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Address for Correspondence: Prof. Sharmeen Yasmeen, Professor & Head, Dept. of Community Medicine
Bangladesh Medical College, House # 34, Road # 14A, Dhanmondi R/A, Dhaka-1209
Phone: (88-02) 44812101-6, Fax: (88-02) 9125655
E-mail: sharmeenbmc@yahoo.com, Web: www.bmcjournal.com

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Editorial

Strengthening of infection prevention and control: A stitch in time to combat COVID- 19

Nahar A[a], Yasmeen S[b]

The novel coronavirus causing COVID-19 is a new strain that has not previously identified in humans. It has spread from its initial identification in Wuhan, China, and has been declared a pandemic on 11th March 2020 by the World Health Organization (WHO).[1] COVID- 19 appears to spread more virulently than other coronaviruses such as SARS, but the mortality rate seems to be less, with 2.8% of people dying from COVID-19 compared to 9.6% from SARS.[2]

SARS-CoV-2 is an enveloped, non-segmented, positive sense RNA virus which was sequenced and isolated by January 2020.[3] COVID-19 is transmitted mainly through respiratory droplets; direct human to human transmission occurs through air droplets among persons who are in close contact within 1 meter. Moreover, droplet infection has also been documented indirectly through surfaces of fomites.[4] Air-borne transmission may occur in special situation where aerosol generating medical or surgical procedures are undertaken. However, in a study in China among 75,465 COVID-19 cases no direct airborne transmission was recorded.[5]

Till today, no vaccines and antiviral drugs have been approved. WHO emphasized on implementation of Infection prevention and control programs to control the COVID-19 pandemic. To mount an optimal response to the COVID-19 outbreak, using the strategies and practices recommended, a facility level IPC programme with a dedicated and trained team or at least an IPC focal point should be in place and supported by the national and facility senior management.[6-7] Achieving the comprehensive IPC programmes according to the WHO core components across the whole health system in all countries is essential to sustain efforts to control the COVID-19 pandemic, other emerging infectious diseases health care-associated infections and antimicrobial resistance.[6]

COVID- 19: IPC Priorities are;

1. Screening and triage for early recognition of patients with suspected COVID-19, and rapid implementation of source control
2. Applying standard precautions for all patients: Hand hygiene; respiratory hygiene; use of PPE; environmental cleaning; waste management.
3. Implementing additional precautions: Isolation and cohorting of patients with suspected or confirmed COVID-19; contact and droplet precautions; airborne precautions.
4. Implementing administrative controls: Administrative measures related to health workers; administrative measures to manage visitors.
5. Implementing environmental and engineering controls.[6]

In IPC, maintenance of hand hygiene is one of the effective measures to control spread of COVID-19 infection to others. Hand hygiene includes either cleansing hands with an alcohol-based hand rub (ABHR) containing at least 70% alcohol, or with soap, water and disposable towels.[6] However, using a surgical mask for COVID-19 patients, their care giver and health care workers (HCW) is well accepted. Using an N95 mask or respirators is only restricted to any procedures like bronchoscopy, tracheostomy, manual ventilation, collection of respiratory samples or during other aerosol generating procedures.[8]

In addition to using standard precautions, all individuals, including health workers should use contact and droplet precautions before entering the room in health care facilities where suspected or confirmed COVID-19 patients are admitted.[6] Contact precaution prevents direct or indirect transmission from contaminated surface, fomites or instruments. Personal protective equipment (PPE) that includes medical masks, medical gloves, gown, face shield and goggles are necessary to prevent infection to health care workers. Dedicated equipment (e.g. stethoscopes, thermometers, blood pressure cuffs etc.) should be used for each patient; however, in case of sharing, each equipment must be disinfected with 70% ethyl alcohol.[9] Health care workers' proper training on donning and doffing of PPE is very important to prevent spread of infection among them.[10,11] For a COVID-19 patient who is infected with a multi-drug resistant organism (e.g. *Clostridioides difficile*), a new set of gown and gloves are needed after caring for such patients.[10] Droplet precaution refers to prevention of large droplet transmission of respiratory viruses. As air-droplet seldom crosses beyond 1 meter, performing any work on patient near within 1 meter, all health care workers must wear medical mask along with face shield or goggles to protect eye from accidental spiting from patients.[10] Some aerosol generating procedures (AGPs) have been associated with an increased risk of transmission of coronaviruses (SARS-CoV-1, SARS-CoV-2 and MERS-CoV).[12,13,14] The current WHO list of these AGPs is: tracheal intubation, non-invasive ventilation [e.g. Bilevel positive airway pressure (BiPAP), Continuous positive airway pressure therapy (CPAP)], tracheotomy, cardiopulmonary resuscitation, manual ventilation before intubation, bronchoscopy, sputum induction induced by using nebulized hypertonic saline, and autopsy procedures. It

remains unclear whether aerosols generated by nebulizer therapy or high-flow oxygen delivery are infectious, as data on this is still limited.[15] Health workers performing AGPs or in settings where AGPs are performed among suspected or confirmed COVID-19 patients (e.g. intensive care units or semi-intensive care units) should: perform procedures in an adequately ventilated room – refer to the environmental and engineering control section in this guidance;[15] use appropriate PPE: wear a particulate respirator at least as protective as a US National Institute for Occupational Safety and Health (NIOSH)-certified N95, European Union (EU) standard FFP2, or equivalent.[16,17,18] Although initial fit testing is needed prior to the use of a particulate respirator, many countries and health-care facilities do not have a respiratory fit testing programme. Therefore, it is critical that when health workers put on a disposable particulate respirator, they should always perform the required seal check to ensure there is no leakage.[17] Other PPE items include eye protection (i.e. goggles or a face shield), long-sleeved gown and gloves. If gowns are not fluid resistant, health workers performing AGPs should use a waterproof apron if the procedure is expected to produce a large volume of fluid that might penetrate the gown,[11,16] in the intensive care units, where AGPs are frequently performed, the health worker may choose to wear a particulate respirator throughout his or her shift, in areas of community transmission.[17] Ideally, AGPs should be performed in rooms equipped with negative pressure ventilation systems, according to airborne precautions.[16]

All surfaces in health-care facilities should be routinely cleaned and disinfected, especially high-touch surfaces, and whenever visibly soiled or if contaminated by body fluids. In settings where suspected or confirmed COVID-19 patients are admitted, frequency depends on type of patient areas and surfaces. According to WHO guideline: Clean surfaces thoroughly with water and detergent; apply a disinfectant solution. For COVID-19, either 0.1% (1000ppm) sodium hypochlorite or 70-90% ethanol are effective. However, if there are large spills of blood or body fluids, a concentration of 0.5% (5000ppm) sodium hypochlorite should be used; contact time of a minimum of 1 minute is recommended for ethanol, chlorine-based products and hydrogen peroxide ≥0.5%; after appropriate contact time, disinfectant residue may be rinsed off with clean water if required.[9,19,20] All specimens collected for laboratory investigations should be regarded as potentially infectious. Health workers who collect, handle or transport any clinical specimens should follow WHO laboratory biosafety guidance related to coronavirus disease (COVID -19) guideline.[21] Health-care waste produced during the care of patients with suspected or confirmed COVID-19 is considered to be infectious and should be collected safely in clearly marked lined containers and sharp safe boxes.[22]

In a hospital, infection prevention control measures must be strictly followed. In the hospital there should be a system of well-maintained triage which is a first point of contact of suspected patient where patients are separated according to case definition. It is mandatory for all suspects in the triage to wear mask for source control purpose and be positioned at least 1 meter apart from each other in a designated, well-ventilated, waiting area. The attending physicians should have PPE with surgical mask, however in case of any aerosol generating procedure and during sample collection, a complete PPE is mandatory to protect health care worker. Ideally all health-care facilities in areas with COVID-19, community transmission should implement policies to restrict visitor access. This measure aims not only to protect visitors from getting infected, but also to reduce visitors' potential to introduce the COVID-19 virus into the health-care facilities.[6] Among the preventive measures for COVID-19, including aggressive tracing of cases and contacts, strict quarantine, and screening, as well as education to promote good hand hygiene practices, should be put in place.[23,24] Securing an isolated room for persons who suddenly get sick during work and encourage employee to get self-quarantine when having mild symptoms of COVID-19. According to WHO, for symptomatic patients, these additional precautions can be discontinued 10 days after symptoms onset and at least three consecutive days with neither fever nor respiratory symptoms. For asymptomatic patients, isolation can end 10 days after the initial positive RT-PCR test result.[25] Although some patients have been tested positive for COVID-19 based on molecular assays several days after resolution of symptoms, it is still unknown whether these patients continue to shed the virus, since only RNA viral fragments have been detected.[26]

To minimize the spread and fight against COVID-19 ensure appropriate monitoring, supervision, testing capacity, adequate resources, i.e., protective gear, O2 supply, ICU facilities as essential requirements in the fight against COVID- 19 in hospital setting. Infection prevention and control measures are extremely important to reduce the risk of infection and to protect HCWs. Public health measures are necessary for controlling the spread of the disease in the absence of an effective vaccine or treatment.

Dr. Azizun Nahar; M. Phil, MBBS
Associate Professor, Department of Microbiology
Bangladesh Medical College, Dhaka
Email: azizunnahar26@gmail.com

and

Prof. Sharmeen Yasmeen; M. Phil, MPH, MBBS
Head of the Department of Community Medicine
Bangladesh Medical College, Dhaka
Email: sharmeenbmc@yahoo.com

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MRI evaluation of carcinoma of tongue with clinical and histopathological correlation

Nahar K[a], Begum D[b], Zamal A K M Y[c], Sarkar P C[d], Barua S[e], Begum H[f]

Abstract

Background: Carcinoma of tongue constitutes a vast majority of malignancies of the oral cavity and oropharynx and is commonly evaluated with radiologic imaging. Clinical examination allows direct visualization; it cannot evaluate deep extension of disease. MRI has become the keystone in the pretreatment evaluation of these cancers and provides accurate information about the extent and depth of the disease that can help decide the appropriate management strategy.

Objective: Aim of the present study was to evaluate the role of MRI in staging carcinoma of tongue and to correlate MRI findings with clinical and histopathological findings.

Methods: This cross sectional study was carried out Bangladesh Medical College Hospital and National Institute of ENT, Dhaka between January 2017 and December 2018. Total 100 patients with malignant lesions of tongue were studied. All patients underwent surgical treatment for primary tumor and cervical nodes and later histopathology was performed. The sensitivity, specificity and the accuracy of MRI in the detection of carcinoma of tongue were evaluated and compared to clinical and histopathological diagnosis.

Results: Majority (71.0%) of tongue carcinoma were found in oral tongue. Male was predominant as 81.0%. The sensitivity, specificity and accuracy of clinical examination and MRI in the detection of malignant lesion of tongue were 85.45% vs 100%, 88.24% vs 65.38 and 86.0% vs 91% respectively while the positive and negative predictive values were 97.26% vs 89.16% and 55.56% vs 100% respectively.

Conclusion: Study revealed MRI is more accurate to clinical evaluation for higher tumour stages T2, T3 and T4. Sensitivity and Accuracy and NPV of MRI are higher compared to clinical evaluation.

Keywords: MRI, Carcinoma of tongue, histopathological finding.

Introduction:

The tongue is the centre piece of the oral cavity and the oropharynx. Oral tongue consists of the anterior two-thirds and the posterior (the base) of the tongue is considered part of the oropharynx.[1] The oral tongue is the most common oral cavity subsite for squamous cell carcinoma (SCC).[2,3]

Tumor thickness or depth of invasion of 4-5 mm is associated with an increased risk of nodal metastases.[4] At presentation, approximately 60% of patients with SCC of the tongue base have nodal involvement which is bilateral in approximately 30 % and necessitates meticulous inspection with imaging.[5]

Evaluation of the depth of invasion can be done clinically by tumor palpation and radiologically with the use of magnetic resonance imaging (MRI).[6]

MRI with superior soft tissue characterization is the optimal modality, displaying exquisite anatomical detail including intrinsic and extrinsic muscles, the floor of mouth (FOM) and the lingual vascular bundle .[7]

MRI is used to assess the extent of loco-regional tumor spread, depth of invasion and extent of lymphadenopathy. The invasion of the floor of the mouth by the tumor is depicted well in the coronal plane.[8,9]

a. Dr. Kamrun Nahar; FCPS, MBBS
Associate Professor, Department of Radiology & Imaging
Bangladesh Medical College, Dhaka

b. Dr. Delara Begum; MD, MBBS
Associate Professor, Department of Radiology & Imaging
National Institute of ENT, Dhaka

c. Dr. AKM Yunus Zamal; M. Phil, MBBS
Professor, Department of Histopathology
Universal Medical College, Dhaka

d. Dr. Polash Chandra Sarkar; FCPS, MBBS
Assistant Professor, Department of Otolaryngology
National Institute of ENT, Dhaka

e. Dr. Saikat Barua; M. Phil MBBS
Assistant Professor, Department of Radiology & Imaging
Bangladesh Medical College, Dhaka

f. Dr. Halima Begum; M. Phil MBBS
Assistant Professor, Department of Radiology & Imaging
Bangladesh Medical College, Dhaka

Correspondence to:
Dr. Kamrun Nahar; FCPS, MBBS
Associate Professor, Department of Radiology & Imaging
Bangladesh Medical College, Dhaka
E-mail: knmili01@gmail.com

Perinural spread is best assessed on MRI and may be seen as excessive enhancement within foraminae and loss of fat density. [7]

The need for elective neck dissection in patients with N0 neck is often based on clinical and/or radiographic assessment of tumor depth of invasion in addition to tumor size.[10,11] The aim of the present study is to define the accuracy of MRI in the evaluation of the T stage, correlating MRI to clinical and pathological data. In the subgroups of the tumor close to the mandible, the relationship between tumor and mandible was determined, comparing clinical examination and MRI to pathological data.

Material and Methods:

The cross sectional study was carried out in Bangladesh Medical College Hospital and National Institute of ENT, Dhaka between January 2017 and December 2018. One hundred patients of all age groups willing to do MRI with malignant lesions of tongue excluding those who have any contraindication to MRI or refused to do MRI were studied. The oral cavity was examined looking for any sign of trismus, visible or palpable lesions, evaluating dental status, tongue movement and protrusion. Palpation of the tongue and floor of the mouth was extremely useful in detecting small lesion infiltration and superficial extension. All patients underwent surgical treatment for primary tumor and cervical nodes. The histopathological reports were collected and correlated with MRI findings. The histopathology was found to be positive to squamous cell carcinoma in 99 cases and to adenoid-cystic carcinoma in one).

MR Imaging technique and procedure

Magnetic Resonance Imaging (MRI) was obtained on a 1.5 Tesla (Hitachi, Model Echelon smart) superconductive system using a head and neck phased array coil. The study, before the infusion of contrast medium, consisted of fast spin-echo (FSE) T1 weighted sequences on axial and coronal or sagittal planes; axial and sagittal FSE T2 weighted sequences and short-tau-inversion-recovery (STIR) T2 weighted sequences on the axial plane and post contrast axial, coronal and sagittal T1 with T2 Fat sat axial sequences. The sequences were acquired at 4 mm thickness with 1 mm interslice gap. The matrix used is 256 x 256 and FOV 240 mm. Echoplanner diffusion weighted imaging is performed with b value 0 and 1000 sec/mm^2. Non contrast T1W sequences demonstrate cortical erosion and marrow invasion. Contrast enhanced T1W images help to assess marrow invasion, perineural spread, soft tissue extent, tumour thickness and best demonstrate necrosis in nodes. T2W sequences depicts extrinsic muscles, floor of mouth (FOM) involvement as well as nodes.

The pathological staging (PT) was achieved considering the maximum tumor size after fixation of the specimen in formalin. The tumor was oriented and cut along its major diameters; the assessment of the mandibular involvement was made through the examination of the EE slides after decalcification. All data were finally tabulated and cross-tabulations were prepared and sensitivity, specificity, diagnostic accuracy and predictive value MRI was evaluated with that of clinical and histopathological tools.

Results:

Table 1: Demographic characteristics of the study patients (n=100)

Demographic characteristics	Number of patients	Percentage
Age (years)		
≤30	11	11.0
31-40	14	14.0
41-50	29	29.0
51-60	26	26.0
61-70	18	18.0
>70	2	2.0
Sex		
Male	81	81.0
Female	19	19.0

Majority (29.0%) patients belonged to age 41-50 years. Male were predominant (81.0%) and female were 19(19.0%). Male female ratio was 4.3:1 (Table-1).

Table 2: Site of tumour of the study patients (n=100)

Site of tumor	Number of patients	Percentage
Oral tongue	71	71.0
oropharyngeal tongue	29	29.0

Majority (71.0%) patients were found as oral tongue malignancy and 29.0% with oropharyngeal tongue malignancy (Table-2).

Table 3: Association between MRI and clinical tumours staging (n=100)

Clinical T staging	Total	MRI T staging				p value
		T1	T2	T3	T4	
T1	3	3	0	0	0	0.001[s]
T2	27	0	25	2	0	
T3	36	0	8	23	5	
T4	34	0	2	12	20	
Total	100	3	35	37	25	

Most of the patients (36) had clinical stage T3 among them 8 patients had T2, 23 had T3 and 5 had T4 evaluation of MRI tumour stage (Table-3).

Table 4: Association between MRI and clinical nodal staging (n=100)

Clinical N staging	Total	MRI T staging			p value
		T1	T2	T3	
T0	27	15	7	5	0.001[s]
T1	48	2	24	22	
T2	25	0	0	25	
Total	100	17	31	52	

Most of the patients (48) had clinical stage N1 among them 2 patients had N0, 24 had N1 and 22 had N2 evaluation of MRI nodal stage (Table-4).

Table 5: Association between MRI and histopathological tumours staging (n=100)

MRI T staging	Total	Histopathological T staging				p value
		T1	T2	T3	T4	
T1	3	3	0	0	0	0.001[s]
T2	35	0	34	1	0	
T3	37	0	4	33	9	
T4	25	0	1	0	24	
Total	100	3	39	34	24	

Most of the patients (37) had MRI stage T3 among them 4 patients had T2 and 33 had T3 evaluation of histopathological tumour stage (Table-5).

Table 6: Association between MRI and histopathological nodal staging (n=100)

MRI N staging	Total	Histopathological N staging			p value
		T0	T1	T2	
T0	17	17	0	0	0.001[s]
T1	31	5	21	5	
T2	52	4	0	48	
Total	100	26	21	53	

Most of the patients (52) had MRI stage N2 among them 4 patients had N0 and 48 had N2 evaluation of histopathological nodal stage (Table-6).

Table 7: Association between histopathological and clinical tumour staging (n=100)

MRI T staging	Total	Histopathological T staging				p value
		T1	T2	T3	T4	
T1	3	3	0	0	0	0.001[s]
T2	27	0	26	1	0	
T3	36	0	11	22	3	
T4	34	0	22	11	21	
Total	100	3	39	34	24	

Most of the patients (36) had clinical stage T3 among them 11 patients had T2, 22 had T3 and 3 had T4 evaluation of histopathological tumour stage (Table-7).

Table 8: Association between histopathological and clinical nodal staging (n=100)

MRI N staging	Total	Histopathological N staging			p value
		T0	T1	T2	
T0	27	24	2	1	0.001[s]
T1	48	2	19	27	
T2	25	0	0	25	
Total	100	26	21	53	

Most of the patients (48) had clinical stage N1 among them 2 patients had N0, 19 had N1 and 27 had N2 evaluation of histopathological nodal stage (Table-8).

Table 9: Sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV) of MRI and clinical data in the evaluation of malignant lesion of tongue

Test of validity	**MRI**	**Clinical**
Sensibility	100.0	85.45
Specificity	65.38	88.24
Accuracy	91.0	86.0
PPV	89.16	97.26
NPV	100	55.56

The sensitivity, the specificity and the accuracy of clinical examination in the detection of malignant lesion of tongue were 85.45%, 88.24% and 86.0% respectively while the positive and negative predictive values were 97.26% and 55.56% respectively. The sensitivity, the specificity and the accuracy of MRI in the detection of malignant lesion of tongue were 100%, 65.38% and 91% respectively while the positive and negative predictive values were 89.16% and 100% respectively (Table-9).

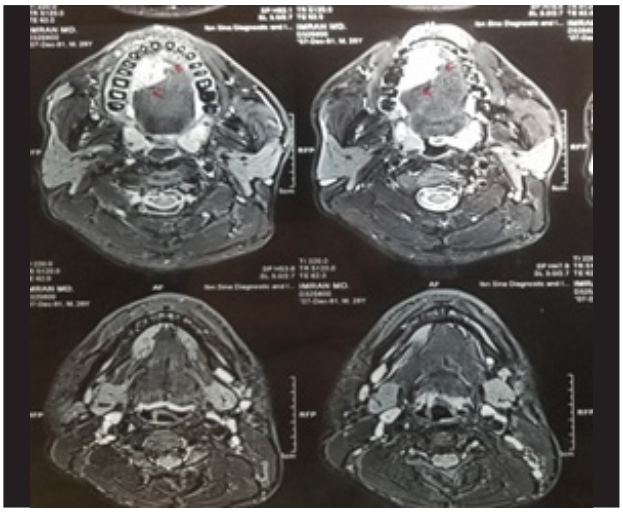

Figure 1: CE T2W fat sat MR images depict oral tongue Ca in right half of tongue that extends up to midline with level Ia and right lb cervical lymphnodes

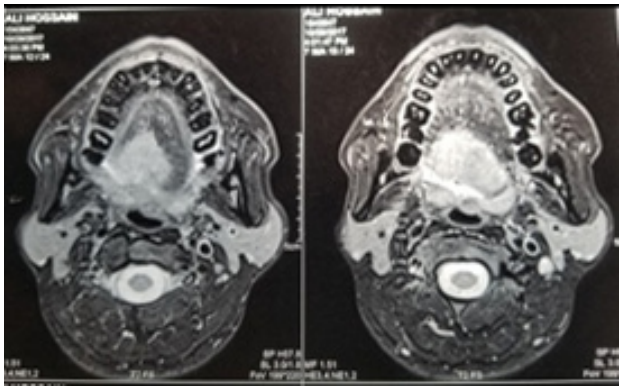

Figure 2: CE T2W fat sat MR images show base tongue Ca that crosses midline, involves RMT with left level ll lymph node.

Discussion:

In this study observed that the majority (29.0%) patients belonged to age 41-50 years. Male were predominant (81.0%) and female were 19(19.0%). Male female ratio was 4.3:1. Singh et al.[12] observed in his study almost one third (32.0%) patients belonged to age 51-60 years and 96.0% patients were male. Vidiri et al.[13] showed that the median age was 50 years (range 35-86). Similar observation also found Alsaffar et al.[15] they showed the mean age was found 64 years and 34 cases were male. Agarwal et al.[16] showed out of 47 patients, 34(72.34 %) and 13(27.66%) were male and female respectively. Dikshit et al.[14] which showed male predominance. Also, according to Bhat et al.[17] study, majority (74.3%) were males with a male to female ratio of 3:1.

In current study showed the majority (71.0%) patients were found in oral tongue malignancy and 29(29.0%) in oropharyngeal tongue. In the Agarwal et al., study MR detected nodal metastasis in oral tongue in 70 % and FOM (floor of the mouth) in 67% cases. Singh et al.[12] observed that the highest number of patients was found to have tongue malignancy constituting about 82% of the patients.

In this study observed that most of the patients (36) had clinical stage T3 among them 8 patients had T2, 23 had T3 and 5 had T4 evaluation of MRI tumour stage. Singh et al.[12] reported there was moderate agreement (k=0.537) for the T stage between the clinical and MRI staging assessments. This is consistent with the studies performed by Rogerio et al.[18] and Hirunpat et al.[19] which also showed that misstating by clinical examination in the overall stage grouping was high. MRI was used to determine the local extension of oral-cavity and base of the tongue carcinoma.[20]

In this study showed most of the patients (48) had clinical stage N1 among them 2 patients had N0, 24 had N1 and 22 had N2 evaluation of MRI nodal stage. Singh et al.[12] reported that N stage agreement between MRI and clinical staging assessments was fair (k=0.328).

In current study showed most of the patients (37) had MRI stage T3 among them 4 patients had T2 and 33 had T3 evaluation of histopathological tumour stage. Singh et al.[12] reported the confirmatory diagnosis was made by surgery/histopathology.Good/substantial(k=0.790) agreement for the T stage was seen between MRI and histopathology staging assessments. These results are consistent with the study conducted by Tetsumura et al.[21] in which the tumor depth and width were measured on both MR images and histopathological sections and the authors observed a high correlation between the values measured by MRI and histopathology. Lam et al.[22] also conducted a study in which the radiological tumor thickness on contrast-enhanced T1-weighted and T2-weighted images was compared with the histological tumor thickness. They concluded that MR images provide satisfactory accuracy for the measurement of tumor thickness and staging of oral tongue cancer. Vidiri et al.[13] also observed similar observation they showed their study. Agarwal et al.[16] reported on correlating MRI data with pathological findings, three cases each of down staging and up staging was seen in T stage evaluation. One case each was down staged from T2 to T1, T3 to T2 and T4 to T2. On the other hand, one case each was upstaged from T0 to T1, T2 to T3 and T2 to T4. The accuracy of MRI seems to be far higher than clinical examination in case of middle-size tumors and larger tumors. Heissler et al.[23] observed accuracy of MRI to be 87% in identifying the T stage, as compared with the histopathologic result.

In this study showed most of the patients (52) had MRI stage N2 among them 4 patients had N0 and 48 had N2 evaluation of histopathological nodal stage. Singh et al.[12] reported that the agreement for the N stage was moderate (k=0.458) between MRI and histopathology staging assessments. Zeng et al.[24] also conducted similar studies

and founded that MRI showed good performance in displaying tumor invasion, invasion depth and extension. Agarwal et al.[16] comparison of nodal stages by MRI and HPE, MRI correctly identified 44 out of 47 cases in comparison to histopathological examination. Only three cases were changed by HPE. The three cases under staged by MRI were one case of N2a was changed to N2c and two cases of N0 were changed to N1 by HPE.

In this study observed the most of the patients (36) had clinical stage T3 among them 11 patients had T2, 22 had T3 and 3 had T4 evaluation of histopathological tumours stage. Alsaffar et al.[15] reported that evaluated SLN for oral and oropharyngeal cancer however most of these studies included advanced T stage and did not study specific subsite. [25,26] Sagheb et al.[27] did a pilot study to examine the role of SLN in early T stage tongue SCC with N0 neck.

In this study observed most of the patients (48) had clinical stage N1 among them 2 patients had N0, 19 had N1 and 27 had N2 evaluation of histopathological nodal stage. Singh et al.[12] reported agreement for the N stage was poor (k=0.185) between the clinical and histopathology staging assessments. In their study showed that MRI is an adequate technique for the assessment of oral cavity malignancies, in the evaluation of depth invasion, presence and extension of mandibular involvement (T stage), and shows excellent agreement with the final T staging by histopathology. This is consistent with the study conducted by Vidiri et al.[13] which also shows similar results.

In this study observed that the sensitivity, the specificity and the accuracy of clinical examination in the detection of malignant lesion of tongue were 85.45%, 88.24% and 86.0% respectively while the positive and negative predictive values were 97.26% and 55.56% respectively. The sensitivity, the specificity and the accuracy of MRI in the detection of malignant lesion of tongue were 100%, 65.38% and 91% respectively while the positive and negative predictive values were 89.16% and 100% respectively. Vidiri et al.[13] reported similar observation they showed their study the sensitivity, the specificity and the accuracy of MRI in the detection of mandibular involvement were 94.1%, 60% and 81.5% respectively, while the positive and negative predictive values were 80% and 85.7% respectively. The sensitivity, the specificity and the accuracy of clinical examination in the detection of mandibular involvement were 100%, 30% and 74.1% respectively while the positive and negative predictive values were 70.8% and 100% respectively. Bolzoni et al.[20] found high sensitivity, specificity and accuracy using MRI (93%); the NPV was 87.5% and the negative value was 96%. Imaizumi et al.[28] found a sensitivity of MRI and CT for mandibular invasion to be 96 % & 100 % respectively and of sensitivity of MR and CT for marrow involvement to be 81% and 88% respectively, however without any statistical difference.

Conclusion:

MRI is more accurate than clinical evaluation for higher tumour stages T2, T3 and T4. Sensitivity, Accuracy and NPV of MRI are higher compared to clinical evaluation, although there are strong relations between radiological and clinical evaluation.

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Role of HydroMark for neoadjuvant chemotherapy patient: Bangladesh experience

Ahmed S K F[a], Nafisa A[b], Khan H I[c], Priam S M[d], Ferdous H[e], Kumkum F J[f]

Abstract

Background: In order to perform breast conserving surgery following complete, good response to neoadjuvant chemotherapy, localization of primary tumour site is a prerequisite. Due to lack of localization technique, Bangladeshi patients face significant psychological and social impact due to unnecessary mastectomy. We have revolutionized breast cancer management in Bangladesh by introducing many techniques and concepts. HydroMark marker insertion at tumour centre with US guidance is one such example.

Objective: To share this new development in breast cancer management in Bangladesh and to present early outcome data of HydroMark insertion for suitable patients with breast cancer having NAC (Neoadjuvant Chemotherapy), which may aid in breast conserving surgery following downstaging of cancer.

Methods: In this prospective cross-sectional study, a total number of fourteen patients were selected for neoadjuvant chemotherapy by MDT at the AKMMCH, Dhaka during the period from December 2018 to April 2020. Patients with triple assessment confirmed, palpable breast cancer who deemed suitable for NAC, had USG guided marker clip inserted at the centre of the mass under local anesthesia. Tumour grade, hormone receptor status and other markers were established from the core biopsy. Clinical staging, including palpable tumor size and lymph node status were recorded. Post NAC radiologic evaluation done to assess radiological response half way of treatment and at the end. Decision about NAC (6-8 cycles) was made through virtual MDT.

Results: Patient's age ranged between 28 to 60 years with an average 41.42 years. Pre NAC tumour sizes ranged between 3 cm to 7cm with an average of 4.03 cm on clinical examination, and 2.5 cm to 5.5 cm with an average 4.71 cm on imaging. Post NAC clinical findings showed complete response in 6 case and on imaging, 3 showed complete radiological response and 1 case showed 15 mm and 1 with 10 mm and 1 case showed 16mm on USG. On core biopsy, 5 cases were Grade-3, 8 cases were Grade-2 and 1 with Grade-1 invasive ductal carcinoma. Four cases were ER positive and 10 cases were ER negative. HER2 was positive in 3 and negative in 11 cases. Post NAC clinical examination showed complete response in 6 cases and one patient did not attend our unit post NACT and other seven still receiving chemotherapy. Therefore, 6 cases will have post-operative histology details available in this paper. Histology revealed three cases with Grade-2, two with Grade-3 and Grade-1 IDC. Three showed complete pathological response, one 10 mm, one 12 mm and one 8 mm size of invasive cancer with clear margins.

Conclusion: Our early outcome data shows that HydroMark localisation technique has shown great success in breast conservation for patients with good/complete clinical response post NAC who would have subjected to unnecessary mastectomy. This paved the way for other organizations to adapt this technology and likely to serve benefit of many Bangladeshi patients avoiding unnecessary mastectomy post neoadjuvant chemotherapy.

Keywords: HydroMark, Invasive ductal carcinoma, Complete pathological response, Neoadjuvant chemotherapy, Breast conserving surgery.

a. Dr. SK Farid Ahmed; FRCS, MBBS
Breast & Oncoplastic Breast Surgeon, Wycombe Hospital
Buckinghamshire Healthcare NHS Trust, UK
Visiting Consultant and Advisor, Anwer Khan Modern Breast Care Unit and Research Centre, Dhaka.

b. Dr. Ali Nafisa; FCPS, MBBS
Associate Professor, Department of Surgery
Anwer Khan Modern Medical College, Dhaka.

c. Dr. Humaira Islam Khan
Consultant Sonologist, Anwer Khan Modern Hospital & Diagnostic Centre, Dhaka.

d. Dr. Samanta Meharin Priam; MBBS
Medical Officer, Department of Surgery
Anwer Khan Modern Medical College Hospital, Dhaka.

e. Dr. Hasnatul Ferdous; MBBS
Medical Officer, Department of Surgery
Anwer Khan Modern Medical College Hospital, Dhaka.

f. Dr. Farzana Jahan Kumkum; MBBS
Honorary Medical Officer, Department of Surgery
Shaheed Suhrawardy Medical College Hospital, Dhaka.

Correspondence to:
Dr. SK Farid Ahmed; FRCS, MBBS
Breast & Oncoplastic Breast Surgeon, Wycombe Hospital
Buckinghamshire Healthcare NHS Trust UK
Visiting Consultant and Advisor, Anwer Khan Modern Breast Care Unit and Research Centre, Dhaka
Email: skfahmed406@yahoo.com

Introduction:

Neoadjuvant therapy is the pre-operative treatment of tumours with chemotherapy, radiation therapy, and endocrine therapy. It was originally used for its impact on surgery, down staging tumours, and allowing breast-

conserving surgery rather than mastectomy. In addition, neoadjuvant therapy offers potential opportunities for response prediction[1] and relatively quick assessment for drug development and approval in breast cancer[2] by monitoring benefit from the intervention at early stages of disease. Neoadjuvant chemotherapy and endocrine therapy are widely used and studied in breast cancer.[3] Due to down-staging of the tumour by NAC (Neoadjuvant Chemotherapy), patients who were initially planned for mastectomy could receive BCS (Breast Conserving Surgery).

HydroMark is the only biodegradable hydrogel polymer containing a central permanent metal marker which provides exceptional visibility. HydroMark marker hydrates to provide unmatched long-term visibility. It is Ultrasound visible even after Neoadjuvant Chemotherapy. It hydrates to provide 12-15 months of Ultrasound visibility after neoadjuvant chemotherapy.

We are looking at the initial experience of HydroMark marker clip insertion prior NAC; this concept is introduced in Bangladesh by first author which has revolutionised breast cancer management in Bangladesh. Due to inability to locate residual breast cancer, post NAC, patients ended up by unnecessary mastectomy. Although this technology is well established in western world, we wanted to introduce this to benefit breast cancer patients in Bangladesh. One of the biggest benefit of NAC is down staging of breast cancer and avoiding of mastectomy but Bangladeshi patient were deprived of the benefit due to lack of availability of this technology.

The advantages of BCS compared to mastectomy obviously include less morbidity and thereby improved aspects of quality of life.[4] Another benefit of NAC includes the opportunity to de-escalate surgical treatment of the axilla.[5] BCS after NAC introduces challenges as identification of original tumour location and monitoring tumour response using imaging.[6] These promising results have led to challenging new trials investigating the potential of non-operative therapy for invasive breast cancer by utilizing accurate image-guided percutaneous biopsy to document pathologic complete response.[7] While improved breast imaging and the promising concept of non-operative therapy in patients that reach pCR (Complete pathological response) after NAC are currently being investigated, surgical management with the Neoadjuvant chemotherapy has been established in downstaging large or locally advanced tumours allowing breast-conserving surgery, thereby avoiding mastectomy since the 1970s.[8] Patients with tumours that achieve a pathological complete response (pCR) to neoadjuvant chemotherapy have been shown to have lower recurrence rates compared with those with partial response.[9] However, pCR is achieved only in 20% to 30% of patients[10] and its predictive value depends on the tumour biology. Patients with human epidermal growth factor receptor (HER) 2-positive and triple-negative tumours are good candidates for neoadjuvant chemotherapy as they have higher probability of achieving pCR.[11] The efficacy of NAC to downsize or achieve a pathologic complete response (pCR) has improved due to more efficient targeted drug regimens, and pCR rates of up to 60-80% in the triple negative and ER-ve, HER2 positive are now being reached.[12] Residual cancer burden (RCB) and number and size of nodal metastases provides a standardised procedure for the prospective evaluation of specimens to report response to neoadjuvant chemotherapy.[13]

Material and Methods:

In this prospective cross-sectional study, a total number of fourteen patients were selected for neoadjuvant chemotherapy by MDT at the Anwer Khan Modern Breast Care Unit and Research Centre, Dhaka during the period from December 2018 to April 2020. Patients diagnosed with palpable breast cancer who deemed suitable for NAC, underwent placement of marker clip at the centre of the mass under local anesthesia with USG guidance. Patients were selected for this procedure when the initial diagnosis of breast cancer is made with mammogram, Ultrasound, and subsequent histologic confirmation. Tumour grade, hormone receptor status and other markers were established from the core biopsy. Clinical staging, including palpable tumor size and lymph node status were recorded. Post NAC evaluation was done by radiologic imaging to assess radiological response half way of treatment and at the end. Decision about NAC was made through virtual MDT. Informed written consent is obtained from the patients. Patients were usually given 6-8 cycle of chemotherapy under oncologist guidance.

Procedure

The surgical tray is assembled in a sterile fashion with the following items: gloves, sterile drape, bandage and local anesthetic. The patient is positioned and the breast is prepared and draped. 10ml of 1% bupivacaine local anesthesia injected at the entry point of applicator of the breast and the area where the applicator will travel. The sonographic probe is fitted with the sterile probe cover. Sonographic guidance locates the tumour and determines the center. Before HydroMark clip deployment, the applicator is placed on the sterile field, breast was cleaned and draped, USG probe was placed and the HydroMark applicator was inserted through the pre-determined area of skin of the breast and applicator is pushed into the centre of the palpable breast cancer (Figure -1). Location of the tip of the applicator at the centre of the mass was confirmed with Ultrasound. The plunger pushed and hydrogel is deployed under direct sonographic guidance (Figure 2). The applicator unit were pulled out and manual pressure applied to the site. Water proof bandage is placed at entry point of application. USG confirmation of centre localisation of hydrogel was made (Figure 3). Marker placement is now documented for subsequent definitive surgical treatment after neoadjuvant chemotherapy.

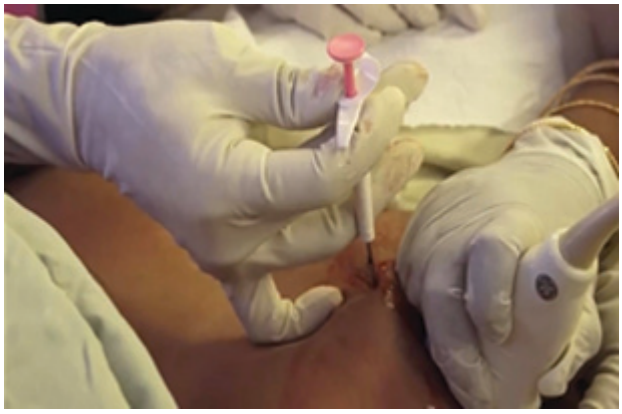

Figure 1: US guided insertion of HydroMark

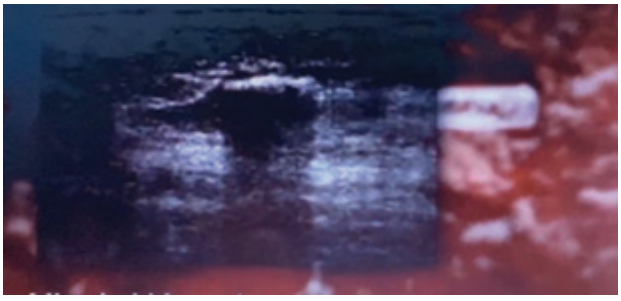

Figure 3: Microbubbles enhance immediate hyperechoic USG visibility at initial deployment.

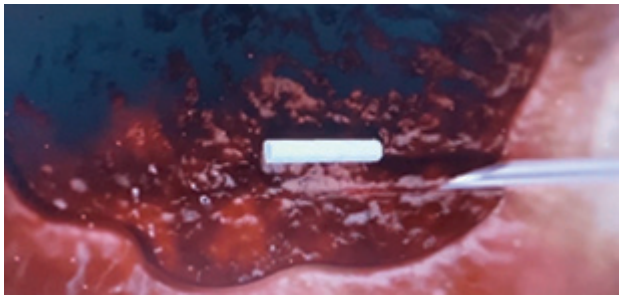

Figure 2: HydroMark deploys quickly and smoothly

Results:

A total of fourteen patients were inserted with HydroMark before commencement of neoadjuvant chemotherapy. Age ranged between 28 to 60 years with an average 41.42 years.

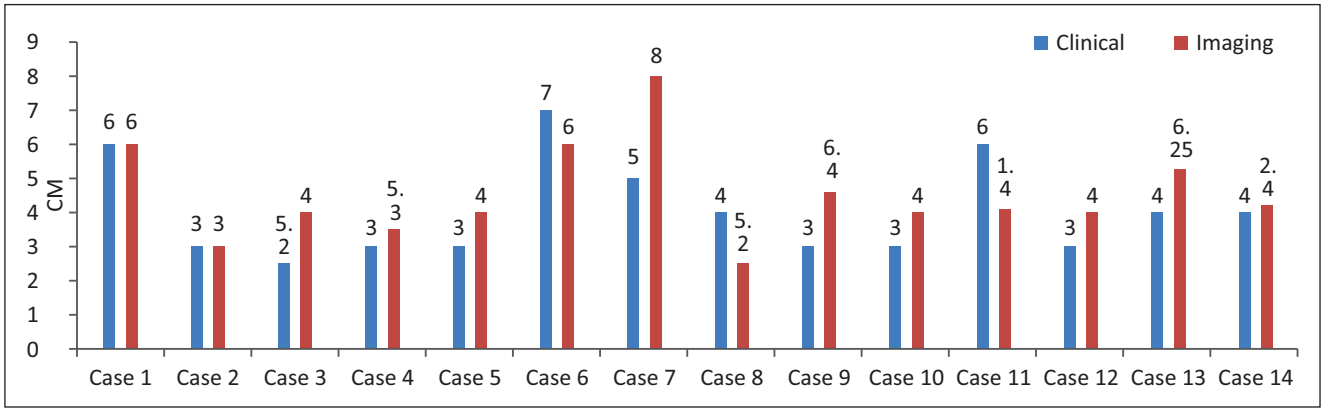

Figure 4: Pre NAC size comparison, clinical to radiological.

Pre NAC tumour sizes ranged between 3 cm to 7cm with an average of 4.03 cm on clinical examination and 2.5 cm to 5.5 cm with an average of 4.71 cm on imaging (Figure 4).

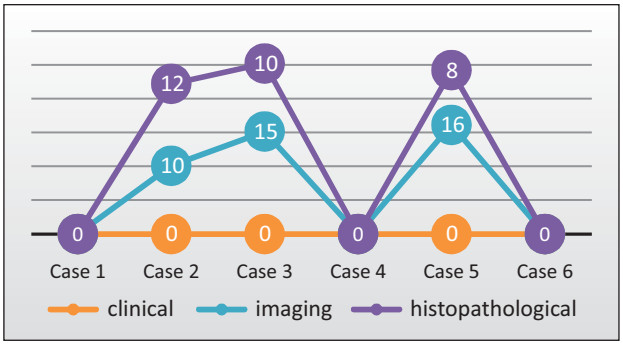

Figure 5: Post NAC size comparison, clinical, Imaging & histopathology

Post NAC clinical findings showed complete response in 6 cases and on imaging, 3 showed complete radiological response and 1 case is 15 mm, one case is 10 mm and one case 16 mm on USG, one patient was lost. Three showed complete pathological response, one with 10 mm, one with 12 mm and 8 mm size of invasive cancer with clear margins (Figure 5).

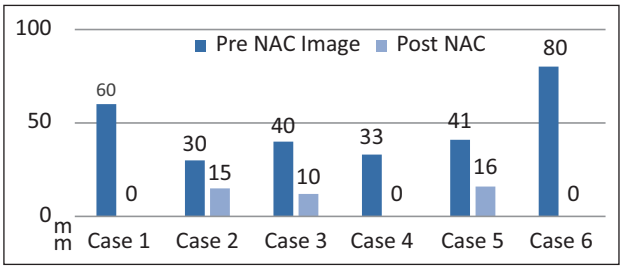

Figure 6: Imaging size of tumour; pre and post NAC

On imaging, 3 showed complete radiological response and 1 case is 15 mm, one case is 10 mm and one case 16 mm on USG (Fig-6)

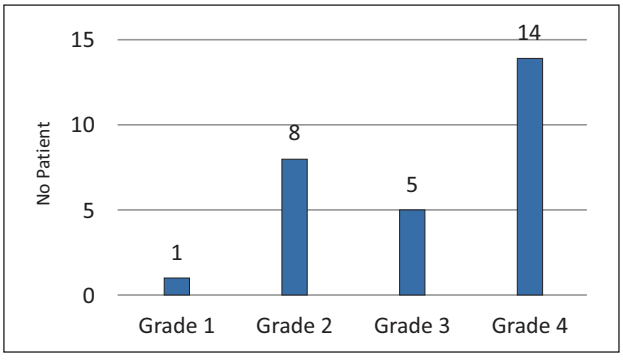

Figure 7: Grades on histology

On core biopsy, 5 cases were Grade-3, 8 cases were Grade-2 and one with Grade-1 invasive ductal carcinoma (Figure 7).

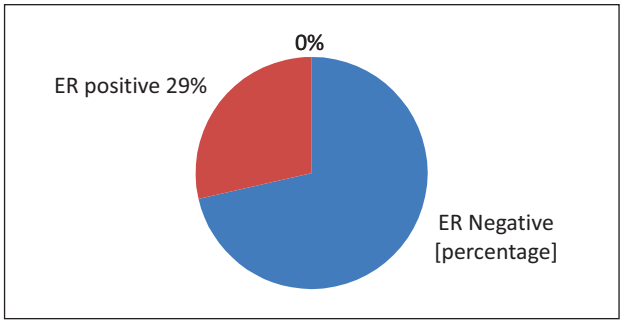

Figure 8: ER (Estrogen receptor) status

Four cases were ER positive and 10 cases were ER negative (Figure 8).

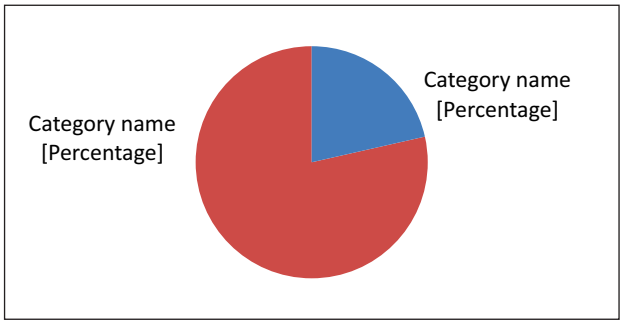

Figure 9: HER2 status

HER2 was positive in 3 and negative in 11 cases (Figure 9).

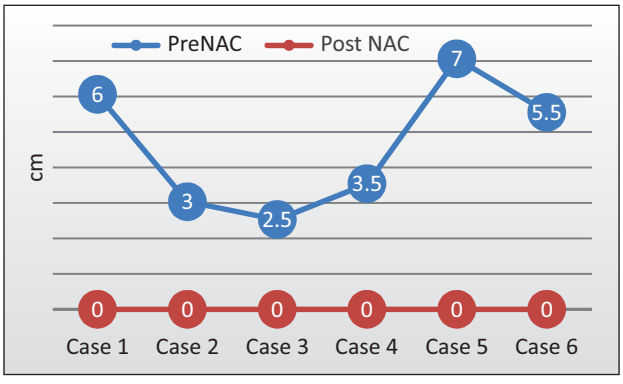

Figure 10: Clinical size; pre vs post NAC

Post NAC clinical examination showed complete response on 6 cases (Figure 10) and other seven still receiving chemotherapy, one patient was lost.

Therefore, 6 cases will have post-operative histology details available in this paper. Histology revealed three cases with Grade-2, two with Grade-3 and one with Grade-1 IDC. Staging of axilla with surgery (SNB, axillary clearance) were performed as per need.

Discussion:

HydroMark is the only biodegradable hydrogel polymer containing a central permanent metal marker which provides exceptional visibility. HydroMark marker hydrates to provide unmatched long-term visibility. It is ultrasound visible even after Neoadjuvant Chemotherapy. It hydrates to provide 12-15 months of ultrasound visibility after neoadjuvant chemotherapy (Figure 11). Easily seen under uniquely distinguishable during a T2 sequence MRI. This creates a better patient experience. Under localization with ultrasound, provides a faster and more comfortable procedure for the patient.[14]

HydroMark offers three distinct shapes for better tracking of multiple biopsy sites such as open coil, butterfly and barrel (Figure 12 & 13).

Historically, the gold standard for treating large palpable breast cancer has been mastectomy, chemotherapy, and occasionally radiation therapy. However, data from Europe have shown that patients with palpable tumors can benefit from preoperative NAC, thus enabling most to undergo lumpectomy rather than mastectomy.[15] Recently, some patients with palpable breast cancer are initially being offered neoadjuvant chemotherapy before surgery to down stage the primary breast tumour. After treatment, the primary tumour area is surgically excised to verify tumour response and to obtain clear margins before adjuvant radiation therapy. However, a problem faced by the surgeon in this setting is that the tumour frequently responds so dramatically to preoperative neoadjuvant chemotherapy that it is no longer palpable or visible on a mammogram or ultrasound. If the lesion is not visible on the images, it can be difficult to localize the tumour bed before definitive breast conservation surgery. As a result, the surgeon can benefit from having a wire localization to identify the tumour bed to ensure the tumour's removal. To address this issue, we used a simple technique of placing a small marker in the tumour and using sonography to localize and permanently document the tumor site before neoadjuvant chemotherapy. When the tumour has a complete response to the systemic treatment, the tumor bed can be easily identified on a imaging by using the marker to guide a standard wire localization to perform wire guided wide local excision, taking the tumour bed with good margins (Figure 14).

The first case of a breast cancer patient in Bangladesh who had HydroMark inserted by second author under the guidance of first author in 12th December 2018 and created history in breast cancer management. This exemplary step has encouraged other organization, eg: National Institute of Cancer Research and Hospital (NICRH) to start using this technique. In a modern world, Bangladeshi breast cancer patients deserves up-to-date management of breast cancer and we are fully committed to make this change.

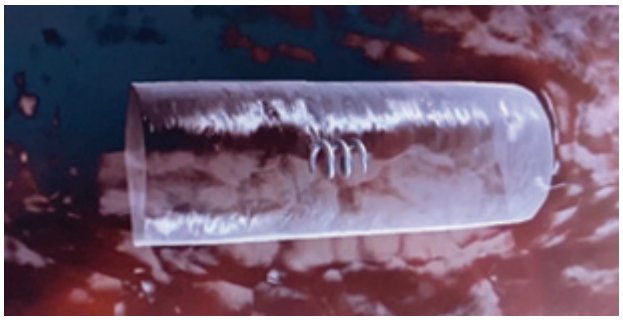

Figure 11: Exclusive hydrogel technology provides up to 12 months of unmatched ultrasound even in patient undergoing neoadjuvant chemotherapy.

Figure 12: Metalic clips permanently visibly within X ray and MRI

Figure 13: Mammotom provides compatible HydroMark site markers for breast biopsy.

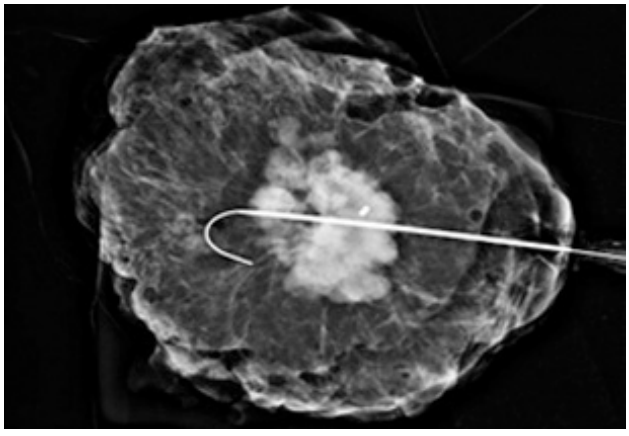

Figure 14: Post-operative X-ray of wire guided wide local excision with marker clip in situ

Conclusion:

Historically, despite having complete clinical and radiological response with Neoadjuvant chemotherapy, all patients were subject to have mastectomy in Bangladesh. As we know that there is no statistically significant survival benefit from mastectomy to breast conserving surgery, having a mastectomy for these group of patients are deemed over treatment along with significant negative impact personally, psychologically, and socially. Due to lack of marker clips even if patients wanted breast conserving surgery, surgeons couldn't offer that as there was no option to locate the site of cancer post NAC if compete clinical or radiological response occurs.

Through technology transfer and delegation of appropriate training, we have introduced HydroMark insertion technique and this will be a game changer for the breast cancer patients of Bangladesh to avoid unnecessary mastectomy post neoadjuvant chemotherapy. The huge negative impact of unnecessary mastectomy causing psychological and social impact can be avoided by simply using this technique.

We anticipate that this will encourage other organisations, both government and private, to come forward to learn and adapt this technology which will benefit enormously for the greater quality of lives of our patients which they rightly deserve.

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Original Article

Effect of Combined Oral Contraceptive Pill on Forced Vital Capacity and Peak Expiratory Flow Rate

Islam F[a], Jahan N[b], Ara T[c], Alam T[d]

Abstract

Background: Bangladesh is one of the most crowded land on earth. In Bangladesh 61% of married women are using contraceptive methods. The most widely used method is Combined Oral Contraceptive Pill (COCP). This COCP may have some effects on different organs including lungs.

Objective: To observe the effects of Combined Oral Contraceptive Pill (COCP) on FVC and PEFR in apparently healthy women receiving COCP.

Methods: This cross sectional comparative study was carried out in the Department of Physiology, Sir Salimullah Medical College (SSMC), Dhaka between July 2013 and June 2014. A total 30 apparently healthy young women, age ranged 20 to 30 years were included in this study who were Combined Oral Contraceptive Pill users (COCP - U) for at least 6 months. Thirty age and BMI matched Combined Oral Contraceptive Pill nonusers (COCP - NU) were taken as control. FVC and PEFR of all the subjects were measured by Digital Auto Spirometer (MINATO AS-507). Statistical analysis was done by Independent sample 't' test.

Results: FVC ($p < 0.001$) and PEFR ($p < 0.001$) were significantly higher in COCP-U than those of COCP-NU. Moreover, the mean serum estrogen ($p < 0.001$) and progesterone ($p < 0.05$) levels were also significantly higher in COCP-U in comparison to those of COCP-NU.

Conclusion: From the result of this study it can be concluded that COCP have beneficial effects on some pulmonary function parameters.

Keywords: Combined Oral Contraceptive Pill, Forced vital capacity , Peak expiratory flow rate, Estrogen, Progesterone.

Introduction:

Contraception means prevention of conception. Contraceptive methods are by definition, preventive methods to help women avoid unwanted pregnancies.[1] Bangladesh is one of the most crowded land on earth with a population of 156.8 million[2] in 143,998 km^2 area.[3] In Bangladesh 61% of married women are using contraceptive methods and of them most widely used method is combined oral contraceptive pill (COCP)which constitutes 27%.[4]

a. Dr. Farhana Islam; M. Phil, MBBS
Assistant Professor, Department of Physiology
Shaheed Suhrawardy Medical College, Dhaka.

b. Dr. Nasim Jahan; M. Phil, MBBS
Professor & Head, Department of Physiology
Enam Medical College, Savar, Dhaka.

c. Dr. Tanzin Ara; M. Phil, MBBS
Assistant Professor, Department of Physiology
Bangladesh Medical College, Dhaka.

d. Dr. Tania Alam; M. Phil, MBBS
Assistant Professor (CC), Department of Physiology
Chandpur Medical College.

Correspondence to:
Dr. Farhana Islam; M. Phil, MBBS
Assistant Professor, Department of Physiology
Shaheed Suhrawardy Medical College, Dhaka.
E-mail: islamfarhana83@gmail.com

Combined oral contraceptive pill (COCP) contain levonorgestrel 150 µgm and ethinylestradiol 30 µgm. Levonorgestrel is a kind of progestogen. Ethinyl estradiol is a synthetic form of estrogen.[5] Estrogen has effects on all systems of the body. It helps to prepare female for reproduction. A primary function of estrogen is to cause cellular proliferation and growth of the tissues of the reproductive organs and other tissues related to reproduction. Estrogen stimulates bone growth, increases protein deposition, body metabolism, causes sodium and water retention by the kidney tubules, it causes the skin to become more vascular, soft and smooth.[6] Oestrogen receptors are present in human respiratory muscles.[7,8] There is a positive correlation between skeletal muscle strength and oestrogen levels.[9] Estrogen influences surfactant production and alveologenesis.[10] Progesterone helps in smooth muscle relaxation and hyperventilation, also has a significant bronchodilator effect.[11,12] Estrogen and progesterone hormones improve pulmonary function in women[13,14] by decreasing the contractility and increasing the relaxation of bronchial muscle.[15]

For assessment of pulmonary functions forced vital capacity (FVC), peak expiratory flow rate (PEFR) are usually measured.[6] Recently significant increase values of FVC have been found in women using COCP.[16,17,18]

PEFR in COCP users[16] increases which may be due to decreased pulmonary airway resistance.[19] Some synthetic form of progesterone causes hyperventilatory changes in COCP users.[20] COCP can increase forced expiratory flow and volume from 6.5% to 15%.[21] Studies investigating the effect of COCP on pulmonary function have reported conflicting results.[14,16] So this study has been designed to observe the effect of COCP on pulmonary function in Bangladeshi women using COCP.

Material and Methods:

This cross sectional comparative study was done in the Department of Physiology, SSMC from July 2013 to June 2014. Ethical permission was taken from the Institutional Ethics Committee (IEC) of SSMC. A total 30 apparently healthy women, combined oral contraceptive pill users (COCP-U) aged 20-30 years were taken as study group. They were selected from Family Planning Unit of SSMC. Another 30 apparently healthy age and BMI matched combined oral contraceptive pill nonuser (COCP-NU) women were also included as control for comparison. They were selected from personal contact from different area of Dhaka city. Subjects having history of pulmonary diseases, diabetes mellitus, hypertension, angina, epilepsy, cancer, metabolic disorder, history of bleeding disorder were excluded from the study. After selection and proper counseling, the risk, benefit and procedure of the study were explained in details to each subject. They were asked to attend the Department of Physiology between 9.00 AM to 2.00 PM on the day of examination. Informed written consents were taken from them. All information about personal and medical were recorded in a pre-fixed questionnaire. Then a thorough clinical examination of all the subjects were done. After taking 5 minutes' rest, for assessment of pulmonary function FVC and PEFR of all the subjects were measured by using Digital Auto Spirometer (MINATO AS-507). Then under aseptic precautions 5 ml of venous blood was collected from every subject for estimation of serum estrogen and progesterone levels. Estimation of serum estrogen and progesterone were done by chemiluminescent method in Microbiology laboratory of Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag Dhaka. Data were analyzed by Independent sample 't' test.

Results:

Mean age of group- A is 24.57 ± 1.8 years and that of group-B is 25.87 ± 2.71 years. There is significant difference of mean age between both groups.

Table 1: Percentage of predicted value of FVC and PEFR in both groups (n=60)

Parameters	COCP-NU (n=30)	COCP-U (n=30)	P value
FVC %	82.53 ± 3.64	92.23 ± 2.50	0.000***
PEFR%	73.97 ± 5.95	81.93 ± 5.46	0.000***

Mean percentage of predicted values of FVC & PEFR were significantly ($p < 0.001$) higher in COCP-U, than those of COCP-NU. Values are mean ± SD. Statistical analysis was done by independent sample t-test (Table 1).

Table 2: Serum estrogen and progesterone levels in both groups (n = 60)

Parameters	COCP-NU (n=30)	COCP-U (n=30)	P value
Serum estrogen (pg/ml)	47.04 ± 6.72	59.52 ± 10.42	0.000***
Serum progesterone (ng/ml)	2.37 ± 0.66	3.32 ± 2.34	0.040*

Serum estrogen ($p < 0.001$) and progesterone ($p<0.05$) levels were significantly higher in COCP-U, than those of COCP-NU. Values are mean ± SD. Statistical analysis was done by independent sample t-test (Table 2).

Discussion:

In this study, the value of pulmonary function parameters in healthy control group were within normal limit and were almost similar to that of various investigators from different countries.[16,19]

Here, mean percentage of predicted values of FVC and PEFR were significantly higher in COCP-U than those of COCP-NU.

The beneficial effect of COCP on pulmonary function have been noted from the above finding in COCP-U. There are some postulated mechanism regarding these changes in lung functions of COCP-U.

Progesterone by activating β_2 adrenergic receptors[22] reduces constriction of the airways, relaxes the bronchial smooth muscle,[23] decreases airway hyper responsiveness and ultimately improves the pulmonary function. It has been suggested that high level of progesterone directly stimulates respiratory centre by increasing its sensitivity to CO_2 and thereby causes hyperventilation.[24-27] Progesterone stimulates respiratory center through CNS steroid receptor mediated mechanism[24] and induces hyperventilation through both the central medullary and peripheral chemoreceptors.[26] Several investigators of different countries have suggested that improvement in pulmonary function in COCP users may be due to the effect of estrogen on strengthening respiratory muscle.[9,16] Again, some researchers reported that estrogen also influences surfactant production and alveologenesis.[10] Low dose of estrogen improves lung function may be by opening small airways and by decreasing airway resistance.[21] Estrogen receptors were identified in the nuclei of connective tissue and of the smooth muscle cells of the lung. These receptors participate in maintaining the connective tissue by increasing the synthesis or decreasing the breakdown of collagen. Estrogen increases adenyl cyclase activity which in turn results in potentiation of catecholamine-induced bronchial relaxation and bronchi are widene.[28]

Combination of estrogen and progesterone improve musculoskeletal integrity and thereby increase the total lung capacities.[29] Estrogen increases the number of progesterone receptors, so combined effect of estrogen and progesterone synergistically increases pulmonary function.[30] Estrogen and progesterone have been associated with relaxation of airway smooth muscle in human model.[28] In the present study lung function parameters were improved in COCP-U, as evidenced by measured value of FVC and PEFR may be due to higher concentration of estrogen and progesterone in combined oral contraceptive pill.

Conclusion:

From this study, it may be concluded that, some aspects of pulmonary functions are higher in female who received combined oral contraceptive pill (COCP) in comparison to that of COCP nonusers. All these changes may be associated with higher levels of serum estrogen and progesterone. However, increased strength of respiratory muscles along with decreased airway resistance by estrogen and progesterone content of COCP might be responsible for this improved pulmonary function parameters.

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Dexmedetomidine and Propofol- an integrated approach in controlled sedation for patients undergoing hand surgery

Khan M R H[a], Muhit M S[b], Deepa T C[c], Nazir A[d]

Abstract

Background: Propofol is a widely accepted general anaesthetic agent. However, as it has several adverse effects, very often newer drugs such as Dexmedetomidine is used.

Objective: The objective of the study is to find out an optimized method of sedation with normal cardiovascular and airway function. Several sedatives, analgesics and narcotics are used to achieve these objectives while minimizing adverse effects.

Methods: We conducted a cross sectional comparative study in three groups on 90 adult patients undergoing different surgical procedures in upper limb under brachial plexus block. Patients were selected by purposive sampling for this study. Group-A received 1.5 mcgm/ml of Propofol, Group-B received 0.4 mcgm/kg/h Dexmedetomidine following a loading dose of 1.0 mcgm/kg for 10 min and Group-C received half dose of both drugs simultaneously. Haemodynamic variables, side effects and drug efficacy were observed and compared.

Results: The significantly raised heart rate was observed in Group-A (70±10 beat/min) than Group-B (58±8 beats/min) and Group-C (57±8 beats/min) with $p< 0.001$. Observation revealed significantly higher mean arterial pressure in Group-B (95.0±14.0 mm Hg) than Group-A (88.7±10.2 mm Hg) and Group-C (82±9.0 mm Hg), where $p=0.004$. The onset of action was longer in Group-B ($p <0.001$).

Conclusion: There were remarkable differences in groups regarding haemodynamic stability and adverse effect. Moreover, Propofol and Dexmedetomidine as a combined therapy provided a better option rather than individual drug.

Keywords: Propofol, Dexmedetomidine, Sedation, Hand surgery.

Introduction:

Propofol is most commonly used sedative during surgical and diagnostic procedures that demand sedation and relief from anxiety beside main anaesthetic agents to overcome unwarranted side effects during the operative procedures. Respiratory depression is one of the serious and common patient injuries during monitored sedation. The main goal of sedation is to maintain the sedation with normal cardiovascular and airway function. Several sedatives, analgesics and narcotics are used to achieve these objectives while minimizing adverse effects. Moreover, Propofol provides antiemetic properties along with rapid onset and recovery time. Nevertheless, Propofol has some adverse effects such as severe respiratory depression and hypotension, which highlight the need to find better drugs. The BIS (Bispectral Index) is an electroencephalogram-derived multi-variant scale that, when a drug such as Propofol is used, it correlates with the metabolic rate of glucose. Both, loss of consciousness and awakening from anesthesia are correlated with this scale. The efficacy of BIS index monitoring is not without controversy. Some controlled studies have found that using the BIS reduced the incidence of memory but this was not confirmed in several very large multicenter studies on awareness. Dexmedetomidine, a highly selective α2-adrenergic receptor agonist, has analgesic and sedative properties without significant respiratory depression.[1]

Although less significant respiratory depression is prominent merit of Dexmedetomidine. The adverse effects of it include a dose-dependent decrease in blood pressure and heart rate due to its sympatholytic effects.In the absence of an ideal sedative agent, there is great interest in combining different agents to maximize efficacy and minimize adverse effects, with some studies finding that these combinations have significant benefits over single agents.[2-4] In this study, we tried to find out that the

a. Dr. Md. Rafiqul Hasan Khan; FCPS, MCPS, MBBS
Associate Professor, Department of Anaesthesiology
Bangladesh Medical College, Dhaka.

b. Dr. Md Shahriar Muhit; FCPS, MBBS
Assistant Professor, Department of Anaesthesiology
Bangladesh Medical College, Dhaka.

c. Dr. Taslema Chowdhury Deepa; DA, MBBS
Junior Consultant, Department of Anaesthesiology
Bangladesh Medical College Hospital, Dhaka.

d. Dr. Nazir Ahmed; MBBS
Medical Officer, Department of Anaesthesiology
Bangladesh Medical College Hospital, Dhaka.

Correspondence to:
Dr. Md. Rafiqul Hasan Khan; FCPS, MCPS, MBBS
Associate Professor, Department of Anaesthesiology
Bangladesh Medical College, Dhaka.
Email: azad300769@gmail.com

combination use of Propofol and Dexmedetomidine would reduce adverse effects such as respiratory depression and cardiovascular depression and improve efficacy as measured by early onset and recovery time. Therefore, we performed this cross sectional comparative study to evaluate the efficacy and safety of the combination use of Propofol and Dexmedetomidine.[4]

Material and Methods:

A cross sectional comparative study was carried out in the Department of Anaesthesiology in Bangladesh Medical College Hospital from July 2013- June 2016. There were a total of 90 patients who were selected by purposive sampling. They were divided into three groups; Group-A received 1.5 mcgm/ml of Propofol and Group-B received 0.4 mcgm/kg/h Dexmedetomidine following a loading dose of 1.0 mcgm/kg for 10 min. The Group-C received a half dose of both drugs simultaneously. Inclusion criteria were: 1) Patients with ASA physical status I-II; 2) Patients who have given consent for this study. The exclusion criteria were: 1) Patients with facial and oral cavity deformities; 2) Obese patients. All patients were monitored through ECG, pulse oxymeter and NIBP (noninvasive blood pressure). Brachial plexus block was conducted using the same predefined protocol without premedication. All anesthetic procedures and surgeries were performed by the same anesthesiologist and surgical team. After arrival to the operating room, the patient's vital signs were monitored by measurement, electrocardiography, and pulse oximetry. There are three groups in this study. In Group-A, 1.6 μg/ml of initial target effect site concentration of Propofol was infused through a TCI pump. Patients in the Group-B received an infusion of 0.4 μg/kg/h Dexmedetomidine following a loading dose of 1.0 μg/kg over 10 min. Then, the dose of Dexmedetomidine was adjusted by 0.08 μg/kg/h according to Observer Assessment of Alertness/Sedation score. In Group-C, 0.8 μg/ml of initial of Propofol was infused through a TCI pump and a loading dose of Dexmedetomidine of 0.5 μg/kg was infused over 10 min together. Then, 0.2 μg/kg/h dexmedetomidine was infused for the maintenance dose. During the sedation, the maintenance doses of Propofol and Dexmedetomidine were titrated by the same proportion depending on the Observer Assessment of Alertness/Sedation score (OAAS/S score). The dose of Propofol was adjusted by 0.2 μg/ml and the dose of Dexmedetomidine was adjusted by 0.04 μg/kg/h simultaneously.

After arrival to the operating room, the patient's vital signs were monitored by noninvasive blood pressure measurement, electrocardiography, and pulse oximetry. Respiratory variables such as end-tidal CO_2 and respiratory rate were monitored by a side-stream infrared gas analyzer. Supplemental oxygen (4 L/min) was given to all patients. The Supraclavicular brachial plexus block was performed with 0.25% bupivacaine 20 ml under ultrasound-guided techniques. After adequate surgical anesthesia has been achieved, patients received a sedative in accordance with the method above. During sedation, all patients were maintained in the supine position and the sedation statuses of the patients were evaluated by the Observer OAA/S score and bispectral index (BIS) monitoring.

Monitoring of Drug Effect

The primary endpoints were the changes of mean arterial pressure and the extent of airway obstruction (1 =patent airway, 2 =airway obstruction alleviated by jaw thrust, 3 =airway obstruction relieved by positive mask ventilation). The time to achieving the target depth of sedation (OAA/S score of 3) was measured by calculating the time from injection to an OAA/S score of 3. In addition, the time to achieving BIS score of 70 was also measured. During the sedation procedure, vital signs and sedation status including OAA/S scores, BIS scores, mean arterial pressure, heart rate, SpO_2, end-tidal CO_2 and respiratory rate were recorded at the following times: (1) before the injection of the drug (T0); (2) 5 min after infusion (T1); (3) achieving the target mental status (OAA/S score 3) (T2); (4) 15 min after achieving the target mental status (T3); (5) 30 min after achieving the target mental status (T4); (6) termination of infusion (T5); and (7) an alert mental status (T6).

Data analysis was done by SPSS v25. Significant relationship of variables between three groups were analysed by Anova test.

Results:

Among 142 patients who were assessed for eligibility from July 2013 until June 2016, 52 patients were excluded because of not meeting the inclusion criteria or declining to participate. As a result, 90 patients were purposively selected and 30 patients were distributed in each group by a predefined method.

Table 1: Patient's mean value of age, height, weight and BMI (N=90)

Variable	Group-A	Group-B	Group-C	*p* value
Age (years)	43.5±12.	46.8±15.7	43.6±15.1	0.901
Height (cm)	167.8±9.5	165.8±9.0	166.5±9.4	0.852
Weight (kg)	66.0 ±12.0	62.7±9.9	63.3±10.2	0.112
BMI (kg/m^2)	22.6±3.5	22.7±2.6	22.4±2.9	0.714

Table 1 shows mean age, mean height, mean weight and mean BMI of Group-A, B and C. No significant differences were found between groups in terms of age, height, weight and BMI (p value was 0.901, 0.852, 0.112 and 0.714 respectively)

Table 2: Changes in hemodynamic and respiratory variables

Variable	Group-A	Group-B	Group-C	*p* value
Mean Arterial Pressure	88.7±10.2	95.0±14.0	82.0±9.05	0.004
Heart Rate	70±10	58±08	7±8	<0.001

The reduction of mean arterial pressure in Group-B: 95.0±14.0 mm Hg was significantly less than other groups [Group-A: 88.7±10.2, Group-C: 82.0 ±9; 0, p=0.004] and the reduction of heart rate in Group-A: 70±10 beat/min, was significantly less than other groups [Group-B: 58 ±8, Group-C: 57 ±8; $p < 0.001$] as shown in Table 2.

Table 3: Incidence of adverse events

Variable	Group-A	Group-B	Group-C	*p* value
Hypoxia	11±40.1	3±11.8	1±3.1	0.001
Spontaneous movement	12±32.7	1 ±3.4	0	<0.001
Cough	4±17.9	2±10.3	1±3.3	0.16
Nausea	0	0	0	1.00
Vomiting	0	0	0	1.00
Agitation	7 ±25.3	0	0	0.001
Bradycardia requiring atropine	1 ±3.6	6 ±21.6	0	0.001
Hypotension requiring ephedrine	0	0	0	1.00

The Group-A had a higher incidence of hypoxia (p=0.001), spontaneous movement ($p < 0.001$) and agitation (p=0.001) than other groups. The incidence of bradycardia requiring atropine was significantly greater in Group-B (p=0.001). No episodes of nausea, vomiting, or hypotension were found and there were no differences in the occurrence of cough (p=0.16) between groups (Table 3).

Table 4: Comparison of onset and recovery time and dose rate of drug infusion

Variable	Group-A	Group-B	Group-C	*p* value
Onset time (seconds)				
Time to OAA/S score 3	504.8±147.5	711.1±103.0	548.9±80.0	<0.001
Time to BIS 70	588.3±145.8	807.3±105.7	623.1±98.0	<0.001
Recovery time (seconds)				
Time to OAA/S 5	476.8±178.4	582.9±178.1	494.5±178.8	0.07
Time to BIS 90	585.2±188.4	682.0±179.2	585.9±188.6	0.08
Dose rate of drug infusion				
Propofol (mg/kg/h)	3.54 ±1.01	-	1.59±0.56	
Dexmedetomidine (µg/kg/h)	-	1.26±0.37	0.61±0.17	

OAA/S score Observer Assessment of Alertness/Sedation score, BIS bispectral index.

Although there was a significantly longer time (seconds) to achieve the target depth of sedation in Group-B [Group-A 504.8±147.5, Group-B 711.1±103.0, Group-C 548.9±80.0, $p < 0.001$], there was no difference in recovery time among the groups (p=0.07) as shown in Table 4. The dose rate of Propofol infusion in Group-A and rate of Dexmedetomidine infusion in Group-B were 3.54±1.01 mg/kg/h and 1.26±0.37µg/kg/h, respectively. In total, 1.59 ±0.56 mg/kg/h of Propofol and 0.61±0.17 µg/kg/h of Dexmedetomidine were infused in Group-C. In comparison with the half-dose of drug infusion in Group A and B, there were no differences in the dose rates of drug infusion.

Discussion:

We demonstrated through our study that Propofol and Dexmedetomidine as a combination provided cardiovascular stability, early onset time and higher satisfaction scores without delayed recovery time and adverse effects such as airway obstruction, hypoxia, and spontaneous movement.

The rapid injection of a loading dose of Dexmedetomidine can have biphasic effects on blood pressure, with temporary increases in blood pressure by a direct α_2-adrenoceptor-induced vasoconstrictive response in the peripheral vasculature followed by a lower mean arterial pressure due to decreased sympathetic outflow. This biphasic trend in blood pressure was observed in the B group, but temporary increases of blood pressure were not

observed in Group-C.[5,6,7] In terms of heart rates, Dexmedetomidine can cause bradycardia due to its well-known sympatholytic effects.[8,9] The heart rates in both the A and C groups were decreased after infusion. After taking these results into consideration, we suggest that the combination of Propofol and Dexmedetomidine provided cardiovascular stability.[10,11]

In order to avoid transient hypertension, the slow injection of Dexmedetomidine was required, which can result in slower onset of sedation.[12,13] The time to OAA/S 3 or BIS 70 of the B group, which was longer than the other groups by about 3 min, also implies the delayed onset of sedation for Dexmedetomidine, which correlates well with the results of a previous study. The combined use of Propofol and Dexmedetomidine overcomes this limitation and results in an onset time similar to that of Propofol.[14] As the recovery time from sedation with Dexmedetomidine and Propofol are known to be equivalent, there were no differences in recovery time between the three groups.[15,16]

Our study has several limitations. First, although one of the advantages of Dexmedetomidine is its analgesic property, we could not evaluate its analgesic effects because this study was conducted under brachial plexus block. Therefore, further studies are needed to evaluate the analgesic effect when Dexmedetomidine is used in combination with Propofol. Another limitation is that we did not use premedication, which could have an influence on sedation level.[17] Anxiety due to the unfamiliar operating room environment and undergoing regional anesthesia could have increased baseline blood pressure, heart rate and respiratory rate. Lastly, the accuracy of end-tidal CO_2 monitoring is also a limitation. Although we placed the airway adapter as close as possible to the patient's airway, some degree of measurement error of end-tidal CO_2 is inevitable in non-intubated patients.[18]

We expected a synergistic effect between Propofol and Dexmedetomidine. However, judging from the requirement of half of the usual doses of Propofol and Dexmedetomidine to maintain the target sedation level, the combined use of Propofol and Dexmedetomidine seemed to have an additive effect. Further studies are needed to accurately assess whether the combined use of Propofol and Dexmedetomidine has an additive effect or not.

Conclusions:

We demonstrated that hypertension and bradycardia can be avoided with combination of Propofol and Dexmedetomidine. The combination of these two agents also improved patient safety by decreasing the incidence of airway obstruction, hypoxia, spontaneous movement and agitation during deep sedation. Moreover, the use of Propofol and Dexmedetomidine had a similar onset time as that of Propofol without a delayed recovery time, and achieved higher satisfaction scores than with the use of a sole agent.

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Original Article

Level of dental phobia affecting the oral health seeking behavior among medical and dental students

Shah S[a], Shahed L[b]

Abstract

Background: Dental phobia may make dental visits very fearful. It may also adversely affect the oral health seeking behavior of the individual.

Objective: To determine levels of dental phobia affecting oral health seeking behavior among the medical and dental students.

Methods: A cross sectional study was conducted on 50 medical and dental undergraduates of Bangladesh Medical and Dental College by non-probability sampling. Informed consent was taken from each of the respondents. Face to face interview method was used for data collection. Two standard questionnaires based on Corah's Dental Anxiety Scale (DAS) and Dental Concern Assessment were used as data collection tool in this study. Data were analyzed by SPSS software version 20.0.

Results: According to Corah's Dental Anxiety Scale, 56% medical students and 36% dental students suffered from moderate level of anxiety. As per Dental Concern Assessment, 40% medical students got moderately anxious by sound of the drill, 72% got highly anxious by the sight of the injection, 56% got anxious during RCT and 64% got anxious during extraction. On the other hand, 28% dental students got moderately anxious by sound of the drill, 76% got highly anxious by the sight of injection, 52% got anxious during RCT and 44% got anxious during extraction.

Conclusion- Moderate level of phobia was seen among the respondents. Injection followed by sound of the drill and dental procedures namely RCT and extraction were reported to be the most feared procedures. Effective communication along with educational session and behavioral therapy might help to reduce dental phobia among patients.

Keywords: Dental Phobia, Medical and dental students, Corah's Dental Anxiety Scale, Dental Concern Assessment.

Introduction:

Phobia is an irrational, severe fear that leads to avoidance of a feared situation, object as well as any activity. Dental phobia is the extreme fear of dentists and the dental procedure. It is a serious condition characterized by severe anxiety at the thought of seeing a dentist.[1,2]

Dental phobic tends to spend most of their time worrying about their dental condition. They try to avoid dental attentions from dentists as much as possible. They usually let initial pathologies to progress gradually becoming something severe and are forced to seek dental care. Treatment of such pathologies in dental clinic are not very comfortable to the patient. For example- extractions, root canal treatment.[3]

a. Dr. Saiquat Shah; MPH, MSD, BDS
Assistant Professor, Department of Dental Public Health
Bangladesh Dental College, Dhanmondi, Dhaka

b. Lameea Shahed
Final Year BDS Student
Bangladesh Dental College, Dhanmondi, Dhaka

Correspondence to:
Dr. Saiquat Shah; MPH, MSD, BDS
Assistant Professor, Department of Dental Public Health
Bangladesh Dental College, Dhanmondi, Dhaka
Email: saiquatshah@gmail.com

Dental phobic suffer from different psychiatric disorders such as generalized anxiety disorder, agoraphobia, depression etc. Such phobic with poor oral condition avoid public interactions or taking jobs which have public contact. They laugh rarely as they try to cover their teeth. People with high dental phobia, both children and adults, may prove difficult to treat. They require more time and present with behavioral problems which can result in a stressful and unpleasant experience for both the patient and the dentist. If the patients are not managed properly, it is quite possible to establish what has been referred as 'vicious cycle of dental fear.[4]

Dental phobia results due to both direct and indirect experiences. Direct experience such as traumatic and painful dental experience and perceived manner of the dentist may result in dental phobia. Dentists who are considered 'impersonal', 'uncaring' and 'cold' may develop high dental fear in patient. Moreover, indirect experiences like hearing about others traumatic experience, negative portrayal about dentistry shown on mass media are also the reasons of dental phobia.[5,6]

Individuals with dental phobia represent a difficult population to treat and present special challenges to dentists in terms of the management of care. The fear and anxiety of an individual could affect the dentist-patient relationship. It affects not only general adult population but also students who are going to become health professionals. Most people

encountered dental fear and anxiety when having their dental treatments.[7,8,9]

Several studies have been done in other countries like Australia, Malaysia, Sweden, Jordan, Yemen etc. to find out the effects of dental phobia on among the medical and dental students.[10-12]

However, information about the levels of dental phobia affecting the oral health seeking behavior among the medical and dental students of Bangladesh has not been published. In addition, until now no information is available about the effect of dental phobia among Bangladeshi population. Hence, this study was designed and conducted to assess the level of dental phobia affecting the oral health seeking behavior among the medical and dental students.

Material and Methods:

A cross sectional study was conducted among the students of Bangladesh Medical College and Bangladesh Dental College located in Dhaka, Bangladesh. The study group included 1st year-3rd year medical and dental undergraduate students of both the colleges. Fifty (50) respondents were chosen by non-probability convenient sampling method which comprised 25 students in each college. Informed consent was taken from each of the respondents. Face to face interview method was used for data collection. Two standard questionnaires based on Corah's Dental Anxiety Scale (DAS) and Dental Concern Assessment were used as data collection instrument in this study.

Corah's Dental Anxiety Scale consisted of four questions as follows with five choices measured in scores of 1 to 5;

1. If you had to go to the dentist tomorrow, how would you feel about it?
2. When you are waiting in the dentist's office for your turn in the chair, how do you feel?
3. When you are in the dentist's chair waiting while he gets his drill ready to begin working on your teeth, how do you feel?
4. You are in the dentist's chair to have your teeth cleaned, while you are waiting and the dentist is getting out the instruments which he will use to scrape your teeth around the gums, how do you feel?

The score of each of the four questions were summed to give the level of dental phobia. The overall maximum score is 20 as follows-

Scoring of Dental Anxiety Scale

(1)= 1, (2)= 2, (3)= 3, (4)= 4, (5)= 5

Anxiety rating

- 1-8 = Normal.
- 9-12 = Moderate anxiety. They have specific stressors that should be discussed and managed
- 13-14 = High anxiety.
- 15-20 = Severe anxiety (or phobia). Maybe manageable with the Dental Concern Assessment but might require the help of mental health therapist.

Dental Concern Assessment was provided to each respondent to rank their concern or anxiety over the dental procedures. It consisted of 26 questions with four choices- Low, Moderate, High and Don't Know. Guidelines and instructions on how to fill the questionnaire was given.

The contact information such as name, age, sex, year of study and number of family members of each respondent were included in the questionnaire. Responses to the questionnaire were obtained. No clinical examinations were performed.

The collected data were and analyzed by using Microsoft Excel 2013 and Statistical Package for Social Science (SPSS Inc., version 20, Chicago, Illinois, USA). Occurrences of various variables was computed in means, percentages and standard deviation. Adjusted odds ratio with 5-10% confidence intervals was calculated for all significant variables in the final model. The result was obtained in the form of table, charts and pie graphs.

Results:

Table 1: Distribution of respondents by age (N=50)

Age of the respondents	Medical students		Dental students	
	Frequency	Percentage	Frequency	Percentage
19	1	4	8	32
20	7	28	12	48
21	17	68	5	20
Total	25	100	25	100

Among the respondents, 1(4%) respondents from medical and 8 (32%) respondents from dental background were of 19 years of age, 7(28%) respondents from medical and 12(48%) respondents from dental were of 20 years of age and, 17(68%) respondents from medical and 5(20%) respondents from dental were of 21 years of age. (Table 1)

Table 2: Distribution of respondents by sex (N=50)

Sex of the respondents	Medical students		Dental students	
	Frequency	Percentage	Frequency	Percentage
Male	12	48	8	32
Female	13	52	17	68
Total	25	100	25	100

Out of the respondents, 12(48%) respondents from medical and 8 (32%) respondents from dental background were male and 13 (52%) respondents from medical and 17(68%) respondents from dental were female. (Table 2)

Table 3: Distribution of respondents by level of dental phobia, according to Corah's Dental Anxiety Scale (N=50)

Normal		Moderate		High		Severe	
Medical No. (%)	Medical No. (%)	Medical No. (%)	Medical No. (%)	Medical No. (%)	Medical No. (%)	Medical No. (%)	Medical No. (%)
4 (16%)	4 (16%)	4 (16%)	4 (16%)	4 (16%)	4 (16%)	4 (16%)	4 (16%)

Among the respondents, 4(16%) respondents from medical and 5(20%) respondents from dental background had no sort of anxiety towards dental procedures, 14(56%) respondents from medical and 9(36%) respondents from dental had moderate anxiety, 4(16%) respondents from medical and 8(32%) respondents from dental had high anxiety and 3(12%) respondents from both medical and dental respectively had severe anxiety. (Table 3)

Table 4: Distribution of respondents by concern or anxiety over the dental procedures, according to Dental Concern Assessment (N= 50)

Dental Procedure	Low (100%)		Moderate (100%)		High (100%)		Don't Know (100%)	
	Medical	Dental	Medical	Dental	Medical	Dental	Medical	Dental
1) Sound of the drill	24	16	40	28	24	20	12	36
2) Not being numb enough	20	28	32	20	20	8	28	44
3) Dislike the numb feeling	8	16	28	16	8	12	56	56
4) Injection	4	8	24	16	72	76	0	0
5) Probing	16	12	12	12	12	8	60	68
6) Sound of scraping	48	36	28	24	16	12	8	28
7) Gagging	16	44	32	20	40	24	12	12
8) X-ray	52	60	20	4	20	0	8	36
9) Rubber dam	8	16	16	32	12	0	64	52
10) Jaws get tired	24	8	44	40	28	40	4	12
11) Cold air	8	8	52	44	32	20	8	28
12) Lack of information	20	28	56	20	16	4	8	48
13) RCT	16	8	12	8	56	52	16	32
14) Extraction	0	0	0	20	64	44	36	36
15) Fear of being injured	20	8	44	28	36	56	0	8
16) Panic attacks	28	32	48	24	24	28	0	16
17) Unable to stop dentist	20	36	40	24	16	12	24	28
18) Unable to ask question	20	32	32	20	12	0	36	48
19) Not being taken seriously	28	36	16	24	12	0	44	40
20) Being criticized	4	4	40	28	48	52	8	16
21) Smells in dental office	32	32	28	40	24	8	16	20
22) Need for further treatment	16	28	36	28	24	12	24	32
23) Cost of the treatments	20	12	48	56	32	20	0	12
24) No. of appointments and the time required for further treatments	44	20	24	48	16	16	16	16
25) Feeling embarrassed about the condition of the mouth	20	8	40	28	36	56	4	8
26) Don't like feeling confined	36	48	12	12	8	4	44	36

Sound of the drill being the 2nd most feared procedure made 10(40%) respondents from medical and 7(28%) respondents from dental moderately anxious. Out of total respondents, majority got highly anxious at the sight of injection among which 18(72%) respondents were from medical and 19(76%) respondents were from dental. RCT

and extraction were considered as the most feared procedure. When asked about their experience during RCT, 14 (56%) respondents from medical and 13(52%) respondents from dental became highly anxious. During extraction, none of the respondents from medical and dental were found to be less anxious. It made 16(64%) respondents from medical and 11(44%) respondents from dental highly anxious.

Among the total respondents,8(32%) respondents from medical and 5(20%) respondents from dental became moderately anxious as they were not being numb enough during the procedure. On the other hand,7(28%) from medical and 4(16%) respondents from dental became moderately anxious as they disliked the numb feeling.

When asked about other procedures, probing made 4(16%) medical and 3(12%) dental students less anxious. During tooth cleaning 12(48%) medical and 9(36%) dental students were reported to get less anxious by the sound of scraping. Gagging during dental procedures made 4(16%) medical and 11(44%) dental students less anxious. Again, 13(52%) medical and 15(60%) dental respondents became less anxious towards x-ray. The use of rubber dam made students anxious at different level but majority didn't know what exactly it was among which 16(64%) were medical and 12(52%) were dental.

Out of total respondents, 11(44%) medical and 10(40%) dental students became moderately anxious when jaws got tired during the dental procedures. Again 13(52%) medical and 11(44%) dental students got moderately anxious when cold air hurt teeth during any dental procedure. Lack of information about the procedure made 14(56%) medical and 5(20%) dental students moderately anxious

Among the total respondents, 9(36%) medical and 14(56%) dental students became highly anxious due to the fear of getting injured. Again,12(48%) medical and 6(24%) dental students were moderately anxious when they had panic attacks. Many respondents were found to get anxious when they were unable to stop the dentist. Among them,10(40%) were from medical and 6(24%) were from dental. Due to difficulty in asking any question during dental treatments, 8(32%) medical and 5(20%) dental students got moderately anxious. Some patients got less anxious when they were not taken seriously. Among them, 7(28%) were from medical and 9(36%) were from dental. Again, 12(48%) medical and 13(52%) dental students became highly anxious since they had the fear of being criticized.

Smells in the dental office made 7(28%) medical and 10(40%) dental students moderately anxious. Some respondents were found to get moderately anxious as they worry about a lot of treatments. Among them, 9(36%) respondents were from medical and 7(28%) respondents were from dental. Regarding the cost of dental treatments, 2(48%) respondents from medical and 14(56%) respondents from dental were moderately anxious. Moreover,6(24%) respondents from medical and 12(48%) respondents from dental got moderately anxious about the time required for the dental treatments.

Out of total respondents, 9(36%) respondents from medical and 14(56%) respondents from dental were highly embarrassed about the condition of their mouth. Again, 9(36%) respondents from medical and 12(48%) respondents from dental became less anxious as they don't like the feeling of being confined during any dental procedures (Table 4).

Discussion:

Despite the technological advances made in modern dentistry, anxiety about dental treatment and fear of pain associated with it is still seen among many individuals. Improvements have not been able to eliminate or substantially reduce dental phobia. Studies have shown that different procedures, namely, dental drills and sight and sensation of a dental local anesthetic injection, sight, sound and vibrational sensation of rotary are the major causes of dental fear and anxiety.[10]

To measure the level of phobia among the students, Corah's Dental Anxiety Scale was used. Majority (46%) of the respondents were found to have moderate anxiety. Among them, medical students (56%) were found to be more anxious than dental students (36%). On asking, most of them had negative past dental experiences where the local anesthesia didn't work and they had to undergo severe pain during the procedures. In a study carried out in Jordan with undergraduate students of medicine and dentistry, it was seen that medical students had highest percentage (13.58%) and dental students had lowest percentage (11.22%) of dental anxiety.[13] On the other hand, an article by Hakim H and Razak AI published in The Scientific World Journal showed a different picture.[14] Dental students (96%) were found to be more anxious than medical students (90.4%) in the study. But the reasons were quite similar, that is, the dental students encountered more traumatic dental experiences in the past.

With the help of the Dental Concern Assessment, the students were asked to rank their concerns or anxiety over the dental procedures. Noticeably, the sense of fear varied because each individual had special fear responses due to different dental treatment.

The study revealed that 40% medical students and 28% dental students got moderately anxious by sound of the drill. According to the study, sound of the drill was considered as the 2nd most feared procedure. The finding of the current study is similar with the previous study done by Ahmed A. Madfa et al.[15] This was because the sound of the fast running drill operated with compressed air hurt their teeth.

Injections as a way of administering local anesthesia during different procedures are one of the major causes of dental anxiety. It was seen that all the respondents became anxious at different levels by injections. Among the total respondents,72% medical and 76% dental students were found to get highly anxious by the sight of injection. This was due to the fact that most of the students could not

withstand the sight of the approaching needle in the oral cavity. Similar findings were seen in a study done by Ahmed A. Madfa et al where injection was considered as the most feared procedure.[15] In 1995, Milgrom P et al. surveyed at University of Washington regarding the fear of dental injection.[5] More than 25% adults expressed at least one clinically significant fear of injections. The study revealed that, the most feared dental procedure reported was root canal treatment and dental extraction. During the RCT, 56% medical and 52% dental students were found to get highly anxious. During extraction, 64% medical and 44% dental students were found to get highly anxious. According to them, these are the most fear-inducing procedures because these procedures have the ability to invoke severe pain.

It's quite expected that dentist will use medications to numb the area to ensure you are comfortable throughout any procedure. It was seen that some respondents were not numb enough during the procedures. They felt severe pain in the specific tooth as the local anesthetic didn't work for them. As a result, they ended up feeling pain during the procedure. Some of the respondents disliked the numb feelingbecause it symbolizes the loss of control for them, some had the fear of suffocating whereas some suffered from panic attacks.

When asked about other dental procedures, it was seen that during teeth cleaning, the sound of scraping made 48% medical and 36% dental students highly anxious because they faced painful cleaning experience caused by sore gum disease. Moreover, 52% medical and 60% dental students got anxious during x-raybecause they had no idea about the dental x-ray and was not aware of what it was. The study also showed that 16% medical and 32%dental students got moderately anxious by the use of rubber dam. Again, 40% medical and 24% dental students got anxious due to gagging because these students faced more difficulty in breathing and suffered from gag reflexes.

Beside the different dental procedures, it was seen that some other reasons also work behind dental fear. The study revealed that 56% medical and 20% dental students got moderately anxious for not having enough information about the procedure. This was because the medical students were not aware of what will happen which resulted in fear.36% medical and 56% dental studentsgot highly anxious because they had the fear of being injured. 48% medical and 24% dental students suffered from panic attacks. This was because most of the medical students who had panic attacks got anxious right after seeing the dental needle. Moreover, 40% medical students and 24% dental studentsgot moderately anxious when they were not able to stop the dentist. On the other hand, 32% medical and 24% dental studentsgot moderately anxious when they were not feeling free to ask the dentist anything. In both cases, the medical students were more anxious because they had the feeling of helplessness while sitting in a dental chair with their mouth wide open, unable to see what's going on.

Some respondents were found to get anxious when they were not taken seriously. Among them, only 12% medical students were found to get highly anxious. Besides this, criticism plays a vital role behind dental phobia. Forty-eight percent medical and 52% dental students were found to get highly anxious due to this. Upon asking, it was seen that similar reasons work behind both the situations. The perceived manner of the dentist is the major reason behind it. Smell in the dental office got respondents anxious at different level. It's because the typical odor in many dental practices resulted in causing panic attacks to most of them. Most of the respondents were seem to feel moderately anxious regarding the feeling that they might need a lot of dental treatment due to poor health condition. This was followed by the cost of the dental treatments and time required for necessary appointments. Majority of the respondents were worried about the cost of the dental treatments. Usually, the cost of dental treatments is high and they were worried whether they will be able to afford it or not. Again, some respondents were worried about the time required for necessary appointments. Since, they are students of medicine and dentistry, they usually don't get enough time away from their studies.

One of the major reasons of dental phobia found was the condition of the mouth. The study revealed that 36% medical and 56% dental students felt anxious due to this. Most of them felt nervous to go to the dentist due to such condition and never felt free to talk about it. This increased the level of fear or anxiety among them.

The limitation of the current study was that the sample size was small and data collection was done from one college only. Under limitations of the current study, it can be said that dental phobia remains as a significant problem. The results obtained from this study must, however, be interpreted with care due to small sample size. Further studies should be carried out using larger sample size.

Conclusion:

Overall prevalence of dental phobia was moderate. While medical students exhibited higher prevalence of dental phobia compared to dental students, some situations indicated dental students being more fearful towards dental procedures. Fear of injection is the most common hindrance in seeking good dental care. Sound of the drill was ranked as the 2nd most fearful procedure. The 3rd most fearful procedure was the root canal treatment.

To minimize the rate of dental phobia among the individuals, identifying a fearful patient is very important. The earlier a dental practitioner can identify a patient with dental phobia, the greater the likelihood of success in working with the patient. Moreover, communication between the dentist and patient is also important for successful treatment. Dentists should pay attention to every word the patient says with patience and should try to understand his/her condition before adopting an appropriate treatment approach. Educational sessions and

behavioral therapy at an initial stage of dental treatment may decrease the anxiety regarding dental procedures as well.

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Review Article

Zika Virus Disease: An Updated Overview

Nahar A[a], Sauda T H[a], Ahmed S R[c], Sikder M H[d], Quader F[e], Yasmeen S[f]

Abstract

Zika virus (ZIKV) is an emerging mosquito-borne virus transmitted primarily by Aedes mosquitoes (Aedes aegypti and Aedes albopictus). Zika virus is a positive-sense single-stranded RNA virus in the family *Flaviviridae.* Newborns of women infected with ZIKV during pregnancy have a 5 to 14% risk of congenital Zika syndrome and a 4 to 6% risk of ZIKV-associated microcephaly. Reverse transcription (RT)-PCR of acute-phase serum samples is the test of choice. Virus isolation from samples collected up to five days after the onset of symptoms can be beneficial. Serologic test can be done but there are some limitations. ZIKV infection has been reported in South East Asian countries including Bangladesh. Bangladesh is at high risk for emerging threat of ZIKV infection and currently, there is no active surveillance system on it. Therefore, it is necessary to establish national ZIKV surveillance, increase public awareness and mosquito control for the prevention and control of ZIKV infection in South East Asia. Here literatures like original article, review article and WHO guideline were considered from PubMed, Google Scholar, MEDLINE source.

Keywords: Zika virus disease, Zika virus, Aedes mosquito, Congenital zika syndrome, RT-PCR.

Introduction:

Zika virus (ZIKV) is an emerging mosquito-borne virus transmitted primarily by Aedes mosquitoes (Aedes aegypti and Aedes albopictus). They transmit also dengue (DENV), West Nile virus (WNV), Japanese encephalitis virus (JEV), and yellow fever virus1 (YFV).[1] ZIKV was first isolated from a sentinel rhesus monkey in the Zika Forest in Uganda in 1947 and from Aedes africanus mosquitoes in 1948.[1] It was then emerged in Africa as sporadic benign-human infections during the early 1960s through the middle of 1980s. Later, in 1969, ZIKV appeared as a potential pathogen in Asian-continent. The first ZIKV was isolated from Aedes mosquitoes in Malaysia [2] and human cases were confirmed in Indonesia and Pakistan in the early 1980s.[3,4,5] Several studies also documented widespread population exposure with ZIKV[4,5] but with mild clinical manifestations and since no outbreak had been reported, therefore, ZIKV failed to attract enough attention, globally. Concerns started growing since 2007 when ZIKV-epidemics broke out in Yap Island, Micronesia and another large outbreak in French Polynesia during 2013-2014.[6] More severe public health implications started revealing since early 2015, when a huge ZIKV outbreak swept over Brazil being associated with microcephaly &/or other neurological disorders.[7] In March 2017, WHO confirmed active ZIKV infections in 61 countries, the majority of which are from America, Africa and Western Pacific regions. In South and South-East Asia except Singapore, ZIKV cases are remain unexpectedly low comparing to America and Caribbean countries.[8] Nevertheless, epidemiology, geographical location and factors like distribution of Aedes-mosquito, effect of global warming on climate change in vector density [9] and trans-continental traveling suggest that there should be more ZIKV-cases in Asian regions since previous serological evidence attested this assumption clearly. [6]

In Bangladesh, some epidemiological, clinical and outbreak studies were conducted on dengue [10] and chikungunya[11] in contrast to ZIKV, which might have been missed or ignored due to lack of its attention earlier than 2015.[12] A retrospective surveillance was performed on 200 samples by Institute of Epidemiology, Disease Control & Research (IEDCR), Dhaka, Bangladesh where they found one sample was positive for ZIKV by real time RT-PCR and further confirmed by genome sequencing. A dendrogram was constructed using sequencing data (630 bp contig) obtained from study sample and reference strains from different geographical regions and period/ times available in GenBank database. The case was a 65 years old male from a metropolitan city of Bangladesh who had no history of travel outside Bangladesh. Phylogenetic

a. Dr. Azizun Nahar; M. Phil, MBBS
Associate Professor of Microbiology
Bangladesh Medical College, Dhaka

b. Dr. Tunazzina Hossain Sauda; MBBS
Supervising Council, BMSS

c. Dr. Samia Rashna Ahmed; MBBS
Ex. Hony. Medical Officer, Department of Medicine
Bangladesh Medical College Hospital

d. Dr. Munimul Hasan Sikder; MPH, MBBS
Ex-Assistant Registrar, Department of Cardiology
Bangladesh Medical College Hospital

e. Dr. Fuad Quader; MBBS
Honorary Lecturer of Microbiology
Bangladesh Medical College

f. Prof. Sharmeen Yasmeen; M. Phil, MPH, MBBS
Professor and Head, Department of Community Medicine
Bangladesh Medical College

Correspondence to:
Dr. Azizun Nahar; M. Phil, MBBS
Associate Professor of Microbiology
Bangladesh Medical College, Dhaka
Email: azizunnzhar26@gmail.com

analysis of partial E gene sequences from Bangladeshi isolates demonstrated a close relationship with ZIKV from Brazil and current South American strains clustering within a monophyletic clade distinct from African lineage.[12]

Virology:

Zika virus is a positive-sense single-stranded RNA virus in the family *Flaviviridae*.[13] Its closest relative is Spondweni virus, the only other member of its clade.[13,14] The Zika virus genome contains 10,794 nt (nucleotide) encoding 3,419 aa (amino acid). Like other flaviviruses, Zika virus is composed of 2 noncoding regions (5' and 3') that flank an open reading frame, which encodes a polyprotein cleaved into the capsid, precursor of membrane, envelope, and some nonstructural proteins.[14] The virus can be inactivated by potassium permanganate, ether and temperature $>60^0$C but neutralization with 10 percent ethanol is not effective.[1]

Epidemiology:

Zika virus was first isolated from humans was carried out in 1952, in Uganda and Tanzania.[1] In a study conducted in Nigeria in 1968 and during 1971-1975, ZIKV was also isolated from humans and in another study it was evident that 40 percent of the tested persons had neutralizing antibody to ZIKV.[15,16] From various studies viz., virological, serological and case reports of human ZIKV infection, the virus was identified and reported from various other African countries (Uganda, Senegal, Ivory Coast, Nigeria, Gabon, Egypt, Tanzania, Sierra Leone, Central African Republic), Asian countries (Cambodia, Indonesia, Malaysia, India, Pakistan, Singapore, Thailand, Philippines and Vietnam), Pacific islands (Micronesia/ Yap, FP, Cook Islands and New Caledonia) and Oceania.[17]

Tropical countries in Asia are believed to be endemic for many arboviral diseases including DENV, JEV, and chikungunya virus (CHIKV). In contrast to DENV, studies on ZIKV in Asia have been scarce, due to its apparent limited public health importance and the initial belief- prior to knowledge of the neurological complications- that the disease is mild in character.[18]

ZIKV strains are divided into two major lineages: the African lineage and the Asian/American lineage. These two lineages differ in approximately 90% of their nucleotide sequence.[19] Strains belonging to the Asian/American lineage have been isolated in Southeast Asia, in the Pacific Islands, and in the Americas. Within the Asian/American lineage, the strains from the Americas have formed a new American cluster.[20-22] Molecular analysis of strains isolated in Brazil has suggested that there was a single introduction of the virus into the Americas between May and December 2013, but the study did not identify specific molecular markers associated with microcephaly.[21]

To date, there is no clear evidence to explain the relatively low prevalence of ZIKV infection in Asia and why ZIKV has not been associated with similarly large outbreaks in Asia to those seen in the Pacific and the Americas. The mild character and non-specific clinical presentation of ZIKV infection, coupled with the low burden to public health prior to 2007, led to ZIKV disease being of less interest in scientific studies. Additionally, ZIKV was not recognized, was misdiagnosed, or was simply overlooked in clinical settings such as hospitals and private clinics, even during testing for arbovirus infections in the framework of national surveillance. This may explain why the circulation of ZIKV in some Asian countries is often documented based on cases in which travellers experiencing a febrile disease after returning to their home country are subsequently diagnosed following a broad investigatory panel of aetiology that includes Zika. Another challenge is in the laboratory diagnosis. The great extent of cross-reactivity between flavi viruses in the IgM and HI assays could lead to erroneous conclusions in Asian countries where DENV and JEV are predominantly circulating and where these assays are more widely available than molecular methods.[13]

Bangladesh Situation

On 22 March 2016 Reuters reported that Zika was isolated from blood sample of an elderly 67 years' man in Chittagong as a part of retrospective study done in Institute of Epidemiology, Disease Control and Research (IEDCR), Dhaka Bangladesh.[23] After WHO's emergency call on Zika virus, the government in February decided to test again old samples stored at IEDCR that had earlier tested negative for dengue and chikungunya virus. IEDCR had tested 101 samples randomly selected from 1070 samples they had earlier collected from their surveillance sites- two Dhaka, one Khulna and the other in Chittagong. According to GULF NEWS, BANGLADESH (June 16, 2016), IEDCR authorities test blood samples from a further 159 people who were neighbors or had close contact with the patient, and find no sign of virus.[24]

The host range and transmission pattern

Human-vector-human cycle of transmission occurs during outbreaks, which are rare events where arboviruses become established as a cause of human disease, spread in a mosquito-human-mosquito cycle, instead of enzootic mosquito-monkey-mosquito cycle. ZIKV is transmitted by Aedes mosquitoes, which are daytime active and aggressive biters.[25] The *Ae. aegypti* mosquito appears to be the major vector in Asia [3] and was the suspected primary vector for the French Polynesia outbreak.[26] In humans, male-to-female sexual transmission can occur whether the male partner with ZIKV infection is symptomatic or asymptomatic and has been observed more frequently than female-to-male and male-to-male transmission.[27] Although the effect of sexual transmission in areas in which the virus is endemic is difficult to assess, estimates are that 1% of ZIKA infections reported in Europe and United States were acquired through sexual transmission.[28]

ZIKA RNA has been detected in semen, by reverse-transcriptase-polymerase-chain-reaction assay, up to 370 days after onset of illness, but shedding of infective viral particles is rare after 30 days from the onset of illness.[27,29]

Maternal-fetal transmission of ZIKV may occur in all trimesters of pregnancy, whether infection in the mother is symptomatic or asymptomatic.[30-34] Vertical transmission has been estimated to occur in 26% of fetuses of ZIKV-infected mothers in French Guiana, a percentage similar to transmission percentages that have been observed for other congenital infections. Among fetuses that were exposed to ZIKV by vertical transmission, fetal loss occurred in 14% and severe complications compatible with congenital Zika syndrome occurred in 21%. In addition 45% of the fetuses that were exposed to ZIKV by vertical transmission had no signs or symptoms of congenital Zika syndrome in the first week of life.[34] Intrauterine transmission is supported by the finding of Zika virus RNA by reverse transcription PCR (RT-PCR) in amniotic fluid of 2 mothers with symptoms of Zika virus infection during pregnancy; both delivered babies with microcephaly.[35] However, ZIKV can be transmitted to humans by non-vector borne mechanism such as blood transfusion.[36]

Pathogenesis:

Most of the flavivirus replication is thought to occur in cellular cytoplasm but perhaps it might not be the case with the Zika virus as one of the studies detected antigens in infected cell nuclei.[37] After mosquito inoculation of a human host, cellular entry likely resembles that of other flaviviruses, whereby the virus enters skin cells through cellular receptors, enabling migration to the lymph nodes and bloodstream. Few studies have investigated the pathogenesis of Zika virus infection. One study showed that human skin fibroblasts, keratinocytes, and immature dendritic cells allow entry of Zika virus.[38] Several entry and adhesion factors (e.g., AXL receptor tyrosine kinase) facilitate infection, and cellular autophagy, needed for flaviviral replication, enhances Zika virus replication in skin fibroblasts.[38] After cellular entry, flaviviruses typically replicate within endoplasmic reticulum-derived vesicles. However, Zika virus antigens were found exclusively in the nuclei of infected cells; this finding suggests a location for replication that differs from that of other flaviviruses and merits further investigation.[37]

Clinical Manifestations:

In humans, the incubation period from mosquito bite to symptoms onset is≈3-12 days. Infection is likely asymptomatic in ≈ 80% of cases.[39,40] Symptoms of infection with the virus begin with mild headache followed by maculopapular rash (neck, face, trunk, and upper arms, and spread to palms and soles), fever, malaise, conjunctivitis and joint pains. Other manifestations include diarrhoea, constipation, abdominal pain, anorexia, dizziness and conjunctivitis. Rashes are not the consistent feature of this disease.[13] Some less frequent manifestations are myalgia, vomiting, oedema, and retro-orbital pain.[41] Among the complications, following are important to mention;

1. ZIKV-Associated Guillain-Barré Syndrome

The incidence of ZIKV-associated Guillain-Barré syndrome is estimated to be 2 to 3 cases per 10,000 ZIKV infections, which is similar to the risk associated with campylobacter infection.[42,43] The interval between antecedent illness and on- set of the Guillain-Barré syndrome is 5 to 10 days, which has led to speculation about a contributory parainfectious process.[44] Acute inflammatory demyelinating polyneuropathy, acute motor axonal neuropathy, and the Miller–Fisher syndrome (a subset of the Guillain–Barré syndrome characterized by ophthalmoplegia, ataxia, and areflexia) have been observed with ZIKV-associated Guillain-Barré syndrome, but the relative proportions of these subtypes vary across studies and regions. [44-46] Several case series showed thatthe prognosis of ZIKV-associated Guillain-Barré syndrome was similar to that of Guillain–Barré syndrome associated with other infectious or noninfectious processes; however, findings from a case-control study suggest that ZIKV-associated Guillain-Barré syndrome results in higher morbidity and more frequent cranial neuropathy. [44,47]

2. Congenital Zika Syndrome

Newborns of women infected with ZIKV during pregnancy have a 5 to 14% risk of congenital Zika syndrome and a 4 to 6% risk of ZIKV-associated microcephaly.[30-34,48,49] Prominent features of congenital Zika syndrome include fetal brain disruption sequence, a condition that arises from partial brain disruption during gestation with subsequent collapse of the fetal skull caused by decreased intracranial hydrostatic pressure; subcortical calcifications; pyramidal and extrapyramidal signs; ocular lesions of chorioretinal atrophy and focal pigmented mottling of the retina and congenital contractures that appear to be caused by a neurogenic process.[50] Neonatal mortality in the first week of life among infants with congenital Zika syndrome may be as high as 4 to 7%; better estimates of neonatal mortality past the first week of life are needed.[30,34] The absence of clinical and radiologic abnormalities indicative of congenital Zika syndrome at birth does not exclude the risk of abnormalities such as seizures, hearing loss, visual impairment, dysphagia, and developmental delay later in life. Among U.S. children who were born to mothers infected with ZIKV during pregnancy and who had no identified birth defects, 9% had at least one neurodevelopmental abnormality before they reached 2 years of age, a finding that underscores the need for long-term surveillance of children born to mothers with ZIKV infection.[29,49,51,52]

Four recently published mouse-model studies have addressed the causal relationship between ZIKV infection in pregnancy and pathologic changes in fetuses.[53,54,55,56]

Three of the studies introduced different ZIKV strains into pregnant mice through peripheral inoculation routes

(intravenous, intraperitoneal, or subcutaneous),[53,54,56] and two studies inoculated ZIKV directly into the fetal brain.[55,56] Early in pregnancy, ZIKV infection may lead to severe placental vascular damage and a reduction in fetal blood vessels and blood flow. Alternatively, ZIKV could cross the placental barrier without excessive and spread to the fetal brain, where it preferentially infects and injures neuronal progenitor cells. This outcome may be more typical of infection later in pregnancy because of enhanced interferon-λ-induced innate immunity in trophoblasts.[57]

Diagnosis:

The symptoms of Zika virus are similar to those in case of dengue and chikungunya; therefore, the diagnostic molecular techniques are employed on the acute samples and serological tests are applied on samples 5-6 days after onset of symptoms. Reverse transcription (RT)-PCR of acute-phase serum samples is the test of choice. It is evident that the viruria can last longer than viraemia and hence the RT-PCR based detection of viral RNA in patients' urine samples could be an alternative method in case genetic material disappears from the serum.[25,58,59] An alternative to the RT-PCR is the "pan flavivirus" amplification technique combined with sequencing data. [25,14,60,61] Real time RT-PCR can also be very useful for diagnostic purpose.[41] Virus isolation from samples collected up to five days after the onset of symptoms can be beneficial. The plaque reduction neutralization test (PRNT) by neutralizing antibody that appears as early as five days after onset of illness has greater specificity with respect to immunoassays, but the drawback is that it may give cross-reactive results in case of secondary flavivirus infections. Immunoglobulin (Ig) M to Zika virus can be detected as early as three days after onset of illness by ELISA.[13] Zika virus IgM and IgG are notoriously cross-reactive with those against other flaviviruses, limiting specificity. [45, 13] Blood samples should be collected from febrile illness cases and must be tested for common viral diseases; DENV and CHIKV and then ZIKV. Blood samples negative for DENV and CHIKV should be processed for detection of Zika virus aetiology. [62]

Treatment and Prevention:

No antiviral agents have been approved for the treatment of ZIKV infection and supportive care for clinical management of acute ZIKV infection. The therapeutic approach to ZIKV-associated Guillain-Barré syndrome is the same as that for classic Guillain-Barré syndrome and includes the use of therapeutic plasma exchange or intravenous immunoglobulin.[63] Recommendations regarding the care of infants are stratified according to the clinical and imaging findings in the infant and laboratory evidence of ZIKV infection in the mother during pregnancy.[64]

Prevention of sexual transmission relies on abstinence or protected sexual intercourse after suspected infection for 2 months if the partner with suspected infection is female and for 3 months if the partner with suspected infection is male. [27] Prevention of congenital Zika syndrome relies on avoidance of infection during pregnancy or postponement of pregnancy.[65] Protection of ZIKV infections against mosquito bites during the day and early evening is needed. Public awareness should develop to destroy the breeding place of Aedes mosquitoes like covered water storage containers, stagnant water in flower pots, and tires. Larvicides and insecticides should be used to reduce mosquito populations and disease spread.

Conclusion:

ZIKV infection has been reported in South East Asian countries including Bangladesh. Bangladesh is at high risk for emerging threat of ZIKV infection and currently, there is no active surveillance system on it. Therefore, it is necessary to establish national ZIKV surveillance, increase public awareness and mosquito control for the prevention and control of ZIKV infection in South East Asia.

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Case Report

Methotrexate induced pulmonary toxicity in a male patient with rheumatoid arthritis: a case report

Saber S[a], Alam M T[b], Hossain M M[c], Momen A B I[d], Alam R F[e]

Abstract

Interstitial lung disease (ILD) is a common pulmonary manifestation that may be related to the inflammatory process itself, infectious complications and to the treatments use. Drug-induced interstitial lung disease (ILD) is a rare but serious adverse event. Both synthetic and biologic immunosuppressive agents have been related to the onset or worsening of ILD, making the adoption of safe and effective therapeutic approach difficult. Methotrexate-Induced ILD is the prototype of drug-induced lung toxicity in patients with rheumatoid arthritis (RA). Here we report the case of a 57-year-old gentleman being treated with methotrexate for rheumatoid arthritis, developed respiratory symptoms and signs. These improved on drug withdrawal and with eight weeks of steroid treatment.

Keywords: Rheumatoid arthritis, Interstitial lung disease, Methotrexate, Pulmonary toxicity..

Introduction:

Rheumatoid arthritis (RA) is the most common inflammatory arthritis with a worldwide prevalence of about 1% and a female predominance of about 3:1. It is an inflammatory chronic autoimmune disease generally characterized by a progressive and disabling symmetric polyarthritis accompanied by specific autoantibodies.[1] While there are numerous synthetic and biologic disease-modifying anti rheumatic drugs (DMARDs) that can halt progression of the articular manifestations of the disease, data on extra articular manifestations are less conclusive. Over the past few years, the lung has become a major focus in terms of pathophysiology and overall prognosis.[2] Even though the majority of RA-related deaths are linked to cardiovascular disease, pulmonary complications are common and cause 10–20% of overall mortality.[3] In clinical practice, there are perceived discrepancies regarding pulmonary toxicity between pulmonologists and rheumatologists, especially regarding methotrexate (MTX) and the potential risks of long-term pulmonary fibrosis. Methotrexate is one of the most widely used broad spectrum immunomodulatory drugs. It can be used upfront as a primary option or as a combination drug in various immunological conditions. Methotrexate is generally safe in the dosages used. However, a clinician has to be alert regarding some of its less common side-effects. We discuss here a patient who developed methotrexate-induced pulmonary toxicity.

Case Presentation:

A 57-year-old male with a diagnosis of RA on 22/11/18, started prednisolone 10mg/day and MTX 10mg/week with an increase in dose to 15mg/week on 12/07/19, and prednisolone was gradually tapered-off and discontinued after 4 weeks. Six months later, while still on methotrexate, he presented with gradually progressive exertional breathlessness and dry cough of two months' duration. He had high grade, intermittent fever with chills along with anorexia and worsening breathlessness since ten days.

On examination, he was tachypnoeic with a respiratory rate of 32/minute and had a temperature of 39°C. Chest auscultation revealed bilateral, fine inspiratory crepitations in the infra-axillary and infra-scapular areas. The rest of the systemic examination was normal. His WBC count was 13,500/cu mm with differential counts of Neutrophil-69%, Lymphocyte-33%, Monocyte-1%, and Eosinophil-7%. Chest x-ray (CXR) showed haziness in both lower zones. Sputum could not be examined, as he did not produce any. Contrast enhanced computed tomography (CECT) of the thorax showed patchy areas of ground glass haziness in both middle and lower lobes, suggestive of alveolitis.

a. Dr. Sadia Saber; FCPS, MRCP (UK), MRCP (Ireland), MBBS
Assistant Professor (CC), Department of Medicine
Bangladesh Medical College, Dhaka

b. Dr. Md. Tarek Alam; MD (USA), MBBS
Professor (CC) and Head, Department of Medicine
Bangladesh Medical College, Dhaka

c. Dr. Mohammad Monower Hossain; MBBS
Medical Officer, Department of Medicine
Bangladesh Medical College Hospital, Dhaka

d. Dr. Abdul Basit Ibne Momen; MRCP (UK), MBBS
Registrar, Department of Medicine
Bangladesh Medical College, Dhaka

e. Dr. Rafa Faaria Alam; MBBS
Medical Officer, Department of Medicine
Bangladesh Medical College Hospital, Dhaka

Correspondence to:
Dr. Sadia Saber; FCPS, MRCP (UK), MRCP (Ireland), MBBS
Assistant Professor (CC), Department of Medicine
Bangladesh Medical College, Dhanmondi, Dhaka
Email: sadiasaber201477@gmail.com

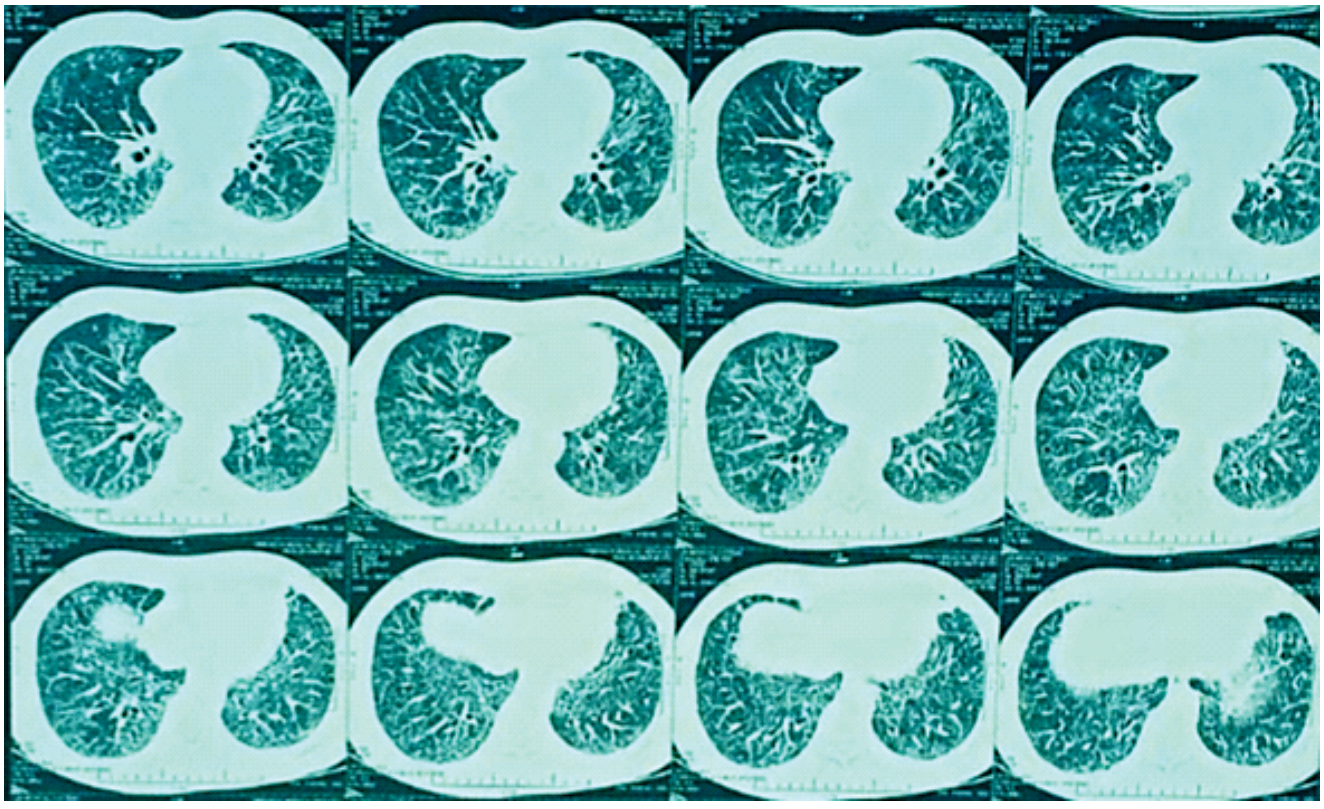

Fig 1: CECT scan of thorax showing areas of ground glass haziness, suggestive of alveolitis

Bronchoscopy was suggested but the patient did not give his consent for the procedure. Blood and urine cultures were sterile. Blood gas analysis on room air revealed respiratory alkalosis with mild hypoxaemia. The patient was unable to perform pulmonary function tests as he had unrelenting cough and tachypnoea. He had an ejection fraction of 64% on echocardiography; and pulmonary artery systolic pressure of 33 mm Hg.

A diagnosis of methotrexate-induced pulmonary toxicity was made. The drug was stopped, and he was started on antibiotics and high dose steroids, with other supportive treatment.

His fever started settling down and he symptomatically started to improve with lesser cough and breathlessness. His repeat WBC was 8,200/cu mm and chest X-ray after four weeks was normal. It has taken another four weeks to taper down his steroid dose.

Discussion:

Methotrexate is a folate antagonist used as a chemotherapeutic agent as well as for the treatment of non-neoplastic inflammatory diseases, rheumatoid arthritis (RA) being the commonest prototype. Methotrexate induced pulmonary toxicity occurs in 1-5% patients with RA and is most commonly seen in the first year of treatment.[4]

Current guidelines of the British Society for Rheumatology for the management of patients with RA have proposed to perform pulmonary function tests as a screening procedure before starting MTX thus helping to identify occult lung disease.[5] Despite the association between pneumonitis and MTX is generally accepted, the ILD/MTX link is not clearly demonstrated and has been questioned by other authors. Dawson and colleagues performed chest HRCT and pulmonary function test in 128 RA patients and found no differences in the dose or duration of MTX therapy in the 28 patients presenting pulmonary fibrosis, suggesting no evidence of MTX-related chronic ILD.[6] Finally, a recent meta-analysis of Conway and colleagues have demonstrated a mild increased risk of respiratory adverse events in patients with RA treated with MTX compared with other disease-modifying anti rheumatic drugs (DMARDs) and biologic agents, however not higher increased risk of death.[7]

Patients on low-dose methotrexate are at increased risk for opportunistic infections.[8] These include *Pneumocystis carinii* pneumonia, disseminated histoplasmosis, and herpes zoster. Therefore, exclusion of opportunistic pathogens is important in the differential diagnosis of methotrexate pneumonitis. It is a diagnosis of exclusion (Table II).[9] Radiologically, bilateral mixed interstitial-alveolar pulmonary shadows, pleural effusion, hilar lymphadenopathy may be present. Pulmonary function tests show a restrictive ventilatory defect with decreased

diffusing capacity. The pathogenesis of this entity is not known. It probably has a hypersensitivity mechanism suggested by the frequent finding of peripheral eosinophilia and lymphocytosis on bronchoalveolar lavage. BAL lymphocyte CD4: CD8 may be increased, decreased, or normal. It may be an idiosyncratic immune reaction. Thus, different mechanisms may be operative in different subjects.

On histology, mononuclear cell infiltrates with type II pneumocyte hyperplasia in acute cases, and interstitial fibrosis in chronic cases, may be present. Isolated areas of bronchiolitis obliterans and non-caseating granulomas may be present.

Factors that increase risk for methotrexate lung toxicity are: higher daily and cumulative doses, renal insufficiency, concomitant high-dose aspirin or non-steroidal anti-inflammatory drug therapy, and pre-existing lung disease.

The treatment of methotrexate pneumonitis includes withdrawal of the drug and supportive care. Oral or intravenous pulse corticosteroid therapy[10] may be useful and is initiated after infection has been excluded. However, there are no clear guidelines for the optimal dose or duration of therapy. Patients with significant hypoxia will require oxygen therapy and intensive care with mechanical ventilation. Cyclophosphamide has been used successfully in significant pneumonitis.[11] Although there are instances of successful reintroduction of methotrexate after pneumonitis, there is not enough evidence to support this.[12]

The prognosis with methotrexate-associated lung injury is generally favorable. The overall mortality is approximately ten per cent.[13]

Our patient had a probable diagnosis of methotrexate induced pulmonary toxicity (Table I). Also, as per the causality assessment scale provided by Naranjo CA et al[14], he had a probable adverse drug reaction to methotrexate (score - 6). He responded well to drug withdrawal and steroids, the latter having been tapered off in four weeks' time. A re-challenge of methotrexate was not attempted.[12]

Table 1: Pulmonary involvement with methotrexate use.[15]

Pulmonary Syndrome	Treatment	Comments
Chronic pneumonitis/ pulmonary fibrosis	Discontinue drug; give corticosteroids	Most common type
Hypersensitivity-type lung disease	Discontinue drug; give corticosteroids	May resolve even if drug is continued; may progress to fibrosis
Acute chest pain syndrome	Discontinue drug	Often associated with pleural effusion
Non-cardiogenic pulmonary edema	Discontinue drug; Supportive care	Associated with intrathecal administration.

Table 2: Criteria of Searles and McKendry for diagnosis of methotrexate pneumonitis.[9]

1. Acute onset dyspnoea
2. Fever > 38° C
3. Tachypnoea >/= 28/min, and dry cough
4. Radiological evidence of pulmonary interstitial or alveolar infiltrates
5. WBC < 15,000/cu mm with or without eosinophilia
6. Negative blood and sputum cultures (mandatory)
7. Restrictive defect and decreased DLCO on PFT
8. PO2 < 60 mm Hg on room air
9. Histopathology consistent with bronchiolitis or interstitial pneumonitis with giant cells and without evidence of infection

Definite ≥ 6 criteria; Probable: 5 of 9 criteria; Possible: 4 of 9 criteria.

Conclusion:

Although rare, this is a well-documented case of MTX-induced ILD. The diagnosis of MTX-induced ILD is based on clinical evaluation, imaging and biopsy, as well as on the improvement with the use of corticosteroids and MTX suspension. The clinician should be alert for ILD-induced MTX in elderly patients with sudden onset of dyspnea.

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Case Report

Klinefelter's syndrome associated with hand deformity: A case report

Aktar Y[a], Munir H K[b]

Abstract

Klinefelter syndrome is the most common sex chromosome disorder that affects 1 in 500 males. Additional X chromosome in the affected males results in male hypergonadotropic hypogonadism, androgen deficiency, and impaired spermatogenesis. Testosterone replacement therapy should be provided to correct the androgen deficiency for appropriate virilization. Radioulnar synostosis is a very rare malformation behind Klinefelter syndrome. We report here a 14-year-old boy presented with tall stature for his age. He had bilateral gynaecomastia and lack of pubic and axillary hair. The boy had also difficulty in pronation and supination of his upper limbs. X-ray of both elbow joints revealed bilateral radioulnar synostosis. Biochemically he had hpergonadotropic hypogonadism and karyotype showed 48, XXYY. Radioulnar synostosis can be associated in individuals with Klinefelter syndrome, but usually found in patients with karyotype 48, XXYY and rarely in 47, XXY.

Keywords: Klinefelter syndrome, Karyotype 48, XXYY, Androgen, Testosterone, Radioulnar synostosis..

Introduction:

Klinefelter syndrome is relatively common and affects 1:500 to 1:1000 male live births.[1] It is a group of chromosomal disorders in which there is at least one extra X chromosome added to the normal 46, XY male karyotype.[1] Variants of Klinefelter syndrome are rare but may found when more than one extra sex chromosome is present in each cell, e.g. 48, XXXY or 49, XXXXY. Hypogonadism, gynaecomastia, azoospermia or oligospermia and increased levels of gonadotropins are the characteristic features.[2] Klinefelter syndrome is also associated with an increased risk for other congenital malformations, additional medical problems and complex psychological involvement.[3]

Case Presentation:

A 14-year-old boy was referred to an out-patient department for his tall stature and reduced mobility of the right forearm since childhood. The complaints were mild, having difficulty in different movement specially writing. Initially after birth his family members could not detect the hand deformity but day by day his disability comes forward. There were no similar cases in the family. He had also complaints of increasing height in comparison to the boys of similar age. Other than this he had also history of delayed appearance of pubic, axillar and facial hair. He was psychologically depressed about his body configuration. He had two other brothers who were healthy. His developmental milestone was normal; had no learning difficulties and an average academic performance.

Physical examination revealed his body weight was 64.8 kg, height- 182 cm, arm span- 174 cm, BMI-19.5 kg/m^2, BP-100/60 mm Hg, bilateral gynaecomastia shown in Fig-1 (similar to breast Tanner stage 3), testicular volume 4 ml bilaterally, stretched penile length- 7.2 cm, no pubic, axillary and facial hair (Fig-2). Examination of both upper limbs revealed reduced range of movement on pronation and supination which led him to having difficulty in opening bottle-caps and door-knobs, also difficulty in writing. The rest of his physical examination was normal.

Investigation results are listed in Table-1. He received 125 mg intramuscular testosterone injection every 4 weeks for 3 months at the age of 14 years to initiate his pubertal development. After that he is on intramuscular testosterone 250 mg every 4 weeks. Corrective surgery for radioulnar synostosis (Fig-3) is also planned after the age 22 years.

a. Dr. Yasmin Aktar; MD, MBBS
Consultant, Department of Endocrinology
Bangladesh Medical College Hospital, Dhaka

b. Dr. Hasan Khalid Munir; D. Ortho, MBBS
Resident Assistant Professor, Department of Orthopedics
Bangladesh Medical College Hospital, Dhaka

Correspondence to:
Dr. Yasmin Aktar; MBBS, MD
Consultant, Department of Endocrinology
Bangladesh Medical College Hospital, Dhaka
Email: yasminaktar18@gmail.com

Table 1: Investigation results of the patient

Name of investigations	Result	Normal Value
Haemoglobin	12.3	13-17 gm/dl
FBS(Fasting blood sugar)	4.74 mmol/l	3-6.37 mmol/l
2 Hour after 75gm glucose	5.0 mmol/l	<7.8 mmol/l
Free T4 (Thyroxine)	0.748 ng/dl	0.89-1.76 ng/dl
TSH (Thyroid stimulating hormone)	0.74 µIU/ml	0.40-4.0 µIU/ml
Serum Testosterone	0.38 ng/ml	2.4- 12 ng/ml
Serum LH (Luteinizing hormone)	30.1 mIU/ml	1-15 mIU/ml
Serum FSH (Follicle stimulating hormone)	66.3 mIU/ml	2-10 mIU/ml
Basal Cortisol	225.02 nmol/l	138-690 nmol/L
Plasma ACTH (Adrenocorticotropic hormone)	57.48 pg/ml	05 to 46 pg/ml
MRI of Pituitary gland- Normal pituitary gland		
Karyotyping: 48, XXYY		

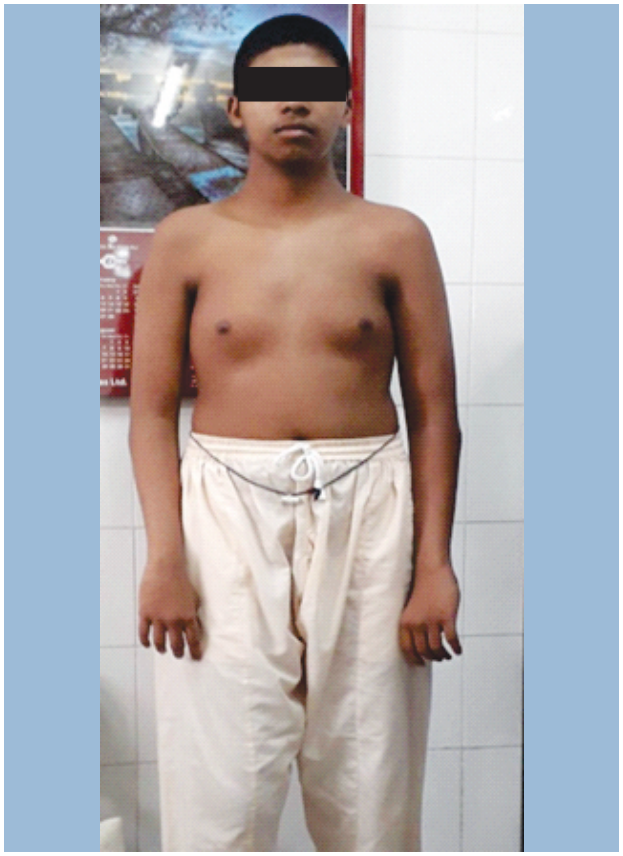

Fig 1: Bilateral Gynaecomastia

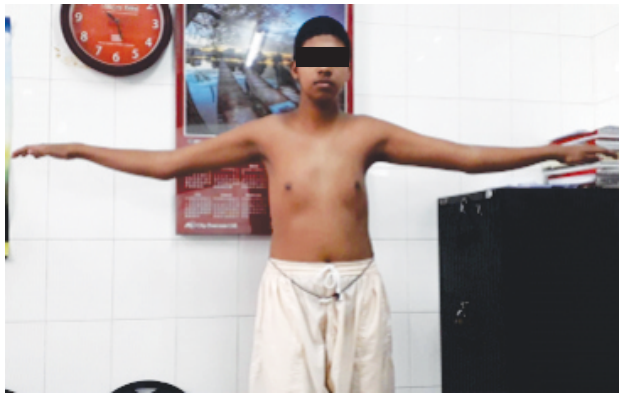

Fig 2: No hair in axillary & beard area, long arm span

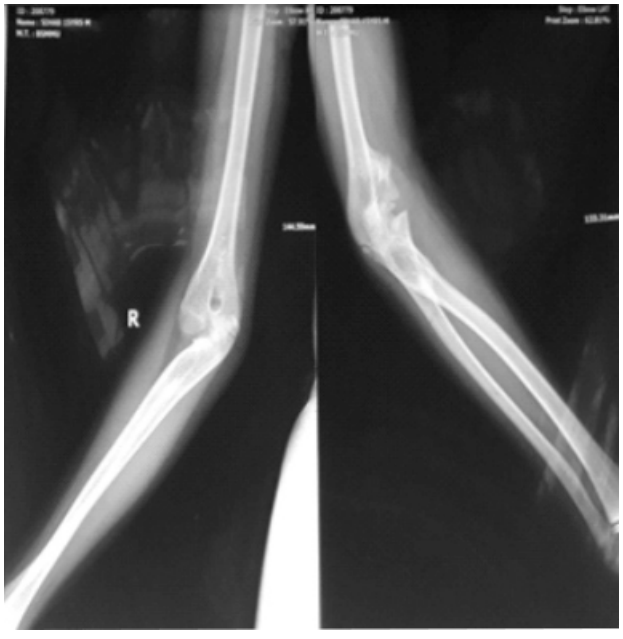

Fig 3: Radioulnar synostosis

Discussion:

The incidence of the 48, XXXY and 49, XXXXY variants is considerably lower; of 1 in 17000 to 1 in 50000 live births and 1 in 85000 to 1 in 100000 live births, respectively.[3] Klinefelter syndrome is associated with high stature, as does the 48, XXXY variant.[3] My patient also had bilateral radioulnar synostosis. A review of literature reporting Klinefelter's syndrome and its chromosomal variations showed 18 cases of proximal radioulnar synostosis.[4] The finding of proximal radioulnar synostosis in a single generation should alert clinicians to suspect a disorder of sex chromosome abnormality[4] and hence karyotyping should be ordered. In addition, James et.al found a mosaic karyotypes 46, XY/47, XYY/48, and XYYY in a 3-year-old boy with bilateral radioulnar synostosis.[6] In a large cohort study included 40 Klinefelter's patient and observed for prevalence of musculoskeletal disorders particularly hypotonia (85%),

radioulnar synostosis (75%), pes planus (65%), asymmetric hip rotation (67.5%), and clinodactyly (60%).[5] There are two forms of radioulnar synostosis: acquired or post-traumatic and congenital. The last form can be isolated or secondary to other malformations or syndromes. The clinical manifestation can be subtle in early childhood and many times the syndrome is under-diagnosed.[4]

Conclusions:

Many operative procedures have been developed for patients with congenital radioulnar synostosis to mobilize the fixed forearm though long-term results are still unsatisfactory. Whenever this type of deformity detected in early childhood, should exclude the sex chromosomal disorder behind this.

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Case Report

Emphysematous Pyelonephritis: A Rare Disease

Kabir M M[a], Sikder M[b], Kabir M[c], Mahmood I H[d], Rahman R[e], Nahar A[f]

Abstract

Emphysematous pyelonephritis (EPN) is a severe, acute necrotizing renal parenchymal infection with formation of gas. The aim of this case study is to share our experience regarding diagnosis and treatment of the patient of Emphysematous pyelonephritis at our institution. USG – Ultrasound examination of KUB revealed mildly increased cortical echogenicity of both kidneys with mildly swollen right kidney. There were also echogenic shadows both within the cortex and medulla. Abdominal computed tomography (CT) showed gas in renal calyces, bilateral nephrolithiasis and uniform thickening of wall of the urinary bladder. Due to improvement of imaging technique and newer antibiotic surgical option may be delayed. Our clinical experience and data suggest that early goal directed therapy with IV antibiotics, fluid resuscitation and strict management of DM together can provide viable alternatives to nephrectomies in early stages of EPN. In case of a patient of old age with multiple risk factors where any surgical procedures can initiate another life threating episode to the patient, medical management with cautious monitoring can be an important alternative. More case reports and study will be helpful to develop a proper and complete picture and guideline to manage such cases in different clinical setups.

Keywords: Emphysematous pyelonephritis (EPN), Diabetes mellitus, Meropenem.

Introduction:

Emphysematous pyelonephritis (EPN) is a severe, acute necrotizing renal parenchymal and perirenal infection with formation of gas. Emphysematous pyelonephritis predominantly affects females with uncontrolled diabetes and can occur in type I as well as type II DM.[1] The pathogenesis of this disease is thought to involve many different predisposing factors including high tissue glucose concentrations, presence of gas-forming organisms, impaired vascular supply, impaired immune system, and ureteric obstruction.[1] Because of its rarity, most of the information has been from case reports. CT scan is the modality of choice for the staging of the parenchymal gas and to rule out obstruction.[2] The aim of this case study is to share our experience regarding diagnosis and treatment of the patient of Emphysematous pyelonephritis at our institution.

Case Presentation:

A 50-year-old female presented to the emergency department of with the complaints of fever, anorexia, vomiting for 15 days, loin pain radiating from loin to groin and high coloured urine for one day. She was a known case of diabetes mellitus and hypertension. The patient appeared alert and oriented but dehydrated. On examination, patient appeared ill with tachycardia, dehydration, fever (101^0F) and tenderness in the right loin region.

Laboratory investigation revealed Hb: 11.8 g/dl, total leukocyte count: 14,500 with polymorphs 90%, platelet: 70.0 10^9/L blood urea nitrogen (BUN): 109.8 mg/dl, creatinine: 3.67 mg/dl, serum Na^+: 129 mmol/L, random blood glucose: 13 mmol/L. The urine analysis showed – RBC; plenty, pus cells: 15-20/HPF, sugar: 1+, albumin: 1+. Urine culture showed no growth but blood culture revealed growth of *Enterococcus* species. USG – Ultrasound examination of KUB revealed mildly increased cortical echogenicity of both kidneys with mildly swollen right kidney. There were also echogenic shadows both within the cortex and medulla (Fig 1). Abdominal computed tomography (CT) showed gas in renal calyces, bilateral nephrolithiasis and uniform thickening of wall of the urinary bladder (Fig 2). There was minimal right sided pleural effusion present in X-ray chest P/A view. Conservative treatment was started with I/V insulin, I/V fluid and I/V meropenem 500 mg thrice daily for 14 days.

a. Dr. Muhib Muhammed Kabir; MBBS
Medical Officer, Department of Nephrology
Bangladesh Medical College Hospital

b. Dr. Munimul Hasan Sikder; MBBS, MPH
Ex- Assistant Registrar, Department of Cardiology
Bangladesh Medical College Hospital, Ex- Project Coordinator
National Anti-Tuberculosis Association of Bangladesh

c. Dr. Mehnaz Kabir, MBBS, MPH
Lecturer, Department of Community Medicine
Bangladesh Medical College

d. Dr. Iqbal Hasan Mahmood; MBBS
Assistant Registrar, Department of Nephrology
Bangladesh Medical College Hospital

e. Dr. Rezwanur Rahman; MD (Nephrology), MBBS
Associate Professor, Department of Nephrology
Bangladesh Medical College

f. Dr. Azizun Nahar M. Phil, MBBS
Associate Professor, Department of Microbiology
Bangladesh Medical College

Correspondence to:
Dr. Azizun Nahar; M. Phil, MBBS
Associate Professor, Department of Microbiology
Bangladesh Medical College
Email: azizunnahar26@gmail.com

Patient started recovering clinically and was subsequently discharged home in a stable condition and had no complaint at the time of follow up, USG showed no gas in the renal area, bilateral pyelonephritis with renal stone on right side. Routine urine examination showed plenty of pus cells and culture showed no growth, so she was treated with broad spectrum antibiotic to prevent sepsis and was discharged from the hospital in good condition. No surgical intervention was advised. She was advised to further follow up in Urology department and Nephrology OPD if symptoms reappear.

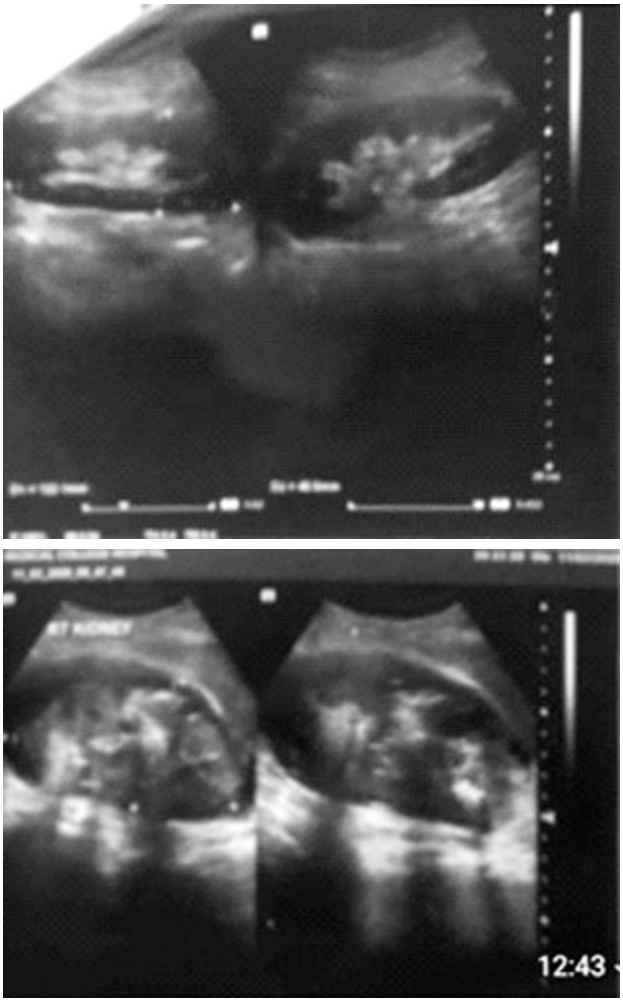

Fig 1: USG of KUB revealed mildly increased cortical echogenicity of both kidneys with mildly swollen right kidney. There were also echogenic shadows both within the cortex and medulla

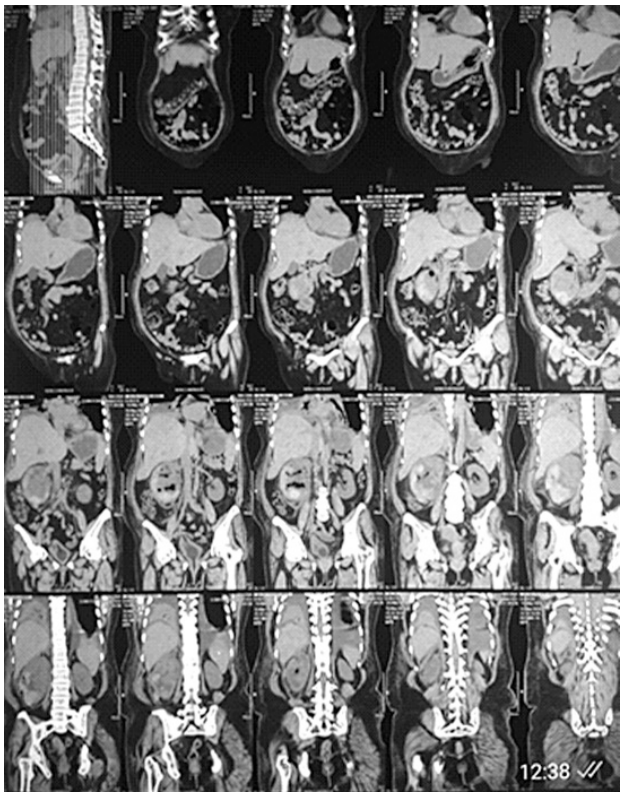

Fig 2: Abdominal computed tomography (CT) showed gas in renal calyces, bilateral nephrolithiasis and uniform thickening of wall of the urinary bladder

Discussion:

EPN is a rare necrotizing infection with high mortality and morbidity. The predisposing factors EPN are diabetes mellitus and ureteric obstruction. All the documented cases of emphysematous pyelonephritis have been in adults.[3] Juvenile diabetic patients do not appear to be at risk, and women are affected more often than men. Almost all patients display the classic triad of fever, vomiting, and flank pain.[4] We also found similar findings with our patient. Pneumaturia is absent unless the infection involves the collecting system. Bacteriuria, positive blood culture results, and leukocytosis are often present. Results of urine cultures are invariably positive. *E. coli* is the most frequently identified pathogen; *Klebsiella* and *Proteus* are less common.[5] In this case study urine culture had no growth but blood culture showed growth of *Enterococcus* species. Another case series in USA had three patients with *E. coli* positive urine cultures, one patient had a blood culture that grew *Staphylococcus epidermidis*.[6] The pathogenesis of gas formation requires pathogenic bacteria capable of mixed acid fermentation, a hyperglycemic environment, and localized tissue ischemia. Because a hyperglycemic environment is one of the requirements in gas formation, it only makes sense that diabetes is a significant predisposing factor. It has been estimated that up to 95% of EPN cases have underlying uncontrolled diabetes mellitus.[7] Furthermore, hyperglycemia in association

with impaired blood supply to the kidneys from vasculopathy- both of which are prevalent in diabetic patients- facilitates the process of anaerobic metabolism.[8]

Diabetes is the predisposing factor for EPN development and some of the patients had predisposing factors such as ureteric obstruction or immunological impairment, our patient also had history of diabetes which correlates with this study.[9] Our case presents the patient with renal calculi. Risk of developing EPN in patients with urinary tract obstruction is about 25-40%, with ureteral obstruction being the second most common predisposing factor in those diagnosed with EPN.[7,10] Current evidence suggests females are more susceptible to EPN because they are also more susceptible to urinary tract infections.[4,11,12] Ureteral obstruction causes local tissue ischemia which can provoke an infection in a number of ways such as exacerbating local tissue destruction, encouraging purulent infection, and inhibiting the removal of locally produced gas.[4,12,13] Multiple reasons exist, as a result of which obstructive calculi increase the likelihood of infection. One possibility is the stone providing a nidus for infection from where the disease could spread further on. Another possibility is that the obstructing calculus causes stagnation/reflux of urine and therefore a lack of laminar flow in the ureteral system. This would make it easier for the pathogens to ascend proximally up the urethra and ureters resulting in infection. In a case series four out of the five patients had hypertension.[14] Our patient also had hypertension. As mentioned earlier, ischemia is a known predisposing factor for EPN. Hypertension causes ischemia through mechanisms such as arteriosclerosis and glomerulosclerosis.

The clinical approach to treating patients with EPN has changed over the years. Due to advances in medical imaging, interventional radiology, newer more effective antibiotic therapy, and readily available intensive care integrated with dialytic support, patients with EPN have much better outcomes. Managing EPN more conservatively has thus become the standard of care.[15] Our approach to patient management is in accordance with current evidence based protocols. The patient was treated with broad spectrum antibiotics, which was subsequently adjusted based on culture results. She received early goal directed therapy for her sepsis. Recent reviews of the management of EPN propose that percutaneous drainage should be part of the initial management strategy for EPN.[16]

The mortality rate of EPN is 60-75% with antibiotic therapy and 21-29% after antibiotic treatment and nephrectomy. When this infection extends into the perinephric space, the mortality rate increases sharply to 80%; the overall mortality is 43%.[17] As the number of case was single, so no mortality was reported in this study.

We attempted to explain this phenomenon by studying the current literature. One large review covering 10 studies on 210 patients with EPN found that the mortality from medical management alone was 50%, medical management combined with emergency nephrectomy was 25%, and medical management combined with percutaneous drainage was 13.5%.[18] Mortality was significantly less in patients undergoing percutaneous drainage compared to other treatments. Of the patients who underwent medical treatment with percutaneous drainage, a small number underwent elective nephrectomy and mortality was 6.6%.[18] Percutaneous drainage should therefore be a part of the initial management strategy for EPN. This strategy is associated with a lower mortality than medical management or emergency nephrectomy. Delayed elective nephrectomy may be eventually required in some patients. The advantages of percutaneous drainage include increased patient stability for subsequent reversal of some of the underlying contributory factors. This in turn then decreases the risk of adverse events should a nephrectomy be eventually needed.

Conclusions:

In our case, surgical procedures were not attained but, aggressive and goal directed approach with methodical clinical evaluation and laboratory support helped to get a better outcome. Due to improvement of medical imaging and newer antibiotics surgical option may be delayed. Our clinical experience and data suggest that early goal directed therapy with IV antibiotics, fluid resuscitation and strict management of DM together can provide viable alternatives to nephrectomies in early stages of EPN. In case of a patient of old age with multiple risk factors where any surgical procedures can initiate another life threating episode to the patient, medical management with cautious monitoring can be an important alternative. More case reports and study will be helpful to develop a proper and complete picture and guideline to manage such cases in different clinical setups.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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College News

College Events:

- International Mother Language Day was observed in Bangladesh Medical College and Hospital on 21st February 2020 at the local premises.
- Bangladesh Medical College and Hospital celebrated 100th birth anniversary of Father of Nation, Bangabandhu Sheikh Mujibur Rahman on 17th March,2020. Following events were organized in this occasion;
  - Complete recitation of Holy Quran followed by dua mahfil and special prayer for Bangabandhu and his family members.
  - A presentation on life history of Bangabandhu including his glorious contribution and a discussion meeting in the Auditorium of BMC.
  - Free treatment of poor patients on 17th March, 2020 in Emergency Dept. of Bangladesh Medical College Hospital.
  - Free treatment for poor patients on 18.03.2020 at the outpatient department of Bangladesh Medical College Hospital.

Seminars:

- Seminar on "Delayed puberty- a disorder in timing?" was held on 15th January, 2020 in BMC. The speaker was Dr. Yasmin Aktar, Consultant, Dept. of Endocrinology, BMCH.
- Seminar on "Pain Management" was held on 4th February, 2020 in BMC. The speakers were: Prof. Dr. Zafor Md. Masud, Professor & Head, dept. of Oncology, BMC and Prof. Dr. Md. Nurul Amin, Professor, dept. of Anesthesia, BMC.
- A seminar on "Novel Corona Virus-(2019-nCoV): A global public health emergency" was held on 13th February, 2020 in BMC. The speaker was Prof. Dr. Nilufar Begum, Professor & Head, dept. of Microbiology, BMC.

Participation in the International Conferences/Seminars/Workshop/ Congress/Meetings:

- Prof. Dr. Mahmood Hasan, Professor & Head, Dept. of Psychiatry, Bangladesh Medical College attended the 72nd Annual National Conference of Indian Psychiatric Society (ANCIPS) 2020, held at Kolkata, India on 22-25 January, 2020.
- Prof. Dr. Md. Zahid Hasan Bhuiyan, Professor, Dept. of Urology, Bangladesh Medical College attended the 53rd Annual Conference Urological Society of India held in India from 23-26 January, 2020.
- Dr. Asma Habib, Assistant Professor, Dept. of Gynae & Obstetrics, Bangladesh Medical College attended the RCOG World Congress 2020 held in Muscat, Oman from 28-30 January,2020.

Obituary:

Prof. SAM Golam Kibria, honorable member of BMSRI, former Chairman of dept. of Urology, BSMMU died from COVID-19 on 5th June,2020 at the age of 74. Members of BMSRI, teachers, doctors, students and staff of BMC and BMCH expressed their deep condolence at the demise of this legendary Professor of health profession in Bangladesh.

New Appointment:

Professor Dr. Paritosh Kumar Ghosh, Head of the department of Pathology, appointed as Principal of Bangladesh Medical College on regular basis on 25th March 2020.

Prepared by:
Shahana Akter Dalia
Sr. Administrative Assistant
Bangladesh Medical College