Volume-04
Number-01
January-2021
ISSN: 2616-6178

The **BEACON** Medical Journal

Journal of Current Medical Practice

The Advisory Board

Prof. Dr. Quazi Deen Mohammad
Director & Professor of Neurology
National Institute of Neuroscienes
Sher-E-Bangla Nagar, Dhaka.

Prof. Dr. T. A. Chowdhury
Advisor of Dept. of Obstetrics and Gynecology
BIRDEM, Dhaka.

Prof. ABM Abdullah
Ex. Dean & Professor, Faculty of Medicine
Bangabandhu Sheikh Mujib Medical University.

Prof. Dr. Rashidul Hassan
Professor & President
Bangladesh Lung Foundation (BLF).

Prof. Mohammod Shahidullah
Professor & Chairman of Dept. of Neonatology
Bangabandhu Sheikh Mujib Medical University.

Prof. Dr. Khan Abul Kalam Azad
Principal & Professor
Department of Medicine
Dhaka Medical College.

Prof. Dr. Md Billal Alam
Professor, Dept. of Medicine
Dhaka Medical College and Hospital.

Prof. Dr. Md. Nurul Hooda
Professor & Director
National Institute of Kidney Diseases & Urology (NIKDU)

Prof. Dr. Shahedur Rahman Khan
Director
National Institute of Diseases of The Chest & Hospital & National Asthma Centre.

Prof. Dr. Md. Faruq Alam
Professor & Director
Department of Psychiatry
National Institute of Mental Health.

Prof. Dr. Golam Mostafa
Director cum Professor
National Institute of Ophthalmology (NIOH).

Prof. Dr. Mirza Mohammad Hiron
Former Director cum Professor, NIDCH.
President, The Chest & Heart Association of Bangladesh.

Prof. Dr. Shamsun Nahar
Prof. & Chairman
Dept. of Physical Medicine & Rehabilitation.
Bangabandhu Sheikh Mujib Medical University.

Prof. Dr. Begum Hosne Ara
Ex. Executive Director & Head
Department of Obstetrics and Gynecology
Institute of Child and Mother Health.

Prof. Dr. A K M Musa
Ex. Professor & Head
Department of Medicine
BIRDEM.

Prof. Dr. Md. Saifullah
Professor
National Institute of Ophthalmology (NIOH).

The Advisory Board

Prof. Dr. Syed Modasser Ali
Chairman
Bangladesh Medical Research Council (BMRC)

Prof. Dr. Md. Abul Kalam
Professor & Head
Department of Burn & Plastic Surgery
Dhaka Medical College.

Prof. Dr. Md. Zulfiqur Rahman Khan
Prof. & Chairman, Dept. of Hepatobillary Pancreatic & Liver Transplant Surgery
Bangabandhu Sheikh Mujib Medical University.

Prof. Dr. A.B.M. Bayezid Hossain
Professor and Head of the Dept. of Surgery
Sir Salimullah Medical College and Hospital.

Prof. Dr. Md. Shamsuzzaman
Professor & Head,
Department of Orthopedic Surgery
Dhaka Medical College and Hospital.

Prof. Dr. Golam Faruque
Professor, Dept. of Orthopedic Surgery
National Institute of Traumatology & Orthopaedic Rehabilitation.

Prof. Dr. Rowshan Ara Begum
Advisor of Obstetrics and Gynecology
Holy Family Red Crescent Medical College & Hospital, Dhaka.

Prof. Dr. Md. Selimuzzaman
Prof. & Head, Dept. of Child Health
Dhaka Shishu (Children) Hospital.

Prof. Dr. A Z M Mustaque Hossain
Professor & Head, Department of Surgery.
Dhaka Medical College and Hospital.

Prof. Dr. Faruque Pathan
Professor & Advisor
Department of Endocrinology, BIRDEM.

The Review Board

Prof. M A Azhar
Principal & Head
Department of Medicine
Green Life Medical College & Hospital.

Prof. Md. Mazibar Rahman
Professor, Department of Surgery
Professor of Surgery (Rtd.)
Dhaka Medical College and Hospital.

Prof. Dr. M. A. Mohit (Kamal)
Professor, Department of Psychiatry
National Institute of Mental Health.

Prof. Lt. Col Dr. Md. Abdul Wahab
Professor, Dept. of Dermatology and Venereology
Bangabandhu Sheikh Mujib Medical University.

Prof. Dr. Md. Sazzad Khondoker
Professor, Dept. of Burn & Plastic Surgery
Dhaka Medical College & Hospital.

Prof. Dr. Fatema Ashraf
Head, Dept. of Obstetrics and Gynecology
Shaheed Suhrawardy Medical College and Hospital.

The Review Board

Prof. Dr. Faruque Ahmed
Professor & Head,
Department of Gastroenterology.
Dhaka Medical College and Hospital.

Prof. Dr. Sayeda Anwar
Professor & Head,
Department of Pediatric and Neonatology.
Dhaka Medical College and Hospital.

Prof. Dr. Wahida Khanam
Professor & Head,
Department of Pediatrics and Neonatology.
Institute of Child and Mother Health.

Prof. Dr. Md. Mozaffer Hossain
Professor & Head,
Department of Anaesthesia, Analgesia, Palliative & Intensive Care Medicine.
Dhaka Medical College and Hospital.

Prof. Dr. A. F. Mohiuddin Khan
Prof. & Head, Dept. of ENT, DMCH

Prof. Dr. Sarwar Iqbal
Prof. & Head, Department of Nephrology, BIRDEM

Prof. Dr. Md. Anower Hussain
Dean, Faculty of Public Health
Bangladesh University of Health Sciences

Editor's choice

This is a pleasure for us that we are going to publish "The Beacon Medical Journal" volume-04, number-01 in January 2021. Next issue will be published in July 2021. The journal has been published 2 issues/year as regular basis. Ten thousand copies have been distributed to graduate doctors throughout the country by our field colleagues. Already we had built a strong advisory and review board to draw the attention of its authors & readers nationally & internationally. Editorial of this issue is postpartum hemorrhage which is the most common obstetric emergency. PPH is a leading cause of maternal morbidity & mortality worldwide. In this issue, epidemiology, common causes, updated management of PPH are nicely described. Apart from that this issue also contains six original articles, one review article and two case reports.

Your opinion and suggestions will highly encourage us for the development of the journal. The journal is freely available at www.beaconpharma.com.bd for contributing the advancement of public health and medical research.

I do believe this journal will scientifically help doctors in their daily practice.

Dr. G.M. Raihanul Islam
Executive Editor
The Beacon Medical Journal

Editorial Board

Executive Editor
Dr. G. M. Raihanul Islam
MBBS, MPH.
Vice President, Medical Service Department.
Beacon Pharmaceuticals Limited.
Email-dr.raihan@beaconpharma.com.bd
Mobile:-01985550111.

Chief Editor
Prof. Dr. Nazneen Kabir
Ex. Executive Director & Head of Obstetrics & Gynecology,
Institute of Child and Mother Health (ICMH),
Matuail, Dhaka.

Associate Editors
1. **Dr. Tamoshi Showkat**
2. **Dr. Shafaet Hossain**
3. **Dr. Md. Moniruzzaman**
4. **Dr. Badhan Kumar Das**
5. **Dr. Israt Azmi Rolin**

Information for authors

Common Rules for Submission of Manuscript in The Beacon Medical Journal

01. Manuscript written in English on bio medical topics will be considered for publication provided these have not been published previously and are not under consideration for publication elsewhere.

02. The author should obtain written permission from appropriate authority if the manuscript contains any table, data or illustration from previously published in other Journal. The letter of permission should be submitted with manuscript to the editorial board.

03. Authors should keep one copy of their manuscript for reference & three hard copies along with soft copy should be sent to the Executive Editor, The Beacon Medical Journal.

04. The authors should sign a covering letter mentioning that final manuscript has been seen and approved by all authors. Relevancy and contribution of coauthors should clearly mentioned by first author. Irrelevant person or without any contribution should not be entitled as coauthors.

05. The materials submitted for publication may be in the form of an original research, review article, special article, a case report, recent advances, new techniques, books review on clinical / medical education, adverse drug reaction or a letter to the editor.

06. An author can write review article only if he / she has written a minimum of two(2) original research articles and four(4) case reports on the same topic.

07. The manuscript may be submitted by the author online following appropriate criteria as mentioned.

08. Each component of the manuscript should begin on a new page in the sequence of-
    a. Title page
    b. Abstract
    c. Text- Introduction, Material & methods, Result and Discussion.
    d. References
    e. Acknowledgement

09. The title page should include the title of the paper, name of the authors, name of the departments in which they worked, email address & phone number.

10. The title should be concise, informative & self explanatory.

11. The Abstract should be structured as-introduction with objectives, materials & methods, result, discussion with conclusion including key words number of figures, tables, reference & correspondence

12. The text should be presented in the form of-
    a. **Introduction:** This should include the purpose of the article. The rational for the study or observation should be summaries. Only strictly pertinent reference should be cited. The subject should not be extensively reviewed. Data or conclusion from the work being reported should not be presented in introduction.
    b. **Materials & method:** study design & sampling method should be mentioned. Consent from respondents / patients should be taken in the form before interview / study. All drugs & chemicals used should be identified precisely, including generic name, dose route of administration. For all quantitative measurement SI unit should be used.
    c. **Results:** This should be presented in a logical sequence in the text, tables & illustration. For Statistical Analysis standard procedure to be maintained. It should be done by a recognized statistician or subject expert related to statistics.
    d. **Discussion:** Authors comment on the result supported with contemporary references including arguments and analysis of identical work done by other workers may be elaborately discussed. A summary is not required. Brief acknowledgement may be made at the end.
    e. Tables: Number and titles of tables to be clearly written.
    f. Source of Illustrations & Figures should be mentioned.
    g. Abbreviations and Symbols: Use only standard abbreviations; avoid abbreviations in the title of the article.

13. References-
    a. Reference should be numbered in order to which they appear in the text as superscript.
    b. Reference should be in Vancouver style.

Editorial

Postpartum Hemorrhage: The Most Common Obstetric Emergency

Postpartum hemorrhage (PPH) is a leading cause of maternal morbidity and mortality worldwide. Recognition of PPH is challenging, but once hemorrhage is recognized, management needs to focus on achieving adequate uterine tone and maintaining maternal hemodynamic stability. There have been several advances in the management of postpartum hemorrhage, many of which can be implemented at the labor and delivery unit level.[1] Hemorrhage remains as one of the top 3 obstetric related causes of maternal mortality, with most deaths occurring within 24-48 hours of delivery.[2]

Traditionally, postpartum hemorrhage (PPH) has been defined as greater than 500 ml estimated blood loss in a vaginal delivery or greater than 1000 ml estimated blood loss at the time of cesarean delivery. This was redefined in 2017 by the American College of Obstetrics and Gynecology as a cumulative blood loss greater than 1000 ml with signs and symptoms of hypovolemia within 24 hours of the birth process, regardless of the route of delivery. While this change was made with the knowledge that blood loss at the time of delivery is routinely underestimated, blood loss at the time of vaginal delivery greater than 500 ml should be considered abnormal with the potential need for intervention. Primary postpartum hemorrhage is bleeding that occurs in the first 24 hours after delivery, while secondary postpartum hemorrhage is characterized as bleeding that occurs after 24 hours to 12 weeks of delivery.[3-5]

Primary causes of postpartum hemorrhage include uterine atony, genital tract lacerations, retained placenta, uterine inversion, abnormal placentation, and coagulation disorders. Uterine atony, or lack of effective contraction of the uterus, is the most common cause of postpartum hemorrhage. Secondary causes of postpartum hemorrhage include retained placenta, infection, subinvolution of the placental site, and inherited coagulation deficits.[6-9] Postpartum hemorrhage is the leading cause of morbidity and mortality in childbirth. PPH occurs in approximately 1% to 6% of all deliveries. Uterine atony, the primary cause of PPH, accounts for 70% to 80% of all hemorrhage. In low income setting incidence is 6% to 10% of all birth.[10]

Risk factors for postpartum hemorrhage are dependent on the etiology of the hemorrhage. Risk factors for uterine atony include high maternal parity, chorioamnionitis, prolonged use of oxytocin, general anesthesia, and conditions that cause increased distention of the uterus such as multiple gestation, polyhydramnios, fetal macrosomia, and uterine fibroids. Risk factors that can lead to uterine inversion include excessive umbilical cord traction, short umbilical cord, and fundal implantation of the placenta. Genital tract trauma risk factors include operative vaginal delivery and precipitate delivery.[11] Retained placenta and abnormal placentation are more common if an incomplete placenta is noted at delivery, a succenturiate lobe of the placenta is present, or if the patient has a history of previous uterine surgery. Coagulation abnormalities are more common in patients presenting with fetal death in utero, placental abruption, sepsis, disseminated intravascular coagulopathy (DIC), and in those with a history of an inherited coagulation defect.[10-13]

Patients present with acute bleeding post-partum from the vagina. The patient may also have an increased heart rate, an increased respiratory rate, and feeling faint while standing up. As the patient continues to lose blood, they may also feel cold, have decreased blood pressure, and may lose consciousness. Patients may also have signs and symptoms of shock, such as confusion, blurry vision, clammy skin, and weakness. Initial evaluation of the patient should include a rapid assessment of the patient's status and risk factors. In postpartum women, signs or symptoms of blood loss such as tachycardia and hypotension may be masked, so if these signs are present, there should be a concern for considerable blood volume loss (greater than 25% of total blood volume). Continuous assessment of vital signs and on-going estimation of total blood loss is an important factor in ensuring safe care of the patient with PPH.

An examination of the patient at the time of hemorrhage can help to identify the probable cause of bleeding focused on any specific risk factors the patient may have. A rapid assessment of the entire genital tract for lacerations, hematomas, or signs of uterine rupture should be performed. A possible manual exam, speculum examination or assessment by bedside ultrasound may be a part of the evaluation. A soft, "boggy" or non-contracted uterus is the common finding with uterine atony. Uterine inversion presents as a round bulge or mass with palpation of the fundal wall in the cervix or lower uterine segment and is often associated with excessive traction on the umbilical cord or abnormally adherent placenta. Widespread bleeding, such as from venipuncture sites, is a sign of disseminated intravascular coagulation (DIC).

Laboratory studies can be ordered in a PPH to help evaluate and manage the patient, although interventions such as medication or blood product administration should not be withheld, pending the results of such studies. Type and screen or crossmatch may be ordered to prepare for possible blood transfusion. Complete blood count to assess hemoglobin, hematocrit, and platelets can be evaluated at intervals, although lab values often lag behind the clinical presentation. Coagulation studies and fibrinogen will be useful in the patient where DIC is suspected.

The treatment and management of postpartum hemorrhage are focused on resuscitation of the patient while identifying and treating the specific cause.[1] Maintaining hemodynamic stability of the patient is important to ensure continued perfusion to vital organs. Ample intravenous (IV) access should be obtained. Careful direct assessment of cumulative blood loss is important, and a focus should be on early initiation of protocols for the release of blood products and massive transfusion protocols.

Rapid identification of the cause of postpartum hemorrhage and the initiation of treatment should be made simultaneously. Transfer to an operating suite with anesthesia assistance may be indicated for help with a difficult laceration repair, to correct uterine inversion, to help provide analgesia if needed for removal of retained products, or if surgical exploration is indicated. If the postpartum hemorrhage is due to uterine atony, treatment modalities include medical management with uterotonic agents, uterine tamponade, pelvic artery embolization, and surgical management.

Medical management with uterotonic and pharmacologic agents is typically the first step if uterine atony is identified. While oxytocin is given routinely by most institutions at the time of delivery (see prevention), additional uterotonic medications may be given with bimanual massage in an initial response to hemorrhage. Uterotonic agents include oxytocin, carbetocins, and prostaglandins. Commonly used uterotonics include oxytocin, carbetocin, carboprost, misoprostol.

If bimanual massage and uterotonic medications are not sufficient to control hemorrhage, uterine tamponade may be considered. An intrauterine balloon tamponade system can be used, typically by filling an intrauterine balloon with 250 to 500 mL of normal saline. If there is not an intrauterine balloon readily available, the uterus may be packed with gauze, or multiple pads Foley catheters may be placed concurrently. It is important to keep an accurate count of anything placed in the uterus to prevent retained foreign bodies. Uterine artery embolization may be considered in a stable patient with persistent bleeding. Fluoroscopy is used to identify and occlude bleeding vessels. While the unstable patient is not a candidate for this modality, it has the benefit of uterine conservation and possible future fertility. Exploratory laparotomy is typically indicated in the setting where less invasive measures for postpartum hemorrhage have failed or if the suspected reason for postpartum hemorrhage such as morbidly adherent placenta, demands it. A midline vertical abdominal incision should be considered to maximize exposure; however, if the patient had a cesarean delivery, the existing incision may be utilized. Vascular ligation sutures may be attempted to decrease pulse pressure at the uterus. Bilateral uterine artery ligation [16] sutures may be placed as well as bilateral utero-ovarian ligament ligation sutures. Ligation of the internal iliac arteries may also be performed; however, as this entails a retroperitoneal approach, it is rarely used. Uterine compression sutures may also be used as a treatment for atony.[17] The B-Lynch suture technique, the most commonly performed of the compression sutures, physically compresses the uterus looping from the cervix to the fundus. The definitive treatment for postpartum hemorrhage is a hysterectomy. A peripartum hysterectomy is associated not only with permanent sterility but also increased surgical risk with a higher risk of bladder and ureteral injury. Supracervical hysterectomy may be performed alternately as a faster surgery with potentially fewer complicated risks.

Postpartum hemorrhage is a leading cause of maternal and fetal morbidity worldwide. Correct and timely institution of treatment can vastly improve the patient outcomes. As the loss of blood occurs in postpartum hemorrhage, the patient is at risk of hypovolemic shock. When the patient loses 20% of the blood, they develop tachycardia, tachypnea, narrowed pulse pressure, and delayed capillary refill. This may lead to ischemic injury to the liver, brain, heart, and kidney. Sheehan syndrome or postpartum hypopituitarism is one of the complications of excessive blood loss seen in postpartum hemorrhage. The complications related to management include transfusion-related acute lung injury, infections, hemolytic transfusion reactions.

Preventative techniques can be used in patients to prevent atony and PPH, including active management of the third stage of labor with oxytocin administration, uterine massage, and umbilical cord traction. Identifying high-risk patients before delivery is one of the most important factors in preventing morbidity and mortality associated with PPH. This allows for planning appropriate routes and timing of delivery in the appropriate medical resource setting. Patients with previous cesarean delivery should have ultrasound evaluation antepartum to help determine the appropriate route and place of delivery. Treatment of patients with anemia by either oral or parenteral iron supplementation should be considered, especially in patients with hematocrit less than 30%. Additionally, consideration for erythropoietin stimulating agents with hematology consultation should be undertaken in high-risk patients, especially in those who do not accept a blood transfusion.

Standardized, multidisciplinary protocols have been used to help decrease severe maternal morbidity associated with postpartum hemorrhage that involves a focus on unit readiness, recognition and prevention, response, and reporting/systems learning. The nursing and anesthesia teams should be aware of the postpartum hemorrhage and be available to assist. Simulation activities can be utilized in event training in PPH and have been shown to improve outcomes. Postpartum hemorrhage is one of the surgical emergencies in obstetrics. The condition is best managed by an interprofessional team that also includes laboratory personnel and labor and delivery nurses.

Although postpartum hemorrhage itself may not be preventable, early identification of blood loss, and mobilization of resources may prevent adverse outcomes. Multidisciplinary planning at the system level, ensuring that hemorrhage protocols exist, as well as for management of high-risk patients is important for improving patient outcomes.[14,15,18]

Prof. Nazneen Kabir
Ex. Executive Director &
Head of obstetrics and Gynecology
Institute of Child and Mother Health (ICMH), Matuail, Dhaka

References

1. *Higgins N, Patel SK, Toledo P. Curr Opin Anaesthesiol. Postpartum hemorrhage revisited: new challenges and solutions. [PubMed]*

2. *Haeri S, Dildy GA . Semin perinatal. Maternal mortality from hemorrhage. 2012 Feb;36(1):48-55. doi: 10.1053/j.semperi.2011.09.010. [PubMed]*

3. *Oliveira MI, da Costa VS, Mer S, Osório J, Martins AP. Thrombocytopenia in pregnancy, a challenge in the intensive care unit (ICU). Rev Esp Anestesiol Reanim. 2019 Aug - Sep;66(7):385-389. [PubMed]*

4. *Arnold MJ, Keung JJ, McCarragher B. Interventional Radiology: Indications and Best Practices. Am Fam Physician. 2019 May 01;99(9):547-556. [PubMed]*

5. *Alemu FM, Fuchs MC, Martin Vitale T, Abdalla Mohamed Salih M. Severe maternal morbidity (near-miss) and its correlates in the world's newest nation: South Sudan. Int J Womens Health. 2019;11:177-190. [PMC free article] [PubMed]*

6. *Lin L, Chen YH, Sun W, Gong JJ, Li P, Chen JJ, Yan H, Ren LW, Chen DJ. Risk factors of obstetric admissions to the intensive care unit: An 8-year retrospective study. Medicine (Baltimore). 2019 Mar;98(11):e14835. [PMC free article] [PubMed]*

7. *Changede P, Chavan N, Raj N, Gupta P. An Observational Study to Evaluate the Maternal and Foetal Outcomes in Pregnancies Complicated with Jaundice. J Obstet Gynaecol India. 2019 Feb;69(1):31-36. [PMC free article] [PubMed]*

8. *Joseph CM, Bhatia G, Abraham V, Dhar T. Obstetric admissions to tertiary level intensive care unit - Prevalence, clinical characteristics and outcomes. Indian J Anaesth. 2018 Dec;62(12):940-944. [PMC free article] [PubMed]*

9. *Gillissen A, van den Akker T, Caram-Deelder C, Henriquez DDCA, Bloemenkamp KWM, de Maat MPM, van Roosmalen JJM, Zwart JJ, Eikenboom J, van der Bom JG., TeMpOH-1 Study Group. Coagulation parameters during the course of severe postpartum hemorrhage: a nationwide retrospective cohort study. Blood Adv. 2018 Oct 09;2(19):2433-2442. [PMC free article] [PubMed]*

10. *Shamsuddin L, Kobir N, pot partum Hemorrhage Esscntials of obstctrics and Gynaecology (1st ed) 2020.*

11. *Precipitate and Emergency delivery, http:/www. sweet have 02.com/ PDF Health 922 les 03. pdf last edited August 2020.*

12. *Shakur H, Beaumont D, Pavord S, Gayet-Ageron A, Ker K, Mousa HA. Antifibrinolytic drugs for treating primary postpartum haemorrhage. Cochrane Database Syst Rev. 2018 Feb 20;2:CD012964. [PMC free article] [PubMed]*

13. *Tanaka H, Matsunaga S, Yamashita T, Okutomi T, Sakurai A, Sekizawa A, Hasegawa J, Terui K, Miyake Y, Murotsuki J, Ikeda T. A systematic review of massive transfusion protocol in obstetrics. Taiwan J Obstet Gynecol. 2017 Dec;56(6):715-718.*

14. *Vasquez DN, Plante L, Basualdo MN, Plotnikow GG. Obstetric Disorders in the ICU. Semin Respir Crit Care Med. 2017 Apr;38(2):218-234. [PubMed]*

15. *Downes KL, Grantz KL, Shenassa ED. Maternal, Labor, Delivery, and Perinatal Outcomes Associated with Placental Abruption: A Systematic Review. Am J Perinatol. 2017 Aug;34(10):935-957. [PMC free article] [PubMed]*

16. *Post partum hemorrhage: Management Approaches during laparotomy, Nov 14 2019, (Ref:24)*

17. *Post partum hemorrhage: Management Approaches during laparotomy, Nov 14 2019, (Ref:40)*

18. *Maswime S, Buchmann E. A systematic review of maternal near miss and mortality due to postpartum hemorrhage. Int J Gynaecol Obstet. 2017 Apr;137(1):1-7. [PubMed]*

Original Article

Presentation of Covid-19 Disease and the Impact of Patient's Comorbidities on it's Hospital Outcome : An Observational Study in a Covid-19 Dedicated Hospital

Bodiuzzaman M M [1], Hossain M I [2]

ABSTRACT

Background: Coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a global pandemic that initially started in Wuhan, China, and spread exponentially across the globe infecting human being irrespective of age,sex and ethnicity. Given the nature of this virus, there is much still to be learned. People with COVID-19 have had a wide range of symptoms reported – ranging from mild symptoms (e.g. common cold) to more severe diseases such as bronchitis, pneumonia, severe acute respiratory distress syndrome (ARDS), multi-organ failure, and even death. Comorbidity is an important factor in COVID-19 pandemic outcome often leading to rapid and severe progression of the disease process, even death.

Objective: This study was carried out to see the socio-demographic characteristics and presenting features of COVID-19 disease as well as to assess impact of comorbidities on its hospital outcome.

Methods: This observational study was carried out in the COVID-19 dedicated hospital of Faridpur from April 2020 to September 2020 for a period of 06 month. All clinically suspected patients confirmed by RT-PCR were included as cases. Data were collected by detailed history from patients then those were checked, verified for consistency and edited for result. After editing and coding, the coded data were analyzed by using the SPSS software package.

Results: A total of 627 patients were included in the study of which 552 were treated in covid ward and 75 patients were treated in ICU. Among Covid ward admitted (552) patients 354 (64.13%) were male and 198 (35.86%) were female with a male to female ratio of 1:0.56; young adult patients (19 to 50 years) were more affected and admitted (62.86%) and people living in urban area were more affected (52.71%) than rural area (47.28%). Fever, cough and shortness of breath (63.04%, 45.47% and 42.39% respectively) were predominant symptoms. Regarding comorbidities, 44.20% patients have one or more comorbidities where as 55.79% patients have no comorbidity. Hypertension (17.57%) was the predominant comorbid condition followed by Diabetes (15.94%), ischemic heart disease (05.61%), Chronic obstructive airway disease (05.61%), Chronic kidney disease (2.3%), Stroke (1.44%), Heart failure (0.54%) and Cancer (0.36%). A total of 75 patients needed ICU support; most of them were elderly patients (64 out of 75). Regarding hospital outcome, 96.74% (534 out of 552) covid ward patients and 45.34% (34 out of 75) of ICU admitted patients discharged uneventfully whereas 03.2% covid ward patients and 54.66%of ICU admitted patients expired. Deaths were more in elderly patients (n=43; 72.88%). Common comorbidities found among the patients who expired were Hypertension, Diabetes and Ischemic heart diseases (42.37%, 37.28% and 16.94% respectively).

Conclusion: The predominant number of patients presented with fever, cough and shortness of breath in our setting. The percentage of COVID-19 hospitalizations resulting in death remains high among elderly patients and those with one or more comorbid conditions. Therefore, elderly patients and those with comorbidities should take all necessary precautions to avoid getting infected with SARS CoV-2.

Keywords: Coronavirus, COVID-19, SARS-CoV-2, Clinical features, Comorbidity.

1. * Dr. M. M. Bodiuzzaman
MBBS, FCPS (Medicine)
Assistant Professor, Department of Medicine
Faridpur Medical College, Faridpur.
Email: drbodiuzzaman72@gmail.com
Mobile: 01763-771144

2. Dr. Mohammad Iqbal Hossain
MBBS, FCPS (Medicine)
Assistant Professor, Department of Medicine
Faridpur Medical College, Faridpur.

Introduction

An outbreak of novel coronavirus (SARS-CoV-2) emerged in December 2019 in Wuhan of China has led to a global pandemic, affecting around 250 countries across the globe. The virus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causes a clinical syndrome termed coronavirus disease 2019 (COVID-19). SARS-CoV-2 is predominantly spread by respiratory droplets and by contaminated fomites as well as by aerosols in certain circumstances.[1]

Several studies have estimated the incubation period of COVID-19. Based on the experience in China, the typical incubation period of COVID-19 infection has been estimated to be a median of 5.1 days. The reported mean incubation period for COVID-19 varied from 4 days to 10.9 days. Incubation period distributions of different age groups are significantly different. Of symptomatic cases in any age group, about 95% will show symptoms within 14 days. This supports the currently practiced length of quarantine in many countries.[2,3]

The virus infects humans in all age groups, of all ethnicities, both males and females. Older age, male sex, obesity, hypertension, diabetes, cardiovascular disease and chronic lung disease, Chronic kidney disease(CKD) have shown worse prognosis and are risk factors for COVID-19 mortality.[4,5,6]

Hypertension and diabetic patients have increased morbidity and mortality rates and have been linked to more hospitalization and intensive care unit (ICU) admissions.4,5 Pre-existing COPD is likely to worsen the progression and prognosis of COVID-19.[7] Elderly population is more susceptible to this illness and is more likely to be admitted to the ICU with a higher mortality rate. The age-related changes in the geriatric population may be due to the changes in lung anatomy and muscle atrophy which results in changes in physiologic function, reduction of lung reserve, reduction of airway clearance, and reduction of the defense barrier function.[8]

COVID-19 infection has a broad spectrum of severity ranging from an asymptomatic form to a severe acute respiratory syndrome that requires mechanical ventilation. Among symptomatic patients, about 80% showed a mild clinical course characterized by a dry cough, sore throat, low-grade fever, or malaise; in 20% of cases, the general condition worsened in about seven days from the beginning of the symptoms, culminating in respiratory failure.[9]

As the novel coronavirus continues to evolve, there are still many limitations to our knowledge of who exactly this virus would impact critically.

Methods and Materials

This observational study was carried out in the COVID-19 dedicated hospital of Faridpur (situated in Faridpur Medical College Hospital, Faridpur) from April 2020 to September 2020 for a period of 06 months. All clinically suspected patients confirmed by RT-PCR were included as cases and those who were not confirmed, excluded from this study. Cases were selected irrespective of age and sex on a random basis. Patients admitted in corona ward were selected for symptom analysis, comorbidities and hospital outcome whereas patients admitted in ICU were excluded from symptom analysis. Data were collected by detailed history from patients or their relatives followed by thorough physical examination as well as diagnostic evaluation; then those were checked, verified for consistency and edited for result. After editing and coding, the coded data were analyzed by using the SPSS software package.

Results:

A total of 627 patients were included in the study of which 552 were treated in Covid ward and 75 patients were treated in ICU. Among Covid ward admitted (552) patients 354 (64.13%) were male and 198 (35.86%) were female with a male to female ratio of 1:0.56;young adult patients (19 to 50 years) were more affected and admitted (62.86%) and people living in urban area were more affected (52.71%) than rural area (47.28%) (Table I).

Table I: Distribution of patients according to age, sex and residence (n= 552)

Demographics	Frequency (%)	
Age group	<19 years	24 (4.3)
	19-50 years	347 (62.86)
	>50 years	181 (32.78)
Sex	Male	354 (64.13)
	Female	198 (35.86)
Residence	Urban	291 (52.71)
	Rural	261 (47.28)

Fever, cough and shortness of breath (63.04%, 45.47% and 42.39% respectively) were predominant symptoms followed by asymptomatic and other symptoms like sore throat, headache , generalized body ache and other non -respiratory problems. (Table II).

Table II: Distribution of patients according to presentation (n=552)

Symptoms	Frequency (%)
Fever	348 (63.04)
Cough	251 (45.47)
SOB	234 (42.39)
Sore throat	24 (4.34)
Headache	16 (2.8)
Generalized bodyache	13 (2.3)
Asymptomatic	46 (8.33)
Others	14 (2.3)

Regarding comorbidities, 44.20% patients have one or more comorbidities whereas 55.79% patients have no comorbidity. Hypertension (17.57%) was the predominant comorbid condition followed by diabetes (15.94%), ischemic heart disease (05.61%), COAD (05.61%), CKD (2.3%), Stroke (1.44%), Heart failure (0.54%) and Cancer (0.36%) (Table III).

Table III: Distribution of patients according to comorbidities (n=552)

Comorbidities	Frequency (%)
Hypertension (HTN)	97 (17.57)
Diabetes Mellitus (DM)	88 (15.94)
Ischemic Heart Disease(IHD)	31 (5.61)
Heart failure (HF)	03 (0.54)
Chronic Obstructive Airway Diseases (COAD)	31 (5.61)
Chronic kidney disease (CKD)	13 (2.3)
Cerebrovascular disease (CVD)	08 (1.44)
Cancer	02 (0.36)

Regarding hospital outcome, 96.8% covid ward patients and 45.34% of ICU admitted patients discharged uneventfully whereas 03.26% covid ward patients and 54.66%of ICU admitted patients expired. Deaths were more in elderly patients (n=43; 72.88%). Common comorbidities found among the patients who expired were Hypertension, Diabetes and Ischemic heart diseases (42.37%, 37.28% and 16.94% respectively). A total of 75 patients needed ICU support that was 11.96% of total cases; most of them were elderly patients (64 out of 75 i.e. 85.33%). Out of total mortality, death rate was much more higher in ICU than in COVID ward (69.49% vs 30.50%).The male to female ratio of ICU death was 3.2:1.The mortality rate in ICU was higher in those with one or more comorbid conditions; the predominant comorbidities were hypertension (42.37%) and diabetes (37.28%) followed by IHD, COAD, CKD and CVD. No comorbidity was found in 27.11% of ICU death (Table IV, V, VI).

Table IV: Distribution of Patients according to ICU Treatment and Outcome

Age Group of ICU Treated Patients (n=75, 11.96%)		<51 year	11 (14.66%)
		>51 year	64 (85.33%)
Outcome (n=627)	Recovery (n=568)	Covid Ward	534 (96.74%)
		ICU	34 (45.34 %)
	Death in Total cases (n=627)	Covid Ward	18 (2.87%)
		ICU	41 (6.53%)
	Comparison of death (n=59)	Covid Ward	18 (30.50%)
		ICU	41(69.49%)

Table V: Distribution of mortality according to age, sex and comorbidities (n=59)

		Frequency (%)
Age group	<19 years	02 (3.38)
	19-50 years	14 (23.72)
	>50 years	43 (72.88)
Sex	Male	45 (76.27)
	Female	14 (23.72)
Comorbidities	Comorbidity present	43 (72.88)
	Comorbidity absent	16 (27.12)

Table VI: Distribution of mortality according to pattern of comorbidities (n=59)

Co morbidity in dead patients	Comorbidities	Frequency (%)
Present (n=43)	HTN	25 (42.37)
	DM	22 (37.28)
	IHD	10 (16.94)
	COAD	07 (11.86)
	CKD	04 (6.77)
	CVD	04 (6.77)
	Others	04 (6.77)
Absent (n=16)		16 (27.11)

Discussion

In this study a total of 627 patients were included (552 from Covid ward and 75 from ICU) and demographic, clinical presentation as well as pertinent data regarding impact of comorbidities on COVID-19 disease outcome were collected.

In our study, adult patients especially the economically productive age group i.e.19-50 were mostly affected (62.86%) followed by elderly population (32.78%). The percentage of under 19 with confirmed COVID-19 cases is far lower (4.3%) than the standard population percentage. These findings were closely related to a review done by Dominic Cortis, where three studies were included. Two studies were from China by Zhang and Guan et al. and another one from South Korea by Korea Centers for Disease Control and Prevention. Those studies showed that the percentage of youths with confirmed COVID-19 cases is far lower than the standard population percentage. The proportion of COVID-19 confirmed cases for youths (age group 0-14 year:) is lower in China (1.55%, 0.89%) than South Korea (4.04%).The predominant population affected in all three studies were 15-64year groups (76.93%, 83.98% in China and 78.60% in S.Korea) followed by elderly population (21.53%,15.13% in China and 17.36% in S.Korea).[10] A study conducted in China showed the age distribution for all patients where 61.5% were aged <60 years and the other cases were aged ≥60 years; this is consistent with our studies (67.16% in below 50 group vs 32.78% in above 50 group).[11] A study conducted in India showed that 21–50 age group, contributes to the maximum proportion (60%) of the total cases followed by those below 20 years of age constituting nearly 13% of the cases.[12] There is a deviation of this study to ours as well as to China and South Korean studies in respect of younger peoples' Covid-19 positivity.

Regarding sex distribution, in a study that included a total of 5700 patients admitted into 12 different hospitals of USA found 39.7% female and 60.3% male as Covid 19 positive.[13] In another study conducted in India males contribute to 66% of the total positive cases.[12] In a study in India, it is observed that women are half as likely to be infected by COVID-19 as men.[14] These above-mentioned results almost matches with our study result (male 64.13% and female 35.86%).

In our study we found, urban population affected more (52.71%) than rural population (47.28%). There may be some explanations linking urban areas and coronavirus, emphasizing densities; connectivity; crowded living conditions; and exposed occupations.

Regarding presentation, in this study, most of the patients presented with fever (63.04%) , cough (45.47%) and shortness of breath (42.39%).The less predominant symptoms were sore throat (4.34%), headache (2.8%) followed by with chest pain, abdominal pain, diarrhoea, vomiting, bleeding manifestation and psychosis in a minor of patients. There were 8.33% of asymptomatic patients. In a meta-analysis that included seven articles published from 24th Jan to 16th March, 2020 revealed that fever was the predominant symptom (88.8%) followed by dry Cough(68%) fatigue (33%), productive cough (28.5%), muscle pains (14.4%), diarrhoea (4.4%), nausea or vomiting (4.1%), rhinorrhea(3.2%), chest and abdominal pain(0.15%).15 Similarly, a study in a hospital of Wuhan, China found fever (98%),cough (76%), dyspnoea (55%),myalgia or fatigue (44%), sputum production (28%), headache (8%), haemoptysis (5%), and diarrhoea (3%) as common symptoms.[16] In another meta-analysis, found similar result, where most prevalent clinical symptom was fever (91.3%), followed by cough (67.7%), fatigue (51.0%) and dyspnea (30.4%). [17] These above-mentioned studies closely matched with the result of this study.

Considering comorbidity, 44.24% patients had one or more comorbidities and 55.79% presented in isolation. Common comorbid conditions found were as follows: HTN (17.57%), DM(15.94%), IHD (5.61%),COAD (5.61%) followed by CKD (2.3%), CVD (1.44%), Heart failure (0.54%) and Cancer(0.36%).

In a meta-analysis, as mentioned above revealed hypertension (15.8%) as the most common comorbidity followed by other cardiovascular and cerebrovascular conditions (11.7%) , endocrine disorder primarily diabetes (9.4%), co-existing infection like HIV and Hepatitis B (1.5%),malignancy (1.5%), respiratory system disorder ,e.g. COPD and others (1.4%), renal disorders (0.8%) and immunodeficiency states(0.01%).[15] Almost similar results were found in another retrospective, multicenter cohort study, where 48% patients had comorbidities, with hypertension being the most common (30%), followed by diabetes (19%) and coronary heart disease (8%).[18] In a population-based surveillance for laboratory-confirmed COVID-19–associated hospitalizations in the United States, among 1,482 patients, 12% adult patients had one or more underlying conditions; the most common were hypertension (49.7%), obesity (48.3%), chronic lung disease (34.6%), diabetes mellitus (28.3%) and cardiovascular disease (27.8%).[19]

The results of first two studies closely resemble with our study (Hypertension, Coronary artery disease and Diabetes as predominant comorbidities), but the third one revealed obesity as an important comorbidity which was not included in our study.

In our study, 96.8% covid ward patients and 45.34% of ICU admitted patients discharged uneventfully whereas 2.87% covid ward patients and 6.53% of ICU admitted patients expired. These matches with the following two studies.

Approximately 10% of the global population may have been infected by October 2020, with an estimated overall IFR of 0.15% to 0.2% (0.03% to 0.04% in those <70 years of age).20 In another study, roughly 80% of COVID-19-positive cases result in full recovery from the illness without any hospitalizations or interventions.[5]

In our study, death were more in elderly patients (n=43; 72.88%). A total of 75 patients needed ICU support that was 11.96% of total cases; most of them were elderly patients (64 out of 75 i.e. 85.33%). Out of total mortality, death rate was much more higher in ICU than in COVID ward (69.49% vs 30.50%). These results are coherent with the studies done in other centers.

COVID-19 can cause severe disease leading to hospitalization in ICU and potentially death, especially in the elderly with comorbidities. According to the CDC, 8 out of 10 deaths reported in the USA occurred in adults 65 years old and above.5 According to a report by CDC, data from China have indicated that older adults, particularly those with serious underlying health conditions, are at higher risk for severe COVID-19-associated illness and death than are younger persons. In the same report, COVID-19 cases in the United States, Overall, 31% of cases, 45% of hospitalizations, 53% of ICU admissions, and 80% of deaths associated with COVID-19 were among adults aged ≥65 years with the highest percentage of severe outcomes among persons aged ≥85 years.[21] People <65 years of age have a very small risk of death even in pandemic epicenters, and deaths in people <65 years of age without any underlying conditions is rare.[22] In our study, the mortality rate in ICU was higher in those with one or more comorbid conditions; the predominant comorbidities were hypertension (42.37%) and diabetes (37.28%) followed by IHD,COAD,CKD and CVD. No comorbidity was found in 27.11% of death. In Italy only 12% of death certificates reported direct causality from COVID-19, while 88% of patients who died had at least one comorbidity.[23,24] In New York state, just over 86% of reported COVID-19 deaths involved at least one comorbidity, according to the state's department of health. The leading comorbidity, seen in 55.4% of all deaths, was hypertension. the rest of the 10 most common comorbidities in COVID-19 fatalities were diabetes (37.3%), hyperlipidemia (18.5%), coronary artery disease (12.4%), renal disease (11.0%), dementia (9.1%), chronic obstructive pulmonary disease (8.3%), cancer (8.1%), atrial fibrillation (7.1%), and heart failure (7.1%). [25]

Hyperlipidemia and Dementia were not included in ours.

Limitations

The first limitation of this study is the relatively small number of patients included; vast majority of the patients were either treated outside the hospital or were asymptomatic. Secondly, all possible comorbidities were not included in the study.

Conclusion

In our study, HTN, DM and COAD patients shows more mortality rates than New York City study. Most of the patients presented with fever, cough and respiratory distress in our setting. The elderly patients and those with one or more comorbid conditions reflected poor outcomes.

Acknowledgement

Authors of the study are thankful to all healthcare providers of Covid-19 dedicated hospital of Faridpur for their cooperation.

Reference

01. *Brewster DJ, Chrimes N, Do TB, Fraser K, Groombridge CJ, Higgs A, et.al.Consensus statement: Safe Airway Society principles of airway management and tracheal intubation specific to the COVID-19 adult patient group.Med J Aust. 2020 Jun; 212(10): 472-81. doi: 10.5694/mja2.50598.Epub 2020 May 1.Erratum in: Med J Aust. 2020 Oct;213(7):312.*

02. *Lauer SA, Grantz KH, Bi Q,Jones FK, Zheng Q,Meredith HR,et al.The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application.Ann Intern Med.2020 Mar ;172: 577– 82. doi:10.7326/M20-0504.*

03. *Dai J, Yang L, Zhao J. Probable Longer Incubation Period for Elderly COVID-19 Cases: Analysis of 180 Contact Tracing Data in Hubei Province, China.Risk Manag Healthc Policy. 2020; 13: 1111–17.doi: 10.2147/RMHP.S257907.*

04. *Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: prevalence, pathophysiology, prognosis, and practical considerations. Diabetes Metab Syndr. 2020;14(4):303–10.doi: 10.1016/j.dsx-.2020.04.004.*

05. *Sanyaolu A,Okorie C,Marinkovic A,Patidar R,Younis K,Desai P,et al. Comorbidity and its Impact on Patients with COVID-19.SN Compr Clin Med. 2020 Jun 25 : 1–8.doi: 10.1007/s42399-020-00363-4 .*

06. *Gansevoort RT,Hilbrands LB.CKD is a key risk factor for COVID-19 mortality.Nat Rev Nephrol. 2020 Aug.https://-doi.org/10.1038/s41581-020-00349-4.*

07. *Zhao Q, Meng M, Kumar R, Wu Y, Huang J,Lian N,et al.The impact of COPD and smoking history on the severity of COVID-19: a systemic review and meta-analysis. J Med Virol. 2020 May;92(10)1–7.doi: 10.1002/jmv.25889*

8. *Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: a comparison with young and middle-aged patients. J Infect. 2020 Mar; 80(06):E14-E18.DOI:https://doi.org/10.1016/j.-jinf.2020.03.005.*

09. *Macera M,Angelis GD,Sagnelli C,Coppola N,Vanvitelli COVID-19 Group. Clinical Presentation of COVID-19: Case Series and Review of the Literature.Int J Environ Res Public Health. 2020 Jul; 17(14): 5062.doi: 10.3390/ijerph17145062*

10. *Cortis D.On Determining the Age Distribution of COVID-19 Pandemic.-Front Public Health. 2020 May; 8: 202. doi:10.3389/fpubh.2020.00202*

11. *Liu Y,Mao B,Liang S,Yang J-W,Lu H-W,Chai Y-H,et al.Association between age and clinical characteristics and outcomes of COVID-19.Eur Respir J.2020 May;55(5):2001112. doi:10.1183/13993003.01112-2020.*

12. *Kulkarni SV,Chauhan H.COVID-19 in Different Age Groups of Children: Initial Impression from Integrated Disease Surveillance Programme (IDSP) under National Centre for Disease Control (NCDC).Indian J Pediatr. 2020 Jul;87:674–5.https://-doi.org/10.1007/s12098-020-03457y.*

13. *Richardson S,Hirsch JS, Narasimhan M,Crawford JM,McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA.2020;323(20):2052-59. doi:10.1001/jama.2020.6775*

14. *Gupta S.The age and sex distribution of COVID-19 cases and fatalities in India.medRxiv 187953 [preprint].2020 [Jul 16].Available from doi:https://doi.org/10.1101/2020.07.14.20153957.*

15. *Paudel SS.A meta-analysis of 2019 novel corona virus patient clinical characteristics and comorbidities. Research Square 148580 [preprint].2020 [Apr 08].Available from doi: 10.21203/rs.3.rs-21831/v1.*

16. *Huang C,Wang Y,Li X,Ren L,Zhao J,Hu Y ,et al.Clinical features of patients infected with 2019 novel coronavirus in Wuhan,China.Lancet.2020 Feb 15;395 (10223):497-506.https://-doi.org/10.1016/S0140-6736(20)30183-5.*

17. *Yang J,Zheng Y,Gou X,Pu K,Chen Z,Guo Q,et al.Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis.Int J Infect Dis.2020 May;94:91-5.doi:10.1016/j.ijid.2020.03.01. Epub 2020 Mar 12.*

18. *Zhou F,Yu T,Du R,Fan G,Liu Y,Liu Z,et al.Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.Lancet.2020 Mar 28 ;395 (10229): 1054-62.https://doi.org/10.1016/S0140-6736(20) 30566-3.*

19. *Garg S,Kim L,Whitaker M,O'Halloran A,Cummings C,Holstein R ,et al.Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 — COVID-NET, 14 States.MMWR. 2020 April 17;69(15):458_64.*

20. *Ioannidis JPA. Global perspective of COVID-19 epidemiology for a full-cycle pandemic. Eur J Clin Invest. 2020;00:e13423. doi: 10.1111/eci.13423 21.Bialek S,Boundy E,Bowen V,Chow N,Cohn A,Dowling N et al. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) - United States, February 12-March 16, 2020.MMWR Morb Mortal Wkly Rep.2020 Mar 27;69(12):343-46.doi: 10.15585/mmwr.mm6912e2.*

22. *Loannidis JPA, Axfors C, Contopoulos-Ioannidis DG. Population-level COVID-19 mortality risk for non-elderly individuals overall and for non-elderly individuals without underlying diseases in pandemic epicenters. Environ Res. 2020 Sep;188:109890.doi https://-doi.org/10.1101/2020.04.05.20054361.*

23. *Oke J, Heneghan C.Global COVID-19 case fatality rates. 2020 [internet publication].Centre for Evidence-Based Medicine;2020.*

24. *Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy.JAMA. 2020;323(18):1775-6. doi:10.1001/jama.2020.4683*

25. *Franki R. Comorbidities the rule in New York's COVID-19 deaths. Hospitalist. 2020; [Accessed June 1, 2020,https://www.the-hospitalist.org/hospitalist/article/220457/coronavirus-updates/comorbidities-rule-new-yorks-covid-19-deaths].*

Original Article

Carbetocin Versus Oxytocin in the Active Management of 3rd Stage of Labour Following Vaginal Delivery: An Open Label Randomized Control Trial

Akther P [1], Yasmin N [2], Islam J A [3], Ashraf F [4], Akther M [5], Rahman M R [6]
Ahmad S A [7], Faruquee M H [8], Islam G M R [9]

ABSTRACT

Background: Every day, more than 220 women around the world die from severe bleeding after childbirth. Globally, post-partum hemorrhage is the number one direct cause of maternal mortality. Most postpartum hemorrhages are caused by uterine atony and occur in the immediate postpartum period. Most of these tragic deaths can be prevented by active management of third stage of labour. Active management of the third stage of labor should be practiced routinely to decrease the risk of postpartum hemorrhage. Oxytocin is used for enhancing uterine contraction after delivery.But oxytocin has some limitations like shorter half- life, less contraction time and more side effects, whereas carbetocin has prolonged duration of action which ensures more contraction time and less adverse effects. So, carbetocin considered as a good alternative over oxytocin for the prevention of PPH after vaginal delivery.

The Aim of Study: To see the efficacy and safety of Carbetocin over Oxytocin for the prevention of PPH after vaginal delivery.

Methods: A randomized-controlled trial was conducted in the Department of Obstetrics and Gynecology,Shaheed Suhrawardy Medical College and Hospital,Dhaka, Bangladesh over a period of 9 months from January 2015 to September, 2015 .Ninety four patients who had included undergoing vaginal delivery at term were randomized into two groups receiving either 10IU oxytocin or 100µg carbetocin.Outcome measures such as primary PPH, massive blood loss, need for additional uterotonic drug, additional blood transfusion as well as adverse effects were all documented.

Results: In this study, massive blood loss did not occur none of patients in carbetocin group. But massive blood loss occured 6.4% women in oxytocin group. Further fundal massage , immediate blood transfusion and additional uterotonics didn't need any patient in carbetocin group. In oxytocin group, fundal massage required 8.5% of women, blood transfusion were needed for 10.6% patients and additional uterotonics needed for 10.6% women .Average amount of blood loss were 88 ml less in carbetocin group and adverse effects of drugs were almost similar in both group. Primary PPH was developed 8.5% in oxytocin group but none of patients had developed PPH in carbetocin group.

Conclusion: Carbetocin appears to be an effective new drug than Oxytocin for the prevention of postpartum hemorrhage in vaginal delivery.

Key Words: Carbetocin, Oxytocin, Postpartum hemorrhage

01. * Dr. Pervin Akther
Assistant Professor, Obstetrics and Gynecology
Mugda Medical College & Hospital, Dhaka
E-mail: aktherpervin121@gmail.com
Mobile: 01713-452345

02. Dr. Nilofar Yasmin
Associate Professor, Department of Obstetrics & Gynecology
Shaheed Suhrawardy Medical College and Hospital

03. Dr. Jinnat Ara Islam
Associate Professor, Department of Obstetrics & Gynecology
Shaheed Suhrawardy Medical College and Hospital

04. Prof. Dr. Fatema Ashraf
Professor and Head, Department of Obstetrics & Gynecology
Shaheed Suhrawardy Medical College and Hospital

05. Dr. Mahbuba Akhter
Ex. Asst. Registrar, Department of Obstetrics & Gynecology
Shaheed Suhrawardy Medical College and Hospital

06. Prof. Dr. Md. Ridwanur Rahman
Clinical Monitor, WHO, Professor and Ex. Head,
Department of Medicine, Shaheed Suhrawardy Medical College and Hospital

07. Prof. Dr. Sk. Akhtar Ahmad
Professor, Occupational and Environmental Health
Bangladesh University of Health Sciences (BUHS)

08. Dr. M. H. Faruquee
Associate Professor
Department of Occupational and Environmental Health
Bangladesh University of Health Sciences (BUHS)

09. Dr. G. M. Raihanul Islam
Vice President & Head of Medical Services Department
Beacon Pharmaceuticals Ltd.

Introduction

In every minute one mother dies due to postpartum hemorrhage in this modern world[1]. Postpartum hemorrhage occurs in approximately 4 percent of vaginal deliveries and estimates are that it causes significant morbidity and 25 percent of all maternal childbirth-related deaths[2]. In developing countries, mortality from PPH remains high[3]. In low income setting, PPH accounting for 30% of maternal death3, while in Bangladesh it is 31%[4]. The majority of these deaths occur within 4 hours of delivery, which indicates that they are a consequence of the third stage of labour[5,6]. That's why active management during third stage of labour is recommended.

The third stage of labor is the time from the delivery of the baby until delivery of the maternal placenta[7]. Primary PPH is defined by the World Health Organization as the loss of blood estimated to be >500ml from the genital tract within 24 hours of vaginal delivery[8] Volume of blood loss depends on how long it takes the placenta to separate from the uterine wall and how effectively the uterine muscle contracts in the immediate postpartum period. Attempts to prevent postpartum hemorrhage have focused on the prophylactic use of uterotonic agents and the active clinical management of the third stage of labor. Active management of labor incorporates three main interventions: administration of a uterotonic medication after delivery of the baby; early cord clamping and cutting; and controlled traction on the umbilical cord while awaiting placental separation and delivery[9,10].

If obstetric hemorrhage is not managed efficiently and effectively, this will lead to shock, hemostatic failure from disseminated intravascular coagulation and ultimately death[11]. Conventional uterotonics like oxytocin has used for preventing PPH but it has some limitations like shorter half-life[12], less contraction time and more side effects like fluid overload, convulsion, arrhythmia and pulmonary edema. In addition, the ergot alkaloids cannot be used in 10-15% of women who have gestational hypertension[13]. Further, oxytocin and ergot preparation require protection against light to preserve its effectiveness and stability[14]. In our country cold chain is not properly maintained for oxytocin. So, there is a chance of its effectiveness and stability problems. As a result, treatment failure may occur Bleeding due to uterine atony, can be prevented by an effective uterotonic agent[15]. Till now it is recommended that Oxytocin should be used as uterotonic agent either in the form of intramuscular injection or intravenous infusion.Carbetocin is a long-acting synthetic analogue of oxytocin with agonist properties[16,17]. Carbetocin has prolonged duration of action (approximately 1 hour) which ensures more contraction time and less adverse effect[18,19].The clinical and pharmacological properties of carbetocin are similar to those of naturally occurring oxytocin.Carbetocin binds to oxytocin receptors present on the smooth musculature of the uterus, resulting in rhythmic contractions of the uterus, increased frequency of existing contractions and increased uterine tone[14].A single dose of carbetocin has been hypothesis to act upto 16 hours in comparison to intravenous oxytocin infusion regarding the increase in uterine tone and the reduction of the risk of PPH in vaginal delivery[13].Moreover, carbetocin ensures more effective contraction and less adverse effect like headache, tremor, hypotension, nausea, abdominal pain, and pruritus[14]. Several data of literature suggest that prophylactic administration of carbetocin may be a good alternative to oxytocin to prevent post-partum hemorrhage[20].

Material and Method

This randomized control trial was done from January'2015 to September'2015 in the Department of Gynecology and Obstetrics, Shaheed Suhrawardy Medical College and Hospital, Dhaka, Bangladesh. About ninety four pregnant women were included in this study. The participants were enrolled in the study after fulfilling the inclusion and exclusion criteria. According to computer generated randomization sequential number was allocated for the cases. A written informed consent was taken from eligible women on admission. The study protocol was approved by the ethical committee of Shaheed Suhrawardy Medical College and Hospital, Dhaka, Bangladesh .

Inclusion criteria were women with a single pregnancy undergoing vaginal delivery above 36 weeks or greater (gestational age was recorded according to the last menstrual period and was confirmed by ultrasound report).Exclusion criteria were placenta previa, multiple gestation, placental abruption (determined by history and ultrasound report) hypertensive disorders in pregnancy, preeclampsia, and known case of cardiac, renal, liver diseases, epilepsy, moderate anemia and unwilling to participate in the study.

During the study period 47 women were enrolled who received Carbetocin 100 µg I/V as a single dose and 47 women who received 10 IU of oxytocin after vaginal delivery. The primary outcome was measured by the amount of blood loss within 24 hours after delivery.The research team provided a standardized delivery mat (Quaiyum's mat) and five (05) pre-weighed standard sanitary pads for blood collection after delivery to each of the pregnant woman to measure blood loss in 24 hours postpartum period. Women were advised to preserve the soaked mat and all soaked pads in a container which was provided by the study staff members. The secondary outcomes were massive blood loss, need for additional uterotonic drug, additional blood transfusion as well as adverse effects within 24 hours of delivery. Uterine tone was evaluated by palpation and administration of additional uterotonics was the decision of the investigator.

Analysis was performed by using a computer based statistical program SPSS (Statistical Package for Social Sciences) version 16. Quantitative data were expressed as means ±SD. 95% confidence interval was calculated and p value of <0.05 was considered as significance.

Result

A total of 107 pregnant women with a single pregnancy were initially recruited for inclusion in this study. 13 cases were excluded (4 had pre-eclampsia,3 eclampsia,3 multiple gestation,3 severely anaemic). Thus 94 women formed the

final study group and were included in the final analysis. Mean age of study population were 23.9 ± 3.2 in carbetocin group and 23.3 ±3.2 in oxytocin group (Table I). Among the study patients 36.1% (17) had mild anemia in Carbetocin group and 42.6% (20) had mild anemia in oxytocin group. Mean systolic BP of patients were 112±5.6 mm of Hg and Diastolic BP were 75 ±4.3 mm of Hg in Carbetocin group and mean systolic BP were 110±1.7 mm of Hg and Diastolic BP were 72±11.5 mm of Hg in Oxytocin group. Mean gestational age at delivery were 38.01±1.1 weeks in Carbetocin group and 38.09± 1.7 weeks in Oxytocin group (Table-1). Massive blood loss occurs 6.4 %, fundal massage required 8.5 %, blood transfusion needed 10.6 % and additional uterotonic needed for 10.6% patients in Oxytocin group but in carbetocin group massive blood loss, fundal massage and immediate blood transfusion did not need to any patient and no patient was required additional uterotonics (Table-2). There was no major adverse effect observed in both the groups (Table-3). Average blood loss was 320 ml in carbetocin group and 408 ml in oxytocin group. Average 88 ml more blood loss was observed in oxytocin group (Table-4). No patients had developed PPH in carbetocin group. But 8.5% (4) patients had developed PPH in oxytocin group (Table-5).

Table-1. Baseline characteristics of study patients (n=94)

	Carbetocin Group (47)	Oxytocin Group (47)	P value
Age	23.9 ± 3.2	23.3 ±3.2	0.439
Mild Anemia	36.1% (n=17)	42.6% (n=20)	0.386
Systolic BP	112±5.6 mm of Hg	110±1.7	0.210
Diastolic BP	75 ±4.3 mm of Hg	72±11.5 mm of Hg	0.509
Gestational Age	38.01±1.1 weeks	38.09± 1.7 weeks	0.799

Table-1. Data are presented as mean ±SD. The mean differences were not statistically significant (P>0.05)

Table - 2. Outcome of Third stage of Labour (n = 94)

Outcome of 3rd stage of Labour	Carbetocin Group (47)		Group (47)		P value
	Yes (%)	No (%)	Yes (%)	No (%)	
Massive blood loss	00%	100%	6.4% (3)	93.6%(44)	0.07
Fundal massage required	00%	100%	8.5%(4)	91.5%(43)	0.002
Blood transfusion	00%	100%	10.6%(5)	89.4%(42)	0.002
Need for additional uterotonics	00%	100%	10.6%(5)	89.4%(42)	0.002

Table-2.Shows that massive blood loss occurs in 6.4% patient, fundal massage required 8.5% patients, blood transfusion needed for 10.6% patients and additional uterotonic needed for 10.6% patient in Oxytocin group but in carbetocin group massive blood loss, fundal massage and blood transfusion did not need to any patient and none of patient was required additional uterotonics.

The mean differences were statistically significant (P<0.05).

Table – 3 Adverse effects (n = 94)

Side effects	Carbetocin (n=47) n (%)	Oxytocin (n=47) n (%)	P value
Nausea	0(0.0)	0(0.0)	0.50
Vomiting	0(0.0)	0(0.0)	0.50
Fever	0(0.0)	0(0.0)	0.50
Arrhythmia	0(0.0)	0(0.0)	0.50
Pulmonary edema	0(0.0)	0(0.0)	0.50
Abdominal Pain	0(0.0)	1(2.1)	0.30
Headache	0(0.0)	1(2.1)	0.30
Tremor	0(0.0)	0(0.0)	0.50
Hypotension	0(0.0)	0(0.0)	0.50
Pruritus	0(0.0)	0(0.0)	0.50

Table-3. There were no major adverse effects observed in both groups. The differences were not statistically significant (P>0.05).

Table – 4 Blood loss in 24 hours (n = 94)

Amount of blood loss	Carbetocin group (47)	Oxytocin group (47)	Difference	P Value
Average blood loss in 24 hours(in ml)	320 ml(302 gm)	408 ml (385gm)	88 ml	0.001

Table-4. Shows that average blood loss in carbetocin group is 320 ml and oxytocin group is 408 ml. Average 88 ml more blood loss was observed in oxytocin group. The mean differences were statistically significant (P<0.05).

Table - 5 Outcome of the patient: Primary PPH (n = 94)

Outcome (Primary PPH)	Carbetocin group (47)	Oxytocin group (47)	P Value
Yes	0(0.0)	4(8.5%)	0.002
No	47(100)	43(91.5%)	

Table- 5. Showed no patients had developed PPH in carbetocin group. But 4(8.5%) patients had developed PPH in oxytocin group. The mean differences were not statistically significant (P>0.05).

Discussion

Our results had shown that carbetocin is superior in comparison to oxytocin in the reduction of blood loss during the active management of third stage of labour. Carbetocin also decrease the need for additional uterotonics, uterine massage and massive blood loss in the active management of third stage of labour after vaginal delivery.

Reyes OA and Gonzalez GM et al[21]. performed a prospective double-blind randomized controlled trial with severe preeclampsia for prevention of PPH where the mean age of study patient in carbetocin group were 26.5 years and 26.7 years in oxytocin group. In our study mean age of study patients were 23.9 ± 3.2 years in carbetocin group and 23.3 ±3.2 years in oxytocin group. Debbie-lynuy and Nelindac atherinep et al[22] showed that mean preoperative systolic BP of

study patients in carbetocin group were 117±6.8 mm of Hg and diastolic BP were 69 ±7.7 mm of Hg and mean preoperative systolic BP were 118±8.3 mm of Hg and diastolic BP were 73±8.5 mm of Hg in Oxytocin group. In this study, mean preoperative systolic BP of patients were 112±5.6 mm of Hg and diastolic BP were 75 ±4.3 mm of Hg in carbetocin group and mean systolic BP were 110±1.7 mm of Hg and diastolic BP were 72±11.5 mm of Hg in oxytocin group. All patients of both the groups were with normal blood pressure.

Ahmed Mohamed Maged et al[23]. have randomized 200 women undergoing vaginal delivery in high risk women the average gestational age were 39.4±1.3 weeks in carbetocin group and 39.2±1.4 weeks in oxytocin group, which is almost similar to this study; 39.01±1.1 weeks in Carbetocin group and 39.09± 1.7 weeks in oxytocin group. They also showed that there was no significant difference between the two study groups regarding occurrence of adverse effects of both drugs. In this study, there were no major adverse effects observed in both groups.

Manal M. E Behery et al[24]. showed that none of women in carbetocin group required blood transfusion, while 15.5% in oxytocin group required blood transfusion. In this study, none of patients in carbetocin group were needed blood transfusion but in oxytocin group blood transfusion were required 10.6% patients.

Agnes P. Monteo-Fenix et al[25]. investigated carbetocin versus oxytocin for the prevention of postpartum hemorrhage following vaginal delivery among high risk women and found that fundal massage required 10% patients in carbetocin group and 83% patients in oxytocin group. In this study, none of patients in carbetocin were needed fundal massage but in oxytocin group fundal massage were required 8.5% patients.

Sergio Rosales-Ortiz, Rogelio Perez Aguado et al[26]. also showed that only 1.5% patients need additional uterotonics in carbetocin group and 5.8% patients in oxytocin group. Manal M. E Behery et al24.showed that none of the patient in carbetocin group required additional uterotonics while as high as 71.5% of women in oxytocin group need additional oxytocin to ensure adequate uterine contraction for long period. C. A. G. Holleboom, J. van Eyck et al[27]. also showed the comparison between carbetocin with oxytocin, prophylaxis of uterine atony with carbetocin after an elective caesarean section diminished the need for additional uterotonics by more than 50 % in oxytocin group. Debbie-lynuy et al[22]. showed that only 5.7% patients were need for additional uterotonics in carbetocin group and 34.3% patients in oxytocin group. In this study, none of patients of carbetocin group were required additional uterotonic but in oxytocin group additional uterotonics were required for 10.6% patients.

Sergio Rosales-Ortiz et al[26]. also showed the mean amount blood loss in carbetocin group was 366 ml and oxytocin group were 400 ml when compared the efficacy of carbetocin with oxytocin. Average 34 ml more blood loss was observed in oxytocin group. Ahmed Mohamed Maged[23] showed the mean amount blood loss in carbetocin group was 337 ml and oxytocin group were 378 ml. Average 41 ml more blood loss was observed in oxytocin group.

Mohammed S. E. Elsafty[28] showed that amount blood loss was an average of 207 ml of blood in the oxytocin group and an average of 87 ml of blood loss in carbetocin group. Average 120 ml more blood loss was observed in oxytocin group. In this study average blood loss in carbetocin group was 320 ml and oxytocin group was 408 ml. Average 88 ml more blood loss was observed in oxytocin group.

Ahmed Mohamed Maged et al[23]. also showed the occurrence of PPH were 4% in carbetocin group and 16% in oxytocin group. In this study, occurrence of PPH in oxytocin group was 8.5% patients but in carbetocin group none of patients had developed PPH.

Another similar study was conducted in Department of Gynecology and Obstetrics Institute of Child and Mother Health (ICMH), Matuail, Dhaka. Massive blood loss did not occur none of patients in carbetocin group. But massive blood loss occured 8.5% women in oxytocin group. Further fundal massage required, immediate blood transfusion and additional uterotonics didn't need any patient in carbetocin group. In oxytocin group, fundal massage required 10.6% of women, blood transfusion were needed for 6.4% patients and additional uterotonics needed for 10.6% women .Average amount of blood loss were 64 ml less in carbetocin group and adverse effects of drugs were almost similar in both group. Primary PPH was developed 6.4% in oxytocin group but none of patients had developed PPH in carbetocin group.[34]

Primary postpartum haemorrhage (PPH) is the most common form of major obstetric hemorrhage[29]. It is the most common cause of maternal morbidity in developed countries and a major cause of death worldwide[30,31]. The most common point at which PPH occurs is during the third stage of labour, when the uterus may suddenly loss its ability to contract. Around 80% of cases of postpartum hemorrhage due to uterine atony[32].Bleeding due to uterine atony, can be prevented by active management of third stage labour (AMTSL)[33].The promising findings suggested that carbetocin appears to be an effective new drug in the active management of third stage of labour in vaginal delivery. A single dose of 100 microgram IV carbetocin is more effective than oxytocin for maintaining adequate uterine tone, decreases blood loss and preventing postpartum hemorrhage in women undergoing vaginal delivery. Carbetocin can be considered as a good alternative to oxytocin in managing third stage of labour in vaginal delivery.

Acknowledgment

This study was conducted by department of gynecology & obstetrics, Shaheed Suhrawardy Medical College and Hospital, Dhaka, Bangladesh. The preparation of carbetocin was Duratocin manufactured by Beacon Pharmaceuticals Limited, Bangladesh. The research team would like to thank all doctors, health staff and patients for participating in the clinical trial.

Conflict of interest

The authors declare that there is no conflict of interests regarding the clinical trial

Referrences

01. AbouZahr C. Global burden of maternal death and disability. Br Med Bull 2003;67:1–11
02. Abouzaher C. Antepartum and postpartum haemorrhage. In: Murray CJ, Lopez AD, eds. Health dimensions of sex and reproduction: the global burden of sexually transmitted diseases, HIV, maternal conditions, perinatal disorders, and congenital anomalies. Boston: Harvard University Press, 1998:172-4
03. American Academy of Family Practitioners (AAFP). Advanced Life Support in Obstetrics. Syllabus Updates. Downloaded 21/05/2008 from www.aafp.org/online/en/home/cme/aafpcoursesclinicalcourses /also/syllabus. html#Parsys0003, 2008
04. National Institute of Population Research and Training (NIPORT), MEASURE Evaluation, UNC-CH, USA, ICDDR, B., 2011
05. Ramanathan G, Arulkumaran S. Postpartum haemorrhage. Curr Obstet Gynaecol 2006;16(1):6–13.
06. Kane TT, el-Kady AA, Saleh S, Hage M, Stanback J, Potter L. Maternal mortality in Giza, Egypt: magnitude, causes, and prevention. Stud Fam Plann 1992;23:45–57.
07. Norwitz ER, Robinson JN, Repke JT. Labor and delivery. In: Gabbe SG, Niebyl JR, Simpson JL. Obstetrics: normal and problem pregnancies. 4th ed. New York: Churchill Livingstone, 2002:364
08. World Health Organisation: WHO Guidelines for the Management of Postpartum Haemorrhage and Retained Placenta. http://whqlibdoc.who.int/publications/2009/ 9789241598514_eng. pdf, 2009
09. Prendiville WJ, Elbourne D, McDonald S. Active versus expectant management in the third stage of labor. Cochrane Database Syst Rev 2000;(3):CD000007.
10. Festin MR, Lumbiganon P, Tolosa JE, Finney KA, Ba-Thike K, Chipato T. 2003;81(4):286-91. Epub 2003 May 16.
11. Annette Briley and Susan Bewle: Management of obstetric haemorrhage. In: Sue Pavrod and Beverly Hunt. The Obstetric Hematology Manual. United State of America, Cambridge University Press, ISBN-13 978-0-521-86564- 7, Section 5 Chapter 13a, 2010
12. Oyelese Y, Scorza WE, Mastrolia R, Smulian JC .Post- partum hemorrhage. Obstet Gynecol Clin N Am 2007; 34(3):421–441.
13. G Larciprete, C Montagnoli, M Frigo, V Panetta J, Prenat et al Carbetocin versus oxytocin in caesarean section with high risk of post-partum haemorrhage Med. 2013 Jan-Mar; 7(1): 12–18.
14. Werner R. Prevention of postpartum haemorrhage with the oxytocin analogue carbetocin. European Journal of Obstetrics and Gynecology and Reproductive Biology; 2009; 147 (1): 15-20.
15. Derman R, Kodkany BS, Goudar SS, Geller SE, Naik VA, Bellad MB, Patted SS, Patel A, Edlavitch SA, Hartwell T, Chakraborty H, Moss N.Oral misoprostol in preventing post partum haemorrhage in resource-poor communities: a randomised controlled trial. Lancet2006; 368:1248-53.
16. Gazi R, Quaiyum, A, Islam, M, Hossain, S,Wirtz, A,L, Saha, , N, C, Jesmin, M. Post-Partum Excessive Bleeding among Bangladeshi Women: Determinants, Perceptions, Recognition, Responses. Centre for Equity and Health Systems, icddr, Dhaka, Bangladesh. Published November 15, 2012
17. Attilakos G, Psaroudakis D, Ash J, Buchanan R, Winter C, Donald F, Hunt L, Draycott T. Carbetocin versus oxytocin for the prevention of postpartum haemorrhage following caesarean section: the results of a double-blind randomized trial. BJOG 2010; 117: 929–936
18. Tharakan T, Jha J Randomized double blind prospective trial of active management of the third stage of labor. Arch Med Sci 2008; 4(1):79–82.
19. Sergio RO, RP Aguado et al. Carbetocin versus oxytocin for prevention of postpartum haemorrhage: a randomized controlled trial. Published Online February 26, 2014 School of Clinical and Experimental Medicine, University of Birmingham, UK
20. MP Yuen.Oxytocic Agents for the Management of Postpartum Haemorrhage 2011; 16: 10.
21. Reyes OA, Gonzalez GM : Carbetocin versus oxytocin for prevention of postpartum hemorrhage in patients with severe preeclampsia: a double-blind randomized controlled trial. J obstet gynaecol can 2011; 33(11):1099–1104
22. D Iynuy, N Atherinep et al: Carbetocin versus Oxytocin for the Prevention of Postpartum Hemorrhage Following Elective Cesarean Section: Rizal Medical Center Experience; Philippine Journal of Obstetrics & Gynecology. 2013; 37 (2):71-79
23. AM Maged, A Gany, A Hassan, AA Nesreen & Shehata: Carbetocin versus oxytocin for prevention of postpartum hemorrhage after vaginal delivery in high risk women; J Matern Fetal Neonatal Med,2015; 29(4): 532–536
24. Manal M, El Behery, G Abbas, El Sayeda, Azza A et al: Carbetocin versus oxytocin for prevention of postpartum hemorrhage in obese nulliparous women undergoing emergency cesarean delivery; J Matern Fetal Neonatal Med.2016; 29(8):1257
25. Agnes P, M Fenix , Trinidad R , Vera et al: Double-Blind Randomized Controlled Trial Comparing the Effect of Carbetocin and Oxytocin for the Prevention of Postpartum Hemorrhage Among High Risk Women Following Vaginal Delivery; Philippine Journal of Obstetrics & Gynecology.2011; 35(4):169-175.
26. S R Ortiz, R P Aguado, RS Hernandez, M Castorena et al: Carbetocin versus oxytocin for prevention of postpartum haemorrhage: a randomised controlled trial; The Lancet. 2014 ;383:51
27. CAG. Holleboom, J.VAN Eyck, SV. Koenen: Carbetocin in comparison with oxytocin in several dosing regimens for the prevention of uterine atony after elective caesarean section in the Netherlands. ArchGynecol Obstet 2013; 287:1111–1117
28. Mohammed S. E. Elsafty, Alaa S. Hassanin, M Laban, Ahmed M, Ibrahim et al: Intravenous carbetocin shot is superior to oxytocin infusion for placental delivery in second trimester abortion: a pilot randomized controlled trial: The Journal of Maternal-Fetal & Neonatal Medicine. 2016; 29(5): 850-854
29. Prevention and management of postpartum haemorrhage , Royal College of Obstetricians and Gynaecologists, Green-top Guideline No. 52, Minor revisions November 2009 and April 2011
30. The Prevention and Management of Postpartum Haemorrhage: Report of Technical Working Group, Geneva 3–6 July 1989. Geneva: World Health Organization, 1990
31. Bais JM, Eskes M, Pel M, Bonsel GJ, Bleker OP. Postpartum haemorrhage in nulliparous women: incidence and risk factors in low and high risk women. A Dutch population-based cohort study .Eur J Obstet Gynecol Reprod Biol. 2004; 115:166–72
32. Dutch Association of Obstetrics and Gynaecology (NVOG). Guideline postpartum haemorrhage. 2012;1–9.
33. Chandhiok N, Dhillon BS, Datey S, Mathur A, Saxena NC .Oral misoprostol for prevention of postpartum haemorrhage by paramedical workers in India. Int J GynaecolObstet 2006; 92:170-75
34: Kabir N , Akter D, Daisy TA et al: Efficacy and safety of carbetocin in comparison to oxytocin in the active management of third stage of labour following vaginal delivery: An open label randomized control trial: Department of Gynecology and Obstetrics Institute of Child and Mother Health (ICMH), Matuail, Dhaka, Bangladesh: Bangladesh Journal of Obstetrics and Gynaecology: Vol-30, Number-1, March-2015

Original Article

Control Status of Blood Pressure Among the Hypertensive Patients

Azad M A K [1], Haque M A [2], Jahan S M S [3], Rahman M M [4], Shaheduzzaman A K M [5], Sarker M K [6]
Mondol R N [7], Hossain M M [8], Sarker H [9], Hossain M Z [10]

ABSTRACT

Background: Hypertension is a major cause of morbidity in developing countries which are in a state of epidemiological transition. Of those detected to have hypertension, their blood pressure often remains uncontrolled because they failed to comply with, or dropout of treatment, or that treatment was simply inadequate. We are lacking of such types of data that those who are hypertensive, how many of them achieve the controlled BP after taking treatment in an organized way.

Objective: The objective of this study was to find out the frequency of control status of hypertension among the hypertensive patients and their sociodemographic characteristics.

Methods: A cross sectional descriptive type of study was done during the period of January 2012 to March 2012 among the hypertensive patients who were registered and treated for at-least 3 months in the Hypertension and Research Center, Rangpur, Bangladesh. A purposeful consecutive sampling technique was applied and total 300 hypertensive patients were enrolled. The data were collected by direct interview of the patient and secondary data were taken from their registration book and records. The interested variables are processed, edited and analyzed by SPSS windows version 17.0. The interested data of the study population were expressed in frequency distribution and appropriate statistical tests were applied to see the significance of difference between variables. P value <0.05 was considered as statistically significant.

Result: A total 300 patients were studied. The mean age ± SD of them was 49.37±12.81 years. The study showed the control rate of high blood pressure among the hypertensive patients was 28%. Among the study population 11.7% had high creatinine, 8.3% were diabetic, 79.2% had family history of cardiovascular disease, 7.2% had elevated cholesterol and 15% were smokers, and 5.6% had found LVH, 16.1% IHD, 9.1% CVD and 2.7% retinopathy. Among the study population 74% were taken combined anti-hypertensive drugs and 26% single drug. The controlled rate was significantly higher among the housewives (44%; p=0.000).

Conclusion: Control rate of blood pressure among the hypertensive patients is 28% among the population attended at the hypertension care centre.The control rate is not satisfactory though it's consistent with that of other studies in different countries. Concerted public health effort is required to detect, treat and control hypertension in our country.

Key words: Hypertension, Control status.

01. * Dr. Md. Abul Kalam Azad
Assistant professor (Medicine)
Rangpur Medical College
Email: akazaddmc@yahoo.com
Mobile: 01712177244

02. Dr. Md. Ashraful Haque
Associate Professor of Medicine
Rangpur Medical College

03. Prof. Shah Md. Sarwer Jahan
Professor of Medicine
Rangpur Medical College

04. Prof. Dr. Md. Mahfuzer Rahman
Professor of Medicine, Rangpur Medical College

05. Dr. A.K.M. Shaheduzzaman
Assistant professor (Medicine)
Rangpur Medical College

06. Dr. Md. Kumruzzaman Sarker
Assistant professor (Medicine)
Rangpur Medical College

07. Dr. Ratindra Nath Mondol
Associate Professor of Medicine
Rangpur Community Medical College

08. Dr. Mohammad Mahbub Hossain
Associate Professor of Hepatology
Rangpur Medical College

09. Dr. Horipodo Sarker
Associate Professor of cardiology
Rangpur Medical College

10. Prof. Md. Zakir Hossain
Professor of Medicine
Shaheed Ziaur Rahman Medical College, Bogra

Introduction

Hypertension is the important risk factor for cardiovascular disease[1]. Hypertension is a major cause of morbidity in developing countries which are in a state of epidemiological transition[2]. Hypertension affects nearly 26% of adult population worldwide[3]. Worldwide prevalence estimates for hypertension may be as much as 1 billion individuals and approximately 7.1 million deaths per year may be attributable to hypertension[4]. Studies from India and Bangladesh had shown upward trend in prevalence in hypertension[5]. Prevalence of prehypertension and hypertension, respectively, significantly greater in South India (Trivandarum: W 31.9% ; M 35.5%) and West India (Mumbai: W 29.1% ; M 35.6%) compared to North India (Moradabad: W 24.5% ; M 27.0%) and East India (Kolkata: W 22.4% ; M 24%)[6]. Hypertension is a major modifiable risk factor for cardiovascular diseases (CVDs) and a leading cause of the CVD burden worldwide[7]. The higher the blood pressure the greater the chance of heart attack, the heart failure, stroke, kidney disease and death[8]. Hypertension has been shown to be a major risk factor also for cognitive impairment and dementia[9]. It has been reported to be responsible for 57% of all stroke deaths and 24% of all cardiovascular deaths in East Asians[10]. Hypertension remains silent, being generally asymptomatic during its clinical course. As it is hidden beneath an outwardly asymptomatic appearance, the disease does immense harm to the body in the form of "Target Organ" damage; hence, the WHO has named it the "Silent Killer"[11]. Concerted public health effort is required to detect, treat and control hypertension in the community, as shown by the experiences of many countries[12,13,14]. In the United States (US) over the last two decades the National High Blood Pressure Education Program of the US has been remarkably successful in increasing detection, treatment and control of hypertension in the US population. The concomitant decline in cardiovascular mortality in the US is due in part to this progress in hypertension detection and control. Further, hypertensives often remain undetected in the community until they present with cardiovascular complications[15]. Of those detected to have hypertension, their blood pressure often remains uncontrolled because they failed to comply with or dropout of treatment or that treatment was simply inadequate[16].

The objective of this study was to find out the frequency of control status of hypertension among the hypertensive patients and their sociodemographic characteristics.

Methods

A cross sectional descriptive type of study was done during the period of January 2012 to March 2012 among the hypertensive patients who were registered and treated for at-least 3 months in the Hypertension and Research Center, Rangpur, Bangladesh. A purposeful consecutive sampling technique was applied and total 300 hypertensive patients were enrolled according to inclusion and exclusion criteria. The data were collected by direct interview of the patients and secondary data were taken from their registration book and records.

Inclusion criteria

1. Age 18 years and above.
2. Registered and follow up in the centre for at least 3 months.
3. Gave consent to be enrolled in the study.

Exclusion criteria

1. Age below 18 years.
2. Unwilled to be enrolled in the study.
3. Incomplete data.

Variables of Study

Sociodemographic data, rate of control of hypertension, risk factors for hypertension and its complications, and type of treatment with drug.

Measurement of blood pressure

The auscultatory method of BP measurement with a mercury manometer was used. Persons were seated quietly in a chair for atleast 5 min before measurement of blood pressure by the physician. Phase 1 and phase 5 of Korotkoffsound were considered as SBP and DBP respectively.

Definition of uncontrolled blood pressure

WHO 16 -18
Young patients (aged 40-59 years)
Systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg, or both, with additional risk factors:

- Male sex
- History of left ventricular hypertrophy, ischaemic heart disease, and cerebrovascular disease
- Raised serum creatinine concentration (history of renal failure)
- Diabetes
- Smoking, raised serum cholesterol concentration >7.8 mmol/l
- Family history of cardiovascular disease

Older patients (aged ≥60 years)
Systolic blood pressure ≥140 mm Hg or diastolic ≥90 mm Hg.

Statistical analysis

The interested variables are processed, edited and analyzed by SPSS windows version 17.0. The sociodemographic data of the study population are expressed in frequency distribution and their observed difference was tested by one sample t test and chi square test. Non parametric test was applied to see the associations of qualitative variables with control status. The Pearson's correlations test was used to find out the relation of age with systolic and diastolic pressure. P value <0.05 was considered as statistically significant within the 95% confidence interval. The results were presented in tables and graphs.

Result

Table-1: Sociodemographic Characteristics of the respondents (n=300).

Age Group	Frequency (%)
less than 40 years	63 (21)
40-59 years	164 (54.7)
60 years and above	73 (24.3)
Total	300 (100)
Mean age ±SD	***49.37±12.81***

Sex	Frequency (%)
Male	173 (57.7)
Female	127 (42.3)
Total	300 (100)

Education	Frequency (%)
No formal education	21 (7)
Primary	105 (35)
Secondary	68 (22.7)
Higher secondary	37 (12.3)
Graduate	40 (13.3)
Post graduate	27 (9)
Madrasa	2 (0.7)
Total	300 (100)

Occupation	Frequency (%)
Service	68 (22.7)
Business	47 (15.7)
Agriculture	40 (13.3)
Retired	20 (6.7)
Unemployed	6 (2)
Housewife	119 (39.7)
Total	300 (100)

Monthly income	Frequency (%)
<5000	116 (38.7)
5001-10000	49 (32)
10001-15000	47 (16.3)
>15000	39 (13)
Total	300 (100)

Residence	Frequency (%)
Urban	120 (40)
Sub-Urban	68 (22.7)
Rural	112 (37.3)
Total	300 (100)

Table -2: Frequency of risk factors. (n=300)

Variables	Frequency (%)
Elevated Creatinine ¥	33(11.7)
DM	24(8.3)
Family History of Cardiovascular Disease	228(79.2)
Elevated Cholesterol Π	12(7.2)
Smoking	45(15)

¥ Serum creatinine ≥ 1.4 mg/dl
Π Serum cholesterol ≥ 200 mg/dl

Table -3: Frequency distribution of complications.

Variables	Frequency (%)
LVH Ω	16(5.6%)
IHD	46(16.1%)
CVD	27(9.1%)
Retinopathy	8(2.7%)

Ω Voltage criteria on ECG

Table-4: Frequency of taking single or combination drugs (n=300).

Variables	Frequency (%)
Single	77(25.7)
Combined	223(74.3)
Total	300

Table 5: frequency distribution of Control Status of hypertensive patients (n=300).

Control status of blood pressure	Frequency (%)	Percent
Controlled (BP<140/90 mm Hg without risk factors or BP<130/80 With risk factors)	84	28
Uncontrolled (BP ≥ 140/90 without risk factors or BP ≥ 130/80 with risk factors)	216	72
Total	300	100.0

Table 6: Frequency distribution of sociodemographic characteristics of controlled hypertensive patients (n=84).

Age group	Frequency (%)	P value
< 40 years	17(20.2%)	0.013
40-59 years	39(46.4%)	
60 years and above	28(33.3%)	
Total	84(100%)	

Sex	Frequency (%)	P value
Male	42(50%)	1.000
Female	42(50%)	
Total	84(100%)	

Education	Frequency (%)	P value
No formal education	07(8.3%)	0.000
Primary	35(41.7%)	
Secondary	17(20.2%)	
Higher secondary	9(10.7%)	
Graduates	10(11.9%)	
Post graduates	06(7.1%)	
Total	84(100%)	

Occupation	Frequency (%)	P value
Service	18(21.4%)	0.000
Business	10(11.9%)	
Agriculture	12(14.3%)	
Retired	05(6%)	
Unemployed	02(2.4%)	
Housewife	37(44%)	
Total	84(100%)	

Monthly income	Frequency (%)	P value
<5000	34(40.5%)	0.001
5001-10000	26(31%)	
10001-15000	13(15.5%)	
>15000	11(13.1%)	
Total	84(100%)	

Residence	Frequency (%)	P value
Urban	22(26.2%)	0.005
Sub-Urban	20(23.8%)	
Rural	42(50%)	
Total	84(100%)	

Table-7 Frequency distribution of complication among the controlled hypertensive patients (n=84)

Variables	Frequency (%)
LVH	2(2.5%)
IHD	8(10.1%)
Elevated Creatinine	10(12.7%)
CVD	7(8.3%)
Retinopathy	2(2.4%)

Table-8 Frequency distribution of risk factors among the controlled hypertensive patients (n=84)

Smoking	Frequency (%)	P value
Yes	15(17.9)	0.000
No	68(81.0)	
Ex-smoker	1(1.2)	
Total	84(100.0)	

Diabetes mellitus	Frequency (%)	P value
Yes	11(13.8)	0.000
No	69(86.3)	
Total	80(100.0)	

Elevated Cholesterol	Frequency (%)	P value
Yes	1(2.1)	0.000
No	46(97.9)	
Total	47(100.0)	

Family History of Cardiovascular Disease	Frequency (%)	P value
Yes	51(66.2)	0.004
No	26(33.8)	
Total	77(100.0)	

Table-9: Frequency of taking single or combined drug among the controlled hypertensive patients (n=84).

Drug type	Frequency (%)	P value
Single	21 (25.0)	0.000
Combined	63 (75.0)	
Total	84 (100.0)	

A total 300 patients were studied. The mean age of them was 49.37±12.81 years. According to age group distribution maximum (54.7%) was in between 40-59 years. Among them male were 57.7% and female were 42.3%. Among the study population 7% had no formal education, 35% had primary education, 22.7% had secondary and 12.3% had higher secondary, 13.3% were graduated and 9% were post-graduated and 0.7% had madrasa education. Among the study population 22.7% were service holder, 15.7% businessmen, 13.3 farmer, 6.7% retired person, 2% unemployed, and 39.7% housewives. Among the study population 38.7%, 32%, 16.3%, and 13% had monthly income <5000, 5001-10000, 10,001-15,000 and >15,000 taka per month respectively. Among the study group 40% live in urban, 22.7% in sub-urban and 37.3% in rural areas (Table-1). Among the study population 11.7% had elevated creatinine, 8.3% were diabetic, 79.2% had family history of cardiovascular disease, 7.2% had elevated cholesterol and 15% were smokers and 2% ex-smokers (Table-2). Target organ damage in study group, LVH was found in 5.6%, IHD in 16.1%, CVD in 9.1%, and Retinopathy in 2.7% (Table-3). 74.3% study population were taken combined anti-hypertensive drugs and 25.7% single drugs (Table-4). The control rate of high blood pressure in our study group

was 28% (Table-5). Among the controlled hypertensive patients most patients were in between 40-59 years age (46.4%; p=0.000), control among male and female was same (50% & 50% respectively p= 1.000) which was not statistically significant. The controlled rate was higher in the primary education group than that of other education group (35%; P=0.000). The controlled rate was significantly higher among the housewife (37%; p=0.000). Among the study population most of the people come from rural areas (42% p=0,005). The monthly income of the controlled hypertensive group was found 34% had <5000, 26% had 5001-10000, 13% had 10001-15000 and 11% had >15000 taka, which was statistically significant (p=0.005) (Table-6). Target organ damage in the controlled hypertensives, 2.5% patients had LVH, 10.1%,12.7%,8.3%,2.4% had IHD, high creatinine, CVD and retinopathy respectively (Table-7). Risk factors in the controlled hypertensives 17.9% was smoker 1.2 was ex-smoke, DM, elevated cholesterol and family history of cardiovascular disease had in 13.8%, 2.1% and 66.2% respectively and these were statistically significant (Table-8). Among the controlled hypertensives 25% patients were taken single and 75% were taken combined drugs (Table-9).

Discussion

In our study mean age±SD of hypertensive patients was found 49.39±12.81years. Nazir A, et al found it was 55.8±13.4 years in their study19. GelirliAz, et al (2010) found mean age of their study population was 48.8±13.2 years20. So, our findings are consistent with other findings.

Our study revealed male was 57.7%. Palanisamy S, et al found male were 58.14% in their study[21]. In our study, occupation of maximum population was housewife (39.7%). Ahmed NU et al found 51.5% of hypertensive patients were housewife in their study[22]. In our study 35% of the study population had primary education and among the controlled hypertensive patients it was found 41.7%. In other study it was found 17% and 14.53% respectively[23].In our study, among the hypertensive patients, maximum (62.7%) were urban and sub-urban dwellers. Nazir A, et al found that prevalence of hypertension more (21.6%) in urban areas[20]. In our study, most of the hypertensive (59.5%) had monthly income more than 5000 taka. In other studies it's found that hypertension is more common in effluents society. In our study, it was found that 8.3% had diabetes mellitus, 17% were smokers, 7.2% had high cholesterol, 11.7% had elevated creatinine and 79.2% had family history of cardiovascular disease. Marvin Moser MD, et al found in their study, 37% had diabetes, 29% smoker, 54% had elevated cholesterol24.Papazafiropoulou A, et al found 11% elevated creatinine level[25]. In our study LVH, IHD, CVD and Retinopathy were found 5.6%, 16.1%, 9.1% and 2.7% respectively. In other studies it was found 33% LVH, 2-15% Retinopathy[26].Approximately 60 percent of patients who present with strokes have a past history of hypertension and in those who are hypertensive, approximately 78 percent have not had their blood pressure adequately controlled[27]. Although it is well recognized that blood pressure is one of the three major risk factors for the development of CHD (the other two being high cholesterol and smoking), it has been claimed that CHD events often occur in patients who lack all of these risk factors. An analysis of three large prospective studies found that for both fatal and nonfatal myocardial infarctions, at least one of the big three was present in more than 90 percent of cases.[28] In our study, among the study population control of hypertension was found 28%. JNC-7 report from NHANES described it was 34% in 1999[28]. Marvin Moser MD, et al found that control rate was 52.9% in USA populations[24]. Ahmed et al NU found it was 22%[22]. In our study populations 25.7% were taking single antihypertensive drug and 74.3% combined drug. In other studies it was found that most patients who are hypertensive will require two or more anti-hypertensive medications to achieve their BPgoals[29,30].

Conclusion & recommendation

Control rate of blood pressure among the hypertensive patients is 28% among the populations attended at the hypertension care centre (Hypertension and Research Centre) Rangpur, Bangladesh. The control rate is not satisfactory though it's consistent with that of other countries. Concerted public health effort is required to detect, treat and control hypertension in the community.

Limitations of the study

1. It is a day care centre based study.
2. Consecutive sampling technique was adopted.
3. Cross sectional study.
4. Small scale and short duration study.

Acknowledgement

All the study participants,Hypertension and research centre(Rangpur,Bangladesh) and its staffs, doctors, medical personnel are heartedly acknowledged. We are very much grateful to Professor Dr. Md. ZakirHossain for his continuous initiation, motivation and proper guidance.

References

01. Kannel WB. Blood pressure as a cardiovascular risk factor.JAMA 1996;275:1571-6.

02. Reddy KS, Hypertension control in developing countries:Generic issue. J Hum Hypertens1996;10(Suppl 1): S33-S38.

03. Kearney PM, WheltonM,Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data.Lancet 2005;365:217-23.

04. World Health Organization. World Health Report 2002: Reducing risks, Promoting healthy life.Geneva, Switzerland: World Health Organization;2002.

05. Hypertension study group.Prevalence,awareness,treatment and control of hypertension among the elderly in Bangladesh and India: A multicentrestudy.Bull World Health Organ 2001;79:490-500.

06. Singh RB, Fedacko J, Pella D, Macejova Z, Ghosh S, Amit K, et al. Prevalence and risk factors for prehypertension and hypertension in five Indian cities.ActaCardiol 2011; 66(1):29-37.

07. *Ezzati M, Lopez AD, Rodger A, Vander Hoorn S, Murray CJL. Comparative risk assessment collaborative group: selected major risk factors and global and regional burden of disease.Lancet 2002;360:1347-60.*

08. *Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. The seventh report of the Joint National Committee on Prevention,Detection,Evaluation, and Treatment of High Blood Pressure.The JNC 7 report.JAMA 2003;289:2560-72.*

09. *RigaudAS,Seux ML, Staessen JA, Birkenhager WH, Fortte F. Cerebral complications of hypertension. J Hum Hypertens 2000;14:605-16.*

10. *Rodgers A, Lawes C, MacMohon S. Reducing the global burden of blood pressure related cardiovascular disease. J Hypertens 2000;18(Suppl 1):S3-6.*

11. *Carretero OA, Oparil S. Essential hypertension.Part I: definition and etiology. Circulation 2000;101(3):329-35.*

12. *Henauw SD, Bacquer DD, Fonteyne W, Stam M, Kornitzer M, Backer GD.Trends in the prevalence,detection,treatment and control of arterial hypertension in the Belgian adult population. J Hypertens 1998; 16: 277-84.*

13. *Kastarinen MJ, Salomaa VV, Vartianen EA, Jousilahti PJ, Tuomilehto JO, Puska PM, et al.Trends in blood pressure levels and control of hypertension in Finland from 1982 to 1997. J Hypertens 1998;16:1379-87.*

14. *Burt VL, Whelton K, Roccella EJ, Brown C, Cutler JA, Higgins M, et al.Prevalence of hypertension in the US adult population. Hypertension 1995;25:305-13.*

15. *Joint National Committee on Prevention,Detection,Evaluation, and Treatment of High Blood Pressure. The fifth Report of the Joint National Committee on Prevention,Detection,Evaluation, and Treatment of High Blood Pressure.Archint Med 1993.*

16. *Lim TO, Morad Z, Hypertension Study Group.Prevalence,Awareness,Treatment and Control of Hypertension in the Malaysian Adult population: Results from the National Health and Morbidity Survey 1996.Singapore Med J 2004;45(1): 20-27.*

17. *Subcommittee of WHO/ISH Mild Hypertension Liaison Committee.Summary of 1993 World Health Organisation-International Society of Hypertension guidelines for the management of mild hypertension. BMJ 1993;307: 1541–6.*

18. *Meyers MG, Carruthers SG, Leenen FHH, Haynes RB.Recommendations from the Canadian Hypertension Society consensus conference on the pharmacologic treatment of hypertension. Can Med Assoc J 1989;140: 1141–6.OpenUrlMedline*

19. *Swales J.Guidelines on guidelines. J Hypertens 1993;11: 899–903.OpenUrlCrossRefMedlineWeb of Science*

20. *Ahmed N, Khaliq M A, Shah S H, Anwar W. Compliance to antihypertensive drugs,salt restriction, exercise and control of systemic hypertension in hypertensive patients at Abbottabad. J Ayub Med Coll Abbottabad 2008;20(2):66-69.*

21. *Busari OA, Olanrewaju TO, Desalu OO, Opadijo OG, Jimoh AK, Agboola SM, Busari OE, OlalekanO.Impact of patient's knowledge, Attitude and practices on Hypertension onCompliance with antihypertensive drugs in Resource-poor Setting.TAFperv Med Bull 2010;9 (2): 87-92.*

22. *Palanisamy S, Sumathy A. Intervention to improve patient adherence with Antihypertensive Medication at a tertiary care teaching hospital.International Journal of PharmTech Research 2009;1(2):369-374.*

23. *Ahmed NU, Rahman M, Islam MDU, Ali SY, Hossain AM, Fatema K, Islam MR, SadhyaG. Socio-demographic, Clinical Characteristics and Status of Hypertension Control among Rural Hypertensive Patients.Faridpur Med. Coll. J.2011; 6(1): 05-09.*

24. *Amal M Al-Mehja, Ali A Al-Yahya, Majeda M Al-Qattan, Huda S Al-Duwaisan, Bader NMB Al-Otaibi.Determinants of Poor Blood Pressure Control in Hypertensive Patients – An Area-based Study.Kuwait Medical Journal 2004;36 (4) : 270-274.*

25. *Marvin Moser MD, Stanley S, Franklin MD.Hypertension Management: Results of a NewNational Survey for Hypertension Education: Harris Interactive. The Journal of Clinical Hypertension 2007; 9(5) : 316-323.*

26. *Papazafiropoulou A, Skliros E, Sotiropoulos A, Papafragos C, Gikas A, Apostolou O, Kaliora H, Tountas C. Prevalence of target organ damage in hypertensive subjects attending primary care: C.V.P.C. study (epidemiological cardio-vascular study inprimary care).BMC Family Practice 2011; 12:75*

27. *Droste DW, Ritter MA, Dittrich R, et al. Arterial hypertension and ischaemic stroke. Acta NeurolScand 2003;107(4):241–251. [PMID: 12675696]*

28. *Greenland P, Knoll MD, Stamler J, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. JAMA 2003;290(7):891–897. [PMID: 12928465]*

29. *Joint National Committee on Prevention,Detection,Evaluation, and Treatment of High Blood Pressure. The Seventh Report of the Joint National Committee on Prevention,Detection,Evaluation, and Treatment of High Blood Pressure.Archint Med 2005;4*

30. *Cushman WC, Ford CE, Cutler JA, et al. Success and predictors of blood pressure control in diverse North American settings: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). J ClinHypertens (Greenwich). 2002;4: 393-404.*

31. *Black HR, Elliott WJ, Neaton JD, et al. Baseline characteristics and elderly blood pressure control in the CONVINCE trial. Hypertension.2001; 37:12-8.*

Original Article

The Pattern of Musculo Skeletal Disorders among the Bangladeshi Diabetic Patients Attending the Tertiary Level Hospital

Ahmed S [1], Hossain M D [2]

ABSTRACT

Background: Diabetic patients may present with various musculoskeletal (MSK) disorders. Adhesive capsulitis of shoulder joint is well established as a complication of diabetes.

Objective: To find out the pattern of MSK disorders among the Bangladeshi diabetic patients attending the tertiary level hospital

Methods: Total 120 MSK disorders patients were included in this study. Diagnosis was made from comprehensive history and clinical examinations supplemented by appropriate laboratory investigations. Diabetes was excluded by fasting blood sugar, oral glucose tolerance test and HbA1c. Diabetic patients with MSK disorders who were getting oral hypo- glycaemic agents or insulin were included in diabetic group.

Results: Majority 25(20.8%) patients had rheumatoid arthritis, 22(18.3%) patients had lumbar spondylosis, 20(16.7%) had cervical spondylosis, 19(15.8%) had frozen shoulder, 9(7.5%) had osteoarthritis of knee joint, 7(5.8%) had pelvic inflammatory disease, 6(5.0%) had trigger fingers, 5(4.2%) had non-specific low back pain, 4(3.3%) had planter fosciitis and 3(2.5%) had lateral epicondylitis.

Conclusion: Common pattern of MSK disorders among diabetic patients were rheumatoid arthritis, lumbar spondylosis, cervical spondylosis, frozen shoulder, osteoarthritis of knee joint, pelvic inflammatory disease, trigger fingers, non specific low back pain, planter fosciitis and lateral epicondylitis.

Key word: Musculoskeletal (MSK) disorders, Diabetic patients.

01. * Dr. Saleh Ahmed, MBBS, FCPS
Senior Consultant, Department of Medicine
250 beded General Hospital Chandpur
Mobile: 01731190278
E-mail: pdrc4006@gmail.ocm

02. Md. Delowar Hossain
Research Officer
Medical Academy for professional studies (MAPS)

Introduction

Diabetes is a multi-system disorder affecting 3-7% of the adult population in different geographical areas.1 Diabetic patients may present with various musculoskeletal (MSK) disorders. Adhesive capsulitis of shoulder joint is well established as a complication of diabetes.[1]

Musculoskeletal pain (MSP) comprises a major health problem for the general population, affecting their quality of life, demanding increased health care cost. Musculoskeletal disorders have a major impact on society in terms of morbidity, long-term disability and economics. Diabetes mellitus (DM) is considered as an epidemic in the modern world and much of its morbidity and mortality is related to micro and macro vascular complications.[2]

Diabetes mellitus (DM) is a major public health problem worldwide. It was estimated that in 2017 there are 451 million (age: 18–99 years) people with DM. These figures were expected to increase to 693 million by 2045.[3] A variety of musculoskeletal (MS) disorders has been associated with DM and can cause significant disability.[4, 5]

The aim of study was to find out the pattern of MSK disorders among the diabetic patients attending the Department of Medicine, Chandpur Medical College Hospital.

Methodology

This cross-sectional study was done between period of June 2017 to February 2018 at the department of Medicine, tertiary level Hospital to see the pattern of MSK disorders in diabetic patients. Total 120 MSK disorders patients were included in this study. Diagnosis was made from comprehensive history and clinical examinations supplemented by appropriate laboratory investigations. Diabetes was excluded by fasting blood sugar, oral glucose tolerance test and HbA1c. Diabetic patients with MSK disorders who were getting oral hypo-glycaemic agents or insulin were included in diabetic group. Different serological test like rheumatoid factor (RF), anti citrullinated peptide antibody (ACPA), Human leucocytic antigen-B27, antinuclear antibody, anti double stranded-DNA

were done in relevant cases according to clinical diagnosis. X-Ray and magnetic resonance imaging (MRI) of spines, joints were done where needed. All necessary data were recorded in a preformed data sheet.

Results

Table I shows that majority 41(34.2%) patients belonged to age 41-50 years with mean age was 48.9±13.5 years. Males were predominant (56.7%) whereas females were 52(43.3%). Majority 71(59.2%) patients came from urban area. Among female 45(37.5%) were housewife followed by 42(35.0%) were service holder, 15(12.5%) were businessman, 11(9.2%) were retried and 7(5.8%) were student/others. More than half (54.2%) patients came from lower middle income group family. Table 2 shows that majority 71(59.2%) patients were normal body weight. Almost two third (65.0%) patients had hypertensive disorder. Majority 73(60.8%) patients had DM during <10 years. Regarding treatment pattern of DM, majority 33(27.5%) patients received LM+OHA, 31(25.8%) received insulin+OHA+LM, 27(22.5%) received insulin, 25(20.8%) received oral hypogecemic agent. Normal fasting blood glucose was found in 49(40.8%) and diabetes was 71(59.2%). Normal random blood glucose was 45(37.5%) and diabetes was 75(62.5%). Normal HbA1c was 57(47.5%) and diabetes was 63(52.5%). Majority 77(64.2%) patients changed daily life due to pain. Figure 1 shows that majority 77(64.2%) patients had chronic patients and 43(35.8%) had acute pain. Table 3 shows that majority 25(20.8%) patients had rheumatoid arthritis, 22(18.3%) patients had lumbar spondylosis, 20(16.7%) had cervical spondylosis, 19(15.8%) had frozen shoulder, 9(7.5%) had osteoarthritis of knee joint, 7(5.8%) had pelvic inflammatory disease, 6(5.0%) had trigger fingers, 5(4.2%) had non-specific low back pain, 4(3.3%) had planter fosciitis and 3(2.5%) had lateral epicondylitis.

Table 1: Demographic characteristics of the study patients (n=120)

Age (years)	Frequency (%)	Percentage
≤20	7	5.8
21-30	15	12.5
31-40	29	24.2
41-50	41	34.2
51-60	17	14.2
>60	11	9.2
Mean±SD = 48.9±13.5		

Sex	Frequency (%)	Percentage
Male	68	56.7
Female	52	43.3

Residence	Frequency (%)	Percentage
Rural	49	40.8
Urban	71	59.2

Occupation	Frequency (%)	Percentage
Service holder	42	35.0
Businessman	15	12.5
Housewife	45	37.5
Retried	11	9.2
Student/others	7	5.8

Socioeconomic status	Frequency (%)	Percentage
Lower	37	30.8
Lower middle	65	54.2
Upper middle	13	10.8
Higher	5	4.2

Table 2: Distribution of subjects according to their lifestyle and biochemical factors (n=120)

BMI	Frequency (%)	Percentage
Underweight	7	5.8
Normal weight	71	59.2
Overweight	25	20.8
Obese	17	14.2

Hypertension related status	Frequency (%)	Percentage
Hypertensive	78	65.0
Normotensive	42	35.0

Duration of DM	Frequency (%)	Percentage
<10 years	73	60.8
≥10 years	47	39.2

Treatment pattern of DM	Frequency (%)	Percentage
Lifestyle modification	4	3.3
LM + OHA	33	27.5
Oral hypoglycemic agent	25	20.8
Insulin	27	22.5
Insulin + OHA + LM	31	25.8

Fasting blood glucose status	Frequency (%)	Percentage
Normal (<7 mmol/l)	49	40.8
Diabetes (≥7 mmol/l)	71	59.2

Random blood glucose status	Frequency (%)	Percentage
Normal (<11.1 mmol/l)	45	37.5
Diabetes (≥11.1 mmol/l)	75	62.5

HbA1c level status	Frequency (%)	Percentage
Normal (<7 %)	57	47.5
Diabetes (≥7	63	52.5

Number of subjects changed daily life due to pain	Frequency (%)	Percentage
Yes	77	64.2
No	43	35.8

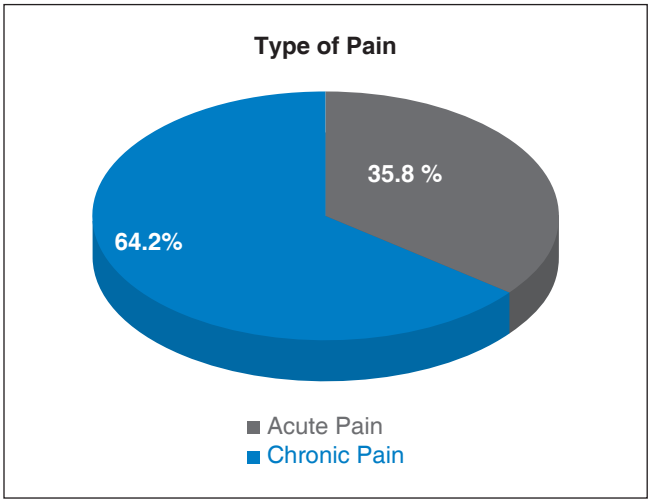


Figure 1: Pie chart showing type of pain of the study patients (n=120)

Table 3: Pattern of MSK disorders among diabetic patients (n=120)

Name of disease	Frequency	Percentage
Rheumatoid arthritis	25	20.8
Lumbar spondylosis	22	18.3
Cervical spondylosis	20	16.7
Frozen shoulder	19	15.8
Osteoarthritis of knee joint	9	7.5
Pelvic imflammatory disease	7	5.8
Trigger fingers	6	5.0
Non specific low back pain	5	4.2
Planter fosciitis	4	3.3
Lateral epicondylitis	3	2.5

Discussion

In this study observed that the majority 41(34.2%) patients belonged to age 41-50 years with mean age was 48.9±13.5 years. Males were predominant (56.7%) whereas females were 52(43.3%). Majority 71(59.2%) patients came from urban area. Majority 45(37.5%) were housewife followed by 42(35.0%) were service holder, 15(12.5%) were businessman, 11(9.2%) were retried and 7(5.8%) were student/others. More than half (54.2%) patients came from lower middle income group family. Majjad et al[3] reported the participants' median age was 54 years [45–62]. There were as many men as women among the participants (= 188, sex ratio=1). Sultana et al. reported that the mean (±SD) age of the subjects was 52.6(±11.7) years and 55% (n=990) were male. Service holder was found 20.6%, business 25.0%, housewife 41.1%, student or others 13.4%. Rich income was 5.6%, middle class 73.8%, poor 20.5%. Shamsuzzaman et al.2 also observed their study carried on 221 (94 males and 127 females). Mean age 54.02±10.815 years diabetic patients with complains of Musculo skeletal pain. Among the respondents, 19.5% were Service holder, 8.1% were Business person, 51.1% were House maker, 20.8% were Retired person. It was reported that among the respondents, 40.3% were manual worker, 35.3% work in seating position, 23.5% work in both manually and seated position. The monthly family income of the respondents, 35.3% had Tk. 20000, 30.8% had Tk. 20001 - 30000, 12.7% had Tk. 30001 – 40000, 9.5% had Tk. 40001 – 50000, and 11.8% had above Tk. 50000.

In this study observed that majority 71(59.2%) patients were normal body weight. Almost two third (65.0%) patients had hypertensive disorder. Majority 73(60.8%) patients had DM during <10 years. Regarding treatment pattern of DM, majority 33(27.5%) patients received LM+OHA, 31(25.8%) received insulin+OHA+LM, 27(22.5%) received insulin, 25(20.8%) received oral hypogecemic agent. Normal fasting blood glucose was found in 49(40.8%) and diabetes was 71(59.2%). Normal random blood glucose was 45(37.5%) and diabetes was 75(62.5%). Normal HbA1c was 57(47.5%) and diabetes was 63(52.5%). Majority 77(64.2%) patients changed daily life due to pain. The median duration of diabetes was 8 years[4-13]. Sixteen percent of Majjad et al.3 patients had more than 10 years of diabetes. 50.7% were treated with insulin ± oral hypoglycemic. The mean HbA1c value was 8.5 ± 2%. Poor glycemic control was noted in 68.9% of patients. The mean BMI value was 26.4 ± 3.6 kg/m2. 45.7% of the patients were overweight, while 15.4% were obese. Sultana et al.[6] reported underweight was found 5.0%, normal weight 61.7%, overweight 19.4%. Hypertensive disorder 66.7%, majority 62.2% patients had DM during <10 years. Majority 27.2% patients received LM+OHA. Normal fasting blood glucose was found in 42.2% and diabetes was 57.8%. Normal random blood glucose was 40.6% and diabetes was 59.4%. Normal HbA1c was 49.4% and diabetes was 50.6%. Majority 62.8 patients changed daily life due to pain.

In current study observed that majority 77(64.2%) patients had chronic patients and 43(35.8%) had acute pain. Shamsuzzaman et al.[2] study observed acute pain was found 36.4% and chronic pain 63.6%.

In present study observed that majority 25(20.8%) patients had rheumatoid arthritis, 22(18.3%) patients had lumbar spondylosis, 20(16.7%) had cervical spondylosis, 19(15.8%) had frozen shoulder, 9(7.5%) had osteoarthritis of knee joint, 7(5.8%) had pelvic inflammatory disease, 6(5.0%) had trigger fingers, 5(4.2%) had non specific low back pain, 4(3.3%) had planter fosciitis and 3(2.5%) had lateral epicondylitis. Majjad et al.3 reported Osteoarthritis was found 19.4%, shoulder capsulitis 12.5%, Carpel Tunnel Syndrome 8.8%, Limited joint mobility 2.9%, Trigger Finger 5.9%, Dupuytren's contracture 0.5%. Khan et al.[1] reported rheumatoid arthritis was the commonest (20.1%) inflammatory arthropathy while lumber and cervical spondylosis constituted about 37% of all disorders. In the present series as well as in other studies, degenerative disorder of the locomotor system was found to be a common (50%) condition.[7-9] Back pain was the most frequent MSK complain (32.9%) in our series which was similar to the findings of Bjella et al.[7] Rheumatoid arthritis was the commonest inflammatory arthropathy in the present series which was also reported by Alam et al.[8]. In Sultana et al.[6] study, 43.9% had osteoarthritis, 29.4% had shoulder adhesive capsulitis, 15.6% had ankylosing spondylitis, 15% had planter fascitis, 12.2% had Charcot's joint, 6.7% had carpal tunnel syndrome, 5.6% had rheumatoid arthritis, 5% had trigger finger, 2.8% had Dupuytren's contracture. Shamsuzzaman observed shoulder capsulitis (25%), carpal tunnel syndrome (20%), tenosynovitis9. Study by Zamani[10] also found Carpal tunnel syndrome (49.8%), knee osteoarthritis (45%), sclerodactyly (27.2%), Dupuytren's contracture (14.1%), trigger finger (11.9%), adhesive capsulitis (11.9%), limited joint movement's syndrome (8%) and Charcot joint (0.6%) were seen in patients[11]. Almost similar finding was also reported in the study by the study conducted in Libya[12] and study in Greece[13].

Conclusion

Common pattern of MSK disorders among diabetic patients were rheumatoid arthritis, lumbar spondylosis, cervical spondylosis, frozen shoulder, osteoarthritis of knee joint, pelvic inflammatory disease, trigger fingers, non specific low back pain, planter fosciitis and lateral epicondylitis.

Reference

01. *Khan MS, Ahmed A, Zaman A, Haque H, Hosain M, & Doza A. Pattern of Musculo-Skeletal Disorders in Diabetic and Non-diabetic Patients Attending in a Tertiary Care Hospital in Dhaka. BIRDEM Medical Journal, 2017;8(1), 68-71.*

02. *Shamsuzzaman M, Harun-Ar-Rashid, Yasmin N, Faruquee MH and Akter J. Pattern of musculoskeletal pain among diabetic patients in a specialized health care facility in Dhaka. Daffodil International University Journal of Allied Health Sciences.2014;1(2):51-54.*

03. *Majjad A, Errahali Y, Toufik H, Djossou JH, Ghassem MA, Kasouati J et al. Musculoskeletal Disorders in Patients with Diabetes Mellitus:A Cross-Sectional Study, International Journal of Rheumatology,2018:3839872:1-6.*

04. *Merashli M, Chowdhury TA and Jawad ASM. "Musculoskeletal manifestations of diabetes mellitus," QJM: An International Journal of Medicine,2015;108(11): 853–857.*

05. *Mueller MJ. "Musculoskeletal impairments are often unrecognized and underappreciated complications from diabetes,"Physical Therapy in Sport, 2016;96(12):1861–1864.*

06. *Sultana SR, Das M, Faruque M, Mondal R, Nurani RN, Hossain M, Banik PC. Musculoskeletal Disorders among Bangladeshi Type 2 Diabetic Subjects. SMU Medical Journal 2015; 2(2): 67-80.*

07. *Bjella Allender E, Magi M. Rheumatic disorders in Swedish population and health care system. J Rheumatol 1980; 7: 877-85.*

08. *Alam MN, Haq SA, Moyeenuzzaman M. Rheumatological disorders in IPGMR. Bangladesh J Medicine 1996; 7: 1-7.*

09. *Ramchurn N. Mashamba C. Leitch E. Arutchelvam V. Narayanan K. Weaver J. Hamilton J. Heycock C. Saravanan V. Kelly C. Upper limb musculoskeletal abnormalities and poor metabolic control in diabetes. 2009; 20(7): 718.*

10. *Zamani B. Matini SM. Jamali R. Taghadosi M. Frequency of musculoskeletal complications among the diabetic patients referred to Kashan diabetes center during 2009-10. Feyz Journal of Kashan University of Medical Sciences. 2011; 15(3).*

11. *Attar SM. Musculoskeletal manifestations in diabetic patients at a tertiary center. Libyan Journal of Medicine. 2012; 7.*

12. *Bagher OM. Golbarg M. Hossein S. Pattern of rheumatic diseases in two outpatient clinics in Iran. Indian J Med Sciences. 2011; 65:7-17.*

Original Article

A Comparative Study of Result between "Choledocholithotomy and ERCP assisted Stone Extraction" in the Treatment of Choledocholithiasis

Nuruzzaman G M [1], Rahman M A [2], Alfazzaman M [3], Saha K P [4], Sobhan S A [5]

ABSTRACT

Background: Choledocholithiasis is the stones in the extra biliary tree. The patients may be asymptomatic and choledocholithiasis may be diagnosed incidentally. Sometimes patients may present with upper abdominal pain, persisting jaundice, fever with chills and rigor.

Objective: Aim of the study was to compare the result in between "Choledocholithotomy and ERCP assisted stone extraction" in the treatment of Choledocholithiasis.

Method: This is a prospective study on differnt level hospitals in Bangladesh. Study duration was 6 months. Total 40 cases were included in each group of Choledocholithiasis after fulfilling the criteria. Patients were selected randomized in each alternative case for either choledocholithotomy or ERCP assisted stone extraction who are attended in Zainul Hoque Sikder Women's Medical College & Hospital and other tertiary level hospitals in Dhaka.

Result: In this study, outcome of 40 patients with symptomatic cholelidocholithiasis undergoing ERCP assisted stone extraction was compared with that of 40 patients treated by open choledocholithotomy procedure. The two patient groups were more or less simillar in age, sex and biliary tree stone burden. The presence of symptomatic bile duct stones was required for entry into this study. All patients had cholelidocholithiasis was diagnosed and assessed only by ultrasonography of hepatobiliary system. Open choledocholithotomy required more than double operative time than ERCP assisted stone extraction. The complication rate is more in conventional choledocholithotomy than in ERCP assisted stone extraction.

Conclusion: ERCP assisted stone extraction as a new approach to surgical management of bile duct stones offers the patients shorter hospital stay, faster return to work, markedly reduced postoperative pain and much improved cosmetic result as compared to open choledocholithotomy.

Key word: Choledocholithotomy, ERCP, Choledocholithiasis.

1. * Dr. G.M. Nuruzzaman
MBBS, FCPS (Surgery), FACS (USA)
Junior Consultant Surgery, Sader Hospital, Narail
E-mail: drzaman82@gmail.com
Cell: 01714-593563

2. Prof. Dr. M. Ataur Rahman
MCPS, FCPS (Surgery)
ZH Sikder Wemens Medical College Hospital

3. Dr. Md. Alfazzaman
MBBS, PhD (Surgery)
MH Samorita Medical College Hospital

4. Dr. Krishna Pada Saha
Junior Consultant (Surgery)
Shaheed Suhrawardy Medical College Hospital

5. Dr. Sarwar Ahmed Sobhan
FCPS
Medical officer and MS (Phase B)
Hepatobilliary pancreatic surgery
BSMMU

Introduction

Choledocholithiasis is stones in the extra hepatic biliary tree. It may be primary or secondary. Primary stones are formed in CBD (Common bile duct) and biliary tree itself, and are multiple, often sludge like, commonly pigment or mixed type. Primary stones are rare and usually caused by defective pathophysiology causing stasis, biliary dyskinesia, congenital conditions like choledochal cyst, infections, infestations like ascariasis, low protein diet, malnutrition, obesity, females, old age. Secondary biliary stones are common, usually cholesterol or black pigment stone. Secondary biliary stones are associated with 15% of gallstone disease. These are formed in gall bladder, passes through cystic duct to CBD. Here CBD and biliary tree are otherwise normal. Commonly stones are impacted in supraduodenal part of CBD.[1,3]

Gall bladder stones are associated in most of the patients with choledocholithiasis. The patient may present with cholelithiasis or years after cholecystectomy. The patients usually present with features of cholangitis- jaundice, fever with chills and rigor and abdominal pain with generalized itching, pale stool etc. The patients may be asymptomatic and choledocholithiasis may be diagnosed incidentally. Sometimes patients may present with persisting upper

abdominal pain, persisting jaundice and fever with chills and rigor. With the help of proper history taking, physical examination and by some investigations diagnosis can be made. On general examination patient is usually icteric and dehydrated. On abdominal examination upper abdominal tenderness may be present, Gallbladder is not usually palpableGallbladder will be palpable in primary choledocholithiasis, double impacted stones- one at CBD and one at cystic duct with mucocele of gallbladder, large stone in Hartman's pouch and other causes of obstructive jaundice except stones). The differential diagnosis are Carcinoma of head of pancreas, Peri-ampullary carcinoma, Cholangio-carcinoma, biliary stricture, choledocal cyst, Hepatitis etc Some investigations are done to reach the diagnosis and to exclude differential diagnosis and to know the general condition of the patient and the fitness for anesthesia. Choledocholithiasis may be classified as primary choledocholithiasis which is rare and secondary choledocholithiasis which is common. Primary biliary stones are formed in common bile duct and biliary tree itself and they are multiple, commonly pigment or mixed type. Secondary biliary stones are formed in gall bladder and pass through cystic duct to common bile duct commonly black pigment or cholesterol stones. The causes are defective pathophysiology of biliary tree causing stasis, biliary dyskinesia, choledochal cyst, caroli's disease, infections and infestations like clonorchiasis, ascariasis, obesity, malnutrition, old age, haemolytic diseases, ileal resection, fasting for long time, TPN for long time. Retained stones mean if stones are found in CBD within 02 years of cholecystectomy. Recurrent stones mean if stones are found after 02 years of cholecystectomy. The usual required investigations are ultra sonogram of hepato-biliary system and pancreas, LFT (Liver Function Tests: serum bilirubin-both direct and indirect, alkaline phosphatase, PT (Prothrombin Time) with INR, serum total protein and albumin globulin ratio), MRCP (Magnetic Resonance Cholangio Pancreatography), ERCP (Endoscopic Retrograde Cholangio Pancreatography), Endo-ultrasonography, RFT (Renal Function Test) etc. After diagnosis patient should be treated according to clinical features; if the patient presents with features of cholangitis, acute pancreatitis and septicemia then conservative treatment should be started by nothing per oral, broad spectrum antibiotics, correction of dehydration and electrolyte imbalance, correction of prolonged prothombin time by vit-k or FFP (Fresh Frozen Plasma). Sometimes sphincterotomy by ERCP and biliary drainage with stenting is done for improving the condition. Then stones from biliary tree are extracted by Choledocholithotomy or ERCP (Endoscopic Retrograde Cholangio Pancreatography) assisted procedures (Endoscopic Papillotomy/ sphincterotomy and stone extraction by Dormia basket or balloon catheter; or fragmenting the stones by means of lithotripter or ESWL and extraction with CBD stent is placed in situ if required). If calculus cholecystitis is associated-cholecystectomy is done before, after or at same sitting. In asymptomatic choledocholithiasis, cholecystectomy done before treatment of choledocholithiasis or both is treated at same sitting.[1,2,3]

In case of Choledocholithotomy a T-Tube is placed in CBD which is removed after 10-14 days after T-Tube cholangiography and this tract may be used for further stone removal if needed. ERCP (Endoscopic Retrograde Cholangio Pancreatography) is possible where facilities are available. The usual complications of Choledocholithotomy are bleeding, sepsis, post operative biliary stricture. The complications of ERCP (Endoscopic Retrograde Cholangio Pancreatography) are-bleeding, sepsis, pancreatitis, perforation of upper GIT etc. By this comparative study the clinicians as well as the patients can accept the safe, effective, economical modality in between "Choledocholithotomy and ERCP assisted stone extraction" in the treatment of Choledocholithiasis in selected cases.[4]

Endoscopic Retrograde Cholangiopancreatography (ERCP) is a combined endoscopic and radiological procedure which plays an essential role in the diagnosis and management of diseases of biliary tract and pancreas. The diagnostic technique was first introduced in 1968. This was quickly followed by development of therapeutic procedures. Although ERCP requires expensive equipment and technical skill it is now widely available.

ERCP provides direct visual observation of the esophagus, stomach, duodenum and ampulla of Vater. Inflammatory or neoplastic lesion visualized in any part of the upper gastrointestinal tract may entirely explain the clinical picture. Endoscopic biopsy with forceps, brush cytology, aspiration of pancreatic juice for cytology is possible and provides valuable informations. Retrograde pancreatogram and/or the retrograde cholangiogram often provide information indicative of the presence of tumor, worm, stone or inflammatory disorders.

Certain lesions can be treated or palliated by therapeutic ERCP e.g. papillotomy, stone removal, worm extraction, nasobiliary drainage, dilation of a stricture and stent insertion across bile ducts obstruction to improve their drainage. ERCP is generally well tolerated procedure when performed by surgeons who have had special training and experience in this technique.

The main complications are cholangitis, pancreatitis and haemorrhage. The morbidity and mortality for a diagnostic ERCP are about 1 percent and 0.1 percent respectively, whereas after an endoscopic sphincterotomy the figures are 10 percent and 1 percent. There is a particular risk of haemorrhage after a sphincterotomy. Less frequent problems are retroperitoneal perforation of the duodenal wall and impaction of a basket because a stone is trapped but is too large to remove.[4,6]

Another potential risk of ERCP is an adverse reaction to the drugs used. This risk must be balanced against the potential benefit of the procedure and the risk of alternative surgical treatment of the condition. These complications can be managed conservatively but occasionally they do require corrective surgery.[6]

Materials And Methods

This is a prospective study on different level hospitals in Bangladesh. Study duration was 6 months. Total 80 cases were included 40 in each group of Choledocholithiasis after

fulfilling the criteria. Patients were selected randomized in each alternative case for either choledocholithotomy or ERCP assisted stone extraction who are attended in Zainul Hoque Sikder Women's Medical College & Hospital and other tertiary level hospitals in Dhaka.

Variables of the study were per operative findings, per operative and post operative complications of choledocholithotomy or ERCP assisted stone extraction, primary and secondary outcome of choledocholithotomy or ERCP assisted stone extraction of choledocholithiasis.

Result in between "Choledocholithotomy and ERCP assisted stone extraction" in the treatment of Choledocholithiasis and follow up findings at regular intervals were also done. Diagnostic tools were both clinical and investigations.

Data was collected by researcher himself personally using of structured questionnaire designed for this study. Descriptive analysis was done using mean and standard deviation. Nominal data were analysed by their frequencies and percentages. Presentation is made by tables and charts. Statistical inference is made using SPSS computer software (SPSS inc. ver.11.5) with 5% significance level and 95% confidence level and appropriate test is done.

Result

The study was a prospective cross sectional study. The sample size was constructed by 40 patients in each group whereas total sample size is 80. The patient underwent choledocholithotomy and ERCP assisted stone extraction were two groups taken here to see the efficacy, cost effectiveness and hospital stay after performing each method as a treatment of choledocholithiasis.

The comparison between two types of intervention was observed and their comparison that has been come out in my study has been decorated by different tabular forms and figures that are displayed in this chapter.

Table-1: Distribution of patients by age and sex in choledocholithotomy (n=40)

Distribution of patients by age and sex in choledocholithotomy (n=40)

Age	Male		Female		Total		P value
(years)	No	%	No	%	No	%	
18- 25	0	0.0	01	2.5	01	2.5	
26-35	0	0.0	04	10.0	04	10.0	
36-45	2	5.0	11	27.5	13	32.5	0.184089^{NS}
46-55	2	5.0	12	30.0	14	35.0	
56-65	4	10.0	04	10.0	08	20.0	
Total	8	20.0	32	80.0	40	100	

The test is done by chi-square test.
NS: Non significant

Total 40 patients underwent choledocholithotomy as a treatment for choledocholithiasis. Among 40 patients male were 8 and female were 32 in number which were 20% and 80% of the total population. Among the 8 male patients 2 in number each belong to the age group between 36 to 45 years and between 46 to 55 years and the rest 4 male patients were from the age group between 56 to 65 years. Among the 32 female patients 1 patient from 18 to 25 years age group, 4 patients each belong to the age group between 26 to 35 years and between 56 to 65 years, 11 patients were from 36 to 45 years and the rest 12 female patients were from the age group between 46 to 55 years.

Table-2. Distribution of patients by age and sex in ERCP assisted stone extraction (n=40).

Distribution of patients by age and sex in ERCP assisted stone extraction (n=40)

Age	Male		Female		Total		P value
(years)	No	%	No	%	No	%	
18- 25	0	0.0	02	5.0	02	5.0	
26-35	2	5.0	08	20.0	10	25.0	
36-45	1	2.5	13	32.5	14	35.0	0.47711^{NS}
46-55	3	7.5	06	15.0	09	22.5	
56-65	1	2.5	04	10.0	05	12.5	
Total	7	17.5	33	82.5	40	100	

The test is done by chi-square test.
NS: Non significant

Total 40 patients underwent ERCP assisted stone extraction as a treatment for choledocholithiasis. Among 40 patients male were 7 and female were 33 in number which were 17.5% and 82.5% of the total population. Among the 7 male patients 2 patients were from 26 to 35 years age group and 1 in number each belong to the age group between 36 to 45 years and between 56 to 65 years and the rest 3 female patients were from the age group between 46 to 55 years. Among the 33 female patients 2 patient from 18 to 25 years age group, 8 patients from age group between 26 to 35 years, 13 patients from 36 to 45 years age group, and rest 6 and 4 patients were from 46 to 55 years and from the age group between 56 to 65 years respectively.

Figure 1: Presenting complaints of the patients in choledocholithotomy (n-40)

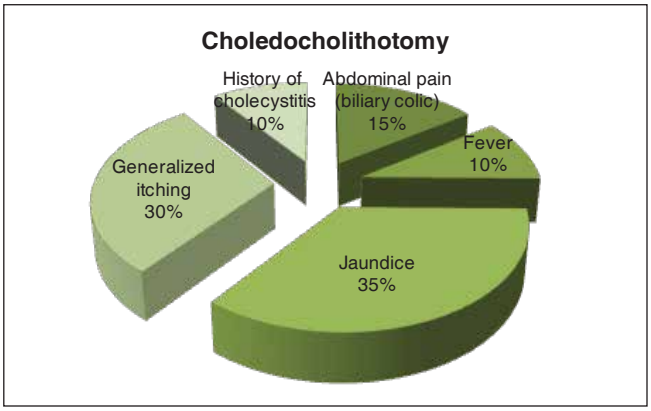
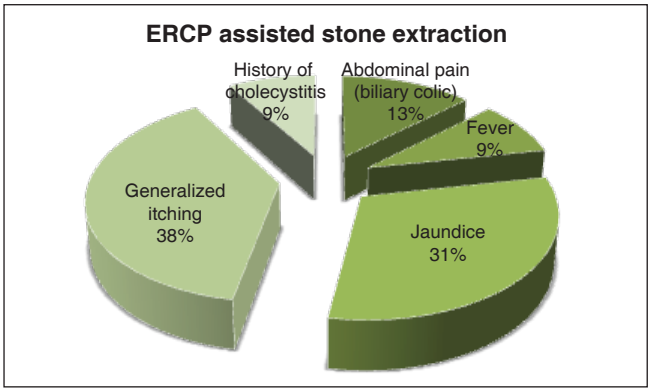


Figure 1: Presenting complaints of the patients in choledocholithotomy (n-40)

Among the 40 patients undergoing choledocholithotomy highest 14 (35%) patients had Jaundice, 12 (30%) presented with generalized itching, 6 (15%) patients presented with abdominal pain i,e. biliary colic and 4 (10%) patients each presented with fever and history of cholecystitis.
Figure 2: Presenting complaints of the patients in ERCP assisted extraction of stone (n-40)

Figure 2: Presenting complaints of the patients in ERCP assisted stone extraction (n-40)



Among the 40 patients undergoing ERCP assisted stone extraction the highest 15 (38%) patients had generalized itching , 13 (31%) presented with Jaundice, 6(13%) patients presented with abdominal pain i,e. biliary colic and 3 (9%) patients each presented with fever and history of cholecystitis

Table- 3. Peroperative findings of both groups (n=40 in each group)

Peroperative findings of Choledocholithotomy & ERCP assisted stone extraction

Peroperative findings	Choledocholithotomy		ERCP assisted stone extraction		P value
	No	%	No	%	
Impaction of stones	8	(20%)	6	(15%)	0.915486^{NS}
Dilatation of CBD	36	(90%)	34	(75%)	
Position of stones - distal CBD	16	(40%)	19	(47.5%)	
Clearance of stones	40	(100%)	34	(85%)	
Cholangiography	40	(100%)	40	(100%)	

The test is done by chi square test.
NS: Not Significant

Among the 40 patients underwent choledocholithotomy in 8 (20%) impaction stone were seen, in 36 (90%) patients CBD was dilated , stone was lodged in the distal CBD in 16 (40%) patients , clearance of stone were achieved in 40 (100%) patients as well as intraoperative cholangiography.
On the other hand, among the 40 patients underwent ERCP assisted stone extraction impaction of stone were observed in 6 (15%) patients, CBD were dilated in 34 (75%) patients, stones were slodged in distal CBD in 19 (47.5%) patients, clearance of stones were achieved in 34 (85%) patients and finally intraoperative cholangiography done in 40 (100%) patients.

Table- 4: Peroperative complications of both groups (n-40 in each group)

Peroperative complications of both groups

Peroperative complications	Choledocholithotomy		ERCP assisted stone extraction		P value
	No	%	No	%	
Haemorrhage	05	(12.5)	02	(5.00)	0.06281^{NS}
Failure	00	(00)	06	(15.0)	
Gut injury	00	(00)	00	(00)	

The test is done by chi-square test.
NS: Non significant

Considering the peroperative complications in both techniques of choledocholithiasis problem the very much specific complications came in front are two like hemorrhage and technical failure. Among the 40 patients each of both groups I observed that in choledocholithotomy patients surgeons faced moderate hemorrhage in case of 5 patients which was 12.5% of the study population of that group. On the contrary, no cases was found as technical failure in that group.

In the group of patients undergoing ERCP assisted stone extraction surgeons faced hemorrhage in case of 02 patients which were 5.00 % of the total population of that group and 6 cases found technically failed in expert hand which is about 15% of that group population

Table-5: Postoperative complications of both groups (n=40 in each group):

Postoperative complications of both groups

Complications	Choledocholithotomy		ERCP		P value
	No	%	No	%	
Cholangitis	02	(05.0)	04	(10.0)	0.024167^{S}
Pancreatitis	05	(12.5)	01	(2.5)	
Fever	15	(37.5)	05	(12.5)	
Wound infection	06	(15.0)	00	(00)	
Post operative bile duct stricture	05	(12.5)	03	(7.5)	

The test is done by chi-square test.
S: Significant

I observed cholangitis, pancreatitis, fever, wound infection, post operative bile duct stricture as the common post operative complications in these 80 patients of both groups. Among them 6 (7.5%) patients each suffered from cholangitis, pancreatitis. Wound infection 06 (15%) only in Choledocholithotomy, 20 (25%) patients suffered from fever and 8 (20%) patients suffered from post operative bile duct stricture.

Table-6: Morbidity and mortality of both groups: (n=40; in each group):

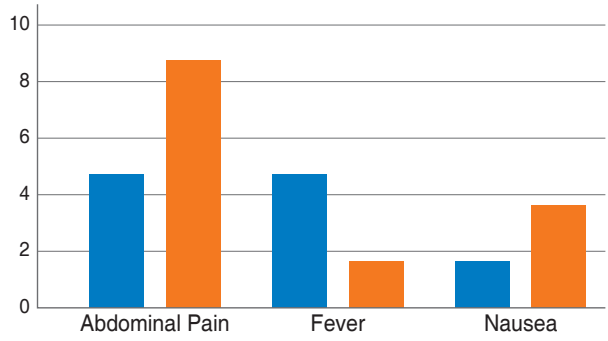
Morbidity and mortality of both groups

Type of complication	Choledocholithotomy		ERCP		P value
	No	%	No	%	
Injury to CBD/ hepatic duct / cystic artery /hepatic artery	00	(0.0)	00	(0.0)	0.045897[S]
Injury to duodenum / intestine	00	(0.0)	00	(0.0)	
Spillage of stone	08	(20)	00	(0.0)	
Postoperative bile leak	00	(0.0)	00	(0.0)	
Postoperative voiting	02	(5)	03	(7.5)	
Superficial wound infection	06	(15)	00	(0.0)	
Decreased pulmonary function and chest infection	10	(25)	01	(2.5)	
Overall morbidity	12	(27.5)	02	(5.0)	
Mortality	00	(0.0)	00	(0.0)	

The test is done by chi-square test.
S: Significant

Morbidity and mortality after both procedures occurred in some patients due to different causes like spillage of stone, postoperative vomiting, superficial wound infection, decreased pulmonary function and chest infection etc. Among the 80 patients of both groups spillage of stone and superficial wound infection occurred in 06(15%) patients in choledocholithotomy, postoperative vomiting occurred in 5 (6.25%) patients, 11 (13.75%) patients suffered from decreased pulmonary function and chest infection and maximum 13 (16.25%) patients were suffered from overall morbidity.

Figure-3: Symptoms of post operative follow up (both groups):



	Abdominal Pain	Fever	Nausea
ERCP assisted stone extraction	3	3	2
Choledocholithotomy	9	2	4

Figure-3: Symptoms in postoperative follow up (both groups):

Abdominal pain, nausea, fever were given emphasized as the important findings in follow up period by the surgeons. Among the 40 patients of each group 9, 2 and 4 patients suffered from abdominal pain, fever and nausea respectively in choledocholithotomy group whereas 3 patients each suffered from abdominal pain and fever plus 2 patients from nausea in ERCP assisted stone extraction group.

Table - 7: Operation time in both groups (n=40; in each group):

Operation time in both groups

Operative duration	Choledocholithotomy	ERCP assisted stone extraction	P value
< 60 min	4	34	< 0.00001.[S]
60-120 min	26	6	
>120 min	10	00	
Mean±SD	101.525± 23.96	52.475±10.52	

The test is done by student t test.
S: Significant

Operation time is an important observation in this study. In both groups of choledocholithotomy and ERCP assisted stone extraction maximum 34 procedures among the 40 patients of latter group completed within 60 minutes. The statistics is 85% of that group population and rest 6 (15%) of that group population took 60-120 minutes time.

On the other hand, choledocholithotomy came out as a time consuming procedure through this study as 26 (65%) procedures were completed between 60 to 120 minutes, 10 (25%) procedures completion took >120 minutes and only very small number of people like 4 (10%)in numbers were completed within 60 minutes.

Table-8 : Hospital stay of both groups (n=40; in each group):

Hospital stay of both groups

Post Operative Hospital stay (days)	Choledocholithotomy	ERCP assisted stone extraction	P value
10-18	10	00	0.000723[S]
<09	30	40	
Mean ± SD	10±3.76	3.725± 1.42	

The test is done by chi-square test.
S: Significant

To observe the total hospital stay after each procedure was one of our specific objectives of the study. Among the 40 patients underwent choledocholithotomy 10 patients had to be admitted into the hospital 10-18th POD whereas no patient underwent ERCP assisted extraction of stone stayed in the hospital upto 10th POD. 30 patients of initial group and 40 patients of latter group left the hospital within 9th POD. So the mean hospital stay in case of choledocholithotomy is 10 days and in case of ERCP assisted stone extraction is 3.75 days.

Table-9 : Total cost of treatment both groups (n=40; in each group):

Total cost of treatment

Expenses (approx.)	Choledocholithotomy	ERCP assisted stone extraction	P value
<10,000 tk	10	00	0.042522[S]
10,000-20,000 tk	28	32	
>20,000 tk	2	8	

The test is done by chi square test.
S: Significant

The cost of treatment includes hospital admission; daily expenses, operation charge, OT charge; Medicine charge and also surgeon's charge in case of different hospitals of Dhaka city. Here mostly 10,000-20,000 BDT expenditure was observed in 28 and 32 patients in case of choledocholithotomy and ERCP assisted stone extraction respectively.
Whereas only 10 patients cost <10,000 BDT in open surgery but no patient could achieve ERCP assisted stone extraction with such expenditure. Conversely, maximum expenditure valued choledocholithotomy by >20,000 BDT in case of 2 patients undergoing choledocholithotomy and 8 patients in case of ERCP assisted stone extraction.

Fig-4: Patients satisfaction in both groups (n=40; in each group):

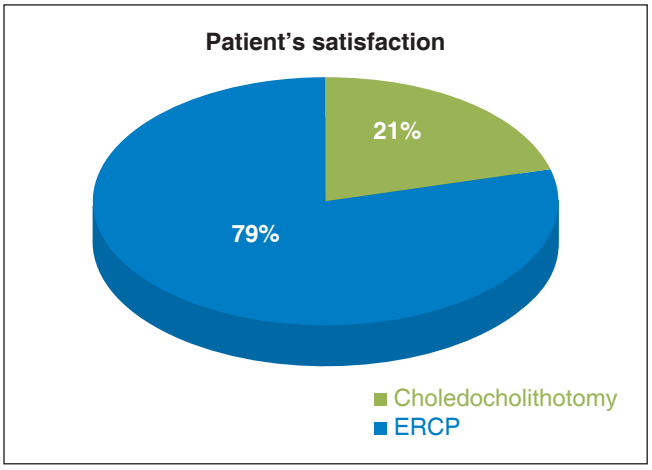


Fig-4: Patients satisfaction in both groups: (n=40; in each group):

Shows that 79% patients were satisfied in ERCP assisted stone extraction and 21% patients were satisfied in Choledocholithotomy.

Discussion

Although Open choledocholithotomy has been performed quite successfully for more than 100 years its pre-eminent position in the treatment strategy for patients with choledocholithiasis has been challenged by the recent introduction and widespread application of ERCP assisted stone extraction. Almost more than 100 years later now a days, ERCP assisted stone extraction that has gained the acceptance as the standard of care for patients requiring biliary tract stone removal though open choledocholithotomy still required for some cases. ERCP assisted stone extraction is the preferred treatment for choledocholithiasis. It is associated with better out come, lesser hospital stay and lower cost as compared to conventional open Choledocholithotomy. Minimum pain-where strong analgesic are not required, no scar, resuming early activity are all major advantages of this precedure.

A study shows a total of 1177 ERCP were included in the analysis of which 56.2% were therapeutic. The 30 days complication rate was 15.9%. The procedure related mortality rate was 1.0%. Post ERCP pancreatitis occurred in 3.8% of patients (3 deaths). Haemorrhage or perforation occurred with 0.9% and 1.1% respectively; of the procedures (3 deaths). One perforation that resulted in the death of the patient occurred after placement of an endoprosthesis. Cholangitis occurred in relation to 5% of the ERCP procedures (3 deaths). Cardio-respiratory complications occurred in 2.3% (2 deaths).[4,6,18]

40 patients undergoing ERCP assisted stone extraction were compared with another 40 patients undergoing open choledocholithotomy during the same period in Zainul Hoque Sikder Women's Medical College & Hospital and other tertiary level hospitals in Dhaka. All patients in both groups were selected on the basis of ultrasonographic evidence of CBD stones and had symptoms consistent with biliary colic and or dyspepsia. Patient with acute severe cholangitis and acute pancreatitis as evidenced by preoperative fever, leucocytosis and peritonitis, patients had undergone previous surgical treatment of the upper part of abdomen previously, patients with severe comorbiditis and major coagulopathy were excluded from both groups. All patients were evaluated clinically and by performing relevent investigations. Operative procedure, preoperative findings, time of operation any complications or problems during operation were noted. Postoperative pain and discomfort (assessed clinically) and hospital stay were also recorded.

The age of the patient ranges from 18 to 65 years with a mean age and standard deviation 40±15.6 years. The most common age group was 35-55 years. Among all the patients 18.75% were male and 81.25% female with a male female ratio of 1:4.33. The age and sex distribution of the patients treated by choledocholithotomy and ERCP assisted stone extraction shows highest female patients four to five times more likely to suffer from choledocholithiasis. In this study most of the patients (90%) present with features of itching and cholangitis. Cholelithiasis was associated in (20%) of patients. Most of the stones are multiple in number and situated in proximal CBD. In choledocholithotomy, all stones are cleared and T-tube was placed in situ. In case of ERCP assisted stone extraction, in 06 patients stone clearance was not possible and converted into choledocholithotomy. In all cases per-operative cholangiogram was done. In case of ERCP assisted stone extraction, stent was kept in situ in selected cases and removed later without major complications. No major per-operative and post –operative

complications except minor cholangitis, pancreatitis, fever,wound infection, biliary stenisis; which were more in choledocholithotomy. The overall morbidity was little-bit higher in choledocholithotomy. The total hospital stay and mean cost were much higher in choledocholithotomy. Patients satisfaction was higher in ERCP assisted stone extraction.

Open choledocholithotomy was done either by a right subtotal incision (Kocher's) 94% or upper midline incision 6.0%. No incision is required in ERCP assisted stone extraction. So the cosmetic result is better in ERCP assisted stone extraction than conventional choledocholithotomy.

The mean operative time for ERCP assisted stone extraction was 52 minutes and mean operative time required for open choledocholithotomy was 101 minutes which is comparable with other study. Operative time is much higher for open choledocholithotomy than ERCP assisted stone extraction which is also consistent with other study. In ERCP assisted stone extraction every part of operative field is illuminated. So there is less chance of injury to nearby structures. But its drawback is bleeding, that can not be managed by direct vision.[4]

In case of ERCP assisted stone extraction, peropertive problems were experienced in 13 patients (32.5%). Most common problems were large stone size (3-4 cm), impacted stone in CBD, failure of clearance of stones in 06 cases. This type of peroperative problems or difficulty were encountered in previous studies.[6,20] But no such peroperative problems or difficulties were encountered in open choledocholithotomy of present study.

Bleeding is undoubtedly a great problem during surgery. In case of acute cholangitis increase tissue vascularity & incase risk of vascular injury. In this series oozing occurred in 23% cases, the fields were cleaned by irrigation followed by aspiration then those were managed by swab compression for few minutes. Minor arterial bleeding occurred in 32% cases. In case of minor arterial bleeding sucker was inserted close to the bleeding points. With active aspiration bleeding vessels were visualized, these were then grasped by insulated grasper and were coagulated though the grasper or clipped.

Bowel is more vulnerable to injury during ERCP assisted stone extraction in acute gallbladder disease. In this study there was no incidence of bowel injury. All hollow visceral injuries during dissection are preventable by careful dissection & avoidance of unnecessary electocautery. There were no gross post operative wound infection, intra-abdominal sepsis, major pulmonary complications, postoperative pancreatitis, major vascular or visceral injuries, bile leakage in either group.

ERCP assisted stone extraction was successful in 34 out of 40 attempted, the remaining 6 patients were converted to laparotomy and choledocholithotomy. Overall failure rate was 15% in present study which is consistent with other studies. Analgesics required in case of ERCP assisted stone extraction for 2 days and open choledocholithotomy was 7 days on an average. In other study, use of parental narcotic analgesic had markedly reduced during the first 24 hours of ERCP assisted stone extraction. This is probably due to early mobilization with combined analgesics. More Analgesics required on open cholecystectomy due to more tissue injury.

The resumption of an oral solid diet was significantly faster after ERCP assisted stone extraction (mean 1.6 days) than open choledocholithotomy (mean 3.45 days) which is comparable with other studies[41]

The mean cost of surgery was higher for ERCP assisted stone extraction than conventional choledocholithotomy. However consideration of total cost involving loss of working hour after open choledocholithotomy, ERCP assisted stone extraction is more cost effective in context of socio-economic consideration.Most of the patients of the ERCP assisted stone extraction group were discharged from the hospital on fourth postoperative day which is consistent with other study. Incase of open choledocholithotomy discharge of the patient from the hospital was on an average at tenth post operative day. A shorter period was requied before return to work (or full activity) for those patient treated with ERCP assisted stone extraction (average 10 days) than in those undergoing open choledocholithotomy (average 30 days) in present study. This finding is coincide with other studies regarding return to full activity.

In spite of increase technical difficulty ERCP assisted stone extraction is safe, effective and well established treatment of choledocholithiasis. ERCP assisted stone extraction is technically more demanding to surgeon & beneficial to patient.

Considering all the above circumstances, I like to put forward a few suggestions to improve surgical skill, minimize complications, and ensure patients benefit. These are:

1. Arrangement of training program for surgeons, who are in their initial stage of performing ERCP assisted stone extraction.
2. To ensure availability of technical personnel, instruments & all logistic supports in all the tertiary level hospitals throughout the Bangladesh.
3. Surgeons should be more confined throughout the procedure to minimize complications.
4. Preoperative assessment & optimization of patients to reduce conversion rate.

It shall also be considered that sample size of this study was not large enough to predict that such results represent the true picture of the whole population, and hence large-scale studies are required to validate the findings of this study.

Conclusion

ERCP assisted stone extraction as a new approach to surgical management of bile duct stones offers the patients shorter hospital stay, faster return to work, markedly reduced postoperative pain and much improved cosmetic result as compared to open choledocholithotomy. In this study, outcome of 40 patients with symptomatic cholelidocholithiasis undergoing ERCP assisted stone extraction was compared with that of 40 patients treated by

open choledocholithotomy procedure. The two patient groups were more or less simillar in age, sex and biliary tree stone burden. The presence of symptomatic bile duct stones was required for entry into this study. All patients had cholelidocholithiasis was diagnosed and assessed only by ultrasonography of hepatobiliary system. Open choledocholithotomy required more than double operative time than ERCP assisted stone extraction. The complication rate is more in conventional choledocholithotomy than in ERCP assisted stone extraction. But all the complications were insignificant. No major complications occur in any group. The length of hospital stay and time lost from work were significantly reduced in the group treated by ERCP assisted stone extraction. The mean cost of surgery was higher for ERCP assisted stone extraction than conventional choledocholithotomy. ERCP assisted stone extraction is more cost effective in context of socio-economic consideration. Patient satisfaction and overall cosmetic result is better after ERCP assisted stone extraction than after conventional choledocholithotomy.

ERCP assisted stone extraction is a better choice than conventional choledocholithotomy in cases of anticipated uncomplicated CBD stone disease on account of its better patient satisfaction, shorter hospital stay, better cosmetic result, earlier resumption to work.

Limitations of the present study

1. This is a small scale study comprising only 40 subjects in each group.
2. Hospital based study of the patients who suffering from cholidocholithiasis.
3. This study only reflects the defined age and sex group of people who were suffering from cholidocholithiasis.
4. Personal biasness of data collector may present

References

01. *NORMAN S. WILLIAMS, CHRISTOPHER J. K. BULSTRODE & P. RONAN O'CONNELL, Bailey and Loves SHORT PRACTICE of SURGERY, 26th edition; 1097-1117.*

02. *CURRENT Diagnosis & Treatment of SURGERY 13th edition; 573-601.*

03. *FARQUHARSON'S TEXTBOOK OF OPERATIVE GENERAL SURGERY. 9TH edition. P: 317-337*

04. *E J Williams, J Green, I Beckingham, R Parks, D Martin, M Lombard Guidelines on the management of common bile duct stones (CBDS)-2008.*

05. *Treerawood Gomuthura, Risk factors & Techniques affecting surgical outcome of therapeutic Endoscopic Retrograde Cholangiopancreatography difficulties, J Med Assoc Thai 2005; 88(8): 1103-9.*

06. *Sabri Selçuk ATAMANALP1, Mehmet İlhan YILDIRGAN1, Abdulmecit KANTARCI2- Endoscopic retrograde cholangiopancreatography (ERCP): outcomes of 3136 cases over 10 years 2011; 41 (4); 615-621.*

07. *R M Kirk, General Surgical Operations. 5th edition, London Churchill Livingstone; 2006, p: 285-315.*

08. *Cuschieri A. 2002. "Disorders of the Biliary Tract' in Essential Surgical Practice. Higher Training in General Surgery, 4th edn. eds. Sir Alfred Chuschieri, Robert J.C. Steele, Abdool Rahim Moossa. K.M. Varghese company, Mumbai, pp. 321-374.*

09. *Lygidakis NJ. Operative risk factors of cholecystectomy-choledochotomy in the elderly. Surg Gynecol Obstet 1983;157:15–9*

10. *Martin L. Freeman et al., Complications of endoscopic biliary sphincterotomy, The New England Journal of Medicine. Vol 335: 909-919, Sep. 26, 1996, Number 13*

11. *Gurusamy KS, Samraj K. Primary closure versus T-tube drainage after laparoscopic common bile duct stone exploration. Cochrane Database Syst Rev 2007:CD005641.*

12. *Halme L., Doepel M, Von Numers H, Edgren J., Ahonen J., Complications of diagnostic & therapeutic ERCP , Ann Chir Gynaecol. 1999; 88(2): 127-31.*

13. *Hacker KA, Schultz CC, Helling TS. Choledochotomy for calculous disease in the elderly. Am J Surg 1990; 160:610–2; discussion 3.*

14. *Johnson AS, Ferrara JJ, Steinberg SM, Gassen GM, Hollier LH, Flint LM. The role of endoscopic retrograde cholangiopancreaticography: sphincterotomy versus common bile duct exploration as a primary technique in the management of choledocholithiasis. Am Surg 1993;59(2):78-84.*

15. *667-710. Barteau JA, Castro D, Arregui ME, et al. A comparison of intraoperative ultrasound versus cholangiography in the evaluation of the common bile duct during laparoscopic cholecystectomy. Surg Endosc 1995;9:490–6.*

16. *J. Lizcano G C J, A. Martin J G J, Arinoad J M A, Sola A P, Service of Diagnostic Diseases Hospital Virgen de la Luz. Cuenca, Spain. Complications of Endoscopic Retrograde Cholangiopancreatography: A study in a small ERCP unit. Rev. esp. enferm dig Vol 196 no. 3 Madrid Mar. 2004.*

17. *Christensen M, Matzen P, Schulze S, Rosenberg J, Complications of ERCP: A Prospective study. Gastrointest Endosc 2004; 60: 721-31.*

18. *Meyrs, W.C. Ricciardi, R, Chari, R.S. 2001. "Liver Anatomy and Development" in Sabiston's Text Book of Surgery Book 1. 16th edn. Eds. Courtney M. Townsend Jr, Daniel Beauchamp, B. Mark Evers, Kenneth L. Mattox. Harcourt Asia Pt. Ltd. Delhi, pp 997-1004.*

19. *Suc B, Escat J, Cherqui D, Fourtanier G, Hay JM, Fingerhut A, et al. Surgery vs endoscopy as primary treatment in symptomatic patients with suspected common bile duct stones: a multicenter randomized trial. French Association for Surgical Research. Arch Surg 1998;133(7):702-8.*

20. *Huang LY,Liu YX, Wu CR,Cui J, Zhang B. - Application of ERCP in biliary and pancreatic diseases-chinease med J 2009;122:2967-72.*

21. *Pungpapong S, Kongkan P, Rerknimitr R, Kullavanijaya P. Department of Internal Medicine, Mayo Clinic Jacsonville, USA, Department of Internal Medicine, Faculty of Medicine, Chulanlongkorn University, J. Med Assoc Thai 2005; 88(2):238-46.*

22. *Pagana TJ, Stahlgren LH. Indications and accuracy of operative cholangiography. Arch Surg 1980; 115:1214–5.*

23. *Steven A, Pitt H A, Sabiston's Text Book of Surgery, 17th edition, W.B. Saunder Company, Philadelphia, 2001; pp1599-1600.*

24. *Jones WB, Roettger RH, Cobb WS, Carnobell AM. ERCP in general surgery: how much are we outsourcing? Am Surg 2009; 75: 1050-3*

25. *Gomuthura T, Risk factors & Techniques affecting surgical outcome of therapeutic Endoscopic Retrograde Cholangiopancreatography difficulties, J Med Assoc Thai 2005; 88(8): 1103-9.*

26. *Berci G, Morgenstern L. Laparoscopic management of common bile duct stones. A multi-institutional SAGES study. Society of American Gastrointestinal Endoscopic Surgeons. Surg Endosc 1994;8:1168-74; discussion 74–5*

27. *Blumgart LH (ed.) Surgery of the liver and biliary tract, 4th edn. London: WB Saunders, 2006.*

28. *Kurtz, R.C. 1994. "Diagnostic Endoscopic Retrograde Cholangiography" in Surgery of the Liver and Biliary Tract 2nd edn. vol. ed. L. H. Blumgart Churchill Livingstone pp. 309-323.*

29. *Bland KI, Sarr MG, Buchler MW et al (eds) Liver and biliary surgery: hand books in general surgery. Newyork: Springer, 2010.*

30. *SRB's MANUAL OF SURGERY, 4th edition;*

31. *Ong TZ, Khor JL, Selamat DS, Yeoh KG, Ho KY. Complications of Endoscopic Retrograde Cholangiopancreatography in the post -MRCP era: A Tertiary Center experience. World J Gastroenterol.2005 Sep 7; 11 (33): 5209-12*

32. *Peter L. Williams, Gray's Anatomy the Anatomical Basis of Medicine and Surgery 38th edition, 1995 p-1810.*

33. *Franklin ME Jr., Pharand D, Rosenthal D. Laparoscopic common bile duct exploration. Surg Laparosc Endosc 1994;4:119–24*

34. *Cotton, P. Williams. C, Practical gastrointestinal endoscopy, 4th edition,Blackwell, Science Ltd. 1996: 105-138.*

35. *Garg PK, Tandon RK, Ahuja V, et al. Predictors of unsuccessful mechanical lithotripsy and endoscopic clearance of large bile duct stones. Gastrointest Endosc 2004; 59:601–5.*

36. *Chummy S. Sinnatamby, Last's Anatomy, Regional and applied, 10th edition, 1999, reprint-2005, pp 257-264.*

37. *Sackmann M, Holl J, Sauter GH, et al. Extracorporeal shock wave lithotripsy for clearance of bile duct stones resistant to endoscopic extraction. Gastrointest Endosc 2001;53:27–32.*

38. *Neuhaus H, Zillinger C, Born P, et al. Randomized study of intracorporeal laser lithotripsy versus extracorporeal shock-wave lithotripsy for difficult bile duct stones. Gastrointest Endosc 1998;47:327–34.*

39. *Gil S, de la Iglesia P, Verdu JF, et al. Effectiveness and safety of balloon dilation of the papilla and the use of an occlusion balloon for clearance of bile duct calculi. AJR Am J Roentgenol 2000; 174:1455–60.*

40. *William F. Ganong. "Review of Medical Physiology", 18th edition, 1997. Appleton & Lange. P 468.*

41. *Boerma D, Rauws EA, Keulemans YC, et al. Wait-and-see policy or laparoscopic cholecystectomy after endoscopic sphincterotomy for bile-duct stones: a randomised trial. Lancet 2002;360:761–5.*

42. *Hammarstrom LE, Holmin T, Stridbeck H. Endoscopic treatment of bile duct calculi in patients with gallbladder in situ: long-term outcome and factors. Scand J Gastroenterol 1996;31:294–301.*

43. *Stiegmann GV, Goff JS, Mansour A, et al. Precholecystectomy endoscopic cholangiography and stone removal is not superior to cholecystectomy, cholangiography, and common duct exploration. Am J Surg 1992;163:227–30.*

44. *Erickson RA, Carlson B. The role of endoscopic retrograde cholangiopancreatography in patients with laparoscopic cholecystectomies. Gastroenterology 1995; 109:252–63.*

45. *Urbach DR, Khajanchee YS, Jobe BA, et al. Cost-effective management of common bile duct stones: a decision analysis of the use of endoscopic retrograde cholangiopancreatography (ERCP), intraoperative cholangiography, and laparoscopic bile duct exploration. Surg Endosc 2001;15:4–13*

46. *Fan ST, Lai EC, Mok FP, et al. Early treatment of acute biliary pancreatitis by endoscopic papillotomy. N Engl J Med 1993; 328:228–32.*

47. *Howden JK, Baillie J. Preoperative versus postoperative endoscopic retrograde cholangiopancreatography in mild to moderate pancreatitis: a prospective randomized trial. Gastrointest Endosc 2001;53:834–6*

48. *Leung JW, Chung SC, Sung JJ, et al. Urgent endoscopic drainage for acute suppurative cholangitis. Lancet 1989; 1:1307–9.*

49. *Tham TC, Vandervoort J, Wong RC, et al. Safety of ERCP during pregnancy. Am J Gastroenterol 2003; 98:308–11.*

Original Article

Safety and Efficacy of Oral Azithromycin and Daily Topical Clindamycin in the Treatment of Acne Vulgaris

Akter A [1], Afroz R [2], Rahman M M [3]

ABSTRACT

Background: Combination therapy is an effective approach to simultaneously target multiple pathogenic factor of acne. A unique combination of oral azithromycin and daily topical clindamycin in the treatment of acne vulgaris.

Objective: To evaluate the safety and efficacy of oral azithromycin thrice weekly and daily topical clindamycin has been developed for treatment of acne vulgaris.

Methods: It was an open, controlled clinical trial; conducted on 57 out patients with acne vulgaris. Patients were clinically assessed on first visit and 4 weekly for 3 months. Evaluation included success rate (subjects 'clear' or 'excellent' improvement, good response), lesion count, and percentage change in lesion count from baseline, cutaneous tolerability and adverse events.

Results: In this study the concomitant use of oral azithromycin thrice weekly and daily topical clindamycin in the treatment of acne vulgaris is assessed. A total of 57 patient with acne vulgaris those fulfilled the inclusion criteria were enrolled. Azithromycin, 500mg orally thrice weekly for 3 month & daily topical clindamycin at night is used. Patients were clinically evaluated at 4 weekly interval. At base line and all follow up visits all parameters were examined and graded by using Michaelsson acne severity index. Both the total scores and number of each type of acne lesion were compared to base line scores and five comparative categories were generated i.e. cleared, excellent, good and poor improvement and worse. In this study the number of female patients were 42 (73.68%) and male patients were 15 (26.32%). Most of the patient were students and belongs to upper middle socioeconomic class. Mean age of the patient was 18.56±3.35 years. At the end of first 4 weeks, 72.12% comedones, 67.63% papuler lesion, 51.44% pastular lsion and 29.14% infiltrated lesion were cleared; cystic lesion remained unchanged. At the end of 12 weeks treatment 99.5% comedones, 97.52% papuler lesion, 94.34% pastular lsion and 89.23% infiltrated lesion were cleared. Percent reduction of Michaelsson Acne Severity Index was 54.73% after 4 weeks of treatment, 79.09% after 8 weeks and 95.32% after 12 weeks of treatment, which was statically highly significant. Adverse effects i.e. 13(22.81%) complained of heart burn, 8(14.04%) abdominal cramp, 6(10.53%) tinnitus and 4(7.02%) headache. 16(28.07%) patients complained of mild burning sensation (irritation) and erythema on facial skin. Adverse events that occurred early in the study, and were transient. So combination therapy of oral azithromycin and topical clindamycin is safe and effective in the treatment of acne vulgaris.

Conclusion: This study revealed that combination regimen of oral azithromycin and daily topical clindamycin is safe and effective in the management of acne vulgaris.

Key words: Acne vulgaris, Azithromycin, Clindamycin

1. * Dr. Ayesha Akter, MBBS, FCPS
Assistant Professor, Cumilla Medical College
E-mail: drayeshaakter1996@gmail.com
Mobile: 01813-932926

2. Dr. Rozina Afroz
Assistant Professor (Skin & VD)
Shaheed Ziaur Rahman Medical College, Bogura

3. Dr Mohammad Mozibur Rahman
Senior Consultant, Paediatrics
250 Bed Sadar Hospital Brahmanbaria

Introduction

Acne vulgaris is a self-limited disorder of the pilosebaceous unit that is seen primarily in adolescents. It is sufficiently common that it often has been termed physiologic[1]. It occurs in 85% of all teenager with greatest frequency between the ages of 15 and 16 in both sexes[2]. In men and women older than 25 years, 40% to 54% have some degree of facial acne and clinical facial acne presents into middle age in 12% of women and 3% of men. A few will have inflammatory papules into late adult hood[2]. Acne occurs most commonly during adolescence and often continuous into adulthood. Acne is usually caused by an increase in testosterone in both sexes during puberty[3].The pathogenesis of acne is multifactorial. It involves excessive sebum production, abnormal epithelial

hyperkeratinization in sebaceous follicles, the presence of microbial organisms, notably the anaerobic Propionibacterium acnes (P.acnes), and inflammation[4]. In the very young patients the predominant lesions are comedones. In girls, the occurrence of acne may precede menarche by more than 1 year. Like other countries a quite number of adolescents and young adults both male and female suffer from acne vulgaris in our country and many suffer from high degree of morbidity and psychological trauma due to post acne scar that develop due to lack of proper and adequate treatment. A review conducted by J.K.L.TAN et al suggested that psychological abnormalities including depression, suicidal tendency, anxiety, pshychosomatic symptoms including pain and discomfort, embarrassment and social inhibition. Various regimens and treatment modalities have been tried with varying rate of success. For example when tazarotene (0.1%) gel applied once daily for 12 weeks in acne vulgaris, at the end of treatment 93.6% of patients showed almost complete clearance of acne lesions[32] ; azithromycin 500mg thrice weekly for 12 weeks used in acne vulgaris 80% clearance observed at 12 weeks10, topical 1% clindamycin gel applied twice daily for 8 weeks 88% reduction of acne lesion at the end of treatment[25]. Neither oral therapy (antibiotics and retenoids) nor the topical therapy is being considered as an ideal and fruitful treatment of acne vulgaris. Systemic oral therapy is not free of poor compliance and side effects unless treated for long duration. The treatment armamentarium of acne contains many different therapeutic options, including topical and oral antibiotics, topical and oral retinoids, topical benzoyl peroxide, azelaic acid, topical clindamycin, hormonal agents and surgical modalities[6]. Topical clindamycin preparation are used in acne vulgaris as antimicrobial agent for last several years. Clindamycin penetrates the skin and retains its biological activity against P. acnes even in contact with skin. The concentration of clindamycin in the comedonal material is more than sufficient to suppress the growth of P. acnes. There is a concurrent reduction in the free fatty acid levels on the skin surface[7]. Clindamycin are available in our country and can be used as monotherapy and in combination with other agent. Systemic antibiotic most commonly used in acne vulgaris to act against P. acnes are tetracycline, erythromycin, minocycline and doxycycline[8]. They often required frequent and long term administration. Therefore they failed to gain acceptance more over they are sometimes associated with side effects contributing to reduce compliance. Azithromycin belongs to the azalide group of antibiotics and structurally related to macrolides like erythromycin. It is more tissue stable, penetrates deeply into tissue and for a higher terminal half life than erythromycin. It is approved mainly for the treatment of streptococcal pharyngitis and uncomplicated skin infections[35]. It appears to have a broad spectrum of activity in vitro against P.acnes. The efficacy and safety of azithromycin therapy in acne vulgaris has been reviewed in many western journals[9,10] and articles on clinical trials have been published. There are no reports in the literature of P.acnes resistance to azithromycin[11]. Recently some studies have been published on the effective use of azithromycin in treating acne in adults, but until now there is scant published information on azithromycin use for acne in the adolescent population[10,11,12,13,14]. The effect of azithromycin (500 mg) orally thrice weekly for 12 weeks, appear to be a safe and effective treatment for acne vulgaris with excellent patient compliance. So, combination of oral azithromycin (500 mg.) thrice weekly and daily topical clindamycin at night might be a good option for the treatment of acne vulgaris.

Method

A double blind study has been conducted with purposive method to examine the effectiveness of topical 1% clindamycin hydrochloride hydrate in a hydroalcoholic vehicle as compared to the effect of the vehicles above. Fourteen patients applied clindamycin or vehicle alone twice daily for eight weeks. Free fatty acid, surface lipid percentages, quantative bacterial counts and clinical responses were assessed every two weeks. A signifiacant reduction (88%) in the percentage of free fatty acid in the surface lipids was seen in the clindamycin treated group and not in the vehicle treated group. There was no significant change in the surface microflora. Despite the short duration of treatment, objective clinical improvement was seen in three of nine treated patients, while none was observed in the placebo-treated patients.[25]

An open label, non comparative study was carried out to see the efficacy, safety and compliance of 500 mg. azithromycin thrice weekly for 12 weeks in acne vulgaries at the out patient clinics of Aga khan University Hospital, Pakistan.[10] After the baseline visit, patients were scheduled to return four weekly for 12 weeks, Efficacy was judged by the percentage clearance. The study was conducted in out patient department of Dermatology & Venereology, Comilla Medical College Hospital; Comilla. A total of 57 patients having acne vulgaris were included. Patients of 13-30 years of age group with moderate to severe acne taking no other drugs for acne treatment were included. Age below 13 years and above 30 years of either sex and who had received topical anti-acne drugs within 2 weeks and systemic anti-acne drugs within 2 months before the study were excluded. Pregnant and lactating mothers, women planned for pregnancy were excluded.

Procedure

Selection of case was done according to inclusion and exclusion criteria of the study and this was recorded. The diagnosis was made on clinical basis by assessing nature and number of the acne. To reach a clinical diagnosis, detailed history, thorough physical examination including comedone expression and identification of papules, pustule, nodule and cyst on the face, neck, trunk, or shoulder region was done.

Management of the sample respondent

All patients included in the study was managed in the following way:

Base line week 0	1st Follow up week 4	2nd Follow up week 8	3rd Follow up week12
a. Consent	a. Interview	a. Interview	a. Interview
b. Interview	b.Clinical examination	b.Clinical examination	b. Clinical examination
c. Clinical examination	c. Treatment	c. Treatment	
d. Laboratory investigation			
e. Treatment			

Baseline Visit (Week0)

a. Informed consent
b. Interview
c. Clinical examination
d. Laboratory investigation:

Blood sample-5 ml. of blood was drawn from antecubital vein with aseptic precaution and following investigation were done.

1. CBC, ESR.
2. Serum billirubin, SGPT, SGOT, S. Alkaline phosphatase.
3. Blood urea, Serum creatinine.

e. Treatment

Patients were randomly assigned to the following treatment regimens;

1. Tab/Cap. Azithromycin 500mg. orally (three times in a week for 12 weeks).
2. Topical clindamycin daily at night for 12 weeks.

Scoring of acne vulgaris

Acne lesions graded according to the severity index described by Michaelsson et al[35]. Five point scaled used; 0.5 for comedone, 1 for papule, 2 for pastules, 3 for ifiltrated lesions and 4 for cystic lesions. Multliplying each type of lesion with its severity index and adding them together calculate the total severity score of acne. Patients clinically assessed at 4 weeks interval. At all follow-up visits all parameters examined and graded. Both the total scores and number of each type of acne lesions compared to the baseline scores.

Statistical assessment

Efficacy and safety was evaluated at 4th, 8th and 12th week of study period. In addition to the required data on patients history and diagnosis, the efficacy of the drug was documented by type and site of lesions at baseline and at the end of treatment. The efficacy of the medications was expressed as improvement of the lesion. Safety of the medications were assessed by observing the side effects during follow up schedule. Intolerability was recorded are known side effects of abdominal pain, headache, burning sensation and erythema on facial skin. A final medical assessment of safety and efficacy was made at the end of treatment period using a five point scale (Categories: cleared, when 100% resolution occurred; excellent, when 75% or greater reduction observed; good, when 50%- 74% reduction observed; poor, when <50% reduction observed and worse, if exacerbation of disease occurred) and the assessment result was recorded and analyzed to prepare the final result.

Statistical analysis

Standard deviation and confidence interval were used for the measure of dispersion. Paired T test was applied to asses the differences for statistical significance.

Socio-Demographic Data

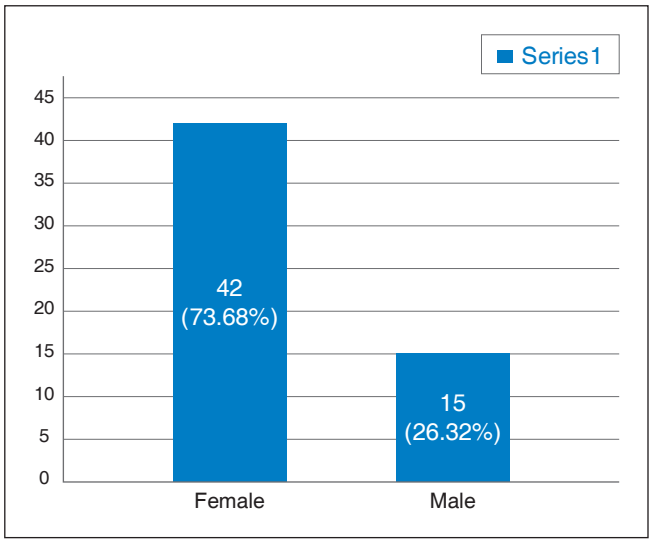
Table-2.3.1: Shows the age group of study population (N=57).

Age Group	Total N (%)	Mean ±SD (Range)
11 – 15 years	11 (19.30)	18.56±3.35 years (13-30 years)
16 – 20 years	36 (63.16)	
21 – 25 years	5 (8.77)	
26 -30 years	5 (8.77)	
Total	57 (100.0)	

Age distribution of patients with acne vulgaris are presented in Table-2.3.1. The youngest patient age was of 13 years while the oldest one aged 30 years. The average age was 18.56±3.35 years and most of the patients were belonged to<_ 20 years age groups (82.46%).

Sex

Figure-2.3.1. Shows sex distribution (N=57).



Sex distribution of patients with acne illustrated in figure-2.3.1. Among the study population 42(73.68%) were female and 15(26.32%) were male.

Clinical Data

Age at Onset of Acne Vulgaris

Table-2.3.2: Shows duration of symptoms (N=57)

Age Group	Total N (%)	Mean ±SD (Range)
<15 years	29 (50.88)	16.35±2.94 years (11-21 years)
16-20 years	23 (40.35)	
21-25 years	5 (8.77)	
Total	57 (100.0)	

Distribution of patient by age at the onset of acne vulgaris are presented in Table-2.3.2. The lowest age was of 11 years while the highest age was 21 years. The average age was 16.35±2.94 years when most of the patients experienced acne vulgaris.

Site of Involvement

Table -2.3.3 Shows site of involvement (N=57)

Site of Acne Involvement	Yes		No		Total	
	N	(%)	N	(%)	N	(%)
Cheek	57	100.0	0	0.0	57	100.0
Chin	52	91.23	5	8.77	57	100.0
Forehead	51	89.47	6	10.53	57	100.0
Nose	29	50.88	28	49.12	57	100.0
Back of the neek	3	5.26	54	94.74	57	100.0
Shoulder	8	14.04	49	85.96	57	100.0
Chest	5	8.77	52	91.23	57	100.0
Upper back	14	24.56	43	75.44	57	100.0

Facial distribution of acne was present in 57 patients. In addition to this 5 patients had acne on their chest, 8 patients had on their shoulder and 14 patients had acne on their upper back.

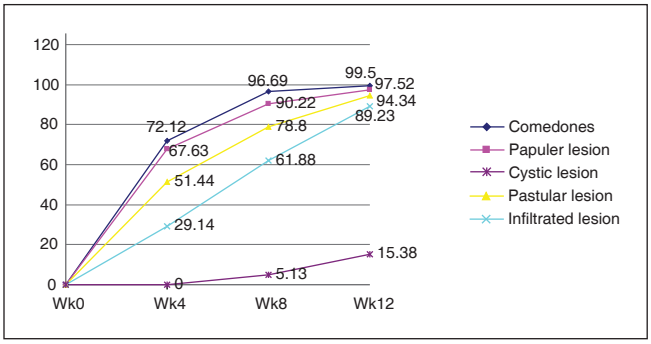
Assesssment
Reduction in the number of acne.

Table- 2.3.4. Reduction in the number of different type of acne lesion in response to study regimens.

Site of Acne Involvement	Number of lesion Mean±SD			
	Week 0	Week 4	Week 8	Week12
Comedones	24.35±22.75	6.79±5.75	0.81±1.55	0.12±0.57
Papular lesion	52.42±14.04	16.96±5.42	5.12±5.50	1.30±1.67
Pastular lesion	34.11±13.67	16.56±6.23	7.23±5.83	1.93±2.17
Infiltrated lesion	11.74±16.32	8.32±11.40	4.47±6.54	1.26±1.88
Cystic lesion	2.74±6.10	2.74±6.10	2.60±5.68	2.52±5.48

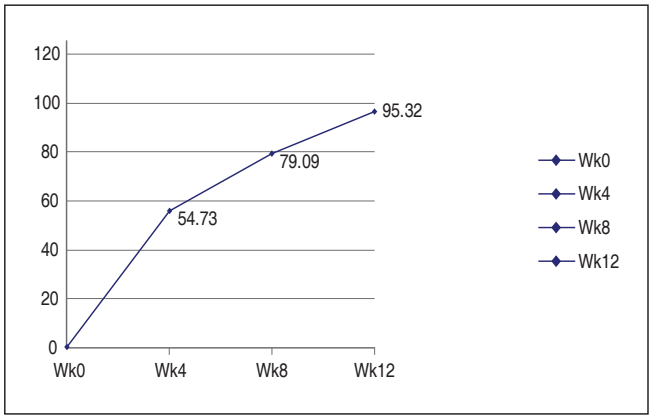
At the end of first four weeks there was significant reduction in uhe number of comedones (95% CI of the difference = 12.65-22.47, p=0.000) and these reduction remained significant throughout the treatment period(week8: 95% CI of the difference =17.73-29.36,p=0.000) and week12: 95% CI of the difference = 18.25-30.20, p=0.000). Similarly papular acne significantly reduced in number throughout the treatment period (week4: 95% CI of the difference = 31.61-39.30, p=0.000, week8: 95% CI of the difference = 43.23-51.37,p=0.000 and week12: 95% CI of the difference = 47.29-54.96, p=0.000). Treatment remain also reduced the number of pastuler acne in same fashion(week4: 95% CI of the difference = 14.73-20.35, p=0.000, week8: 95% CI of the difference = 23.70-30.05, p=0.000 and week12: 95% CI of the difference = 28.59-35.77, p=0.000). In case of infiltrated lesion the reduction was gradul but significant in all follow-ups (week4: 95% CI of the difference = 1.22-5.62,p=0.003, week8: 95% CI of the difference = 4.15-10.38, p=0.000 and week12: 95% CI of the difference = 6.49-14.45,p=0.000), but cystic lesion showed no improvement through out the treatment period (week4: p=1.000, week8: p=0.159 and week12: p=0.083)

Percent reduction in the number of acne
Figure. 2.3.4: Precent reduction in the number of different type acne lesion in response to study regimen.



Percent reduction in the number of acne lesion showed highly significant improvement in case of comedones, papular and pastular lesion throughout the treatment period.
Infiltrated lesion also showed significant response to the treatment regimen but cystic lesion showed no significant improvement

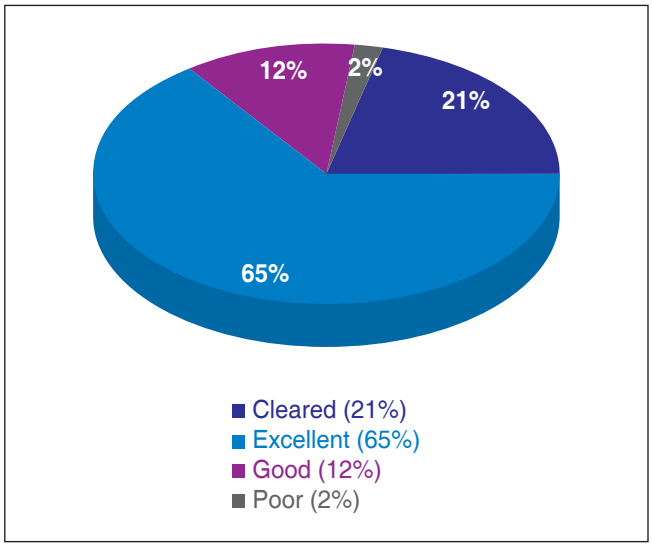
Michaelsson Acne Severity Index
[Figure-2.3.5. Changes in the Michaelsson Acne Severity Index and its precent reduction during treatment]



Percent reduction of ASI

Precent reduction of michaelsson Acne Severity Index in response to stydy regimens is illustrated in figure-2.3.5. The study regimens showed highly significant percent reduction of Michaelesson Acne Severity Index throughout the treatment period.

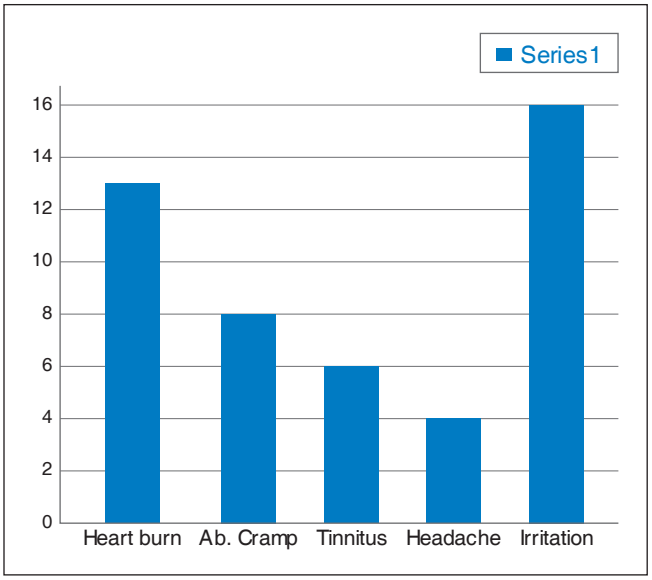
Overall Assessment
Figure-2.3.6. Overall evaluation of Acne Vulgaris at the end of 12 weeks treatment with study regimens.



Presented in fig-2.3.6. Investigator's evaluation carried on 57 patients who have completed the study with compliance. Among them Acne lesion cleared in 21.0% cases, excellent improvement observed in 65% cases and 12% showed good and 2% showed poor response.

Adverse Effects

Figure - 2.3.7. Adverse effect of study regimens observed during treatment period.



Adverse effects of two drug regimens observed during treatment period illustrated in Figure-2.3.8. of 57 patients 13 (22.81%) complained of heart burn during treatment period, 8(14.04%) patients reported abdominal cramp, 6(10.53%) patients reported tinnitus and 4(7.02%) reported headache. 16(28.07%) patients complained of mild burning sensation (irritation) and erythema on facial skin.

Discussion

The main objective of this study was to evaluate the safety and efficacy of oral azithromycin and topical clindamycin in the treatment of acne vulgaris. This study was conducted among the patients who sought health care for acne vulgaris in the Dermatology and Venereology Out-patient Department, Comilla Medical College Hospital, Comilla from Nov.2011- May2012. Fifty seven patients were enrolled in this study who were treated with oral azithromycin three times in a week for twelve weeks and daily topical clindamycin in the treatment of acne vulgaris.

Topical retinoides have been a mainstay of acne therapy for approximately a quarter of century. Their clinical effectiveness in treating comedones and micro-inflammatory acne remains unequalled by other topical agents. In the treatment of acne they have the typical irritation that limits their use. Systemic antibiotic most commonly used are tetracycline, erythromycin and doxycycline. They often require frequent or long-term administration. Therefore, they failed to gain acceptance. In many Western journal, the efficacy and safety of azithromycin in the treatment of acne have been reviewed and articles on clinical trials published.[35,9,10] Topical clindamycin promotes comedonal drainage, clear current inflammatory and non-inflammatory lesions and prevents formation of new acne lesion. On the other hand oral azithromycin causes suppression of P.acnes[23] thus reduces the production of free fatty acids and other irritant enzyme produces by the bacteria. Further it also shows anti-inflammatory activity by impending neutrophil chemotaxis. So, concomitant use of these two drugs might have synergistic effect in the management of acne vulgaris. As they have two different route of administration and there is no possibility of drug interaction, suggest that the use of oral azithromycin and topical clindamycin at the same time may improve the cure rate of acne vulgaris. The mean age of the respondents was 18.56±3.35 years with a range of 13 to 30 years. This finding was supported by Saple DG et al, Odom RB et al and Sharquie KE et al.[31,32,33] In this study the number of female patients were 42 (73.68%) and male patients were 15 (26.32%). From this study it was observed that females are predominant. This result was largely accord with Singhi MK et al[35] and Fernandez et al[9] but differ from Federico BMD et al.[33] Most of the patient were students (71.93) and belongs to upper middle socioeconomic class (43.86%). The mean age of first acne onset was observed at 16.35 years (SD±2.94).

Acne lesions most commonly develop in areas with the greatest concentration of sebaceous glands, which include the face, neck, chest, upper arm and back[26]. Facial distribution of acne was present in 57 patients. In addition to this 5 patients (8.77%) had acne on their chest, 8 patients (14.03%) had on their shoulder and 14 patients (26.58%) had acne on their upper back. While the types of Acne lesions were analysed, at the base line visit (week 0) the (Mean±SD) of comedones was 24.35±22.75, papular lesion was 52.42±14.04, pustular lesion was 34.11±13.67, infiltrated lesion was 11.74±16.32, cystic lesion was 2.74±6.10. At the 1st follow up (week 4) the (Mean±SD) of comedones was 6.79±5.75, papular lesion was 16.96±5.42, pustular lesion was 16.56±6.23, infiltrated lesion was 8.32±11.40, cystic lesion was 2.74±6.10. At the 3rd follow up (week 12) the (Mean±SD)of comedones was 0.12±0.57, papular lesion was 1.30±1.67, pustular lesion was 1.93±2.17, infiltrated lesion was 1.26±1.88, cystic lesion was 2.52±5.48. In my study, the treatment regimens showed highly significant improvement from the first follow- up visit. At the end of 12 weeks treatment 93% was improvement observed in term of percent reduction of Michaelsson Acne Severity Index. These findings were superior to those observed in different studies by using azithromycin[9,10,23] and clindamycin in different settinings.[7,15,25]

Nearly 90% of comedones and papular lesion and more than half of the pustular and infiltrated lesion healed after 8 weeks. At the end of 12 weeks nearly all of the comedones, papules and pustular lesion were cleared, but only few infiltrated lesion persist. On the other hand, the number of cystic lesion remained almost unchanged. Therefore the study regimen failed to show any efficacy against cystic type of acne, which are usually recalcitrant to topical and oral anti-acne drugs. Percent reduction of Michaelsson Acne Severity Index was 54.73% after 4 weeks of treatment, 79.09% after 8 weeks and 95.32% after 12 weeks of treatment, which was statically highly significant.[28,29,35] After 12 weeks among 57 patients acne lesion cleared in 21% cases, excellent improvement observed in 65% cases and 12% showed good response and 2% patients showed poor response.

Adverse effects i.e. 13(22.81%) complained of heart burn during treatment period, 8(14.04%) patients reported

abdominal cramp, 6(10.53%) patients reported tinnitus and 4(7.02%) reported headache due to Azithromycin intake and 16(28.07%) patients complained of mild burning sensation (irritation) and erythema on facial skin after topical use of Clindamycin.

These findings were largely differing from Buck ML et al(2005)30 where they mentioned abdominal cramp as a side effect only for 1-4%, heart burn 6.8%, headache 2.3% and nausea for 0.5-2%.

During my study period, none of these reaction were severe and most occurred within the first week of initiation of therapy and was observed to resolve with continued use of the drugs adding Ranitidine and anti-spasmodic in some patient. As the adverse effects of the drugs used in our setting was a bit higher than others, so there may remain different aspect of consideration.

Conclusion

This study revealed that combination regimen of azithromycin and topical clindamycin is efficacious and safe in the management of acne vulgaris. Study with larger group of patients for longer period may result in superior out comes and assess the relapse rate in clinical practice through improved compliance.

References

01. *Wolf K, Goldsmith, LA, Katz SL, Gilchrest BA, Paller AS, Leffel DJ, Fitz Patricks Dermatology in General Medicine, 7th Edn, USA. The Megraw Hill: 2008, P 687-703.*
02. *JAMES WD, Bergre TC, Elston, DM Andrew's Diseases of the Skin clinical determotology , 10th edn, Philadelphia, W.B. Saunders, Company 2006, P 231-250.*
03. *James WD(April 2005). "Clinical Practice Acne ." N Engl J Med 352(14):1463-72.*
04. *Webster GF The pathophysiology of acne. Cutis. 2005; 76 (2suppl):4-7*
05. *TAN JK: Phychosocial impact of acne Vulgaris, evaluating the evidence, Skin therapy Lett. 2004. Aug-Sep; 9 (7): 1-3, 9.*
06. *Riddle CC, Amin K, Schweiger ES, A Review of Azithromycin for the Treatment of Acne Vulgaris Cosmetic Dermatology, 2007; 20(5); 299-302*
07. *Khanna VN. Topical clindamycin hydrochloride 1% in acne vulgaris. Indian J. Dermatol Venereol Leprol 1990;56:377-80.*
08. *Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report form a global alliance to improve outcomes in acne. J Am Acad Dermatol 2003,49(Suppl 1): S1-37.*
09. *Adolfo C, Fernandez- obergon. Azithromycin for the treatment of acne. Int. J. Dermatol 2000; 39 (1):45*
10. *Kapadia, N. Talib A. Acne treated successfully with azithromycin Int. J. Dermatol 2004: 43 (10): 766-767.*
11. *Kus S, Yucelten D, Aytug A. Comparison of efficacy of azithromycin vs. doxycycline in the treatment of acne vulgaris. Clin EXP Dermatol 2005 May; 30(3):215-20.*
12. *Duran JM, Amsden GW. Azithromycin: indications for the future? ExpertOpinPharmacother.2000Ma;1(3):489-505.*
13. *Caputo R, Barbareschi M, Veraldi S. Azithromycin: a new drug for systemic treatment of inflammatory acneic lesions. G Ital Dermatol Venerol.2003;138:327-331.*
14. *Fernandez-Obregon AC. Azithromycin for the treatment of acne. Int J Dermatol. 2000 jan; 39(1):45-50.*
15. *NilFroushzadeh MA, Siadat AH, Baradaran EH, Moradi S. Cindamycin lotion alone versus combination lotion of clindamycin phosphate plus tretinoin versus combination lotion of clindamycin phosphate plus salicyclic acid in the topical treatment of mild to moderate acne vulgaris: a randomized control trial. Indian J. Dermatol Venereol Leprol 2009 May-Jun;75(3):279-82.*
16. *Acne. The American Heritage Dictionaries' Answers, com.2006 Available from. http://www.answers.com/*
17. *Zaenglein AL, Graber EM, Thiboutot and Strauss JS. Acne. In: Klaus Wolf, Lowell A. Goldsmith, Stephen I. Katz, Barbara A. Giilchrest, Amy s. Paller, David J, editors. Fitzpatrick's Dermatology in General Medicine. 7th Ed: New York, USA The McGraw-Hill Companies, 2008: 690-703.*
18. *Cunliffe WJ, Holland DB, Clark SM, et al. Comedogenesis: some new aetiological, clinical, and therapeutic strategies. Dermatology. 2003;206:11-16.*
19. *Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report form a global alliance to improve outcomes in acne. J Am Acad Dermatol 2003,49(Suppl 1): S1-37.*
20. *Tan AW, Tan HH. Acne vulgaris: a review of antibiotic therapy. Expert Opin Pharmacother. 2005 Mar; 6(3): 409-18.*
21. *Scheinfeld NS, Tutrone WD, Torres O, Weinberg JM. Macrolides in dermatology. Clin Derm 2003; 21:40-9.*
22. *Julie C Harper C Acne Vulgaris: medicine. 2009-08-06. Retrieved 2009-12-21*
23. *Gurber F, Gribisic-Greblo H, Kastelen M, et al. Azithromycin compared with minocycline in the treatment of acne comedonica and papulo-pustulosa. J Chemother 1998:10:269-273.*
24. *Feldman S, Careccia RE, Barham KL, Hancox J, Diagnosis and Treatment of Acne. Am Fam Physician 2004;69(9):2135-6*
25. *Thomsen RJ, Stranieri A, Knutson D, Strauss JS. Topical clindamycin treatment of acne. Clinical, surface lipid composition, and quantitative surface microbiology response. Archives of Dermatology 1980;116(9):1031-1034*
26. *Merck Manual the Online Medical Library, sec: Dermatologic Disorders, Sub: Acne and Related Disorders. www.merck.com/mmpe/sec10/ch111/ch111b.html*
27. *Md Abdul Wahab, M. Hasibur Rahman, Nasrin sultana Monamie. Isotretinoin versus weekly pulse dose azithromycin in the treatment of acne- a comparative study. Department of Dermatology and VD, Bangabandu Sheikh Mujib Medical University and Combined Military Hospital, Dhaka,Bangladesh 2004-2007.*
28. *Le Federico B MD, Francesco Savoia MD, Gianluca P MD. Azithromycin: A new therapeutical strategy for acne in adolescents. Dermatology Online Journal 13(4):4.*
29. *Skidmore R, Kovach R, Walker C, Thomas J, Bradshaw M, Leyden J et al. Effects of subantimicrobial-dose Doxycycline in the treatment of Moderate Acne. Arch Dermatol 2003 Apr: 123:459-464.*
30. *Buck ML. Pediatric therapy update: Azithromycin. Pediatric pharmacotherapy 2005 Apr; 11(4)*
31. *Odom RB, James WD, Berger TG. (editor) Andrews' diseases of the Skin. Clinical Dermatology, 9th ed. W. B. Saunders Company, Philadelphia; 2000. pp. 284-306*
32. *Saple DG. Torsekar RG , Pawanarkar V. An open study to evaluate the efficacy and safety of tazarotene gel(0.1%) in acne vulgaris. Indian J. Dermatol Venereol Leprol 2004; 70:92-5*
33. *Sharquie KE. Noaimi AA. Mijtab ZM (2012) Chronic Scalp Folliculitis Versus Acne Vulgaris(Observational Case Series Study. J Clin EXP Dermatol Res 3:153*
34. *Federico B MD, Francesco Savoia MD, Gianluca P MD. Azithromycin: A new therapeutical strategy for acne in adolescents. Dermatology Online Journal 13(4):4.*
35. *Singhi MK, Ghiya BC, Dhabhai RK. Comparison of Oral azithromycin with daily doxycyclin in the treatment of acne vulgaris. Indian J. Dermatol Venereol Leprol 2003; 69; 274-276.*

Review Article

Favipiravir: A New and Emerging Antiviral Option in COVID-19

Islam G M R [1], Mahbuba M S [2], Faruquee M H [3], Showkat T [4]
Mozumdar S H [5], Das B K [6], Zaman M [7]

ABSTRACT

A recent outbreak of coronavirus disease 2019 (COVID-19) caused by the novel coronavirus designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started in Wuhan, China, at the end of 2019. On March 11, 2020, WHO declared COVID-19 a global pandemic. As of 01, December, 2020, at least 6,35,89,977 cases and 14,73,927 deaths had been identified across the world. In Bangladesh, 4,64932 cases and 6,644 deaths had been identified. About 16%–21% of people with the virus in China became severely ill, with a 2%–3% mortality rate. The mortality rate has greatly increased in Italy, France, Brazil, India, Spain and USA. However, there is no specific treatment against this new virus. Therefore, it is urgently necessary to identify effective antiviral agents to combat the disease and explore the clinical effect of antiviral drugs. No drugs or biologics have been proven to be effective for the prevention or treatment of COVID-19. Numerous antiviral agents, immunotherapies, and vaccines are being investigated for development of potential therapies. One of the drugs which has recently draw much attention, especially in Bangladesh, is an anti-viral drug originally designed for influenza, called favipiravir. The drug, which works by preventing certain viruses from replicating, seemed to shorten the duration of the virus clearance as well as improve lung conditions (as seen in X-rays) in tested patients.

In this article, we have tried to provide a comprehensive, evidence-based review of this drug in the context of the present pandemic in the management of COVID-19.

Key words: Favipiravir, Covid-19

1. * Dr. G. M. Raihanul Islam, MBBS, MPH
Vice President, Head of Medical Services Department
Beacon Pharmaceuticals Limited
E-mail: dr.raihan@beaconpharma.com.bd
Mobile: 01985-550111

2. Dr. Most. Sultana Mahbuba, MBBS, DCH
Medical Officer, Rajshahi Medical College & Hospital

3. Dr. M.H Faruquee, MBBS, MPH
Associate Professor and Head
Department of Occupational and Environmental Health
Bangladesh University of Health Science

4. Dr. Tamoshi Showkat MBBS, MPH
Executive, Medical Services Department
Beacon Pharmaceuticals Limited

5. Dr.Shafaet Hossain Mozumdar, MBBS, MPH
Executive, Medical Services Department
Beacon Pharmaceuticals Limited

6. Dr. Badhan Kumar Das, MBBS
Executive, Medical Services Department
Beacon Pharmaceuticals Limited

7. Dr. Moniruzzaman, MBBS
Executive, Medical Services Department
Beacon Pharmaceuticals Limited

Introduction

One year and more than 63 million confirmed cases later, the COVID-19 pandemic has become the worst public-health crisis of the century. At this moment, in the absence of effective antiviral drugs for COVID-19, healthcare providers treat the clinical symptoms (e.g. fever, breathing difficulty) of patients with supportive care such as fluid management, oxygen therapy, etc. can be highly effective for patients with severe symptoms. Discovery of a new and specific antiviral agent against the SARS-CoV-2 would be the real challenges.

Favipiravir, initially was marketed as an anti-influenza agent in Japan. Favipiravir was first used against Covid-19 in Wuhan, China. Then, as the pandemic spread to Europe, this drug received approval for emergency use in Italy, and currently has been in use in Japan, Russia, Ukraine, Uzbekistan, Moldova, and Kazakhstan. Approval has also recently been granted in Saudi Arabia and the UAE. Thereafter, Turkey, Bangladesh, and most recently Egypt have also seen recent commercial launches. In June 2020, favipiravir received the DCGI (Drug Controller General of India) approval in India for mild and moderate COVID-19 infections. As of the 23rd of July, 2020; there are 32 studies registered on clinical trials.gov to assess the utility of this drug in the management of COVID-19 (3 completed, 12 recruiting)[1]

Pharmacology

Favipiravir (T-705) is a synthetic prodrug, first discovered while assessing the antiviral activity of chemical agents active against the influenza virus in the chemical library of Toyoma chemicals. A lead compound, A/PR/8/34, later designated as T-1105, and its derivatives were found to have antiviral activities. Favipiravir is derived by chemical modification of the pyrazine moiety of T-1105 (Fig. 1).[2] It has been approved in Japan for the management of emerging pandemic influenza infections in 2014.

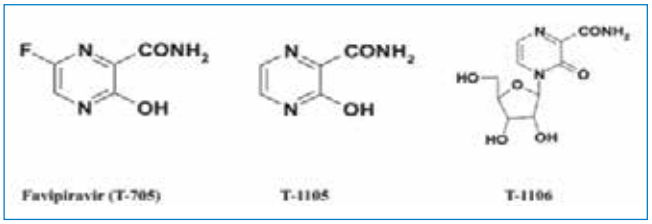


Fig. 1. Chemical structure of favipiravir.[2]

Pharmacokinetics and pharmacodynamics

Favipiravir is administered as a prodrug. It has an excellent bioavailability (~94%), 54% protein binding, and a low volume of distribution (10–20 L). It reaches Cmax within 2 h after a single dose. Both Tmax and half-life increase after multiple doses. Favipiravir has a short half-life (2.5–5 h) leading to rapid renal elimination in the hydroxylated form. Elimination is mediated by aldehyde oxidase and marginally by xanthine oxidase. Favipiravir exhibits both, dose-dependent and time-dependent pharmacokinetics. It is not metabolized by the cytochrome P450 system, but inhibits one of its components (CYP2C8). Thus, it needs to be used with caution when coadministered with drugs metabolized by the CYP2C8 system.[3,4]

Mechanism of action

Within the tissue, the molecule undergoes phosphoribosylation to favipiravir-RTP, which is the active form of this drug. It exerts its antiviral effect through the following mechanisms:

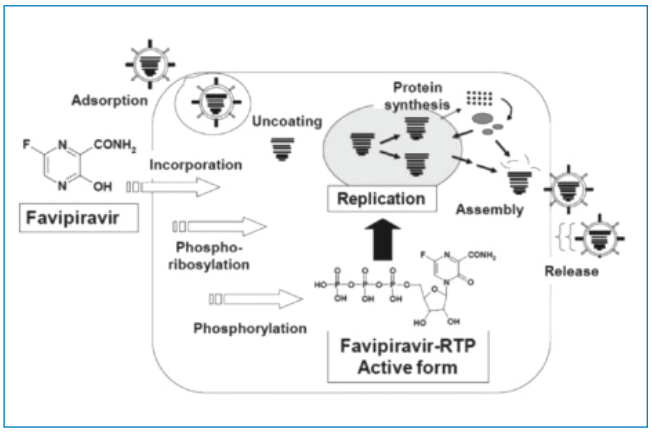


Fig. 2. Mechanism of action of favipiravir.[2]

a. This molecule acts as a substrate for the RNA-dependent RNA-polymerase (RdRp) enzyme, which is mistaken by the enzyme as a purine nucleotide,2 thus inhibiting its activity leading to termination of viral protein synthesis (Fig. 2).

b. It gets incorporated in the viral RNA strand, preventing further extension.[5] This mechanism of action, along with preservation of the catalytic domain of the RdRp enzyme across various RNA viruses, explains the broad spectrum of activity of this drug.

c. It has recently been shown that favipiravir induces lethal mutagenesis in vitro during influenza virus infection, making it a virucidal drug.[6] Whether a similar activity is demonstrated against SARS-CoV-2 or not is uncertain.

Spectrum of antiviral activity

A. **Influenza:** Favipiravir inhibits 53 types of influenza viruses including seasonal strains A (H1N1), A (H3N2), and influenza B; the A (H1N1)pdm09 pandemic virus; highly pathogenic avian influenza virus A (H5N1) isolated from humans; A (H1N1) and A (H1N2) isolated from swine; and A (H2N2), A (H4N2), and A (H7N2). It is also active against drug-resistant strains of the virus, including M2 and NA inhibitors.[7]

B. **Ebola:** During the Ebola virus outbreak in 2014, favipiravir was one of the drugs short-listed for trials by the WHO. Although in vitro studies[8,9] showed encouraging results for this drug, with a trend toward survival benefit showed by clinical studies,[10,11] conclusive evidence of benefit was never found. In the JIKI multicenter trial[10] conducted in 126 patients with Ebola, favipiravir in an initial loading dose of 6000 mg followed by 2400 mg/day for 9 days was shown to have some effect in patients with medium to high viremia but not in those with more severe viremia (Ct value < 20). This large dose seemed to have been well tolerated as well. A subsequent retrospective study also found favipiravir-treated patients had a trend toward improved survival times against Ebola virus, although this effect was not statistically significant.[11]

C. **Activity against other pathogenic RNA viruses:** In addition to its activity against influenza and Ebola viruses, favipiravir has been found to have therapeutic efficacy in cell culture and mouse models of arenavirus, bunyavirus, filovirus, West Nile virus, yellow fever virus, foot-and-mouth-disease virus, and Lassa virus including agents causing viral hemorrhagic fevers and encephalitis.

Role in SARS-CoV-2

Shannon et al.[12] found that the SARS-CoV-2–RDRp complex is at least 10-fold more active than any other viral RdRp known. Favipiravir acts by inhibiting this viral RdRp enzyme, allowing facile insertion of favipiravir into viral RNA while sparing human DNA. They concluded that nucleoside analogs (such as favipiravir) are promising candidates for the treatment of COVID-19. The optimal dose of favipiravir is difficult to establish from the limited preclinical, in vitro data. For instance, the higher dosing of favipiravir used in Ebola

was based on preclinical studies showing the target concentrations needed to inhibit the Ebola virus (EC50: 67 mM)8 were higher than that in influenza (EC50: 0.48 mM).[13] Despite these high doses, the predicted target concentrations could not be achieved when PK studies were performed on 66 patients in the JIKI trial.[14] Wang et al.[15] found that the high concentrations of favipiravir (EC50: 61.88uM) were needed to inhibit SARS-CoV-2 infection in Vero cells. Thus, it is difficult to ascertain the basis on which the current dose of this drug has been established in SARS-CoV-2. Despite this uncertainty, the dose in clinical use in most countries, including India, is 1800 mg bid on day 1, followed by 800 mg bid on days 2–14.

Clinical trials in COVID-19

Over the past few months, clinical studies have been performed all over the world to assess the efficacy of favipiravir in the management of COVID-19. The major clinical studies are summarized here.

China

An open-labeled nonrandomized study[17] from China compared the effect of favipiravir (day 1: 1600 mg twice daily; days 2–14: 600 mg twice daily) vs lopinavir/ritonavir (day 1–14: 400/100 twice daily) in the treatment of COVID 19. Both groups received interferon-alpha (5 million units twice daily) by nasal inhalation. Those aged 16–74 years, positive for SARS-CoV-2, symptom onset within the past 7 days and mild-moderate disease were recruited. From 30 January to 14 February, 56 patients with laboratory-confirmed COVID 19 were screened, of which 35 patients met eligibility for favipiravir. From 24th January to 30th January, 91 laboratory-confirmed COVID-19 patients who were already on lopinavir/ritonavir treatment were screened for eligibility, of which 45 were eligible for control arm. Baseline characteristics of both arms did not show statistically significant differences. Compared with the lopinavir/ritonavir arm, however, patients in the favipiravir arm showed a statistically significant shorter median length of time to viral clearance (4 days vs 11 days, $p < 0.001$), improvement in chest CT findings at day 14 after randomization (91.4% vs 62.2%, $P = 0.004$) and lower incidence of adverse effects (11.43% Vs 55.56% P value < 0.001). Multivariate analysis showed that favipiravir was independently associated with faster viral clearance and chest CT scan improvement. With the limitations of nonrandomized study and the lack of blinding, a potential selection bias may have confounded the results.

Japan

A Japanese observational study group recorded the details of hospitalized COVID-19 patients in Japan to assess the safety and efficacy of favipiravir.[18] From February to May 2020, a total of 2158 cases were registered from 407 hospitals. In more than 90 percent of cases, favipiravir was administered at a dose of 1800 mg orally on day 1 followed by 800 mg twice daily on subsequent days. The median duration of therapy was 11 days. Rates of clinical improvement at 7 and 14 days were 73.8% and 87.8%, 66.6% and 84.5%, and 40.1% and 60.3% for mild, moderate, and severe disease, respectively. Thus, vast majority of patients with mild and moderate disease recovered from the illness, whereas in those with severe disease, the results were not encouraging. The mortality rates at the time of survey were 5.1%, 12.7%, and 31.7% for mild, moderate, and severe disease, respectively. It is to be stressed that this study had no control arm which precludes direct comparison of the clinical course with those who did not receive the agent.

Favipiravir in combination with nafomostat (transmembrane protease serine 2 inhibitor, previously used successfully in MERS-CoV-2 infection, acute pancreatitis and DIC) was found to be useful in a small case series consisting of 11 serious patients with COVID-19 in Japan. The median age, time from symptom onset to admission in the ICU, and PaO2/FiO2 ratio on admission were 68 years (IQR 60–69), 8 days (IQR 7–11), and 131 (IQR 114–198) respectively. All patients needed oxygen therapy, eight patients (73%) needed invasive mechanical ventilation, and 3 patients (27%) needed extracorporeal membrane oxygenation (ECMO). Of the 11 patients, 7 were successfully weaned from mechanical ventilation, 1 patient with DNR order died. Nine and 7 patients were discharged from the ICU and the hospital, respectively. One patient had been weaned of ventilation was still in the hospital at the time the paper was published. A prospective clinical trial (jRCTs031200026) with this combination is expected to be initiated in Japan soon.[19]

Bangladesh

The Study on safety and efficacy of Favipiravir (Favipira) for COVID-19 patient in selected hospitals of Bangladesh is a double-blind, placebo-controlled Randomized control study. The study was conducted by Bangladesh Society of Medicine. Study starting period from May, 2020 to June, 2020, 50 COVID 19 positive (by RT- PCR) patients were randomly selected based on the inclusion criteria.

There were no significant differences between Groups A (Favipiravir) and Group B (Placebo) regarding demographic characteristics. We observed significant levels of viral clearance at Day-4 (48.0%), Day-7 (76.0%) and Day-10 (96.0%) in Group A(Favipiravir) patients. But viral clearance was significantly lower at Day-4 (00.0%), Day-7 (36.0%) and Day-10 (52.0%) in Group B (Placebo) patients. P values- at Day-4: 0.001; at Day-7: 0.005; at Day-10: 0.001).

Regarding laboratory test result including WBC Count, Neutrophil Count, Lymphocyte Count, ALT, AST, Serum Uric Acid, CRP, RBS after 10 days treatment had also observed. There was no major difference observed in both groups. The differences were not statistically significant (P>0.05).

In addition, Chest X ray findings after 10 days treatment was observed. Lung condition improvement in Groups A (Favipiravir) 65.3% patients and only 34.7% in Group B (Placebo) patients. (P<0.05). No major adverse effects observed in both groups. The differences were not statistically significant (P>0.05). There were no major

observable differences in adverse events between Group A and Group B patients.

Beacon Pharmaceuticals Limited, Bangladesh assisted the research by making the Favipira (Favipiravir) free of cost for the study.

ONGOING TRIALS

Russia

A phase 3 Russian trial COVIDFPR 01 (ClinicalTrials.gov Identifier: NCT04434248) is ongoing and includes 330 patients from 30 medical centers across 9 Russian regions. Phase 1 of the trial ended within 10 days, after recruiting 60 patients with coronavirus infection with moderate illness. They were randomized in a 1:1:1 ratio of high-dose favipiravir (1800 mg twice daily on day 1 followed by 800 mg twice daily for next 13 days) vs low-dose favipiravir (1600 mg twice daily on day 1 followed by 600 mg twice daily for next 13 days) vs standard of care (SOC). Favipiravir was quite safe with no demonstrable side effects. Fever returned back to normal in 68% of patients on favipiravir within 3 days as compared with 6 days in the control group. After first 4 days of treatment, 65% of the 40 patients who took favipiravir tested negative for the virus, twice as many compared with the standard therapy group. At the end of day 10, 35 of 40 (87.5%) patients tested negative for the virus. In the pivotal phase of the trial, the dose of favipiravir was selected based on results from the pilot study and compared with the SOC as previously mentioned. The study aims to look upon the rate of viral elimination by day 10, time to viral elimination in a time frame of 28 days, and time to clinical improvement.[20]

Saudi Arabia

An ongoing open-labeled randomized controlled trial from Saudi Arabia is evaluating the efficacy of favipiravir and hydroxychloroquine combination therapy Identifier: NCT04392973] in the management of moderate to severe COVID-19. The experimental arm consists of favipiravir (dose: 1800 mg twice daily on day 1 followed by 800 mg twice daily for a total period of 10 days or till hospital discharge) plus hydroxychloroquine (400 mg twice daily on day 1 followed by 200 mg twice daily for next 4 days). The control arm includes the SOC treatment in COVID 19. The primary endpoint of the trial is time to clinical improvement and time to a negative PCR test.[21] Results of this trial are eagerly awaited.

The USA

The research team at Stanford Medicine have recently commenced a double-blind, placebo-controlled trial (favipiravir vs placebo for 10 days) to assess the utility of favipiravir in reducing symptoms and the duration of viral shedding in outpatients with COVID-19.About 120 patients are expected to be enrolled beginning July 6, 2020.[22]

Indian trial

A randomized, multicenter, open-labeled clinical trial in Indian patients has just been completed, with results expected to be published soon. This trial evaluated the efficacy and safety of favipiravir in patients hospitalized with mild to moderate COVID-19 infection. Conducted in hospitals across India, 150 patients were randomized, with 72 to the favipiravir arm and 75 to the SOC arm. Those in the favipiravir arm received 3600 mg on day 1, then 1600 mg on days 2–14. Daily nasopharyngeal swabs were collected from all participants till two consecutive swabs were negative. The primary endpoint was time to cessation of shedding of SARS-CoV-2 as determined by two consecutive negative swabs. Other secondary endpoints analyzed in this study were clinical cure rates as determined by the treating physician with recovery of fever, respiratory rate, oxygen saturation, and cough relief. The trial also looked at other secondary endpoints such as time from randomization to initial requirement of high flow supplemental oxygen or ventilatory support and time from randomization to hospital discharge. Final data are being analyzed and under review but we can reveal23 that there was 28.7% faster viral clearance in the favipiravir-treated patients compared with those who received SOC (5 versus 7 days) with 2/3rd of favipiravir-treated patients achieving viral clearance in week 1. Treating clinicians judged 70% of patients in the favipiravir limb to be clinically cured by day 4 versus 44% in the SOC arm. These initial results were indeed promising but need to be confirmed in larger studies.

Side effects/adverse effects

The Japanese study[18] discussed previously found that adverse reactions were seen in around 20% of the patients who received favipiravir (at a dose lower than approved for COVID-19). The adverse effects were relatively minor and included hyperuricemia and diarrhea in 5% of the participants and reduced neutrophil count and transaminitis in 2% of the participants. One study showed occurrence of psychiatric symptoms in association with favipiravir. Effect of favipiravir in QTc prolongation is still uncertain, with some pharmacodynamic studies suggesting a positive association,[24] but a Japanese study suggesting otherwise.[25] Overall, favipiravir has a good safety profile, as was confirmed by a large systematic review.[26] In the following sections, we give a brief overview of the adverse effect profile of this drug:

Hyperuricemia

Favipiravir use results in a dose-dependent increasing trend in the prevalence of hyperuricemia.[24] A systematic review conducted by Pilkington et al. found similar trends across multiple studies.[26] This is however not associated with clinical manifestations. There has been no evidence that hyperuricemia caused by favipiravir leads to clinical manifestations; however, longer follow-up periods would be required to fully assess this risk.

Teratogenicity

There is evidence that favipiravir has a teratogenic potential and embryotoxicity. The Japanese drug safety bureau approval advises that favipiravir be given a strong warning against use in women of reproductive age and recommends precautionary statements on packaging and prescription alerts. The bureau also recommends that favipiravir should be avoided where alternative drugs could be used.[24] Effective contraceptive methods during and for 7 days after the end of treatment need to be instructed to men who have received this treatment. Before favipiravir is prescribed to women of child-bearing age, it is imperative to rule out pregnancy with a negative urine pregnancy test.

The following figure lists the adverse effect profile of this drug and the frequency with which these are encountered (Fig. 3).

	≥1%	0.5-<1%	<0.5%
Hypersensitivity		Rash	Eczema, pruritis
Hepatic	AST(GOT) increased ALT(GPT) increased ¥-GTP increased		Blood ALP increased, blood bilirubin increased
Gastrointestinal	Diarrhoea	Nausea, Vomiting, Abdominal pain	Abdominal discomfort, duodenal ulcer, haematochezia gastritis
Hematologic	Neutrophil count Decreased, white blood Cell count decreased	Glucose urine present	White blood cell count increased, reticulocyte count decreased, monocyte increased
Metabolic disorders	Blood uric acid increased (4.79%) Blood triglycerides increased		Blood potassium decreased
Respiratory			Asthma,oropharyngeal pain, Rhinitis,nasopharyngitis
Others			CPK increased,blood urine present, tonsil polyp, Pigmentation,dysgeusia, Bruise, vision blurred,eye pain, vertigo

Fig. 3. Figure depicting adverse effects of Favipiravir

Dose

The recommended dosage of favipiravir for adults is 1600 mg orally twice daily on 1st day followed by 600 mg orally twice daily, up to maximum of 10 days.

Drug interactions

Pyrazinamide: Concomitant use of pyrazinamide with favipiravir increases the levels of uric acid. Regular uric acid level monitoring is mandatory when these drugs are used together.

Repaglinide: Favipiravir inhibits the metabolism of repaglinide through the CYP2C8 pathway, thus increasing its potential to cause toxicity (hypoglycemia, headache, increase incidence of upper respiratory tract infections, etc). Cautious concomitant use is recommended.

Theophylline: Theophylline increases the blood levels of favipiravir and adverse reactions to favipiravir may occur.

Famciclovir, sulindac: Efficacy of these drugs may be reduced when coadministered with favipiravir.

Acyclovir: Acyclovir may delay the conversion of favipiravir into the active moiety, thus reducing its antiviral efficacy.[27]

Conclusion

The frightening speed with which the COVID-19 pandemic has spread across the world has only served to expose how inadequate our available antiviral drug options are. Repurposed antiviral drugs have all been accelerated into treatment after rapidly conducted clinical trials. Older, pre-existing antiviral drugs such as oseltamivir and ribavirin have not been shown to be effective against SARS-CoV-2. The most promising antiviral drug to date is another repurposed drug, remdesevir, which has been shown to be effective in several well-conducted trials. When used in moderately severe, nonventilated patients, it has been shown to improve time to clinical recovery,[28,29] and a trend toward reduced mortality,[28] although a significant mortality benefit has not been demonstrated. The effect of this drug appears modest at best, with further large scale trials urgently needed to evaluate its place in the management of COVID-19.

Favipiravir, a drug which has a similar mechanism of action to remdesivir but is orally administered, has less strong supportive data to back its use, but is nevertheless emerging as an agent that is worth considering in mild to moderate cases. The preliminary results from the first Indian study with this drug have been encouraging with small but significant improvement in time to clinical recovery and a two-day shorter viral shedding time. Put in perspective, a Cochrane review of 20 trials of oseltamivir in influenza showed this widely used drug reduced the time to clinical alleviation of symptoms by 16.8 h only.[30]

The main advantages of favipiravir are that it is administered orally and that it can be given in patients who are symptomatic but not ill enough to be hospitalized. As most COVID-19 patients (85%) have mild to moderate disease and can be treated at home, this drug could potentially be used in large numbers of patients. As with any antiviral, it should be stressed that favipiravir should be administered early after the onset of symptoms for it to be effective in reducing viremia. Its role in potentially shortening the duration of viral shedding could also have an epidemiological impact as it could reduce viral transmission at home and in the community. The role of favipiravir in prophylaxis in exposed but healthy contacts is also being looked at in an ongoing trial.[31] Favipiravir is also being evaluated in combination with other antiviral drugs such as umifenovir to see if these drugs act in a complimentary or synergistic manner.[32]

The side-effect profile of the drug also seems acceptable with asymptomatic hyperuricemia and mild, reversible elevation in transaminases being the most frequently reported adverse effects. In the Indian trial, no special safety signal was elicited. It is however teratogenic and must never be used in pregnant women. The main disadvantage is a high pill burden which works out to a loading dose of 18 tablets on the first day and then 8 tablets a day for the rest of the course. With the recent launch of 400 mg dose with one of the manufacturers, these concerns about the high pill burden will be partially alleviated. The recommended duration of

treatment, extending to 2 weeks may also be a disadvantage. Here again, the manufacturers specify that the drug can be stopped in a week if the patient has made a complete recovery by then.

Thus, in conclusion, favipiravir may emerge as a valuable drug in the treatment of mild to moderate symptomatic SARS-CoV-2–infected cases. Furthermore, larger RCTs are urgently needed before this drug can be unreservedly recommended however.

Disclosure of competing interest

The authors have none to declare.

References

01. *Clinicaltrials.gov.Search of: favipiravir | Covid19 - list results - clinicaltrials.Gov [online] Available at: https://clinicaltrials.gov/ct2/results?cond=Covid19&term=favipiravir&cntry=&state=&city=&dist (2020), Accessed 23rd Jul 2020 Google Scholar*

02. *Y. Furuta, B.B. Gowen, K. Takahashi, K. Shiraki, D.F. Smee, D.L. BarnardFavipiravir (T-705), a novel viral RNA polymerase inhibitor Antivir Res, 100 (2013 Nov), pp. 446-454 ArticleDownload PDFView Record in ScopusGoogle Scholar*

03. *Toyama Chemicals. Summary of Product Characteristics of Avigan. Google Scholar*

04. *V. Madelain, T.H. Nguyen, A. Olivo, et al.Ebola virus infection: review of the pharmacokinetic and pharmacodynamic properties of drugs considered for testing in human efficacy trialsClin Pharmacokinet, 55 (2016 Aug), pp. 907-923, 10.1007/s40262-015-0364-1 CrossRefView Record in ScopusGoogle Scholar*

05. *Z. Jin, L.K. Smith, V.K. Rajwanshi, B. Kim, J. DevalThe ambiguous base-pairing and high substrate efficiency of T-705 (favipiravir) ribofuranosyl 5 -triphosphate towards influenza A virus polymerase PloS One, 8 (2013), Article e68347 CrossRefGoogle Scholar*

06. *T. Baranovich, S.S. Wong, J. Armstrong, et al.705 (favipiravir) induces lethal mutagenesis in influenza A H1N1 viruses in vitro J Virol, 87 (2013), pp. 3741-3751 View Record in ScopusGoogle Scholar*

07. *K. Sleeman, V.P. Mishin, V.M. Deyde, Y. Furuta, A.I. Klimov, L.V. GubarevaIn vitro antiviral activity of favipiravir (T-705) against drug-resistant influenza and 2009 A(H1N1) viruses Antimicrob Agents Chemother, 54 (2010), pp. 2517-2524 View Record in ScopusGoogle Scholar*

08. *L. Oestereich, A. Lüdtke, S. Wurr, T. Rieger, C. Muñoz-Fontela, S. GüntherSuccessful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal modelAntivir Res, 105 (2014 May), pp. 17-21 ArticleDownload PDFView Record in ScopusGoogle Scholar*

09. *S.J. Smither, L.S. Eastaugh, J.A. Steward, M. Nelson, R.P. Lenk, M.S. LeverPost-exposure efficacy of oral T-705 (Favipiravir) against inhalational Ebola virus infection in a mouse model Antivir Res, 104 (2014 Apr), pp. 153-155 ArticleDownload PDFView Record in ScopusGoogle Scholar*

10. *D. Sissoko, C. Laouenan, E. Folkesson, et al.Experimental treatment with favipiravir for ebola virus disease (the JIKI trial): a historically controlled, single-arm proof-of-concept trial in Guinea PLoS Med, 13 (2016 Mar 1), Article e1001967 CrossRefGoogle Scholar*

11. *R. Kerber, E. Lorenz, S. Duraffour, et al.Laboratory findings, compassionate use of favipiravir, and outcome in patients with ebola virus disease, Guinea, 2015-A retrospective observational study J Infect Dis, 220 (2019 Jun 19), pp. 195-202 CrossRefView Record in ScopusGoogle Scholar*

12. *A. Shannon, B. Selisko, N. Le, et al.Favipiravir Strikes the SARS-CoV-2 at its Achilles Heel, the RNA Polymerase bioRxiv (2020 May 15) Google Scholar*

13. *Y. Furuta, K. Takahashi, Y. Fukuda, et al.In vitro and in vivo activities of anti-influenza virus compound T-705 Antimicrob Agents Chemother, 46 (2002), pp. 977-981 View Record in ScopusGoogle Scholar*

14. *T.H. Nguyen, J. Guedj, X. Anglaret, et al.Favipiravir pharmacokinetics in Ebola-Infected patients of the JIKI trial reveals concentrations lower than targeted PLoS Neglected Trop Dis, 11 (2017 Feb 23), Article e0005389 CrossRefGoogle Scholar*

15. *M. Wang, R. Cao, L. Zhang, et al.Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro Cell Res, 30 (2020 Mar), pp. 269-271 CrossRefView Record in ScopusGoogle Scholar*

16. *C. Chen, Y. Zhang, J. Huang, et al.Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial medRxiv (2020) 2020 Apr 15 Google Scholar*

17. *Q. Cai, M. Yang, D. Liu, et al.Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study (2020 Mar 18) Engineering (Beijing) Google Scholar*

18. *M. James IvesPreliminary report of favipiravir observational study in Japan released [Internet]. News-Medical.net, [cited 23 July 2020]. Available from: https://www.news-medical.net/news/20200602/Preliminary-report-of-Favipiravir-Observational-Study-in-Japan-released.aspx (2020) Google Scholar*

19. *K. Doi, M. Ikeda, N. Hayase, K. Moriya, N. Morimura, Covid-Uth Study GroupNafamostat mesylate treatment in combination with favipiravir for patients critically ill with Covid-19: a case series Crit Care, 24 (2020 Jul 3), p. 392 Google Scholar*

20. *RDIF and ChemRar launch final stage of favipiravir clinical trial [Internet]. Prnewswire.com, [cited 23 July 2020]. Available from: https://www.prnewswire.com/ae/news-releases/rdif-and-chemrar-launch-final-stage-of-favipiravir-clinical-trial-301064181.html (2020) Google Scholar*

21. *Search of: NCT04392973 - list results - ClinicalTrials.gov [Internet]. Clinicaltrials.gov, [cited 23 July 2020]. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=NCT04392973&cntry=&state=&city=&dist= (2020) Google Scholar*

22. *Investigational antiviral study finds faster clinical improvement in patients with COVID-19 [Internet]. Pharmacy Times, [cited 24 July 2020]. Available from: https://www.pharmacytimes.com/news/favipiravir-study-finds-faster-clinical-improvement-in-patients-with-covid-19 (2020) Google Scholar*

23. *Personal Communication.. Google Scholar*

24. *Pharmaceuticals and Medical Devices AgencyReport on the Deliberation Results – Avigan. Japan Evaluation and Licensing*

Division, Pharmaceutical and Food Safety Bureau (2011) Available at: www.pmda.go.jp/files/000210319.pdf, Accessed Jul 2020 Google Scholar

25. *Y. Kumagai, Y. Murakawa, T. Hasunuma, et al.Lack of effect of favipiravir, a novel antiviral agent, on the QT interval in healthy Japanese adults Int J Clin Pharm Ther, 53 (2015) 866–674 Google Scholar*

26. *V. Pilkington, T. Pepperrell, A. HillA review of the safety of favipiravir – a potential treatment in the COVID-19 pandemic? J Virus Erad, 6 (2020 Apr 30), pp. 45-51 ArticleDownload PDFView Record in ScopusGoogle Scholar*

27. *M. Catherine, S. Neil, G. Brian, N. WayneFavipiravir and Remdesivir Appear to Be Relatively Unencumbered with Drug-Drug Interactions - Anesthesia Patient Safety Foundation [Internet] Anesthesia Patient Safety Foundation (2020) [cited 14 August 2020]. Available from: https://www.apsf.org/article/favipiravir-and-remdesivir-appear-to-be-relatively-unencumbered-with-drug-drug-interactions/Google Scholar*

28. *J.H. Beigel, K.M. Tomashek, L.E. Dodd, et al.Remdesivir for the treatment of covid-19 - preliminary report N Engl J Med (2020 May 22) Google Scholar*

29. *J. Grein, N. Ohmagari, D. Shin, et al.Compassionate use of remdesivir for patients with severe covid-19 N Engl J Med, 382 (2020 Jun 11), pp. 2327-2336 CrossRefView Record in ScopusGoogle Scholar*

30. *C.J. Heneghan, I. Onakpoya, M.A. Jones, et al.Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data Health Technol Assess, 20 (2016 May), pp. 1-242 CrossRefView Record in ScopusGoogle Scholar*

31. *[Internet] Appili Set to Evaluate Favipiravir as Preventive Measure against Covid-19, Pharmaceutical Business review (2020) [cited 24 July 2020]. Available from: https://www.pharmaceutical-business-review.com/news/appili-therapeutics-favipiravir-canada-trial/ Google Scholar*

32. *D. Tirumalaraju, D. TirumalarajuGlenmark Starts Phase III Favipiravir Combination Trial for Covid-19 [Internet] Clinical Trials Arena (2020) [cited 26 July 2020]. Available from: https://www.clinicaltrialsarena.com/news/glenmark-favipiravir-combo-trial/ Google Scholar*

Case Report

Brenner tumour of the ovary: A rare case report

Barkat S [1], Hasan K M M [2]

ABSTRACT

Brenner tumour is a rare ovarian tumour, mostly benign and is a part of the surface epithelial group of ovarian neoplasm. It is usually asymptomatic and frequently found as an incidental pathological finding. Here we present a case of Mrs Chowma Marma 73 years tribal menopausal lady treated surgically for ovarian tumour and histopathological findings revealed Brenner Tumour of the ovary.

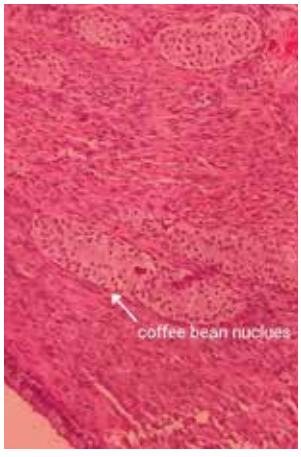
1. * Dr. Sabreena Barkat, FCPS
Consultant (Obs & Gynae), Emanuel Medical Centre, Bandarban, Chittagong hill district
E-mail: barkatsabreena5122@gmail.com
Mobile: 01816-816171

2. Dr. Kazi Mohammad Mahmudul Hasan
Assistant Professor, Dept of Anaesthesia and pain
Monno Medical College, Manikganj, Dhaka

Case Report

Mrs Chowma Marma a tribal 73 years menopausal lady having 5 children came to the general practitioner with the complaints of heaviness in the lower abdomen for last 6 months, dull aching continued lower abdominal pain and loss of appetite for the same duration. USG revealed a left sided adenexal mass (8.9cm X 11.7cm, with multiple internal echoes).Thereafter she was referred to the gynecologist.

At the time of examination her vitals were normal. She was a known case of Hypertension and Type II Diabetes Mellitus. Both blood pressure and blood sugar were controlled. A palpable mobile lump (approximately 6cm X 8cm)with well defined margins, partly solid partly cystic in consistency was found in the pelvic region. On speculum examination cervix looked apparently healthy, deviated to the right. On bimanual examination uterus was atrophied, left fornix was full. CA 125 was 18.9. Paps smear was normal. The patient was prepared for laparatomy.



During laparatomy a solid ovarian tumour was found on the left side. Right ovary and Fallopian tube was healthy. Total abdominal hysterectomy with bilateral salpingo ophorectomy done with proper haemostasis.

Grossly the tumour was 8cm x 9cm white smooth with glistening capsule. Cut surface showed partly solid partly cystic areas. Cystic areas contained hemorrhagic fluid. Solid areas were well circumscribed, nodular surrounded by fibromatous tissue. On histopathological examination epithelial cells are ovoid to polygonal with pale cytoplasm. Some of the nuclei have pale central longitudinal groove (coffee bean nucleus). All the above findings go in favor of Brenner tumour of ovary. No malignant cells were seen. The post operative period was uneventful. Both blood pressure and blood sugar remained controlled during postoperative period. She was discharged on 7th postoperative day with advice for regular follow up.

Incidence

Ovarian tumour are the 3rd common tumour among women. However the incidence of brenner tumour is very rare (1.4 - 2.5%) of which only 2 - 5% are malignant.[1,2,3]

Introduction

Brenner tumour was named after Fitz Brenner, a German scientist in the year 1907[1] These are an uncommon subtypes of surface epithelial arrival tumour. Majority are benign tumours rarely may become malignant.

Signs and symptoms

Most of the tumours are asymptomatic and are an incidental pathological finding.[2,3] If the tumour is large it may cause pain, abdominal distension, heaviness of the abdomen or difficulty in bowel control[3]

Cause: The exact cause of benign or malignant Brenner tumour is unknown. About 30% of the Brenner tumour are found along with mucinious cystadenoma.[4]

Diagnosis : Although these tumours are diagnosed during

routine pelvic examination or an USG[2,3,5]the final diagnosis is done after surgical biopsy.

Gross and microscopic examination: Brenner tumour is a solid ovarian tumour and generally asymptomatic. In 30% of cases it is associated with serous or mucinious cystadenoma. Most of the time the tumour is unilateral. Bilateral is seen only in 5-7 % cases.[4]

On nakyed eye examination benign Brenner tumour are well circumscribed with gray white glistening capsules[8]. Borderline Brenner tumour are cystic with unilocular or multilocular papillomatous mass protruding into one or more of the locules.[6] Malignant Brenner tumour may be solid or cystic with moral nodules[7].
It is seen that Brenner tumours are generally derived from the surface epithelium of the ovary or the pelvic mesothelium.[8]

Microscopically there are abundant dense fibrous stroma with epithelial nests of transitional cells. The fibrous component is less prominent in borderline or malignant tumours.[9] The nucleus is typically grooved and is known as coffee bean nucleus.[10]

Almost in all types of brenner tumour surgery is the main treatment. Benign tumours have an excellent prognosis. Malignant tumours if diagnosed early complete resection is possible.

Discussion

Only a few cases of brenner tumours has been reported. One case has been documented in Assam India, a 45 years old multiparous women who presented with abdominal pain and lump.[2] After hysterectomy histopathology confirmed Brenner tumour.

In Japan 2 cases were reported the first is a 55 year old lady with abdominal lump and constipation. The second case is a 70 years menopausal lady who presented with a pelvic mass underwent TAH with bilateral salpingo ophorectomy with histopathology revealed brenner tumour of ovary.[11]

Treatment : Treatment of Brenner tumour is always surgical. Since the tumours occurs in post menopausal women removal of both ovaries, fallopian tubes and uterus are recommended. For younger women removal of the tumour is the choice of surgery.[9]

Prognosis : For individual with Benign Brenner tumour and no other findings there is a good to excellent long prognosis. These tumours usually do not recur.

Reference

01. *Philip, Elliot Elias, O Dowd Michael J. (2000) the history of obstetrics and Gynaecology. Carnforth; Lancs: Parthenon. p 586*

02. *Borah T, Mahanta RK, Bora BD, Saikia S. Brenner tumor of the ovary: An incidental finding. J Midlife Health. 2011 Jan-Jun; 291:40-41. https://www.ncbi.nlm.nih.gov/pmc/articles/P-MC3156501.*

03. *Douherty D, Onyemkpa C, Engel M, Oyasijic T. A case report of an incidental Brenner tumor found after resection of a large ovarian mucinous neoplasm. Int J Surg Case Rep. 2018; 49:40-43.*

04. *Moon WJ, Koh BH, Kim SK, Kim YS, Rhim HC, Cho OK, et al. Brenner tumor of the ovary: CT and MR findings. J Comput Assist Tomogr. 2000;24:72–6. [PubMed] [Google Scholar]*

05. *Nasioudis D, Sisti G, Holcomb K, Kanninen T, Witkin S. Malignant Brenner tumors of the ovary; a population-based analysis. Gynecol Oncol. 2016; 142:44-49. https://www.ncbi.nlm.nih.gov/pubmed/27130406.*

06. *Lang SM, Mills AM, Cantrell LA. Malignant Brenner tumor of the ovary: Review and case report. Gynecol Oncol Reports. 2017; 22:26-31.*

07. *Arey LB. The origin and form of the Brenner tumor. Am J Obstet Gynecol. 1961;81:743–51. [PubMed] [Google Scholar]*

08. *Green GE, Mortele KJ, Glickman JN, Benson CB. Brenner tumors of the ovary sonographic and computed tomographic imaging features. J Ultrasound Med. 2006;25:1245–51. [PubMed] [Google Scholar]*

09. *Clemet PB, Young RH. Ovarian Surface Epithelial – Stromal Tumors. In: Mills SE, editor. Sternberg's Diagnostic Surgical Pathology. 5th ed. Philadelphia: Lippincott Williams and Wilkins, A Wolters Kluwer business; 2010. pp. 2278–308. [Google Scholar]*

10. *Takahama J, Ascher SM, Hirohashi S, Takewa M, Ito T, Iwasaki S, et al. Borderline Brenner tumor of the ovary: MRI findings. Abdom Imaging. 2004;29:528–30. [PubMed]*

11. *Japanese journal of clinical oncology, vol 29, issue 6, June 1999, pages 308-313*

Case Report

Ectopic Spleen Presented as Intestinal Obstruction: A rare case report

Hossain M M [1], Hosen M M A [2], Shahid S M A [3], Ahsan M S [4]
Begum N [5], Ahmed P [6], Ahmed T [7], Alam S N [8]

ABSTRACT

Background: Ectopic spleen is a very uncommon congenital anomaly. In this study ectopic spleen presented as intestinal obstruction.

Case Presentation: A four years old girl presented with history of abdominal pain with repeated vomiting for 10 days and absolute constipation for 3 days.

Results: USG findings were ectopic and mildly enlarged spleen which was placed in hypogastric region with evidence of infarction.

Conclusion: Transabdominal ultrasonography is a very useful diagnostic procedure for the detection of ectopic spleen.

Keywords: Ectopic Spleen, Intestinal Obstruction.

1. * Dr. Md. Mosharruf Hossain
Associate Professor (PMO),
Institute of Nuclear Medicine and Allied Science, Rajshahi
Rajshahi Medical Collage Hospital Campus, GPO- 6000,
Rajshahi, Bangladesh.
Email: drmhossainbaec@gmail.com
Mobile: 01984955533

2. Dr. M. M. Arif Hosen
Assistant Professor (SMO),
Institute of Nuclear Medicine and Allied Science, Rajshahi

3. Dr. S. M. Ahsan Shahid.
Assistant Professor,
Department of Pediatric Surgery
Rajshahi Medical Collage & Hospital, Rajshahi

4. Dr. Mostofa Shamim Ahsan
Director & Professor (CMO)
Institute of Nuclear Medicine and Allied Science, Rajshahi

5. Dr. Nasrin Begum
Associate Professor (PMO)
Institute of Nuclear Medicine and Allied Science, Rajshahi

6. Dr. Parvez Ahmed
Assistant Professor (SMO)
Institute of Nuclear Medicine and Allied Science, Rajshahi

7. Dr. Tasnim Ahmed
Assistant Professor (SMO)
Institute of Nuclear Medicine and Allied Science, Rajshahi

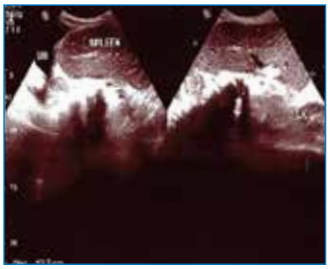
8. Dr. Shibli Nishad Alam
Medical Officer (MO)
Institute of Nuclear Medicine and Allied Science, Rajshahi

Introduction

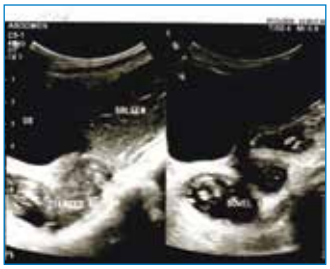
Ectopic spleen is a very rare congenital anomaly. Though accessory spleen has an incidence rate up to 16% of patients undergoing contrast enhanced abdominal CT, incidence of ectopic spleen is very low < 0.5 %. Recently we have diagnosed such type of rare diagnosis by transabdominal ultrasonogram.

Case report

A 4 year old girl was referred from pediatric surgery department of Rajshahi Medical Collage Hospital to our Institute for ultrasonogram of whole abdomen with the history of abdominal pain with repeated vomiting for 10 days and absolute constipation for 3 days. She had no history of dysentery or blood with stool. We scanned her by curvilinear (5mHZ) transducer of Philips Affinity 70G ultrasound machine. We found some dilated and fluid filled bowel loops but no definite intestinal obstruction. Spleen was not seen on left hypochondrium region but there was a solid mass of about 13.4 x 6.5 cm seen on hypogastriac region. The mass was homogenous and mimic with splenic tissue. Hilum was directed downwards and left laterally with another margin just beneath the parietal wall. Doppler study shows no definite vascularity within it. Final comment by USG was ectopic and mildly enlarged spleen which was placed in hypogastric region with evidence of infarction (Figure: 1a and 1b). The dilated bowel loops were due to the pressure effect of ectopic & enlarged spleen over bowel loops. Afterwards laparotomy was done and revealed that the hypogastric mass was an infarct spleen (Figure: 2a and 2b). Histopathology reveals splenic tissue with necrosis.



(Figure: 1a)



(Figure: 1b)

(Figure: 2a)

(Figure: 2b)

(Figure 1a & 1b shows USG images of spleen in hypochondriac region adjacent to left lateral margin of urinary bladder with dilated bowel loops; Figure 2a & 2b shows photograph of spleen during operation and after resection of spleen).

Discussion

Spleen is an intraperitoneal organ located in the left upper quadrant beneath 9, 10 and 11th ribs with a smooth serosal surface. Its normal position is provided by two fatty ligaments: the gastrosplenic ligament, which connects the greater curvature of the stomach to the ventral aspect of the spleen, and the splenorenal ligament between the left kidney and the spleen, attaching the spleen to the posterior abdominal wall. The splenic hilum is directed anteromedially. Splenic size changes according to the age and weight. Configuration of the spleen is also variable according to the indentations of the organs including stomach, colon, pancreas, and kidney which are in close relation to the spleen[1-4].

Wandering or ectopic spleen is a very rare congenital anomaly in which the spleen is located outside of its normal location. Though accessory spleen has an incidence rate up to 16% of patients undergoing contrast enhanced abdominal CT, incidence of ectopic spleen is very low < 0.5 %. Ectopic spleen is mainly detected in children and women between 20 and 40 years of age[5]. In our case patient was a 4 year old girl. Wandering spleen can be an elusive diagnosis as its presentation is greatly variable and intermittent torsion can cause non-specific signs and symptoms. Torsion of the vascular pedicle may be acute or chronic. It can present as an asymptomatic or painful abdominal mass, intermittent abdominal pain or as an acute abdomen (e.g. bowel obstruction, acute pancreatitis)[6-8]. In this case patient presented with abdominal pain, repeated vomiting with features of bowel obstruction. The abnormal mobility of the spleen was caused by an abnormality of its suspensory ligaments. There may be a congenital absence or underdevelopment of these ligaments, or an acquired laxity of the ligaments caused by various conditions, such as pregnancy or diseases causing splenomegaly. Due to these abnormal ligaments a long vascular pedicle may form, containing the splenic vessels, predisposing the spleen to torsion and consequently splenic infarction[7].

Ultrasonography and CT scan are the most useful methods for diagnosis. Imaging findings of wandering spleen are the absence of the spleen in its normal position and a mass located anywhere in the abdomen or pelvis with enhancement pattern of a normal splenic tissue. In case of torsion, a “whirl” appearance of its twisted pedicle and impaired enhancement of the mass can also be helpful. Doppler ultrasonography and contrast enhanced CT can be used to evaluate splenic vascularization. In splenic torsion, Doppler ultrasonography shows no flow within the spleen and a low diastolic velocity with an elevated resistive index in the proximal splenic artery. Contrast enhanced CT can show a total absence or heterogeneous enhancement pattern within the spleen related to partial or total infarction. Technetium sulfur colloid liver-spleen scan can be used to identify an abnormal abdominal mass as the spleen. The treatment choice of a wandering spleen is splenopexy. Splenectomy is required only in case of infarction[9-11]. In our case on Doppler study no blood flow was seen within the spleen and splenectomy was done.

Conclusion

In conclusion we can say, thought ectopic spleen is a very rare condition but it can be diagnosed by transabdominal Ultrasonogram with careful evaluation, so ultrasonogram can be taken as a useful first line screening modality for detection of ectopic spleen.

References

01. *G. Gayer, R. Zissin, S. Apter, E. Atar, O. Portnoy, and Y. Itzchak, “CT findings in congenital anomalies of the spleen,” British Journal of Radiology, vol. 74, no. 884, pp. 767–772, 2001.*
02. *W. J. Dodds, A. J. Taylor, S. J. Erickson, E. T. Stewart, and T. L. Lawson, “Radiologic imaging of splenic anomalies,” American Journal of Roentgenology, vol. 155, no. 4, pp. 805–810, 1990.*
03. *L. S. Rabushka, A. Kawashima, and E. K. Fishman, “Imaging of the spleen: CT with supplemental MR examination,” Radiographics, vol. 14, no. 2, pp. 307–332, 1994.*
04. *K. M. Elsayes, V. R. Narra, G. Mukundan, J. S. Lewis, C. O. Menias, and J. P. Heiken, “MR imaging of the spleen: spectrum of abnormalities,” Radiographics, vol. 25, no. 4, pp. 967–982, 2005.*
05. *Wallace S, Herer E, Kiraly J et-al. A wandering spleen: unusual cause of a pelvic mass. Obstet Gynecol. 2008;112 (2, Part 2): 478-80.*
06. *Lebron R, Self M, Mangram A et-al. Wandering spleen presenting as recurrent pancreatitis. JSLS. 2009;12 (3): 310-3.*
07. *Bouassida M, Sassi S, Chtourou MF et-al. A wandering spleen presenting as a hypogastric mass: case report. Pan Afr Med J. 2012;11: 31.*
08. *Taori K, Sanyal R, Deshmukh A et-al. Pseudocyst formation: a rare complication of wandering spleen. Br J Radiol. 2005;78 (935): 1050-2.*
09. *Paterson, D. P. Frush, L. F. Donnelly, J. N. Foss, S. M. O'Hara, and G. S. Bisset, “A pattern-oriented approach to splenic imaging in infants and children,” Radiographics, vol. 19, no. 6, pp. 1465–1485, 1999.*
10. *Ben Ely, R. Zissin, L. Copel et al., “The wandering spleen: CT findings and possible pitfalls in diagnosis,” Clinical Radiology, vol. 61, no. 11, pp. 954–958, 2006. D. C. Desai, A. Hebra, A. M. Davidoff, and L. Schnaufer, “Wandering spleen: a challenging diagnosis,” Southern Medical Journal, vol. 90, no. 4, pp. 439–443, 1997.*

Favipira 200

1ST TIME IN BANGLADESH

Favipiravir INN 200 mg tablet

The Only Clinically Proven Drug in the Management of COVID-19 Patients of Bangladesh

BEACON®
Pharmaceuticals Limited
Light for life

Gaviflux

Sodium Alginate USP, Sodium Bicarbonate USP & Calcium Carbonate BP

Faster Action, Faster Relief

from **Heartburn** & **Acid Reflux**

BEACON®
Pharmaceuticals Limited
Light for life

Published by **Beacon Pharmaceuticals Ltd.**

Corporate Office : 9/B/2 Toyenbee Circular Road, Motijheel, Dhaka, Bangladesh,
Tel : +88-02-57165371-79, Fax : +88-02-57165380, Web : www.beaconpharma.com.bd