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Editorial

# Monkey Pox
# An upcoming threat

Despite the name the animal reservoirs for monkey virus are squirrels and rodents. It causes rare zoonotic infection in communities in the rainforest belt of central Africa, producing a vesicular rash that is indistinguishable from small pox but differentiated by the presence of lymphadenopathy,less infectious. Little person to person transmission occurs. Outbreak outside Africa has been linked to importation of African animals as exotic pets. People with monkey pox get a rash that may be located on or near the genitals (penis, labia, vagina, or anus) and could be on other areas like hands, feet, chest, face or mouth. The rash will go through several stages including scabs before healing. The rash can initially look like pimples or blisters and may be painful or itchy. Other symptoms can include fever, chills, swollen lymphadenopathy exhaustion, muscle aches, backache, and respiratory symptoms. Sometimes peoples have flu like symptoms before the rash, some peoples get rash first followed by others symptoms, and others only experience rashes.

Monkey pox symptoms usually start within 3 weeks of exposureto the virus. It can be spread from the time symptom start until the rash has healed, all scabs have fallen off and a fresh layer of skin has formed. The illness typically last 2-4weeks.

The monkey pox is often transmitted through close sustained physical contactsalmost exclusively associated with sexual contact in the current outbreak. It can also be transmitted to humans through close contact with infected person, or animals or the material contaminated with the virus and close contact with the lesion, body fluids, respiratory droplets, and contaminated materials such as bedding.

Infected animals can spread monkey pox virus to peoples and it is possible that people who are infected can spread virus to animals through close contact.

Vaccine used during the smallpox eradication programme also provided protection against monkey pox. Newer vaccine Jynneosand ACAM 2000 is also approved. An antiviral agent known as Tecovirimat that was developed for small pox was licensed by the European medicines agencies (EMA) for monkey pox in 2022.

Raising awareness of risk factors and educating people about the measures they can take to reduce exposure to the virus is the main prevention strategy for monkey pox.

**Prof. Dr. Md. Ashif Mashud Chowdhury**
Department of Medicine
Dhaka National Medical College

**References**

1. Monkey Pox-Davidsons Principles and Practice of Medicine-24th Edition
2. Centre for Disease Control (CDC)-USA, August 5, 2022
3. Monkey Pox-WHO, May 19, 2022

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## Instruction for Authors:

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Title of the article (Should be concise, informative and self explanatory).
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**Introduction**

States the purpose of the article and summarizes the rational of the study.
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Organization as author

Hypertension Prevention Program Research Group Hypertension, Insulin, and Proinsulin in Participants with Impaired Glucose Tolerance Hypertension. 2010; 20(6): 576-82

Volume with supplement

Genaud G, Spierings EL, Keywood C. Tolerability and safety of Frovatriptan with Short and Long Term Use for Treatment of Migraine and in Comparison with Sumatriptan. Headache. 2009;25 supple: 541-47

Books

Personal author(s)

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical Microbiology 4th ed St.Louis:Mosby; 2002.

Editor(s) /compiler(s) as author

Gilstrap LC, Cunningham FG, VandorstenJP, editors. Opetative Obstetrics. 2nd ed. New York: McGraw-Hill; 2002

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Chapter in a book

SE. Strous. Influenza and its viruses M. Schaechter, G. Medoff, D. Schlessinger In : Mechanisms of Microbial diseases. P. 393-406.

Journal Article on the Internet

Abood S. Quality Improvement Initiative in Nursing Homes: the ANA Acts in an Advisory Role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12]; 102 (6) Available from : http:/www.nursingworld. org/AJN/2002/june/Wawatch.htmArticle.

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Cancer-Pain.org [Internet]. New York: Association of Cancer Online Resources [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/.

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J. Dhaka National Med. Coll. Hos. 2022; 28 (01): 07-09

**Original Article**

# Detection of Gallbladder Carcinoma Incidentally After Laparoscopic Cholecystectomy for Cholelithiasis, in a Tertiary Level Hospital

**Md. Alamgir Hossain Sikder[1], Fahim Hasan[2], Shahidur Rahman[3], Jamal Abu Naser[4]**

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## Abstract

**Background:** Carcinoma of gallbladder is a rare disease but extremely variable by geographical region and racial-ethnic group. The incidence of intra or postoperative incidental carcinoma of gallbladder diagnosed is estimated 0.2 and 2.8.

**Objective:** To detect incidental gallbladder carcinoma after laparoscopic cholecystectomy & to correlate it with age variable and findings of gallbladder pathology postoperatively.

**Methods:** A total 960 patients of gallbladder stone/cholelithiasis were carried out laparoscopically by laparoscopic cholecystectomy in the Department of Surgery of Dhaka National Medical College Hospital retrospectively during the period from January 2017 to December 2020.

**Results:** Incidental gallbladder carcinoma were diagnosed in 3(0.41%) out of 960 patients undergone laparoscopic cholecystectomy.

**Conclusion:** Gall bladder carcinoma is rare disease with poor prognosis. The use of meticulous laparoscopic technique seems to be important for the diagnosis and avoidance of early complication of the disease and microscopic examination is very much important for the depth of invasion, range of mucosal spread and lympho-vascular involvement.

**Keywords:** Cholelithiasis, Incidental gallbladder carcinoma, Laparoscopic cholecystectomy.

## Introduction

Gallbladder carcinoma is a rare but high malignancy neoplasm with incidence rate of 0.3-1.5%.[1-3] The incidence of intra or post-operative incidental gallbladder carcinoma diagnosis is estimated between 0.2 and 2.8% in this group, 15-30% of patients prove to be asymptomatic at the time of presentation, without clinical evidences of intra or preoperative neoplasm.[1-3] Gallbladder carcinoma is the sixth most common gastrointestinal malignancy worldwide.[4] Complete surgical removal is the only modality that can provide a chance of cure. However, the overall prognosis of patients with gallbladder carcinoma has been dismal because the majority of cases have been judged to have unresectable disease at presentation because it is very difficult to diagnose GBC (Gallbladder Cancer) preoperatively. Gallbladder cancer, incidentally diagnosed during pathological examination of gallbladder specimen after cholecystectomy performed for other indication, is defined as incidental gallbladder carcinoma (IGC).[5-9]

## Methods

A total 960 patients with chronic cholecystitis due to cholelithiasis where wall thickness is within normal limit underwent laparoscopic cholecystectomy done during the period from January 2017 to December 2020 in the Department of Surgery of DNMCH. We excluded preoperative malignancy from this study. We have taken history, then physical examination, then investigation like Liver function test, S. Bilirubin, SGPT, S. Alkaline Phosphatase, Prothrombin time, Ultrasound of HBS & Pancreas, Renal function test. Also postoperative findings of gallbladder after laparoscopic cholecystectomy was documented in each of the cases. All the specimens of gallbladder were sent for histopathological examination. The histological slides were reviewed for all the cases.

## Results

A total of 960 patients underwent laparoscopic cholecystectomy in our Department of Surgery during the study period of 4 years. 3 cases (0.41%) were confirmed histologically as carcinoma gallbladder (adenocarcinoma) incidentally.

**Table-I: Incidental Gall bladder carcinoma: Age and Sex distribution with duration of symptoms of 3 patients have been summerized**

| Sl. No. | Age (years) | Sex | Total duration of symptoms |
|---|---|---|---|
| 1 | 65 | Female | Chronic right upper abdominal pain for 2 years |
| 2 | 55 | Female | Chronic right upper abdominal pain for 4 years |
| 3 | 58 | Female | Chronic right upper abdominal pain for 5 years |

**Table-II: Incidental Gall Bladder Carcinoma: Operative procedure and findings with microscopic and pathologic stage.**

| Sl. No. | Operative Procedure | Postoperative Findings | Pathological Grading & Staging |
|---|---|---|---|
| Case-1 | Laparoscopic Cholecystectomy | Multiple gallstones with thick walled gallbladder was found | Well differentiated adenocarcinoma, Pathological stage pT1a (Intramucosal) |
| Case-2 | Laparoscopic Cholecystectomy | Multiple gallstones with thick walled gallbladder was found | Moderately differentiated adenocarcinoma, Pathological stage pT1a (Intramucosal) |
| Case-3 | Laparoscopic Cholecystectomy | Multiple gallstones with thick walled gallbladder was found | Well differentiated adenocarcinoma, Pathological stage pT1a (Intramucosal) |

Case-2 showed moderately differentiated adenocarcinoma. Case-1 and Case-2 showed well differentiated adenocarcinoma. After the histological diagnosis, all the 3 patients were referred to the Cancer Hospital, Mohakhali, Dhaka.

## Discussion

Gallbladder carcinoma (GC) is the most common malignancy of the biliary tract and the sixth most common malignancy of the gastrointestinal tract worldwide.[10] It is an aggressive and late symptomatic disease and most of the patients are treated at advanced stages. The prognosis is usually dismal and the 5 years survival rates have been reported to be less than 5% for the more advanced stages.[9,11] The countries with higher incidence of gallbladder cancer include Chile, Poland, India and Japan. A high incidence of this cancer has been reported among women in northern India (21.5/100000) and among female Native American Indians (14.5/100000).[12,10]

The early stage of carcinoma is typically diagnosed incidentally because of the inflammatory symptoms which are related to the coexistent cholelithiasis or cholecystitis.[1] Incidental gallbladder carcinoma (IGBC) is the carcinoma of gall bladder which is suspected for the first time during cholecystectomy or which is found on the histological examination of the gallbladder.[2,8] With the increasing widespread acceptance of LC (Laparoscopic Cholecystectomy) and the difficulties in diagnosing gallbladder carcinoma preoperatively, the number of cases of IGBC during and after LC has increased.[4,6] The female gender and advanced age are the demographic risk factors for GBC. All the three cases of the incidentally detected gallbladder carcinoma in this series were females and their average age was 58 years. A review of literature showed that 0.19% to 3.3% of the patient who underwent laparoscopic cholecystectomy for cholelithiasis were found to have carcinoma of gall bladder.[1-5] In a study of LC(Laparoscopic Cholecystectomy) cases from the Indian metropolis of Kolkata,reported an incidence of 0.59% of IGBC.[7] The present study which was based on DNMCH (Dhaka National Medical College Hospital) showed an incidence of 0.41% of IGBC among laparoscopic cholecystectomy cases over a period of 4 years.

GBC (Gallbladder Carcinoma) either remains asymptomatic for a longtime or it presents with non-specific symptoms like pain in the abdomen, vomiting, anorexia, jaundice, a gall bladder mass and fever. In this study, 3 patients presented with the features of chronic calculus cholecystitis. The association of GBC with cholelithiasis and chronic gallbladder inflammation is well known. It has been presumed that a longstanding chronic inflammation which is caused by cholelithiasis plays a role in the tumor progression and that carcinogenesis and gallstones are seen in 54-97% of the patients of GBC.[11,13] However, while most of the patients of GBC will have a history of cholelithiasis, only 0.3-3% of the patients with gallstones develop GBC. In this series all the 3 patients who were detected to have IGBC had symptomatic gallstone disease for which LCS were undertaken.[12,14] The other risk factors includea porcelain (calcified) gallbladder, a typhoid carrier state and gall bladder polyp.[12-14]

The ultrasonographic findings in early stage GBC (Gallbladder Carcinoma) are subtle, with considerable overlaps with the findings of acute and chronic cholecystitis. The features such as thickened gall bladder wall, gallbladder stones or CBD stones, a gallbladder mass and a pericholecystic collectionare not characteristics of GBC and they can be associated with cholecystitis.[15] Multiple gallstones with thickened

gallbladder were seen in all the 3 cases of IGBC (incidental gallbladder carcinoma) in this series.

Surgical resection with curative intent in post laparoscopic cholecystectomy gallbladder carcinoma is: for stage T1a surgery is not proved to be necessary but watchful follow up only seems to be required.

**Conclusion**

In our study, incidental gallbladder cancer was found to be 0.41%. Female gender, advanced age, multiple stones and wall thickness > 3 mm were common in our series. Gall bladder cancer runs a short course with poor prognosis. The use of meticulous laparoscopic techniques seems to be important for the diagnosis and avoidance of early complication of this disease.

**References**


1. Ferrase AG, Solej M, Enrico M, Falcone A, Catalano S, Pozzi G, et al. Diagnosis of incidental gallbladder cancer after laparoscopic cholecystectomy: our experience. BMC surgery 2013; 13: 19-22.
2. Clemente G, Nuzzo G, De Rose AM, Giovanini I, LaTorre G, Ardito F. Unexpected gallbladder cancer after laparoscopic cholecystectomy for acute cholecystitis; a worrisome picture. Journal of gastrointestinal surgery 2012; 16: 1462-1468.
3. Bertran E, Heise K, Andia ME, Ferreccio C. Gallbladder cancer: incidence and survival in a high risk area of chile. Int J Cancer 2010; 127: 2446-2454.
4. Zhang WJ, Xu GF, Zou XP. Incidental gallbladder carcinoma diagnosed during or after a laparoscopic cholecystectomy. World J surgery. 2009; 33: 2651-2656.
5. Zhang WJ, Xu GF, Tian ZQ, Wu GZ, Wang H, Guan WX. Surgical approach does not influence the outcome of incidental gallbladder carcinoma. Int J Clin Exp Med 2015; 8(1): 869-875.
6. Ahn Y, Park CS, Hwang S, Jang HZ, Choi KM, Lee SG. Incidental gallbladder carcinoma after cholecystectomy: when should be suspect it preoperatively and what are predictors of patient survival? Ann Surg Treat Res. 2016; 90(3): 131-138.
7. Tantia O, Jain M, Khanna S, Sen B. Incidental carcinoma gallbladder during laparoscopic cholecystectomy for symptomatic gall stone disease. Surg Endos. 2009; 23: 2041–2046.
8. Shrestha R, Tiwari M, Ranabhat SK, Aryal G, Rauniyar SK, Shrestha HG. Incidental Gallbladder carcinoma : value of routine histological examination of cholecystectomy specimens. Nepal Med Coll J. 2010; 12(2): 90–94.
9. Choi SB, Han HJ, Kim CY, Kim WB, Song TJ, Suh SO, et al. Incidental gallbladder cancer diagnosed following laparoscopic cholecystectomy. World J Surg. 2009; 33(12): 2657–2663.
10. Fong Y, Heffernan N, Blumgart LH. Gallbaldder carcinoma discovered during laparoscopic cholecystectomy. Aggressive reresection is beneficial. Cancer. 1998; 83:423–427.
11. Albores-Saavedra J, Henson DE. Tumors of the Gallbladder and Extrahepatic Bile Ducts. Washington DC Armed Forces Institute of Pathology 1986: 108. Atlas of Tumor Pathology, Second series Fascicle. 22.
12. Wakai T, Shirai Y, Yokoyama N, Nagakura S, Watanabe H, Hatakeyama K. Early gallbladder carcinoma does not warrant radical resection. Br J Surg. 2001; 88(5): 675–678.
13. Wakai T, Shirai Y, Hatakeyama K. Radical second resection provides survival benefit for patients with T2 gallbladder carcinoma first discovered after laparoscopic cholecystectomy. World J Surg. 2002; 26(7): 867–871.
14. Goetze TO, Paolucci V. Immediate re-resection of T1 incidental gallbladder carcinomas: A survival analysis of the German registry. Surg Endosc. 2008; 22(11): 2462–2465.
15. Martins-Filho ED, Batista TP, Kreimer F, Martins AC, Iwanaga TC, Leao CS. Prevalence of Incidental Gallbladder Cancer in a Tertiary-Care Hospital from Pernambuco, Brazil. Arq Gastroenterol. 2015; 52: 247-249.

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**Original Article**

# A comparative study of Widal test with blood culture in the diagnosis of typhoid fever in febrile patients

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## Abstract

**Background:** Typhoid fever is a major health problem in developing countries and its diagnosis on clinical ground is difficult. Diagnosis in developing countries including Bangladesh is mostly done by Widal test. However, the value of the test has been debated. Hence, evaluating the result of this test is necessary for correct interpretation of the result. Objective of the study was to compare the result of Widal test with Blood Culture in the diagnosis of typhoid fever in febrile patients in Dhaka National Medical Institute Hospital.

**Methods:** Blood samples were collected from 270 febrile patients with symptoms clinically similar to typhoid fever and visiting Dhaka National Institute Hospital from December 2015 to April 2016. Blood culture was used to isolate S.typhi andS.paratyphi. Slide agglutination test and tube agglutination tests were used for the determination of antibody titer. An antibody titer of $\geq$1:80 for anti TO was taken as a cut of value to indicate recent infection of typhoid fever.

**Results:** One hundred and eighty six (68.9%) participants were females and eighty four (31.1%) were males. 7 (2.6%) cases of S. typhiand 4 (1.5%) cases of S. paratyphi were identified with the total prevalence of typhoid fever 4.1%. The total number of patients who have indicative of recent infection by O antigen is 160 (59.2%). The sensitivity, specificity, positive predictive value(PPV) and negative predictive value(NPV) of Widal test were 71.4%, 41.06%, 3.1% and 98.1% respectively.

**Conclusions:** Widal test has a low sensitivity, specificity and PPV, but it has good NPV which indicates that negative Widal test result have a good indication for the absence of the disease.

**Keywords:** Widaltest , Blood culture, Typhoid Fever.

## Background

Typhoid fever is a systemic prolonged febrile illness caused by certain Salmonella serotypes including Salmonella typhi, S. paratyphi A, S. paratyphi B and S. paratyphi C. Human beings are the only reservoir host for typhoid fever, and the disease is transmitted by faecally contaminated water and food in endemic areas especially by carriers handling food. The World Health Organization (WHO) estimates about 21 million cases of typhoid fever with >600,000 deaths annually. The cases are more likely to be seen in India, South and Central America, and Africa i.e. in areas with rapid population growth, increased urbanization, and limited safe water, infrastructure and health systems.[1,2]

Accurate diagnosis of typhoid fever at an early stage is important not only for diagnosis of etiological agent, but also to identify individuals that may serve as a potential carrier, who may be responsible for acute typhoid fever outbreaks.[3] Options for the diagnosis of typhoid fever are clinical signs and symptoms, serological markers, bacterial culture, antigen detection and DNA amplification.[4,5] Blood, bone marrow and stool culture are the most reliable diagnostic methods but they are expensive techniques and some bacterial culture facilities are often unavailable.[6,7,8] In many countries including Bangladesh, the Widal test is the most widely used test in typhoid fever diagnosis because it is relatively cheaper, easy to perform and requires minimal training and equipment.[9,10]

Although Widal test has been in use for more than a century, the value of the test to diagnose typhoid fever has been debated for as many years as it has been

available.[11] It relies classically on the demonstration of a rising titer of antibodies in paired samples 10 to 14 days apart. In typhoid fever, however, such a rise is not always demonstrable, even in blood culture-confirmed cases.[11] In addition, Interpreting the test has been such a problem that different cut-offs have been reported from different places.[9,12] Furthermore, patient management cannot wait for results obtained with a convalescent-phase sample. For practical purposes, a treatment decision must be made on the basis of the results obtained with a single acute-phase sample.[7,13] So evaluating the result of a single Widal test is necessary for correct interpretation.

This study was carried out to evaluate the value of a single acute-phase Widal test result by blood culture for the diagnosis of typhoid fever in febrile patients in Dhaka National Medical Institute Hospital, Dhaka, Bangladesh in collaboration with other renowned laboratories in Dhaka City.

Study area and period: The study period was 1st December 2015 to 30th April 2016. The study was conducted inDhaka National Medical Institute Hospital,the largest private Medical College Hospital in Bangladesh, located in old Dhaka which is densely populated area in capital city.

**Study design and patient population**

A prospective study on febrile patients was conducted in which patients were screened for typhoid fever and suspected patients were enrolled in the study, then blood samples were collected and tested for confirmation of the disease. Patients were screened by their physician for the clinical symptom of typhoid fever which is fever of 2 or more days before admission accompanied by other clinical symptoms of typhoid fever in the absence of any other known febrile illnesses. Febrile patients whose presumptive clinical diagnosis were typhoid fever sent to the laboratory by their physician for Widal test were included in the study. However, those febrile patients who had received antibiotic treatment for their symptom within two weeks before coming to the hospital and those who diagnosed for other known febrile illness were not included in this study. By using these inclusion and exclusion criteria 277 suspected febrile patients were recruited for this study then data and blood sample were collected and analysed from270 patients.

**Blood sample collection and inoculation**

Using a sterile syringe and needle, about 8–10 ml of blood collected from each study subject,then dispensed into the culture medium bottle containing 45 ml of Tryptic Soya broth (OXOID, England) and then incubated at 37°C.

**Sub culturing and biochemical identification**

After 24 hours' incubation sub-culturing was performed from the Tryptic Soya broth on XLD agar (OXOID, England). After overnight incubation, sensitivity test was done for positive cultures while negative broth cultures were incubated for seven days and sub cultured before reported as negative. Suspected colonies obtained on the above media were screened by biochemical tests using Triple Sugar Iron agar (TSI) (BBL™), citrate utilization test, motility (Difco™), urease test (Himedia ltd. India) and lysine decarboxylation (LDC) [Difco™] test.

**Widal test**

Qualitative slide agglutination and semi quantitative tube agglutination (titration) were performed using febrile antigen kits of Salmonella typhi (Chromatest Febrile Antigens kits, Linear chemicals, Barcelona, Spain). The slide agglutination test is used as a screening test for the presence of anti TO antibodies in the patient's serum. For the slide agglutination test a drop of Salmonella typhi O antigen is added on a drop of serum on card and rotated at 100 rpm for one minute and reported as reactive or non-reactive. For those slide agglutinations whose results are reactive and weakly reactive titer was determined. In the tube agglutination test (titration), serum sample was serially diluted by using fresh 0.95% saline preparation from 1:20 to 1:640 for anti TO separately in 12 test tubes. Then a drop of O antigens are added in the test tubes, equal amount in all. Based on the manufacturer manual, an antibody titer of 1:80 and higher for anti TO antibodies were taken as a cut of value to indicate recent infection of typhoid fever.

**Quality controls**

Standard operational procedures were followed during processing of each sample and all the instruments used for sample processing were checked every morning for proper functioning. E.coli ATCC 25922 was used as a reference strain.

**Data analysis**

Statistical software package (SPSS Version 16) was used for the analysis of the data. Sensitivity, Specificity, Positive Predictive Value (PPV and Negative Predictive Value (NPV) were calculated for Widal test.

## Results

Although 277 febrile patients from the hospital involved in the study, data from 270 patients (where 68.9% patients were female) were analysed, because three missed due to insufficient serum samples to perform Widal test, other three missed due to incomplete sociodemographic data, and one missed due to both insufficient serum sample and incomplete sociodemographic data. The study participants' age ranged from 15–80 years (M = 35.82 ± 12.4 [SD]) and most of them were 15–40 years (94.3%).

### Qualitative slide agglutination Widal test

Qualitative slide agglutination Widal test was performed in the hospital laboratory as a primary screening test of serum for presence or absence of the O antigen of S.typhi. Slide agglutination reaction for O antigen showed that 127 (47.0%) of the patients had reactive agglutination result. 110 ( 40.7%) patients had non-reactive reaction result for O antigen of Salmonella typhi (Table-I).

**Table-I: Qualitative slide agglutination reaction results of Widal test of febrile patients suspected of typhoid fever in Dhaka National Medical Institute Hospital**

| Reaction result | O antigen | |
|---|---|---|
| | Frequency | (%) |
| Reactive | 127 | (47.0) |
| Weakly reactive | 33 | (12.5) |
| Non reactive | 110 | (40.7) |
| **Total** | **270** | **(100.0)** |

### Semiquantitative tube agglutination test (titration)

Titer was performed for those patients whose slide agglutination test result indicated reactive and weakly reactive reactions. One hundred sixty 160 (59.3%) patients had reactive and weakly reactive reaction for anti TO antibody. The frequency distribution of titration result is presented on Table-II.

**Table-II: The frequency distribution of semi quantitative tube agglutination titration test of Widal test in febrile patients suspected of typhoid fever in Dhaka National Medical Institute Hospital**

| Titer | O antigen | | |
|---|---|---|---|
| | Frequency | % (n = 160) | % from total (n = 270) |
| No agglutination | 40 | 25.0 | 14.8 |
| 1:20 | 32 | 20.0 | 11.9 |
| 1:40 | 15 | 9.4 | 5.6 |
| 1:80 | 42 | 26.3 | 15.6 |
| 1:160 | 21 | 13.0 | 7.8 |
| 1:320 | 6 | 3.8 | 2.2 |
| 1:640 | 4 | 2.5 | 1.5 |
| Total | 160 | 100 | 59.3 |

Serum from 40 (25.0%) patients with reactive (12/40) and weakly reactive (28/40) reaction of slide agglutination for anti TO antibody did not show any agglutination in tube agglutination titration test. Among those who had agglutination reaction results, 42 (15.6%) had titer of 1:80 for O antigen.There were only 4 (1.5%) patients whose titer of O antigen was 1:640 and higher.

Antibody titer of 1:80 for O antigen was taken as cut of values to indicate recent typhoid infection (positive titer). Taking O ≥ 80 as a cut of value, we found 73 (27%) patients had indicative of recent typhoid infection. The total number of patients who had indicative of recent infection by O antigen is 88 (32.6%). Among these, 20 (7.4%) patients had antibody titer indicative of recent infection by O (≥1:80) antigen tests.

The agreement between qualitative slide agglutination and semi quantitative tube agglutination test (titration) indicates that there was a moderate agreement between slide agglutination test and tube agglutination titer for O antigen (Kappa = 0.406). In doing these, weakly reactive slide agglutinations reactions were considered as reactive because their titer was determined.

### Blood culture

Of the 270 blood cultures, only 7 (2.6%) S. typhi were isolated from the patients while S. paratyphi were identified from 4(1.5%) patients. The blood cultures of 51 (18.9%) patients' were positive for bacteria other than salmonella species (Table-III).

**Table-III: The distribution of blood culture results of febrile patients suspected of typhoid fever in Dhaka National Medical Institute Hospital**

| Bacteria | Number of isolates (%) |
|---|---|
| S. typhi | 7 (2.6) |
| S. paratyphi | 4 (1.5) |
| Non typhoidal salmonella | 7 (2.6) |
| Other bacteria | 51 (18.9) |
| Negative blood culture | 201 (74.4) |
| **Total** | **270 (100.0)** |

Based on the above results of Widal test and blood culture for Salmonella typhi and Salmonella paratyphi, an evaluation of Widal titration results for the diagnosis of typhoid fever was performed for O (≥1:80) (Table 4 and 5).

**Table-IV:The distribution of anti TO titers among culture positive febrile patients in Dhaka National Medical Institute Hospital.**

| Intensity of pain | Culture positive | Culture Negative | Total |
|---|---|---|---|
| Test positive (Widal test) | 5 | 155 | 160 |
| Test Negative (Widal Test) | 2 | 108 | 110 |
| **Total** | **7** | **263** | **270** |

**Table-V: The sensitivity, specificity, PPV, and NPV of titers of anti TO (≥1:80) Widal tests for diagnosis of typhoid fever from febrile patients in Dhaka National Medical Institute hospital**

| Measurement | O antigen (%) |
|---|---|
| Sensitivity | 71.4 |
| Specificity | 41.06 |
| PPV | 3.1 |
| NPV | 98.1 |

Anti TO agglutination titer of 1:80 and higher were detected among 5/7 (71.4%) of culture confirmed typhoid cases byS. typhi as compared with 2/4 (50%) of S. paratyphi and 3/7 (42.9%) of nontyphoidal salmonella. 46 (27%) patients with a negative blood culture result had a positive Widal titer of anti TO. The antibody titer of culture confirmed typhoid fever caused by S. typhi is presented in Table-V. The overall patients which have positive titer for O antigen and culture confirmed typhoid fever cases were presented on Figure-I.

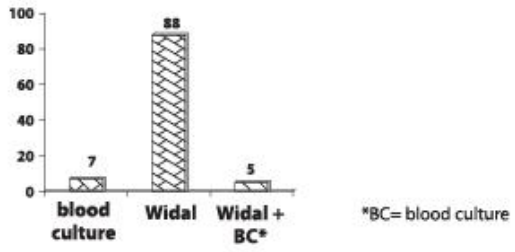


**Figure-I: Diagnostic result of typhoid fever by blood culture and Widal titration of febrile patients suspected of typhoid fever in Dhaka National Medical Institute Hospital, December 2015- April 2016. *BC= blood culture.**

## Discussion

The sensitivity and specificity of Widal titer of anti TO 1:80 and higher in this study were about 71.4% and 41.06% respectively. This is similar with the study conducted in the endemic area of Vietnam by Olsen et al. for the evaluation of serodiagnostic assay of acute enteric fever.[14]

Another study done in Kenya has shown that Widal testing done on acute phase serum of patients suspected to have typhoid fever had limited diagnostic capability given its low sensitivity in which among all typhoid cases only 26% had diagnostic titer while 53.6% had O titer less than 1:4015.With the cut off value of anti TO ≥1:80 Widal titer in this study, Widal test had relatively good NPV (98.9%), but PPV was very low (5.7%).Positive predictive value is more important than other measure of clinical diagnostic methods because it gives the proportion of patients with positive test results that are correctly diagnosed but it is highly affected by a prevalence of the disease. In this study only 7 (2.5%) had culture proven febrile typhoid fever. So a negative Widal test result has a good predictive value for the absence of the disease but a positive result would have a low predictive value for the presence of typhoid fever.[9]

A similar study conducted in Egypt indicates that a negative result of Widal test would have a good predictive value of the disease (NPV=98%) but positive result would have a very low predictive value for typhoid fever (PPV = 5.7%).[16] Low sensitivity for Widal test may also be related to the data collection time. In this study Widal test was performed just at the admission of the patient in the hospital.False positive results of Widal titer were so high in this study (PPV = 5.7%). These false positive results may be associated with cross reacting antibodies from serum of febrile patient other than typhoid fever.

In a study conducted in Cameroon to study the prevalence of typhoid fever of febrile patients with clinically compatible symptom of typhoid fever, 45% of the patients has the true diagnosis of malaria but only 2.5% of the patients had culture proven typhoid fever4.On the other hand, the presence of Widal agglutination under condition of negative malaria smear, negative S. typhi culture and without prior immunization against typhoid suggests that other infections may also share common antigenic determinant with S. typhi.[11] Typhus, C. neoformance meningitis, immunological disorder and chronic liver disease are best example for this.[5]

A similar study conducted in Nigeria in apparently healthy students indicates a higher significant titer of antibody for anti TO antibody of S.typhi.[17] This may

have two negative outcomes in the patient and also in the community. One is that patients are treated (mismanaged) for salmonella having another febrile disease which in turn results in the development of drug resistance.[18] The other is the highly fatal disease of febrile illness such as malaria, non typhoidal salmonellosis, endocarditis and urinary tract infection might be missed.[5]

False negative results were also found in our study. 2 cases among seven culture confirmed typhoid fever cases had a negative titer. The false negative Widal test results were there probably because blood was collected too early in the disease processes, or inoculated bacterial load is inadequate to induce the antibody production.[11] Previous antibiotic treatment may also contribute to negative Widal agglutination test but there was no patient who explained taking antibiotic within two weeks before coming for the diagnosis during this study.

The positivity of slide agglutination and tube titration in this study was about 49.3% and 38% respectively. Similar positive results were obtained by slide agglutination reaction. Statistically there was moderate agreement (kappa = 0.406) between slide agglutination and tube agglutination titer of anti TO. A study conducted in Jimma, south-western Bangladesh, indicated fair agreement (kappa = 0.225) for anti TO.[19] The current study was conducted in febrile patients while Mamo and his colleagues conducted on healthy population, and this could be one reason for the agreement differences. But still the agreement of slide agglutination and tube titration was very low.

The slide agglutination test is rapid and is used as a screening procedure. An initial positive screening test requires the determination of the strength of antibody. But in many developing countries where the disease is endemic a laboratory professional performs the test, makes diagnosis and reports as positive or negative (reactive and non-reactive).[11] This is also the case of Dhaka National Medical Institute Hospital where this study was conducted. Normally the result of Widal test should be reported as either of 'agglutination' or 'no agglutination' and if agglutination is present, in titers (1:20, 1:40…) rather than in reactive or non-reactive terms. This type of reporting may be misleading and contribute to the incorrect interpretation of the test result by the physicians.[11]

In addition to S.typhi and S.paratyphi other bacteria were identified from blood culture of the febrile patients who had positive or negative Widal titer. In the current study seven (2.6%) cases of non typhoidal salmonella and 51 (18.8%) cases of other bacteria were identified from blood culture. The result of non typhoidal salmonella (2.6%) was similar to a study done in Tanzania; the study identified 2.9% of non typhoidal salmonella from blood culture.[9,20] Positive Widal titers were also seen in cases of nontyphoidal salmonella and in blood culture positive cases for other bacteria. 3 out of 7 (42.9%) of nontyphoidal salmonella cases and 17 of the 51 (33.3%) other bacteria positive cultures had a positive titer of anti TO.[21]

## Conclusion

The qualitative slide agglutination tests had a moderate agreement with standard tube agglutination test (titration). Therefore, laboratories should perform the standard laboratory procedure of Widal test and follow the standard reporting instead of in 'reactive' and 'non-reactive' terms. The sensitivity, specificity, PPV and NPV of Widal test were 71.4%, 41.06%, 3.1% and 98.1% respectively. A high antibody titer development is also seen in nontyphoidal febrile infections. In addition,Widal test in the laboratory should also be performed using O antigen of S.paratyphi A, S.paratyphi B and S.paratyphi C. Nevertheless, using Widal test as the only laboratory test for the diagnosis of typhoid fever will result in misleading diagnosis.

## Acknowledgement

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## References

1. Willke A, Ergonul O, Bayar B;Widal test in diagnosis of typhoid fever in turkey. Clin Diagn Lab Immunol. 2002, 9 (4): 938-941.PubMedPubMed Central
2. Crump JA, Luby SP, Mintz ED; The global burden of typhoid fever. Bull World Health Organ. 2004, 82 (5): 346-353.PubMedPubMed Central
3. Gopalakrishnan V, Sekhar WY, Soo EH, Vinsent RA, Devi S; Typhoid fever in Kuala Lumpur and a comparative evaluation of two commercial diagnostic kits for the detection of antibodies to salmonella typhi. Singapore Med J. 2002, 43 (7): 354-358.PubMedPubMed Central

4. Nsutebu EF, Martins P, Adiogo D; Prevalence of typhoid fever in febrile patients with symptoms clinically compatible with typhoid fever in Cameroon. Trop Med Int Health 2003; 8 (6): 575-578. 10.1046/j.1365-3156.2003.01012.x.PubMedView Article

5. Onyekewere CA: Typhoid fever; misdiagnosis or over diagnosis. Niger Med Pract. 2007; 51 (4): 76-79.

6. Wain J, Hosoglu S; The laboratory diagnosis of enteric fever. J Infect DevCtries. 2008, 2 (6): 421-425.PubMedView Article

7. Parry CM, Tuyet HNT, Diep TS, Wain J, Chinh NT, Vinh H, et al. Value of a single-tube widal test in diagnosis of typhoid fever in Vietnam. J Clin Microbiol. 1999, 37 (9): 2882-2886.PubMedPubMed Central

8. Wain J, Diep TS, Be Bay PV, Walsh AL, Vinh H, Duong NM, et al. Parry CM, Day NPJ; Specimens and culture media for the laboratory diagnosis of typhoid fever. J Infect DevCtries. 2008, 2 (6): 469-474.PubMedView Article

9. Ley B, Mtove G, Thriemer K, Thriemer K, Amos B, Seidlein LV et al.; Evaluation of the Widal tube agglutination test for the diagnosis of typhoid fever among children admitted to a rural hospital in Tanzania and a comparison with previous studies. BMC Infect Dis. 2010, 10: 180-10.1186/1471-2334; 10-180.PubMedPubMedCentralView Article

10. Beyene G, Asrat D, Mengistu Y, Aseffa A, Wain J.; Typhoid fever in Ethiopia. J Infect DevCtries. 2008, 2 (6): 448-453.PubMedView Article

11. Olopoenia LA, King AL; Widal agglutination test-100 years later; still plagued by controversy. Postgrad Med J. 2000; 76: 80-84. 10.1136/pmj.76.892.80.PubMedPubMed CentralView Article

12. Bhutta ZA; Current concepts in the diagnosis and treatment of typhoid fever. BMJ. 2006, 333: 78-82. 10.1136/bmj.333.7558.78.PubMedPubMed CentralView Article

13. Khoharo HK, Ansari S, Qureshi F;Evaluating single acute-phase widal test for the diagnosis of typhoid fever. Med Channel. 2010, 16 (1): 42-44.

14. Olsen SJ, Pruckler J, Bibb W, Thanh NT, Trinh TM, Minh NT et al.; Evaluation of rapid diagnostic tests for typhoid fever. J Clin Microbiol. 2004, 42 (5): 1885-1889. 10.1128/JCM.42.5.1885-1889.2004.PubMedPubMed CentralView Article

15. Omuse G, Kohli R, Revathi G; Diagnostic utility of a single widal test in the diagnosis of typhoid fever at Aga khan university hospital (AKUH), Nairobi. Kenya Trop Doct. 2010; 40 (1): 43-44. 10.1258/td.2009.090109.PubMedView Article

16. Youssef FG, Daba AS, Kabeil SS, Parker TM; A comparative study of blood culture and antibody response with the duration of illness in diagnosis of typhoid fever. Aust J Basic Appl Sci. 2010, 4 (4): 609-614.

17. Udeze AO, Abdulrahaman F, Okonko IO, Anibijuwon II;Seroprevalence of S.typhi among the first year students of university of Ilorin, Ilorin, Nigeria. Middle East J Sci Res. 2010; 6 (3): 257-262.

18. Nsutebu EF, Ndumbe PM, Koulla S; The increase in occurrence of typhoid fever in Cameroon; over diagnosis due to misuse of the Widal test. Trans R Soc Trop Med Hyg. 2002; 96 (1): 64-67. 10.1016/S0035-9203(02)90243-9.PubMedView Article

19. Mamo Y, Belachew T, Abebe W, Gebre-Selassie S, Jira C; Pattern of widal agglutination reaction in apparently healthy population of Jimma town, southwest Ethiopia. Ethiop Med J. 2007; 45 (1): 69-77.PubMed

20. Feasey NA, Archer BN, Heyderman RS, Sooka A, Dennis B, Gordon MA et al.; Typhoid fever and invasive nontyphoid Salmonellosis, Malawi and South Africa. Emerg Infect Dis. 2010, In press article

21. Aftab R, Khurshid R;Widal agglutination titre; a rapid serological diagnosis of typhoid fever in developing countries. Pak J Physiol. 2009; 5 (1): 65-67.

J. Dhaka National Med. Coll. Hos. 2022; 28 (01): 16-19

**Original Article**

# Functional outcome of Unstable Distal Radial Fracture Management by External Fixator using the Principle of Ligamentotaxis

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**Abstract:**

**Objective:** The aim of the present study was to asscess the functional outcome of Unstable Distal Radial Fracture managed by External Fixator using the Principle of Ligamentotaxis.

**Methods:** A prospective observational study was conducted from July 2016 to June 2018 among 32 patients attending at Orthopaedics and Traumatology department of the Dhaka Medical College Hospital after obtaining requisite consent from the patients. The collected data were entered into the computer and analyzed by using SPSS (version 20.1) to asscess the functional outcome of Unstable Distal Radial Fracture managed by External Fixator using the Principle of Ligamentotaxis. The study was approved by the institutional ethical committee.

**Results:** 32 patients were enrolled for the study. The mean age of the patients was 37.56±11.82. More than half of the respondents were male (68.75%). Results were assessed by Demerit point system of Gartland and Werley for functional outcome In this study satisfactory result was seen in 84.37% and unsatisfactory result was seen in 15.63%. All fractures (100%) were united nicely.

**Conclusion:** Unstable distal radial fracture management by external fixator using the principle of ligamentotaxis is an effective method of treatment.

**Keywords:** Distal radius fracture, External fixator.

## Introduction

Distal radius fracture has been estimated to account for one-sixth of all fractures that are seen and treated in emergency rooms.[1] It occurs in middle aged and elderly women commonly. But it can also occur in young men with high velocity injury though less in number. Patients with fracture of distal end of radius have serious complications more frequently than generally appreciated and failure in management may cause permanent disability.[2] Recently surgical management has been widely recommended and performed to prevent disability. Several studies have shown convincingly that functional outcome is good when the anatomy is restored by obtaining good reduction of fracture fragments, maintaining the angulations of the articular surface of radius and radial length.[3] Various surgical interventions are available presently, like percutaneous pinning, intra focal pinning, external fixator and plate fixation. In this clinical study only the unstable distal radius fractures have been selected for external fixation, which are not amenable to treatment by closed reduction and plaster cast immmobilization. As these fractures have an inherent capacity for loss of reduction or shortening or both. The instability can be recognized by the presence of much communition, severe dorsal angulation (≥20°) or extensive intra articular involvement. In these cases it is difficult to align the fracture fragment, and to maintain the reduction.[4] External fixator may be performed in a bridging technique and a non bridging technique. Bridging external fixator allows distraction across the radio carpal joint. Anderson and O Neil were first to maintain fracture reduction using an external fixator using in 1977, but Vidal Jacques described original method of treatment of these fractures with ligamentotaxis.[5] The moulding of fracture fragments into alignment by traction force applied across the fracture through the surrounding soft tissue is known as ligamentotaxis. The same ligaments, retinaculae, tendons and the periosteum that envelop the fracture

which are the surgical barrier for open reduction of the fracture fragments, help to achieve reduction of the fracture by ligamentotaxis.[6] Multiple studies have documented the efficacy of this technique. If unstable distal radial fracture management by external fixator using the principle of ligamentotaxis shows acceptable outcome, it would help many patients in the rural areas. Because it less invasive and comparatively easy procedure.

## Materials & method

A prospective observational study was conducted from July 2016 to June 2018 among 32 patients attending at Orthopaedics and Traumatology Department of the Dhaka Medical College Hospital after obtaining requisite consent from the patients. Purposive sampling was done to collect the data. The collected data were entered into the computer and analyzed by using SPSS (version 20.1).

## Result

Table-I shows distribution of patients by age. In this study the highest number of patients 9 (28.13%) were within 35-43 years. The mean age was 37.56±11.82 years.

**Table-I: Age distribution of the study population (n=32)**

| Age in years | Frequency | Percentage (%) |
|---|---|---|
| 18 – 25 years | 7 | 21.88 % |
| 26 – 34 years | 8 | 25 % |
| 35 – 43 years | 9 | 28.13 % |
| 44 – 52 years | 3 | 9.38 % |
| ≥53 years | 5 | 15.63 % |
| **Total** | **32** | **100 %** |

Among the study population male (68.75%) was found 22 and female (31.25%) was 10 (Figure-I).

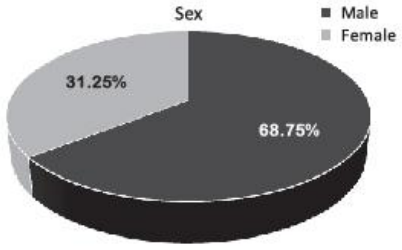



**Figure-I: Pie chart showing percentage of sex distribution of patient**

According to table-II, most of the patients had closed fractures. Number of such cases was 25 (78.12%)

**Table-II: Distribution of patients according to soft tissue involvement (n=32)**

| Type of fracture | Frequency | Percentage (%) |
|---|---|---|
| Open fracture | 3 | 9.37 % |
| Closed fracture | 25 | 78.12 % |
| Technically open fracture | 4 | 12.5 % |
| **Total** | **32** | **100 %** |

According to table 3, majority (37.50%) injury was AO/ASIF type C3 fracture. It signifies that majority of injuries were as a result of high velocity.

**Table-III: Distribution of patients according to AO/ASIF type of the fractures of the distal radius (n=32).**

| AO / ASIF Type | Frequency | Percentage (%) |
|---|---|---|
| A3 | 1 | 3.13% |
| B1 | 2 | 6.25% |
| C1 | 8 | 25 |
| C2 | 9 | 28.13 |
| C3 | 12 | 37.50 |

Majority cases were operated on the day of injury. It was 20 in number (62.50%). No cases were delayed more than 7 days. The mean time interval between injury and fixation was 2.12±1.43 days

**Table-IV: Distribution of time interval between injury and fixation (n=32)**

| Group | Time interval between injury and fixation (days) | Frequency | Percentage (%) |
|---|---|---|---|
| 1 | 0-1 | 20 | 62.50% |
| 2 | 2-3 | 8 | 25% |
| 3 | 3-7 | 4 | 12.50% |

In majority cases (68.75%) external fixators were kept for 6 weeks. Only in 10(31.25%:= 25% + 6.25%) cases more than 6 weeks were required but no cases got more than 8 weeks of immobilization. The mean time of keeping the fixator was 6.69±0.61 weeks.

**Table-V: Distribution of duration of immobilization by external fixator (n=32).**

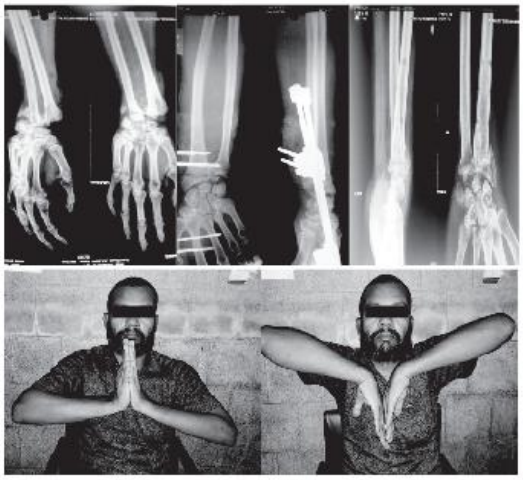
| Group | Duration of immobilization (weeks) | Frequency | Percentage (%) |
|---|---|---|---|
| 1 | 6 | 22 | 68.75% |
| 2 | 7 | 8 | 25% |
| 3 | 8 | 2 | 6.25% |

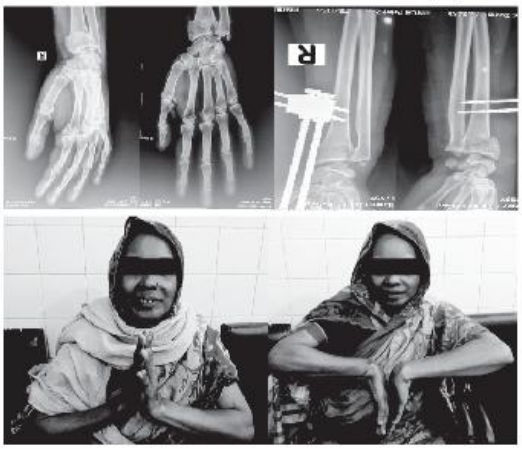
In this series 32 patients were available finally for functional evaluation. It shows excellent results in 25%, good results in 59.37% cases, fair results in 9.37% cases and poor result in 6.25% cases. The mean functional score was 6.78±5.69 ranging from 1 to 22 points.

**Table-VI: Distribution of the study patients according to functional score Gartland and Werley (n=32)**

| Result | Score | Frequency | Percentage (%) |
|---|---|---|---|
| Excellent | 0-2 | 8 | 25% |
| Good | 3-8 | 19 | 59.37% |
| Fair | 9-20 | 3 | 9.37% |
| Poor | >20 | 2 | 6.25% |

According to Demeritpoint system of Gartland and Werley, excellent and good outcome are considered as satisfactory & fair and poor outcome are considered as unsatisfactory.Satisfactory= Excellent + Good= 25% + 59.37%= 84.37% Unsatisfactory= Fair + Poor= 9.37%+ 6.25%= 15.62%.





## Discussion

In this study it is observed that mean age of the patient was 37.56 ± 11.82 years and the maximum number of the patients belonged to the age range between 35 to 43 years. Bacron & Kurtzke in a study with two thousand cases in New York between the period of 1945 to 1949 had found that the average age of the patients was 48.2 years.[7] In this study 22 patients were male (68.75%) and 10 were female (31.25%). Dissimilar results were obtained in the study conducted by Baron, JA et al.[8] study. In their study they stated that womens were approximately 4.88 times more likely than men to obtain a distal forearm fracture.[8] In our study out of 32 patients we found 84.37% satisfactory and 15.63% unsatisfactory result. In a popular study Vaughan et al. assessed 52 patients for a period of 58 months and produced 85% satisfactory result.[9] Alamgir et al. assessed the result of 15 patients of unstable distal radial fractures with/without intraarticular extension and produced 86% satisfactory and 14% unsatisfactory result.[10] So there is no significant difference of result of present series with that of the previous work. Maruthi & Shivanna produced 76.68% satisfactory result in 30 patients with external fixator with an average follow up of 9 months. The dissimilarity may be contributed to the different scoring system used by the authors. He used modified Green-O'Brein clinical scoring system.[5]

## Conclusion

It is concluded that unstable distal radial fracture management by uniplanar static external fixator using the principle of ligamentotaxis is a satisfactory and effective method of treatment. Moreover, it is simple

technique, less invasive procedure, learning curve is also short and hardware can be removed in outpatient basis.

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**Conflict of Interest**

Authors declare no conflict of Interest.

**References**

1. Jupiter, J.B., (1991), "Current concepts review: fractures of the distal end of the radius", The Journal of bone and joint surgery, American vol.73(3), pp.461-469.
2. Wadsworth, T.G., (1990), "Colles' fracture: Failure in management may cause permanent disability", British medical journal, 301, pp.192-94.
3. McQueen, M. and Caspers, J., (1988), "Colles fracture: does the anatomical result affect the final function", Bone & Joint Journal, vol 70(4), pp.649-651
4. Cooney, W.P., Dobyns, J.H. and Linscheid, R.L., (1980), "Complications of Colles' fractures", The Journal of bone and joint surgery, American vol. 62(4), pp.613-619.
5. Maruthi, C.V., Shivanna, (2015), "Management of fracture of distal radius by external fixator using the principle of ligamentotaxis a prospective study", Indian Journal of Orthopaedics Surgery, vol 2(1), pp.19-26.
6. Agee J.M., (1993), "External fixation: Technical advances based upon multiplanar ligamentotaxis", Orthopaedic Clinic North America, vol 24(2), pp.265-274.
7. Bacorn, R.W. and Kurtzke, J.F., (1953), "Colles' Fracture : A Study of Two Thousand Cases From the New York State Workmen'S Compensation Board", JBJS, vol 35(3), pp.643-658.
8. Baron, J.A., Karagas, M. et al. (1996), "Basic epidemiology of fractures of the upper and lower limb among americans over 65 years of age" vol. 6, pp. 612-628
9. Vaughan, P.A., Lui, S.M., Harrington, I.J. and Maistrelli, G.L. (1985) , "Treatment of unstable fractures of the distal radius by external fixation", Bone & Joint Journal, vol 67(3), pp.385-389.
10. Alamgir, M.M., Islam, M.M., Haque, M.E., Islam, M.N. and Kader, A.(2014), "Treatment of Comminuted Intra-articular Fractures of Distal Radius by External Fixator", Journal of Current and Advance Medical Research, vol 1(2), pp.30-34

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**Original Article**

# Comparison between tonsillotomy and tonsillectomy of young children 2 years post surgical followup

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**Abstract:**

**Objectives:** To study the long-term effect of tonsillotomy and tonsillectomy in young children after two years in comparison to the results after six months.

**Method:** Children, age 4-5 with Sleep Disordered Breathing (SDB) and tonsil hyperplasia, were randomized to TE (32) or TT (35). TT was performed by diathermy. An adenoidectomy with cold steel (Universal Dissection Method) was performed in the same session for 80% of cases. The patients were assessed prior to surgery, at six and 24 months postoperatively. Effects of surgery were evaluated clinically, through questionnaire (general health/snoring/ENT-infections), Quality of Life (QoL), survey of pediatric obstructive sleep apnea with OSA-18, and children's behavior with the Child Behavior Checklist.

**Results:** After two years there was still no difference between the groups with respect to snoring and frequency or severity of upper airway infections. Both TT and TE had resulted in large improvement in short and long term QoL and behavior. Three TT-children and one TE child had been re-operated due to recurrence of obstructive problems, the TE-child and one of the TT-children with adenoidectomy and two of the TT-children with tonsillectomy. Three of the TT-children had tonsil tissue protruding slightly out of the tonsil pouch and twelve TE-children had small tonsil remnants within the tonsil pouches, but with no need for surgery.

**Conclusion:** Younger children have a small risk of symptom-recurrence requiring re-surgery within two years after TT. For the majority, the positive effect on snoring, infections, behavior and quality of life remain and is similar to TE.

**Keywords:** Tonsillotomy, Tonsillectomy, Quality of Life, Methodology.

## Introduction

At present, the most common indication for tonsil surgery in children is upper airway obstruction causing Sleep Disordered Breathing (SDB).[1] SDB is a symptom-complex including not only snoring and sleep apnea, but also restless sleep, frequent awakenings, failure to thrive and behavioral disturbances. Oral breathing is often associated with SDB and may cause subsequent bite aberrations.[2] Daytime health related quality of life (HRQL) and level of functioning have been found to be affected by SDB.[3-7] Simple snoring without other symptoms of SDB, usually does not qualify a child or an adult for tonsil-surgery.

SDB in children is most commonly caused by a relative hypertrophy of the Waldeyer ring, which usually peaks in size around the age of five.[8-10] That is why tonsil surgery due to SDB is especially common in the pre-school age groups.[3]

During the past decade, tonsillotomy, or intracapsular tonsillectomy, partial removal of the tonsils, has become accepted as the surgical method for tonsil hyperplasia because it causes less surgical trauma, carries less risk for serious bleedings than total tonsillectomy, and allows for a more rapid recovery.[1,11]

The aim of the present investigation is to study the long-term effect of tonsillotomy and tonsillectomy in young children after two years in comparison to the results after six months and to assess whether the beneficial effects persisted that were observed after six months on snoring, infections, HRQL and behavior.[4]

## Methods

Children (4.5–5.5 yrs), who all had tonsil hypertrophy and obstructive problems (SBD), assessed by an

ENT-surgeon and been put on the waiting-list for tonsil surgery, had been randomized to either TT(35) or TE(32).4 No sleep studies had been performed on these "otherwise healthy" children, who were neither obese nor had signs of severe OSAS. Sixty-seven children were enrolled, 28 girls and 39 boys, aged 50–65 months (mean age, 56 months; 4.8 years old). Twenty per cent had had one or a few bacterial upper airway infections (tonsillitis) prior to the last three months before surgery. These infections did not exclude them from the study.

Exclusion criteria were recurrent tonsil infections during the last few months, small tonsils, obesity, bleeding disorder.

Randomization had been done from the waiting list (a sequentially numbered list generated by a computer), and families had been informed about the study and the randomization outcome by mail before giving informed consent.[4] Before surgery, the parents had also answered: a disease-specific quality of life questionnaire about general health, snoring, eating difficulties and infections,[12-14] OSA-18 (Obstructive Sleep Apnea-18)[4,15] and a standardized assessment of child behavior, CBCL (Child Behavior Check List).[4,16]

TE had been performed on 22 boys and 10 girls and 17 boys and 18 girls underwent TT. 80% (28TT/25TE) underwent adenoidectomy at the same time as primary tonsil surgery and 10% (5TT/1TE) had had an adenoidectomy earlier.

The tonsillectomies were all performed using cold steel (Dissection Methods)

All tonsillotomies were performed using diathermy. All children participated in the six month follow-up.[4] Two years after surgery, the children were called in for a clinical follow-up, which was not blinded. An ENT-specialist performed a structured interview and examination, which included an estimation of the remaining tonsil tissue inside or outside the pillars in both groups. The interview covered the parents' evaluation of snoring using a Visual Analogue Scale/VAS (no snoring to severe snoring before, immediately after, and at present two years after surgery). Parents were asked about episodes of upper respiratory infections (URI) with or without treatment with antibiotics, onset of allergies, voice problems/changes, appetite, enuresis and mouth breathing.

The same questionnaires that had been given six months after surgery were administered: the questionnaires about general health, snoring, eating difficulties and infections, OSA-18, and CBCL, were used, with the specific instruction that the same parent as before filled them out. The patients who reported episodes of antibiotic-treated URTI after surgery were further investigated and characterized after their medical charts had been obtained from the treating physician.

Questionnaire (Qu) included 11 questions comparing the time before and after surgery concerning general health, temper, stamina/energy, concentration, snoring prevalence and snoring loudness, appetite, ENT-infections, antibiotic treatment and satisfaction. The questions were assessed on a five-step Likert scale.[4,14]

The OSA-18 consists of 18 items grouped into 5 domains: sleep disturbance, physical symptoms emotional distress, daytime function, and caregiver concerns.[4,15] Items are scored on a 7-point ordinal scale that assesses the frequency of specific symptoms, scored from 1, "none of the time" to 7, "all of the time". Item responses are summed to produce a total score ranging from 18 to 126. A total score less than 60 suggests minor impact on disease-specific QoL, 60–80, a moderate impact, and greater than 80. a major impact. A mean survey score and individual domain mean scores are calculated. The OSA-18 change scores are calculated by subtracting the follow-up mean survey score and the individual domain mean scores from the baseline mean and individual domain mean scores. Positive values indicate clinical improvement and negative values indicate deterioration. The OSA-18 also provides a direct global rating of SDB-related Health Related Quality of Life (HRQL) via 10-point visual analogue scale with specific semantic anchors.

The CBCL was scored to obtain a total problem score, as well as scores for "Internalizing behavior" (sub scores: Withdrawn, Somatic Complaints, Anxious/Depressed) and "Externalizing behavior" (sub scores: Delinquent Behavior and Aggressive Behavior).[16,17] Normative data was available from 1991 for the Swedish population for the version of the instrument used. Each item is scored from 0, "not true" to 2, "very true"/"often true". The scores from the present study were compared to the normative data for a group of school children 6–15 years old.[18] The instrument consists of two parts: social competence and behavioral/emotional problems. In the present study, only the items from the latter part have been used. Parents completed the same parts of CBCL, as at the time of surgery and at the six month's assessment.

**Results**

At the two year follow-up, all 67 children answered the questionnaires and 64 children (95.5%) came to the clinical examination.

At the six-month follow-up, no differences in frequency and loudness of snoring or ENT-infections had been noted between the TT and the TE group.[4]

At the present two year follow-up, the structured interview showed no difference between the TT and the TE group concerning snoring although three children had been re-operated.

At the ENT examination, one of the 33 TT-children was found to have tonsil tissue slightly outside the tonsil pouch. The parents noted some snoring (VAS 4), but less than before surgery and felt there was no need for re-surgery. 12/32 TE-children had small remnants of tonsil tissues within the tonsil pouches, but none of them reported any significant snoring.

The median value for parental evaluation of severity of snoring before versus two years after surgery with VAS was 8.4 before and 1.3 after TE(n = 32) and 8.5 before and 1.6 after TT(n = 33) (ns).

One TT-child and one TE-child had undergone adenoidectomy due to recurrence of snoring later than the six-month control. Two TT-children (5.9%) were tonsillectomized due to recurrence of snoring after the six-month control, both being of normal weight. One of them had also had two episodes of tonsillitis after 6 months. After re-surgery with TE, this child started to snore again and a new recurrence of adenoid was diagnosed. This time the snoring was alleviated with nasal steroids. A third child with no recurrence of snoring had a re-TT due to severe enuresis and encopresis, which, according to the parents, had been temporarily improved after the first surgery with TT. No positive effect on encopresis was noted after the second operation. This child has since then had continued contact both with the Paediatric clinic and the Child Psychiatric clinic.

No generally increased tendency for upper airway infections was noticed in either group. Antibiotic-treated throat infections were reported by eight TT-children and one TE. The charts of these patients were acquired, showing that three were diagnosed with a positive Rapid Strep Test, the rest (5) had been diagnosed without any objective measures. Two had suffered from recurrent infections preoperatively and one of them had also undergone re-surgery. One child of the five had been treated because of streptococcal infections in the family although asymptomatic himself. One TE-child reported three antibiotic-treated episodes of throat infections after surgery, which was, however, still fewer than he had had before surgery.

Oral breathing was reported in 17/65 children equally in the groups, compared to 40/67 before surgery and 8/65 after six months.19 In three TT children and two TE children, the oral breathing was only during sleep (ns). No change of voice quality was observed by the parents or the examiner in either group. No child in either group had developed any allergies after surgery.

The questionnaire about general health (Qu) did not show any significant changes between six months and two-years concerning general health, frequency or loudness of snoring (Figure-I) or number of ENT infections (otitis and URI including sore throat, Figure-II).

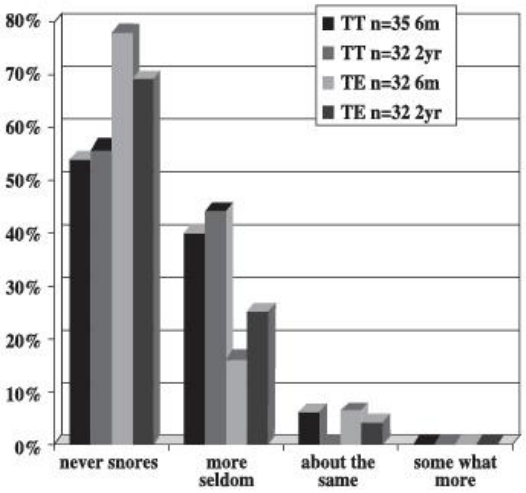


**Figure-I: The frequency of snoring after surgery (six months and two years) in comparison with snoring before surgery (Qu) rated by parents. The children reoperated with tonsil surgery are excluded in the two year follow-up.**

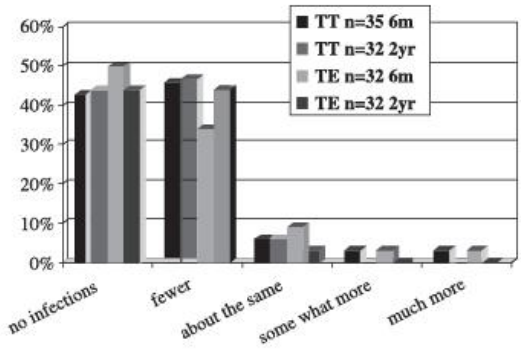


**Figure-II: Assessment of prone to ENT infections children (Qu) were after surgery, six months and two years. The children reoperated with tonsil surgery are excluded in the two year follow-up.**

The results from OSA-18 are shown in Table-I where the preoperative data are compared with the 6-month results and the 2-year follow-up. "Sleep disturbance" and "physical suffering" were the highest rated domains. There was no difference between the TT and TE groups in the improvement of scores after two years, (Table-II and Figure-III). The total OSA-18 score and each of the domain scores and the visual scale showed large improvement for both tonsillectomy and tonsillotomy after six months ($p<0.0001$), an improvement which persisted after two years (Figure-III). After six months, the "emotional distress" change was moderate and after two years, a major change was noted (Table-II). A fair to good correlation was seen between OSA-18 total score and CBCL total problems preoperatively, and also the postoperative changes in those measures correlated fairly well. After two years there was no difference compared to normative value and the study groups' for "externalization" and "total problem" (Table-II) and no differences between the groups.

**Table-I: Preoperative responses for the OSA-18 and change scores in TT and TE**

| | TT pre | TT change score[b] at 6 mo | TT pre | TE change score[b]at 6 mo | P-valuec TT/TE change scores at 6 mo | TT change score[b]pre to 2yr | TE change score[b]pre to 2yr | P-valuec TT/TE change scores pre to 2 yr |
|---|---|---|---|---|---|---|---|---|
| | | n=35 | n=35 | n=32 | n=32 | | n=32 | n=32 |
| Total | 3.5±1.0 | 1.8±1,0 | 3.4±1.0 | 1.8±1,0 | NS | 1.8±1,2 | 1.9±1,4 | NS |
| Sleep disturbance[a] | 4.2±1.3 | 2.7±1.5 | 3.9±1.4 | 2.6±1.5 | NS | 2.9±1.5 | 2.5±1.3 | NS |
| Physical symptoms[a] | 3.9±1.3 | 1.9±1.7 | 3.8±1.4 | 2.1±1.6 | NS | 2.1±1.5 | 2.0±1.4 | NS |
| Emotional distress[a] | 3.2±1.7 | 1.0±1.4 | 3.1±1.4 | 1.1±1.5 | NS | 1.6±2.1 | 1.7±1.8 | NS |
| Daytime function[a] | 3.1±1.4 | 1.2±1.5 | 3.3±1.3 | 1.7±1.2 | NS | 1.5±1.3 | 1.3±1.3 | NS |
| Caregiver concerns[a] | 3.0±1.6 | 1.6±1.5 | 2.8±1.4 | 1.5±1.3 | NS | 1.5±1.5 | 1.5±1.3 | NS |

[a]mean ± standard deviation (SD; bChange score=The follow-up mean survey score and the individual domain scores subtracting from the baseline mean and individual domain mean scores cMann-Whitney U-Test. (Change score<0.5=trivial change; 0.5 to 0.9= small change; 1.0 to 1.4 =moderate change; and ≥1.5= large change). The children reoperated with tonsil surgery are excluded in the two year follow-up.

**Table-II: Child Behavior Checklist before and after surgery, TE resp. TT and compared with normal range**

| | TT | TE | P-value TT CBCL/ normal range[a,c] | P-value TE CBCL/ normal range[a,c] | P-value TT/TE CBCL |
|---|---|---|---|---|---|
| Before surgery | n=35 | n=32 | | | |
| Internalization[b] | 5.8±4.6 | 4.2±3.6 | <0.01 | NS | NS |
| Externalization[b] | 9.8±7.0 | 7.8±6.1 | NS | NS | NS |
| Total problems[b] | 25.6±19.1 | 20.9±12.4 | <0.001 | <0.01 | NS |
| Six months after surgery | n=35 | n=32 | | | |
| Internalization[b] | 3.7±5.4 | 2.4±2.7 | NS | <0.05 | NS |
| Externalization[b] | 7.6±6.7 | 6.3±4.5 | <0.05 | NS | NS |
| Total problems[b] | 19.5±18.4 | 13.5±9.8 | <0.05 | NS | NS |
| Two years after surgery | n=32 | n=32 | | | |
| Internalization[b] | 3.1±3.9 | 2.9±5.8 | NS | <0.05 | NS |
| Externalization[b] | 5.6±6.0 | 5.6±6.9 | NS | NS | NS |
| Total problems[b] | 13.9±12.9 | 13.6±21.7 | NS | NS | NS |

NS= not significant. [a]Normal range. Swedish population [18][b]Mean ± SD [c]Mann-Whitney U-test. The children reoperated with tonsil surgery are excluded in the two year follow-up.

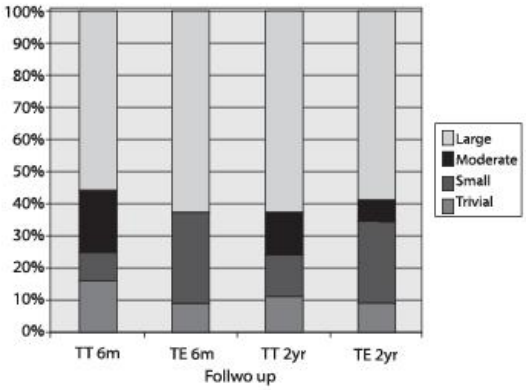


**Figure-III: TT=32/TE=32 Change in disease-specific quality of life 6 months and 2 years after.Tonsillotomy and Tonsillectomy. The children reoperated with tonsil surgery are excluded in the two year follow-up.**

After two years there was no difference compared to normative value and the study groups' for "externalization" and "total problem" (Table-II) and no differences between the groups.

**Discussion**

Concerns about re-growth and recurrence of obstructive problems have been raised after partial removal of tonsils, especially with respect to younger children with a naturally rapid growth of the lymphatic tissue in the Waldeyer ring and at the same time narrow dimensions of the upper airway.[8,10] The present study demonstrates equally good long-term results on recurrence of SDB for RF-tonsillotomy as for traditional tonsillectomy in a young group of patients.

There is however a certain risk of re-growth of tonsil tissue and recurrence of obstructive problems. How great that risk is, is not possible to evaluate with the power of the present study although recurrence rates of six to seven per cent among very young children[20,21] and around three per cent or lower[22-25] among older children have been noted in other studies. Large material, such as those in register studies, are needed for these kinds of analyses. In the present study, a couple of the TT children had undergone further tonsil surgery within two years due to recurrence of snoring and one child in each group had had another adenoidectomy.

Tonsillotomy diathermy tonsillotomy methods do vary considerably, with some techniques aiming at removing as much tonsil tissue as possible, leaving only a thin layer as a "biological dressing". In the present study, we aimed at only removing the obstructing tonsil tissue protruding medially of the pillars, thereby reducing the risk of bleeding, and also resulting in less pain as well as shorter operating time. Due to the study plan, TE was performed after recurrence of snoring (in two children), but re-TT would probably have been just as effective, and in our clinical praxis, re-TT is often the parent's choice, although tonsillectomy could be advocated to avoid yet another setback.[21]

Apart from the fear of re-growth, infections have been considered a risk after tonsillotomy, but no significant difference between the TT and TE group was observed in the frequency of upper airway infections. This is consistent with earlier findings.[14] One explanation could be that a high proportions of TE-children also were shown to have remnants of tonsil tissue in the tonsil pouches, which might have equalized the groups with respect to immunological defense. Most authors and clinicians recommend TE as method of choice in cases with recurrent infections, although very few studies have addressed throat infections after tonsil surgery. In the present study, more TT-children had been treated with antibiotics for throat infections than among the TE-children. However, most of them were not diagnosed objectively. Our previous study,[14] including older children, showed an equal rate of infections, 12%, in both the TT and TE group. A possible confounding factor concerning antibiotic treatment is that a physician could be more prone to prescribe antibiotics to a child with parts of the tonsils left than to a patient thought to have no tonsils left at all. Contrary to most other studies, which exclude children with recurrent tonsillitis, we suggest that TT can be performed also on children with obstructive symptoms and a "normal" rate of throat infections, a number that would not per se qualify for tonsillectomy. Since we could not require that the parents should seek an ENT specialist when their child came down with a sore throat, it was difficult to get a thorough assessment of a diagnosed tonsillitis; the family doctor did not always take a bacterial swab or motivated the rationale for antibiotic treatment.

The children in the present study were "otherwise healthy" without any severe obesity, craniofacial aberration or other diseases, so sleep-studies had not been regarded as necessary.[26-28]

Improvements in scores on both the OSA-18 instrument and CBCL noted at the six-month follow-up visit persisted at the two-year follow-up. These improvements in behavior and HRQL could be result of the surgery, but also might be the result of the child's normal development, which in turn might not have occurred if the SDB had persisted or returned.

Several surgeons were involved in the study, but no calibration of surgical methods was performed. There is risk for a slide in surgical methods towards own preferences and tonsil surgery is performed in several slightly different manners. Fewer, "calibrated" surgeons, preferably just one, would have ensured less "surgeon-bias". The surgeons attempted to calibrate their view of tonsil size in an attempt to standardize this part of the study. Records of differences in tonsil size before surgery should have been made, providing an opportunity to stratify the material, for example using the Brodsky-scale rating tonsil size and percentage of the obstruction from one to four.[10]

We strongly believe that most parents would object to having their children undergo surgery without knowing the character of the procedure and that it would be unethical, although the actual difference between the operations may be seen as slight in a layman's eyes. Quite probably, it would also have affected the drop-out ratio negatively. A surgeon would also object, since the possibility to affect the method of surgery would be eliminated. However, since tonsillotomy has gained increasing popularity among ENT-doctors, more parents know about the method and its possible benefits. Thus, it would have been interesting to perform a single-blinded study to avoid the risk of response bias and observer bias from overly positive expectations from the parents in the TT-group, and perhaps correspondingly negative expectations in the TE-group.

Internal validity also has to be discussed: Did the children stop snoring due to surgery or due to general growth and maturation? We assume that the general growth of children in this age group should provide a "self-healing" effect. In a previous study with children 5–15 years of age,[17] a number of included children recovered spontaneously from obstructive sleep disorder and were subsequently excluded and removed from the waiting list.

Pre-school children with tonsillar hyperplasia do however seem to continue to have large tonsils throughout their childhood, as implied by Kaditis et al.[10] Also, in a non-longitudinal study, Löfstrand-Tideström and Hultcrantz, found that a child who snored at age 4, had a six times greater risk for snoring at age 12 than a child who did not snore at age 4. This was regardless of whether surgery had been performed or not.[26]

**Conclusion**

Tonsillotomy with RF for children between 4–6 years of age with tonsil hyperplasia comes with/results in a small risk of recurrence within two years. This has to be weighed against the lessened risk for severe pain and dangerous bleedings. The long-term good effect on snoring, infections, behavior and quality of life is similar to that of tonsillectomy.

**References**

1. Koempel JA, Solares CA, Koltai PJ. The evolution of tonsil surgery and rethinking the surgical approach to obstructive sleep-disordered breathing in children. J Laryngol Otol. 2006; 120(12): 993-1000.
2. Chan J, Edman JC, Koltai PJ. Obstructive sleep apnea in children. Am Fam Physician. 2004; 69(5): 1147-1154.
3. Aronen ET, Liukkonen K, Simola P, Virkkula P, Uschakoff A, Korkman M, et al. Mood is associated with snoring in preschool-aged children. J Dev Behav Pediatr. 2009; 30(2): 107-114.
4. Ericsson E, Lundeborg I, Hultcrantz E. Child behavior and quality of life before and after tonsillotomy versus tonsillectomy. Int J Pediatr Otorhinolaryngol. 2009; 73(9): 1254-1262.
5. Goldstein NA, Pugazhendhi V, Rao SM, Weedon J, Campbell TF, Goldman AC, et al. Clinical assessment of pediatric obstructive sleep apnea. Pediatrics. 2004; 114(1): 33-43.
6. Liukkonen K, Virkkula P, Aronen ET, Kirjavainen T, Pitkaranta A. All snoring is not adenoids in young children. Int J Pediatr Otorhinolaryngol. 2008; 72(6): 879-884.
7. Landau YE, Bar-Yishay O, Greenberg-Dotan S, Goldbart AD, Tarasiuk A, Tal A. Impaired behavioral and neurocognitive function in preschool children with obstructive sleep apnea. Pediatr Pulmonol. 2012; 47(2): 180-188.
8. Abramson Z, Susarla S, Troulis M, Kaban L. Age-related changes of the upper airway assessed by 3-dimensional computed tomography. J Craniofac Surg. 2009; 20(1): 657-663.

9. Jeans WD, Fernando DC, Maw AR, Leighton BC. A longitudinal study of the growth of the nasopharynx and its contents in normal children. Br J Radiol. 1981; 54(638): 117-121.

10. Kaditis AG, Lianou L, Hatzinikolaou S, Kalampouka E, Gartagani-Panayiotopoulou P, Zintzaras E, et al. Tonsillar size in 2- to 14-year-old children with and without snoring. Pediatr Pulmonol. 2009; 44(12): 1216-1222.

11. Acevedo JL, Shah RK, Brietzke SE. Systematic Review of Complications of Tonsillotomy versus Tonsillectomy. Otolaryngol Head Neck Surg. 2012; 146(6): 871-879.

12. Hultcrantz E, Linder A, Markstrom A. Tonsillectomy or tonsillotomy?–A randomized study comparing postoperative pain and long-term effects. Int J Pediatr Otorhinolaryngol. 1999; 51(3): 171-176.

13. Hultcrantz E, Ericsson E. Pediatric tonsillotomy with the radiofrequency technique: less morbidity and pain. Laryngoscope. 2004; 114(5): 871-877.

14. Ericsson E, Graf J, Hultcrantz E. Pediatric tonsillotomy with radiofrequency technique: long-term follow-up. Laryngoscope. 2006; 116 (10): 1851-1857.

15. Franco RA, Rosenfeld RM, Rao M. First place--resident clinical science award 1999. Quality of life for children with obstructive sleep apnea. Otolaryngol Head Neck Surg. 2000; 123(1): 9-16.

16. Achenbach TM, Edelbrock CS. Behavioral problems and competencies reported by parents of normal and disturbed children aged four through sixteen. Monogr Soc Res Child Dev. 1981; 46(1): 1-82.

17. Ericsson E, Hultcrantz E. Tonsil surgery in youths: good results with a less invasive method. Laryngoscope. 2007; 117(4): 654-661.

18. Larsson B, Frisk M. Social competence and emotional/behaviour problems in 6–16 year-old Swedish school children. Eur Child Adolesc Psychiatry. 1999; 8(1): 24-33.

19. Lundeborg I, McAllister A, Graf J, Ericsson E, Hultcrantz E. Oral motor dysfunction in children with adenotonsillar hypertrophy-effects of surgery.Logoped Phoniatr Vocol 2009; (34): 111–116.

20. Unkel C, Lehnerdt G, Schmitz KJ, Jahnke K. Laser-tonsillotomy for treatment of obstructive tonsillar hyperplasia in early childhood: a retrospective review. Int J Pediatr Otorhinolaryngol. 2005; 69(12): 1615-1620.

21. Doshi HK, Rosow DE, Ward RF, April MM. Age-related tonsillar regrowth in children undergoing powered intracapsular tonsillectomy. Int J Pediatr Otorhinolaryngol. 2011; 75(11): 1395-1398.

22. Eviatar E, Kessler A, Shlamkovitch N, Vaiman M, Zilber D, Gavriel H. Tonsillectomy vs. partial tonsillectomy for OSAS in children-10 years post-surgery follow-up.Int J Pediatr Otorhinolaryngol 2009; (73): 637–640.

23. Hultcrantz E, Linder A, Markstrom A. Long-term effects of intracapsular partial tonsillectomy (tonsillotomy) compared with full tonsillectomy. Int J Pediatr Otorhinolaryngol. 2005; 69 (4): 463-469.

24. Vlastos IM, Parpounas K, Economides J, Helmis G, Koudoumnakis E, Houlakis M. Tonsillectomy versus tonsillotomy performed with scissors in children with tonsillar hypertrophy. Int J Pediatr Otorhinolaryngol. 2008; 72(6): 857-863.

25. Korkmaz O, Bektas D, Cobanoglu B, Caylan R. Partial tonsillectomy with scalpel in children with obstructive tonsillar hypertrophy. Int J Pediatr Otorhinolaryngol. 2008; 72(7): 1007-1012.

26. Lofstrand-Tidestrom B, Hultcrantz E. Development of craniofacial and dental arch morphology in relation to sleep disordered breathing from 4 to 12 years. Effects of adenotonsillar surgery. Int J Pediatr Otorhinolaryngol. 2010; 74(2): 137-143.

27. Stewart MG, Glaze DG, Friedman EM, Smith EO, Bautista M: Quality of life and sleep study findings after adenotonsillectomy in children with obstructive sleep apnea. Arch Otolaryngol Head Neck Surg. 2005; 131(4): 308-314.

28. Roland PS, Rosenfeld RM, Brooks LJ, Friedman NR, Jones J, Kim TW, et al. Clinical practice guideline: Polysomnography for sleep-disordered breathing prior to tonsillectomy in children. Otolaryngol Head Neck Surg. 2011; 145(1): S1-S15.

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**Original Article**

# Clinical profile and commonly used Drugs and their response in chronic headache patients at OPD in DNMCH

**Nurul Amin Khan[1], Shaheen Wadud[2], Torikul Islam[3], Asif Masud Chowdhury[4], Shyamal Chandra Banik[5]**

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**Abstract:**

**Background:** Headache is the most commonest presentation in Neurology Outpatient Department. Headache patient may present in different ways. It may vary in duration, character, severity, location, associated features, and trigger factors. In our clinical practice many drugs are used for treatment of headache. Responses of those drugs may vary from patient to patient.

**Objectives:** To see the clinical profile of chronic headache patients and commonly used drugs and their responses in those patients.

**Methodology:** It was a descriptive, cross sectional observational study. 100 patients presenting with chief complaints of headache to the Neurology OPD in Dhaka National Medical College Hospital between January 2018 to June 2018 were included. Patients with secondary cause of headache were excluded for the study. Results were tabulated and analyzed.

**Results:** Tension headache was the commonest headache type (72%), followed by migraine headache (28%).Intensity was severe in majority of cases (65%), frequency of headache was 9.5±4.4 (Min 2 –Max 20) times per month with duration of 2.8±1.4 (Min 1-Max 12) days. Bilateral band like pain was the commonest (45%) clinical presentation. Among the associated features, vomiting (86%) and vertigo (56%) were common and journey was the commonest aggravating factor (78%). Commonly prescribed drugs were Amitriptyline (70%) and Propranolol (48%).Drug response was good among 66% patients.

**Conclusion:** Clinical presentation of headache may vary patient to patient. The diversity of headache presentations and response to the drugs need to know very well for accurate diagnosis and management of headache patients.

**Key words:** Chronic headche, Drugs.

## Introduction

Headache is the most common disorder in our clinical practice. Headache has wide spectrum presentations. It varies patient to patient, region to region. As in other parts of the world, in Bangladesh too, Headache is the commonest one in our Neurology Outpatient Department. Tension-type headache is very common, with a lifetime prevalence in the general population ranging in different studies between 30% and 78% and Migraine ranked as third most prevalent disorder in the world.[1] In GBD 2015, it was ranked third–highest cause of disability worldwide in both males and females under the age of 50 years.[2] There is lack of study about Headache presentations and its variation, drugs uses in the headache and their responses. The present study designed to study the clinical profile of headache, drugs used in the headache and their responses.

## Materials and methods

In this descriptive, observational study, total number of 100 headache patients were randomly selected clinically from the period of January 2018 to June 2018 at neurology department of Dhaka National Medical College Hospital.

For each patient a routine clinical questionnaire was completed. The questionnaire consisted of details on the onset and lifetime duration of the illness, the pattern of headache, associated factors. Patients with secondary cause of headache was excluded for the study.

The International classification of headache disorder, version 3 was applied and as many diagnosis as was necessitated by the criteria and as was clinically justified, were assigned to each patient.

Statistical analysis was done using STATA 10 software.

**Results:**

Out of 100 cases, most of the cases were diagnosed as Tension type headache (72%) then Migraine headache (28%).

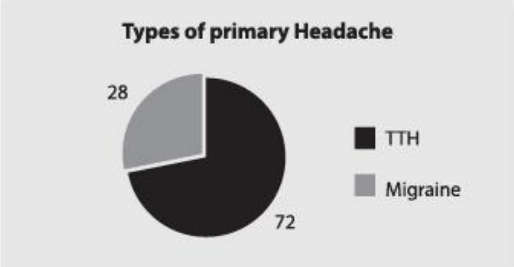


**Figure-I: Types of Headache**

**Table-I: Headache frequency and duration among study population**

| Headache Character | |
|---|---|
| Frequency | 9.5±4.4 (Min 2- Max 20) times per month. Above 10 times per month 44 persons (44%) |
| Duration | 2.8±1.4 (Min 1 - Max 12) days. |

Among headache patient, headache frequency were 9.5±4.4 (Min2-Max 20) times in one month. Above 10 times in each month were found among 44% patient. In each patient of headache, pain was persisted averagely 2.8±1.4 (Min 1-Max 12) days

**Table-II: Intensity of pain among population**

| Intensity of pain | Frequency | Percentage | Cum. |
|---|---|---|---|
| Moderate | 35 | 35.00 | 35.00 |
| Severe | 65 | 65.00 | 100.00 |
| **Total** | **100** | **100.00** | |

Headache was severe in 65% of the cases and moderate in 35 % of the cases (Table-II)

**Table-III: Location of pain among population**

| Location of pain | Frequency | Percentage | Cum. |
|---|---|---|---|
| Unilateral | 18 | 18.00 | 18.00 |
| Bilateral | 45 | 45.00 | 63.00 |
| Frontal | 30 | 30.00 | 93.00 |
| Occipital | 7 | 7.00 | 100.00 |
| **Total** | **100** | **100.00** | |

Location of the headache may vary patient to patient and bilateral headache was 45%, frontal 30%, unilateral 18% (Table-III).

**Table-IV: Associated Features with Headache in population**

| Associated feature | Present in cases (in number) |
|---|---|
| Aura | 08 |
| Photophobic and Phonophobia | 68 |
| Nausea/Vomiting | 86 |
| Lacrimation | 06 |
| Vertigo | 56 |

Headache was associated with several associated factors like nausea and vomiting (86%), Photophobia & Phonophobia (68%), vertigo (56%) (Table-IV)

**Table-V: Aggravating factor of headache patients**

| Aggravating factor | Present in cases (in number) |
|---|---|
| Movement | 26 |
| Smoke | 12 |
| Journey | 78 |
| Any Smell | 38 |
| Fasting | 52 |

There were some aggravating factors causing aggravation of intensity as well as frequency of headache. Those were Journey (78%), Fasting (52%), Smell (38%), Movement (26%), and Smoke (12%) (Table-V)

**Table-VI: Drugs used among headache patients**

| Drug used | Present in cases (in number) |
|---|---|
| Amitriptyline | 70 |
| Flupenthixol | 36 |
| Nortriptyline | 12 |
| Propranolol | 48 |
| Sodium valproate | 8 |
| Tolfenamic acid | 4 |
| Pizotifen | 2 |
| Escitalopram | 2 |
| Clonazepam | 2 |

Most of the headache patient were treated with single or combination drugs and those were amitriptyline (70%), propranolol(48%), flupenthixol(36%), nortriptyline(12%), sodium valproate(8%), pizotifen(2%), escitalopram(2%), clonazepam(2%). Responses were better in amitriptyline and propranolol combinations as well as amitriptyline and sodium valproate.

The International classification of headache disorder, version 3 was applied and as many diagnosis as was necessitated by the criteria and as was clinically justified, were assigned to each patient.

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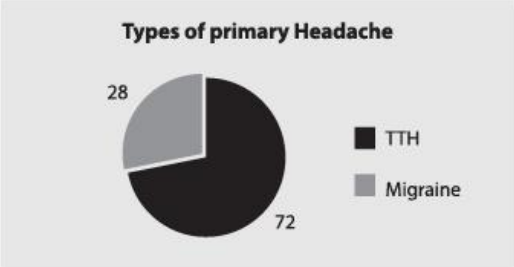


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Most of the headache patient were treated with single or combination drugs and those were amitriptyline (70%), propranolol(48%), flupenthixol(36%), nortriptyline(12%), sodium valproate(8%), pizotifen(2%), escitalopram(2%), clonazepam(2%). Responses were better in amitriptyline and propranolol combinations as well as amitriptyline and sodium valproate.

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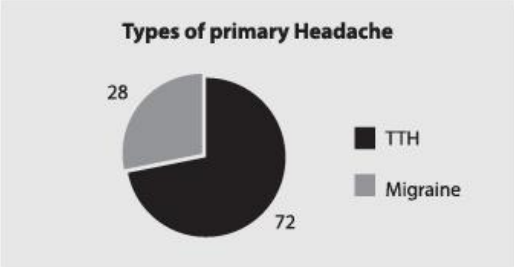


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Most of the headache patient were treated with single or combination drugs and those were amitriptyline (70%), propranolol(48%), flupenthixol(36%), nortriptyline(12%), sodium valproate(8%), pizotifen(2%), escitalopram(2%), clonazepam(2%). Responses were better in amitriptyline and propranolol combinations as well as amitriptyline and sodium valproate.

**Table-VII: Response to drugs among headache patients**

| Respond to drug | Freq. | Percent. | Cum. |
|---|---|---|---|
| Marked to moderate | 66 | 66.00 | 66.00 |
| Slight | 24 | 24.00 | 90.00 |
| Unchanged | 10 | 10.00 | 100.00 |
| **Total** | **100** | **100.00** | |

Among the treated patient 66% patient were marked to moderate responder, 24% were slight responder and 10% were unchanged to the drugs. Analgesic or abortive drugs were avoided as because they induce rebound or medication over use headache.

## Discussion

This observational study estimated the prevalence of different types of headaches among the study populations. It showed that 72% patients suffered from TTH and 28% from migraine headache. Tension type headache has been observed in higher prevalence than migraine in most of the population based studies.[3] We found the similarities in other studies done in different countries like: in Isfahan[4] (44.2% TTH versus 14.2%migraine); Jordan[5] (36.9% TTH versus 7.7% migraine); Zagreb[6] (57.69 versus 8.86%); while in Oman[7] both were equal (12.2%).

In addition to headache, there were some associated features, commonly found during taking history of headache patient. Those are Nausea &vomiting 86%, vertigo 56%, Photophobia 44%, Phonophobia 24%, Aura 8%, and Lacrimation 6%. These accompanying symptoms increase the disability of the patient and are usually more problematic for the patient. These associated symptoms, known as migraine variant, when more prominent than the headache, it makes the diagnosis difficult and delay the Management. These findings of associated features are in almost consistent with other studies.[8,9]

We also noticed some aggravating factors which were influencing the headache intensity. Those are journey (78%), fasting (52%), smell (38%), movement ((26%), smoke (12%). Mustaq et al.[10] found similar aggravating factors in their study and sleep deprivation was an important aggravating factor for headache.

Headache patients were treated commonly with amitriptyline (70%), propranolol (48%), flupenthixol (36%), nortriptyline (12%), sodium valproate(8%), pizotifen (2%), escitalopram (2%), clonazepam (2%). Those drugs were used either single or combination to treat the migraine and tension headache. Other researchers had found that amitriptyline was most effective drug for Tension headache.[11,12] Islam et al.[13] found that amitriptyline and propranolol combination were more effective than monotherapy for migraine headache. We also found that combination drugs superior than monotherapy in headache treatment. Lenaerts et al.[14] and Rothrock et al.[15] found that sodium valproate were effective in chronic tension headache and migraine as well. SSRI drugs are recently used in headache patient but showed no superiority than the tricyclic antidepressant.[16] In our study, we also found that Sodium valproate, SSRI were not superior than the tricyclic antidepressant.

Drug responses were varied, it depend upon types of drugs and doses of drugs. We have documented the drugs responses of commonly used drugs in our study and we stratified the response on the basis of Physician Global Assessment, response to treatment (PGART scale). We found that marked to moderate responder were 66%, slight responder were 24%, Unchanged 10%. Gopalakrishnan S et al.[17] found the similar drug response to the prophylactic drugs.

## Conclusion

Primary headache was the commonest clinical presentation in our outpatient department and also in daily practice. Tension headache was more common than migraine headache. Nausea, vomiting, photophobia, phonophobia were commonly found associated features and journey, fasting, smell, movement were common aggravating factors. Amitriptyline, propranolol, flupenthixol, sodium valproate were commonly used drugs for headache patients. Most of the headache patients were good responder with those drugs in single use as well as combination.

## References

1. Internation Headache society. (2021) Tension-type Headache (TTH) [online] https://ichd-3.org/2-tension-type-headache/
2. Internation Headache society. (2021) Migraine [online] https://ichd-3.org/1-migraine/
3. Stovner LJ, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher AI,et al. The global burden of headache: a documentation of headacheprevalence and disability worldwide. Cephalalgia 2007; 27:193–210.
4. Ghorbani A,Abtahi S-M,Feridian-Esfahani M,Abtahi

S-H,Shemshaki H,Akbari M,et al.Prevalence and clinical characteristics of headache among medical students,Isfahan,Iran.J.ResMed Sci(internet)2013 March,18(Suppl1):S24-27.

5. Alzoubi KH, Mhaidat N, Azzam SA, Khader Y, Salem S, Issaifan H, et al. Prevalence of migraine and tension-type headache among adults in Jordan. J Headache Pain 2009; 10(4): 265–270.
6. Galinović I, Vuković V, Troselj M, Antić S, Demarin V. Migraine and tension-type headache in medical students: a questionnaire study. Coll Antropol. 2009; 33(1):169-173.
7. Deleu D, Khan MA, Humaidan H, Al Mantheri Z, Al Hashami S. Prevalence and clinical characteristics of headache in medical students in Oman. Headache. 2001; 41(8):798-804.
8. Menon B, Kinnera N. Prevalence and characteristics of migraine in medical students and its impact on their daily activities. Ann Indian Acad Neurol. 2013; 16(2): 221-225.
9. Nandha R, Chhabra MK. Prevalence and clinical characteristics of headache in dental students of a tertiary care teaching dental hospital in Northern India. Int J Basic Clin Pharmacol. 2013; 2: 51-55.
10. Ahmed M, Bota R, Ariff M. Prevalence of different types of headache and Migraine disability assessment: A cross sectional study among University students.Int.J Medical Science and Innovative Research.2017; 2(5): 371-377.
11. LANCE JW, CURRAN DA. TREATMENT OF CHRONIC TENSION HEADACHE. Lancet. 1964; 1(7345): 1236-1239.
12. Diamond S, Baltes BJ. Chronic tension headache--treated with amitriptyline--a double-blind study. Headache. 1971; 11(3): 110-116.
13. Islam MA, Shaikh AK, Alam SM, Sultana D, Islam MS, Rashid MM. Safety & Efficacy of Propranolol and Amitriptyline Combination Therapy in Migraine Prophylaxis: A Randomized Control Trial. Journal of National Institute of Neurosciences Bangladesh 2018; 4(1): 3–7.
14. Lenaerts M, Bastings E, Sianard J, Schoenen J. Sodium valproate in severe migraine and tension-type headache: an open study of long-term efficacy and correlation with blood levels. Acta Neurol Belg. 1996; 96(2): 126–129.
15. Rothrock JF, Mendizabal JE. An analysis of the "carryover effect" following successful short-term treatment of transformed migraine with divalproex sodium. Headache 2000; 40(1): 17–19.
16. Ramadan NM, Schultz LL, Gilkey SJ. Migraine prophylactic drugs: proofof efficacy, utilization and cost. Cephalalgia. 1997; 17(2): 73–80
17. Srinish G, Chethan KG, Gopakumar KP. Efficacy of amitriptyline in migraine prophylaxis: a comparative study of two different doses of amitriptyline. Int J Health Sci Res. 2014; 4(7): 89-96.

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**Original Article**

# Frequently Prescribed Anti-Diabetic Medication at Initiation of Treatment in Upazilla Hospital

**Md. Shahedul Kabir[1], Farhana Islam[2], Md. Shafiqur Rahman[3], Bhagyoshree Karmokar Jyoti[4]**

[1]Junior Consultant, Department of Cardiology, Sitakundo, Chittagong, [2]Senior Lecturer, Department of Pharmacology, Dhaka National Medical College, [3]Associate Professor, Department of Paediatrics, Dhaka National Medical College, [4]Medical Officer, Department of Surgery, Dhaka Medical College

**Abstract:**

**Objective:** To assess the frequently prescribed anti-diabetic medication at initiation of treatment.

**Methods:** A descriptive, cross sectional study was conducted from January 2019 to June 2019 among 300 patients attending at medicine outpatient department of upzilla health complex, Sitakundo, Chittagong after obtaining requisite consent from the patients. Data were collected through the assessment of patients in the Outpatient Department. The collected data were entered into the computer and analyzed by using SPSS (version 20.1) to assess the frequently prescribed anti-diabetic medication at initiation of treatment. The study was approved by the institutional ethical committee.

**Results:** In a pool of 300 type 2 diabetes, most patients (57.3%) belonged to the middle age group 41-60 years. Female patients (74.3%) were more than the male patients at the outpatient department. Type 2 DM is more common in urban area (65.7%). Most of the patients were initially treated with metformin (38.3%) followed by sulfonylureas (20.0%) and insulin (10.7%).

**Conclusion:** Most of the patients were initially treated with metformin followed by sulfonylureas and insulin.

**Keywords:** Metformin, Diabetes mellitus.

## Introduction

Diabetes mellitus is one of the oldest diseases known to man, which was the first reported in Egyptian literature about 3000 years ago.The name diabetes was first given by the Greek physician Aretaeus. Avicenna is the famous Arabian physician who first described the complications and progression of the disease. In 1889, Joseph von Mering and Oskar minkowski discovered the role of pancreas in diabetes. Sir Edward Albert Sharpey-Schafer in 1910 found that diabetes resulted from lack of insulin. Bantin, Best and Collip purified the hormone insulin from pancreas of cows at the University of Tornoto. This led to the availability of an effective treatment for diabetes in 1922. Trials to prepare an orally administered anti-diabetic agent ended successfully after first marketing of tolbutamide and carbutamide in 1955.[1] The prevalence of diabetes mellitus is growing rapidly worldwide and is reaching epidemic proportions.[2] Type 2 diabetes characterized by high level of blood glucose due to the impaired action of insulin and insufficient insulin production by pancreas.[3] Because of the progressive nature of the disease, an evolving treatment strategy is necessary to maintain both fasting and postprandial glycemic control. The goal of type 2 diabetes treatment is to lower the blood glucose with diabetic meal plan, physical activity, weight loss (if needed) and medication (if needed).[4] Medications for diabetes mellitus need to be taken for the entire life and factors like efficacy, side effects, drug interactions and cost of therapy need to be taken into consideration.[5]

## Methods

A descriptive, cross sectional study was conducted from January 2019 to June 2019 among 300 patients attending at medicine outpatient department of upzilla health complex, Sitakundo, Chittagong after obtaining requisite consent from the patients. Purposive sampling was adopted for collecting data. The assessment of patients were held directly in the Outpatient Department. The relevant information was entered into the predesigned proforma to assess the frequently prescribed anti-diabetic medication at initiation of treatment. The collected data were entered into the computer and analyzed by using SPSS (version 20.1).

## Results

According to table-I, the age structures of the patients have been categorized in years into three groups. Overall 77 (25.7%) patients were in ≤ 40 years old while 172 (57.3%) patients were 41-60 years old, 51 (17.0%) patients belong to > 60 years age group. Most patients belonged to the middle age group 41-60 years

**Table-I: Age distribution of the study population (n=300)**

| Age (years) | Number | Percentage |
|---|---|---|
| ≤ 40 yrs | 77 | 25.7 |
| 41-60 yrs | 172 | 57.3 |
| > 60 yrs | 51 | 17.0 |
| Total | 300 | 100.0 |
| Mean ±SD | 50.59±12.57 | Range 30-90 yrs |

Figure-I shows that, total numbers of patients as both male and female were 300. It comprised of 77 (25.7%) male and 223 (74.3%) female in outpatient. Female patients were more than the male patients at the outpatient department.

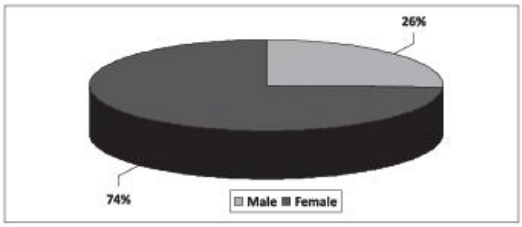


**Figure-I: Pie chart showing sex distribution of the study population**

According to table-II, out of 300 patients, 197 patients came from urban area and 103 patients from rural area. Type 2 DM is more common in urban area.

**Table-II: Residential status of the study population (n=300)**

| Residence | Number | Percentage |
|---|---|---|
| Urban | 197 | 65.7 |
| Rural | 103 | 34.3 |
| Total | 300 | 100.0 |

According to table-III, out of 300 patients, 115 patients (38.3%) were initially treated with biguanides, 60 patients (20.0%) were initially treated with sulfonylureas, 32 patients (10.7%) were initially treated with insulin, 1 patient (0.3%) was initially treated with incretin mimetics, and 92 patients (30.7%) could not mention the drug name which was initially used.

Most of the patients were initially treated with metformin.

**Table-III: Most frequently prescribed anti-diabetic medication at initiation of treatment**

| Treatment starts with | Number | Percentage |
|---|---|---|
| Sulfonylureas | 60 | 20.0 |
| Biguanides | 115 | 38.3 |
| Insulin | 32 | 10.7 |
| Could not mention | 92 | 30.7 |
| Incretin mimetics | 01 | 0.3 |
| **Total** | **300** | **100.0** |

## Discussion

This study showed that diabetes mellitus is more prevalent in female patients than in male patients. This may be assigned to the fact that women are more obese than men. The other reasons might be due to lack of physical activity, life style changes, dietary habit and stress. Almost similar results were obtained in the other studies.[1] However other studies reported higher prevalence of DM in men.[6,7]

This study also found a higher prevalence of diabetes was among the middle aged patients, with a high percentage (57.37%) in the age group of 41-60 years where the mean age was 50.59±12.5 years. This result correlates with the study of sajith et al.[2] A study from the Nepal reported that higher mean age 58.1 ± 11.6 years in type 2 diabetic patients. So this present study does not correlate with the Nepal study. In general elderly patients are at a greater risk of developing type 2 diabetes mellitus. In the present study, type 2 DM is more common in urban people (65.7%). Our study findings are also similar to the study conducted in Bangladesh by Akter et al.[8] Similar findings have been reported in china (11% versus 8%). Diabetes may be more common among urban residents due to sedentary life style or different dietary habits. In our study we observed that a large number of patients (38.3%) initially treated with metformin. This prescribing pattern is according to guidelines of American Diabetes Association. They recommended that metformin should be started along with lifestyle changes at the time of diagnosis. In our study, 10.7% patients initially treated with insulin. In case of newly

diagnosed type 2 diabetes mellitus patients short term aggressive insulin therapy preserve beta cell function, reduce insulin resistance and maintain optimal glycemic level. Our result is not consistent with the result of Sharma, Nazareth and Petersen study.[9] In their study they observed that 1.7% patients with newly diagnosed type 2 diabetes mellitus were prescribed with insulin as first line therapy.

**Conclusion**

Most of the patients were initially treated with metformin followed by sulfonylureas and insulin. This prescribing pattern is according to guidelines of American Diabetes Association. They recommended that metformin should be started along with lifestyle changes at the time of diagnosis. Although, newer & expensive agents like DPP4 inhibitors & GLP-1 agonists are available in the market. Older & cheaper agents like metformin & sulfonylureas are still the mainstay of treatment in the context of our country.

**Acknowledgement**

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**Conflict of interests:** None

**References**

1. Alam M, Aqil M, Shah Qadry S, Kapur P, Pillai K. Utilization pattern of oral hypoglycemic agents for diabetes mellitus type 2 patients attending out patient department at a university hospital in new Delhi. Pharmacology and pharmacy 2014; 5: 636-645.
2. Sajith M, Pankaj M, Pawar A, Modi A, Sumariya R. Medication adherence to anti-diabetic therapy in patients with type 2 diabetes mellitus. International Jounal of Pharmacy and Pharmaceutical Science 2014; 6(2): 564-570.
3. Kannan A, Arshad, Kumar S. A study on drug utilization of hypoglycemic agents in type 2 diabetic patients. Asian Journal of Pharmaceutical and Clinical Research 2011; 4(4): 60-63.
4. Asif M. Information on the effects of physical workout and diet on diabetic patients. African Journal of Medical & Sciences 2013; 12(1): 38-43.
5. Yusefzadeh G, Sepheri G, Goodarzi H, Shokoohi M. Prescription pattern study in type 2 diabetes mellitus in diabetic out patients in private clinics in Kerman, Iran. British Journal of Medicine and Medical Research 2014; 4(32): 5144-5153.
6. Mann DM, Ponieman D, Leventhal H, Halm EA. Predictors of adherence to diabetes medications: the role of disease and medication beliefs. Journal of Behavioral Medicine 2009; 32: 278-284.
7. Abebaw M, Messele A, Hailu M, Zewdu F. Adherence and associated factors towards anti-diabetic medication among type 2 diabetic patients on follow up at university of Gondar hospital, northwest Ethiopia. Advances in nursing 2016; p.7.
8. Akter S, Rahman MM, Abe SK, Sultana P. Prevalence of diabetes and prediabetes and their risk factors among Bangladeshi adults: a nationalwide survey. Bull world health organ. 2014; 92(3): 204-213.
9. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. BMJ Open. 2016; 6(1): e010210.

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**Original Article**

# A study on Anti-diabetic effects of ethanolic extract of Pomelo (Citrus Maxima Linn) and Glibenclamide on blood glucose level of diabetic rats

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**Abstract:**

**Background:** Diabetes mellitus is a one of the major public health problem adversely affecting health and socio-economic status of people at both national and global level.

**Objective:** To evaluate the effects of ethanolic extract of Pomelo (Citrus maxima linn) fruit juice on blood glucose level in alloxan induced diabetic rats.

**Methods:** This experimental study was carried out in two parts on 30 albino rats. In experiment-I; 12 rats were divided into 2 groups; each comprising of 6 rats. Group-I: Normal non-diabetic rats are fed with normal feed only and Group-II: Normal non-diabetic rat were fed with normal feed with Citrus maxima extract for 21 days. In experiment-II, 18 rats were divide into three groups; Group III (diabetic control), Group IV (experimental group) and Group V (standard drug group). To induce diabetic, these 18 rats were injected alloxan 120 mg/kg body weight intraperitoneally. Then group III and IV were treated with the Citrus maxima ethanol extract and Glibenclamide respectivelyfrom day1 to day 21.

**Results:** Blood glucose level of group IV decreased significantly ($p<0.05$) from 12.10-13.30 to 7.00-7.50 mmol/l. Blood glucose level of group V also decreased significantly ($p<0.05$) from 12.50-13.50 to 6.50 to7.90 mmol/l.Difference of blood glucose results between group IV and V was not statistically significant.

**Conclusion:** The ethanolic extract of Citrus maxima has shown significant activity like Glibenclamideto reduce blood glucose in hyperglycemic rats.

**Keywords:** Diabetes Mellitus, Citrus maxima, Ethanolic extract, Glibenclamide

## Introduction

Diabetes mellitus, a metabolic endocrine disorder, has become a common global health problem and one of the leading causes of death and disability.Diabetes was one of the four priority non-communicable diseases (NCDs) targeted by world leaders in the 2011.[1] Epidemiological studies on urbanization and aging influences have shown the prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% increase in 2000 and 4.4% in 2030.[2] The IDF diabetic atlas 10th edition reveals that approximately 537 million adults (20-79) years were living with diabetes and this number is predicted to rise to 643millions by 2030 and 783 million by 2045.[3] USD 10 billion was spent on healthcare for people with diabetes in 2021— the second lowest expenditure of all IDF regions.[4] In Bangladesh, there were 8.4 million adults living with diabetes in 2019, and projected to almost double (15.0 million) by 2045.Studies, including a systematic review and meta-analysis, and national survey reports showed that the prevalence of diabetes among adults has increased substantially in Bangladesh, from ~5% in 2001 to ~14% in 2017.[5-8]

According to WHO (1999) Diabetes mellitus is a metabolic disorder of multiple etiologies characterized by chronic hyper[1]glycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both.[4]

Patient complains of symptoms suggesting of diabetes is diagnosed by test urine for glucose and ketones, measure random or fasting venous blood glucose and testing of level of glycosylated hemoglobin (HbA1c). Diagnosis is confirmed by fasting blood glucose ≥ 7.0mmol/l (120mg/dl) or plasma glucose ≥ 11.1mmol/l (200mg/dl) two hours after a 75g oral glucose load in glucose tolerance test. HbA1c of 6.5% is recommended as the cut point of diagnosis.[9-11] Diabetes is an incurable disease. The goal of diabetes management is to maintain the level of blood glucose; this goal should be achieved through an anti-diabetic agent (either natural or chemical) that will be effective, affordable, and available and with less side effects. Type-1 diabetes requires absolute insulin therapy, whereas Type-2 can be treated with oral anti-diabetic drugs or Insulin or as a combination of both with life style modification.[1,12] Despite considerable progress in the treatment of diabetes by oral hypoglycemic agents, search for newer drug continues because the existing synthetic drugs have several limitations. For a developing country like Bangladesh herbal plants may be the most attractive target for their availability, low cost and safety margin.[13]

Citrus maxima, the pomelo in rutaceae (Citrus family), is known as batabilebu in Bengali is the biggest citrus fruit. Like other citrus fruits, pomelos also are rich in vitamin C and contain polyphenol, proteins and polysaccharide. In the field of polyphenol compound, It contains flavonine, narginin and hesperidine.[13-16] Citrus maxima cited for its various medicinal properties, especially analgesic, anti-inflammatory, antibacterial, antioxidant, hepatoprotective, antidiabetic, Anti-depressant, anti-tumor and antihyperlipeadimic properties.[13-20]

## Materials and Method

**Place and Period of Study:** This experimental (animal) study was carried out in the Department of Pharmacology and Therapeutics of Sir Salimullah Medical College in collaboration with institution of Nutrition and Food Science (INFS) from July 2016 to June 2017. Total 30 male Swiss albino rats were taken for the study.

### Materials

**Animals:** A total number of 30 healthy Swiss albino male rats were purchased from the animal resource division of ICDDRB, Mohakhali Dhaka. The age of the rats was between 8-10 weeks weighing about 150 to 170 grams. They were kept in metallic cage (1 rat /cage) in the animal house of Institute of Nutrition and Food science in a well-ventilated room and a temperature of about 26-28˚C. the animal room was maintained under a constant 12-hours light: 12- hours dark cycle. They were allowed to feed standard rat food pellets and drink water ad libitum, except during the day of blood sampling when animals were kept an overnight fasting.21

**Drugs:**

a) Alloxan Monohydrate (Sigma Chemical Co.USA) was purchased. Alloxan Monohydrate was administered by single intraperitoneal (i.p) injection at a dose of 120 mg/kg body weight.[22]

b) Glibenclamide: as Diabenol (Square pharmaceutical Pvt Ltd), which was purchase from Lazz pharma, Dhaka. It was then crushed into powder and dissolved in water given at a dose of 10 mg/kg body weight.[23]

**Medicinal plant:** Citrus maxima linn (pomelo) batabilebu was purchased from local market.

**Procedure of obtaining ethanolic extract of Citrus maxima linn (pomelo):** Pomelo was brought from local market, the pulp was collected by peeling off and washed thoroughly with water. By using a commercial blender fruit juice was made (600mg). 600 mg of citrus fruit juice was soaked in 300ml ethanol alcohol with continuous shaking (40 rpm) at 25˚C for three days and filtered. The organic extract was evaporated under vacuum to obtain a semisolid residue (4g). The extract was kept in refrigerator.[24]

**Experimental dose:** Ethanolic extract of pomelo with a dose of 200 mg/kg body weight was given to Group II and Group IV rats with laboratory diet and water for 21 days. The dose was selected from Parixitet al.[23] Pomelo extract was weighed according to group wise body weight accurately by electric analyzer. Extract was then dissolved in 2.9 ml of water. The liquid form of extract was administered through a micropipette.

**Design of experiment:**

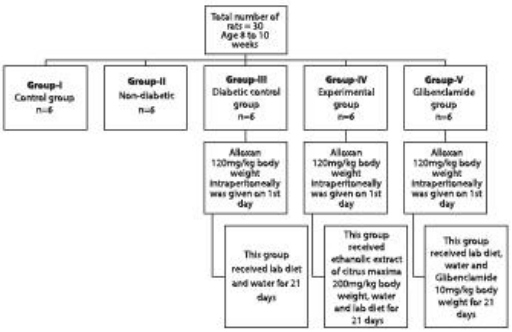
Group-I (Normal non-diabetic rat normal feed only): In this group, the rats were given normal feed and water for 21 days and fasting blood was estimated on day 1, 4, 7, 21.

Group-II (Normal nondiabetic rat normal feed with Citrus maxima extract): rats were given normal feed with Citrus maxima extract (200mg/kg) for 21 days and fasting blood glucose was estimated day 1, 4, 7 and 21 of the experiment.

**Group-III (Alloxan induced diabetic control group):** Alloxan 120 mg/kg body weight was administered intraperitoneally for induction of diabetes at day 1.[25] After peritoneal injection rats were given standard food and water. Fasting blood glucose level was estimated onday 1 (before alloxan), on day 4 (after alloxan to confirm induction of diabetes mellitus) and on day 7, 14, 21 of the experiment.

**Group-IV (Diabetic rat normal feed with Citrus maxima extract):** The rats were administered ethanolic extract of Citrus maxima 200mg/kg body weight orally along with standard food and water for 21 days.

**Group-V (Diabetic rat normal feed with Glibenclamide):** In this group, 10mg/kg body weight Glibenclamide was given orally with normal feed for 21days of the experiment.




**Sacrifice of the Animals and collection of blood:** Blood sample were collected via tail vein by aseptically cutting the tip of tail with a sharp sterile blade after an overnight fast for measurement of fasting blood glucose levels. All the animals were sacrificed under light chloroform anesthesia after completion of treatment. Blood was collected in epindroff and kept in standing position till clotting of blood had occurred. The blood sample were centrifuged for 15 minutes in a tabletop clinical centrifuge at 3000 rpm for serum separation, the serum was then used for biochemical analysis.

**Determination of blood glucose level:** Estimation of serum glucose concentration by using an oxidase and peroxidase (GOD-POD) method.[26]

**Statistical Analysis:** The results are given as Mean ± SD for the six independently performed experiments. Unpaired student "t" test was used to see the level of significance. p-value <0.05 was considered statistically significant.

## Result

Table-I shows average weight of rats of different group. Each group consists of six rats.

**Table-I: Weight of the subjects in different groups (n=30)**

| Parameters | Groups | | | | |
|---|---|---|---|---|---|
| | I (n=6) | II (n=6) | III (n=6) | IV (n=6) | V (n=6) |
| Weight (gm) | 155.0±8.3 (150-170) | 156.6±10.3 (140-170) | 158.3±7.5 (150-170) | 158.3±9.8 (150-170) | 158.3±9.8 (140-160) |

**Table-II: Mean blood glucose of the subjects in different groups at different followups (n=30)**

| Experimental animal group (n=6) | Serum blood glucose level (mmol/L) | | | | |
|---|---|---|---|---|---|
| | Day-01 | Day-04 | Day-07 | Day-14 | Day-21 |
| Group-I | 4.47 ± 0.48 (4.10 -5.40) | 5.43±0.20 (5.20-5.70) | 4.93±0.61 (4.10-5.60) | 5.37±0.20 (5.10-5.60) | 5.50±0.16 (5.30-5.70) |
| Group-II | 4.20 ± 0.14 (4.00 -4.40) | 5.18±0.27 (4.70-5.50) | 5.25±0.33 (4.70-5.70) | 5.42±0.27 (5.10-5.80) | 5.61±0.27 (5.20-5.90) |
| Group-III | 4.28 ± 0.54 (3.50 -4.90) | 13.20±0.24 (12.80-13.50) | 13.35±0.33 (13.00-13.80) | 13.47±0.32 (13.00-13.90) | 13.58±0.36 (13.10-14.10) |
| Group-IV | 3.97 ± 0.23 (3.70-4.20) | 12.67±0.46 (12.10-13.30) | 9.85±0.30 (9.50-10.30) | 8.58±0.36 (8.10-9.10) | 7.20±0.18 (7.00-7.5) |
| Group-V | 5.82 ± 2.55 (3.90-9.10) | 12.97±0.37 (12.50-13.50) | 10.02±0.29 (9.50-10.30) | 8.95±0.46 (8.30-9.70) | 7.00±0.48 (6.50-7.90) |

**Unpaired t-test:**

| Groups | P-value | | | | |
|---|---|---|---|---|---|
| | Day-01 | Day-04 | Day-07 | Day-14 | Day-21 |
| I vs II | 0.22 | 0.098 | 0.288** | 0.722** | 0.391 |
| I vs III | 0.578 | 1.000 | 0.092$^{ns}$ | 0.341* | <0.001*** |
| I vs IV | 0.045 | <0.001*** | <0.001*** | <0.001*** | <0.001*** |
| I vs V | 0.232 | <0.001*** | <0.001*** | <0.001*** | <0.001*** |
| II vs III | 0.721 | <0.001*** | <0.001*** | <0.001*** | <0.001*** |
| II vs IV | 0.063 | <0.001*** | <0.001*** | <0.001*** | <0.001*** |
| II vs V | 0.232 | <0.001*** | <0.001*** | <0.001*** | <0.001** |
| III vs IV | 0.216 | 0.031 | <0.001*** | <0.001*** | <0.001*** |
| III vs V | 0.181 | 0.220 | <0.001*** | <0.001*** | <0.001*** |
| IV vs V | 0.108 | 0.242 | 0.349 | 0.157 | 0.363 |

Results are expressed as mean ± SD. Unpaired t test was performed to compare between groups. The test of significance was calculated &p value < 0.05 was accepted as level of significance.

n = number of subjects; ns = not significant; */**/*** = significant

Group I: Normal feed only (Control group)

Group II: Normal feed+ ethanol extract of Citrus maxima (Non-diabetic group)

Group III: Alloxan + normal feed (Diabetic group)

Group IV: Diabetic rats + ethanol extract of Citrus maxima (Experimental group)

Group V: Diabetic rats + Glibenclamide (Standard group)

**Table-III: Effect of ethanolic extract of Citus maxima on fasting blood glucose level in non diabetic rats**

| Group | No of rats (n) | Fasting blood glucose level (mmol/L in mean±SD) | p-value |
|---|---|---|---|
| Group-I (Normal feed rats group) | 6 | 5.50±0.20 | 0.391 |
| Group-II Rats feed on ethanolic extract ov Citrus maxima | 6 | 5.61±0.27 | |

p-value is not significant (>0.05)

Comparison between fasting blood glucose level of Group-II with that of normal control Group I was done by unpaired student's t-test. There is a non significant difference (p>0.05) between Group I and Group-II.

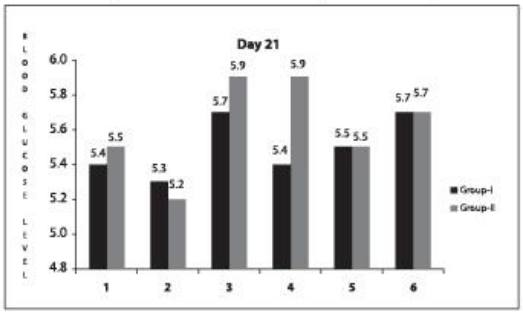



**Fig-I: Bar graph showing fasting blood glucose level of Group-I (normal feed rats group) and Group-II (ethanolic extract of Citrus maxima feed rats group)**

**Table-IV: Administration of alloxan on blood glucose level of adult rats**

| Group | No of rats (n) | Fasting blood glucose level (mmol/L) | p-value |
|---|---|---|---|
| Group-I (Normal feed rats group) | 6 | 5.50±0.20 | *0.001 |
| Group-III (Alloxan-induced diabetic Rats) | 6 | 13.58±0.36 | |

*p-value is highly significant (<0.01)

Significant at p<0.001 level in unpaired student's t-test of significance of difference when compared with the control.

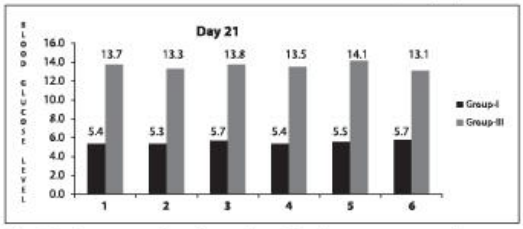



**Fig-II: Bar graph showing fasting serum glucose level in Group-I (normal feed rats group) and Group-III (Alloxan-induced rats group)**

**Table-V: Effect of ethanolic extract of Citrus maxima on fasting blood glucose levels of alloxan induced hyperglycemic rats**

| Group | No of rats (n) | Duration of tratment (day 4-21) | Fasting blood glucose level (mmol/L in mean±SD) | p-value |
|---|---|---|---|---|
| Group-III (Alloxan-induced Rats group) | 6 | | 13.58±0.36 | 0.001 |
| Group IV ( Alloxan induced diabetic rats fed on ethanol extract of CM) | 6 | | 7.20±0.16*** | |

***highly significant (<0.001)

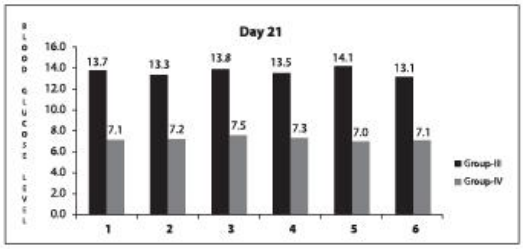



**Fig-III: Bar graph showing the blood glucose level in Group-III (alloxan-induced rats group) and Group-IV (alloxan-induced diabetic rats treated with ethanolic extract of Citrus maxima) on day 21**

**Table-VI: Effect of Glibenclamide on fasting blood glucose level of alloxan induced hyperglycemic rats**

| Group (Mean±SD) | No of rats (n) | Duration of tratment | Fasting blood glucose level (mmol/L in mean±SD) | p-value |
|---|---|---|---|---|
| Group-III (Alloxan –induced rats group) | 6 | (4-21days) | 13.58±0.36 | 0.001 |
| Group-V (Alloxan induced Diabetic rats treated with Glibenclamide) | 6 | (4-21days) | 7.00 ±0.48 *** | |

***highly significant (<0.01)

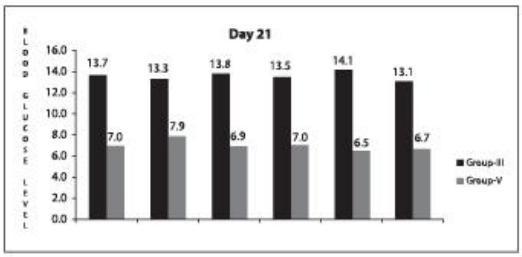



**Fig-IV: Bar graph showing the blood glucose level in Group-III (alloxan-induced rats group) and Group-V (alloxan-induced diabetic rats treated with Glibenclamide) on day 21**

**Table-VII: Comparison of fasting blood glucose level of rats with the ethanolic extract of Citrus maxima treated rats and the Glibenclamide treated hyperglycemic rats**

| Group of | No of rats (n) | Duration of tratment | Fasting blood glucose level (mmol/L in mean±SD) | p-value |
|---|---|---|---|---|
| Group-IV (Alloxan–induced diabetic rats Treated with extract of CM) | 6 | (day 4-21) | 7.2±0.18 | 0.363 |
| Group-V (Alloxan induced diabetic rats treated with Glibenclamide) | 6 | (day 4-21) | 7.00 ±0.48 | |

ns : non-significant

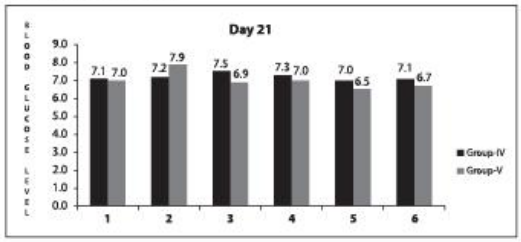



**Fig-V: Bar graph showing the blood glucose level in Group-IV (ethanolic extract Citrus maxima treated rats group) and Group-V (alloxan-induced diabetic rats treated with Glibenclamide) on day 21**

## Discussion

In recent, the world is facing an unprecedented increase in the incidence of diabetes mellitus. Most of the commonly used anti-diabetic agents have some significant side effects and are not cost effective. An increasing interest in herbal and complementary medicine has led to a search for effective natural therapies that have significant effect on blood glucose level.[27] Herbal treatment can be a safe and cost-effective way to combat diabetes.

This research work has been conducted on the basis of the prospect mentioned above. The mentioned parameter was also tested in non-diabetic as well as experimentally induced diabetic rats after 21 days of treatment, the glucose lowering effect of the extract of Citrus maxima was compared with a standard drug, Glibeclamide.

In the present study, diabetes was induced by alloxan monohydrate. The dose and route of administration of alloxan was selected from.[22] The blood glucose levels in animals were measured 72 hours after administration of alloxan which was done according to experiment of Shamim et al.[28] In this study, intraperitoneally (i.p) administration of single dose of alloxan (120mg/Kg), increased blood glucose level significantly ($p<0.001$).The mean ± SD of blood glucose level in rats of Group III was 13.20±0.24 mmol/L and in Group I it was 5.43±0.20 on day 4; in day 21, the mean ± SD of Group III was 13.58±36 mmol/L and 5.50±0.16 mmol/L in Group I. similar observation was reported by number of researchers .Shamim et al.[28] observed that blood glucose level was increasing after 72 hours of intraperitoneal injection of freshly prepared alloxan monohydrate solution at a dose of 120 mg/kg body weight in Swiss alibino rats. Etuk et al.[29] observed that the condition of diabetes after 48 hours of intraperitonel administration of freshly prepared alloxan monohydrate at a dose of 150mg/Kg b.w. In that study, the rise of blood glucose level in experimental rats was also highly significant as $p<0.001$. so it may be concluded that alloxan is a potent hyperglycemic agent in rats.[29]

The study was divided into two parts: Experiment-I and Experiment-II. Experiment-I includes Group I and II. Experiment-II includes Group III, IV and V. blood was collected from Group I and II on day 1, 7, 14 and 21of experiment. Similar experimental design was found in other studies as experiment design-I and experiment design-II.[28,30]

The dose of ethanolic extract of Citrus maxima (200mg/Kg body weight) used in this study was selected based on the dose used in the research done by Bhandurge et al.[23] & Kharjul et al.[24]

The experiment-I of the present study has demonstrated that normal rats group's serum glucose levels was 5.50±0.16 mmol/L (Group I- received only

laboratory diet for 21 days) and the same in group of non-diabetic rats treated with ethanol extract of Citrus maxima juice (Group II) at 200 mg /kg b.w for 21 days; the serum glucose concentrations were 5.61±0.27 mmol/L (mean ± SD), there was no statistically significant difference ($p>0.05$) in the mean value of blood glucose level between two groups. Sriparna K et al.31 also found similar result in her research. So, it may be concluded that Citrus maxima ethanolic extract has no effect on blood glucose level of non-diabetic rats.

In the experiment-II, the effect of ethanolic extract of Citrus maxima was observed in alloxan induced hyperglycemic rats and compared it with Glibenclamide. Decrease in the mean value of blood glucose level was observed in the experimental hyperglycemic group when treated with ethanolic extract of Citrus maxima at a dose of 200mg/Kg (Group IV) and compared with Glibenclamide after 21 days. Diabetes was induced in all groups first by administration of single dose i.palloaxan (120mg/Kg).

The mean ± SD of serum glucose concentration in ethanolic extract of Citrus maxima treated group (Group IV) was 7.20±0.18 mmol/L and in Group III was 13.58±0.36 mmol/L. The mean reduction of serum glucose concentration in Group IV compared to Group III was statistically significant ($p<0.001$). Therefore,the findings of this study are in a well agreement with the fidings of other researchers.[22,23,31,32]

So it may be concluded that ethanolic extract of Citrus maxima has glucose lowering effect in experimentally induced hyperglycemic rats.

The exact mechanism of ethanolic extract of Citrus maxima in reduction of blood glucose level is not well understood. Kim Y et al.[33] suggested in their research that polyphenols isolated from Citrus maxima produced antididiabetic effect by inhibiting the α-amylase and α-glucosidase activities. Polyphenols also enhanced insulin-mediated glucose uptake, a glucose transporter 4-mediated process. This compound inhibited cytokine-induced β-cell damage through suppression of nuclear kappaB (NF-κB) activation in rat pancreatic cells (RINmF5 cells). They observed that the polyphenols also helped to maintain the liver glucose homeostasis.[33]

Guocong et al.[34] evaluated the chemical composition and α-amylase and α-glucosidase enzyme inhibitory effect of crude polysaccharide of citrus maxima endodermis. In his study, it was found that citrus maxima reduced the blood glucose level by inhibiting these two enzymes.

Another study showed that it reduced blood glucose level in mice by activating the PPARα and GLUT4 pathway.[35]

Natarin C et al.[37] investigated the protective effects of pomelo against fructose mediated protein oxidation and glycation. They found that pomelo reduced the blood glucose level and chronic complications of diabetic mellitus due accumulation of AGEs (advanced glycation end products). The polyphenols and flavonoids present in polmelo were responsible for inhibition of the glycation, Sugar-mediated non-enzymatic protein glycation and oxidation.

In the last experimental part, the mean ± SD of serum glucose concentration in Glibenclamide treated group (Group V) was 7.00±0.48 mmol/L and in Group III was 13.58±0.36 mmol/L. The mean reduction of serum glucose concentration in Group V compared to Group III was statistically significant ($p<0.001$). Result is shown in table-VI. So, the Glibenclamide significantly reduces the serum glucose level. Similar observation was made by Bhandurge P et al.[23] who used Glibenclamide at a dose of 10 mg/kg body weight in alloxan induced diabetic rats and found the effect of the drug statistically significant.

The mean ± SD of serum glucose concentration in Glibenclamide treated rats (7.00±0.18) was compared to ethanolic extract of Citrus maxima treated rats (7.20±0.18 mmol/L). The both group was effective for decreasing blood glucose level. But the mean reduction of glucose in Group IV compared to Group V was not statistically significant ($p>0.05$). These result were similar with the results of other studies.[31,32] So, it may be suggested that the glucose lowering effect of ethanol extract of Citrus maxima is almost nearly effective to that of Glibenclamide.[31]

From all above results, it was observed that the ethanolic extract of Citrus maxima has blood glucose lowering effect in alloxan induced hyperglycemic rats as like Glibenclamide but it has no effect on blood glucose level in non-diabetic rats. The result is suggestive of ethanolic extract of Citrus maxima as a useful glucose lowering agent in the treatment of diabetes mellitus. Due to time constrain the following parameters could not be taken in the present study ; 2 hours after blood glucose , plasma insulin level, HbA1c, liver glycogen level and free radicals in the tissues after

treatment with ethanol extract of Citrus maxima. Different extract of Citrus maxima was not used. Despite of all these limitations, interpretation of the results obtained in this study was made carefully and cautiously.

**Conclusion**

The observations and results of this study provide information that Citrus maxima ethanolic extract have glucose lowering effect at a dose of 200mg/Kg body weight in experimental diabetic rats. Thus, it provides a rationale for its use in development of new drug, required for treatment and prevention of diabetes mellitus. However, if these experimental data are endorsed in the clinical trials in future, Citrus maxima may be considered as a natural alternate or adjuvant remedy for type 2 diabetes mellitus.

**References**


1. WHO: diabetes in South East Asia region, 2016 available athttp://apps.who.int/iris/bitstream/10665/204979/1/Vol5%20Issu1.pdf.
2. Wild S, Rogelic G, Green a, Sincree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes care 2004; 27 (5): 1047-53.
3. IDF atlas 10th edition available at https://diabetesatlas.org/

4. WHO Global report on diabetes available at http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf

5 .https://www.idf.org/our-network/regions-members/south-east-asia/diabetes-in-sea.html

6. Akter S, Rahman MM, Abeb SK, Sultanac P. Prevalence of diabetes and prediabetes and their risk factors among Bangladeshi adults: a nationwide survey. Bull World Health Organ. 2014;92:204–13A.
7. National Institute of Population Research and Training (NIPORT) Ma, and ICF International,. Bangladesh Demographic andHealth Survey 2011. Dhaka, Bangladesh and Calverton, Maryland, USA:NIPORT, Mitra and Associates, and ICF International 2013.
8. Research NIoP, Training - NIPORT, Health Mo, Family Welfare, ICF. Bangladesh Demographic and Health Survey 2017-18. Dhaka, Bangladesh: NIPORT/ICF; 2020.
9. WHO/. Report of a WHO Consultation, definition, diagnosis and classification of Diabetes Mellitus and its complications. Department of noncommunicable diseases Surveillience. Geneva :1999:p 1-23. Available at http:/www.staff.ncl.ac.uk/Philip.home/who_dmc.htm.
10. WHO/IDF consultation: Defination and diagnosis of diabetes meliitus and intent hyperglycemia, 2006: 21-29.
11. Frier BM, Fisher M. Davidson's Principles and practice of medicine. 21st ed. 2011. p. 806.
12. Saquib N, Saquib J, Ahmed T, Khanam MA, Cullen MR. Cardiovascular diseases and type 2 diabetes in Bangladesh: a systematic review and meta-analysis of studies between 1995 and 2010. BMC public health. 2012; 12: 434.
13. Antidiabetic Potential of Medicinal Plants and Their Active Components Biomolecules. 2019 Oct; 9(10): 551; Published online 2019 Sep 30. doi: 10.3390/biom9100551;PMCID: PMC6843349; PMID: 31575072
14. Vijaylakshmi P, Radha R. An overview of Citrus maxima. The Journal of Pharmacology 2015; 4(5): 263-267.
15. Dubey NK, Kumar R, Tripathi P. Global promotion of herbal medicines: India's Opportunity. Current Science 2004; 86(1): 37-41.
16. Mabberley DJ. A classification for edible Citrus (Rutaceae). Telopea 1997; 7: 167-72
17. Okwu DE. Citrus fruits: a rich source of phytochemicals and their roles in human health. Int J Chem Sci. 2008; 6(2): 451-471
18. Cordenonsi LM, Sponciado RM, Camapanharo SC, Garcia CV, Ralfin RP, Schapoval EES. Study of flavonoids present in Pomelo (Citrus maxima) by DSC UV-VIS, IR, 1H, and 13C NMR and MS. Drug Anal. Res. 2017; 01: 31-37.
19. Feng B, Pei Y. Study on the coumarins from Citrus grandis. Shenyang Yaoke Daxue Xuebao 2000; 17(4): 253-255.
20. Feng BM, Shah Y, Pei YH, Hua HM, Li W. Structure determination of the constituents from Citrus gandis Osbeck. In China Journal of Chinese Meteria Medica 2001; 26(11): 764-765.
21. Kim K, Kim H, Kwon J, Lee S, Kong H, Im SA, et al. Hypoglycemic & hypolipidemic effects of

processed Aloe vera gel of non-insulin dependent diabetes mellitus.

Phytomedicine 2009, available at www.scien cedirrect.com.

22. Qureshi SA, Hasnain SN. Hyperglycemic and antidiabetic activities of aqueous leaf extracts of Azadiractaindica (Neem) in alloxan-induced diabetic rats. Proceedings of ISSBP symposium of biochemistry & Biophysics 1997; 2: 267-270.
23. Bhandurge P, Rajarajeshwari N, Alagawadi KR, Agrawal S. Antidiabetic and hyperlipaemic effects of citrus maxima linn fruits on alloxan-induced diabetic rats. International Journal of Drug development and research 2010; 2(2): 273-278.
24. Khajrul M, Gali V, Khajrul A. Antidiabetic potential of ethanolic extract of Citrus maxima fruit peel and Anvilleagarcinii. Int. Journal of pharmaceuticals Innovations 2014; 4.
25. Chouglae AD, Panaskar SN, Gurao PM, Arvindekar AU. Optimization of Alloxan dose is essential to induce stable diabetes for prolong period. Asian Journal of biochemistry 2007; 2(6): 402-408.
26. Trinder P. Determination of glucose by enzymatic colorimetric method. Ann. Clin. Biochem. 1969; 6: 24.
27. Diabetes Action Research and Education Foundation 2010 available at http://www.diabe tes action.org./site/pageServer?pagename=complem entary_7_10 accessed on 20-4-17
28. Qureshi SA, Asad W, Sultana V. The Effect of Phyllantusemblica Linn on Type - II Diabetes, Triglycerides and Liver - Specific Enzyme. Pakistan Journal of Nutrition 2009; 8(2): 125-128.
29. Etuk EU et al. Animals models for studying diabetes mellitus. Agriculture and Biology Journal of North America 2010; 1(2): 130-134.
30. Kim SH, Hyun SH, Choung SY. Anti-Diabetic Effect of Cinnamon Extract on Blood Glucose in db/db Mice. Journal of Ethnopharmacology 2006; 104: 119-123.
31. Kundusen S, Gupta M, Majumder UK, Haldar PK, Saha P, Battachariya S et al. Antihyperglycemic effect and antioxidant properties of Citrus maxima leaf in streptozocin- induced diabetic rats. Diabetologia Croatica 2011; 40(4): 113-120.
32. Abdul MMT, Ashok S, Karunakar H, Sayed A, Shabaraya AR. Evaluation of antidiabetic activity of Citrus maxima stem berk on streptozocin induced diabetic rats. Int. Journal of Pharmaceuticals and chemical sciences 2014; 3(3): 647-650.
33. Kim Y, Keogh JB, Cliftoin PM. Polyphenol and glycemic control. Nutrients 2016; 8(1): 17.
34. Guocong L. Chemical compositions, A-Glucosidase and A-amylase inhibitory activities of crude polysaccharide from the endodermis of Shaddock (Citrus maxima). Archives of Biological Sciences 2012; 64(1): 10.2298/ABS12010712.
35. Xu GH, Liu DH, Chen JC, Ye XQ, Ma Y, Shi J. Juice components and antioxidant capacity of Citrus varieties cultivated in China. Food Chemistry 2008; 106(2): 545–551.
36. Yang XH, Zhang GX, Cui P. Gc/Ms analysis of the chemical constituents of Pomelo peel volatile oil. Wuhan Huagong Cueyuan Xuebao 2001; 23(2): 13-15.
37. Caengprasath N, Ngamukote S, Makynen K, Adisakwattana S. The protective effect of pomelo extract [Citrus grandis ] against fructose mediated protein oxidation and glycation. EXCLI Journal 2013; 12: 491-502.

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**Review Article**

# Treatment with a proton pump inhibitor improves glycaemic control in type 2 diabetic patients.

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**Abstract**

Oral hypoglycemic medications sometimes do not control type 2 diabetes well. Proton pump inhibitors as adjunctive therapy might improve diabetes control through increasing serum gastrin & fasting insulin levels. Proton pump inhibitor therapy also associated with lower glycosylated hemoglobin levels in diabetes.

## Introduction

Proton pump inhibitors are first introduced in the late 1980 & they are used for the treatment of acid-peptic disorders. PPIs are now most widely prescribed drugs worldwide due to their outstanding efficacy and safety.[1] PPIs available for clinical uses are-omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole.

All the PPIs are substituted benzimidazoles that resembles $H_2$ antagonists in structure that have a completely different mechanism of action. PPIs inhibit both fasting and meal-stimulated secretion because they block the final common pathway of acid secretion, the proton pump1. In standard doses, PPIs inhibit 90-98% of 24-hour acid secretion.

## Clinical uses of PPI[1]:

a) Gastro-esophageal reflux disease.
b) Peptic ulcer disease:
   1) H. pylory-associated ulcers.
   2) NSAID-associated ulcers.
   3) Prevention of re-bleeding from peptic ulcers.
c) Nonulcer dyspepsia.
d) Prevention of stress-related mucosal bleeding.
e) Gastrinoma and other hypersecretory conditions.

Proton pump inhibitors might be useful as adjunctive therapy for type-II diabetes mellitus.[2]

## DM:

Type-II diabetes is characterized by insulin resistance and/or deficient pancreatic β-cell mass or production and secretion of insulin.[2]

Common treatments of type 2 diabetes may modify insulin sensitivity, increase insulin secretion, or in some cases either reduce beta-cell dysfunction or slow their degradation.[3]

## Effect of PPIs:

A physiological effect of acid suppression with PPIs is a mild/modest hypergastrinemia which occurs with all PPIs.[4] Gastrin is known to be the major regulator of the secretory response to a protein meal, while somatostatin is a potent inhibitor of gastrin and histamine synthesis and release and therefore, of gastric acid secretion.[5]

In rodents, gastrin induces islet β-cell neogenesis[6,7] and in vitro studies, this hormone increases the β-cell mass.[8] A few retrospective studies in adults with diabetes appear to have shown that PPIs are associated with better glycemic control. Mefford et al[9] compared HbA1c levels from type 2 diabetic patients taking PPIs (7%) and type 2 diabetic not taking them (7.6%), obtaining significant differences.

Gastrin has shown to induce β-cell proliferation and neogenesis in various model systems, and also appears to increase the insulin content of individual β-cells.[10] By blocking gastric acid production, proton pump inhibitors (PPIs) remove negative feedback on gastrin production by entero-chromaffin cells. In a rodent model of type 2 diabetes treatment with the PPI lansoprazole increased serum gastrin that was associated with improved glycemic and increased pancreatic insulin content.[11]

## Different research evidence:

A research work was done from hospital of spain by Diana Boj et el.[12]

**Glycemic control result shown in Table:**

| | Total | Insulin | Metformin | Sulfonylurea | Others antidiabetic drugs |
|---|---|---|---|---|---|
| **Withou PPI** | | | | | |
| HbA1C (%) | 7.3 | 7.6 | 7.4 | 7.2 | 8.0 |
| SD(%) | 1.4 | 1.5 | 1.6 | 1.1 | 1.2 |
| n | 43 | 19 | 24 | 11 | 4 |
| **With PPI** | | | | | |
| HbA1C (%) | 6.7 | 6.8 | 6.7 | 6.7 | 7.2 |
| SD(%) | 1.0 | 0.8 | 1.0 | 0.7 | 1.2 |
| n | 54 | 28 | 2.3 | 10 | 13 |
| Absolute difference | -0.6 | -0.8 | -0.7 | -0.5 | -0.8 |
| ρ value | 0.018 | 0.022 | NS | NS | NS |

This study was conducted within total 97 patients admitted to hospital of the year 2010 who had a recent $HbA_1c$ measurement. It compared $HbA_1c$ levels of those taking PPIs and those not. The average $HbA_1c$ level was 7.0% ± 1.2%. Overall PPI consumption was 55.7%. $HbA_1c$ was significantly lower in individuals who took PPIs – 0.6%, people who used PPIs with some type of insulin therapy had a $HbA_1c$ reduction by – 0.8%. For the rest of subgroup analysis based on the antidiabetic drug used, PPI consumption always exhibited lower $HbA_1c$ levels.[12]

Another research was done in USA by I.N.Mefford et al.[13] It was a case report. A 43 year old man with type 2 diabetes, opposed to insulin use and poorly responsive to oral agents over 6 years, was placed on 40-mg twice daily omeprazole. A linear decline in daily fasting blood glucose was observed throughout the first two months treatment. Initial fasting blood glucose, 240mg/dl at the start of treatment, declined to 138mg/dl at the end of 8 weeks. HbA1c was reduced from 11.9% to 8.2%, then sustained at 8.1% after four months. Glucose, insulin, and C-peptide response to a 2-hour glucose tolerance test were consistently improved across this time period.[13]

**Fig. -I: Effect of twice daily 40mg omeprazole treatment on serum gastrin and hemoglobin A1c in a type 2 diabetic.**

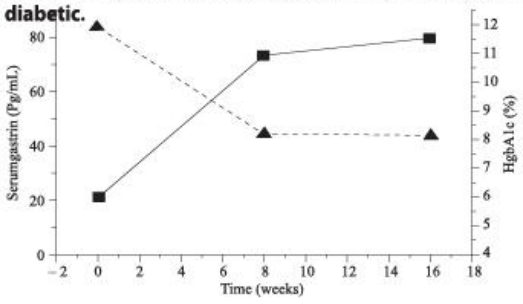
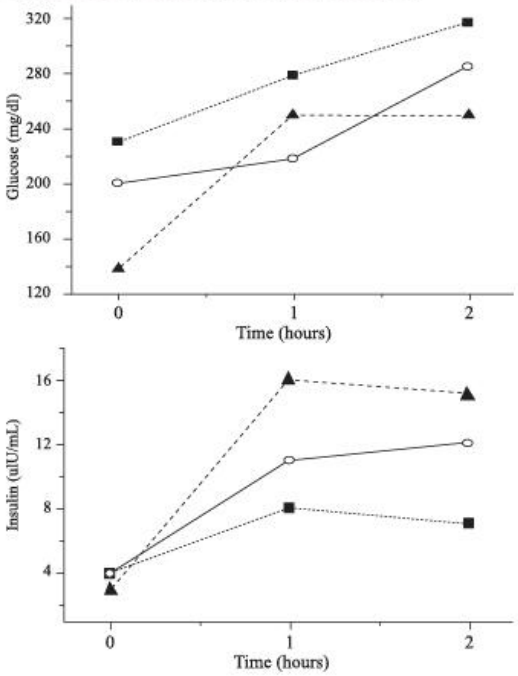



**Fig.-II: 2hr glucose tolerance test effects on blood glucose (a), insulin (b) after twice daily 40mg omeprazole treatment in a type 2 diabetic.**




Calculated β cell mass increased by 67% by HOMA method. We believe this response is consistent with activation or neogenesis of pancreatic beta cells, possibly through a gastrin-mediated mechanism.

Hove et al[14] conducted a case-control study to investigate whether treatment with esomeprazole improved $HbA_1c$ levels in a group of type 2 diabetic patients. They found a border line significant reduction of $HbA_1c$ by 0.7%.

A study was conducted by Michael A. Crouch, Ivan N. Mefford and Ekpedema U. Wade to investigate whether proton pump inhibitor therapy associated with lower glycosylated hemoglobin level in Type 2 Diabetes.[2] In that study 73 individuals were reviewed with type 2 diabetes (not taking insulin), for whom PPI were prescribed. Values for $HbA_1c$ for periods of time when a PPI had been prescribed were compared with HbA1c levels for periods of time with no record of PPI prescribing or over-the-counter PPI use. The mean HbA1c or patients not taking insulin was 7.11 during periods with recorded prescribing or over-the-counter

use of PPI, compared with 7.70 during periods without recorded PPI therapy (P=0.001). Mean $HbA_1c$ for metformin monotherapy was not significantly different (6.81 with PPI vs. 7.10 without PPI; n=16; p=.25). Mean $HbA_1c$ was significantly different for combination therapy that included metformin and/or sulfonylurea and/or glitazone (7.26 vs. 7.80; n=27; p=.002).

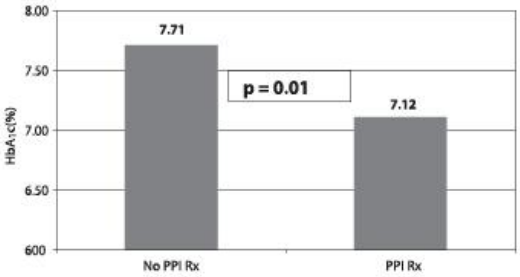



**Fig.-III: Mean hemoglobin $A_1c$ with and without an active proton pump inhibitor (PPI) prescription.**

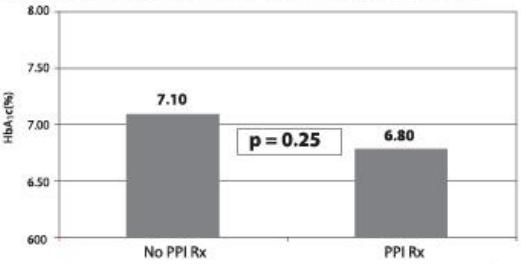



**Fig.-IV: Mean hemoglobin $A_1c$ with a prescription for metformin with and without a concomitant proton pump inhibitor (PPI).**

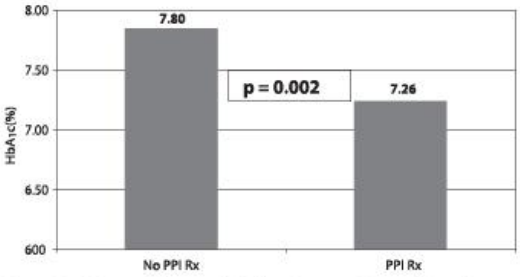



**Fig. -V: Mean hemoglobin $A_1c$ with sulfonylurea and/or glitazone and/or metformin with and without a prescription for a concomitant proton pump inhibitor (PPI).**

## Conclusion

PPIs have a secondary effect on glycemic control. It could be a new antidiabetic drug with a good profile: no hypoglycemic events, good tolerability and safety, and with a limited price.

## References:

1) Mc Quaid KR. Drugs used in the treatment of gastrointestinal diseases. Basic & clinical pharmacology. Edited by Bertram G. Katzung, Susan B. Masters, Anthony J. Trevor. 12th edition, 2012: P. 1085.

2) Michael A. Crouch, Ivan N. Mefford, and Ekpedeme U. Wade. Proton pump inhibitor therapy associated with lower glycosylated hemoglobin levels in type 2 diabetes. JABFM, January-February 2012, Vol. 25, no.1, PP.50-54.

3) P.Marchetti, R. Lupi, S.Del Guerra et al. Goals of treatment for type 2 diabetes: β-cell preservation for glycemic control. Diabetic care, Vol.32, suppl. 2, PP. S178-S183, 2009.

4) Sheen E, Triadafilopoulos G. Adverse effects of long-term proton pump inhibitor therapy. Dig Dis Sci 2011; 56: 931-950.

5) Schubert ML. Gastrin secretion. Curr opin Gastroenterol 2010; 26: 598-603.

6) Rooman I, Lardon J, Bouwens L. Gastrin stimulates beta-cell neogenesis and increases islet mass from transdifferentiated but not from normal exocrine pancreas tissue. Diabetes 2002; 51: 686-690.

7) Suarez-Pinzon WL, Yan Y, Power R, Brand SJ, Rabinovitch A. Combination therapy with epidermal growth factor and gastrin increases beta-cell mass and reverses hyperglycemia in diabetic NOD mice. Diabetes 2005; 54: 2596-2601.

8) Suarez-Pinzon WL, Lakey JR, Brand SJ, Rabinovitch A. Combination therapy with epidermal growth factor and gastrin induces neogenesis of human islet {beta}-cell from pancreatic duct cells and an increase in functional {beta}-cell mass. J Clin Endocrinol Metab 2005; 90: 3401-3409.

9) Mefford IN. Wade EU. Proton pump inhibitors as a treatment method for type II diabetes. Med Hypotheses 2009 Jul; 73(1): 29-32.

10) Michael R. Rickels and Dauiush Elahi. Raising Serum Gastrin to improve Glycemic Control in (Type 2) Diabes: Another Limb of the enteroinsular axis? J Clin Endocrinol Metab, November 2012, 97(II): 3915-3916.

11) Bodvarsdottir TB, Hove KD, Gotfredsen CF, Pridal L, Vaag A, Karlsen AE, Petersen JS 2010. Treatment with a Proton pump inhibitor improves glycemic control in Psammomys obesus, a model of type 2 diabetes. Diabetologia 53: 2220-2223.

12) Boj-Carceller D et al. Are proton pump inhibitors a new antidiabetic drug? Across sectional stydy. World J Diabetes 2011 December 15; 2(12): 217-220.

13) Mefford IN, Mefford JT., and Burris CA. Improved Diabetes Control and Pancreatic Function in a Type 2 Diabetic after Omeprazole administration. Hindwi publishing Corporation. Case reports in endocrinology, Vol 2012, Article ID 468609.

14) Hove KD, Faerch K, Bodvarsdottir TB, Karlsen AE, Petersen JS, Vaag A. Treatment with a proton pump inhibitor improves glycemic control in type 2 diabetic patients – a retrospective analysis. Diabetes Res Clin Pract 2010; 90(3): e72-e74.

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**Case Report**

# A case of Leptospirosis

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**Abstract:**

We describe a case of a patient with fever and jaundice initially diagnosed as a case of dengue with viral hepatitis, but his occupation, persistence of fever and jaundice, subconjunctival hemorrhage and renal involvement provide the clue to diagnose the case as Leptospirosis.

## Introduction

Leptospirosis is a zoonotic disease caused by infection with Leptospira species which is prevalent in both tropical and temperate regions,[1] but more common in tropics as the pathogenic bacteria survives longer in tropical environment. Leptospira species lives in kidneys of mammalian species like rodents, cattle, sheep and pig but rodents are the most common reservoir in transmission of the disease. Humans are infected incidentally after being exposed to infected animal tissue or excreta.[2]

The disease appeared with complex clinical features varying from subclinical infection and self-limiting anicteric illness to multiple-organ failure and death. Severe leptospirosis is the same with Weil's disease which is characterized by kidney and liver failure. Antibiotics should be started as soon as the diagnosis is suspected.[3,4]

According to WHO guidelines treatment regimen for less severe cases is DOXYCYCLINE, TETRACYCLINE, AMPICILLIN, AMOXICILLIN, third generation cephalosporins like CEFTRIAXONE, CEFOTAXIME and QUINOLONE antibiotics.[4] Severe cases usually treated with high doses of BENZYLPENICILLIN (30mg/kg up to 1.2g IV 6-hourly for 5-7 days). Along with antibiotics supportive care should be provided.[5]

## Case Presentation

A 55-year-old farmer hailing from Kapasia, Gazipur got admitted in Dhaka National Medical College Hospital with the complaints of high-grade intermittent fever for 14 days, yellowish discoloration of both eyes for the same duration. His fever was associated with anorexia, nausea and mild itching. On query he gave history of cough with expectoration of scanty mucoid sputum, initially 3 Days after development of symptoms he got admitted at Kapasia upazila health complex, where he developed right sided subconjunctival hemorrhage and his jaundice was gradually increasing, so he shifted to Dhaka for better treatment. He does not have history of hematemesis, melena or other bleeding manifestation.

On examination he was non anemic, deeply icteric, right sided subconjunctival hemorrhage was present. His pulse was 100 b/min regular. BP 90/60 mm/Hg. RR - 16 breathe/ mm, temperature was 100° F. He had no stigmata of chronic liver disease. On abdominal examination the liver was palpable 4 cm from rt costal margin, firm, non-tender, upper border of liver dullness was present in rt 5th intercostal place. After sending first line investigation, we started injection ceftriaxone 2gm twelve hourly. After five days, as fever was not responding, we started doxycycline 100mg BD along with ceftriaxone.

Repeated CBC is presented in table-I.

**Table-I: CBC of patient for 4 different days.**

| | 19.05.19 | 22.05.19 | 25.05.19 | 28.05.19 |
|---|---|---|---|---|
| Hemoglobin H GB. (g/dl) | 10.7 | 11 | 13 | 11.3 |
| WBC/mm^3 | 13000 | 15000 | 19000 | 1000 |
| Neutrophil (%) | 78 | 76 | 74 | 71 |
| Lymphocyte (%) | 19 | 18 | 18 | 24 |
| Monocyte (%) | 2 | 2 | 3 | 3 |
| Eosinophil (%) | 1 | 3 | 5 | 2 |
| PLT(/mm^3) | 20,000 | 70,000 | 3,40,000 | 4,10,000 |
| ESR (mm/1st hour) | 120 | 95 | 105 | 85 |

PBF showed - Neutrophilic leucocytosis with thrombocytopenia.

Urine RME showed 7-8 pus cell and scanty albumin. His initial serotonin was 2.1 mg/dl, RBS was - 6.8 mmol/L;

His liver function test showed in table-II.

**Table-II: Liver functions of patient in 3 different days**

| Parameters | 19.05.19 | 27.05.19 | 05.06.19 |
|---|---|---|---|
| S. bilirubin (mg/dl) | 17 | 14 | 3 |
| SGPT (10/L) | 65 | 60 | 25 |
| SGOT(10/L) | 60 | 62 | 40 |
| ALP (10/L) | 220 | 120 | 115 |
| Serum albumine (gm/L) | 27 | 30 | 35 |
| Prothrombin time (s) | 13 | 13 | 12 |

His HBs Ag, Anti HEV IgM, AntiHAV Igm, Anti HEV-IgM were negative. Ultrasonography of whole abdomen showed Hepatomegaly and mild splenomegaly. Chest X - ray showed bilateral pulmonary inflammatory lesion. MT was negative.

ICT for Dengue, ICT for Malaria, ICT for Kela-azar was negative. Anti-leptospiral Ab was positive but urine for leptospira (DGI) was negative. With injection cefrtiaxone patient was not responding initially, but with addition of the doxycycline his fever subsided after 14 days of antibiotic and after around one month his jaundice subsided.

## Discussion

Leptospirosis has been an emerging global public health problem because of its increasing incidence in both developing and developed countries. The incubation phase from the exposure to the onset of symptoms averages from 7 to 12 days. The step in the pathogenesis of leptospirosis is a penetration of tissue barriers to gain come to the body. Chances portals of entry include the skin by cutting or abrasion the mucous membranes of the conjunctivae or oral cavity. The next step in pathogenesis is hematogenous dissemination and persist there during the leptospiremia phase of the illness.[6] As our patient was a farmer and had a history of working in the dirty water for long, he was a risky patient to develop leptospirosis.

Leptospirosis is diagnosed by serology because the capacity for culture and PCR is limited. IgM antibodies are detectable in the blood 5–7 days after the onset of symptoms. In the microscopic agglutination test (MAT), patient's sera are reacted with active antigen suspensions of leptospiralserovars. After incubation, the serum/antigen mixtures are checked microscopically for agglutination, and the titers are determined.[7] IgM antibody was detected in our patient.

The most case of leptospirosis are mild and resolve spontaneously. Soon initiation of antimicrobial therapy may prevent some patients from progressing to more severe disease. Empirical treatment should be as soon as the diagnosis of leptospirosis is suspected. We treated our case with injection cefrtiaxone and doxycycline for 14 days.

## Conclusion

It was a case of a 55-year-old farmer with moderate manifestation of leptospirosis which was diagnosed with presence of IgM leptospiral antibody. Detail history taking, good clinical guess and early starting of empirical antibiotic can prevent further deterioration and complication.

## Reference

1. Kobawaka Gamage KK, Fernando H. Leptospirosis complicated with Guillain Barre syndrome, papillitis and thrombotic thrombocytopenic Purpura; a case report. BMC Infect Dis. 2018; 18(1): 691.
2. Maroun E, Kushawaha A, El-Charabaty E, Mobarakai N, El-Sayegh S. Fulminant Leptospirosis (Weil's disease) in an urban setting as an overlooked cause of multiorgan failure: a case report. J Med Case Rep.2011; 5: 7.
3. Haake DA, Levett PN. Leptospirosis in humans. Curr. Top. Microbiol. Immunol. 2015; 387: 65–97.
4. Zein U. Leptospirosis Buku ajar ilmu penyakit dalam. 2014; 3(83): 633-639.
5. Bal AM. Unusual clinical manifestations of leptospirosis. J Postgrad Med. 2005; 51(3): 179-183.
6. Levett PN, Haake DA. Leptospira species (leptospirosis) Principles and practice of infectious diseases. Churchill Livingstone Elsevier,2010.p. 73059-65.
7. Maroun E, Kushawaha A, El-Charabaty E, Mobarakai N, El-Sayegh S. Fulminant leptospirosis (Weil's disease) in an urban setting as an overlooked cause of multiorgan failure: a case report. J. Med. Case Rep. 2011.


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