 mEn/L, a significant drop in mean arterial presume occurred as a result of low cardiac contractility[46].

Summary:
Magnesium is the fourth most abundant mineral in the human body. It plays several important evidence-based health benefits in the body.

1. Mg^{2+} is involved in hundreds of biochemical reactions in the body including energygeneration from food, protein formation from aminoacids, DNA & RNA synthesis & repair, muscle contraction and relaxation, neurotransmitters regulation, etc.

2. Mg^{2+} helps to move blood sugar in the muscles and to dispose lactate, that is build up during exercise and cause fatigue. Mg^{2+} supplements can boost exercise performance for athletes, and improves tiredness, fatiguenessin the people with or without chronic illness.

3. Mg^{2+} plays a critical role in mood and low levels are linked to an increased risk of depression. Mg^{2+} supplements can improves mood and irritability.

4. Mg^{2+} supplements have been shown to lower blood sugar and blood pressure in some people. Mg2+ also reduces insulin resistance.

5. Mg^{2+} has been shown to help fight against inflammation. It reduces the inflammatory marker, C reactive protein (CRP).

Normal range of serum magnesium level is 0.75 to 1 mmol/L or 1.5-2 mEq/L or 1.8 - 2.4 mg/dl. If the Mg2+ level is below the range, it is called hypomagnesemia and if the level is above the range, it is called hypermagnesemia. Both are harmful just like a double edged sword.

About 12% of hospitalized patients have hypomagnesemia. Most common causes are chronic use of loop and DCT (thiazide) diuretics, recovery from acute tubular necrosis (ATN), recovery from obstructive uropathy& nephropathy, use of nephrotoxic drugs, like amphoterecin B, aminoglycosides, cyclosporine, cisplatin, etc, inherited diseases like Gitelman's syndrome, Bartter's syndrome. These diseases cause loss of magnesium in urine.

Magnesium also may be lost in gut. The main causes are prolonged diarrhea, vomiting, N/G suction, intestinal surgery, malabsorption, pancreatitis andchronic alcoholism. Chronic alcohol abuse can cause magnesium loss both in stool & urine.

Common clinical features of hypomagnesaemia are muscle weakness, muscle cramp, tetany, delirium, convulsion and supra ventricular and ventricular arrhythmias. There is hypokalemia in 50% cases, which is resistant to K^+ supplementation until Mg^{2+} is corrected. After appropriate diagnosis, hypomagnesemia should be treated with oral or intravenous magnesium.

In CKD and ESRD, the ability of the kidney to regulate Mg level in the body disappears. Low levels of Mg in the body are associated with cardiovascular disease (CVD). It is therefore advised to measure serum magnesium level more frequently. Knowing the results of Mg^{2+}, a tailor made dialysate Mg $^{2+}$ should be implemented in daily clinical practices.

Conclusion:
Actually hypomagnesemia is a neglected topics in medical practice. Both hypomagnesemia as well as hypermagnesemia are dangerous. Both conditions may cause sudden cardiac death from supraventricular and ventricular arrhythmias. Magnesium imbalance is associated with many genetic and acquired rare and common kidney and gastro-intestinal diseases which may lead to grave outcomes. Physicians are habituated with common electrolytes imbalance (e.g. sodium, potassium). They also should be cautious about magnesium imbalance (along with calcium) when patients present with difficult to control common electrolytes imbalance, recurrent arrhythmias, dizziness, convulsion, acute and chronic kidney diseases and gastro-intestinal upset.

This extended thinking may save the lives of many patients.

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Case Report

DCIMCJ 2020 January;7(1):69-71

A Case of COVID-19 Presenting as Cerebral Venous Sinus Thrombosis

Mamun KAA[1], Ali M[2], Nomany BMS[3]

Abstract:

Corona virus disease 2019 (COVID-19) is a highly infectious disease caused by severe acute respiratory syndrome corona virus 2. Here we describe a case of 41years old man who presented with headache, seizures and hemiparesis. He had a prior history of fever with cough. Magnetic resonance venography brain revealed a cerebral venous sinus thrombosis .Ultimately patient was proved to be a case of COVID-19.

Keywords: Corona virus disease 2019, Cerebral venous sinus thrombosis, seizures, hemiparesis

Introduction:

Corona Virus disease 19 is caused by severe acute respiratory syndrome Corona Virus 2 (SARS-CoV-2). It was first recognized in December 2019 in Wuhan, China. It was declared a pandemic in March 2020 bythe World Health Organization. COVID-19 is primarily a disease of respiratory system[1], but there are increasing reports of neurological complications[2,3]. These are caused mainlyby systemic inflammation and coagulopathy[4].

Case report:

A 41years old male presented with new onset severe headache and secondary generalized tonicclonicseizure. Later he reported a history of fever, cough, breathlessness and diffuse bodyache prior to this illness. He took no regular medications.

1. Dr. Kazi Abdullah Al Mamun, Associate Professor, Department of Neuromedicine, Dhaka Central International Medical College.

2. Dr. Md. Ali, Associate Professor, Department of Medicine, Dhaka Central International Medical College.

3. Dr. Bakhtiare Mohammad Shoeb Nomany, Associate Professor, Department of Medicine (Nephrology wing), Dhaka Central International Medical College.

Correspondence: Dr. Kazi Abdullah Al Mamun
E-mail: abdalmamun39@gmail.com

He was afebrile and he had an oxygen saturation of 97% without oxygen inhalation. While in outpatient department he had a seizure and was given Diazepam. He wasalso given Levetiracetam 500 mg IV and then it was continued 12 hourly. Initial neurologic examination revealed a GCS score 12, leftsided facial palsy and left sided weakness (upper extremity was more affected than lower limb). Nasal swab polymerase chain reaction (PCR) was positive for COVID-19. He had a lymphocyte count of 12% on admission. Other laboratory findings, consistent with COVID-19 included elevated CRP (45mg/l), Ferritin (610µg/l) and D-dimer (16 µg/mL) levels.

Coagulation profile was normal. MRI brain showed hyperintense DWI signal of the right temporoparietal infarct with mass effect. MR venography demonstrated absence of flow in the right transverse and sigmoid sinus and right internal jugular vein secondary to venous thrombosis. He was initially treated with intravenous heparin (enoxaparin 60 mg subcutaneously every 12 hourly. The day after admission, he continued to have a decreased level of consciousness. On examination, there were bilateral 6th nerve palsies and fundal photograph showed bilateral papilloedema.

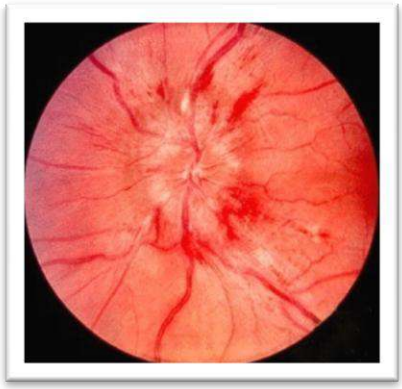

Figure 1: Fundal Photograph revealed Papilloedema

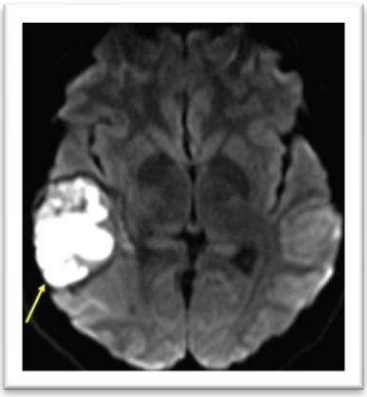

Figure 2: MRI showed hyperintense DWI signal in right temporoparietal region consistent with infarct.

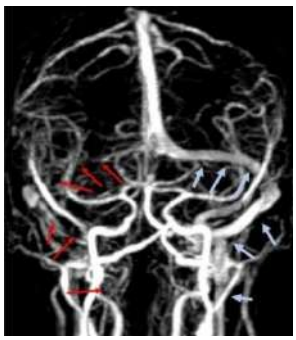

Figure 3: MR venography with red arrows showed absence of flow in the right transverse and sigmoid sinus and right internal jugular vein secondary to venous thrombosis. Light blue arrows show normal flow in the left transvers and sigmoid sinus.

He was given acetazolamide 250 mg twice daily. Over the next seven days, he improved clinically in alertness with persistent bilateral 6th nerve palsies and left sided hemiparesis.

Discussion:

COVID-19 is primarily a disease with respiratory manifestations[1]. But there are increasing reports of neurological complications[5]. There is a pro-inflammatory immune response during infection with COVID-19[6]. The severity of the disease determines the severity of inflammation[7]. High levels of inflammatory processes are associated with a hypercoagulable state[8]. Coagulopathy has been observed in similar diseases including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), caused by the SARS-CoV and MERS-CoV coronaviruses, respectively[9]. Experts suggest initial treatment with low molecular weight heparin(1 mg /kg body weight 12 hourly) followed by oral anticoagulants for 3 months in established Cerebral venous sinus thrombosis in patients with COVID-19[10]. Clinicians need to consider this option for treatment during admission and beyond discharge in patients with multiple risk factors[4]. Cerebral venous sinus thrombosis accounts for only 0.5–1% of strokes[5]. It can present with a wide range of clinical features predominantly affecting younger patients, with a female to male ratio of 3:1[11]. There are inherited and acquired risk factors for cerebral venous sinus thrombosis[12]. In this case, inherited causes were thought unlikely due to age and a lack of prior thrombotic events. Acquired causes include brain tumours, head trauma and local central nervous system infection, none of which were present in this patient. A prothrombotic state is a risk factor for Cerebral venous sinus thrombosis and this patient was positive for COVID-19. Thrombotic complications and prothrombotic states are now well recognized in COVID-19. So we can say that COVID-19 was the risk factor for precipitating cerebral venous sinus thrombosis in this patient.

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Medical Quiz: Images

Mamun KAA[1], Parvin A[2]

A 7 years old girl presented with recurrent focal seizure and poor school performance. The child had multiple hyper-pigmented papules over the face. He also had patches over the lower back. She was suggested CT head.

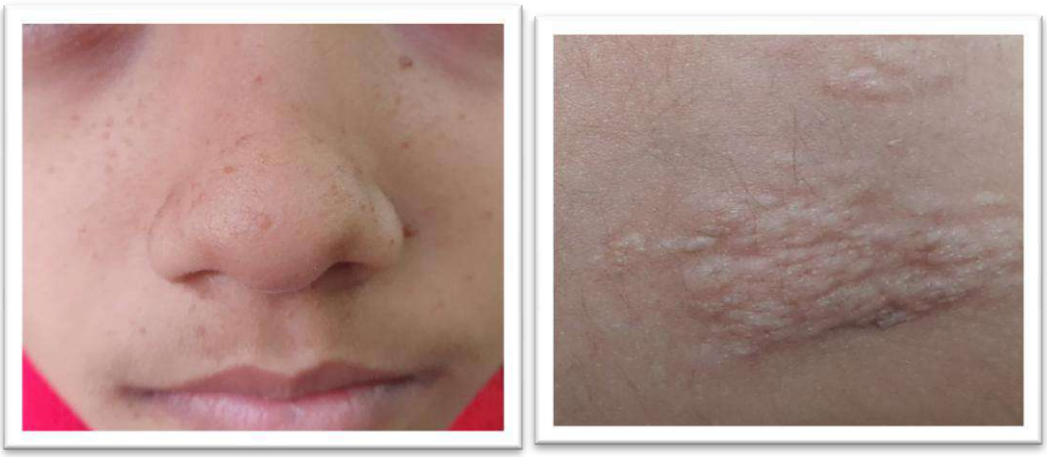

Figure 1: hyper-pigmented papules over face & patches over lower back.

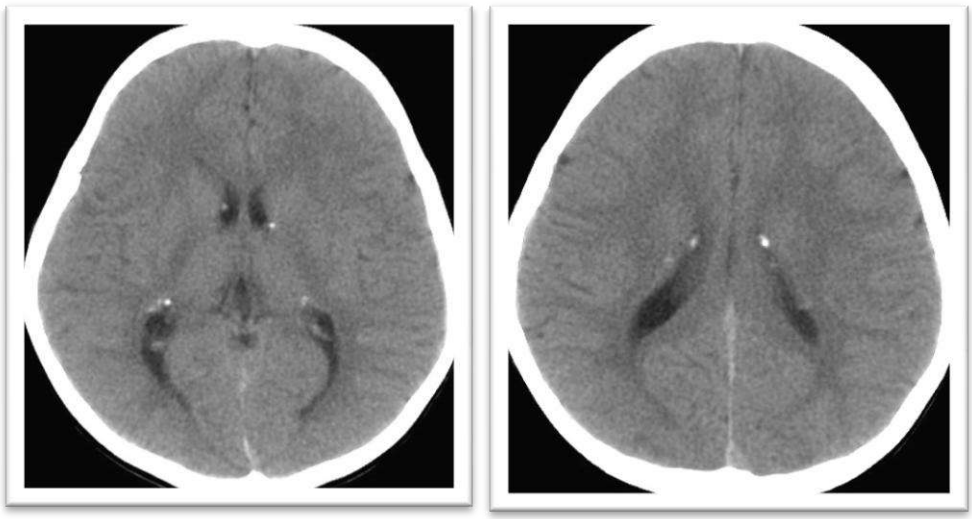

Figure 2: CT head: Multiple calcified subependymal tubers in both lateral ventricles.

1. Dr. Kazi Abdullah Al Mamun, Associate Professor (Neuromedicine), Dhaka Central International Medical College.

2. Dr. Afroza Parvin, Assistant Professor (Radiology), Dhaka Central International Medical College.

- **Q1**.What is the lesion seen on the face ?
- **Q2**. What is the lesion seen on the lower back?
- **Q3**. Mention the abnormal CT findings.
- **Q4.** What is the diagnosis?
- **Q5**.What other investigations should be done?

Answer to Medical Quiz: Images

- ✓ Adenoma sebaceum
- ✓ Shagreen patch
- ✓ Sub ependymal nodules(calcified tubers).
- ✓ Tuberous sclerosis
- ✓ EEG, Genetic testing

Discussion:

Tuberous sclerosis complex (TSC) is one of the neurocutaneous syndromes inherited in autosomal dominant fashion affecting almost all organs[1]. It is due to inactivating mutation in one of the two genes, TSC1 or TSC2[2] .

The major neurological manifestations of tuberous sclerosis complex are seizures, autism, developmental delay and behavioral and psychiatric disorders[3].

TSC has dermatologic manifestations like hypomelanotic macule(90%), facial angiofibromas (75%), Shagreen patch (20-30%)[4].

CT/MRI brain shows sub ependymal nodules .

Seizures are managed with anticonvulsantdrugs like Lamotrigine[5].

Adolescent children may have cosmetic issues, so recent trial support the use of topical 0.1% Rapamycin on facial angiofibromas[6] .

Clinical diagnosis complementing with DNA testing allows precise genetic counseling, which is important.

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