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Editorial

Deaths due to COVID-19: different aspects of handling and disposal of the bodies

The emergence of a novel human coronavirus, SARS-CoV-2, causing severe respiratory tract infections in humans, is affecting all countries of the world and has become a global health concern. Due to the fact that the COVID-19 pandemic does not discriminate its victims, it is of paramount importance to construct a plan for management of the dead for all suspected or confirmed COVID-19 cases, including the unidentified deceased. Different guidelines and protocols have been proposed based on the fact that the limited information we have acquired about this novel virus.

The Directorate of health services, Bangladesh has improvised procedures and guidelines for management of the dead within the existing regulations in order to achieve a balance between medicolegal requirements and the safety of personnel managing the bodies of the deceased with suspected or confirmed COVID-19 infection; at the site of death, during transport, during postmortem procedures, storage and preparation before and during burial or cremation as well as environmental cleaning and disinfection, involving various agencies in the country.

The Principles of handing the dead bodies should be comprised of:

- Ensuring safety and wellbeing of those involved in managing and handling the dead from COVID-19.
- Ensuring the proper and dignified management of all COVID-19 fatalities with respect for their families and communities.
- Ensuring the reliable documentation, identification and traceability of COVID-19 fatalities to prevent them from being missing persons.
- Ensuring the management of COVID-19 fatalities does not impede medico legal investigation where required by the authorities(e.g. suspicious deaths, deaths in custody)

Standard Precautions for Health Care Worker while handling dead bodies like hand hygiene, use of personal protective equipment (e.g. water resistant apron, gloves, masks, eyewear), safe handling of sharp instruments, disinfecting bag housing dead body; instruments and devices used on patient, disinfecting linen etc. Clean and disinfect environmental surfaces etc. should be practiced rigorously. All the staffs assigned to handle dead bodies in isolation area, mortuary, ambulance and those who works in burial ground/ crematorium should be trained in infection prevention control practices. Mortuary staff handling COVID dead body should observe standard precautions. The dead bodies should be stored in cold chambers maintained at approximately 4°C. Mortuary must be kept clean. Environmental surfaces, instruments and transport trolleys should be properly disinfected with 1% Hypochlorite solution.

During removal of body from isolation room or area, followings need to be ensured:

- Health worker attending dead body should perform hand hygiene; ensure proper use of PPE (water resistant apron, goggles, N95 mask, gloves).
- All tubes, drains and catheters on dead body should be removed.
- Any puncture holes or wounds (resulting from removal of catheter, drains, tubes, or otherwise) should be disinfected with 1% hypochlorite and dressed with impermeable material.
- Apply caution while handling sharps such as intravenous catheters and other sharp devices. They should be disposed into a sharps container.
- Plug oral, nasal orifices of dead body to prevent leakage of body fluids.
- If family of patient wishes to view body at time of removal from isolation room or area, they may be allowed to do so with application of standard precautions.
- Place dead body in leak-proof plastic body bag. Exterior of body bag can be decontaminated with 1% hypochlorite. Body bag can be wrapped with mortuary sheet or sheet provided by the family members.

- Body will be either handed over to relatives or taken to mortuary.
- All used/ soiled linen should be handled with standard precautions, put in bio-hazard bag and outer surface of bag disinfected with hypochlorite solution.
- Used equipment should be autoclaved or decontaminated with disinfectant solutions in accordance with established infection prevention control practices.
- All medical waste must be handled and disposed of in accordance with Biomedical waste management rules.
- Health staff who handled body will remove personal protective equipment and will perform hand hygiene.
- Provide counseling to family members and respect their sentiments.

During transportation, the bodies are to be secured in body bag, exterior of which is decontaminated poses no additional risk to staff transporting dead body. Personnel handling body may follow standard precautions (surgical mask, gloves). The vehicle used for transfer the bodies need to be decontaminated with 1% Sodium Hypochlorite.

The burial Ground/ crematorium staff should be sensitized that COVID-19 does not pose additional risk. But the staffs should practice standard precautions of hand hygiene, use of masks and gloves. Viewing of dead body by unzipping face end of body bag (by the staff using standard precautions) may be allowed, for relatives to see body for one last time. Bathing, hugging etc. of dead body should not be allowed. Large gathering at burial ground/crematorium should be avoided as a social distancing measure as it is possible that close family contacts may be asymptomatic and/or shedding virus. After removing body, chamber door, handles and floor should be cleaned with sodium hypochlorite 1% solution. And embalming of dead body should not be encouraged.

Autopsies on COVID-19 related deaths should be avoided; unless absolutely necessary. If autopsy is required be performed for special reasons, infection prevention control practices should be adopted, like:

- Team should be well trained in infection prevention control practices.
- Number of forensic experts and support staff in autopsy room should be limited.
- Team should use full complement of PPE (coveralls, head cover, shoe cover, N 95 mask, goggles, face shield etc.).
- Round ended scissors should be used
- PM40 or any heavy duty blades with blunted points to be used to reduce prick injuries
- Only one body cavity should be dissected at a time
- Unfixed organs must be held firm on table and sliced with a sponge – care should be taken to protect hand
- Negative pressure to be maintained in mortuary. An oscillator saw with suction extraction of bone aerosol into a removable chamber should be used for sawing skull, otherwise a hand saw with a chain-mail glove may be used
- Needles should not be re-sheathed after fluid sampling – needles and syringes should be placed in a sharps bucket.
- Reduce aerosol generation during autopsy using appropriate techniques especially while handling lung tissue.
- After procedure, body should be disinfected with 1% Sodium Hypochlorite and placed in a body bag, exterior will again be decontaminated with 1% Sodium Hypochlorite solution.
- Body thereafter can be handed over to relatives.
- Autopsy table to be disinfected as per standard protocol.

Forensic disciplines contributes equally in the combat of COVID-19, integrating law and medicine and working closely with police, funeral directors and other related authorities in managing the dead. Issues with storage and decomposition, shortages of staff and appropriately equipped mortuaries and other crippled resources, can cause bodies to accumulate if they are not managed in a timely manner. Improvised procedures and guidelines for the management of large numbers of decedents have to be put in place to handle the increased volume of bodies. There is a need to integrate sufficient legal complexities into the social context as well as the consideration of the safety of personnel managing the dead during this unprecedented time. It is imperative to plan and take every necessary step during this pandemic for the management of the dead in the country as a basic human right.

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Original Article

Radiological Findings in Patients of COVID -19 Positive Cases those Who were Admitted in Mugda Medical College Hospital, Dhaka

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ABSTRACT

Patients with COVID-19 positive cases were admitted in Mugda Medical College Hospital, Dhaka from 20th April 2020. The patients were confirmed by RT- PCR test. Chest X-ray of the patients were done to assess the severity of the disease. In this study all positive cases were tested by x-ray of chest from 1st week of May 2020 to 9thJune 2020. Among 126 cases male were 76(60.3%) and female were 50(39.7%), that means male are affected in larger number than female. The age ranges from 11 years-78 years. The peak age group were between 61-70 years and the next two age group were between 31-40 years & 51-60 years. Among them 79.37% patient have abnormal chest radiograph. According to age group distribution the abnormal chest radiograph found in 25% cases in 0- 20 years age group, 35.29% in 21-30 years age group, 64% in 31-40 years age group, 90.91% in 41-50 years age group, 96% in 51-60 years age group and 100% abnormal chest found in 61-70 and 71-80years age group. Higher number of abnormal chest radiograph are noted in higher age groups. Mild pleural effusion was noted in 04% cases, 12% cases have mild cardiomegaly and 04% cases have evidence of sternotomy. Though 20.63% chest radiograph appear normal that does not mean out of danger but requires follow up.

Key words: *COVID-19, RT- PCR test, SARS-CoV-2, HRCT scan.*

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INTRODUCTION

COVID-19 (coronavirus disease 2019) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first cases were seen in Wuhan, China, in late December 2019 before spreading globally. The current outbreak was officially recognized as a Pandemic by the World health organization (WHO) on 11th March 2020. Definitive diagnosis of COVID -19 requires a positive RT- PCR test. Current best practice advises that CT chest is not used to diagnose COVID -19, but may be helpful in assessing for complications. The non-specific imaging findings are most commonly atypical or organizing pneumonia, often with a bilateral, peripheral, and basal predominant distribution. No effective treatment or vaccine exists currently.[1] Mugda Medical College Hospital, Dhaka was selected as a dedicated COVID hospital in the outbreak of COVID-19 infection in Bangladesh. In our country the disease was mainly transmitted by the immigrant workers or people travelling in COVID -19 affected countries. The first case was diagnosed on 8th March 2020. Mugda Medical College Hospital, Dhaka, started its journey as COVID-19 Hospital on 20th April 2020. Patients with COVID-19 positive cases were admitted in this hospital those who were confirmed by next generation sequencing or RT- PCR test. In this hospital chest X-ray of the patients were

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one of the tools of testing severity of the cases. All positive cases with varying degree of sign & symptoms were also tested by chest x-ray.

Human to human strong transmission of SARS- CoV-2 occurs mainly by respiratory drop-lets, close contacts & contacts with contaminated surface and which enters into the body through mucous membrane of eyes, nose & mouth.

The clinical features of the initial 41 patients confirmed to be infected with SARS- CoV-2 includes lower respiratory tract illness with fever, dry cough and dyspnea [2]. A manifestation similar to those two other diseases caused by coronaviruses severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).[3-4]

We want to evaluate the deadly disease COVID-19 pneumonia by chest x-ray those who attend in the Radiology & Imaging department of Mugda Medical College Hospital, Dhaka.

METHOD & MATERIALS

Type of study: This is a cross sectional descriptive study.

Study area & duration: The study is carried out in the Radiology & Imaging department of Mugda Medical College Hospital, Dhaka from 1st week of May 2020 to 9thJune 2020.

Participants: The participants are confirmed COVID-19 cases, those who are under treatment in this hospital and all cases was confirmed by real-time RT-PCR test done in this hospital and referred cases from other hospitals of Dhaka. Consent of patients are waived due to highly contagious, life threatening infectious character of the disease. Sample of the study is purposive, all COVID-19 positive cases are included without exclusion.

Study tool: - X-ray of chest.

Sample size: 126.

Funding source: There are no funding source for the study.

Variables: Age, sex. Chest x-ray and characterization of x-ray findings.

Acquisition of x-rays: X-ray of Chest are done at patient's convenient time by digital x-ray machine in the Radiology & Imaging department of Mugda Medical College Hospital, Dhaka and printed on appropriate size film.

Image interpretation: X-ray images were interpreted by Assistant professor of Radiology & Imaging having about 18 years' experience and one radiologist of 4 years' experience, those who are working in Radiology & Imaging department of Mugda Medical College Hospital, Dhaka.

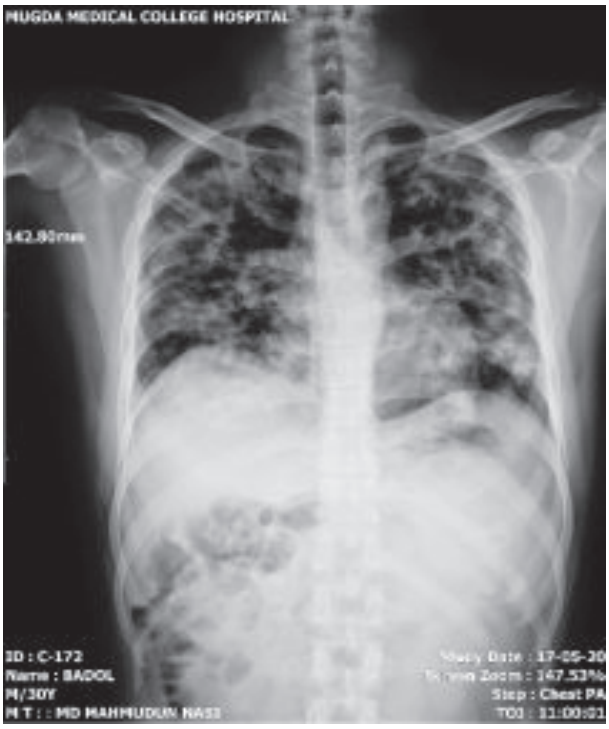

Fig.-1: *Scattered irregular opacities distributed in all zones of both lung fields*

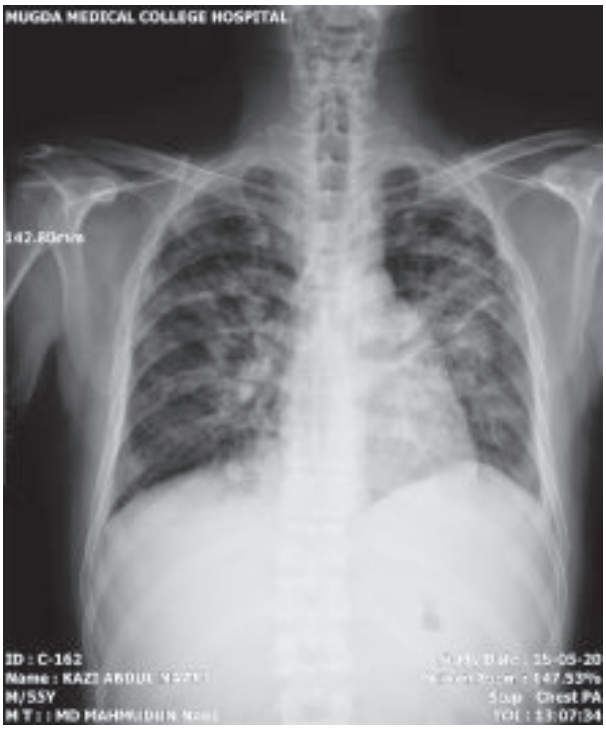

Fig.-2: *Patchy & wooly opacities in all zones of both lungs*

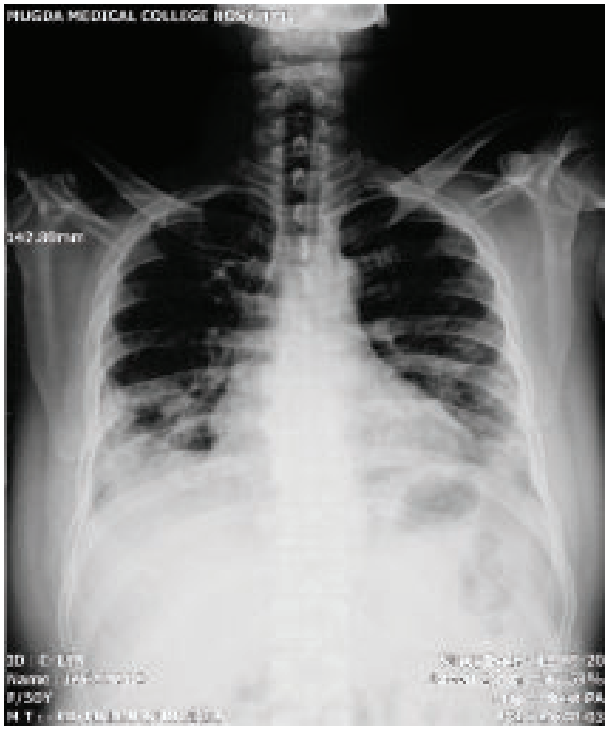

Fig.-3: I*nhomogeneous opacities in mid & lower zones of both lungs with mild cardiomegaly*

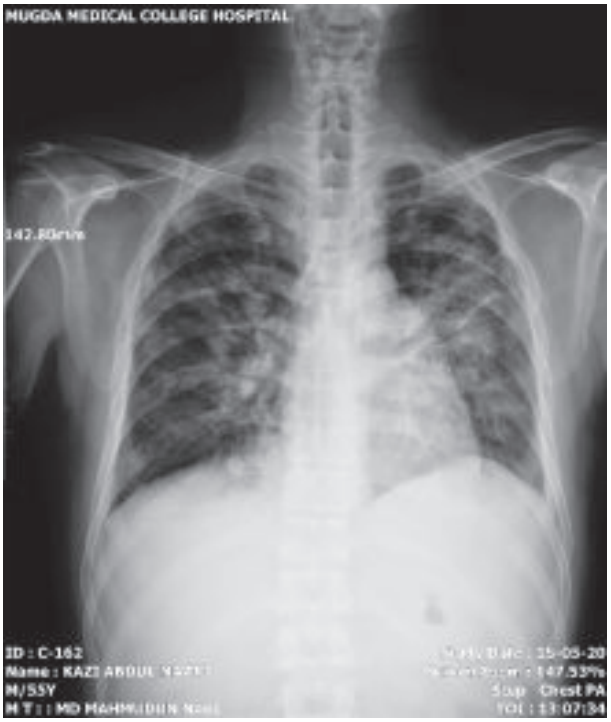

Fig.-4: *Irregular opacities in peripheral sub-pleural regions of both lungs with mild cardiomegaly.*

RESULT

126 patients of confirmed COVID cases are enrolled in this study. The patients come to Radiology & imaging department for chest x-ray from 2nd week of May to 9th June, 2020. The age ranges from 11years-78years Table-I showed. Number of males were 76(60.3%) and female were 50(39.7%) shown in Table-II. The peak age group were between 61-70 years and the next two age group were between 31-40 years & 51-60 years. Among them 79.36% patient have abnormal chest radiograph. According to age distribution abnormal chest radiograph found in 25% in 0- 20 years age group, 35.29% in 21-30 years age group, 64% in 31-40 years age group, 90.91% in 41-50 years age group, 96% in 51-60 years age group and 100% abnormal chest radiograph found in 61-70 and 71-80years age group as shown in Table-III. Both lung involvement was noted in 69% of abnormal chest radiograph. Lung opacities are patchy, wooly, irregular, linear–branching and inhomogeneous type, distribution of opacities was predominantly in mid & lower zones, some had discrete type opacities distributed at lung periphery and in sub-pleural regions. Single lung involvement was noted in 31% cases, among them majority was in left lung (28 out of 31). Mild pleural effusion was noted in 04% cases, 12% cases have mild cardiomegaly and 04% cases have evidence of sternotomy. 20.64% chest radiograph appear normal which is shown in Table-IV, among them majority were female and are in lower age group (17 out of 26) which requires further evaluation. The most common patterns were discrete irregular opacities of peripheral distribution and have a predilection in mid & lower zones with some clear apical regions.

Table I: *Age distribution*

Age Range	No. of Population
0-20	04
21-30	17
31-40	25
41-50	22
51-60	25
61-70	28
71-80	05

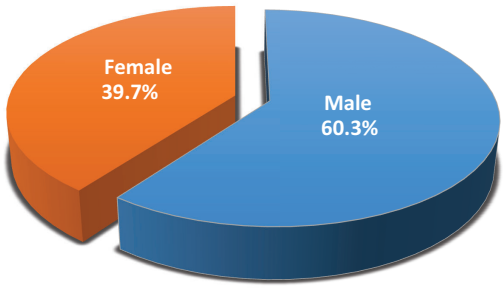

Fig.-5 : *Sex distribution in pie chart*

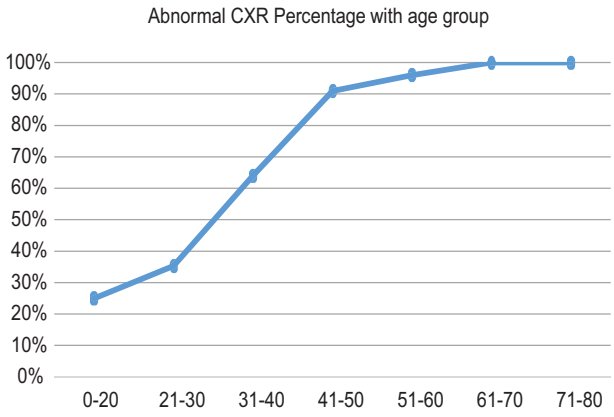

Fig.-6 : *Graphical representation of Abnormal CXR percentage with age group*

Table II : *Pulmonary findings on chest X-ray*

Involvement of lung	Number of patients	Percentage of patient
Both lung parenchyma	69	54.76
Single lung parenchyma	31	24.60
No lung involvement	26	20.64

DISCUSSION

The novel corona virus SARS- CoV-2 is the seventh member of the coronavirus family known to infect humans. It is enveloped RNA virus. The mortality rate of COVID-19 so far lower than that of SARS or MERS corona virus disease; however, SARS-CoV-2 is highly infectious and could be a significant health threat. The *Coronaviridae* family of viruses includes previously known human corona viruses, which are enveloped non segmented positive sense RNA viruses re broadly distributed in human and other nals[5]. Although four of this corona viruses cause nild respiratory symptoms similar to the on cold, epidemics caused by two Corona s SARS-CoV in 2002 and MERS-CoV in 2012, e more than 8000 patients and 1000 patients tively[6-7] with high mortality rate (10% for SARS- nd 37% for MERS-CoV).

Most of the initial cases of corona virus disease 2019(COVID-19), the disease caused by SARS-CoV-2, were epidemiologically linked to exposure to Wuhan's Huanan seafood market, where wild animals are traded.[2-3]

SARS- CoV-2 has been shown to infect human respiratory epithelial cells through an interaction between the viral S protein and the angiotensin converting enzyme 2 receptor on human cells, thus, SARS- CoV-2 possesses a strong capability to infect human.[8] This study shows 79.36% patient have abnormal chest radiograph. There was male preponderance. Lung opacities are noted predominantly in mid & lower zones with some have sub-pleural & peripheral in distribution.

CONFLICT OF INTEREST

There is no conflict of interest only the information produced may help the physicians in management of COVID-19 cases.

CONCLUSION

Chest radiograph of COVID-19 cases have information about approximate involvement of lung parenchyma, areas of distribution with rough estimation of the severity. In this study majority have bilateral lung parenchymal involvement having peripheral and basal distribution with male preponderance.

REFERENCES

1. (Radiopaedia org./articles/ COVID-19-3 by Dr. Daniel J Bell et al. on 9th June 2020)
2. Na Z, Ding Z, Wen W, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497–605
3. Tsang KW, Ho PL, Ooi GC, et al. A cluster of cases of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003; 348: 1977–85.

4. Assiri A, Al-Tawfq JA, Al-Rabeeah AA, et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infect Dis 2013; 13: 752–61.

5. Richman DD, Whitley RJ, Hayden FG, eds. Clinical virology, 4th edn. Washington: ASM Press, 2016

6. de Groot RJ, Baker SC, Baric RS, et al. Middle East respiratory syndrome coronavirus (MERS-CoV): announcement of the Coronavirus Study Group. J Virol 2013; 87: 7790–92.

7. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 2012; 367: 1814–20.

8. Xu X, Chen P, Wang J, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci 2020; published online Jan 21. DOI: 10.1007/s11427-020-1637-5.

Original Article

Phenotypic and Molecular Detection of Extended-spectrum Beta-lactamase among *Pseudomonas Aeruginosa* Isolated from Burn Wound Swab

Sultana S[1], Akter R[2], Naher H[3], Ali MA[4], Rahaman MA[5], Jannat T[6], Uddin N[7], Muhmmod S[8]

ABSTRACT

Pseudomonas aeruginosa *is a Gram negative bacteria causing severe nosocomial infections which are difficult to treat because of resistance to many antimicrobials. Extended spectrum beta lactamase (ESBL) is one of the causes of resistance among* Pseudomonas aeruginosa. *The study was undertaken to determine ESBL producing* Pseudomonas aeruginosa *by phenotypic method and to detect* bla *OXA-10 ESBL gene by molecular method isolated from burn wound swab. A cross sectional observational study was conducted from January, 2016 to December, 2016 among the patients of Burn unit of Mitford Hospital and Dhaka Medical College Hospital. Total 174 burn wound infection cases were taken purposively.* Pseudomonas aeruginosa *were isolated and subjected to antimicrobial susceptibility test by Kirby-Bauer modified disc diffusion technique. ESBL production was detected by CLSI phenotypic confirmatory disc diffusion test (PCDDT) and* bla *OXA-10 ESBL gene was identified by conventional PCR among the phenotypically ESBL producing* Pseudomonas aeruginosa. *Culture of 174 burn wound swab yielded 149 (85.63%) growths. Among 149 growths, 142 (95.3%) were Gram negative bacteria. The most frequent isolates of Gram negative bacteria were found to be* Pseudomonas aeruginosa *75 (52.82%). Phenotypic method detected 40 (53.33%) ESBL producing* Pseudomonas aeruginosa *by CLSI phenotypic confirmatory disc diffusion test and out of them conventional PCR detected 35 (87.5%) positive strains for* bla *OXA-10 ESBL gene. Phenotypically positive ESBL producing* Pseudomonas aeruginosa *showed 100% sensitivity to polymyxin followed by colistin 95%, imipenem 75%, meropenem 57.5%, piperacillin-tazobactam 32.5%, amikacin 12.5%, cefepime 10% and ciprofloxacin 5%. The result of our study suggest that ESBL producing* Pseudomonas aeruginosa *isolates are alarming in our country and it is essential to find out these resistant strains for effective treatment purpose as well as for control of infection.*

***Key words**: Pseudomonas aeruginosa, ESBL, PCDDT, bla OXA-10 gene.*

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INTRODUCTION

Microbial infection is a major cause of morbidity and mortality in hospitalized burn patients. Microorganisms may be originated from patient's own normal flora or may be transferred to the patient's skin surface via contact with contaminated external environmental surfaces, water, fomites, air and the hands of health care workers[1, 2]. About 45% of mortality in burn patients is due to infections[3].

Pseudomonas aeruginosa is the most important, resistant and dangerous organism that causes infection in burn patients[4]. Infection with *P. aeruginosa* in burn patients results in higher mortality rate, antibiotic costs and hospital stay[5, 6]. It is difficult to treat because of development of resistance to many antimicrobials. The resistance to many antimicrobials

is due to low outer membrane permeability, multidrug efflux pumps, production of inducible AmpC chromosomal â-lactamase, production of various plasmid-mediated â-lactamase enzymes like extended-spectrum â-lactamases (ESBL), metallo â-lactamases (MBL)[7, 8].

ESBLs are plasmid mediated enzymes that mediate acquired resistance to extended-spectrum (third generation) cephalosporins and monobactams but do not affect cephamycins or carbapenems[9]. Various Ambler's class A ESBLs such as TEM-, SHV-, PER-, VEB- type and class D ESBL such as OXA- type ESBL have been found in *Pseudomonas aeruginosa*.

Oxacillinase (OXA) ESBLs are belonging to the molecular class D of Ambler's scheme and 2d of functional group under Bush-Jacoby-Medeiros classification scheme[10, 11]. Oxacillinase is named because of having oxacillin hydrolysing abilities, with hydrolysis rates for cloxacillin and oxacillin being greater than 50% that for benzylpenicillin and predominantly found in *Pseudomonas aeruginosa*[12]. Most OXA-type ESBLs derived from OXA-10 (OXA-11, OXA-14, OXA-16 and OXA-17) or OXA-13 (OXA-19 and OXA-28) or to lesser extent from OXA-2 (OXA-15 and OXA-32)[12, 13, 14].

Different phenotypic methods and molecular methods have been suggested for detection of ESBL. Phenotypic methods are double disc synergy test (DDST), CLSI phenotypic confirmatory disc diffusion test (PCDDT), Three dimentional test, E-test ESBL strips, VITEK system. National Committee for Clinical Laboratory Standards (NCCLS) guideline stated that PCDDT is effective method for detection of ESBL[15]. ESBL can be detected also by molecular method by identification of different ESBL genes. OXA-type ESBL genes are common in *Pseudomonas aeruginosa* and most OXA-type ESBLs are the derivatives of OXA-10. The present study was conducted with the aim to isolate *Pseudomonas aeruginosa* from burn wound swab with phenotypic detection of ESBL production by CLSI phenotypic confirmatory disc diffusion test and alongside genotypic detection of *bla* OXA-10 ESBL gene by conventional polymerase chain reaction (PCR).

MATERIALS AND METHODS

Sample size:

This cross sectional observational study was carried out over 1 year from January, 2016 to December, 2016. Ethical clearance was taken from Ethical Review Committee of Sir Salimullah Medical College and Mitford Hospital. Total 174 burn wound infection cases attending the Burn unit of Dhaka Medical College Hospital and Mitford Hospital were taken for the study irrespective of age, sex and antibiotic use. Out of 174 samples, 150 were collected from Dhaka Medical College Hospital and 24 were collected from Mitford Hospital.

Sample collection:

Wound swab samples were collected by sterile cotton tipped swab moistened with sterile saline. During collection, the swab was taken by zigzag pattern by rotating the swab stick across the wound without touching the surrounding wound edge or skin. The specimens were immediately kept in a sterile test tube, capped properly and labelled. Then swabs were transferred to microbiology lab without any delay. Laboratory works were done in the Microbiology department of Sir Salimullah Medical College, Dhaka. Agarose gel electrophoresis was performed in the Microbiology department of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka for visualization of amplified DNA product.

Isolation and identification of *Pseudomonas aeruginosa*:

All wound swabs were inoculated onto Blood agar media and MacConkey agar media and were incubated aerobically at 37°C for 18-24 hours. Pale colonies on MacConkey agar media; Gram-negative bacilli on Gram staining; pink-red slope and butt without production of gas and H_2S on Kligler iron agar (KIA) media; motile, negative for both urease and indole on Motility indole urea (MIU) agar media; positive for both citrate and oxidase test were primarily identified as *Pseudomonas* spp[16]. Suspected *Pseudomonas* spp. were subcultured on Cetrimide agar media and incubated at 37°C for 18-24 hours for confirmation of *Pseudomonas aeruginosa*. Cetrimide agar is a selective media for *Pseudomonas aeruginosa*[17].

Antimicrobial susceptibility test:

Antimicrobial susceptibility test was done on Mueller-Hinton agar (MHA) plate by Kirby-Bauer modified disc diffusion technique according to the CLSI guidelines, 2015[18]. The antibiotics tested were Amikacin (30µg), Imipenem (10µg), Meropenem (10µg), Ceftazidime (30µg), Cefepime (30µg), Ciprofloxacin (5µg), Piperacillin-tazobactam (100/10µg), Aztreonam (30µg), Colistin (10µg) and

Polymyxin B (300 units) from Oxoid Ltd, UK. *Pseudomonas aeruginosa* ATCC 27853 was used as negative control.

Phenotypic detection of ESBL by CLSI phenotypic confirmatory disc diffusion test:

ESBL production was evaluated phenotypically by CLSI phenotypic confirmatory disc diffusion test (PCDDT) according to the CLSI guidelines, 2015[18]. 0.5 McFarland standard of each isolates was spread on MHA plate. Then Ceftazidime (30 µg) and ceftazidime / clavulanic acid (30/10 µg), cefotaxime (30 µg) and cefotaxime / clavulanic acid (30/10 µg) (Himedia Ltd, Mumbai, India) were placed at a distance of 30 mm apart from center to center and then incubated overnight at 37°C. A ≥5 mm increase in zone diameter for either antimicrobial agent combined with clavulanic acid versus the zone diameter of the agent alone inferred the presence of ESBL production (Figure-1).

Figure-1: *CLSI phenotypic confirmatory disc diffusion test shows ESBL production as evidenced by ≥5mm increase zone diameter of ceftazidime / clavulanic acid (CAC) and cefotaxime / clavulanic acid (CEC) as compared with the zone diameter of Ceftazidime (CAZ) and cefotaxime (CTX) alone.*

Molecular detection of *bla* OXA-10 ESBL gene by conventional PCR:

DNA extraction:

Few isolated bacterial colonies were taken from MHA plate, inoculated into a test tube containing Tryptone soy broth and incubated at 37°C for 24 hours. Then it was centrifuged. Supernatant was removed and pellets were transferred into a microcentrifuge tube for DNA extraction. DNA was extracted from bacterial pellets by boiling method[19]. Extracted DNA was used for amplification of DNA with the help of specific primer by PCR for detection of *bla* OXA-10 ESBL gene.

Primer sequence for *bla* OXA-10 ESBL gene[20]:

Primer name	Sequence (5′ to 3′)	Product size
OXA-10 F	5′- ATTATCGGCCTAGAAACTGG -3′	170 bp
OXA-10 R	5′- CTTACTTCGCCAACTTCTCTG -3′	170 bp

DNA amplification:

PCR was carried out in reaction volume of 25µl in a PCR tube containing 12.5 µl commercially prepared master mix consist of dNTP, taq polymerase, $MgCl_2$, PCR buffer and loaded dye; 1 µl forward primer; 1 µl reverse primer; 5 µl extracted DNA and 5.5 µl Nuclease free water (Promega, U.S.A). Amplification for *bla* OXA-10 gene was performed in a PCR thermal cycler according to the following thermal and cycling condition: pre-denaturation at 94°C for 4 minutes; followed by 35 amplification cycles of 94°C for 1 minute, 55°C for 1 minute and 72°C for 1.5 minutes; with a final extension step of 72°C for 5 minutes[20].

Visualization and interpretation of results:

The PCR product for *bla* OXA-10 ESBL gene was analyzed after electrophoresis in 1.5% agarose gel. The agarose gel was observed under UV trans-illuminator for identification of DNA band according to its molecular size by comparing with 100 bp molecular weight marker loaded in a separate lane. Sample showing the presence of corresponding 170 bp DNA band was considered positive for presence of *bla* OXA-10 ESBL gene (Figure-2)

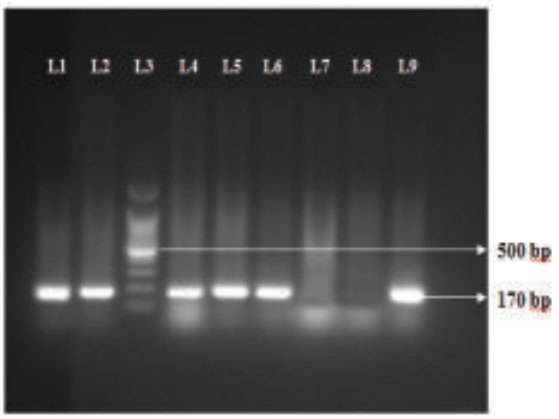

Figure-2 : Amplification of 170 bp of *bla* OXA-10 ESBL gene of *Pseudomonas aeruginosa* Here, Ladder – Lane (L) 3; Negative control – L8; Positive control - L9; Samples detected as positive - L1, 2, 4, 5, 6; Samples detected as negative - L7.

RESULTS

Culture of 174 burn wound swab yielded 149 (85.63%) growths. Among 149 growths, 142 (95.3%) were Gram negative bacteria and 07 (4.7%) were Gram positive bacteria. The most frequent isolates of Gram negative bacteria were found to be *Pseudomonas aeruginosa* 75 (52.82%) followed by *Klebsiella* spp. 24 (16.90%), *Escherichia coli* 14 (9.86%), *Acinetobacter* spp. and *Providencia* spp. 07 (4.93% of each), *Proteus* spp. 05 (3.52%), *Enterobacter* spp. 04 (2.82%), *Citrobacter* spp. 03 (2.11%), other *Pseudomonas* spp. 2 (1.41%) and *Serratia* spp. 01 (0.70%) (Table-I). CLSI phenotypic confirmatory disc diffusion test detected 40 (53.33%) ESBL producing *Pseudomonas aeruginosa* (Table-II). 35 (87.5%) phenotypically positive ESBL producing strains of *Pseudomonas aeruginosa* were positive for *bla* OXA-10 ESBL gene detected by conventional PCR (Table-III). Sensitivity pattern of ESBL producing *Pseudomonas aeruginosa* were to Ciprofloxacin 5%, Cefepime 10%, Amikacin 12.5%, Piperacillin-tazobactam 32.5%, Meropenem 57.5%, Imipenem 75%, Colistin 95% and Polymyxin B 100% (Fig.-3).

Table-I : *Distribution of Gram negative bacteria isolated from burn wound swabs (n=142)*

Isolated bacteria	No (%)
Pseudomonas aeruginosa	75 (52.82%)
Escherichia coli	14 (9.86%)
Klebsiella spp.	24 (16.90%)
Acinetobacter spp.	07 (4.93%)
Proteus spp.	0 5 (3.52%)
Providencia spp.	07 (4.93%)
Enterobacter spp.	04 (2.82%)
Citrobacter spp.	03 (2.11%)
Serratia spp.	01 (0.70%)
Other *Pseudomonas* spp.	02 (1.41%)

Table-II : Result of CLSI phenotypic confirmatory disc diffusion test for phenotypic detection of ESBL among isolated *Pseudomonas aeruginosa* (n=75)

Result	CLSI phenotypic confirmatory disc diffusion test
Positive	40 (53.33%)
Negative	35 (46.67%)

Table-III : *Result of Conventional PCR for bla OXA-10 ESBL gene among phenotypically positive Pseudomonas aeruginosa* (n=40)

Result	*bla* OXA-10 ESBL gene
Positive	35 (87.5%)
Negative	05 (12.5%)

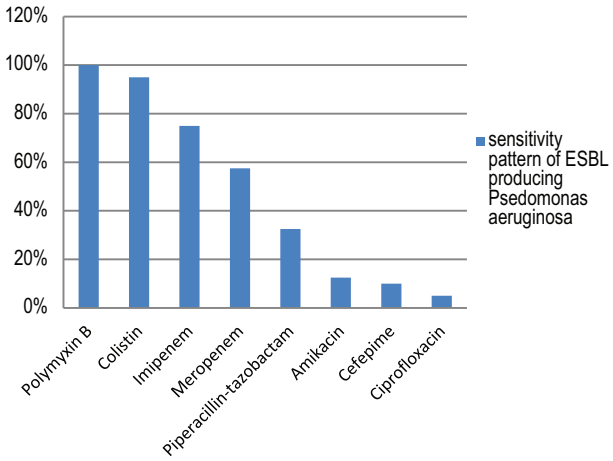

Figure-3 : *Antibiotic sensitivity pattern of phenotypically detected ESBL producing Pseudomonas aeruginosa (n=40).*

DISCUSSION

The study showed that most commonly encountered pathogen among burn patients was *Pseudomonas aeruginosa* 52.82%. A similar observation was made by Farzana (2013)[21] on burn patients in Bangladesh who reported 44.95% *Pseudomonas aeruginosa*. Another study carried out by Rani *et al*. (2016)[22] on burn patients in India found *Pseudomonas aeruginosa* as the maximum isolated pathogen and it was 72.22%.

CLSI phenotypic confirmatory disc diffusion test (PCDDT) detected 53.33% ESBL producing *Pseudomonas aeruginosa*. A study made by Farzana (2013)[21] in Bangladesh reported 43.48% ESBL producing *Pseudomonas aeruginosa* detected by double disc synergy test (DDST). Another study carried out by Begum *et al.* (2013)[23] in Bangladesh detected 37.8% ESBL producing *Pseudomonas aeruginosa* by DDST. Roya *et al.* (2014)[24] reported 39.2% ESBL producing *Pseudomonas aeruginosa* detected by PCDDT in Iran. However, detection of ESBL in AmpC producing Gram negative bacteria is often a problem because of high level expression of AmpC can prevent recognition of ESBL leading to false negative result[25, 26].

PCR is the gold standard method for detection of ESBL producers. In this study, PCR detected 87.5% *bla* OXA-10 ESBL gene among 40 phenotypically positive ESBL producing *Pseudomonas aeruginosa*. A similar observation was made by Farzana *et al.* (2013)[27] who reported 80% *bla* OXA producing *Pseudomonas aeruginosa* in Bangladesh. Another study by Farshadzadeh *et al*. (2014)[28] in Iran reported 68.75% *bla* OXA-10 ESBL gene. Al-Rubaye *et al*. (2015)[20] found 19.4% *bla* OXA-10 ESBL producing *Pseudomonas aeruginosa* in Iraq. This variation might be due to the fact that different regions have different prevalence of resistance determinant genes. Negative strains of *Pseudomonas aeruginosa* for *bla* OXA-10 ESBL gene in our study might be due to presence of other ESBL responsible genes that were not studied in this study.

The study showed sensitivity pattern of ESBL producing *Pseudomonas aeruginosa* were to Ciprofloxacin 5%, Cefepime 10%, Amikacin 12.5%, Piperacillin-tazobactam 32.5%, Meropenem 57.5%, Imipenem 75%, Colistin 95% and Polymyxin B 100%. A study carried by Abedin (2016)[29] in Bangladesh reported colistin sensitive *Pseudomonas aeruginosa* were 91.95%. ESBL producing *Pseudomonas aeruginosa* showed decreased sensitivity to many antibiotics. The cause of resistance may be plasmid of such strain carries resistance genes to different antimicrobials along with ESBL gene[30]. Meropenem, imipenem are stable against extended spectrum beta lactamase and Amp C- beta lactamase[31] and are used as last resort antibiotics for the treatment of severe infection with *Pseudomonas aeruginosa*. However, there has been increasing reports of resistance to this life saving antibiotics in *Pseudomonas aeruginosa*. To overcome this problem, indiscriminate use of antibiotics should be stopped.

CONCLUSION

ESBL producing *Pseudomonas aeruginosa* were found to be frequent isolates in burn wound swab with limited susceptibility to antimicrobials. Decreased susceptibility to broad spectrum antibiotic such as imipenem, meropenem is a great concern as it is the drug of choice in the treatment of severe *Pseudomonas aeruginosa* infection. PCDDT can be used in the laboratory for detection of ESBL as it is easy and inexpensive mehod. The study showed higher rate of presence of *bla* OXA-10 ESBL gene in *Pseudomonas aeruginosa*.

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REFERENCES

1. Weber JM, Sheridan RL, Pasternack MS, Tompkins RG. Nosocomial infections in pediatric patients with burns. Am J Infect Control 1997;25:195–201.
2. Wurtz R, Karajovic M, Dacumos E, Jovanovic B, Hanumadass M. Nosocomial infections in a burn intensive care unit. Burns 1995;21:181–4.
3. Bloemsma GC, Dokter J, Boxma H, Oen IM. Mortality and causes of death in a burn centre. Burns 2008;34:1103–7.
4. Estahbanati HK, Kashani PP, Ghanaatpishels F. Frequency of Pseudomonas aerugunosa serotypes in burn wound infections and their resistance to antibiotics. Burns 2002;28:340-348
5. Aloush V, Navon-Venezia S, Seigman-Igra Y, Cabili S, Carmeli Y. Multidrug-resistant *Pseudomonas aeruginosa*: Risk factors and clinical impact. Antimicrob Agents Chemother 2006;50:43–48.
6. Armour AD, Shankowsky HA, Swanson T, Lee J, Tredget EE. The impact of nosocomially-acquired resistant *Pseudomonas aeruginosa* infection in a burn unit. J Trauma 2007;63:164–71.
7. Poole K. Pseudomonas aeruginosa: resistance to the max. Front Microbiology 2011;2:1-13.
8. Strateva T and Yordanov D. *Pseudomonas aeruginosa* – a phenomenon of bacterial resistance. J Med Microbiol 2009;58(9):1133-48.
9. Centers for Disease Control and Prevention (CDC). Laboratory detection of extended-spectrum â-lactamases (ESBLs), 2010. Available at URL: https://www.cdc.gov
10. Ambler RP. The structure of â-lactamases. Philos Trans R Soc Lond B Sci 1980;289:321-31.
11. Bush K, Jacoby GA and Medeiros AA. A functional classification scheme for â-lactamases and its correlation with molecular structure. Antimicrob Agents Chemother 1995;39(6):1211-33.
12. Naas T and Nordmann P. OXA-type â-lactamases. Curr Pharm Des 1999;5(11):865-879.
13. Hall LM, Livermore DM, Gur D, Akova M and Akalin HE. OXA-11, an extended-spectrum variant of OXA-

10 (PSE-2) â-lactamase from *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 1993;37(8):1637-1644.

14. Toleman MA, Rolston K, Jones RN and Walsh TR. bla_{VIM-7}, an evolutionarily distinct metallo-â-lactamase gene in a *Pseudomonas aeruginosa* isolate from the United States. Antimicrob Agents Chemother 2004;48(1):329-332.

15. David L Paterson and Robert A Bonomo. Extended spectrum beta lactamases: a clinical update. Clin Microbiol Rev 2005;Vol.18, No4: 657-686.

16. Cheesbrough M. Microscopical techniques used in Microbiology, culturing bacterial pathogens, biochemical tests to identify bacteria. In Cheesbrough M, editor. *District Laboratory Practice in Tropical Countries*, Part-2. UK: Cambridge University Press; 2006: p. 65, 67-70, 80-84, 132-143, 180,194.

17. Collee JG and Marr W. Pseudomonas, Stenotrophomonas, Burkholderia. In: Collee JG, Frased AG, Marmion BP, Simons A, eds. Mackie & McCartney Practical Medical Microbiology, 14th ed. USA: Churchill Livingstone, 1996:413-424.

18. Clinical and laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing. Twenty-Fifth Informational Supplement. CLSI document 2015; M100-S25.

19. Ercis S, Sancak B and Hascelik G. A comparison of PCR detection of *mec*A with oxacillin disk susceptibility testing in different media and scepter automated system for both *Staphylococcus aereus* and coagulase-negative *Staphylococci* isolates. Indian Journal Of Medical Microbiology 2008;26(1):21-24.

20. AL-Rubaye DS, Albassam WW, AL-Habobi HM and AL-Rubaye IAHK. Frequency of *blaOxa 10* beta-lactamase gene in *Pseudomonas aeruginosa* isolated from different clinical swab. Iraqi Journal of Science 2015;56(4C):3405-3412.

21. Farzana A. Thesis- Imipenem resistant *bla* NDM1 producing *Pseudomonas* isolated from burn unit of DMCH with their antimicrobial susceptibility pattern and effective combination therapy. Dhaka Medical College, Dhaka; 2013.

22. Rani VS, Rao RK, Ravinder S and Kanakadurga P. Prevalence of extended spectrum beta-lactamase (ESBL) producing *Pseudomonas aeruginosa* isolates from burn patients. International Journal of Contemporary Medical Research 2016;3(5):1297-1300.

23. Begum S, Salam MA, Alam KhF, Begum N, Hassan P, Haq JA. Detection of extended spectrum â-lactamase in Pseudomonas spp. isolated from two tertiary care hospitals in Bangladesh. BMC Research Notes 2013 6:7

24. Rafiee R, Eftekhar F, Tabatabaei SA and Tehrani DM. Prevalence of Extended-spectrum and Metallo â-lactamase production in AmpC â-lactamase producing *Pseudomonas aeruginosa* isolates from burns. Jundishapur J Microbiol 2014;7(9): e16436.

25. Laghawe A, Jaitly N, Thombare V. The Simultaneous Detection of the ESBL and the AmpC â-Lactamases in Gram Negative Bacilli. *J Clin Diag Res* 2012; **6**(4 suppl2): 660 -3

26. Thomson KS. Controversies about extended-spectrum and AmpC beta-lactamases. *Emerg Infect Dis* 2001; **7**(2) : 333 -6

27. Farzana R, Shamsuzzaman SM, Mamun KZ and Shears P. Antimicrobial susceptibility pattern of extended spectrum â-lactamase producing gram-negative bacteria isolated from wound and urine in a tertiary care hospital, Dhaka City, Bangladesh. Southeast Asian J Trop Med Public Health 2013;44(1):96-103.

28. Farshadzadeh Z, Khosravi AD, Alavi SM, Parhizgari N and Hoveizavi H. Spread of extended-spectrum â-lactamase genes of $bla_{OXA-10,}$ bla_{PER-1} and bla_{CTX-M} in *Pseudomonas aeruginosa* strains isolated from burn patients. Burns: Journal of the International Society for Burn Injuries 2014;40(8):1575-1580.

29. Abedin J. Thesis- In vitro and in vivo evaluation of effect of antibiotic combination against imipenem resistant Pseudomonas aeruginosa isolated from burn wound of DMCH. Dhaka Medical College, Dhaka; 2016.

30. Zhao WH and Hu ZQ. â-lactamases identified in clinical isolates of Pseudomonas aeruginosa. Critical Reviews in Microbiology 2010;36(3):245-258.

31. Payne DJ, Bateson JH, Gasson BC, Proctor D, Khusi T, Farmer TH *et al*. Inhibition of metallo-â-lactamases by a series of mercaptoacetic acid thiol ester derivatives. Antimicrob Agents Chemother 1997; 41:135-40.

Original Article

Evaluation of Proton Pump Inhibitor Use among Indoor Patients in Internal Medicine Department in A Tertiary Care Hospital

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ABSTRACT

Gastrointestinal acid related diseases are very common problem in Bangladesh. Current treatment guidelines for acid-related diseases (ARDs) recommend first-line treatment with proton pump inhibitors (PPIs) to reduce gastric acid production. Because of their High efficacy and easy availability irrational use and unnecessary exposure is high. Many drug utilizations studies have reported widespread use of PPIs and that are outside the current prescribing guidelines. The incidence of improper use of PPIs varies from 40% to 70% in various studies. When prescribed in such a large volume the adverse effects, drug interactions and treatment cost increase proportionally. The objective of this study was to assess utilization pattern of PPIs and to evaluate for its rational use. A cross-sectional descriptive study was carried out in a tertiary care teaching hospital for a period of one year, 600 patients were selected as per the inclusion and exclusion criteria and data were collected using standard data entry form. US-FDA guideline, NICE guideline and BNF 74 were used as references for the analysis of these prescriptions. In the study population, Male were found more (53.8 %) than the female (46.2%). The mean age of the study population was 47.9±18.1 years. Anti-ulcerants prescribed were, Proton Pump Inhibitors (PPIs) (90.8%) and H_2 receptor antagonists (9.2%). The most commonly prescribed PPI in this study was Omeprazole (79.5%) followed by Esomeprazole (6.0%), Pantoprazole (5.0%) and Rabeprazole (0.3%). As many as, 50.8% of PPIs were given by parenteral route and the remaining 49.2% by oral route. Approximately 10.3% of the prescribed regimens were considered to be appropriate as they complied with the clinical guidelines. Of them, PPIs were most appropriately being prescribed with Non-Steroidal Anti-inflammatory Drugs (NSAIDS) (78.6%) followed by Peptic ulcer disease (PUD) (14.3%), Gastritis (3.5%), Gastro-esophageal reflux disease (GERD) (1.8%) and Non ulcer disease (NUD) (1.8%). Whereas, the inappropriate use of PPI was revealed in 70.6% of the total prescriptions which were not accepted by the reference guidelines. Moreover, about 19.1% of the prescriptions did not have a clear indication. In this study it was observed that the most of the PPIs were prescribed irrationally without valid indication. So, initiative should be taken immediately to curtail this inappropriate use of Proton Pump Inhibitors.

Keywords: *Evaluation, Proton Pump Inhibitor, acid-related diseases.*

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INTRODUCTION

Acid-peptic diseases include gastro-esophageal reflux disease, peptic ulcer (gastric and duodenal), pathogenic hypersecretory condition (Zollinger-Ellison syndrom) and stress-related mucosal injury. In all these conditions, mucosal erosions or ulceration arise when the caustic effects of aggressive factors (acid, pepsin, bile) overwhelm the defensive factors of the gastrointestinal mucosa (mucus and bicarbonate secretion, prostaglandins, blood flow, and the processes of restitution and regeneration after cellular injury). Over 90% of peptic ulcers are caused by infection with the bacterium Helicobacter pylori or by use of non-steroidal anti-inflammatory drugs (NSAIDs)[1].

There are several treatment options of acid-peptic diseases. Two types of anti-secretory drugs which reduce the gastric HCl are the most important of them - A) H_2 Receptor Antagonists (H_2RAs) - Cimetidine, Ranitidine, Famotidine, and Nizatidine. B) Proton Pump Inhibitors (PPIs) - Omeprazole, Esomeprazole, Lansoprazole, Dexlansoprazole, Rabeprazole, and Pantoprazole[2].

Since the introduction of PPI in the late 1980s, they have demonstrated gastric acid suppression superior to that of H_2RAs. Current treatment guidelines for acid-related diseases (ARDs) recommend first-line treatment with a PPI to reduce gastric acid production. In addition, the PPIs have been found to elicit a relative lack of serious adverse effects or drug interaction[3].

Certain clinical studies stated that PPIs are safe and well tolerated if taken correctly [4]. Because of their high efficacy and easy availability irrational use and unnecessary exposure is high. Many drug utilizations studies have reported widespread use of PPIs and that are outside the current prescribing guidelines[5,6]. The incidence of improper use of PPIs varies from 40-70% in various studies[7]. When prescribed in such a large volume, the adverse effects increase proportionally[8].

Initiation and the continuous use of these drugs without correct indications will result in significant cost to the patient also. Proton pump inhibitors (PPIs) are a major economic burden for the healthcare system in many countries. Concerns have been raised about the increasing costs associated with prescription of these drugs as they are often prescribed for minor symptoms and without clear indications. Studies from the US, Australia and Europe have demonstrated overuse of PPIs in hospitalized patients and in primary care[5,9].

In keeping with the above reflection, it is the time of reappraisal of the appropriate use of PPIs can be useful for both general practitioner and hospital clinician in order to reduce the dangerous overutilization of these drugs. To evaluate the utilization pattern of PPIs, this research was conducted in an inpatient population of Dhaka Medical College Hospital, those were being treated with these drugs.

MATERIALS AND METHODS

This was a descriptive cross sectional study conducted in the in-patient wards of the Internal Medicine Department in Dhaka Medical College Hospital (DMCH), Dhaka for a period of one year from July 2017 to June 2018.The study was approved by institutional ethical review committee. The aim and objectives of this study were explained to the patients. Informed written consent was taken from each patient. They were assured about the confidentiality of the information.

For this study, 600 prescriptions have included from the Internal Medicine Department of Dhaka Medical College Hospital, 200 from each of the selected three units. Consecutive sampling was done in this study according to the inclusion and exclusion criteria. Inclusion criteria includes - patients of either sex aged > 18 years, patients admitted to the Internal Medicine Ward, patients who were prescribed with anti-ulcerants and patients who gave consent. Exclusion criteria includes - patients of either sex aged < 18 years, patients who were not willing to give consent and patients who were not prescribed with Anti-ulcerants.

The study instrument is a self-designed data collection form. The patients' demographics, past and present medical and medication history and other relevant data needed for the study were collected in the form from the treatment-sheets and from direct patient interview. In light of the absence of clear institutional guidelines, the US Food and Drug Administration (USFDA) list of PPI-approved indications, the National Institute for Health and Care Excellence (NICE) guidelines and BNF 74 were considered as references in the assessment of PPIs prescriptions in this study. The evaluation of PPI prescribing was classified into three principal categories, which were "Appropriate," "Inappropriate" and "Unclear". PPI prescription was classified as appropriate when it was done according

to the selected guidelines and it was classified as inappropriate if it was not done in compliance with the guidelines. Finally, the unclear classification was applied to PPIs prescriptions that lack clear justification or indication.

The collected data were analyzed using SPSS software. Descriptive statistics (mean, frequency and percentage) were used to present the findings.

RESULTS

This study was carried out in the three in-patient wards of the Internal Medicine Department in Dhaka Medical College Hospital (DMCH), Dhaka. Total 675 prescriptions in indoor of the internal medicine department were surveyed and of these 600 patients were prescribed with anti-ulcerant. That was 88.9% of the admitted patients in internal medicine department of Dhaka Medical College Hospital were prescribed with anti-ulcerant. The study population consisted of these 600 patients, two hundred from each of the three medicine wards. Out of this 323(53.8%) were males and 277 (46.2%) were females and their mean age was 47.9±18.1 years (Mean ± SD). The highest age group of the study patients was 40-50 years (25.0%).

Anti-ulcerant prescribed with Proton Pump Inhibitors (PPIs) were 90.8% and H_2 receptor antagonists (H_2RA) were 9.2%. Of these Omeprazole was most commonly prescribed PPI 79.5% followed by Esomeprazole 6.0%, Pantoprazole 5.0% and Rabiprazole 0.3%. H_2RAs were Ranitidine and Famotidine. (Table I)

Table I: *Distribution of study patients prescribed with Anti-Ulcerant*

Anti-Ulcerant (n=600)	Frequency	Percentage
PPI	545	90.8
H_2 RA	55	9.2
Total	**600**	**100.0**
PPI (n=545)		
Omeprazole	477	79.5
Esomeprazole	36	6.0
Pantoprazole	30	5.0
Rabeprazole	2	0.3
Total	**545**	**90.8**
H_2RA (n-55)		
Ranitidine	53	8.8
Famotidine	2	0.3
Total	**55**	**9.1**

IV route of administration of PPIs and H_2RA was found to be more which accounts for 50.8% and 72.7% respectively. Oral route of administration was in 49.2% and 27.3% patients respectively. (Table II)

Table-II : *Distribution of Route of administration of Anti-Ulcerant*

Anti- ulcerant	Intravenous	Oral	Total
PPI	277(50.8)	268(49.2)	545(100.0)
H_2RA	40(72.7)	15(27.3)	55(100.0)

*Figures within the parentheses indicate percentage

Majority of the patients were prescribed with PPIs twice daily, 99.5% and only in 0.5% of patients prescribed once daily. (Table III)

Table III : *Distribution of Frequency of administration of Anti-Ulcerant*

Frequency of administration	Frequency	Percentage
Twice daily (BD)	597	99.5
Once daily (OD)	3	0.5
Total	600	100.0

Approximately 10.3% of the prescribed regimens were considered to be appropriate as they complied with the clinical guidelines. Whereas, about 19.1% of the prescriptions did not have a clear indication. Moreover, the inappropriate use of PPI was revealed in 70.6% of the total prescriptions in which PPI prescription were without having any proper valid indications and no justification is available for the prescription of PPI in these types of patients. (Figure 1)

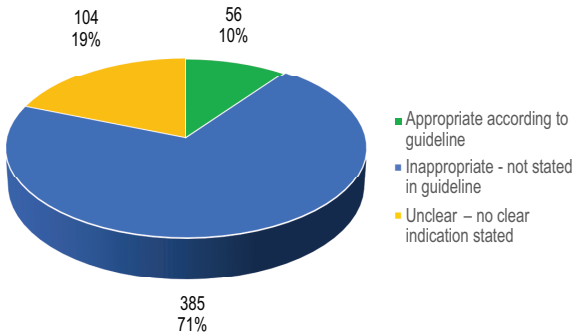

Figure 1: *Distribution of Evaluation of the prescribed PPIs.*

PPIs were most appropriately being prescribed with NSAIDS 78.6% followed by PUD 14.3%, Gastritis 3.5%, GERD 1.8% and NUD 1.8%. (Table IV).

Table IV : *Distribution of Appropriate Indication of prescribed PPIs.*

Indications of PPIs	Number	Percentage
NSAIDS	44	78.6
PUD	8	14.3
Gastritis	2	3.5
GERD	1	1.8
NUD	1	1.8
Total	56	100.0

PUD-Peptic Ulcer Disease, GERD-Gastro-esophageal Reflux Disease, NUD-Non- Ulcer Disease.

DISCUSSION

It was found that 88.8% of admitted patients were prescribed with anti-ulcerant which was similar to the study done in Lebanon (85.0%) by Marwan Sheikh *et al.,* (2012)[10] in USA (71.0%) by Co QD Pham *et al*., (2006)[11] and in Saudi Arabia (53.0%) by Mayet AY (2007)[6].

Among all the Anti-ulcerants prescribed, PPIs were the most common, 90.8% and H_2RAs, 9.2%. In PPIs, Omeprazole was 79.5% followed by Esomeprazole 6.0%, Pantoprazole 5.0% and Rabiprazole 0.3%. In H_2RAs, Ranitidine was 8.8% and Famotidine 0.3%. Similar findings were in study done by Laya Vahdati Rad *et al*., (2016) where PPIs were 91.3% and H_2RA, Ranitidine 8.7%. But in PPIs there were Pantoprazole 55.8%, Rabeprazole 34.05% and Omeprazole 1.45%[12]. Another study conducted by Marwan Sheikh Taha *et al*. in Lebanon revealed PPIs were 95.4% of which Rabeprazole 59.2%, Omeprazole 24.6% & Esomeprazole 11.6% and H_2RA, Ranitidine was 4.6%[10].

The study showed that parental form of PPIs was prescribed more i.e. 50.8% than oral form i.e. 49.2%. This result was in accordance with study conducted by Saurav *et al*. i.e. IV (85.71%) and Oral (14.29%)[13]. But study by Marwan Sheikh *et al.,* (2012) showed 70.8% patients received Anti-ulcerant orally, while 29.2% received it intravenously[10].

Majority of the Patients were prescribed Anti-ulcerant twice daily (BD), 99.5% and only in 0.5% of patients once daily (OD). This result was not in coherence with study conducted by Saurav *et al.,* i.e. OD was found in 60.49% patients and BD was in 31.92% patients[13].

In the absence of the national or institutional guideline, the USFDA list of PPI-approved indications, NICE guideline and BNF 74 were considered as references in the assessment of PPIs prescriptions. In this study, the percentage of appropriate use of PPIs was approximately 10.3% of the total prescriptions. Similar results were observed in studies done by Mohamed Hassan Elnaem *et al*., (2017), 34%[14]; by Nousheen *et al*., (2013), 42 %[15], by Co QD Pham et al., (2006), 36%[11] and by Tze *et al*., (2014) 45.9%[16]. It is noticeable that the reported percentages of appropriate PPI use were not exceeding 50% of the overall number of cases in all reported findings, which indicate the need for more effort towards optimizing the use of PPIs in the hospital setting.

It is reported in the study that 70.6% of the inpatients were prescribed with PPIs inappropriately, which were not accepted by USFDA guideline, NICE guideline and BNF 74. This irrational usage of PPIs increases the Adverse Drug Reaction, Drug interaction and health care cost proportionately. The finding affirmed previous study that revealed a higher percentage of the inappropriate prescriptions of PPIs among hospitalized patients, 64% by Co QD Pham et al., (2006)[11] and 58% by Nousheen *et al*., (2013)[15].

The major issue discovered by this study was, nearly 19.1% of all PPIs prescription were found to have no clear indication which was due to poor documentation. Similar findings were reported, 31.4% in Mohamed Hassan Elnaem *et al*., 2017[14] and in nearly 37% in Saurav *et al*., 2017[13].

From this study, it was evident that PPIs were mostly prescribed with NSAIDs 78.6%, followed by PUD 14.3%, Gastritis 3.5%, GERD 1.8% and NUD 1.8%. This result supported the study done by Blesson Mathew *et al*, revealed PPI was most commonly prescribed along with NSAIDs (38.60%) followed by Polypharmacy (21.22%), APD (14.38%), GERD (12.67%) and PUD (13.10%)[17]. But in the retrospective chart review by Marsha Dangler *et al.,* revealed that the most common indication for PPI use was GERD (55%), then duodenal ulcer, dyspepsia, heartburn, gastritis, GI bleed, abdominal pain and gastric ulcer[18].

CONCLUSION

On the basis of the study findings, the most of PPIs were prescribed inappropriately without having valid indication and do not comply with the reference guidelines- USFDA guideline, NICE guideline and BNF-74. This unnecessary use of PPIs can increase cost, drug interactions and adverse events. The results of our study highlight the need for interventions, including implementation of institutional protocol and prescriber education.

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REFERENCES

1. BG Katzung, AJ Trevor. Basic and Clinical Pharmacology. 13th Edn. New Delhi:McGraw Hill Education (India) Pvt Ltd. 2015; pp.1052.
2. Padmaja Uday kumar. Medical Pharmacology. 5th edn. New Delhi: CBS Publisher and Distributor Pvt Ltd. 2017; pp.399.
3. Chong E, Ensom MHH. Pharmacogenetics of the proton pump inhibitors: a systematic review. Pharmacotherapy. 2003; 23, pp.460-471.
4. Atkins AM, and Sekar C. Proton pump inhibitors: Their misuse, overuse, and abuse. Iosr Journal of Pharmacy. 2013; 3(2), pp.25-29
5. Naunton M, Peterson GM, Bleasel MD. Overuse of proton pump inhibitors. Journal of Clinical Pharmacy and Therapeutics. 2000; 25(5), pp.333-340.
6. Mayet AY. Improper use of antisecretory drugs in tertiary care teaching hospital: An observational study. The Saudi Journal of Gastroenterology. 2007; 13(3), pp.124-128.
7. Sandozi T.A. Comparative Study of Cost Analysis of H_2 Antagonists and Proton Pump Inhibitors in a Tertiary Care Hospital. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2013; 4(1), pp.888-897.
8. Heidelbaugh JJ, Kim AH, Chang R, Walker PC. Overutilization of proton-pump inhibitors: what the clinician needs to know. Therapeutic Advances in Gastroenterology. 2012; 5(4), pp.219-232.
9. Bashford JN, Norwood J, Chapman SR. Why are patients prescribed proton pump inhibitors? Retrospective analysis of link between morbidity and prescribing in the General Practice Research Database. British Medical Journal. 1998; 317, pp.452–456.
10. Marwan Sheikh-Taha, Sarah Alaeddine, Julie Nassif. Use of acid suppressive therapy in hospitalized non-critically ill patients. World Journal of Gastrointestinal Pharmacology and Therapeutics. 2012; 3(6), pp.93-96.
11. Co QD Pham, Randolph E Regal, Thomas R Bostwick, and Kara S Knauf. Acid Suppressive Therapy Use on an Inpatient Internal Medicine Service. Annals of Pharmacotherapy. 2006; 40, pp.1261-1266.
12. Laya Vahdati Rad, Divakar Goli, Binai K Sankar, Shiva Kumar. Evaluation of the use of PPIs and H_2 receptor blockers in inpatient department of general medicine in a teaching hospital in Bengaluru. Journal of Innovations in Pharmaceuticals and Biological Sciences. 2016; 3(2), pp.134-140.
13. Saurav Khanal, Kiana Karamifard, Tenzin Choeku, Ms. Safna Mariyam, Dr. Srinivasa K V. Drug Utilization Evaluation of Proton Pump Inhibitors in General Medicine Department of a Tertiary Care Teaching Hospital. Journal of Biomedical and Pharmaceutical Researc. 2017; 6(4), pp.79-90.
14. Mohamed Hassan Elnaem, Mohamad Haniki Nik Mohamed, AmirulHazim bin Nazar,Rabiatul Nur Khaliesabinti Ibrahim. Evaluation of Proton Pump Inhibitors Prescribing among Non-Critically Ill Hospitalized Patients in a Malaysian Tertiary Hospital. Journal of Applied Pharmaceutical Science. 2017; 7 (12), pp.077-083.
15. Nousheen, Tadvi NA, Shareef SM. Use of proton pump inhibitors in general practice: is it rationale. International Journal of Medical Research & Health Sciences. 2013; 3(1), pp.37-42.
16. Tze C, Chia W, Lim WP, Kien C, Vu F. Inappropriate use of proton pump inhibitors in a local setting. Singapore Medical Journal. 2014; 55, pp.363– 366.
17. Blesson Mathew, Jibin Mathew, Y Kanthi Kiran, Geethu C, Shalin Elsy Varghese, T Irene Ivan, Dona Kurian, T R Ashok Kumar. Study and assessment of appropriateness in the usage of proton pump inhibitors in a tertiary care teaching hospital in south india. Indo-American Journal of Pharmaceutical Research. 2015; 5(09), pp.2849-2856.
18. Marsha Dangler, Leslie Ochs, and Robyn White. Assessing the Appropriate Use of Proton Pump Inhibitors in a Veteran Outpatient Population. Federal Practitioner. 2013; 30(5), pp.21-25.

Original Article

Psychological Impact among Population due to COVID 19 Outbreak in Bangladesh

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ABSTRACT

COVID-19 outbreak is affecting a vast population around the world since it's' onset in the latter part of 2019. The infection has become a pandemic despite different preventive measures taken by countries and organizations. Bangladesh too has been affected by the infectious disease and this is aim to predict the psychological impact of COVID-19 pandemic on Bangladeshi population. Psychosocial impact is described as the effect caused by environmental and/or biological factors on individual's social and/or psychological aspects. Affected persons are more susceptible to develop stress and other mental problems like anxiety, depression because of strenuous social distancing and diverse environment. It is important for the mental health workers to stay ready for psychiatry sequel of the outbreak. Appropriate psychological inter-ventions should be carefully planned to suite the affected and vulnerable individuals. This online survey by Google form was carried among 1056 adult male and female from April 2020 to June 2020 in all over the country. Data were collected by duly pretested a semi-structured questionnaire and DASS 21. This questions were inserted into Google form which was created through Gmail. Data were analyzed by using Statistical Package for Social Sciences (SPSS), version 20. The study revealed that, most of the respondents (57.1%) were residing in the age group of 21-30 years and the mean age of the respondents was 29.98 years among them 50% were male and 50% were female. About 45.7 % completed master level of education, most (89.8%) of the respondents were Muslim, one third (31.3%) were doctor and 74.4% were living in nuclear family. Most of the respondents (73.6%) lived in divisional city and 33.8% of the respondents had income less than BDT 20,000 in a month and the mean monthly income was BDT 32,529.41. It also revealed 525 (49.71%) had depression, 636 (60.22%) had anxiety and 471 (44.60%) suffered from stress. In depression, 159 (14.8%), 198 (18.4%), 75 (7%) and 93 (9.7%) of the respondents have mild, moderate, severe and extremely severe depression respectively. In anxiety, 111 (10.3%) have mild, 258 (24%) have moderate, 105 (9.7%) severe and 162 (15.9%) have extremely severe anxiety. For stress, mild level of stress consists of 144 (13.4%) followed by 150 (13.9%) moderate level of stress, 108 (10.0%) severe level of stress and 69 (7.5%) extremely severe level of stress. A significant association was found between all socio demographic variables with depression, all socio demographic variables with anxiety except educational qualification and all socio demographic variables with stress except age. The study findings demand an intensified effort should be made towards creating awareness about the mental health status and solved this to improve the quality of life.

Key words: *Psychological impact, COVID 19, DASS 21, Bangladeshi population.*

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INTRODUCTION

Cases of pneumonia of unknown origin were reported to the World Health Organization (WHO) on December 31, 2019 in Hubei province in China. A new type of coronavirus (SARS-CoV-2) was isolated from infected patients, characterizing the appearance of a new pathology, later called COVID-19 [1]. It was declared a Public Health Emergency of International Concern on 30th January 2020 [2]. "Novel coronavirus" was the initial term given for this brand-new virus creating havoc on the unprepared communities. Later, it was officially named as COVID-19 by WHO considering many different aspects [3]. The WHO on 11th March 2020 declared COVID-19 a pandemic, emphasizing over 118,000 cases of the condition in more than 110 countries and territories around the world, and the worsening risk of further global spread [4].

China initiated measures to contain the epidemic with the closure of the Wuhan Wet Market, which was identified as the first place of COVID-19 spread on January 1, 2020 [5]. The spread of the epidemic and the confirmation of human-to-human transmissibility led to the lockdown of the Wuhan city on January 23. This measure resulted in travel restrictions to and from Wuhan [6]. Public places such as schools and universities were closed and mass gatherings were prohibited [7]. There is a relative consensus on the use of individual protection measures as these measures have a low capacity to cause damage to health and the economy [8]. Social distancing measures for patients with respiratory infections or symptoms show evidence of effectiveness in controlling the spread of respiratory disease epidemics and, therefore, should be used as a way to reduce the spread of the epidemic. More comprehensive social distancing measures, such as temporary suspension of school activities, events involving large crowds, or closing borders, are also recommended in specific situations, despite the lack of evidence of effectiveness [8].

Strict social distancing measures were adopted and outside activities were extremely limited to reinforce home quarantine. These measures were followed by actions to reduce mobility and mass gatherings across China, using different strategies based on the epidemic situation in each region [7]. Despite these measures, there was an increase in cases and deaths by COVID-19 in China, especially in Hubei province. In early February, community transmission outside of China was confirmed, starting a new phase of expansion of COVID-19 that has culminated in the current pandemic situation [9].

Patients with COVID-19 found to have fear, boredom, loneliness, anxiety, insomnia and anger and they had worries about quarantine and contagion of family members and friends. They also experienced emotional difficulties and anxiety related to uncertainty and stigmatization. Countries, organizations and individuals have taken many different measures to curb this dangerous situation. World Health Organization has instructed the public to adhere to health measures such as staying home when sick, covering mouth and nose with flexed elbow or tissue when coughing or sneezing, Disposal of used tissue immediately, washing hands often with soap and water and cleaning touched surfaces and objects frequently [10]. Countries have taken stringent actions such as locking down areas, imposing curfew, travel restrictions and social distancing. Self-quarantine and quarantine in centers is in place to prevent further spread of the disease from an infected personnel. Testing facilities and hospital capacity have been promptly improved to identify and treat affected patients. Health staff is working 24/7 to manage patients. Many governments are expecting an economic breakdown and unemployment within a short period of time. If a person is economically not stable, it is very usual that the person will go through some mental health problems. For this reason, it is very obvious to know the psychological impact of lockdown due to COVID 19.

COVID-19 pandemic in Bangladesh:

The virus was confirmed to have spread to Bangladesh in March 2020. The first three known cases were reported on 8 March 2020 by the country's epidemiology institute, Institute of epidemiology, disease control and research IEDCR [11]. Infections remained low until the end of March but saw a steep rise in April [12]. In the week ending on 11 April, new cases in Bangladesh grew by 1,155 percent, the highest in Asia, ahead of Indonesia, with 186 percent [13]. As of 20 September 2020, there have been a total of 3,48,916 confirmed cases in the country, with 2,56,565 recoveries and 4,939 deaths [14].

METHODS

This online survey by Google form was carried among 1056 adult male and female who knows to use social media from April 2020 to June 2020 in all over the country. Data were collected by duly pretested a semi-structured questionnaire and DASS 21. DASS 21 (Depression, Anxiety and Stress Scale 21) is a

recognized tool for screening of psychological state. This reliable instrument has 21 items in three domains. Each domain comprises of seven items assessing three dimensions of mental health symptoms: depression, anxiety and stress. Respondents were required to indicate the presence of these symptom(s) over the past week on a four-point Likert scale scoring from 0 to 3. Then this questions were inserted into the Google form which was created through Gmail. This Gmail attached questionnaire, send to the person through Mail, Messenger, WhatsApp, Imo and Viber. Then the answer script with consent received through Mail. All the respondents are free from any psychological state. They have no evidence to taken any drug for depression, anxiety and stress. Then the data were entered into the Statistical Package for Social Sciences (SPSS) statistical software version 20 for the analysis and presented in the form of tables and graphs accordingly.

RESULTS

Table I: *Distribution of respondents by socio-demographic characteristics (n=1056)*

Variables	Sub-variables	Number of respondents	Percentage of respondents
Age	≥20	15 (1.4)	1.4
	21-30	603 (57.1)	57.1
	31-40	312 (29.5)	29.5
	41-50	87 (8.2)	8.2
	51-60	15 (1.4)	1.4
	61-70	18 (1.7)	1.7
	>70	06 (0.6)	0.6
Gender	Male	528 (50)	50
	Female	528 (50)	50
Educational qualification	Primary	03 (0.3)	0.3
	Secondary	81 (7.7)	7.7
	Diploma	09 (0.9)	0.9
	Honors	465 (44.0)	44.0
	Masters	483 (45.7)	45.7
	Doctorate (PhD)	15 (1.4)	1.4
Religion	Islam	948 (89.8)	89.8
	Hindu	96 (9.1)	9.1
	Christian	03 (0.3)	0.3
	Others	09 (0.9)	0.9
Occupation	Student	282 (26.7)	26.7
	Doctor	330 (31.3)	31.3
	Private service	288 (27.3)	27.3
	Government service	45 (4.3)	4.3
	Housewife	45 (4.3)	4.3
	Businessman	30 (2.8)	2.8
	Others	36 (3.4)	3.4
Family type	Nuclear family	786 (74.4)	74.4
	Joint family	270 (25.6)	25.6
Area of residence	Village	24 (2.3)	2.3
	Upazilla	75 (7.1)	7.1
	District town	180 (17.0)	17.0
	Divisional city	777 (73.6)	73.6
Monthly income in BDT	<20,000	357 (33.8)	33.8
	20,001-40,000	258 (24.4)	24.4
	40,001-60,000	153 (14.5)	14.5
	60,001-80,000	99 (9.4)	9.4
	80,001-1,00,000	60 (5.7)	5.7
	>1,00,000	129 (12.2)	12.2

Table I shows, most of the respondents (57.1%) were residing in the age group of 21-30 years and the mean age of the respondents was 29.98 years among them 50% were male and 50% were female. 45.7 % completed master level of education and only 1.4% completed doctorate (PhD). Most (89.8%) of the respondents were Muslim, one third (31.3%) were doctor, about 74.4% were living in nuclear family. Most of the respondents (73.6%) lived in divisional city and 33.8% of the respondents had income less than BDT 20,000 in a month and the mean monthly income was BDT 32,529.41.

Figure 1 shows, in depression status 531 (50.28%) showed no evidence of depression while 525 (49.71%) had depression. For anxiety status 420 (39.77%) of the respondents were free from it while the rest 636 (60.22%) had anxiety. In stress status 585 (55.39%) did not have stress while 471 (44.60%) suffered from stress.

Table II shows, in depression, among 525 (49.71%) respondents, 159 (14.8%), 198 (18.4%), 75 (7%) and 93 (9.7%) of the respondents have mild, moderate, severe and extremely severe depression respectively. In anxiety, among 636 (60.22%) respondents, 111 (10.3%) have mild, 258 (24%) have moderate, 105 (9.7%) severe and 162 (15.9%) have extremely severe anxiety. For stress, among 471 (44.60%) respondents, mild level of stress consists of 144 (13.4%) followed by 150 (13.9%) moderate level of stress, 108 (10.0%) severe level of stress and 69 (7.5%) extremely severe level of stress.

Level of depression, anxiety and stress

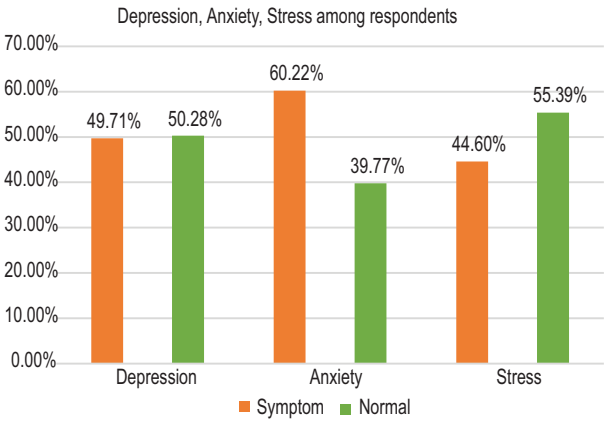

Figure 1: *Bar diagram showing distribution of respondent by level of depression, anxiety and stress (n= 1056)*

Table III shows, in depression status, a significant association was found between all socio demographic variables with depression. For anxiety status, a significant association was found between all socio demographic variables with anxiety except educational qualification. In stress status, a significant association was found between all socio demographic variables with stress except age.

Table-II: *Distribution of respondents by severity level of depression, anxiety and stress according to DASS 21 (n= 1056)*

DASS 21	Depression		Anxiety		Stress	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
Mild	159	14.8	111	10.3	144	13.4
Moderate	198	18.4	258	24.0	150	13.9
Severe	75	7.0	105	9.7	108	10.0
Extremelysevere	93	9.7	162	15.9	69	7.5
Total	525	49.71%	636	60.22%	471	44.60%

Table-III: *Association between socio-demographic characteristics with Depression, Anxiety and Stress (n=1056)*

Variables	P Value		
	Depression	Anxiety	Stress
Age	0.001	0.001	0.095
Gender	0.014	0.001	0.001
Educational qualification	0.001	0.137	0.001
Religion	0.001	0.001	0.037
Occupation	0.001	0.001	0.001
Family type	0.001	0.001	0.001
Area of residence	0.001	0.001	0.001
Monthly income in BDT	0.001	0.001	0.001

DISCUSSION

The study reveals that about 36.61% respondents were found in the age of 21-30 years and the mean age of the respondents was 29.98 years among them 50% were male and 50% were female. The majority of the respondents, about 89.8% of the respondents were Muslim and 45.7 % completed master level of education. One third (31.3%) were doctors and most of the respondents (73.6%) lived in divisional city. Regarding family type, 74.4% were from nuclear families. However, about 33.8% respondents had monthly income <20000 BDT. In depression status 531 (50.28%) showed no evidence of depression while 525 (49.71%) had depression. For anxiety status 420 (39.77%) of the respondents were free from it while the rest 636 (60.22%) had anxiety. In stress status 585 (55.39%) did not have stress while 471 (44.60%) suffered from stress. This mental health status corresponds to another study in Sri Lanka[15]. In depression, among 525 (49.71%) respondents, 159 (14.8%), 198 (18.4%), 75 (7%) and 93 (9.7%) of the respondents have mild, moderate, severe and extremely severe depression respectively. In anxiety, among 636 (60.22%) respondents, 111 (10.3%) have mild, 258 (24%) have moderate, 105 (9.7%) severe and 162 (15.9%) have extremely severe anxiety. For stress, among 471 (44.60%) respondents, mild level of stress consists of 144 (13.4%) followed by 150 (13.9%) moderate level of stress, 108 (10.0%) severe level of stress and 69 (7.5%) extremely severe level of stress. This severity status almost corresponds to another study in China [16]. Statistically no significant association was found between age with stress and educational qualification with anxiety.

CONCLUSION

COVID 19 has several effects on different dimensions of mental health. The effect of COVID 19 cause stress and can lead to anxiety, depression and other psychological and physical illnesses and also cause social abnormalities. The study findings revealed, the psychological impact was higher in the age group of 21-30 years where male and female were affected similarly. The impact was higher in doctor and Muslim population. Most of them were living in nuclear families and a resident of divisional city. Almost half of the respondents were evidences of depression, anxiety and stress. The findings of this study will help in better understanding of mental health status among the Bangladeshi population. Further research should have carried out to find out the reason and psychological interventions among them.

RECOMMENDATION

On the basis of study findings, we have some recommendations that are, implication of psychological care, especially among doctor professional. Reinforce the psychologist and health care professionals to look for mental distress. Supervised psychological interventions considered as an integral part in the management of COVID 19 and increasing awareness of available services for investigations and treatment.

CONFLICT OF INTEREST: None.

REFERENCES

1. Guan WJ, Ni ZY, Hu Y. Clinical Characteristics of Coronavirus Disease 2019 in China N Engl J Med doi: 10.1056. NEJMoa2002032. 2020.
2. Shigemura J, Ursano RJ, Morganstein JC, Kurosawa M, Benedek DM. Public responses to the novel 2019 coronavirus (2019 nCoV) in Japan: Mental health consequences and target populations. Psychiatry and clinical neurosciences. 2020 Apr;74(4):281.
3. Zapata G. Social Economics, Health & Science, Politics & Government. Geopolitics. 2020 May 11.
4. Casale S, Flett GL. Interpersonally-based fears during the covid-19 pandemic: reflections on the fear of missing out and the fear of not mattering constructs. Clinical Neuropsychiatry. 2020 Apr 1;17(2).
5. World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). [Internet]. 2020 [cited 2020 May]. Avaliable from: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf
6. Kucharski AJ, Russell TW, Diamond C, et al. Early dynamics of transmission and control of COVID-19: a mathematical modelling study. Lancet Infect Dis 2020; published online March 11. https://doi.org/10.1016/S1473-3099(20)30144-4
7. Lau, H, Lau H, Khosrawipour V, Kocbach P, Mikolajczyk A, Schubert J, Bania J, et al. The positive impact of lockdown in Wuhan on containing the COVID-19 outbreak in China. J Travel Med [Internet]. 2020;001(714). Available from: http://www.ncbi.nlm.nih.gov/pubmed/32181488
8. European Centre for Disease Prevention and Control. Guidelines for the use of non-pharmaceutical measures to delay and mitigate the impact of 2019-nCoV. ECDC: Stockholm; 2020.
9. World Health Organization. Coronavirus disease 2019 (COVID-19). Situation report 12. February 01,

2020. Geneva: World Health Organization, 2020. [Internet]. 2020 [cited 2020 Mar 21]. Avaliable from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200201-sitrep-12-ncov.pdf?sfvrsn=273c5d35_2

10. World Health Organization. www.who.int/emergencies
11. *"Bangladesh confirms its first three cases of coronavirus". Reuters. 8 March 2020. Archived from the original on 27 March 2020. Retrieved 27 March 2020.*
12. 20-fold rise in Covid-19 cases in Bangladesh since April 1, Dhaka Tribune, 14 April 2020.
13. Mint Covid Tracker: India's corona trajectory has tapered this week but still remains steeper than Asian peers, livemint, 11 April 2020.
14. *Research (IEDCR), Institute of Epidemiology, Disease Control and. করোনা ইনফো. corona.gov.bd (in Bengali).*
15. R ajapakse RP. Foreseeable psychological impact of COVID 19 in Sri Lanka.
16. Wang C, Pan R, Wan X, Tan Y, Xu L, Ho CS, Ho RC. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. International

Original Article

Effectiveness of Metformin-Based Dual Combination Therapies with Sulphonylurea or DPP-4 Inhibitor in Type-2 Diabetic Patients

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ABSTRACT

*The pathophysiology of Type-2 diabetes is mainly focused on insulin resistance and insulin deficiency due to decrease in beta cell mass over time. Metformin is now established as first line monotherapy for treatment of Type-2 diabetes. Patients having uncontrolled diabetes with Metformin, needs to add a second drug which is yet to be established. This type of study compared to glycemic effectiveness of Metformin based dual combination therapies with Sulphonylurea or DPP-4 inhibitor in Type-2 diabetes patients according to baseline HbA1c. This prospective observational study was conducted in three diabetic centers in Dhaka and Tongi over a period of one year, in which 70 Type-2 diabetic patients were selected as per inclusion and exclusion criteria having HbA1c >7.5% to 10%. Subjects were divided into two groups based on the agent combined with Metformin. In **group I** (n= 35) Metformin (500mg) plus Sulphonylurea (gliclazide, 80mg) bid and **group II** (n=35) Metformin (500mg) plus DPP4-inhibitor (vildagliptin, 50mg) bid; HbA1c, FBS, 2-hours ABF were measured initially as baseline and again 12 weeks after treatment in both groups. After 12 weeks of treatment, mean HbA1c decreased significantly from 7.8 ± 0.06% to 6.5 ±0.4% in group I and from 7.9±1.1% to 6.4±0.5% in group II. Both group fulfilled the target of control (HbA1c <7%), but there were no significant differences in the magnitude of HbA1c change among the groups. The two dual therapies using a combination of Metformin and Sulphonylurea or DPP-4 inhibitor showed similar glycemic effectiveness in type-2 diabetic patients. So Sulphonylurea or DPP-4 inhibitor can be used as second line drug with Metformin as add-on therapy.*

***Keyword**: Type-2 diabetes mellitus, Glycated hemoglobin (HbA1c), fasting blood glucose (FBG), blood glucose 2-hours after breakfast (2-hours ABF).*

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INTRODUCTION

Diabetes mellitus is a metabolic disease characterized by hyperglycemic condition resulting from defects in insulin secretion, insulin action or both. Symptoms of hyperglycemia include polyuria, polydipsia, polyphagia, weight loss and blurred vision. Complications of diabetes include retinopathy, nephropathy and peripheral neuropathy. Patients with diabetes have an increased risk of atherosclerotic, cardiovascular, peripheral arterial and cerebrovascular disease.[1] About 425 million people have diabetes in the world and prevalence rate was 8.8% among them 82 million people were from South East Asia. The prevalence of diabetes type-2 is increasing both in urban and rural areas of Bangladesh and they are in the risk of developing diabetes complications early.[2]

Genetic factor and life style have great impact in developing Type-2 diabetes mellitus such as obesity, sedentary life style, physical inactivity, smoking and alcohol consumption.[3] Dietary and life style modification are the first approach to maintain optimum glycemic control. Oral anti-diabetic agents are good options to control Type-2 diabetes for more patient's compliance and are used on the basis of effectiveness, cost and risk of hypoglycemia, weight gain and patient's preference.[4]. In 2012, IDF recommends to keep HbA1c below 7% to improve life expectancy[5, 6]. Initial combination therapy is recommended when HbA1c >8%[7]. The benefits of early combination therapy include reduction of glucotoxicity to cell through early normalization of blood glucose and to avoid diabetes related complications[7, 8].

Metformin is established as first line monotherapy which reduced hepatic glucose production also increasing uptake and utilization of glucose in tissues and improves insulin sensitivity in Type-2 diabetic patients. Metformin does not cause weight gain and hypoglycemia. Sulphonylurea had been using as second line drug as add on with Metformin. It lowers blood glucose concentration by about 20% and HbA_1c by 1 to 2%: but their use entails a greater risk of hypoglycemia and of undesired weight gain, averaging approximately 2 kg[9]. They also increase workload of pancreatic beta cells and cause beta cell exhausted to secrete insulin. But the newer drug DPP-4 inhibitors combination contributes to effective glycemic control, weight neutrality and reduced hypoglycemia[4]. American Diabetic Association recommends a new guideline in which DPP-4 inhibitor is 2nd line drugs used as add on therapy with Metformin especially for obese[4]. In July 2016, ADA recommended glycated hemoglobin (HbA1c) as an important indicator of long term glycemic control and correlates with diabetic complications. Now it is considered the test of choice for monitoring and chronic management of Type-2 diabetes. This study is designed to evaluate the therapeutic effectiveness of newly diagnosed and Metformin failed Type-2 diabetic patients receiving combination therapy of Metformin with Sulphonylurea or DPP-4 inhibitor. The research is also extended to find out the hypoglycemic events and changes in body weight of patients developed during this period.

MATERIALS AND METHOD

This was a prospective observational study, conducted in Endocrine outpatient department of Dhaka Medical College Hospital, NHN (National Healthcare Networks) Uttara, Dhaka and BIHS (Bangladesh Institute of Health Science Hospital) in Tongi Swastho Sheba Kendra, for a period of one year (July 2017 to June 2018).

Total 70 Type-2 diabetic patients were enrolled in this study according to the inclusion and exclusion criteria. Inclusion criteria includes:

i) New patients (who have not taken any anti-diabetic drugs) having initial HbA1c >8% to 10% and mean HbA1c was 9.01 ± 2.35%

ii) Patietst who failed target glycemic control with Metformin alone, having HbA1c >7.5%, mean HbA1c 7.78 ± 1.56%. Exclusion criteria includes : Type-1 diabetic patients, patients taking insulin and HbA1c >10%. This patients were divided into two groups: In group I (n=35) Metformin 500 mg plus Sulphonylurea (Gliclazide 80 mg) and in group II (n= 35) Metformin 500 mg plus DPP-4 inhibitor (Vildagliptin 50 mg) as a combination therapy twice daily for consecutive 12 weeks.

The study instrument is a self-design data collection form. The patient's demographics past and present medical and medication histories also with other relevant data needed for the study were collected in a form, from prescription sheets and direct patient interview. The baseline data of glycemic status HbA1c, FBG, blood glucose 2-hours ABF were collected initially and after 12 weeks of treatment. Later after 12 weeks any history of hypoglycemia and changes in the body weight were recorded. All the relevant information were collected, completed and compiled. Collected data was analyzed by SPSS 22.0. Student t-test and chi-square test were done. The p value d" 0.05 was considered as statistically significant at 95% CI (confidence interval)

RESULTS

This study was done to determine and compare the effectiveness of Sulphonylurea and DPP-4 inhibitors as add on with Metformin as well as their complications (hypoglycemic events, changes in body weight). In this study it was observed that after 12 weeks of treatment mean HbA1c level significantly reduced from 7.8 ± 0.8% to 6.5 ± 0.4% in group I and 7.9 ± 1.1% to 6.4 ± 0.5% in group II. (Table-I). On comparison between two groups there were no statistically significant changes of glycemic control (Table II). Fig 1 shows 88.6% in group I and 91.4% in group II patients achieved glycemic control of HbA1c <7% (parameter of choice) which also shows no significant difference of glycemic control in two study groups. During observation period the mean FBG level

significantly reduced from 8.66 ± 1.38 to 7.01 ± 0.79 mmol/l in group I and 8.70 ± 1.54 to 6.80 ± 0.78 mmol/l in group II (Table I). On comparison between the groups statistically no significant change occurred in FBG level (Table III). Mean blood glucose 2 hours ABF level significantly reduced from 12.16 ± 2.11 to 8.79 ± 1.17 mmol/l in group I and 11.96 ± 1.94 to 8.56 ± 0.68 mmol/l in group II. (Table I) and on comparison between two groups after 12 weeks of treatment statistically no significant difference (Table II).

In this study, target level of HbA1c was set <7%, FBG 4.4-7.2 mmol/l and blood glucose 2 hours ABF <10 mmol/l according to American Diabetes Association in guideline 2019. In group I, 31(88.6%) patients achieved HbA1c target level, 26(74.2%) patients achieved FBG target level, and 18(51.4%) patients achieved blood glucose 2-hours ABF target level. In group II, 32(91.4%) patients achieved HbA1c target level, 28(80.0%) patients achieved FBG target level, and 20(57.2%) patients achieved blood glucose 2-hours ABF target level (Table II).

It was observed total 13(37.1%) patients developed hypoglycemic events out of 70 patients. During the study period, 11(31.4%) patients were in group I and 2(5.7%) patients in group II which was statistically significant hypoglycemic change occur. It showed more hypoglycemic events in group I who was treated with Metformin and Sulphonylurea (Fig 2).

The study shows total 5 (7.14%) patients gained weight after 12 weeks of treatment, 4 (11.4%) patients in group I and 1 (2.9%) in group II. Which was observed, more weight gain in group I patients who took combination of Metformin and Sulphonylurea. There were no significant changes in the mean body weight and was increased in group I (1.17 kg) and decreased in group II (0.86 kg) (Table IV).

Table-I : *Glycemic effects of respondents during study period (0-12 weeks) in two study groups*

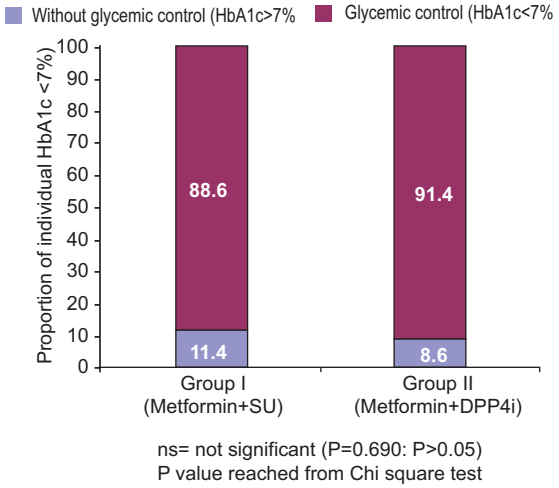
Variables	Before treatment mean± SD	After treatment mean± SD	P value
HbA1c (%)			
Group I (n=35)	7.8±0.8	6.5±0.4	0.008**
Group II (n=35)	7.9±1.1	6.4±0.5	0.001**
FBS (mg/dl)			
Group I (n=35)	8.66±1.38	7.01±0.79	0.003**
Group II (n=35)	8.70±1.54	6.8±0.78	0.001**
2 hrs ABF (mg/dl)			
Group I (n=35)	12.16±2.11	8.79±1.17	0.007**
Group II (n=35)	11.96±1.94	8.56±0.68	0.001**

**significant (P= <0.05) P value reached from pair t-test

Table II : Comparison of glycemic effectiveness, between two study groups after 12 weeks of treatment

Variables	Duration of treatment 0-12 weeks	
	Mean difference	P value
HbA1c (%)		
Group I (n=35)	1.3±0.4	0.155^{ns}
Group II (n=35)	1.5±0.6	
FBS (mg/dl)		
Group I (n=35)	1.65±0.59	0.129^{ns}
Group II (n=35)	1.9±0.76	
2 hrs ABF (mg/dl)		
Group I (n=35)	3.37±0.94	0.881^{ns}
Group II (n=35)	3.41±1.26	

ns= not significant (P= >0.05)
P value reached from unpaired t-test



ns= not significant (P=0.690: P>0.05)
P value reached from Chi square test

Fig.1: *Stack bar diagram showing the proportion of glycemic control in two groups after 12 weeks of treatment*

Table III: *Investigation achieved target glycemic contrast (according to American diabetic association guideline) during study period*

Investigation	Group I (n=35)		Group II (n=35)	
	n	%	n	%
HbA1c (<7%)	31	88.6	32	91.4
FBG (4.4-7.2) mmol/L	26	74.2	28	80.0
Blood glucose 2hrs ABF (<10) mmol/L	18	51.4	20	57.2

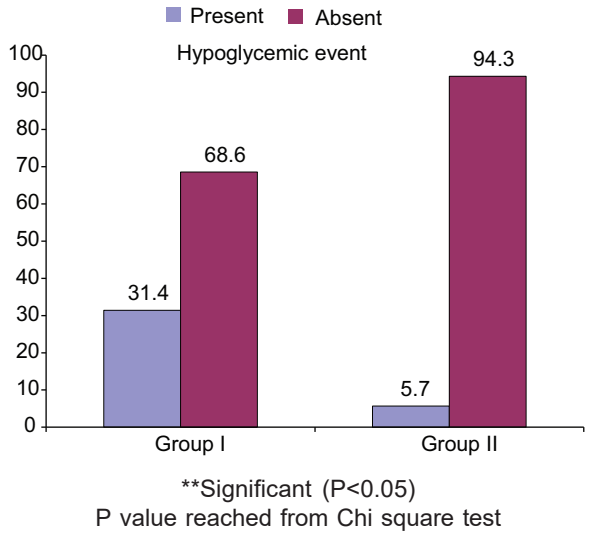


Fig.-2: Bar diagram showing hypoglycemic events of the patients

DISCUSSION

This interventional hospital based study was carried out to compare the effects on glycemic control by combination therapy of Metformin plus Sulphonylurea versus Metformin plus DPP-4 inhibitor in Type-2 diabetes patients.

In this study it was observed that after 12 weeks of treatment mean HbA1c level significantly reduced from 7.8± 0.8% to 6.5 ± 0.4% in group I who were treated with Metformin plus Sulphonylurea and 7.9 ± 1.1% to 6.4 ± 0.5% in group II who were treated with Metformin plus DPP-4 inhibitors. After 12-weeks of treatment, on comparison between two groups, statistically no significant difference (p = 0.155). Similar types of study was conducted by Yung ki Lee, et al., 2013, who compared glycemic effectiveness of Metformin plus Sulphonylurea and Metformin plus DPP-4 inhibitor showed significant decrease in mean HbA1c in both groups (7.8% - 6.5% and 7.9% - 6.4%)[10]. Another study done by Filozof et al., 2010, in 1007 patients was significantly decreased in HbA1c in both groups (8.5% - 7.0%) in one group and (8.5% -7.69%) in other group but on comparison statistically no significant difference between two groups[11].

Mean FBG level significantly reduced from 8.66 ± 1.38 to 7.01 ± 0.79 mmol/l in group I and 8.70 ± 1.54 to 6.8 ± 0.78 mmol/l in group II. After 12-weeks of treatment, on comparison statistically no significant difference. This result is also similar to study done by Yung ki Lee, et al., 2013, also showed that significant reduction of FBG in both group from 9.25 to 5.75 mmol/l and 9.61 to 5.83 mmol/l respectively. But there was statistically no significant difference between two groups[10]. Mean blood glucose 2-hours ABF level significantly reduced from 12.16 ± 2.11 to 8.79 ± 1.17 mmol/l in group I and 11.96 ± 1.94 to 8.56 ± 0.68 mmol/l in groupII. On comparison after 12-weeks of treatment between two groups statistically no significant difference. This result is also similar to the study done by Yung ki Lee, et al., 2013, also showed significant reduction of blood glucose 2-hours ABF in both groups from (9.25- 5.75mol/l and 9.61- 5.83mol/l) respectively. But there was statistically no significant difference between two groups**[10].**

From above discussion it is clear that there is significant reduction of blood sugar level (HbA1c, FBS, blood sugar 2-hours ABF) in both groups but there is no difference of glycemic effectiveness between two groups.

Respondents experienced more hypoglycemia in combination of Metformin plus Sulphonlurea group than Metformin plus DPP-4 inhibitor group (31.4% and 5.7%) respectively. The difference is statistically significant in Sulphonylurea group but not in DPP-4 inhibitor group, which was about similar to the study done by Nauck et at., 2007, which shows hypoglycemic events in 32% and 5% patients respectively[12].

In this study body weight was increased in 5 patients out of 70 (4 in group I and 1 in group II). There was a significant change in mean body weight which was increased in group I (1.17 kg) and decreased in group II (0.86kg). Nauck *et al.*, (2007) showed significant weight gain (1.1 kg) of the patients who took combination of Metformin and Sulphonylurea while significant decrease of body weight (1.5 kg) in patients taking Metformin plus DPP-4 inhibitors[12].

CONCLUSION

On the basis of the study findings that both combinations of drugs are similarly effective in controlling blood sugar but individual group has unique beneficial effect. Metformin and DPP-4 inhibitor combination showed less hypoglycemic events and less weight gain than other combination. So this drug may be prescribed to the patients who are obese and prone to be hypoglycemic (elderly people working patients who do not take their meal properly). On the other hand, combination of Metformin plus Sulfonylurea can be prescribed all patients specially who are not obese. As Metformin plus Sulfonylurea combination has more hypoglycemic events and more weight gain. So, DPP-4 inhibitors can be chosen as second line anti-diabetic drug as add on with Metformin.

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The authors have declared that no competing interest exit.

CONFLICT OF INTEREST: There is no potential conflict of interest to declare.

REFERENCES

1. American Diabetes Association. Classification and Diagnosis of Diabetes. Standards of medical care in diabetes. Diabetes care. 2018; 41(1), pp.13-27.
2. Cho NH, Shaw JE, Karuranga S, Huang Y, Farnandes JD et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Research and clinical practice 2018; 138, pp. 271-281.
3. Wu Y, Ding Y, Tanaka Y, Zhang W. Risk Factors Contributing to Type 2 Diabetes and Recent Advances in the Treatment and Prevention. International Journal of Medical Sciences 2014; 11(11), pp.1185-1200.
4. Inzucchi SE of Hyperglycemia in Type 2 Diabetes. A Patient-Centered Approach Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes care 2015; 38(1), pp. 140-149.
5. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach, position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) Diabetes care. 2012; 35(6), pp.1364-1379.
6. Garber A, Abrahamson M, Barzilay J, Blonde L, Bloomgarden Z et al. AACE comprehensive diabetes management algorithm, Endocrine practice. 2013; 19(2), pp. 327-336.
7. Ko SH, Kim SH, Kim DJ, Oh SJ. Clinical practice guidelines for type 2 diabetes in Korea, Diabetes & Metabolism Journal. 2011; 35(5), pp. 431-436.
8. Bailey T. Options for combination therapy in type 2 diabetes: comparison of the ADA/EASD position statement and AACE/ACE algorithm, The American journal of medicine. 2013; 126(9), pp.10-20
9. Sola D, Rossi L, Piero G, Schianca C, Maffioli P et al. Sulfonylureas and their use in clinical practice.2015; 11(4), pp. 840–848.
10. Lee YK, Seng S, Wang K and Kim J. Glycemic effectiveness of metformin based dual combination therapies with Sulphonylurea, Pioglitazone, or DPP-4 inhibitors in Drug Naïve Korean Type 2 Diabetes DMJ. 2013; 37(6), pp. 465.
11. Filozof C and Gautier JF. A comparison of efficacy and safety of vildagliptin and gliclazide in combination with metformin in patients with Type 2 diabetes inadequately controlled with metformin alone: a 52 week, randomized study. Diabetic Medicine. 2010; 27(3), pp. 318-326.
12. Nauck MA, Meininger G, Sheng D, Terranella L. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab. 2007; (2), pp. 194-205.
13. Zakia S, Ali MA, Akter MS. Study of Evaluation for the Management of Diabetes in Bangladesh. Pharmacology & Pharmacy 2013; 4, pp. 355-361.

Review Article

Managing Urological Issues amidst the COVID-19 pandemic

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ABSTRACT

The COVID-19 pandemic is the latest and biggest global health threat. Medical and surgical practices have changed dramatically to cope with the current challenge. Our objective is to discuss the impact of COVID-19 on Urological practice and their management and to review some of the available recommendations reported in the literature. In the current review the PubMed database was searched to identify all the related reports discussing the impact of COVID-19 on urological field and how the urological issues and cases can be managed is discussed. So it can be concluded that we should adopt triage strategy to avoid wasting of medical resources and endorse sufficient protection procedures to guard against infection when dealing with COVID-19 patients.

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INTRODUCTION

COVID-19 is spreading rapidly around the world, forcing previously unknown changes in our health care systems. This pandemic poses a great burden on medical resources such as hospital beds and protective equipment, in addition to medical personnel. Decisions regarding which type of care is to be continued and which can be postponed must be made and will require revision as the situation improves or worsens. It is yet unpredictable when to expect improvement in the COVID-19 situation, but this will also require a scenario for progressive resumption of medical care. Several medical and surgical societies across the globe have developed lists to guide the decision-making process with regards to reduction of care, mainly focusing on COVID patients in general. We present a statement with recommendations for MuMCH for urological cases based on published studies as well as expert opinion of the urology guidelines panel of different societies.

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Impact of COVID-19: COVID-19 appears similar to Severe Acute Respiratory Syndrome Corona virus (SARSCoV) and Middle East Respiratory Syndrome Corona virus (MERSCoV). To date most reports on COVID-19 describe mild to moderate symptoms such as fever, cough and nasal discharge.[1] The prevalence of severe symptoms is higher among old.[1] While most patients themselves may not be severely ill with COVID-19, this pandemic will impact on urological care. Careful decisions must be made on what care requires postponement and what care is essential to be continued.[2]

Suggested reduction in urological procedures[1]: During various stages of severity of the COVID-19 pandemic, below are recommendations for urological surgical procedures.[1] for stage 1 & 2 suggestions include care that can be postponed. Conversely, for stage 3 & 4 suggestions encompass essential care that should continue if circumstances permit.

Stage 1: Start to reduce Urological cases.

High recommendation to postpone:

- BPH with catheter in situ, Urolithiasis without infection and obstruction.

- Benign scrotal & penile surgery: orchiopexy, hydrocele, hernia, circumcision.
- Functional surgery: incontinence surgery, meatotomy.
- Genital reconstructive surgery: hypospadias, buried penis.
- Benign (hemi) nephrectomy.

Stage 2: Perform only care that is at least semi-urgent.
Recommendation to postpone:

- Stricture urethra with mild obstructive feature.
- Surgery for vesicoureteral reflux: ureteral reimplantation.
- Pyeloplasty in UPJ obstruction without loss of differential function.
- Urolithiasis without infection or obstruction.
- Endoscopic botulinum-toxin for neurogenic bladder

Stage 3: Still perform surgery for urgent cases in which delay will
Cause irreversible progression of disease or organ damage:

- Pyeloplasty in UPJ obstruction with progressive loss of differential function or severe symptoms.

Consider postponing reconstruction and draining the kidney by DJ stent or nephrostomy depending on local situation.

- Urolithiasis with recurring febrile infections
- Ureteric stone associated with fever and infection.
- Nephrostomy for pyonephrosis.
- Posterior urethral valves (PUV).
- Obstructive megaureter with progressive loss of differential function.
- DJ stent removal, check cystoscopy for NMIBC, Intravesical chemotherapy,
- Catherization/ SPC in patient with acute retention of urine.

Stage 4: Perform surgery only in cases of organ-threatening or life-threatening disease:

- Urosepsis with obstruction: e.g. urosepsis with urolithiasis, obstructing ureterocele.
- Suprapubic cystostomy for PUDD, severe stricture utrethra.
- Ureteric obstruction in solitary kidney, Bilateral ureteral obstruction.
- Trauma with hemodynamic instability (endovascular or Surgical procedures) or urinary leakage.
- Patient with haematuria with urinary bladder tumour.
- Acute ischemia: Testicular Trotion
- Paraphimosis (preferably under local anesthesia).[3]
- Cancer surgery: Urinary bladder neoplasm, renal cell carcinoma, Ureteric growth, Carcinoma prostate, Wilms tumor, malignant testicular and penile tumors. Surgical resection may be considered depending on the local situation, condition of the patient and expected duration and stage of tumour.[4]

It is important to note that postponing surgery in patients with obstructive uropathy (e.g. UPJ/UVJ obstruction, PUV and neurogenic bladder) may lead to loss of renal function. Temporary drainage methods may be considered as a bridge to definitive surgery. These delays are likely to have consciences for both clinical and basic science research but faculty mentorship and many current projects can continue. We encourage urolgy residents to enhance their knowledge for research design and analysis by participating free online courses.

Urological Surgery during the COVID-19 pandemic

Every patient should be screened for COVID-19 prior to surgery. If the test-result is unknown, surgery should be performed as if the patient were positive. The effect of surgery on either the susceptibility to COVID-19 or on the severity of symptoms is yet unknown. Still it may be useful to consider regional or local anesthesia whenever possible to prevent the need for mechanical ventilation .[3] This also limits the use of ventilators and other potentially scarce equipment. In case of surgery on a (potentially) COVID-19 positive patient several issues should be considered in order to limit the risk for theatre staff. The operating theatre poses different risks of exposure compared to non-surgical care. Negative pressure rooms are strongly preferred for intubation /extubation for COVID-19 positive and suspected cases. It is important to limit the number of theatre staff present during surgery on a COVID-19 positive patient. [4] Diathermy smoke is a potential risk factor in spreading the Corona virus, as surgical smoke has been shown to contain several viruses in the past.[5,6] Aerosols from ultrasonic scalpels may pose a higher risk due to their lower temperature compared to aerosols from conventional diathermy.[7]It is advisable to use suction devices as much as possible. There is no conclusive evidence regarding the differences in risks of open versus laparoscopic

surgery for the surgical team.[8] However, laparoscopic surgery may be associated with a higher amount of smoke particles than open surgery.[9] During laparoscopy surgical smoke is released into theatre under pressure at several stages of surgery. It is advisable to keep intraperitoneal pressure as low as possible and to aspirate the inflated CO_2 as much as possible before removing the trocars.[7,10] In order to minimize the use of operating room time and optimize the use of resources surgery should be performed by experienced surgeons.[10.] For COVID-19 positive or suspected patients both patients and healthcare workers should wear N95 respirators if available.

Outpatient care with urological problems[7]

While the goal of urologists must be to maintain as high as possible standard of care, the number of patients attending the outpatient clinic must be reduced in order to minimize the chance of infecting patients or health care providers, as well as preserving personal protection equipment. Each individual case should be screened for the possibility of replacing an outpatient visit by consultation via telephone or video-call, when available.[7] A telephone consultation may also be used to screen for the need for physical consultation. If a physical outpatient clinic visit is necessary, the urological patent should be accompanied by only a single caregiver. Prior to the outpatient clinic visit it is also necessary to assess if either patient or caregiver have symptoms that may be COVID-related. If there are COVID-19 symptoms, patient or caregiver has been tested positive for COVID-19 or are in quarantine, they should be seen in a COVID dedicated area of the hospital without interaction with other patients.

Suggested reduction in outpatient clinic visits during various stages of severity of the COVID- 19 pandemic [1,4]

Stage 1: Start to reduce outpatient cases such as benign scrotal and penile pathology or well as incontinence, Uncomplicated UTI, Mild lower urinary tract symptoms, BPH with mild symptoms.

Stage 2: See only cases that are at least semi-urgent, such as varicocele, initial postoperative ultrasound after upper tract reconstruction. Consider postponing prolonged (post-operative) follow up in stable patients.

Stage 3: Continue care for urgent cases in which delay may cause irreversible progression of disease or organ damage. Testicular torsion, genitourinary trauma, follow-up of malignant cases after surgery, evaluation of gross haematuria, acute retention of urine.

Stage 4: Continue all care for cases in which a delay of care is potentially organ-threatening or life-threatening.

Safety measures and precautions for Urology staff

As the infection rate of COVID-19 is reported between 40 and 70%, urology teams should be prepared for the chance to become infected and consider splitting up into 2 teams, aiming to assure the continuity in the hospital of at least 1 team.[4,11] Healthcare workers may be anxious about contracting COVID-19 and this causes an additional stress in already strained working conditions. Hospitals must ensure staff are sufficiently informed about COVID-19 disease, and trained in the use of protective equipment, isolation and infection control measures prior any contact with patients.[12]

When available simulation exercises and e-learning, may aid to ensure optimal quality of care of COVID-19 patients and to maximally reduce the risk of viral transmission to other patients or healthcare workers.[13] Maintaining good mental health of all medical staff is extremely important to ensure a safe working environment [14]. Authority should be aware of the importance the mental health of their staff and maintain contact with all staff members on a regular basis. In addition to following local protocols, staff should be aware that in patients with clinical recovery from COVID-19 both stool and urine may still contain COVID-19 when oropharyngeal swabs have become negative [15.]

Resumption of surgical care after the COVID-19-pandemic peak [7, 10]

While it cannot be predicted when we will be able to revert back from the high stages of the COVID-19 pandemic and resume more normal levels of care, we do need to plan ahead on how to do this.[10] The most logical step will be to reverse back through the aforementioned stages. During this process we will need to confer with our fellow surgical (sub) specialties to prioritize the available surgical time and resources among all surgical patients. While it is wise to postpone surgery in cases of obstructive uropathy during the advanced stages of the COVID-19 pandemic, there is a risk of loss of renal function. The challenge will be to minimize this loss in young patients who have their whole lives ahead of them,

particularly if the pandemic continues for a prolonged period of time.[7]Undoubtedly there will be cases of congenital abnormalities where the optimal surgical timepoint will be surpassed, such as hypospadias and cryptorchidism. These patient may be at risk for suboptimal outcome or increased psychological burden due to delayed surgery and should be prioritized in the long waiting list that we will undoubtedly be facing on the other end of this crisis.

CONCLUSION

While we are working to have a plan to manage this pandemic, much consideration should be given for further planning. There is a serious need for set up with parallel healthcare systems, where we need hospitals that continue to cater for emergencies and cancer management and on the other hand institutions that could potentially share the burden to manage pandemic cases. The current recommendations are based on the limited data available in the literature and are subject to changes.

CONFLICT OF INTEREST: The authors declare that there are no conflicts of interest regarding the PUBLICATIONS OF THIS MANUSCRIPT.

LIMITATIONS: Scarcity of the source of information's.

REFERENCES

1. Ficarra V, Novara G, Abrate A, Bartoletti R, Crestani A, De Nunzio C, et al. Urology practice during COVID-19 pandemic. BJU Int 2002;89:264e8.
2. Ludvigsson JF. Systematic review of COVID-19 in children show milder cases and a better prognosis than adults. Acta Paediatr 2020.https://doi.org/10.1111/APA.15270.
3. Broderick KM, Martin BG, Herndon CDA, Joseph DB, Kitchens DM. The current state of surgical practice for neonatal torsion: a survey of pediatric urologists. J Pediatr Urol 2013;9:542e5.
4. Brindle M, Gawande A. Managing COVID-19 in surgical systems. Ann Surg 2020:1.
5. Capizzi PJ, Clay RP, Battey MJ. Microbiologic activity in laser resurfacing plume and debris. Laser Surg Med 1998;23:172e4.
6. Johnson GK, Robinson WS. Human immunodeficiency virus-1 (HIV-1) in the vapors of surgical power instruments. J Med Virol 1991;33: 47e50.
7. Zheng MH, Boni L, Fingerhut A. Minimally invasive surgery and the novel coronavirus outbreak. Ann Surg 2020:1.
8. The British Association of Paediatric Endoscopic Surgery. BAPES Statement: coronavirus (COVID-19) and endoscopic surgery. 2020. https://static1.squarespace.com/static5c547dd3 d7819e 06b90a 19ae/t/5e77f0e555c6b75f308db801/1584918761408/BAPES+COVID19+2203.pdf.
9. Li CI, Pai JY, Chen CH. Characterization of smoke generated during the use of surgical knife in laparotomy surgeries. J Air Waste Manag Assoc 2020;70:324e32.
10. Mottrie Alex, Puliatti Stefano, Mazzone Elio, ERUS. ERUS (EAU robotic urology section) guidelines during COVID-19 emergency. 2020. https://uroweb.org/wp-content/uploads/ERUSguidelines-for-COVID-def.pdf.
11. American College of Surgeons Committee on Trauma. Maintaining Trauma center access and care during the COVID-19 pandemic: guidance document for Trauma medical directors. 2020. https://www.facs.org/-/media/files/qualityprograms/trauma/acs_cot_statement_on_maintaining_trauma_center_access.ashx.
12. Alsahafi AJ, Cheng AC. Knowledge, attitudes and behaviours of healthcare workers in the kingdom of Saudi Arabia to MERS coronavirus and other emerging infectious diseases. Int J Environ Res Publ Health 2016;13.
13. Wong J, Goh QY, Tan Z, Lie SA, Tay YC, Ng SY, et al. Preparing for a COVID pandemic: a review of operating room outbreak response measures in a large tertiary hospital in Singapore. Can J Anesth Can d'anesthe´sie 2020. https: //doi.org/10.1007/s12630-020-01620-9.
14. Chen Q, Liang M, Li Y, Guo J, Fei D, Wang L, et al. Mental health care for medical staff in China during the COVID-19 outbreak. Lancet Psychiatr 2020;7:e15e6.
15. Ling Y, Xu S-B, Lin Y-X, Tian D, Zhu Z-Q, Dai F-H, et al.Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. Chin Med J (Engl) 2020:1.

Case Report

An Infant of Diabetic Mother with Multiple Congenital Anomalies

Alo D

ABSTRACT

Maternal diabetes has toxic effects on the development of the embryo and significantly increases the risk of congenital malformations in newborns. The incidence of fetal structural defects caused by maternal pregestational diabetes is three- to fourfold higher than that caused by non-diabetic pregnancy.A term female newborn of pregestational diabetic mother was admitted with multiple congenital anomalies involving CNS (spina bifida),Skeletal (Caudal regression syndrome, sacral agenesis, and limb defects)),CVS(VSD,TGA), Renal (Hydronephrosis) . Successful preconception counseling for women with diabetes mellitus and metabolic control will reduce birth defects of newborns and maternal morbidity.

Key words: *Congenital malformation, Infant of pregestational diabetic mother.*

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INTRODUCTION

Pregnant women having fetuses with diabetic embryopathy may have chronic or unrecognized hyperglycemia and elevated levels of glycated hemoglobin. Usually newborn of mothers with pregestational diabetes develops congenital malformations as it is associated with diabetic pregnancy arise before the seventh gestational week [1]. Pre-gestational diabetes mellitus is defined as type 1 or type 2 diabetes that exists before the pregnancy. It has been postulated that hyperglycemia-induced teratogenesis is caused by several mechanisms, such as functional deficiencies of arachidonic acid and myoinositol [1,2]; inhibition of the cellular uptake of dehydroascorbic acid [3]and increased non-enzymatic glycosylation of embryonic proteins[4] decreased catalase activity[5] and increased substrate-induced free-oxygen radical production [6] and abnormal levels of trace metals[2]. The congenital malformations associated with diabetic pregnancy arise before the seventh gestational week[1,7]. Diabetic embryopathy can affect any developing organ system, including the central nervous system (CNS), heart, and renal and urinary tracts, lower limb reduction defects, axial skeleton defects, and caudal dysgenesis complex are more frequent among the children of mothers with pregestational diabetes than among children with non-diabetic mothers [8]. For instance, the frequency of CNS anomalies is 2.9 times higher in children of pregestational diabetic mothers than in children of non-diabetic mothers [8.] Ray et al observed a higher risk of open neural tube defects and urinary tract disorders in association with the presence of pregestational diabetes among women undergoing second-trimester screening [9]

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CASE REPORT

An infant of diabetic mother with multiple congenital anomalies.

A term AGA (3000 gm) female newborn of a diabetic mother got admitted in the newborn unit of pediatrics department of Mugda Medical College Hospital at the age of 1 hr with abnormal limbs. Mother X aged 30 years was diagnosed as diabetic (Pre-pregnancy) one and half year back and was treated with oral hypoglycemic agent (Metformin). During this period she had H/o two abortions at early part of second trimester. She discontinued Metformin before this pregnancy without any consultation with doctor as she thought that her two abortions were caused by Metformin. During this pregnancy she took first antenatal checkup after 3 month of pregnancy. At second trimester mother started insulin as per advice of doctor. Mother had no h/o fever or rash during this pregnancy. Her LUCS was done at term. Baby cried soon after birth. APGAR score was 8/10 at five minute.

On examination baby was plump, plethoric and moonfaced (Fig:1).OFC was 35.8 cm. Micropthalmos, hypertrichosis and hairy pinna were present. Baby was cyanosed but no grunting, her respiratory rate was 48 breaths per minute, heart rate was 120 beats per minute but there was a pansystolic murmur on apical area of heart. Cyanosis was persisting with oxygen. There was shortening of both upper and lower limbs. There were fixed flexion deformity of both knee joints with talipesequinovarus on both feet. (Fig.-2) There were a dimpling and feeling of gap on the back.(fig-4) Serial CBG, full blood count,serum calcium were within normal limit. X-ray limbs with spine revealed hypoplasia of lower limbs with absent fibula and agenesis of sacrum.(Fig.-3). Echocardiography revealed unbalanced atrio-ventricular septal defect with small left ventricle, severe pulmonary stenosis, transposition of great arteries (Fig.-6). USG of whole abdomen revealed left sided mild hydronephrosis (Fig.-5). Baby was discharged with advice for follow up and consultation with paediatric cardiologist, plastic and orthopedic surgeon.

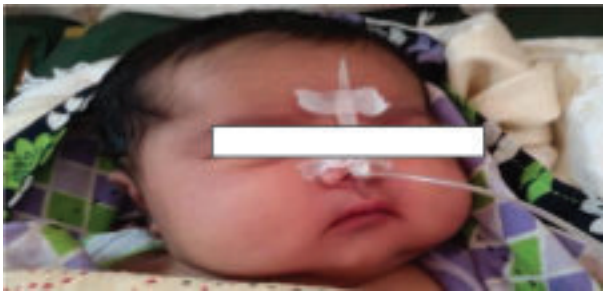

Fig.-1: *Baby was plump, plethoric and moon faced (At 1st day of life)*

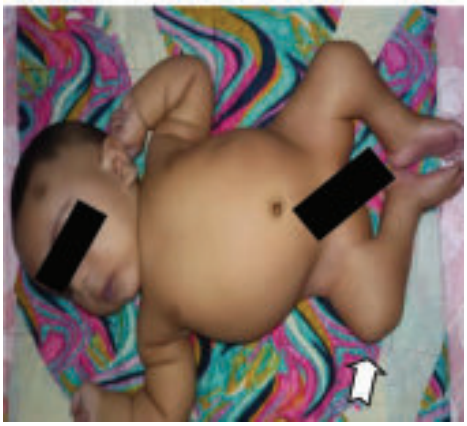

Fig.-2: *Fixed flexion deformity of both knee joints with bilateral talipesequinovarus*

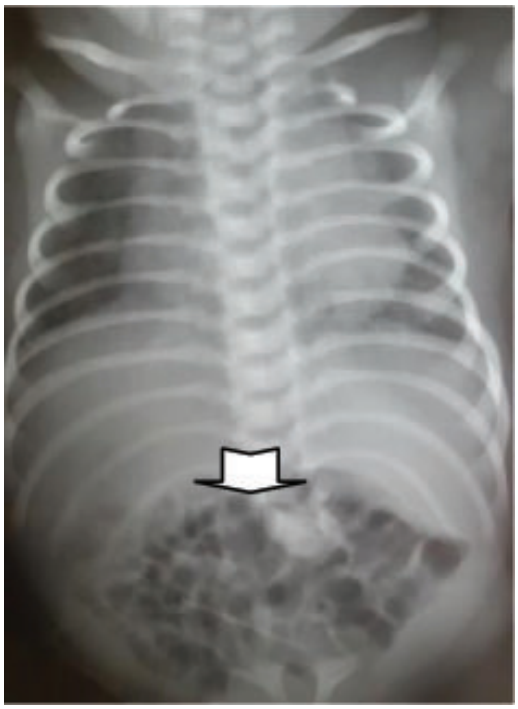

Fig.-3: *Absence of lower part of vertebral column.*

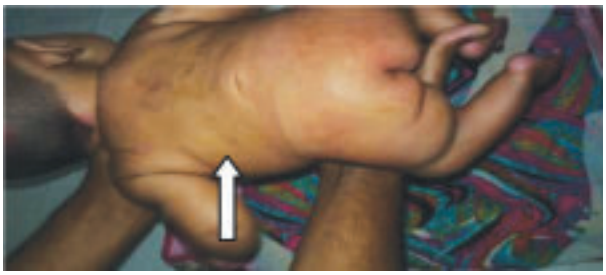

Fig.-4: *Dimpling and swelling on back*

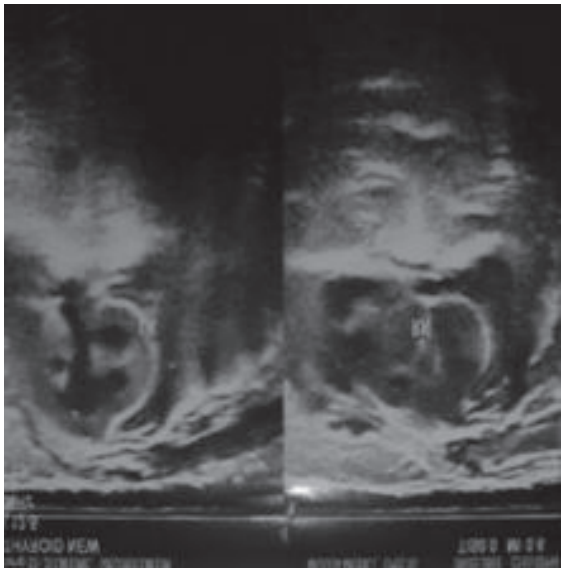

Fig:-5 . *Hydronephrosis in both kidneys*

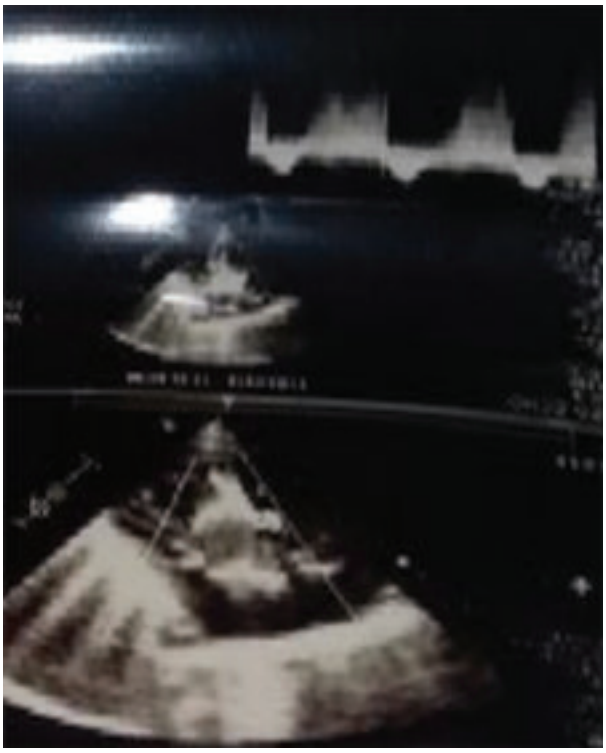

Fig:-6: *Echocardiography*

DISCUSSION

In this infant there is caudal regression syndrome as evidenced by sacral agenesis Fig-3. Caudal regression syndrome is characterized by varying degrees of vertebral anomalies from partial sacral agenesis to complete absence of the lumbosacral spine. It is the most characteristic congenital anomaly observed in the children of diabetic women[8]. Sixteen percent of caudal regression syndrome cases have occurred in the offspring of diabetic mothers, and about 1% of the infants born to non -diabetic mothers exhibit caudal regression syndrome, indicating a risk at least 250 times higher than that of the offspring of non-diabetic mothers [10-11]. Recently, Chan et al found a significantly increased incidence of retinoic acid-induced caudal regression in embryos of diabetic mice compared with embryos of non-diabetic mice and presented evidence that the increased susceptibility to caudal regression is mediated via enhanced down-regulation by retinoic acid of *Wnt-3a* expression in the embryo exposed to a diabetic milieu[11]. Martínez-Frías suggested that the highest risk of congenital defects in the offspring of diabetic pregnant women is caudal dysgenesis[12]. Prenatal sonographic examination of diabetic mothers should include a thorough examination of the fetal spine.

There was a dimpling and feeling of gap on the back that indicates spina bifida in its mild presentation or variety. Mills et al found a twofold ratio of incidence of spina bifida, hydrocephalus, and other CNS defects and a threefold ratio of incidence of anencephaly in infants of diabetic mothers compared with those of controls[7]. Ray et al found an increased risk of having a fetus with an open neural tube defect among pregestational diabetic women undergoing second-trimester maternal serum screening[11]. Recently, impaired expression of developmental control genes has been shown to be a cause of defective morphogenesis in the mouse model of diabetic embryopathy and genotoxicity. For instance, impaired expression of *Pax-3*, a gene that regulates neural tube closure, is sufficient to prevent normal formation of the neural tube [13]. Phelan et al noted a significant reduction in the expression of *Pax-3* in embryos of diabetic mice before the manifestation of morphologic defects [14]. Fine et al showed that hyperglycemia inhibits *Pax-3* gene expression and increases neuroepithelial apoptosis in the embryo, leading to neural tube defects[15]. Chang et al demonstrated that oxidative stress in the embryo caused by maternal hyperglycemia inhibits expression of *Pax-3* and contributes to the occurrence of neural tube defects in diabetic pregnancy [16]. Pani et al provided evidence for polymorphic susceptibility to the molecular causes of neural tube defects during diabetic embryopathy [17]. They also found that *Pax-3* regulates neural tube closure by inhibiting p53-dependent apoptosis[18]. Loeken concluded that maternal diabetes causes birth defects such as neural tube defects by disturbing expression of genes that control essential developmental processes, and that oxidative stress is involved[19].

Echocardiography of this infant revealed congenital heart defect in the form of unbalanced atrio-ventricular septal defect with small left ventricle, severe pulmonary stenosis and transposition of great arteries. Congenital heart defects are the most frequent malformations but are not the most characteristic abnormalities among children of diabetic mothers with or without insulin treatment. Martínez-Frías found that congenital heart anomalies made up 21% of all anomalies among children of diabetic mothers; however, the frequency of congenital heart defects was only 2.8 times higher than that in children of non-diabetic mothers [10]. Schaefer-Graf et al found that the

most commonly affected organs in congenital anomalies caused by pregnancies complicated by type 2 and gestational diabetes were the heart (37.6%), musculoskeletal system (14.7%), and CNS (9.8%)[20].

On USG of abdomen there revealed bilateral hydronephrosis in the this case.The reported congenital malformations of genitourinary system in infants of diabetic mothers include aphallia, hypospadias, megalourethra, urogenital malformation sequence, hydronephrosis, renal agenesis, horseshoe kidneys.Vaux et al found striking abnormalities in sonic hedgehog signaling and these defects in infants of diabetic mothers, and suggest that maternal diabetes may affect sonic hedgehog expression in susceptible tissues during critical stages of development[21]. The reported congenital malformations common to sonic hedgehog abnormalities include aphallia, hypospadias, megalourethra, urogenital malformation sequence, hydronephrosis, renal agenesis, horseshoe kidneys, vertebral segmentation defects, polydactyly, sacral defects, limb deficiency, esophageal atresia, tracheoesophageal atresia, anal stenosis/imperforate anus, urorectal septum malformation sequence, intestinal malrotation/ atresia, holoprosencephaly, and cardiac laterality defects [21].

Mills et al found that malformations in infants of diabetic mothers occur before the seventh gestational week and suggest that any therapeutic intervention aimed at decreasing congenital malformations must be instituted during the critical early period[5]. In fact, patient education and initiating intensive management for glycemic control in diabetic women before conception significantly decrease the risk of congenital malformations[22-25]. For instance, Fuhrmann et al found a 0.8% incidence of congenital malformations in infants born to diabetic mothers with intensive treatment before conception, while there was a 7.5% incidence of congenital malformations in infants born to diabetic mothers with strict metabolic control after 8 weeks' gestation[22]. Kitzmiller et al described a 1.2% incidence of major anomalies among infants in the preconception care group of diabetic mothers compared with 10.9% in the postconception group[24]. Willhoite et al documented a 1.6% incidence of major congenital anomalies among infants born to pregestational diabetic women receiving preconception counseling compared with 6.4% in the group without preconception counseling .[25]

CONCLUSION

In view of the importance of preventing diabetic embryopathy, preconception recognition of the maternal status of glycemic control and early intensive diabetes management are the most beneficial and cost-effective methods for promoting maternal and fetal health in the perinatal management of maternal diabetes.

Key message

Effective control of diabetes / blood sugar is essential during peri-conceptional period and 1st trimester to avoid congenital malformations.

REFERENCES

1. Baker L, Piddington R, Goldman AS, Egler J. Diabetic embryopathy: mechanism involves myo-inositol and arachidonic acid. *Pediatr Res* 1986;20:326A.
2. Goldman AS, Baker L, Piddington R, Marx B, Herold R, Egler J. Hyperglycemia-induced teratogenesis is mediated by a functional deficiency of arachidonic acid. *Proc Natl Acad Sci USA* 1985;82:8227–31.
3. Ely JTA. Hyperglycemia and major congenital anomalies. *N Engl J Med* 1981;305:833.
4. Kennedy L, Baynes JW. Non-enzymatic glycosylation and the chronic complications of diabetes: an overview. *Diabetologia* 1984;26:93–8.
5. Cederberg J, Eriksson UJ. Decreased catalase activity in malformation-prone embryos of diabetic rats. *Teratology* 1997; 56:350–7.
6. Eriksson UJ, Borg LAH. Diabetes and embryonic malformations: role of substrate-induced free-oxygen radical production for dysmorphogenesis in cultured rat embryos.
7. Mills JL, Baker L, Goldman AS. Malformations in infants of diabetic mothers occur before the seventh gestational week: implications for treatment. *Diabetes* 1979;28:292–3
8. Martínez-Frías ML. Epidemiological analysis of outcomes of pregnancy in diabetic mothers: identification of the most characteristic and most frequent congenital anomalies. *Am J Med Genet* 1994;51:108– 13.
9. Ray JG, Vermeulen MJ, Meier C, Wyatt PR. Risk of congenital anomalies detected during antenatal serum screening in women with pregestational diabetes. *Q J Med* 2004;97: *Diabetes* 1993;42:411–9. 10.Banta JV, Nichols O. Sacral agenesis. *J Bone Joint Surg* 1969; 51A:693–703.

11. Chan BWH,Chan KS, Koide T, etal. Maternal-diabetesincreases the risk of caudal regression caused by retinoic acd.diabetes 2002:51;2811-6.

12. Knowler WC. Screening for NIDDM: opportunities for detection, treatment and prevention. *Diabetes Care* 1994;17: 445–50.

13. Chang TI, Loeken MR. Genotoxicity and diabetic embryopathy: impaired expression of developmental control genes as a cause of defective morphogenesis. *Sem Reprod Endocrinol* 1999;17: 153–65.

14. Phelan SA, Ito M, Loeken MR. Neural tube defects in embryos of diabetic mice: role of the *Pax-3* gene and apoptosis. *Diabetes* 1997;46:1189–97.

15. Fine EL, Horal M, Chang TI, Fortin G, Loeken MR. Evidence that elevated glucose causes altered gene expression, apoptosis, and neural tube defects in a mouse model ofdiabetic pregnancy. *Diabetes* 1999;48:2454-562.

16. Chang TI, Horal M, Jain SK, Wang F, Patel R, Loeken MR. Oxidant regulation of gene expression and neural tube development: insights gained from diabetic pregnancy on molecular causes of neural tube defects. *Diabetologia* 2003; 46:538–45.

17. Pani L, Horal M, Loeken MR. Polymorphic susceptibility to the molecular causes of neural tube defects during diabetic embryopathy. *Diabetes* 2002;51:2871–4.

18. Pani L, Horal M, Loeken MR. Rescue of neural tube defects in Pax3-deficient embryos by p53 loss of function: implications for Pax-3dependent development and tumorigenesis. *Genes Dev* 2002;16:676–80.

19. Loeken MR. Free radicals and birth defects. *J Matern Fetal Neonat Med* 2004;15:6–14.

20. Schaefer-Graf UM, Buchanan TA, Xiang A, Songster G, Montoro M, Kjos SL. Patterns of congenital anomalies and relationship to initial maternal fasting glucose levels in pregnancies complicated by type 2 and gestational diabetes. *Am J Obstet Gynecol* 2000; 182:313–20.

21. Vaux KK, Jones MC, Benirschke K, Bird LM, Jones KL. Megalourethra: a report of three cases associated with maternal diabetes and a review of the literature – is sonic hedgehog the common pathway? *Am J Med Genet* 2005;132A: 314–7.

22. Fuhrmann K, Reiher H, Semmler K, Fischer F, Fischer M, Glockner E. Prevention of congenital malformations in infants of insulindependent diabetic mothers. *Diabetes Care* 1983;6: 219–23.

23. Steel JM, Johnstone FD, Hepburn DA, Smith AF. Can prepregnancy care of diabetic women reduce the risk of abnormal babies? *BMJ* 1990;301:1070–4.

24. Kitzmiller JL, Gavin LA, Gin GD, Jovanovic-Peterson L, Main EK, Zigrang WD. Preconception care of diabetes: glycemic control prevents congenital anomalies. *JAMA* 1991; 265:731–6.

25. Willhoite MB, Bennert HW, Palomaki GE, et al. The impact of preconception counseling on pregnancy outcomes: the experience of the Maine Diabetes in Pregnancy.

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