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Editorial

Non Alcoholic Fatty Liver Disease - A Global Epidemic

For defining NAFLD, there must be evidence of – Hepatic steatosis (HS), either by imaging or histology, and Lack of secondary causes of hepatic fat accumulation such as significant alcohol consumption. NAFLD can be categorized histologi - cally into nonalcoholic fatty liver (NAFL) or nonalcoholic steatohepatitis (NASH). NAFL - Is defined as the presence of ≥5% HS without evidence of hepatocellular injury in the form of hepatocyte ballooning and the risk of progression to cirrhosis and liver failure is considered minimal. NASH - Is defined as the presence of ≥5% HS and inflammation with hepatocyte injury (e.g., ballooning), with or without any fibrosis. This can progress to cirrhosis, liver failure, and rarely liver cancer.

Regional incidence of NAFLD in asia is 52.34 / 1000 person per year, is around 28 /1000 person per year. Global prevalence of NAFLD diagnosed by imaging is around 25.24%. The highest prevalence of NAFLD is reported from middle-east (31.79%) and South America (30.45%) whereas lowest prevalence is from Africa (13.48%). Prevalence of NASH in the general population ranges between 1.5% and 6.45%. Prevalence of NAFLD in rural population is 33% in one study and in another study in general population prevalence of NAFLD is 34.34% in Bangladesh.

Features of metabolic syndrome (MetS) are highly prevalent in patients with NAFLD, components of MetS also increase the risk of developing NAFLD. Entire spectrum of obesity, ranging from overweight to obese and severely obese, is associated with NAFLD. >95% of patients with severe obesity undergoing bariatric surgery will have NAFLD. Around one third to two thirds of diabetic patients have NAFLD. The prevalence of NAFLD in individuals with dyslipidemia attending lipid clinics has been estimated to be 50%. 7% of normal weight patient has NAFLD.

Western diet/lifestyle has been associated with weight gain and obesity, and NAFLD. High calorie intake, excess (saturated) fat, high fructose intake, sedentary behaviour leads to obesity and NAFLD. Several genetic modifiers of NAFLD have been identified - A minority have been robustly validated. PNPLA3 I148M and TM6SF2 E167K carriers have a higher liver fat content - Increased risk of NASH. In general, NAFLD is a slowly progressive disease, both in adults and in children. Rate of progression corresponds to 1 fibrosis stage every 14 years in NAFL and every 7 years in NASH. Rate of progression is doubled by arterial hypertension. Progression of fibrosis is more rapid in about 20% of cases.

Prevalence and incidence of CVD is higher in NAFLD than in matched controls. Patients with NAFLD have increased overall mortality compared to matched control populations without NAFLD. The most common cause of death in patients with NAFLD is cardiovascular disease (CVD), indepen- dent of other metabolic co-morbidities. Although liver-related mortality is the 12th leading cause of death in the general population, it is the second or third cause of death among patients with NAFLD. Cancer-related mortality is among the top three causes of death in subjects with NAFLD. CVD should be identified in NAFLD, regardless of traditional risk factors.

US is the preferred first-line diagnostic procedure for imaging of NAFLD, as it provides additional diagnostic information. Quantification of fat content is of limited clinical relevance - Except as a surrogate of treatment effectiveness. A quantitative estimation of liver fat can only be obtained by H-MRS. This technique is of value in clinical trials and experimental studies, but is expensive and not recommended in the clinical setting. Controlled attenuation parameter (CAP) can diagnose steatosis but more data are needed to define the role of CAP.

Fibrosis is the most important prognostic factor in NAFLD - Correlates with liver-related outcomes and mortality, Advanced fibrosis indicates thorough investigation. Biomarkers, fibrosis scores, and transient elastography, are acceptable non-invasive procedures to identify those at low risk of advanced fibrosis/cirrhosis. Biomarkers/scores PLUS transient elastography might confer additional diagnostic accuracy and reduce need for liver biopsy.

Liver biopsy is essential for the diagnosis of NASH - Clinical, biochemical or imaging measures cannot distinguish NASH from steatosis. NAFL encompasses - Steatosis alone plus ONE of lobular or portal inflammation OR ballooning. NASH requires - Steatosis AND Lobular or portal inflammation AND Ballooning. NAS scoring indicates disease severity.

Epidemiology suggests a close relationship between an unhealthy lifestyle and NAFLD. Diet and lifestyle changes are mandatory in all patients. Modest weight loss reduces liver fat, improves hepatic IR, and can result in NASH regression. Structured programmes aimed at lifestyle changes towards healthy diet and habitual physical activity are advisable in NAFLD.
Patients without NASH or fibrosis should receive counselling for healthy diet and physical activity but no pharmacotherapy. In overweight/obese NAFLD, a 7–10% weight loss is the target of most lifestyle interventions, and results in improvement of liver enzymes and histology.

Pharmacotherapy should be reserved for patients with NASH. Treatment should be indicated in: Progressive NASH, Early-stage NASH with risk of fibrosis progression, Active NASH with high necroinflammatory activity. Treatment should reduce NASH-related mortality and progression to cirrhosis or HCC. Resolution of NASH-defining lesions accepted as surrogate endpoint.

Metformin - Two published meta-analyses conclude that metformin therapy did not improve liver histology in patients with NAFLD and NASH and is not recommended for treating NASH in adult patients. Thiazolidinediones-Pioglitazone improves liver histology in patients with and without T2DM with biopsy-proven NASH. Therefore, it may be used to treat these patients. Vitamin E - administered at a daily dose of 800 IU/day improves liver histology in nondiabetic adults with biopsy-proven NASH and therefore may be considered for this patient population. Risks and benefits should be discussed with each patient before starting therapy. UCDA is not recommended for the treatment of NAFLD or NASH. Omega-3 fatty acids should not be used as a specific treatment of NAFLD or NASH, but they may be considered to treat hypertriglyceridemia in patients with NAFLD. Obeticholic acid- A synthetic farnesoid X receptor agonist–, improved insulin resistance in type 2 DM. Until further safety and efficacy data become available, it is not recommended to treat patients with NASH. Available data on pentoxifylline and orlisted are limited or inconclusive. Statins may be confidently used to reduce LDL cholesterol and prevent cardiovascular risk, with no benefits or harm to liver disease.

NAFLD is a global epidemic. NASH has a worse prognosis than steatosis alone. Screening is CVD is mandatory in all patients with NAFLD. The gold standard of diagnosis is liver biopsy.
Diet and lifestyle changes are mandatory in all patients. Pharmacotherapy should be reserved for patients with NASH.

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Original Article

Snodgrass Technique for Hypospadias Repair A Versatile Technique

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Abstract

Background: Hypospadias is a relatively common congenital male external genital defect. Although there are multiple techniques for its reconstruction we are using Snodgrass technique for its high success rate. **Objectives:** To evaluate the result of Snodgrass repair for penile hypospadias. **Method:** The retrospective study was conducted at CoMC and private hospitals from June 2012-June 2017. Total 34 patients under went repair with age 1-12 years mean 6 yrs. All patients were evaluated with detailed history and clinical examination. Reconstruction done under general anesthesia and patients followed up post operatively regularly.

Result: Among 34 cases, 23 (67.64%) had distal, 8 (23.52%) mid and 3 (8.82%) proximal penile hypospadias. 29 (85.29%) patients had successful repair.[4] Patients (11.76%) developed urethrocutaneos fistula and 1 had meatal stenosis. 1 patient developed infection and improved on medical treatment. The shape of meatus was slit like and vertically oriented in almost all cases. **Conclusion:** Snodgrass repair is excellent technique with good result, cosmetic and few manageable complications.

Key words: Hypospadias distal , proximal, Snodgrass repair.

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Introduction:

Hypospadias is a relatively common congenital male external genital defect characterized by a ventral triangular defect whose summit is formed by division of the corpus spongiosum, sides are formed by two pillars of atretic spongiosum and base is formed by the glans itself[1].The incidence of hypospadias is 1/300 male births. It is due to hypoplasia of tissues forming the ventral aspect (ventral radius) of the penis beyond the division of the corpus spongiosum.There are a lot of technique over 200 for its repair but none of them are associated satisfactory outcome. Snodgrass described the tubularised incised plate (TIP) for repair of hypospadias in 1994 as a mean to widen and improve mobilization of the urethral plate when performing a Thiersch-Duplay urethroplasty[2]. Since that time many reports have been published describing the success of this modified procedure to repair distal hypospadias lesions [3, 4]. As a result of the popularity of this procedure, many other currently used techniques for hypospadias repair will probably be used less and less. Results are poorer and complications are greater in extensive procedures such as tube urethroplasty, compared to flaps and TIP[5]. Modern approach in hypospadias repair is to preserve the urethral plate if possible[6]. Given the relative simplicity of the operative concept, low complication rate and good cosmetic result in distal hypospadias, the tubularised incised plate procedure has been progressively applied to more proximal defects[7, 8,] as a relatively straightforward one-stage procedure provided any associated ventral curvature is straightened without transecting

the urethral plate, and that the incised plate appears supple. Similarly, TIP is an option for reoperations if the urethral plate has not been excised previously and still appears healthy without gross scars.

Method:

The retrospective study was conducted at CoMC and private hospitals from June 2012- December 2017. Total 34 patients under went repair with age 1-12 years mean 6 yrs. Among 34 cases, 23 (67.64%) had distal, 8 (23.52%) mid and 3 (8.82%) proximal penile hypospadias.All patients were evaluated with detailed history and clinical examination. Reconstruction done under general anesthesia and patients followed up post operatively regularly.

Table I: Showing Types of Hypospadias

Typs	No.	Percent
Distal	23	67.64%
Mid penile	8	23.52%
Proximal penile	3	8.82%
Total :	**34**	

Surgical Procedure:

Patients are positioned supine for surgery under spinal anaesthesia (less than 3 years under general anaesthesia). A 5–0 polypropylene suture is place into the glans for traction. Next, longitudinal incisions are made along the visible junction of the glans wings to the urethral plate. Proposed lines for incision are first infiltrated with 1 : 100 000 noradrenaline or a tourniquet is used around the base of the penis for haemostasis. After making the skin incision , complete the dissection and glans wings mobilization taking care both to preserve vascularity to the urethral plate and sufficient thickness for the wings to be securely approximated. Relaxing incision is made from within the meatus to the tip of the urethral plate. The depth of incision depends upon whether the plate is grooved or relatively flat, but in all cases extends down to near the corpora cavernosa. Catheter was passed into the bladder. Then the urethral plate is tubularized beginning at the neomeatus, using 5–0 polyglactin suture. The first suture is placed through the epithelium at a point just distal to the midglans so that the meatus has an oval, not rounded, configuration. Tubularization is completed with a running two-layer subepithelial closure, turning all epithelium into the neourethral lumen. A dartos pedicle flap is dissected from the preputial hood and dorsal shaft skin in patients undergoing circumcision, then button-holed and transposed ventrally to cover the entire neourethra. Then glansplasty done with 5–0 polyglactin.

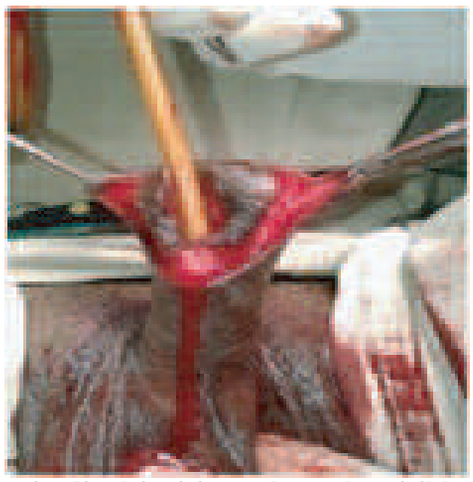

Fig1: Longitudinal incisions along the visible junction of the glans wings to the urethral plate

Fig 2: Tubularization is completed with a running two-layer subepithelial closure.

Fig 3: Skin closed.

Skin closures also used subepithelial 5–0 polyglactin sutures to minimize the risk of suture tracks. During circumcision the dorsal hood is incised down the midline to the level of the subcoronal collar of the inner prepuce. This point is sutured, and then the ventral shaft skin is approximated up the midline, simulating the normal median raphe. Excess skin is next excised and remaining edges sutured. Dressing was applied and catheter fixed with lower abdomen.

Result:

29 (85.29%) patients obtained a functional neourethra with a vertically oriented, slit-like meatus, almost at the tip of the glans penis. A small urethocutaneous fistula occurred in 4 patients . The location of these fistula was subcoronal in 2 patient and distal penile in another 2 patient. All the patients were advised regular urethral dilatation by infant feeding tubes of appropriate sizes and 1 healed spontaneously. Rest 3 patients of fistula later were managed by repair . 1 patients developed meatal stenosis and managed by dilatation .At the follow up, the size of the neourethra was routinely calibrated with infant feeding tube on outpatient basis for all patients. Table 2 shows complications in 34 patients of hyospadias operated by snodgrass procedure.

Table II: Showing complication

Complication	No.	Percent
Urethrocutaneos fistula	4 patients	11.76%
meatal stenosis	1 patients	2.9%
Infection	1 patients	2.9%

Discussion:

The incidence of hypospadias is 1/300 male births and abnormal meatus is located in the glandular [1], coronal and subcoronal levels or in the distal part of shaft, proximal penile, penoscrotal junction and perineal region. Established procedures for correcting distal hypospadias include Thiersch-Duplay, Mathieu, meatal advancement and glanuloplasty (MAGPI), and TIP urethroplasty (Snodgrass). Since its introduction the Snodgrass procedure has been widely adopted which is testament to its successful use. It reliably creates a normal appearing penis with a vertical slit-like meatus unlike the Mathieu or Thiersch-Duplay which create a horizontal, rounded meatus. The TIP urethroplasty is a versatile procedure which can also be used for proximal penile hypospadias repair in all age groups. It is a single stage procedure, thus avoids the need for repeated anaesthesia. In our series 29 patients (85.29%) had successful repair. Results of our study was satisfactory. Din I U reviewed Snodgrass repair results in his study and found satisfactory outcome of the procedure[9]. In comparison to Mathieu procedure the cosmetic results are much superior. Khan MA[10], Moradi M[11] compared the functional and cosmetic aspect of Snodgrass repair to Mathieu repair and found it cosmetically and functionally superior to Mathieu repair. Holland and Smith[12] repaired distal penile hypospadias with tubularized incised plate urethroplasty with complication rate of 22%. Earl et al[13] performed Snodgrass repair for distal and proximal hypospadias and obtained 99% success. Complication rate of Snodgrass repair ranges from 2 to 18%.[16,17]. In our study we had a complication rate of 14.71%, which included fistula formation, meatal stenosis . These results are comparable to the studies done by Snodgrass (16%) [14] and Din et al(16%) [9]. In our study 4 patients (11.76%) developed fistula and this is comparable with most series from leading institutions[3]. Din et al[9] observed urethrocutaneous fistula in 10%, Urethrocutaneous fistula formation remained the major complication in our study (11.76%). Multiple factors could be involved in the formation of urethrocutaneous fistula formation like improper mobilization of flaps during dissection, pressure necrosis due to tight dressing and some degree of meatal stenosis Various techniques were used to avoid urethrocutaneous fistula formation including vascularized dartos flap. All fistula were repaired later on and patients were improved. In our study meatal stenosis occurs in 1 patients after hypospadias repair, result of our study are comparable with other study [3, 15]. Din et al[9] observe meatal stenosis in 6%. Patient developed meatal stenosis was managed by dilatation and maintained by CISC. It is also evident that there was a dramatic improvement in rates of meatal stenosis after surgical technique and management were modified. With regard to surgical technique, tubularisation of urethral plate should not be performed beyond the mid glans region giving a generous oval configuration to the meatus[16]. 1 patient developed wound infection and improved with medical treatment. Majority of the patients had straight urinary stream during followup.

Table III: Cosmetic and functional outcome

Successful repair	29 Patients	85.29%
Urinary stream straight	32 Patient	94.11%

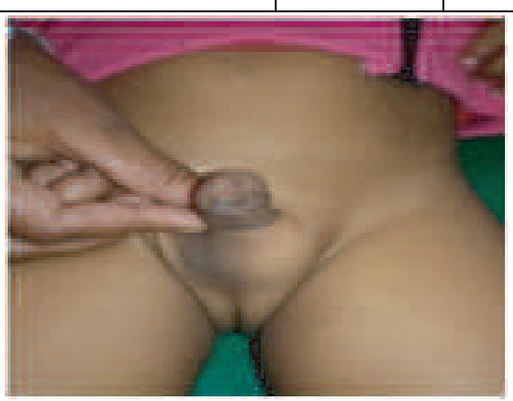

Fig 4: Slit like and vertically oriented neomeaus

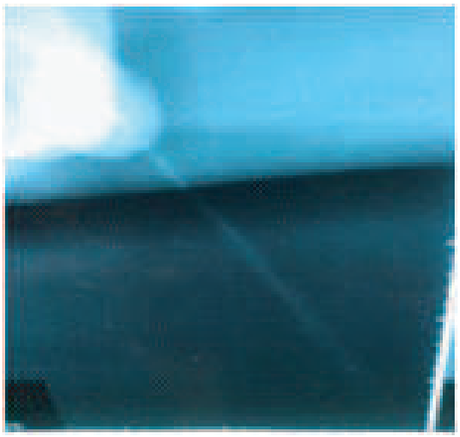

Fig 5: Micturition Good straight urinary stream

Conclusion:

Snodgrass repair is excellent technique for hypospadias repair with good outcome, cosmetic and few manageable complications

References:

1. Prem Puri, Michael Hollwarth. In Paediatric surgery: Chapter 51; Hypospadias.Springer 2005: 529.
2. Snodgrass, W. Tubularized, incised plate urethroplasty for distal hypospadias repair. J Urol 1994; 151:464-465.
3. Snodgrass W, Koyle M, Manzoni G, Horowitz R, Caldamone A, Ehrlich R. Tubularized incised plate hypospadias repair: results of a multicenter experience. JUrol 1996; 156:839-841.
4. Steckler, R. E. Zaontz, M. R. Stent-free Thiersch-Duplay hypospadias repair with the Snodgrass modification. J Urol 1997; 158(3 Pt 2):1178-1180.
5. Retik AB, Atala A. Complications of hypospadias repair. Urol Clin North Am 2002; 29(2):329-339.
6. Upadhyay J, Shekarriz B, Khoury AE. Midshaft hypospadias. Urol Clin North Am 2002; 29(2):299-310.
7. Snodgrass W, Koyle M, Manzoni G, Hurwitz R, Caldamone A, Ehrlich R.Tubularized incised plate 8.Hypospadias repair for proximal hypospadias. J Urol1998; 159(6): 2129.2131.8
8.. Braga LH, Pippi Salle JL, Lorenzo AJ, Skeldon S, Dave S, Farhat WA, Khoury AE, Bagli DJ. Comparative analysis of tubularized incised plate versus onlay island flap urethroplasty for penoscrotal hypospadias. J Urol 2007; 178(4 Pt 1):1451- 1456; discussion 1456-1457.
9. Din IU, Ullah O, Yunas M. Snodgrass repair for anterior hyposadias. JPMI2008;22(1):13-16.
10. Khan MA, Khan K, Ajmal S, Khan MY, Waheed T, Mohammad N. Comparison of MAGPI and Comparison of Snodgrass and Mathieu surgical Mathieu repair in distal hypospadias. J Postgrad Med Inst 2003;18:402-6.
11. Moradi M, Moradi A, Ghadarpanah F. technique in anterior distal shaft hypospadias repair. UNRC/ IUA J Urology 2005;2:28-31. 1.
12. Holland AJ, Smith GHH. Effect of depth and width of urethral plate on tubularized incised plate urethroplasty. J Urol 2000;64:489.
13. Earl YC, Sreenivas NV, Bradley PK, John CP, et al. Snodgrass hypospadias repair with Vascularized dartos flap the perfect repair for virgin cases of hypospadias.J Urol 2002;168:1723-6.
14. Snodgrass W, Bush N, Cost N. Comparative alogram for hypospadias reoperation. J Urology 2009; 182:2885.
15. Jayanthi VR. The modified Snodgrass hypospadias repair: reducing the risk of fistula and meatal stenosis. J Urol. 2003;170(4 Pt 2):1603-5.
16. Elbakry A. Further experience with the tubularized-incised urethral plate technique for hypospadias repair. BJU Int. 2002; 89(3):291-4.rience. J Urol. 1996;156(2 Pt 2):839-41
17. Snodgrass W, Zaida A, Yucel S, Gupta A. Comparison of outcomes of tubularized incised plate hypospadias repair and circumcision: a questionnaire based survey of parents and surgeons. J Paed Urol 2008;4:2

Original Article

Umbilical Artery Doppler Waveform Indices in Second and Third Trimester of Normal Pregnancy of Bangladeshi Women

Sharmin Easmin[1] , Sahera Khatun[2] , Ashikuzzaman[3] , Rosy Perveen[4] , Motiur Rahman[5] Misbah Uddin Ahmed[6]

Abstract

Background: Gestational age, fetal and maternal factors have impact on circulatory changes in both mother and fetus. Assessment of these changes can predict fetal and neonatal status. Doppler ultrasonography (DU) velocimetry of uteroplacental, umbilical, and fetal vessels has now become the established method for antenatal monitoring. Doppler evaluation in pregnancy was first done in the umbilical artery and since then it has become the most widely used investigation tool for fetal evaluation. It is essential that every institute should have its own baseline parameters to apply to its population in evaluation of fetal dynamic status. But, in Bangladesh there is no established, well accepted baseline data available yet. This study was conducted with view to establish normal values of umbilical artery Doppler waveform indices (S/D ratio, R/I, P/I, PSV, EDV) in second & third trimester of pregnancies. **Method:** This observational study was done from January 2014 to December 2014 in Department of Radiology & Imaging, Mymensingh Medical College Hospital, Mymensingh in normal pregnant women from 21 to 40 weeks of gestational age. Pregnant women attending to radiology & Imaging dept. of MMCH for Doppler USG were screened for inclusion in the study. After proper history taking, clinical examination and investigations total 56 cases were selected who met the inclusion and exclusion criteria. Selected cases were evaluated by conventional and Doppler USG. USG was done by using trans-abdominal curvilinear transducers of 3.5 MHz, Medisone machine. Umbilical arterial Doppler flow was obtained by color duplex ultrasound system. After fetal biometry for confirmation of gestational age, Doppler indices were measured by the same examiner at the free loop site where the clearest waveform signal could be visualized. Data were collected in preformed data sheet. Continuous variables were expressed as means±SDs and categorical variables were expressed as percentages. Comparison of mean values of RI, PI, S/D, PSV & EDV at 21weeks of gestational age was done with those at 40 weeks of gestational age by unpaired t test. The correlation of RI, PI, S/D and PSV, EDV with gestational age were assessed by Pearson correlation analysis. A $p<0.05$ will be used to reject the null hypothesis and confidence interval will be set at 95%. Data analysis was done by SPSS computer program version 20 (SPSS Inc., Chicago, IL, USA). **Result:** Mean±SD of age of patients was 23.19±3.53 years with most of the patients in 21-25years age group. Values of EDV,PSV, RI, PI & S/D in 2nd & 3rd trimester were 10.89±3.95 cm/sec, & 13.19±4.09cm/sec with p value 0.03, 36.69±9.69cm/sec & 39.67±7.19cm/sec with p value 0.02, 0.7±0.08 & 0.66±0.079 with p value 0.009, 1.2±0.26 & 1.09±0.245 with p value 0.01 and 3.56±0.85 & 3.168±0.915 with p value 0.01. These values were also evaluated in different gestational age groups which showed progressive changes of these values with gestational age. Gradual increase of values of EDV & PSV and decrease of values of RI, PI & SD was observed. **Conclusion:** This study demonstrated values of umbilical artery waveform indices in different gestational ages from 21 to 40 weeks of gestation. It is concluded that EDV & PSV increased and RI, PI & S/D decreased with advance of gestational age. These findings can be used to evaluate fetal condition during ultrasonography and also to formulate reference values for evaluation of fetal status by Doppler sonography.

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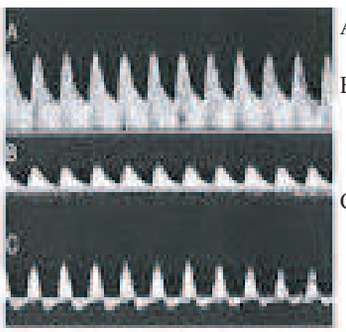
Introduction:

Gestational age, fetal and maternal factors have impact on circulatory changes in both mother and fetus. Assessment of these changes can predict fetal and neonatal status[1,2]. Duplex color Doppler ultrasound is one of the popular imaging modalities to assay the condition of blood vessels and flow pattern[3,4]. For obstetric and fetal evaluation uterine artery, umbilical artery and middle cerebral artery are examined[3]. Various clinico-pathological conditions during pregnancy like fetal hypoxia, acidosis & growth restriction cause uteroplacental insufficiency that increase the umbilical artery resistance and is reflected in umbilical artery Doppler waveforms[7,8,9]. Appropriate analysis of waveforms of these arteries can predict the occurrence and timing of adverse events[3,10]. Considering Considering feasibility, availability and safety, Doppler ultrasonography (DU) velocimetry of uteroplacental, umbilical, and fetal vessels has now become the established method for antenatal monitoring and fetal surveillance. Doppler evaluation in pregnancy was first done in the umbilical artery and since then it has become the most widely used

investigation tool for fetal circulation. Umbilical artery waveform can easily be detected by real time ultrasound associated with pulse wave Doppler ultrasound. In the normal fetus, the resistance to flow (impedance) decreases in the umbilical artery due to increased numbers of tertiary stem villi as the placenta matures. The umbilical artery (UA) impedance indices increase when there is decreased end-diastolic flow due to reduced placental perfusion and "utero-placental insufficiency" as is seen in intrauterine growth restriction (IUGR). Absent or reversed UA end-diastolic flow are particularly ominous findings.[3]



A. Normal velocimetry pattern with S/D ratio <30.
B. The diastolic velocity approaching zero reflects increased placental vascular resistance
C. During diastole, artrerial flow is reversed (negative S/D ratio) which is an ominous sign that may precede fetal

Figure 1: Showing normal and abnormal umbilical artery waveforms.

It is essential that every institute should have its own baseline parameters to apply to its population in evaluation of fetal dynamic status. But, there were very few studies conducted in Bangladesh regarding fetal Doppler indices and there is no established, well accepted baseline data available yet. This study was conducted with view to establish normal values of umbilical artery Doppler waveform indices (S/D ratio, R/I, P/I, PSV, EDV) in second & third trimester of pregnancies.

Method: This observational study was done from January 2014 to December 2014 in Department of Radiology & Imaging, Mymensingh Medical College Hospital, Mymensingh in normal pregnant women from 21 to 40 weeks of gestational age. Normal singleton pregnancies with accurate gestational age based on LMP, adjusted with ultrasound parameters were included. Patients having fetal congenital abnormalities, poly/ oligo-hydramnions, intrauterine growth retardation (estimated fetal weight below 10th percentile) and macrosomia (estimated fetal weight higher than 90th percentile), twin and multiple pregnancies and mothers with Diabetes mellitus, Hypertension, pre-eclampsia, autoimmune conditions, abnormal vaginal discharge and bleeding or any acquired illness were excluded from this study.

The sample size was determined with the formula to calculate sample size with a given proportion, degree of accuracy at a given level of statistical significance. It was 56. Pregnant women attending to radiology & Imaging dept. of MMCH for Doppler USG were screened for inclusion in the study. After proper history taking, clinical examination and investigations total 56 cases were selected who met the inclusion and exclusion criteria. Demographic variables like age of patient in years & gestational age in weeks & trimester were recorded.

Selected cases were evaluated by conventional and Doppler USG. USG was done by using trans-abdominal curvilinear transducers of 3.5 MHz, Medisone machine. Umbilical arterial Doppler flow was obtained by color duplex ultrasound system. After fetal biometry for confirmation of gestational age, Doppler indices were measured by the same examiner at the free loop site where the clearest waveform signal could be visualized. Data were collected in preformed data sheet. Continuous variables were expressed as means±SDs and categorical variables were expressed as percentages. Comparison of mean values of RI, PI, S/D, PSV & EDV at 21weeks of gestational age was done with those at 40 weeks of gestational age by unpaired t test.

The correlation of RI, PI, S/D and PSV, EDV with gestational age were assessed by Pearson correlation analysis. A $p<0.05$ will be used to reject the null hypothesis and confidence interval will be set at 95%. Data analysis was done by SPSS computer program version 20 (SPSS Inc., Chicago, IL, USA).

Result: The study evaluated umbilical artery Doppler waveform indices in 56 cases of normal singleton pregnant Bangladeshi women of 21 to 40 weeks of gestation at Mymensingh medical college hospital.

Age distribution of study population:

Mean±SD of age of patients was 23.19±3.53 years.

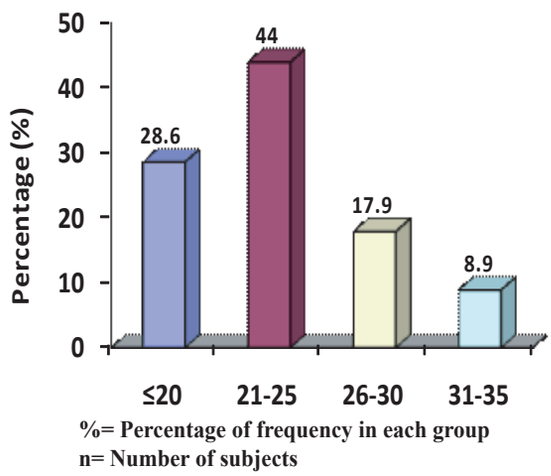


Figure 2: Age distribution of the study population (n=56)

Demographic distribution of patients in different trimesters:

Table I: Demographic distribution of study population in 2nd & 3rd trimesters (n=56)

	Second Trimester	Third Trimester	P value
Frequency (% of Patients)	29 (51.8)	27(48.2)	0.05
Age (in Years) (Mean±SD)	22.72±2.66	23.7±4.27	0.08
Mean±SD of Gestat. age (In weeks)	24±2.42	33.29±3.29	0.002

%= Percentage of frequency in each group
SD= Standard Deviation
n= Number of subject
Analysis was done by unpaired t test

Table I is showing Demographic distribution of study population in 2nd & 3rd trimesters. Frequency & Mean±SD (in years) of age of patients in two groups show no significant difference.

Frequency of patients in different gestational age groups showed that most of the patients were in 21-24weeks. This result is presented in bar diagram in figure III.

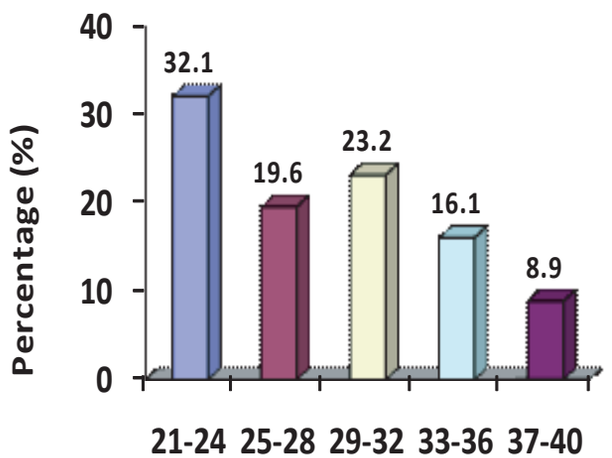


Figure 3: Gestational age distribution of the study population (n=56)

%= Percentage of frequency in each group
n= Number of subjects
Values of umbilical artery Doppler Indices in second and third trimester:
Values of umbilical artery Doppler Indices in second and third trimester are shown in table V.

Table II: Values of Umbilical artery Doppler waveform indices in second & third trimester of pregnancy (n=56).

	2nd Trimester Mean±SD	3rd Trimester Mean±SD	P value
EDV (cm/sec)	10.89±3.95	13.19±4.09	0.03
PSV (cm/sec)	36.7±9.69	39.67±8.19	0.02
RI	0.70±0.08	0.66±0.079	0.009
PI	1.2±0.26	1.09±0.245	0.01
S/D ratio	3.56±0.85	3.168±0.915	0.01

SD= Standard deviation
EDV= End diastolic velocity (cm/sec), PSV=Peak systolic velocity (cm/sec), RI=Resistance index, PI=Pulsatility index, SD= Systolic/Diastolic pressure ratio.
n= Number of subjects

Table II is showing that EDV, PSV, RI, PI & S/D ratio in 2nd & 3rd trimester were significantly different.

Values of umbilical artery Doppler Indices in different weeks of gestation are shown in Table-III.

Table III: Values of umbilical artery Doppler Indices in different gestational age groups by weeks (n=56)

Gestational age group (Weeks)	EDV	PSV	RI	PI	SD
	Mean±SD (Min-Max) (cm/sec)	Mean±SD (Min-Max) (cm/sec)	Mean±SD (Min-Max)	Mean±SD (Min-Max)	Mean±SD (Min-Max)
21-24	8.83±1.74 5.50-11.4	34.36±4.50 25.61-40.71	0.74±0.03 0.68-0.81	1.33±0.18 0.95-1.60	3.98±0.64 3.11-5.28
25-28	14.26±4.28 8.58-22.01	40.51±14.22 25.61-66.49	0.63±0.08 0.45-0.77	0.97±0.23 0.60-1.38	2.87±0.69 1.83-4.44
29-32	11.62±2.85 5.18-15.43	38.69±8.33 25.61-46.48	0.68±0.10 0.45-0.84	1.17±0.31 0.60-1.69	3.52±1.17 1.83-6.33
33-36	12.67±2.84 9.22-16.49	37.45±5.80 30.54-46.48	0.68±0.10 0.61-0.73	1.06±0.13 0.90-1.29	2.98±0.38 2.59-3.71
37-40	18.22±5.30 10.25-27.54	46.16±9.95 37.78-63.41	0.61±0.02 0.57-0.64	0.92±0.07 0.82-1.02	2.56±0.17 2.30-2.78

SD= Standard deviation
EDV= End diastolic velocity (cm/sec), PSV=Peak systolic velocity (cm/sec), RI=Resistance index, PI=Pulsatility index, SD= Systolic/Diastolic pressure ratio.
n= Number of subjects

Progressive changes of values of umbilical waveform indices with gestational age are shown by scatter diagrams in next few pages.

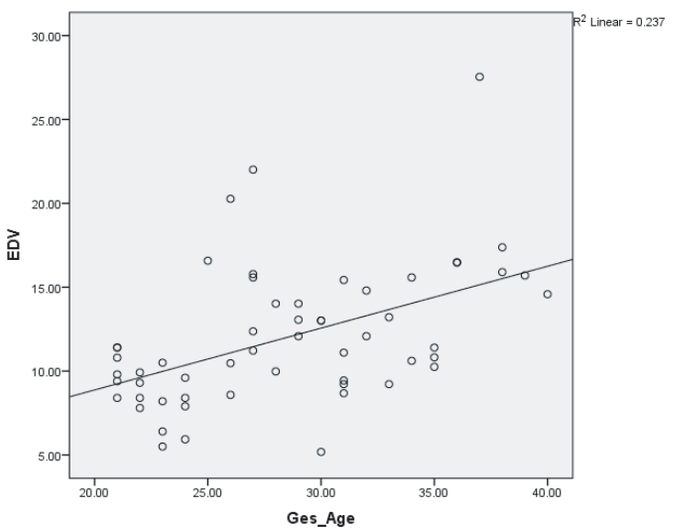


Figure 4: Scatter diagram - Correlation of EDV with progression of gestational age.

EDV= End diastolic velocity (cm/sec), Gest_age= Gestational age (in weeks)
EDV gradually increased from 21 to 40 weeks of gestation.

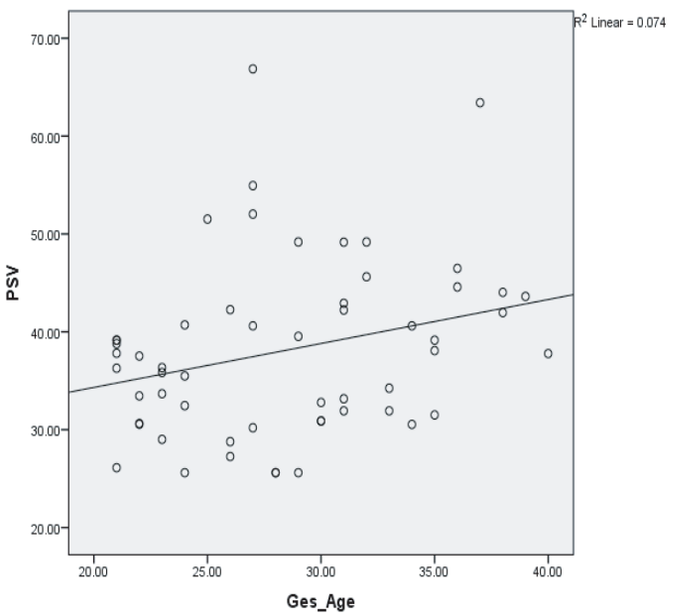


Figure 5: Scatter diagram showing correlation of PSV with gestational age.

PSV= Peak systolic velocity (cm/sec), Gest_age= Gestational age (in weeks)
PSV gradually increases from 21 to 40 weeks of gestation (Positive correlation).

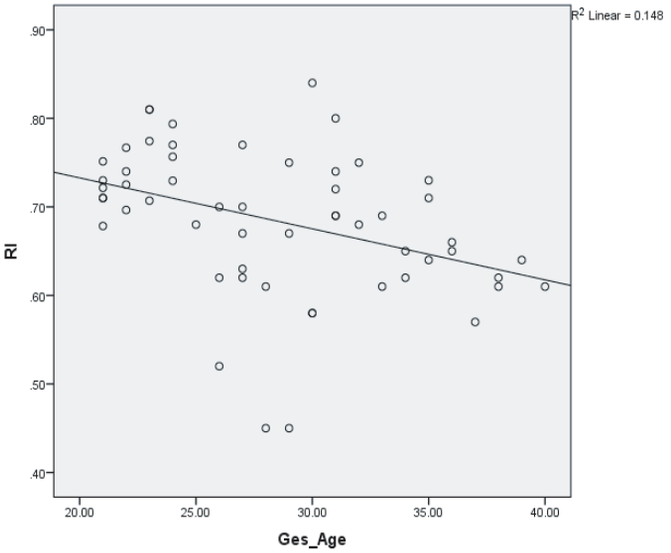


Figure 6: Scatter diagram - Correlation of RI with progression of gestational age.

RI= Resistance Index, Gest_age= Gestational age (in weeks)
Resistance Index (RI) value gradually decreases from 21 to 40 weeks of gestation (negative correlation).

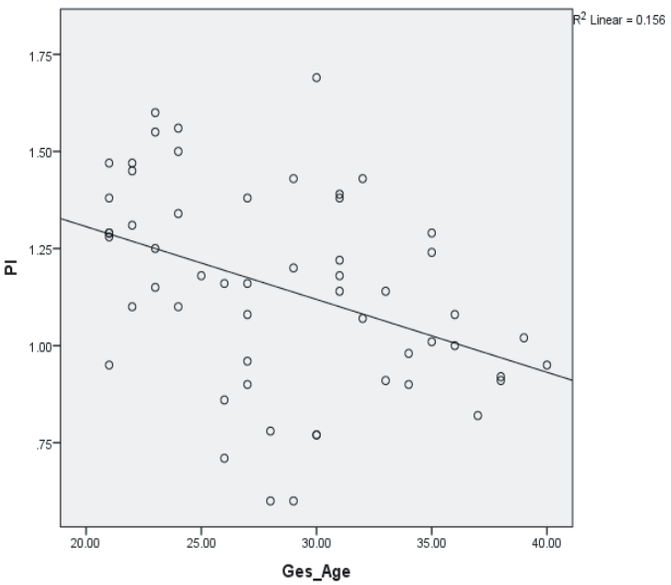


Figure 7: Scatter diagram - Correlation of PI with progression of gestational age.

PI= Pulsatility Index, Gest_age= Gestational age (in weeks)
Pulsatility Index (PI) gradually decreases from 21 to 40 weeks of gestation.

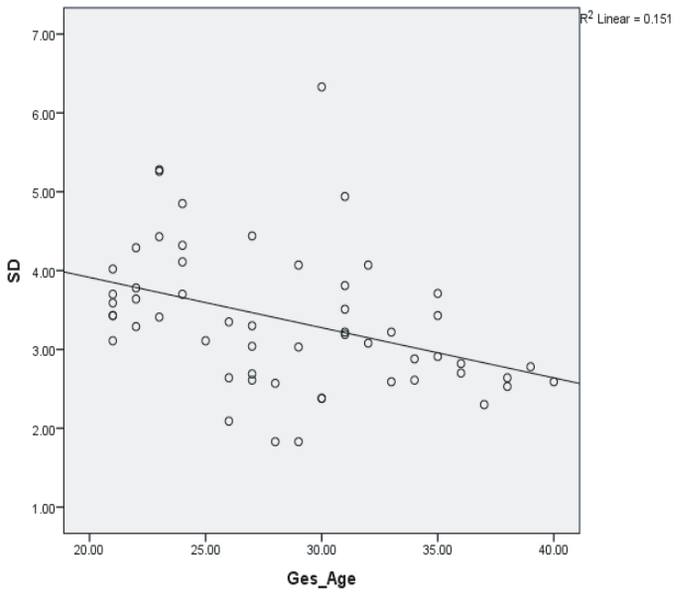


Figure 8: Scatter diagram - Correlation of SD ratio with progression of gestational age.

SD= Systolic/Diastolic pressure ratio, Gest_age= Gestational age (in weeks)

S/D ratio gradually decreases from 21 to 40 weeks of gestation (Negative correlation).

Table IV: Correlation analysis between dependent Doppler indices with independent gestational age (n=56)

Doppler Indices	r value	Level of significance (P value)
EDV (cm/sec)	0.523	0.0001**
PSV (cm/sec)	0.641	0.0001**
RI	-0.690	0.0001**
PI	-0.731	0.0001**
S/D ratio	-0.612	0.0001**

EDV= End diastolic velocity (cm/sec), PSV=Peak systolic velocity (cm/sec), RI=Resistance index, PI=Pulsatility index, SD= Systolic/Diastolic pressure ratio.
n= Number of patients.
R= Correlation co-efficient
**= Highly significant.
Table IV is showing that EDV & PSV has strong positive and RI, PI & S/D ratio have strong negative correlation with gestational age.

Discussion:

Uteroplacental blood flow assessment is an important part of fetal well being assessment. Doppler study of umbilical and uterine arteries of non-gravid & early pregnant state show high pulsatility with high systolic flow and low diastolic flow. A physiological early diastolic notch may be present. Resistance to blood flow gradually drops during gestation as greater trophoblastic invasion of the myometrium takes place. Fetal abnormalities affecting the hemodynamic can change this physiology, like pe-eclampsia, conditions causing IUGR, anemia etc. An abnormally high resistance may persist in pre-eclampsia and IUGR. Low resistance has an excellent negative predictive value with a less the 1% chance of developing pre-eclampsia or IUGR[11].

Doppler evaluation of uteroplacental circulation was done by continuous[12] and pulsed wave Doppler instrument[13,14,15] in different studies. The ISUOG guideline (2013) recommended use of pulsed wave Doppler technique for this purpose[16]. The current study used pulsed wave Doppler technique. On 1989 Abramowitz et al.[17] suggested to use the placental end of umbilical artery for Doppler analysis. Chanprapaph et al.[14] used free loop site of umbilical artery. Ferdousi et al.[15] did not mention the site of umbilical artery examined. In this study free floating part of umbilical artery was examined and placental end of umbilical artery was used to confirm the findings if EDV was found abnormal.

In these respect the technical aspect of Doppler study of umbilical artery of this study was more evidence based.

Different studies analyzed various Doppler indices in umbilical artery. Thompson et al.[18] and Harold et al.[19] worked on A/B ratio i.e. S/D ratio, Chanprapaph et al.[14] worked on S/D ratio, RI & PI, Ferdousi et al. [15] worked on PI of umbilical artery Doppler flow velocimetry in Bangladeshi population. The current study evaluated all parameters viz. EDV, PSV, RI, PI & S/D ratio.

In this study, the values of these parameters were analyzed in second and third trimester and 4weekly groups of gestational age viz. 21-24, 25-58, 29-32, 33-36 and 37-40weeks of gestation.

It was observed that EDV & PSV significant gradual increase from 2nd to 3rd trimester.

Mean±SD of EDV was 8.83±1.74 cm/sec, 34.36±4.50 cm/sec, 0.74±0.03 cm/sec, 1.33±0.18 cm/sec & 3.98±0.64 cm/sec respectively in gestational age groups.

Mean±SD of PSV was 34.36±4.50 cm/sec, 40.51±14.22 cm/sec, 38.69±8.33 cm/sec, 37.45±5.80 cm/sec, 46.16±9.95 cm/sec respectively in gestational age groups.

This result is similar to those found by Ferdousi et al.[15] worked with patients of Dhaka city. Both and EDV and PSV increased from 2nd to 3rd trimester. This revealed that fetal vascular resistance increases with advance of gestational age.

The values of RI were 0.7±0.08 & 0.66±0.079 respectively in 2nd & 3rd trimester respectively with significant difference (P=0.009); the values of PI were 1.2±0.26 & 1.09±0.245 respectively in both groups with significant difference (P=0.01).

Mean±SD of RI was 0.74±0.03, 0.63±0.08, 0.68±0.10, 0.68±0.10 & 0.61±0.02 respectively in gestational age groups. Mean±SD of PI was 1.33±0.18, 0.97±0.23, 1.17±0.31, 1.06±0.13 & 0.92±0.07 respectively in gestational age groups.

Correlation analysis of the values of RI and PI with gestational age demonstrates significant gradual decrease in these values with progression of gestational age.

In the study conducted by Ferdousi et al.[15] the mean±SD of RI in 2nd & 3rd trimester was 0.75±0.06 and 0.69±0.07, mean±SD of PI in 2nd & 3rd trimester was 1.33±0.29 & 1.18±0.29 with progressive decrement from 2nd to 3rd trimester of pregnancy.

Chanprapaph et al.[14] demonstrated values of different Doppler indices as weekly mean±SD from 21 to 40weeks of gestation. The mean±SD values in 21st, 25th, 29th, 33rd & 37th weeks of RI 0.756±0.049, 0.72±0.02, 0.646±0.03, 0.645±0.028 & 0.616±0.028, of PI were 1.27±0.08, 1.256±0.06, 1.061±0.07, 0.974±0.09 & 0.95±0.08.

The mean±SD of these values and their progressive changes with gestational age in the current study are consistent with the findings of Ferdousi et al. (2013), Bewley, Campbell & Cooper (1989), Akiyama et al. (1999) and Chanprapaph, Wanapirak & Tongsong (2000).

The mean±SD of S/D ratio in the current study were 3.56±0.85 & 3.168±0.915 respectively in 2nd & 3rd trimester groups with significant difference (P=0.01). The values were 3.98±0.64, 2.87±0.69, 3.52±1.17, 2.98±0.38 & 2.56±0.17 respectively in gestational age groups.

Correlation analysis of the values of S/D ratio with gestational age showed that its value decreases gradually with advancement of gestation.

These findings correlate with findings of the study by Chanprapaph et al.[14]

The trend of changes of S/D ratio with gestational age but not the values correlate with Harold et al.[19]. The difference in value of S/D ratio may be due to racial variation of study population as that study was done on American people.

The current study was done in patients at Mymensingh medical college hospital and evaluated EDV, PSV, RI, PI & S/D ratio in second and third trimester of gestation. Another study, done By Ferdousi et al.[15] in BIRDEM hospital at Dhaka, evaluated PI in 2nd & 3rd trimester of pregnancy. To form a normal reference value of umbilical artery Doppler wave form indices in Bangladeshi women some other studies need to be done in other part of the country.

Conclusion:

This study demonstrated values of umbilical artery waveform indices in different gestational ages from 21 to 40 weks of gestation. It is concluded that EDV & PSV increased and RI, PI & S/D decreased with advance of gestational age. These findings can be used to evaluate fetal condition during ultrasonography and also to formulate reference values for evaluation of fetal status by Doppler sonography.

References:

1. FitzGerald DE & Drumm JE 1977, 'Non-invasive measurement of human fetal circulation using ultrasound: a new method', Br M Journal, vol.2, pp.1450-1
2. Baschat A & Gembruch U 2003, 'The cerebroplacental Doppler ratio revisited', Ultrasound Obstet Gynecol, vol.21, pp.124 – 127.
3. Maryam R, Norman LM, Rebecca AU & Giancarlo 2011, 'Fetal Surveillance: Doppler Assessment of Pregnancy and Biophysical Profile', in Rumak et al. (eds) Diagnostic ultrasound, 4th edn, Elsevier, Philadelphia.
4. Sushil. G. Kachewar, Siddappa. G. gandage & Hemant.J.Pawer 2012, 'An Indian study of a novel non-invasive method of screening for foetal anaemia', Journal of Clinical and Diagnostic Research, vol.6, pp.688-691
5. Pourcelot L 1974, 'Applications clinique de l.examen Doppler transcutane', in Pourcelot L (eds), Velocimetric Utrasonore Doppler, INSERM, vol.34, pp.213-240.
6. Stuart B, Drumm J, FitzGerald DE & Duignan NM 1980, 'Fetal blood velocity waveforms in normal pregnancy', Br J Obstet Gynaecol, vol.87, pp.780-5.
7. Maulik D, Yarlagadda P, Youngblood JP & Ciston P 1991, 'Comparative efficacy of the umbilical arterial Doppler indices for predicting adverse perinatal outcome', Am J of Obstet Gynecol, vol.164, pp.1434-9.
8. Giles WB,Trudinger BJ & Baird PJ 1985, 'Fetal umbilical artery flow velocity waveforms and placental resistance: pathological correlation', Br J Obstet Gynaecol, vol.92, pp.31–8.
9. Lackman F, Capewell V, Gagnon R & Richardson B 2001, 'Fetal umbilical cord oxygen values and birth to placental weight ratio in relation to size at birth', Am J Obstet Gynecol, vol.185, pp.674–82.
10. Lackman F, Capewell V, Richardson B, daSilva O & Gagnon R 2001, 'The risks of spontaneous preterm delivery and perinatal mortality in relation to size at birth according to fetal versus neonatal growth standards', Am J Obstet Gynecol, vol.184, pp.946–53.
11. Gagnon R & Hof Michiel Van den 2003, 'The use of fetal Doppler in obstetrics': SOGC Clinical practice guideline, J Obstet Gynaecol Can, vol. 25(7), pp.601–7.
12. Morgan MA, Gaillard F et al 2014, 'Uterioplacental blood flow assessment', viewed on 30 December 2014, http://Radiopedia.org.html

13. Yarlagadda, Willoughby L, & Maulik D 1989, 'Effect of fetal heart rate on umbilical arterial Doppler indices', J of ultrasound in Medicine, vol.8(4), pp.215-218.
14. Fong KW, Ohlsson A, Hannah ME, Grsaru S, KingdomJ, Cohen H, Ryan M, Windrim R, Fostyer G & Amankwah K 1999, 'Prediction of perinatal outcomes in fetuses suspected to have intrauterine growth restriction: Doppler US of fetal cerebral, renal and umbilical arteries', Radiology, vol.213(3), pp.681-689.
15. Chanprapaph P, Wanapirak C & Tongsong T 2000, 'Umbilical artery Doppler waveform indices in normal pregnancy', Thai J of Obs & Gynae, vol.12, pp.103-107.
16. Ferdousi MA, Sharif MM, Mohiuddin AS & Shegufta F 2013, 'Normal value of pulsatility index of umbilical artery in second and third trimester of pregnancy', Bangladesh Med Res Counc Bull, vol.39, pp.42-44.
17. Bhide A, Acharya G, Bilardo CM, Brezinka C, Cafici D, Hernandez- Andrade E, Kalache K, Kingdom J, Kiserud T, Lee W, Lees C, Leung KY, Malinger G, Mari G, Prefumo F, Sepulveda W & Trudinger B 2013, 'ISUOG Practice Guidelines: use of Doppler ultrasonography in obstetrics', Ultrasound Obstet Gynecol. Vol. 41, pp.233–239.
18. Abramowicz JS, Warsof SL, Arrington J & Levy DL 1989, 'Doppler analysis of the umbilical artery. The importance of choosing the placental end of the cord', j of ultrasound in medicine, vol.8(4), pp.219-221.
19. Thompson RS, Trudinger BJ & Cook CM 1988, 'Doppler ultrasound waveform indices: A/B ratio, pulsatility index and Pourcelot ratio', Br J Obstet Gynaecol, vol.95, pp.581–8.
20. Harold Schulman, Adiel F, Willium Stem, George F, Naseem J & Peggy B 1984, 'Umbilcal artery wave ratios in human pregnabcy', Am J of Obs & gyne, vol.148(7), pp.985-990.
21. Bewly S, Campbell S. Cooper D 1989, 'Uteroplacental Doppler flow velocity waveforms in the second-trimester- A complex circulation', British Journal of Obstetrics and Gynaecnlogy, vol.96, pp.1040-1046.
22. Akiyama1 M, Kuno A, Tanaka Y, Tanaka H, Hayashi K, Yanagihara T, Hata T 1999, 'Comparison of alterations in fetal regional arterial vascular resistance in appropriate-for-gestational-age singleton, twin and triplet pregnancies', Human Reproduction, vol-14, pp.2635-2643.

Original Article

Haemoconcentration in Preeclampsia and Correlation Between Haematocrit Value and Raised Blood Pressure of Preeclampsia

Sankar Kumar Basak[1], Kohinoor Begum[2], Nahid Yasmin[3]

Abstract

Background: Preeclampsia-eclampsia is a common complication affecting 2% - 8% of pregnancies. In normal pregnancy there is a marked expansion of plasma volume. The increase in intravascular volume is minimal or completely absent in patients with preeclampsia. As a result, preeclampsia represents a state of haemoconcentration and raised haematocrit value. Haemoconcentration in preeclampsia was assessed by estimating haematocrit in different studies in many countries. This study was done on Bangladeshi women to see the correlation between haematocrit and raised blood pressure of preeclampsia. **Method:** This was a cross sectional study conducted in the department of Obstetrics & Gynaecology of Dhaka Medical College Hospital, Dhaka during the period of January 2007 to December 2008. A total of 100 patients were selected and they were divided into two groups – group-A and group-B. Fifty preeclamptic patients were included in the group-A and 50 normal pregnant women were included in the group-B. Blood was drawn from the study subjects and haematological analysis of blood was done. The test statistics used to analyze the data were descriptive statistics, Chi-square (χ^2) and t-tests. **Result:** Among the 50 preeclamptic subjects 16 (32%) had mild hypertension (DBP<110mmHg) and 34 (68%) had severe hypertension (DBP≥ 110 mmHg). But 45 (90%) had severe proteinuria (+++) and only 5 (10%) had moderate (++) proteinuria. The mean haematocrit value of preeclamptic patients was 34.88 ± 3.03 and that of normal pregnant women was 31.94 ± 1.2. It was statistically significant (P value 0.001). The mean haematocrit value of normal pregnant, mild and severe preeclamptic women were 31.94±1.2, 33.31 ± 2.57 and 35.62 ±2.95 respectively. It was also statistically significant (P value 0.001). A statistically significant correlation between haematocrit value and diastolic blood pressure in the preeclamptic women was established (r=0.33 and p value<0.05). It was established a positive but statistically insignificant correlation between haematocrit value and systolic blood pressure in the preeclamptic subjects (r=0.20 and p value>0.05). **Conclusion:** This study can be concluded that the positive correlations were established in between the haematocrit value and both the diastolic (r=0.33,p<0.05) and systolic(r=0.20, p>0.05) blood pressure.

Key words: Pregnancy, Haematocrit, Preeclampsia.

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Introduction:

Preeclampsia/eclampsia is a common obstetric complication leading to maternal mortality and morbidity worldwide, including in the Southeast Asian region[1]. It affects 2%-8% of pregnancies[2]. All over the world preeclampsia is 3rd and 7th leading cause of maternal and perinatal mortality and morbidity respectively[3]. It is responsible for an estimated 16% of global maternal mortality or 63,000 maternal death annually[4]. In a Baseline survey for assessment of Emergency Obstetric Care services in Bangladesh, 5% of the total obstetric admission in health facilities were due to preeclampsia and eclampsia[5].

Plasma volume and haematocrit show a significant correlation[6]. The increase in intravascular volume that normally occurs during pregnancy is minimal or completely absent in patients with preeclampsia. The reduced volume is predominantly of plasma and as a result, haemoconcentration occurs as the disease progresses[7]. Preeclampsia represents a state of haemoconcentratio in and increased haematocrit levels. A fall in repeat haematocrit values may denote clinical improvement[8].

Studies of Lebel et al[9] shown mean haematocrit values were slightly but significantly higher at the early stage of hypertension. Plasma volume was significantly reduced and it can account in part for the increased haematocrit.

Heilmann et al[10] found a higher haematocrit occurred in women of preeclampsia than in normal patients of comparable gestational age. Normal pregnancy is characterized by a marked expansion in plasma volume. Low plasma volume or high haematocrit especially in second trimester are associated with increased frequencies of fetal growth retardation, fetal death, preterm deliveries and preeclampsia[11].

"Maternal haematocrit in labour is related to fetal cord pH at delivery" was demonstrated by Saunders and co-workers[12]. The observed relation between maternal haematocrit and cord pH possibly reflects the fact that adequate plasma volume expansion is the hallmark of successful pregnancy. Instead, it appears that low haematocrits are associated with little or no risk of fetal growth retardation or preterm delivery, whereas high haematocrits are associated with a significantly increased risk of these complications[13].

Haemoconcentration in preeclampsia was assessed by measuring haematocrit and correlation between blood pressure and haematocrit was observed in many studies in different countries. But this study was done on Bangladeshi women to see the correlation between haematocrit value and raised blood pressure of preeclampsia.

Method:

This was a cross sectional study conducted in the Department of Obstetrics & Gynaecology, Dhaka Medical College Hospital (DMCH), Dhaka during the period of January 2007 to December 2008. The study population were patients attending the antenatal clinic and admitted in the department of Obstetrics & Gynaecology, DMCH. A total of 100 subjects were studied. The study population were divided into two groups- Group-A and Group-B. Pregnant women of gestational age between 24 to 40 weeks with preeclampsia were included in the Group-A and the women of same gestational age without preeclampsia were included in the Group-B.

The inclusion criteria for Group-A were gestational age between 24 to 40 weeks, diastolic blood pressure ≥ 90 mm Hg and systolic ≥140 mm Hg and proteinuria (1+or more measured by Dipstick method) and for Group-B were gestational age between 24 to 40 weeks, normal diastolic and systolic blood pressure and having no medical or obstetric complications. The exclusion criteria were patients with diabetes mellitus, renal disease, urinary tract infection, essential hypertension, heart failure, Chronic Obstructive Pulmonary Diseases (COPD) and using diuretics.

The variables included in the study were age, socioeconomic status, parity, gravidity, gestational age, systolic blood pressure, diastolic blood pressure, haematocrit value, and proteinuria.

After taking informed written consent, blood sample and urine sample were collected from the study subjects. Proteinuria was measured by dipstick method. Data were collected from the patients on variables of interest using the structured design by interview, observation, clinical examination, haematological investigations and from the history sheet of the patients. Collected data were processed with the help of software SPSS (Statistical Package for Social Sciences) version- 12.0 and analyzed. The test statistics used to analyse the data were descriptive statistics, Chi-square (χ^2) probability test and t-test. For all analytical tests the level of significance was $p < 0.05$. Ethical clearance for the study was taken from the Ethical Committee, Dhaka Medical College & Hospital.

With all aseptic precaution 1.5 ml of blood was collected from all the subjects using disposable syringe and blood was transferred to test tube containing EDTA, an anticoagulant for haematological analysis. Haematological analysis of blood was done by the Sysmex XS-800i, an automated haematology analyzer in the Department of Haematology, DMCH.

The haematocrit was calculated via the RBC pulse height detection method. Estimation of urine protein was done by reagent strips (Uric 2V GP, Bayer GMBH Germany).

Result:

Among the 100 subjects were studied, 50 were preeclamptic (Group-A) and 50 were normal pregnant women (Group-B).

There was no significant difference of socio-demographic characteristics of the subjects among the groups.

Out of 50 preeclamptic subjects 16 (32%) had mild hypertension (DBP<110mmHg) and 34 (68%) had severe hypertension (DBP≥ 110 mmHg) and among them 45 (90%) had severe proteinuria (+++) and only 5 (10%) had moderate (++) proteinuria (Table-I).

Table I: Severity of preeclampsia of study subjects (n=50)

Parameters	Number of Patients	Percentage (%)
Diastolic Blood Pressure (DBP)		
Mild (DBP <110)	16	32
Severe (DBP ≥110)	34	68
Proteinuria		
Moderate	5	10
Severe	45	90

Haematocrit value of group-A subjects was 34.88±3.03% and that of group-B was 31.94±1.2%. The difference of haematocrit value between the groups was statistically significant (p <0.05) (Table-II).

Table II: Haematocrit of study subjects (n=100)

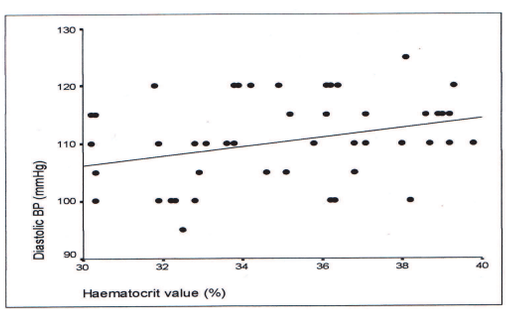
Parameters	Group-A (n=50) Mean±SD	Group-B (n=50) Mean±SD	P value
Haematocrit (%)	34.88±3.03	31.94±1.2	0.001

Table III shows the mean haematocrit of normal pregnant, mild and severe preeclamptic women were 31.94±1.2, 33.31±2.57 and 35.62±2.95 respectively. It shows the significant difference among the groups (preeclamptic and normal pregnant women) (p value <0.05).

Table III: Haematocrit of normal pregnancy, mild and severe preeclampsia (n=100)

Parameters	Group B	Group A		p value
	(DBP <90 mmHg) n=50	(DBP <110 mmHg) n=16	(DBP ≥110 mmHg) n=34	
Haematocrit (%)	31.94±1.2	33.31±2.57	35.62±2.95	0.001

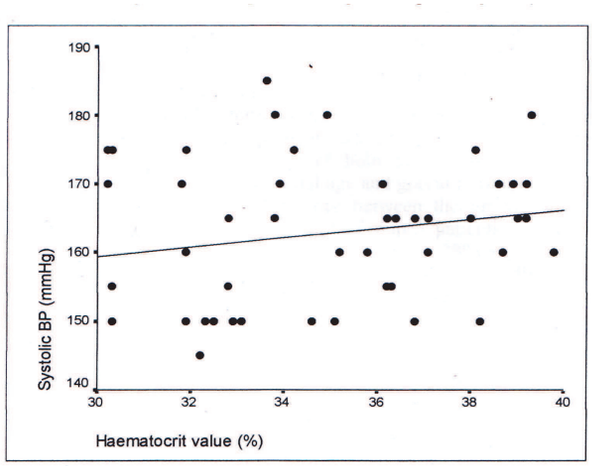
Figure 1: demonstrates that there was statistically significant correlation between haematocrit value and diastolic blood pressure of preeclamptic subjects (r=0.33, p value <0.05)



r=0.33 p value = 0.017 n=50

Figure 1: Correlation of haematocrit with diastolic blood pressure of preeclamptic subjects.

Figure 2 shows the positive but statistically insignificant correlation between haematocrit value and systolic blood pressure of preeclamptic subjects(r=0.20, p value>0.05)



r=0.33
p value = 0.017
n=50

Figure 2: Correlation of haematocrit with systolic blood pressure of preeclamptic subjects.

Discussion:

Preeclampsia is a major cause of maternal and perinatal mortality and morbidity worldwide, particularly in developing countries. Most of the preeclampsia occur in nulliparous women[14].

A severely affected preeclamptic women had marked hypovolaemia and the reduction in plasma volume was particularly marked in association with severe placental failure with a poor fetal outcome[15].

In this study, the group-A and the group-B subjects were almost identical in socio-demographic and obstetric characteristics. It revealed that more than two thirds (68%) of the preeclamptic women (group-A) had severe preeclampsia (diastolic blood pressure ≥ 110 mmHg) and remainders (32%) had mild preeclampsia (diastolic blood pressure < 110 mmHg). Ninety percent had severe proteinuria (+++ on dipstick test) and remaining 10% had moderate (++) proteinuria.

This study revealed that throughout the gestational period (which varies from 24–40 weeks) the haematocrit level of preeclamptic patients remain higher than normal pregnant women. The range of haematocrit in preeclamptic patients varies from 30.2%-39.8% and that of normal pregnant women was 29.2%-34.1%. The higher haematocrit in preeclamptic patients than in normal patients of comparable gestational age was supported by the study of Heilmann L and co-workers[10].

This study demonstrated that the mean haematocrit value of group-A women was 34.88% and that of group-B women was 31.94%. This haematological parameter was significantly higher in group-A women than in group-B women (p value 0.001) (Table II). The result of this study is supported by the study done by Heilmann et al[16]. In comparison between patients with severe preeclampsia and normal pregnant women they found statistically elevated values of haematocrit, haemoglobin and red cell aggregation. They noted higher haematocrit / haemoglobin values in the study groups.

The present study demonstrated that in preeclamptic women the haematocrit values were above those of the normal pregnant women (Table-II). A consequence of increased haemoconcentration is an increase in the viscosity of the blood and that has been found in preeclampsia[17]. In this respect an important observation was found from the study of Aardenburg et al[18] that subnormal plasma volume persisting for at least six month postpartum after a preeclamptic pregnancy identifies women at risk for recurrent disease in their next pregnancy.

From this study it was also found that haematocrit value raised both in mild and severe preeclampsia in comparison to normal pregnant women (Table-III) (p value 0.001). These results were consistent with the study of Heilmann et al[19]. They shown that haematocrit value of both mild and severe preeclampsia were significantly different from that of normal pregnant women. They also found that the lower haematocrit of normal pregnancy is associated with a decreased oxygen capacity but with an increased oxygen delivery. In cases with proteinuric hypertension a haematocrit above normal is associated with reduced systemic oxygen transport rate. Gifford et al[20] recommended haemoglobin and haematocrit value estimation along with other laboratory evaluation for the women in whom hypertension develops after midpregnancy as, haemoconcentration supports diagnosis of preeclampsia and is an indicator of severity.

The present study revealed a statistically significant correlation between heamatocrit value and diastolic pressure in the preeclamptic women (Figure-1)($r=0.33$ and p value<0.05). It also established a positive but statistically insignificant correlation between haematocrit value and systolic blood pressure in the preeclamptic subjects (Figure-2) ($r=0.20$ and p value> 0.05). These finding were supported by the study of Heilmann et al[10]. They found that with preeclampsia haematocrit values were invariably above those in normal pregnant women and there was also correlation between mean arterial blood pressure and haematocrit.

Estimation of haemoglobin levels during severe preeclampsia are valuable supplements to other and more sophisticated placental function tests[21]. The present study demonstrated the significant rise of haematocrit value in preeclamptic women (both mild and severe) over normal pregnant women. So it can be used to monitor the severity of preeclampsia along with other more sophisticated investigations and it was supported by many other studies[20,21,22]. However this study could not say about pregnancy outcome for which large scale prospective study may be performed.

Conclusion:

The mean haematocrit value of both mild and severe preeclamptic patients was significantly higher compared to that of the normal pregnant women ($P<0.05$). The positive correlations were established in between the haematocrit value and both the diastolic ($r=0.33, p<0.05$) and systolic($r=0.20$, $p>0.05$) blood Pressure.

References:

1. Acuin CS, Khor GL, Liabsuetrakul T, Achadi EL, Htay TT, Firestone R et al. Maternal, neonatal and child health in Southeast Asia: towards greater regional collaboration. Lancet 2011; 377 (9764): 516-525.

2. Geographic variation in the incidence of hypertension in pregnancy. World Health Organization International Collaborative Study of Hypertensive Disorders of Pregnancy. Am J Obstet Gynecol 1988; 158(1):80-83.

3. Robson Sc. Hypertension and renal disease in pregnancy. In: Edmonds DK editor. Dewhurts Text Book of Obstetrics and Gynaecology for Post-graduates. 6Th ed. Black well Science Publication, London. 1999: 166-185.

4. Khan KS, Wojdyla D, Say L, Gul mezoglu AM, Van Look PF.WHO analysis of causes of maternal death: a systematic review. Lancet 2006; 367 (9516): 1066-1074.

5. Yasmin HA et al. Baseline Survey for assessment of Emergency Obstetric Care Services in Bangladesh. Bangladesh Institute of Research for Promotion of Essential & Reproductive Health and Technologies (BIRPERT). 1995:10.

6. Brown MA, Zammit VC, Mitar DM. Extracellular fluid volumes in pregnancy induced hypertension. J Hypertans 1992; 10: 61-68.

7. Arias F. Practical guide to high risk pregnancy and delivery, 2nd edition. Harcourt Brace & Company Asia PTE Ltd, Singapore. 1993:186.

8. Ratnam SS, Rao KB, Arulkumaran S. Obstetrics and Gynecology for postgraduates, Vol 1. 2nd Edition. Orient Longman, Hydrabad. 1999:60.

9. Lebel M, Grose JH, Blais R. Increased hematocrit with normal red blood cell mass in early borderline essential hypertension. Clin. Exp. Hypertens A 1989; 11(8):1505-1514.

10. Heilmann L, Siekmann U, Schmid-Schonbein H, Ludwig H. Hemoconcentration and Preeclamsia. Arch-Gynecol Obstet 1981; 231(1):7-21.

11. Heilmann L, Gerhold S, Tempelhoff G.F.V, Pollow K. The role of intravenous volume expansion in moderate preeclampsia. Clin. Hemorheol 2001; 25:83-89.

12. Saunders NJ St. G, Spiby H, Patel D. Maternal haematocrit in labour is related to fetal cord pH at delivery. Br J Obstet Gynaecol 1990; 97:1144-1147.

13. LU ZM, Goldenbarg RL, Cliver SP, Cutter G, Blankson M. The Relationship Betwen Maternal Hematocrit and Pregnancy Outcome. Obstet Gynecol 1991; 77:90-94.

14. Sibai MB. Prevention of preeclampsia: A big disappointment. Am J Obstet Gynecol 1998; 179(5):1275-1278.

15. Soffronof EC, Kaufman BM, Connanghton JF. Intravascular volume determinations and fetal outcome in hypertensive diseases of pregnancy. Am J Obstet Gynecol 1977; 127:4-9.

16. Heilmann L, Rath W, Pollow K. Hemorheological changes in women with severe preeclampsia. Clin. Hemorheol. Microcirc 2004; 31:49-58.

17. Mathews JD, Mason TW. Plasma viscocity and preeclampsia. Lancet 1974; 1: 409.

18. Aardenbug R, Spaanderman MEA, Ekhart TH, van Eijndhoven HW, vander Heijden OWH, Peeters LLH. Low plasma volume following pregnancy complicated by pre-eclampsia predisposes for hypertensive disease in a next pregnancy. Br J Obstet Gynaecol 2003; 110:1001-1006.

19. Heilmann L, Siekmann U. Hemodynamic and hemorheological profile in women with proteinuric hypertension of pregnancy and in pregnant controls. Arch Gynecol Obstet 1989; 246:159-168.

20. Gifford RW, August PA, Cunningham G, Green LA, Lindheimer MD, McNellis D. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gyenecol 2000; 183(1):S1-S21.

21. Sagen N, Koller O, Haram K. Haemoconcentration in severe preeclampsia. Br J Obstet Gynaecol 1982; 89:802-805.

22. Golboni F, Heydarpour S, Taghizadeh, Kajemnezhad A. Predictive value of plasma haematocrit level in early diagnosis of preeclampsia. East Mediterm Health J 2011; 17(10): 744-748.

Original Article

Comparison Between Angiotensin-Converting Enzyme Inhibitor and Angiotensin-Receptor Blocker in Slowing the Progression of Early Chronic Kidney Disease (Renoprotection) in Diabetic Patients

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Abstract

Background: Angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) slows the worsening of the glomerular filtration rate (GFR). Treatment at an early stage of the disease may be beneficial for the patients. The effects of ACE inhibitors and ARBs on renal outcomes (ESKD, doubling of creatinine, prevention of progression of micro to macroalbuminuria) are similarly beneficial. ARBs, have the potential for more complete inhibition of angiotensin action compared with ACEI, because there are enzymes other than ACE that are capable of generating angiotensin II. But there effect on reducing GFR is still controversial. **Method:** A comparative clinical trial was conducted to see the effect of ARB (olmesartan) and ACEi (ramipril) on the patients with early stage chronic kidney disease and DM, who were not treated with ACEi or ARBs previously. 45 patients were selected by purposive and random sampling technique. Patient's serum creatinine, blood pressure and GFR were estimated before the initiation of treatment. The patients were treated with olmesartan 20 mg daily in one group and ramipril 2.5 mg daily in another group for 6 months. **Result:** GFR of olmesartan treated group was significantly decreased from initiation to end point of study (p=0.029). In ramipril treated group, reduction of GFR was also significant (p=0.010). But the change in the glomerular filtration rate between the two treatments groups did not show significant difference before initiation of treatment, at 3 month and at 6 month of treatment (p>0.05 in each follow up). Percent change of GFR in both study group shows non-significant (p>0.05) difference in between or before-after estimation of GFR in our population. **Conclusion:** This study shows that treatment with olmesartan 20 mg/day and ramipril 2.5 mg/day reduced GFR and blood pressure in patients with early stage CKD and DM. The differences between the two treatment regimens were not significant when compared. The serum creatinine level in olmesartan group was increased non-significantly in our study, where ramipril group shows significant increase in serum creatinine level.

Key words: Angiotensin converting enzyme inhibitors, Angiotensin-receptor blockers, GFR, CKD, ACEi, ARB.

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Introduction:

CKD is a global health problem associated with considerable morbidity and mortality and one of the major challenges today. Its prevalence is increasing by approximately 8% per year[1], partially attributable to the increasing prevalence of diabetes mellitus (DM), hypertension, obesity, and an overall aging population[2]. However, despite advances in the treatment of ESRD over the past 20 years, minimal improvement in mortality has been made since the early 1990s, and mechanisms to prevent and delay progression to ESRD are still being sought[3].

The primary cause of ESRD is DM in a percentage reaching 50%, followed by arterial hypertension (HTN) 27%, glomerulonephritis 13% and other causes 10%[1]. Regardless of the primary entity, progression of renal disease is characterized by pathomorphologic changes that comprise early renal inflammation, followed by subsequent tubulointerstitial fibrosis, tubular atrophy, and glomerulosclerosis[4]. The RAAS plays an important role in many of the pathophysiologic changes that lead to progression of renal disease[5].

Kidney disease has the lowest evidence base for clinical interventions of any specialist area of clinical medicine[6].

Interventions to delay the progression of renal disease are limited. The focus of previous research has been blood pressure (BP) reduction and limiting proteinuria. High-quality research in renal medicine has improved recently with the publication of several well-designed, randomised controlled trials (RCTs) including SHARP, EVOLVE and BEACON[7].

Angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor antagonists (ARB) are commonly used in patients with CKD. This is based on large RCTs and a wealth of epidemiological data, although their value in advanced CKD (estimated glomerular filtration rate of <30 ml/min/1.73m2) is unknown. There are no studies assessing the benefits of ACEi or ARB therapy in cardiovascular risk reduction in advanced non-dialysis CKD. Lowering BP reduces cardiovascular events but evidence suggests that ACEi or ARBs are not superior to other antihypertensive agents[7]. Studies in dialysis patients have shown variable effects on cardiovascular events with use of ACE inhibitors, while the rate of decline of renal function remains a strong predictor of mortality[8].

ALLHAT and other studies have shown suppression of the rennin-angiotensin-aldosterone system (RAAS) to be effective in slowing the progression of kidney disease in patients with CKD stage 3 or better. The benefit of ACE inhibitor and ARB cannot be solely attributed to BP reduction in patients with proteinuria. Angiotensin-II suppression results in vaso-relaxation, preferentially of the efferent arteriole in the glomerulus leading to reduced intraglomerular pressure and a significant anti-proteinuric effect[9].

Angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) slows the worsening of the glomerular filtration rate (GFR) and lower the rate of albumin excretion. Treatment at an early stage of the disease may be beneficial[10]. The effects of ACE inhbitor and ARB on renal outcomes (ESKD, doubling of creatinine, prevention of progression of micro to macroalbuminuria, remission from micro to normoalbuminuria) are similarly beneficial[11]. ARBs, have the potential for more complete inhibition of angiotensin action compared with ACEI, because there are enzymes other than ACE that are capable of generating angiotensin II[12]. But there effect on reducing GFR is still controversial.

Method:

A prospective comparative interventional study was conducted in the Department of Pharmacology and Therapeutics, Sylhet MAG Osmani Medical College, Sylhet in collaboration with Outpatient Department of Medicine and Nephrology, Sylhet M A G Osmani Medical College Hospital, Sylhet. The study was conducted during the period from 1st July 2014 to 30th June 2015. Prior to the commencement of the study, the research protocol was approved by the Ethical Committee of Sylhet MAG Osmani Medical College, Sylhet.

At that time period 45 patients with GFR 30-89 ml/min/1.73m2 and the age range of 35-70 years with Hypertension (Blood pressure >135/85 mmHg) were included in this study.

As the study was conducted in a Diabetic center, all patients those only have type 2 Diabetes were included in our studies. Exclusion criteria were- patients with ESRD (End Stage Renal Disease) (GFR<30ml/min/1.73m2), uncontrolled blood pressure (≥179/100mm of Hg), Patient who received ACEI or ARB previously, fever, heart failure, vulvular heart disease, disease that causes proteinuria (Nephrotic syndrome, UTI etc.), serum creatinine level ≥ 1.6mg/dl and Serum potassium value ≥5.1 mmol/l. Also patient taking NSAIDs, steroids, OCP and Cigarettes were not included in the study.

Total 45 patients were selected and on a random fashion, they were allowed to receive olmesartan (ARB) 20mg (n=23) and ramipril (ACEi) 2.5mg (n=22) in two groups. Before starting study drugs, Baseline characteristics (age, sex, body weight, height etc.) were recorded and variables (serum creatinine, systolic and diastolic blood pressure) were measured from collected blood sample of both study groups.

Detail history was taken in a prescribed data collection form. The study participants were divided into two groups. Randomization was done by giving a serial number to the patients who fulfilled the inclusion and exclusion criteria and all the odd numbers were included in group A and all even numbers were included in group B.

The patients of group A were treated with olmesartan 20mg once daily for 6 months and Group B were treated with ramipril 2.5mg once daily for 6 months.

Outcome was measured by monitoring reduction in GFR and Blood pressure (Systolic, Diastolic & Mean) before initiation of treatment, at the end of 3 month and 6 month. Blood pressure of the patients were measure 2 weekly for 1 month and then 4 weekly for 6 month. In course of follow up period 3 patients from olmesartan group and 5 patients from group ramipril were dropped out.

Laboratory analysis: Serum Creatinine was estimated by alkaline picrate method.

Glomerular filtration rate (GFR) was calculated by Cock-Crof & Gault formula.

Statistical analysis: All statistical analysis was done by SPSS (Statistical package for social science) for windows version 16.0.

Result:

In the present study the age of the patients ranged from 41 to 67 years with the mean of 54.00 ± 7.02 years in olmesartan treated group; while the age of the patients ranged from 42 to 70 years with the mean of 57.23 ± 8.81 years in ramipril treated group. The mean age of olmesartan treated group and ramipril treated group did not differ significantly (p=0.222) suggesting an age matched study.

Table I: Glomerular filtration rate (GFR) in olmesartan and ramipril treated group estimated at 0 week, 3 month and 6 month of treatment

Study group	Glomerular filtration rate (mean ± SD)ml/min/1.73m^2			‡p value
	At 0 week	At 3 month	At 6 month	
Olmesartan group (n=20)	70.69 ± 17.25	66.89 ± 16.71	66.66 ± 15.77	p=0.072[a] p=0.029[b] p=0.875[c]
Ramipril group (n=17)	64.62 ± 17.21	59.28 ± 15.44	59.59 ± 13.75	p<0.001[x] p=0.010[y] p=0.808[z]
*p value	p=0.293	p=0.163	p=0.159	

a = Before treatment vs at 3 month, b = Before treatment vs at 6 month, c = 3 month vs 6 month
x = Before treatment vs at 3 month, y = Before treatment vs at 6 month, z = 3 month vs 6 month
*Unpaired t test and ‡Paired t test was applied to analyze data

Table I: shows, before the initiation of treatment the glomerular filtration rate (GFR) was 70.69 ± 17.25 ml/min/1.73m2 in olmesartan group, which decreased to 66.89 ± 16.71 ml/min/1.73m2 at the end of 3 month and 66.66 ± 15.77 ml/min/1.73m2 at the end of 6 month of treatment. This reduction was not significant, before the initiation of treatment to at the end of 3 month (t=1.906; p=0.072[a]), before the initiation of treatment to at the end of 6 month (t=2.357; p=0.029[b]) and 3 month to 6 month (t=0.159; p=0.875[c]) period.

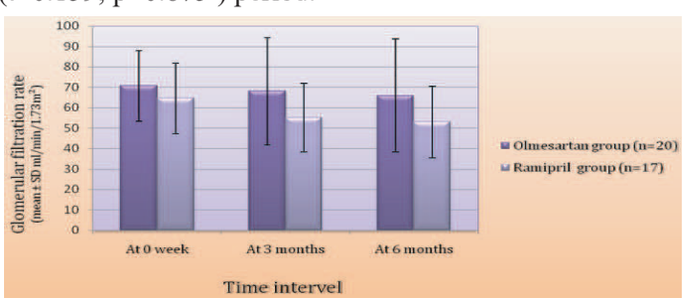

Figure 1: Glomerular filtration rate (GFR) in olmesartan and ramipril treated group estimated at 0 week, 3rd month and 6th month of treatment.

In the ramipril treated group, the GFR was 64.62 ± 17.21 ml/min/1.73m2 at 0 week, which decreases to 59.28 ± 15.44 ml/min/1.73m2 at the end of 3 month and 59.59 ± 13.75 ml/min/1.73m2 at the end of 6 month. The glomerular filtration rate decreased significantly (t=6.147; p<0.001[x]) in 1st 3 month, which was non-significant (t=-0.246; p=0.808[z]) in last 3 month period. The total reduction of GFR in 6 month period was significant (t=2.944; p=0.010[y]).

Glomerular filtration rate of two treatment group was compared and shows, no significant difference statistically at 0 week (t=1.067; p=0.293), at the end of 3 month (t=1.426; p=0.163) and at the end of 6 month (t=1.439; p=0.159).

The percentage reduction of glomerular filtration rate (GFR) was -4.55% at the end of 3 month and to -4.95% at the end of 6 month compared to baseline in olmesartan treated group. The difference in glomerular filtration rate in olmesartan group from before to end point of treatment was not significant (t=0.214; p=0.833).

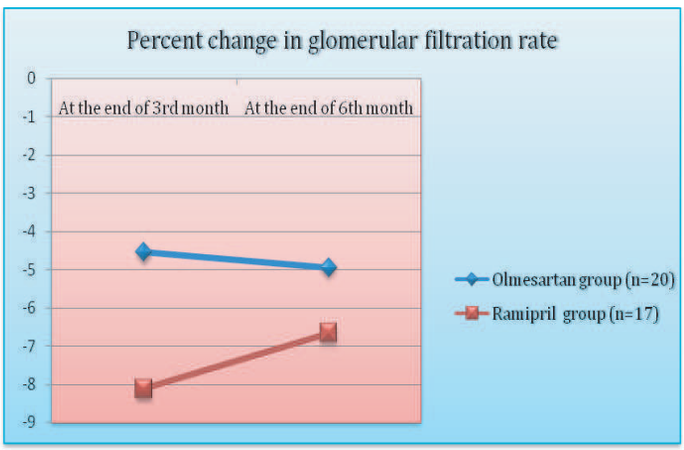

Figure 2: The percent reduction of glomerular filtration rate in both olmesartan and ramipril treated group at 3 month and at 6 month compare to baseline.

Table-II : Comparison of the effect of olmesartan and ramipril on systolic blood pressure, diastolic blood pressure and mean arterial pressure measured at 0 week, 3rd month and 6th month of treatment.

Time period	Systolic blood pressure (mean ± SD mm Hg)			Diastolic blood pressure (mean ± SD mm Hg)			Mean arterial pressure (mean ± SD mm Hg)		
	Group A	Group B	*p value	Group A	Group B	*p value	Group A	Group B	*p value
At 0 week	150.75 ± 8.31	152.35 ± 9.37	p=0.585	94.75 ± 8.19	92.35 ± 12.88	p=0.497	113.42± 6.41	112.35 ± 9.11	p=0.680
At 3rd month	132.75 ± 7.16	136.47 ± 7.86	p=0.141	80.00 ± 7.43	79.41 ± 8.08	p=0.819	97.58 ± 6.70	98.24 ± 5.85	p=0.757
At 6th month	129.75 ± 6.17	132.06 ± 6.14	p=0.263	75.25 ± 6.78	76.18 ± 7.19	p=0.689	93.42 ± 5.98	94.80 ± 5.92	p=0.485
‡p value	p<0.001[a] p<0.001[b] p=0.002[c]	p<0.001[x] p<0.001[y] p<0.001[z]		p<0.001[a] p<0.001[b] p<0.001[c]	p<0.001[x] p<0.001[y] p=0.029[z]		p<0.001[a] p<0.001[b] p<0.001[c]	p<0.001[x] p<0.001[y] p=0.002[z]	

Group A = Olmesartan group (n=20), Group B = Ramipril group (n=17)

*Unpaired t test and ‡Paired t test was applied to analyze data
a = Before treatment vs at 3 month, b = Before treatment vs at 6 month, c = 3 month vs 6 month
x = Before treatment vs at 3 month, y = Before treatment vs at 6 month, z = 3 month vs 6 month

In ramipril treated group, the percentage reduction of glomerular filtration rate was -8.12% at the end of 3rd month and to -6.66% at the end of 6th month treatment period compared to before initiation of treatment. The percentage reduction in glomerular filtration rate was not significant from baseline to end point of treatment (t=-0.745; p=0.467) in ramipril group.

No significant statistical difference in percentage reduction of glomerular filtration rate, between two groups were observed at the end of 3 month (t=1.198; p=0.239) and at the end of 6 month (t=0.536; p=0.595), when compared.

In table-II the effect of olmesartan and ramipril on systolic blood pressure, diastolic blood pressure and mean arterial pressure are shown in different time interval. Systolic blood pressure of both treatment groups were reduced significantly from 0 week to 6 month period. When these changes in systolic blood pressure between the two treatments groups were compared no significant difference was observed.

In the olmesartan treated group, the change in diastolic blood pressure between before the initiation of treatment and at the end of 6 month was significant (t=9.671; $p<0.001^{b}$). In the ramipril treated group, the diastolic blood pressure was reduced significantly (t=5.785; $p<0.001^{y}$) at 6 month period. When these changes in diastolic blood pressure between two treatments groups were compared no significant difference was observed.

In the olmesartan treated group, the serum creatinine was 1.11 ± 0.30 mg/dl before the initiation of treatment which increased to 1.15 ± 0.26 mg/dl at the end of 3 month and to 1.15 ± 0.25 mg/dl at the end of 6 month. The increase in serum creatinine level in olmesartan group was not significant, before to at the end of 3 month (t=-1.630; $p=0.119^{a}$), before to at the end of 6 month (t=-1.917; $p=0.070^{b}$) and 3rd month to 6th month (t=0.000; $p=1.000^{c}$) period.

In the ramipril treated group, the serum creatinine was 1.04 ± 0.21 mg/dl before the initiation of treatment which increase to 1.12 ± 0.21 mg/dl at 3rd month and to 1.11 ± 0.18 mg/dl at 6th month. This increase in serum creatinine level was significant before to at the end of 3rd month (t=-7.50; $p<0.001^{x}$) and before to at the end of 6th month (t=-2.781; $p=0.013^{y}$). But in between 3rd month and 6th month it was non-significant (t=0.717; $p=0.484^{z}$).

When change in the serum creatinine between the two treatments groups were compared, no significant difference was observed before initiation of treatment (t=0.869; p=0.391), at the end of 3 month (t=0.395; p=0.695) and at the end of 6 month (t=0.680; p=0.501).

Discussion:

In the current study, the glomerular filtration rate (GFR) of olmesartan group was significantly decreased from initiation to end point of study where p value was 0.029. In ramipril group, reduction of glomerular filtration rate was also significant (p=0.010). But the change in the glomerular filtration rate (GFR) between the two treatments groups did not show significant difference before initiation of treatment, at 3 month and at 6 month of treatment (p>0.05 in each follow up). Percent change in GFR in both study group shows non-significant (p>0.05) change in between or before-after estimation of GFR in our population.

A study by Lacourciere, shows significant (P≤0.001) reduction in GFR in losartan and enalapril treated group13. Where Hoque, shows eGFR slightly raised in both enalapril and losartan treated group[14]. The ROADMAP study showed that Olmesartan was associated with a significant reduction in eGFR (about 4 ml/min/1.73 m2)[15]. In the post hoc analysis of the IDNT, Irbesartan safely and significantly slowed the rate of change in eGFR (–2.34ml/min/1.73m2/year) compared to amlodipine (–3.76ml/min/1.73 m2/year) and placebo (–3.52 ml/min/1.73m2/year) at similar BP control and conferred renoprotection in patients with diabetic nephropathy (average eGFR 46.4 ml/min/1.73 m2)[16].

In the present study the systolic blood pressure and the percentage reduction of systolic blood pressure; diastolic blood pressure and the percentage reduction of distolic blood pressure; and mean arterial pressure and the percentage reduction of mean arterial pressure were decreased significantly from baseline to endpoint of treatment in olmesartan treated group (p<0.001) and also in ramipril treated group (p<0.001). But the change between the two treatments groups did not show significant difference in their follow up. Lacourciere, found that both losartan and enalapril administered alone or in combination with other agents significantly decreased (p=0.005) systolic BP and diastolic BP without a clear cut difference between the two treatment groups. Indeed, losartan decreased sitting BP from 163.3 (16.2)/97.2 (6.3) mm Hg to 148.3 (17.1)/86.8 (9.6) mm Hg. On the other hand, enalapril decreased sitting BP from 157.7 (15.9)/95.3 (4.8) mm Hg to 145.5 (18.2)/84.4 (8.4) mmHg. Mean changes in standing BP were similar to changes observed in the sitting position[13]. Hoque, showed that, systolic blood pressure decreased from baseline to end point of treatment in both enalapril and losartan treated groups but diastolic pressure did not decrease from baseline to end point of treatment both groups[14].

enalapril and losartan in another study shows no significant difference in mean reductions of blood pressure[13]. It was also observed in DETAIL study that both telmisartan and enalapril reduced blood pressure and their difference of mean reductions was non-significant[17].

The serum creatinine level in olmesartan treated group was increased non-significantly (p=0.070) in our study. In this treatment period serum creatinine was also increased from baseline to 6 month in ramipril treated group, which was significant (p=0.013). But the change in the serum creatinine between the treatment groups did not show any significant difference before initiation of treatment, at 3 month and at 6 month (p>0.05 in each follow up). A study shows mild increase in serum creatinine level in enalapril and losartan treated group in bangladeshi population[14]. In another study Brenner shows, losartan reduce the incidence of serum creatinine doubling[18].

Conclusion:

Our study shows that both Angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) significantly reduced GFR in patients with early stage CKD and DM. But statistically the differences between the two treatment regimens were not significant. Some study shows that patients with diabetic nephropathy and early stage chronic kidney disease may receive benefit from the treatment with ACE inhibitors or ARBs. Worsening of GFR in early stage CKD may be alter with ACE inhibitors or ARBs and should study on a large group of population for a long time period which may show significant delay in the progression to ESRD.

References:

1. Johnson CA, Levey AS, Coresh J, Levin A, Lau J, Eknoyan G. Clinical practice guidelines for chronic kidney disease in adults; Part I. Definition, disease stages, evaluation, treatment and risk factors. Amaerican journal of Family Physician. 2004; 70: 869-876.
2. Rao M, Wang C, Bakris G. Hypertension and CKD: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES), 1999-2004. American Journal of Kidney Diseases. 2008; 51: S30-S37.
3. Foley RN, Collins AJ. End-stage renal disease in the United States: an update from the United States Renal Data System. Journal of American Society of Nephrology. 2007; 18: 2644-2648.
4. Remuzzi G, Benigni A, Remuzzi A. Mechanisms of progression and regression of renal lesions of chronic nephropathies and diabetes. Journal of Clinical Investigation 2006; 116: 288–296.
5. Baltatzi M, Savopoulos Ch, Hatzitolios A. Role of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in hypertension of chronic kidney disease and renoprotection: Study results. HIPPOKRATIA. 2011; 2015: 27-32.
6. Strippoli GF, Craig JC Schena FP. The number, quality, and coverage of randomized controlled trials in nephrology. Journal of American Society of Nephrology. 2004; 15: 411–419.
7. Ahmed A, Jorna T, Bhandari S. Should We STOP Angiotensin Converting Enzyme Inhibitors/ Angiotensin Receptor Blockers in Advanced Kidney Disease? Nephron. 2016; 133: 147–158
8. Zannad F, Kessler M, Lehert P. Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of fosinopril and implications for future studies. Kidney International. 2006; 70 : 1318–1324.
9. Lewis EJ, Hunsicker LG, Bain RP. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The collaborative study group. The New England Journal of Medicine. 1993; 329: 1456–1462.
10. Ruggenenti P, Fassi A, Ilieva AP. Preventing microalbuminuria in type 2 diabetes. The New England Journal of Medicine. 2004; 351: 1941-1951.
11. Bailey J. ACE inhibitor vs. ARBs for patients with Diabetes Kidney Disease. American Family physician. 2007; 76: 68-69.
12. Rayner B. Importance of Modulating the Rennin-Angiotensin System in Preventing Renal Complications of Hypertension. Saudi Journal of Kidney Diseases and Transplantation. 2006; 17: 469-480.
13. Lacourciere Y, Belanger A, Godin C, Halle JP, Ross S, wright N, et al. Long term comparison of losartan and enalapril on kidney fuction in hypertensive type 2 diabetics with early nephropathy. Kidney International. 2000; 58: 762-769.
14. Hoque R, Rahman MS, Iqbal M. Effect of enalapril and losartan on proteinuria in type 2 diabetic nephropathy patients. Bangladesh Medical Resarch Council Bulletin. 2009; 35: 44-48.
15. Haller H, Ito S, Izzo JLJ, Januszewicz A, Katayama S, Menne J, et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. The New England Journal of Medicine. 2011; 364: 907–917.
16. Lewis EJ, Hunsicker LG, Clarke WR, et al. Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. The New England Journal of Medicine. 2001; 345: 851–860.
17. Barnett AH, Bain SC, Bouter P, Karlberg B, Madsbad S, Jervell J et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. The New England Journal of Medicine. 2004; 351: 1952–1961.
18. Brenner BM, Cooper ME, Zeeuw DD, Keane WF, Mitch WE, Parving HH, et al. Effects of Losartan on renal and cardiovascular outcome in patients with type 2 diabetes and nephropathy. The New England Journal of Medicine. 2001; 345(12): 861–869.

Original Article

Detection of Hepatitis C Seropositivity in Patients with Chronic Urticaria

Dilruba Aktar[1], Sharmin Khan[2], Ashik-E-Robbani[3], Farhana Yasmin[4].

Abstract

Background: Urticaria is a common disorder that affects up to 20% of the population at some point during their lifetime. It is well established that Hepatitis B virus causes urticaria. Whether Hepatitis C infection causes urticaria or not is still debated with reports both in favor of and against. There is no clear-cut evidence to affirm or refute a direct link between chronic urticaria and HCV infection in the literature. **Objectives:** To see hepatitis C sero-positivity in patients with chronic urticaria. **Method:** This was a hospital based case-control study conducted in the Department of Dermatology and Venereology, Jalalabad Ragib- Rabeya Medical College Hospital, Sylhet during the period from January 2013 to June 2013. Seventy three patients with chronic urticaria were enrolled in case group. Inclusion criteria were patients with chronic urticaria of all age and both sex. Control subjects were age and sex matched patients with different dermatological disorders other than chronic urticaria and no known association with Hepatitis C virus. Anti HCV antibody was measured in all cases and controls.

Result: Duration of the patients of chronic urticaria and control were6-12 weeks in 25 (34.2%), 3-6 months in 18 (24.7%), 7-12 months in 17 (23.3%), 1-5 years in 8 (10.9%) and above 5 years in 5 (6.8%) patients. Duration of chronic urticaria among male and female patients did not differ significantly (p=0.768).Recurrent type of chronic urticaria was in 28 (39.4%) patients and persistent type was in 45 (61.6%) patients. Types of chronic urticaria among male and female patients did not differ significantly (p=0.665). Disease pattern of the patients of control group were scabies in 24 (39.9%), acne vulgaris in 21 (28.8%), Tinea corporis in 15 (20.5%) , eczema in 8 (11.0%) and vitiligo in 5 (6.8%) patients. There was no sero-positivity for Hepatitis C virus in chronic urticaria group; whereas 1 (1.4%) patient was sero-positve for Hepatitis C virus in control group. The Hepatitis C sero-positivity between the patients of chronic urticaria group and control group did not show any statistically significant difference (p>0.05).

Conclusion: The negative result in this study concludes that there is no role of hepato-trophic virus C in chronic urticaria and the routine investigations for this virus in patients of chronic urticaria are not cost-effective.

Key words: Chronic urticaria, Anti HCV antibody.

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Introduction:

Urticaria is a vascular reaction of the skin characterized by the appearance of wheels, generally surrounded by a red halo or flare and associated with severe itching, stinging or pricking sensation.[1] Urticaria is classified into acute and chronic on the basis of time division of six weeks and chronic urticaria is defined as urticaria that persists for longer than 6 weeks.[2] Urticaria is a common disorder that affects as many as 20% of the population at some point during their life-time. Although a number of triggering factors including drugs,[3] food additives, aeroallergens,[2] connective tissue disorders and infections,[4] have been implicated;[5,6] the etiology still remains largely elusive. Among the various infections suspected, attention has recently been focused on the hepatotrophic viruses.[2] Urticaria has a spectrum of diverse clinical presentations and causes. Clinically, it is classified into ordinary urticaria, physical urticaria, contact urticaria, urticarial vasculitis, and angioedema.[7] Although urticarial vasculitis and urticaria as part of mixed cryoglobulinemia are well known to occur, urticarial vasculitis is a form of small vessel

vasculitis that may present with both urticaria and arthritis. Infections are well recognized as one of the exacerbating factors for urticaria. Infectious agents, such as bacteria, viruses, parasites, and fungi, reported to have association with urticaria. The temporal relationship between infections and urticaria onset, as well as its remission or improvement after treatment of a coincident infection, supports this link.[8] Hepatitis C virus (HCV) is a single-stranded RNA flavivirus that replicates in hepatocytes and peripheral blood mononuclear cells. Hepatitis C infection leads to liver cirrhosis and hepatocellular carcinoma.[9] Reports have also shown that 55–70% of the HCV patients go into the chronic course of the disease affecting organ systems, including joints, muscles, neural and gastrointestinal tissues, and skin.[10] Cutaneous manifestations are often the first signs (observed in 20–40% of the patients with chronic HCV infection).[11] However, the prevalence of skin manifestations varies from one geographic area to another. Blood or blood products constitute the primary transmission routes of HCV. Whether hepatitis C infection is involved in pathogenesis of urticaria or not is still debatable, as conflicting reports have been presented both in favor and against to this topic.[9]

Several studies have suggested that HCV status should be checked in patients presenting with urticaria in areas with a high prevalence.[5,6,12,13] Although clinically significant dermatological manifestations of HCV infection are relatively low, however, under certain conditions it can be associated with significant morbidity and even mortality. Therefore, awareness and immediate recognition of these manifestations is of paramount importance in facilitating early diagnosis and offering better treatment. There is lack of literature regarding hepatitis C sero-positivity in patients with acute and chronic urticaria in Bangladesh. So, this study was designed to see the association of hepatitis C sero-positivity in patients with chronic urticaria.

Method: This hospital based case-control study was conducted in the Department of Dermatology and Venereology, Jalalabad Ragib-Rabeya Medical College Hospital, Sylhet. Protocol of this study was approved by Ethical Review Committee of Jalalabad Ragib-Rabeya Medical College Hospital, Sylhet. Seventy three patients with typical chronic urticaria those attended the Department of Dermatology and Venereology, Jalalabad Ragib-Rabeya Medical College Hospital, Sylhet during the period from January 2013 to June 2013 and those fulfilling the inclusion and exclusion criteria were enrolled in case group. Seventy three age and sex matched patients with different dermatological disorder other than chronic urticaria and not related to any hepatotrophic virus infections were included in the control group. The aims and objectives of the study were explained to the patients or the attendant of each case and control in easily understandable local language and then written informed consent was taken. A thorough history was obtained from each patient about urticaria using the standard questionnaire containing both demographic (age, sex, occupation and marital status) and clinical details (symptoms, sign, past-medical history and predisposing risk factors of urticaria and its duration, presence of any food allergies, underlying infections, or drugs as exacerbating factors). The presence of evanescent urticated plaques was suggestive of urticaria. Patients with drug, food, or infection-induced urticaria were excluded from the study. Similarly, patients with physical urticaria or those with a previous history of connective tissue diseases (urticaria of at least 6 weeks duration) were excluded. Type of chronic urticaria were also noted. Control patients were also evaluated by a thorough history and physical examination. Clinical diagnosis was made to categories types of dermatological disease in control subjects.

Data analysis:

Data were processed and analyzed with the help of computer program SPSS (Statistical Package for Social Sciences) version 21. Quantitative data were expressed as mean and standard deviation and qualitative data as frequency and percentage. Comparison was done by Chi-Square ($\chi 2$) test and Z-test where applied. A probability (p) value of < 0.05 ($p<0.05$) was considered statistically significant.

Result:

The results of this cross-sectional comparative study were as follows:

Distribution of patients by duration of chronic urticaria

Distribution of patients by duration of chronic urticaria was shown in figure-1. Duration of chronic urticaria was 6-12 weeks in 25 (34.2%), 3-6 months in 18 (24.7%), 7-12 months in 17 (23.3%), 1-5 years in 8 (10.9%) and more than 5 years in 5 (6.8%) patients.

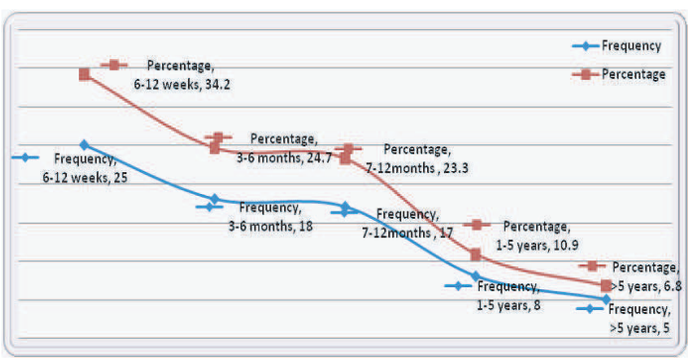

Figure 1: Distribution of patients by duration of chronic urticaria

Distribution of the patients according to types of chronic urticaria:

Figure 2: showed the patients according to types of chronic urticaria. Recurrent type of chronic urticaria was in 28 (39.4%) patients and persistent type was in 45 (61.6%) patients.

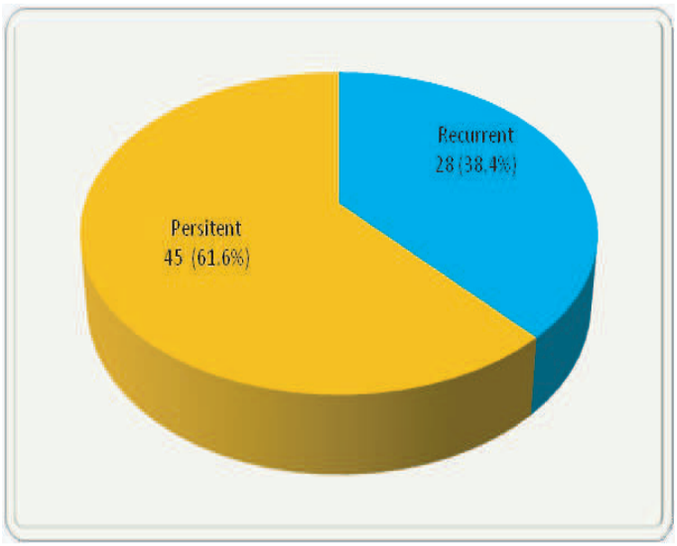

Figure 2: Distribution of the patients according to types of chronic urticaria (n=73)

Distribution of disease pattern of the patients of control group:

Distribution of disease pattern of the patients of control group was shown in figure-3. Disease pattern of the patients of control group were scabies in 24 (39.9%), acne vulgaris in 21 (28.8%), Tinea corporis in 15 (20.5%), eczema in 8 (11.0%) and vitiligo in 5 (6.8%) patients

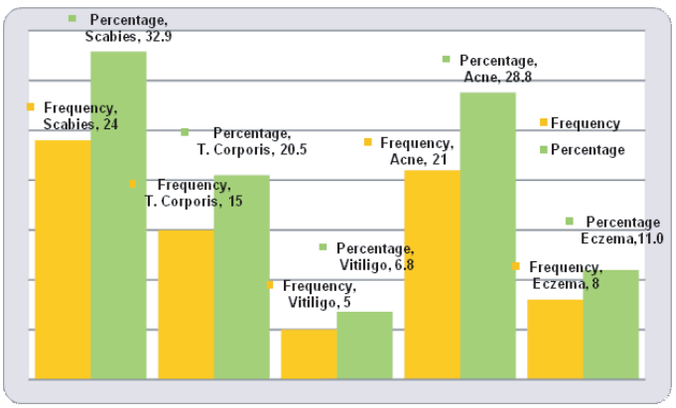

Figure 3: Distribution of disease pattern of the patients of control grou

Distribution of the patients according to Hepatitis C seropositivity:

Table I: Distribution of the patients according to Hepatitis C sero-positivity

Hepatitis C sero-positivity	Study group		p value
	Case (n=73)	Control (n=73)	
Positive	0 (0.0)	1 (1.4)	
Negative	73 (100.0)	72 (98.6)	p>0.05
Total	73 (100.0)	73 (100.0)	

*Chi-square ($\chi 2$) test with Yates' correction was applied to test the level of significance.

Figure in the parenthesis indicates corresponding percentage

.

Discussion:

The hepatitis C virus is an RNA virus that is a major cause of acute and chronic hepatitis. Both acute and chronic hepatitis C are asymptomatic in most patients. Chronic hepatitis C is associated with numerous extra-hepatic manifestations among which skin disorders are quite common.[14]Chronic urticaria may be continuous urticaria, occurring at least twice a week off treatment. While urticaria occurring less frequently than this over a long period is better called episodic (or recurrent), because this presentation is more likely to have an identifiable environmental trigger.[17]Although, urticarial vasculitis and urticaria as part of mixed cryoglobulinemia are well-known to occur with HCV infection, the association of ordinary urticaria remains unclear.[15,18,19] Thiscross-sectional comparative study was conducted in the Department of Dermatology and Venereology, Jalalabad Ragib-Rabeya Medical College Hospital, Sylhet during the period from January 2013 to June 2013 with a view to see hepatitis C sero-positivity in patients with chronic urticaria. For this purpose 73 patients with chronic urticaria were enrolled in case group; and 73 age and sex matched patients with different dermatological disorder other than chronic urticaria were enrolled in control group. The results of the study were as follows:

In this study the age of the patients ranged from 18 to 44 years with the mean age of 29.6 (SD±7.8) years in chronic urticaria group; whereas the age of the patients of control group ranged from 18 to 44 years with the mean age of 30.9 (SD±7.9) years. The mean age of the patients did not differ significantly between two groups (p>0.05).Similar mean age of patients with urticaria was reported in the study of Malik et al.[15] that the mean age of their urticaria

patients was 31.6 years. Bhatt, 2found that the mean age of their chronic urticaria patients was 33.86 (SD ± 13.50) years. This study also showed that 27 (37.0%) patients aged between 25 to 34 years, 24 (32.9%) ,between 35 to 44 years and 22 (30.1%) ,between 18 to 24 years in chronic urticarial group; while 26 (35.6%) patients between 35 to 44 years, 24 (32.9%) ,between 25 to 34 years and 23 (31.5%) ,between 18 to 24 years. There was no significant difference between the age group of the patients in between the groups (p=0.870). In this regards Un this regards Gaig et al.20 found that the age patients of chronic urticaria was above 65 years in 33.3%,25-44 years in 30.0%, 45-65 year in 30.0% and 18-24 years in 6.7%. Bhatt,2 found that the age patient of chronic urticaria was 20-40 years in 57.1%,above 49 years in 27.1% and below 20 year in 15.7% .In the present study there were 31 (42.5%) male and 42 (57.5%) female in chronic urticarial group; whereas 34 (46.6%) male and 39 (53.4%) female in control group. The sex of the patients of chronic urticarial group and control group did not show any statistically significant difference (p=0.617). Similar sex distribution was found in the study of Bhatt,2 that 41.4% of patients with chronic urticaria were female and 58.6% of paients were male. Gaiget al.20 also found the female (75.0%) preponderance of chronic urticaria. Malik et al.15 found 66.7% of their urticaria patients were male. In the current study the duration of chronic urticaria was 6-12 weeks in 25 (34.2%), 3-6 months in 18 (24.7%), 7-12 months in 17 (23.3%), 1-5 years in 8 (10.9%) and more than 5 years in 5 (6.8%) patients. Nearly similar results were observed in the study of Gaig et al.62 that 52.3% of patients who had suffered from chronic urticaria lasted from 6 to 12 weeks, in 18.5% from 3 to 6 months, in 9.4% from 7 to 12 months, in 8.7% from 1 to 5 years and finally in 11.3% of patients the urticaria lasted for more than 5 years. Bhat,2 also support the present study that 50.0% of patients who suffered from chronic urticaria from less than 6 months, in 18.6% from 7 to 12 months, in 18.6% from 1 to 5 years and finally in 12.9% of patients the urticaria lasted for more than 5 years. This study also showed that the duration of chronic urticaria among male patients was 6-12 weeks in 11 (35.5%), 7-12 months in 8 (25.8%), 3-6 months in 7 (22.6%), more than 5 years in 3 (9.7%) and 1-5 years in 2 (6.5%); while duration of chronic urticaria among female patients was 6 -12 weeks in 14 (33.3%), 3-6 months in 11 (26.2%), 7-12 months in 9 (21.4%), 1-5 years in 6 (14.3%) and more than 5 years in 2 (4.8%) patients. Duration of chronic urticaria among male and female patients did not differ significantly (p=0.768). Bhat,2 also support the present study that 58.6% of patients who suffered from chronic urticaria from less than 6 months, 10.3% from 6 to 12 months, 20.9% from 1 to 5 years and finally 10.3% of patients the urticaria lasted for more than 5 years among their male patients; whereas 43.9% of patients who suffered from chronic urticaria from less than 6 months, 24.4% from 6 to 12 months, 17.1% from 1 to 5 years and 14.6% of patients the urticaria lasted for more than 5 years among their male patients. Duration of chronic urticaria among male and female patients did not differ significantly (p=0.407).In this study recurrent type of chronic urticaria was in 28 (39.4%) patients and persistent type was in 45 (61.6%) patients. This result correlates with the study of Bhatt,2 that 42.8% of patients had recurrent type of chronic urticaria and 57.2% of patients had persistent type of chronic urticaria. This study also showed that recurrent type of chronic urticaria was in 11 (35.5%) and persistent type was in 20 (64.5%) among male patients; while recurrent types of chronic urticaria was in 17 (40.5%) and persistent type was in 25 (59.5%) among female patients. Types of chronic urticaria among male and female patients did not differ significantly (p=0.665). This result is in agreement with the study of Bhatt,2 that recurrent types of chronic urticaria was in 51.7% and persistent type was in 48.3% of male patients; while recurrent type of chronic urticaria was in 36.6% and persistent type was in 63.4% of female patients. Types of chronic urticaria among male and female patients did not differ significantly (p=0.207).

In this study there was no sero-positivity for Hepatitis C virus in chronic urticarial group; whereas 1 (1.4%) patient was sero-positve for Hepatitis C virus in control group. The Hepatitis C sero-positivity between the patients of chronic urticarial group and control group did not show any statistically significant difference (p>0.05). This result correlates with the study of Bhatt,2 that anti-HCV antibodies were absent in all patients in the study and the control group; thereby no association of chronic urticaria with hepatotrophic virus C. In another study conducted by Criberet al.[16] to look for the prevalence of hepatitis C virus (HCV) infection in patients with urticaria. HCV infections were detected by serology and RT-PCR for HCV RNA. Hepatitis C virus RNA was detected only by genomic amplification. Antibodies to HCV were found in one patient among 110 patients with chronic urticaria and in one from the control group (0.9% of each group). None had circulating HCV RNA. The study indicated that HCV infections are unlikely cause of urticaria in the general population. Tousiet al.[21] at Loghman Hakim Hospital, Iran carried out a study which included 53 patients with age and sex matched controls attending the same department for different condition. All patients and controls had enzyme linked immune sorbent assay for IgG anti-HCV antibodies which proved negative in both groups. It was therefore concluded that there is no relation between urticaria and HCV infection. Several other studies also supported the present study that lack of association between HCV infection and urticaria.[12,22] But Malik et al.[15] and Halawani,9showed a significant

association between HCV infection and urticaria. There is still a debate among the investigators whether to include hepatitis C workup in chronic urticaria.[23]

Conclusion:

In this study there was no sero-positivity for Hepatitis C in chronic urticaria; whereas 1 (1.4%) patient was sero-positve for Hepatitis C virus in age and sex matched dermatological diseases not having urticaria or known association of Hepatitis C virus. The Hepatitis C sero-positivity between the patients of chronic urticarial group and control group did not show any statistically significant difference ($p>0.05$). The negative result in this study concludes that there is no role of hepato-trophic viruses C in chronic urticaria and the routine investigations for this virus in patients of chronic urticaria are not cost-effective.

Recommendation:

As was no association between Hepatitis virus C and chronic urticaria, the present study does not recommend the routine investigation for Hepatitis virus C in patients of chronic urticaria. But large scale multicentre study required.

Limitation:

This study was conducted in a single center hospital in Sylhet.

Reference:

1. James WD, Berger TM, Elston DM. Andrew's Diseases of the Skin: Clinical Dermatology. 10th ed. Saunders: Canada; 2006. p. 149.
2. Bhatt TA. Chronic urticaria: are Hepato-trophic viruses B and C to blame? Egyptian Dermatology Online Journal 2011; 7(1):3.
3. Grattan C. Aspirin- sensitive urticaria. ClinExp Dermatol 2003; 28:123-7
4. Tebbe B, Geilen CC, Schulzkee JD, Bojarski C, Radenhausen M, Orfanos CE. Helicobacter Pylori infections in chronic urticaria. J Am AcadDermatol 1996; 34:685-6.
5. Hamid S, Cruz PD Jr, Lee WM. Urticarial vasculitis caused by hepatitis C virus infection: response to interferon alpha therapy. J AM Acad Dermatol 1998;39 (2 Pt-1):278-80.
6. Siddique N. Pereira BN, Arshad H. Hepatitis C and urticaria: cause and effect? Allergy 2004;59:668.
7. Grattan CE, Sabroe RA, Greaves MW. Chronic urticaria. J Am Acad Dermatol 2002;46:645–7.
8. Wedi B, Raap U, Kapp A. Chronic urticaria and infections. Curr Opin Allergy ClinImmunol 2004;4:387–96.
9. Halawani M. Screening of Hepatitis C Virus Genotypes in Urticaria Patients in Saudi Arabia. Genetic Testing and Molecular Biomarkers 2012; 16(8): 964–7.
10. Blackard JT, ShataMT, ShireNJ, Sherman KE. Acute hepatitis C virus infection: a chronic problem. Hepatology 2008;47:321–31.
11. Galossi A, Guarisco R, Bellis L, Puoti C. Extrahepaticmani-festations of chronic HCV infection. J Gastrointest Liver Dis 2007;16:65–73.
12. Llanos F, Raison-Peyron N, Meunier L, Ducos J, Meynadier J. Hepatitis C virus infection in patients with urticaria. J Am Acad Dermatol 1998;38: 646.
13. Smith R, Caul EO, Burton JL. Urticaria and hepatitis C. Br J Dermatol 1997;136: 980.
14. Hadziyannis SJ. Skin diseases associated with hepatitis C virus infection. J Eur Acad Dermatol Venerol 1998;10:12–21.
15. Malik LM, Mufti S, Saeed S, Ahmed S, Hussain I. Hepatitis C seroposi-tivity in patients with acute and chronic urticaria. J Pak AssocDermatol 2008;18:144–8.
16. Cribier BJ, Santinelli F, Schmitt C, Stoll-Keller F, Grosshans E. Chronic urticaria is not significantly as-sociated with hepatitis C or hepatitis G infection: a case–con-trol study. Arch Dermatol 1999; 135:1335–9.
17. Grattan CEH. Urticaria and Angioedema. In: Bolognia JL, Jorizzo JL, Schaffer JV, eds. Dermatology. 3rdedn. China: Elsevier, Saunders; 2012. p.294.
18. Ito A, Kazama T, Ito K, Ito M. Purpura with cold urticaria in a patient with hepatitis C virus infection-associated mixed cryoglobulinemia type lll: Successful treatment with interferon beta. J Dermatol 2003; 30: 321-5.
19. Doutre MS, Beylot-Barry M, Beylot C. Urticaria and hepatitis C infection. Br J Dermatol 1998; 138:194-5.
20. Gaig P, Olona M, Muñoz Lejarazu D, Caballero MT, Domínguez FJ, Echechipia S, et al. Epidemiology of urticaria in Spain. J Invest Allergol ClinImmunol 2004; 14(3): 214-20.
21. Tousi P, Rahmati M, Khorshid SM. Urticaria and Hepatitis C infection: is there a relationship? Int J Dermatol 2002; 41:712-15.
22. Raslan HM, Ezzat WM, Abd El Hamid MF, et al. Skin manifestations of chronic hepatitis C virus infection in Cairo, Egypt. East Mediterr Health J 2009; 15:692–700.
23. Cribier B. Urticaria and Hepatitis. Clin Rev Allergy Immunol 2006; 30:25-9.

Original Article

Pharmacoadherence to Anti-diabetic Medication Among Patients with Type 2 Diabetes Mellitus - A Hospital based cross sectional Study

Saleh Ahmed[1], Kamal Hossain Patwary[2], Helalur Rahman[3], AKM Sajedur Rahman[4]

Abstract

Background: Adherence to prescribed medications is an important factor for healthcare and its outcome. It is very much important for chronic diseases care to reduce its mortality and morbidity. Diabetes is a multisystem involving chronic disease and for good glycemic control adherence to prescribed medication and advices are pivotal. This study was done to assess the adherence to anti-diabetic drugs among the patients with Type-2 diabetes mellitus. **Method:** A cross-sectional study was conducted among Type-2 diabetic patients who were admitted in medicine units of Cumilla Medical College and those who came to outpatient department for medical care between June 2017 to May 2018.Assessment of adherence to anti-diabetic medication was based on patient's self-reported recall and observation of treatment order present with him/her.Data were collected for at least three months or the periods between last two visits where the interval between them is at least three months or more. Data were entered and analyzed using Statistical Package for Social science version 16. **Result:** In our assessment of adherence, only 14.11% patients have good adherence, 51.63% have moderate and 34.26% have poor adherence respectively. Patients with only Insulin have very good adherence (83.33%) and with minimum number of oral agents(one drugs) had good adherence (72.22%) whereas non adherence is maximum(100%) in three drugs combination, 39.19% in Insulin and two drugs combination, & 37.50% in two Insulin and one oral drugs combination. Adherence was good in middle aged and elderly group having good educational background. Associated comorbid diseases also increase adherence and patients having only diabetes usually feels better and stop medication at a certain point of their ongoing treatment (43.24%). **Conclusion:** To increase drugs adherence and good glycemic control, patient based motivation and prescribing drugs considering patients are paramount. There is a need for setup policies that will be helpful for patients education and to minimize the cost of anti-diabetic drugs to improve adherence and reduce associated complications.

Key words: Type-2 diabetes, Adherence, Diabetic drugs.

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Introduction:

Diabetes Mellitus is a complex and chronic disease with a growing and ongoing worldwide epidemic. It is estimated that the number of Diabetic patients at present 425 millions and it will reach to 522millions by the year 2030[1]. Diabetes mellitus is a major public-health concern with high morbidity and mortality due to macro-vascular and micro-vascular complications. Most European and American countries have formulated evidence-based guidelines with clear targets and goals [2] but actual diabetic cares are often unable to achieve these targets [3].

Diabetes Mellitus is an important health problems in south east Asia(SEA) and Bangladesh, like the rest of the world. High prevalence of diabetes coupled with both communicable and non-communicable disease make situation more critical. According to international diabetic Federation(IDF), an estimated 96 millions of people have diabetes in SEA region and 90% of whom have Type 2 diabetes which is preventable[4]. In Bangladesh during 2017 there were estimated 6.92 million diabetes cases with prevalence of 6.9[5].The burden associated with diabetes is enormous in the term of increase morbidity and mortality and the economical strains associated with the disease and

its management. Poorly controlled diabetic patients have poor quality of life, associated comorbid diseases and have prolonged & frequent hospital admissions. All the effects of diabetes have an impact on the patients and the family members who have to take care of them. They also impact on the health care system, the government and the society as a whole [6].

In 1996, McLarty et al reported that Diabetes is an important cause of adult mortality in Tanzania, reaching the mortality rate comparable to those reported among diabetic patients in the USA. An investment in diabetes care brings great health care output in other disease areas such as hypertension and coronary artery disease. Low cost strategies such as lifestyle modification, increasing physical activities and effective and rational use of anti-diabetic drugs have enormous effects on diabetes control and reducing associated diseases mortality and morbidity[7].

Previous studies in Mexico, Jamaica, United States of America and India which were conducted in between 1999 and 2002 found adherence to diabetic treatment generally to be sub-optimal ranging from 23 to 77%[8,9]. In another study among patient with type 2 diabetes mellitus, adherence was found 65 to 85% for oral anti-diabetic agents and 60% to 80% for Insulin therapy[10].Despite compelling evidence of effectiveness of medication, adherence to treatment is recognized as a major problem in patient of chronic illness like Diabetes Mellitus. A large proportion of patients become non-adherent to medication at a certain point of time from initial treatment initiation[11,12]. Rates of non-adherence with any long term medication vary from 17% to 60%, depending onpatient's characteristics, treatment pattern, disease severity and the setting of treatment. It is more important to noticed that non-adherence is the highest when the patients are symptoms free[13].

Vermeire E et al showed that regimen complexity,number of drugs, number of dose per day, cost of drugs, side effects have strong influence on non-adherence of diabetic drugs. Patients who are not well understood their drugs regimens are at high risk of non-adherence[14]. Previously Drugs non-adherence has been demonstrate with advancing age due to advance age associated with cognitive impairment and polypharmacy due to multiple comorbid diseases[15]. In a study conducted in Mulago hospital in Uganda showed that age is not a significant factors in drugs adherence but sex and educational level have significant influence which is also similar to finding of a study in Brazil by Heloisa et al[16]. Several studies have reported that patients with multiple medical conditions associated with increased age actively choose which treatment to forego when cost pressure become a problem[17]. Results from different studies revealed other socio-demographic factors like marital status, occupation and religion of the respondent were not significantly associated with non-adherence, but duration of disease, number of drugs, routes of administration had a significant influence on non-adherence[18]. Recently it was found in ENTRED study, a large population study among patients with Type-2 diabetes in Europe on overall medication adherence including anti-diabetic drugs, showed that factors including age, sex, education, financial level, duration and complication of diabetes were associated with poor medication adherence[19].

There is paucity of information on medication adherence in patients with Type -2 diabetes in Bangladesh. Thus, this study was conducted to assess the extent of anti-diabetic drugs adherence and determine factors associated with non-adherence among the patients with Type -2 diabetes mellitus.

Method:

A cross-sectional study was conducted among known cases of Type-2 diabetic patients who were admitted in medicine units of Cumilla Medical College and those who came to outpatient department for medical care between June 2017 to May 2018. All known diabetic patients what may be the glycemic status either good controlled or not are included in this study. Those who are newly diagnosed at present admission or visit and those are not agree to participate in this study are excluded from this study. Here we observed the adherence to previously prescribed medication only. As we do the study in time period of one year all participant are included in our study. Assessment of adherence to anti-diabetic medication was based on patients self-reported recall and observation of treatment order present with him/her. Data were collected for least three months or the periods between last two visits where the interval between them is at least three months or more.

Assessment of Adherence:

In this study, Medication adherence was determined by using a Six items self-administered questionnaire, drawing upon the works by Girerd et al [20]. Patients responded Yes or No to each of the following questions: (1) do you sometimes forget to take your medicine, (2) have you ever run out of your medicine,(3) do you sometimes take your medicine late, (4) do you sometimes decide not to take your medicine because someday you feel that your treatment do more harm than good, (5) do you think that you have too many pills to take, (6) when you feel better, do you sometimes stop taking your medicine.

It has been shown that such a questionnaire has sufficient validity reliability. When "No" was answered to the 6 items it was "Good Adherence" , When 1 or 2 "Yes" it was "Medium Adherence" and When 3 or more "Yes" it was designated as "Poor adherence"[20]. Data were entered and analyzed using Statistical Package for Social science version 16.

Result:

The study included a total of 680 Type -2 diabetic patients, with a median age of 51.0 years (18 -72 years). About 56.47% of study populations were male and 43.53% were females. Maximum patients were in age group 40-60 years(35%). About half of patients (49.41%,) had diabetes in between 2 to 5 years and one third(30.59%,) had diabetes more than 5 years. Majority of patients had no known comorbid diseases(58.88%) like Hypertension, Chronic kidney Diseases,Stroke, Ischemic heart disease, Bronchial asthma and COPD etc.

Table I: Characteristics of study Patients with Type -2 DM

Demographic Factors	n=680	Percentage (%)
Age in years		
<30 yrs	124	18.24%
30-45 yrs	214	31.47%
46-60 yrs	238	35.00%
>60 yrs	104	15.29%
Gender		
Male	384	56.47%
Female	296	43.53%
Religion		
Muslim	594	87.35%
Hindhu	86	12.65%
Education level		
Below class - V	151	22.20%
Class – V to IX	236	34.70%
Class – X to XI	186	27.36%
> Class –XII	107	15.74%
Duration of disease		
< 2 yrs	136	20.00%
2 – 5 yrs	336	49.41%
> 5 yrs	208	30.59%
Co-morbid disease (HTN, CKD, Stroke, IHD, CHF, Br. Asthma, COPD and Others)*		
Yes (at least presence of any one)	334	49.12%
No	346	50.88%

*HTN – Hypertension, CKD – Chronic Kidney Disease, IHD – Ischaemic Heat Disease, CHF – Congestive Heart Failure, COPD – Chronic Obstructive Pulmonary Disease.

Good adherence on diabetic drugs was sub-optimal (14.11%) and female are more adherent to drugs than male (53.13%). Good adherence is maximum in 40 to 60 years age group, and low in both end of age group.Muslims are less adherent than Hindus (12.28% vs 26.74%). Duration of diabetes is strongly related to adherence and increase duration decrease the rate of adherence. Presence of associated comorbid diseases increases the rate of adherence. Patients with only Insulin are more adherent than Insulin oral combination. Increase number of oral drugs decreases the rate of adherence.

Table II: Characteristic of patients and drug adherence

Demographic Factors	n=680	Good (%)	Medium (%)	Poor (%)
Age in years				
<30 yrs	124	12 (12.50%)	66 (18.80%)	46 (19.74%)
30-45 yrs	214	32 (33.33%)	97 (27.64%)	85 (36.48%)
46-60 yrs	238	38 (39.58%)	152 (43.48%)	48 (20.60%)
>60 yrs	104	14 (14.58%)	36 (10.26%)	54 (23.48%)
Gender				
Male	384	45 (46.87%)	227 (64.67%)	112 (48.07%)
Female	296	51 (53.13%)	124 (35.33%)	121 (51.93%)
Religion				
Muslim	594	73 (12.28%)	303 (51.01%)	218 (36.70%)
Hindhu	86	23 (26.74)	48 (55.81%)	15 (17.44%)
Education level				
Below class - V	151	15 (9.94%)	91 (60.26%)	45(29.80%)
Class – V to IX	236	31 (13.13%)	151(63.98%)	54(22.88%)
Class – X to XI	186	34 (18.28%)	68 (36.56%)	84(45.16%)
> Class –XII	107	16 (14.95%)	41 (38.31%)	50(36.3%)
Duration of disease				
< 2 yrs	136	44 (32,35%)	66 (48.53%)	26 (19.12%)
2 – 5 yrs	336	34 (10.11%)	186 (55.36%)	116 (34.52%)
> 5 yrs	208	18 (8.65%)	99 (47.60%)	91 (43.75%)
Co-morbid disease (HTN, CKD, Stroke, IHD, Br. Asthma, COPD & Others)				
Yes (at least presence of any one)	334	94 (28.14%)	230 (68.86%)	10 (2.99%)
No	346	02 (0.57%)	121 (34.97%)	223 (64.46%)
Drugs				
Only insulin	6	1 (16.66%)	5 (83.33%)	0 (00%)
1 ODA*	108	78 (72.22%)	28 (25.92%)	02 (1.85%)
2 ODA	328	17 (5.18%)	184 (56.09%)	127(38.72%)
3 ODA	9	0 (00%)	0 (00%)	9 (100%)
1 insulin + 1 ODA	68	0 (00%)	49 (72.05%)	19 (27.94%)
1 insulin + 2 ODA	74	0 (00%)	45 (60.82%)	29 (39.19%)
2 insulin + 1 ODA	32	0 (00%)	20 (62.50%)	12 (39.50%)
2 insulin + 2 ODA	30	0 (00%)	20 (66.66%)	10 (33.34%)
No medication	25	0 (00%)	0 (00%)	25 (100%)

*** ODA - Oral Anti-diabetic agent.**

Patients with poor adherence reported several reasons for them not adhering to anti-diabetic medications. Feeling better and when symptoms subside majority of patients (43.24%) stop medication at some point of their treatment. Too many pills, cost of drugs, side effects, drugs are not acting properly, forgetting to take drugs or use of traditional drugs are important. It was important to note that a few patients (3.67%, n=25) did not started anti-diabetic medication still they have high level of blood glucose. (Figure 1)

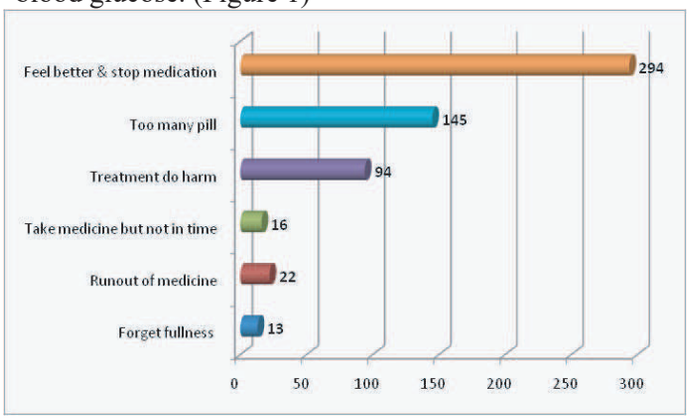

Figure 1: Reasons of Poor Adherence

Discussion:

Drugs Adherence is a key component of management and glycemic control for patients with diabetes mellitus. The prevalence of anti-diabetic drugs adherence found in this study group was suboptimal. Since adherence information was based on patients' recall, the actual prevalence may be even lower than that was found in our study. Similar rates of adherence have been reported in studies done in India, Jamaica, Uganda and France [10,16,17,19]. Adherence to treatment in this study differed between weeks, months and years. This may be due to the fact that it easier to recall the number of skipped days without medication at weeks than the past months.

In previous studies done by Vermeire E et al, several factors modifiable and un-modifiable factors were associated with poor adherence to anti-diabetic drugs. These were cost, regimen complexity, number and dosages of drugs, routes of drugs, age and sex, ethnicity of patients, duration of disease, educational level of patients, comorbid diseases[14,15,17,18,19]. In this study good adherence was found in increased age and in female patients. This positive effect of age and sex on adherence was also reported in United Kingdom [21].

In current study, patient with low age group had the poorest adherence and this is compare able with study done in Uganda where majority of patients were in age group 21-30 and 31-40 years [16]. Another interesting factor that was associated use of non –diabetic medications with diabetic drugs.

The use of other medication in addition to diabetic drugs was significantly associated with a good adherence. These patients are likely to have multiple comorbidities,attended different clinics and hence more information on the benefits of compliance to medications. Multiple comorbidities are also likely to occur with aging. Thus age-related improvement in adherence may be explained by increased comorbidities [13]. Similar to a study done in the USA, there was higher glycemic status difference in between gender and adherence to medications [22].

Social and family supports are also crucial. Family members are frequently involved and recognized as supportive: they act as counselors encouraging diet and exercising behavior and helping in adherence of medications. Support of family and family member were important as it was found in a study of France[23]. This type of study has its benefits, as it helps clinicians to identify patients who are more likely to have poor adherence, and determine the aspects of diabetes that they can focus to improve patients' outcome[24]. Management of diabetes mellitus has three core components namely dietary adherence, regular physical exercise and regular self-monitoring of blood sugar by patients were not addressed in this study.

Limitation:

This study had several limitations, such as purposive sampling; data was collected from a single centre and from only hospitalized patients. On the other hand, data were collected by self-reported methods to assess adherence to medications, which is very much associated with recall bias; there is a tendency to overestimate drug adherence.

Conclusion:

Adherence to anti-diabetic drugs was found suboptimal. High cost, complex treatment regimen and multiple drugs are associated with poor adherence. Responsible authorities and related physician should set policies to improve adherence and to reduce complications, morbidity and mortality.

References:

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetic Care. 2004; 27:1047-1053.
2. Campbell SM, Roland MO, Middleton E, Reeves D. Improvements in quality of clinical care in English general practice 1998-2003: longitudinal observational study. BMJ.2005;331:1121.

3. Pornet C, Bourdel-Marchasson I, Lecomte P, Eschwege E, Romon I, et al. Trends in the quality of care for elderly people with type 2 diabetes.Diabetes Metab.2011;37: 152-161.
4. SicreeR,Shaw J, Zimmet P. The Global burden: Diabetes and Impaired Glucose Tolerance.Diabetes Atlas.2009; 112-115.
5. Biswas T, Islam A,RawalLB,IslamSM.Increasing prevalence of diabetes in Bangladesh: a scoping review.Public Health.2016.
6. Victoria H ,Reimar T ,Ole H, Nicolai L. Diabetes in Sub Saharan Africa: Epidemiology and public health implications.BMC Public Health.2011;11:564.
7. McLarty D, Unwin N, Kitange HM, AlbertiG.Diabetes mellitus as a causes of death in Sub-saharan African: results of community-based study in Tanzania.Diabet Med.1996;13(11):990-4.
8. Swaby P, Wilson E, Swaby S, Sue-Ro R, Pierre R. Chronic disease control and compliance. The HOPE, worldwide Jamaica's experience.PNG Med J.2001;44(3-4):171-175.
9. Joel S, Nadkarni MM, Voss J. The association between diabetes metabolic control and drugs adherence in an indigent population. Diabetes Care.2002;25(6):1015-1021.
10. Rubin Richard. Adherence to pharmacological therapy in patient with type 2 diabetes mellitus. Am J Med.2005;118(5):27-34.
11. Paul C, Katon WJ, Russo J. Impact of Depressive symptoms oAdherence,function and costs.ArchIntern Med.2000;160(21):3278-3285.
12. Melikian C, Vanderplas A, Dezil CM, Chang E. Adherence to oral diabetic therapy in a managed care organization. A comparison of monotherapy, combination therapy and fixed dose combination. Clinical therapeutics.2002;24(3):460-467.
13. Lars O, Tererence B. Adherence to medication.NEngl J Med.2005;353(5):487-497.
14. Joan k, Owino E, NambuyaA.Non- adherence to diabetes treatment at Mulago hospital in Uganda: prevalence and Associated factors.Afr Health sci.2008;8(2):67-73.
15. Robert H, John W. Patients beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. J Psychosom Res.1999;47(6):555-567.
16. Heloisa G, Zanneti ML, Vanderlei H. Factors related to patient adherence to antidiabetic therapy. Revista Latino-American de Enfermagem.2009;17(1): 321-327.
17. Chapman R, Benner JS, Tierce JC, Collins R, David B et al. Predictors of adherence with antidiabetic and lipid lowering therapy. Arch Intern Med.2005;165(19):1147-1152.
18. Grant R, Devita NG, Singer DE, Meigs JB. Polypharmacy and medication adherence in patient with type-2 diabetes. Diabetes Care.2003;26(5):1408-1412.
19. Michel T, Viel JF, Mauny F, Eschwege E, Weill A, Fournier C, et al.Medication Adherence in Type -2 Diabetes: The ENTRED study 2007, a French population based Study.PloSONE.2012;7(3):32412.
20. Girerd X, Hanon O, Anangnostopoulos K, Ciupek C, Mourad JJ et al.Evaluation de I'observance du traitment anti-hypertenseur par un questionnaire: mise au point et utilization dans un service specialise. Presse Med 30:1044-1048.
21. Diamond Jared. The double puzzle of diabetes. Nature.2003;423(6940).599-602.
22. McCabe B. Barrier to adherence in a free medication program for low income individual with Type 2 diabetes.Louisiana,USA.1999; 122-143.
23. Mosnier-paudar H, Hochberg G, Eschwege E, virally ML, Hamili S, et al. How do patients with type -2 diabetes perceive their disease? Insights from the Frence DIABASIS survey. Diabetes Metab.2009;35:220-227.
24. Devin M, Ponieman D, Leventhal H, Halm E. Predictors of adherence to diabetes medications: the role of disease and medication benefits. J Behav Med.2009;32(3):278-284.

Original Article

Prevalence of Hepatitis B Surface Antigen in Pregnant Women in Tersiary Care Hospital, Cumilla, Bangladesh.

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Abstract

Background: Hepatitis B virus (HBV) is a double-stranded DNA virus belonging to the Hepadnaviridae family. Chronic hepatitis B is a potentially life-threatening liver disease caused by HBV. It is a major global health problem and the most serious type of viral hepatitis. Children born to HBsAg+ and HBeAg+ mothers have 70-90% chance of prenatal acquisition of HBV infection and over 85-90% of them will eventually become chronic carriers of the disease. The screening of antenatal clinic attenders for HBV is a relatively routine practice in most health settings in Bangladesh. These study have evaluated the prevalence of HBV among antenatal pregnant women.

Method: This was a cross-sectional study on pregnant women, who were attend in the outpatient department of Gynae and Obstetric from March 2018 to July 2018 in Eastern medical college hospital. Total 400 patients were included in this study. Data were analyzed by SPSS version 16.0.

Result: Among the 400 patients, the ages varied between 18 and 37years with a minimum age 18 and maximum age 37. The majority of cases were in the age group of 18-27 years. HBsAg was detected in the plasma of 11women, giving an overall HBsAg prevalence of 2.75%. The prevalence of HBsAg was the highest among the 18 -27-year-old group.

Conclusion: HBV infection has a low prevalence among pregnant women in rural Bangladesh indicating a low risk of vertical transmission. The existing hepatitis B vaccination regimen in the current EPI program is appropriate for rural Bangladesh. Further research should be carried out in other parts of the country to compare regional variations in HBsAg prevalence.

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Introduction:

Hepatitis B virus (HBV) is a double-stranded DNA virus belonging to the Hepadna viridae family. Chronic hepatitis B is a potentially life-threatening liver disease caused by HBV. It is a major global health problem and the most serious type of viral hepatitis. It can cause chronic liver disease and put people at high risk of death from cirrhosis of liver and liver cancer[1]. Perinatal transmission is one of the most common routs of HBV transmission worldwide [2].Routine screening of pregnant women for hepatitis B surface antigen (HBsAg) is recommended by the World Health Organization[3] .Chronic HBV infection affects approximately 350 million people worldwide, half of whom acquire the infection from perinatal transmission or in early childhood[4].The prenatal transmission of HBV leads to severe long term sequelae. Children born to HBsAg+ and HBeAg+ mothers have 70-90% chance of prenatal acquisition of HBV infection and over 85-90% of them will eventually become chronic carriers of the disease. Chronic carriers of HBV are main reservoirs for continued transmission of HBV and have a higher risk of hepatocellular carcinoma and liver cirrhosis. Many of them eventually become mothers themselves; thus, they perpetuate the cycle[5].

The screening of antenatal clinic attenders for HBV is a relatively routine practice in most health settings in Bangladesh. These study have evaluated the prevalence of HBV among antenatal pregnant women.

Objectives:

The aim of this study was to determine the prevalence of HBsAg among pregnant women attending Eastern medical college gynae & obs dept in 2018.

Method:

This was a cross-sectional study on pregnant women, who were attend in the outpatient department of Gynae and Obstetric from March 2018 to July 2018 in Eastern medical college hospital. Ethical approval to conduct this study was obtained from the ethical committee.

The sample size was calculated using the standard formula for sample size calculation: N = z2pq/d2(where z = the standard normal deviation at 1.96 (which corresponds to a 95% confidence interval), p = the prevalence of hepatitis B in general Iranian population, q = 1 – p; d = the degree of precision expected to be 0.05).

The inclusion criteria were positive pregnancy test and written informed consent. Each woman who refused to give consent was excluded. After obtaining the consents, all the participants were interviewed by an interviewer .According to the inclusion criteria, 425 subjects were included and then 25 were excluded. At first, the advantages of the test were explained for the participants and the consent forms were obtained. A questionnaire including socio - demographic information and HBV infection-associated risk factors was filled. Afterwards, 5 mL blood was aseptically taken from each patient and the blood specimens were transmitted to a laboratory. At the laboratory, after plasma separation, test for HBsAg using the Monalisa HBsAg ultra ELISA kit was performed. We used statistical package for social sciences (SPSS) version 16.0 software. Simple descriptive statistics such as mean and standard deviation were used to describe the data, as appropriate.

Result:

Table I : Age distribution of study population

Age	HBsAg Negative	HBsAg positive	Percentage (%) HBsAg Positive
18-27	318	10	3
28-37	71	1	1.38
Total	389	11	2.75

Among the 400 patients, the ages varied between 18 and 37years with a minimum age 18 and maximum age 37. The majority of cases were in the age group of 18-27 years. HBsAg was detected in the plasma of 11women, giving an overall HBsAg prevalence of 2.75%. The prevalence of HBsAg was the highest among the 18 - 27-year-old group.

Table II : Epidemiological profile of study population

Characteristics		Total	HBsAg Positive	HBsAg Negative
Level of education	Primary school	85	3 (3.53%)	82 (96.47%)
	High school and above	315	8 (3.53%)	307 (96.47%)
Residence	Urban	41	1 (2.43%)	40 (97.57%)
	Rural	359	10 (2.78%)	349 (97.22%)
Gestational age	1st Trimester	61	1 (1.64%)	60 (98.36%)
	2nd Trimester	265	7 (2.64%)	258 (97.36%)
	3rdTrimester	74	3 (4.05%)	71 (95.95%)
H/O Jaundice	Yes	26	1 (3.84%)	25 (96.16%)
	No	374	10 (2.67%)	364 97.33%)
H/O Blood transfusion	Yes	16	0 (0%)	16 (100%)
	No	384	11 (2.86%)	373 (97.14%)

Discussion:

The results of our study indicated that the prevalence of HBsAg among pregnant women was 2.75%.Bangladesh has an intermediate prevalence of hepatitis B with a 4% HBsAg-positive population[6]. Up to now,there are no data on the prevalence of hepatitis B among women of child-bearing age in this country. The observed lower rate among pregnant women is not unexpected because the prevalence of HBsAg is more common among males[7,8]

A wide range in HBsAg prevalence among the pregnant women has been seen in different countries of the world (Merrill and Hunter, 2011), and in different regions of the same country (Batham et al, 2007). Studies from around the world have found the prevalences of HBsAg among pregnant women varies from 0.1% to 25.3% (Ndumbe et al, 1992; Salleras et al, 2009). A similar HBsAg prevalence was seen in the USA in the early 1990s (Desheda et al, 1995). HBsAg prevalence was not consistent with three previous studies from Bangladesh (Akhter et al, 1992; Rumi et al, 1998; Francisco et al, 1999). Those studies were conducted more than a decade ago.

Studies in other countries have reported different rates of prevalence of HBsAg among pregnant women. The HBsAg prevalence among pregnant women was reported 8.3% by Luka et al.[9] and Eke et al.[10] in Nigeria. They are comparable with the 6.4% HBsAg prevalence reported in Ghana[11] , the 6.5% in Congo [12] ,the 9.3% in Kenya [13], the 10.7% in Burkina Faso[14] and the 7.7% in Cameroon[5]..All these countries are generally considered the areas of hyperendemicity for hepatitis B infection (prevalence > 8%)

Conclusion:

In conclusion, HBV infection has a low prevalence among pregnant women in rural Bangladesh indicating a low risk of vertical transmission. The existing hepatitis B vaccination regimen in the current EPI program is appropriate for rural Bangladesh. Further research should be carried out in other parts of the country to compare regional variations in HBsAg prevalence.

References:

1. Kolawole OM, Wahab AA, Adekanle DA, Sibanda T, Okoh AI. Seroprevalence of hepatitis B surface antigenemia and its effects on hematological parameters in pregnant women in Osogbo, Nigeria. Virol J.2012;9:317.
2. Jonas MM. Hepatitis B and pregnancy: an underestimated issue. Liver Int.2009;29 Suppl 1:133–9.
3. Kane MA. Global status of hepatitis B immunisation. Lancet.1996;348(9029):696.
4. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepat.2004;11(2):97–107.
5. Fomulu NJ, Morfaw FL, Torimiro JN, Nana P, Koh MV, William T. Prevalence, correlates and pattern of Hepatitis B among antenatal clinic attenders in Yaounde-Cameroon: is perinatal transmission of HBV neglected in Cameroon? BMC Pregnancy Childbirth.2013;13:158.
6. Kane M, 1994.Global Plan of Action for Hepatitis B Immunization: Global Program for Vaccine and Immunization.Expanded Program on Immunization. Geneva: World Health Organization.
7. Chaudhary RK, Nicholls ES, Kennedy DA, 1981. Prevalence of hepatitis B markers in Indochinese refugees.Can Med Assoc J 125:1243–1246.
8. Kaur S, Rybicki L, Bacon BR, Gollan JL, Rustgi VK, Carey WD, and The National Hepatitis Surveillance Group, 1996.Performance characteristics and results of a large-scale screening program for viral hepatitis and risk factors associated with exposure to viral hepatitis B and C: results of the national hepatitis screening survey.Hepatology 24:979–986
9. Luka SA, Ibrahim MB, Iliya SN. Sero-prevalence of hepatitis B surface antigen among pregnant women attending Ahmadu Bello University Teaching Hospital, Zaria, Nigeria. Nigerian Journal of Parasitology.2008;29(1):38–41.
10. Eke AC, Eke UA, Okafor CI, Ezebialu IU, Ogbuagu C. Prevalence, correlates and pattern of hepatitis B surface antigen in a low resource setting. Virol J.2011;8:12.
11. Acquaye JK, Mingle JA. Hepatitis B viral markers in Ghanaian pregnant women. West Afr J Med.1994;13(3):134–7.
12. Itoua-Ngaporo A, Sapoulou MV, Ibara JR, Iloki LH, Denis F. [Prevalence of hepatitis B viral markers in a population of pregnant women in Brazzaville (Congo)]. J Gynecol Obstet Biol Reprod (Paris).1995;24(5):534–6.
13. Okoth F, Mbuthia J, Gatheru Z, Murila F, Kanyingi F, Mugo F, et al. Seroprevalence of hepatitis B markers in pregnant women in Kenya. East Afr Med J.2006;83(9):485–93.
14. Nacro B, Dao B, Dahourou H, Hien F, Charpentier-Gautier L, Meda N, et al. [HBs antigen carrier state in pregnant women in Bobo Dioulasso (Burkina Faso)]. Dakar Med.2000;45(2):188–90

Original Article

A Study on Efficacy of Oral Pregabalin in Attenuation of Pain on Propofol Injection

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Abstract

Background: Propofol is one of the widely used intravenous anesthetic agents, although pain on injection still remains a considerable concern for the anesthesiologists. A number of techniques has been tried to minimize propofol-induced pain with variable results. The aim of this randomized, placebo-controlled, double-blind study was to determine whether pre-treatment with oral pregabalin, would reduce incidence and severity of pain on propofol injection (POPI).

Method: Eighty adult patients, American society of Anesthesiologists (ASA) grading I–II, scheduled for elective ENT surgery under general anesthesia at national institute of ENT, Dhaka were randomly assigned to one of the two groups. Group I (pregabalin group) was scheduled for taking 150 mg pregabalin orally 2 hours before induction of anesthesia and group II (placebo group) was scheduled for taking one placebo tablet 2 hours before induction. During injection of propofol for induction of anesthesia, pain was estimated as per McCrirrick and Hunter scale. Data were entered and analyzed using Statistical Package for Social science version 16.

Result: The incidence of pain experienced in group I(pregabalin group) was 45% patients and in group II (placebo group) was 75% patients, which was statistically significant $p<0.05$.The severity of POPI was also lower in pregabalin group than the placebo group ($p<0.05$).The incidence of mild and moderate pain in groups I versus group II was 25% versus 45% and 20% versus 30% respectively $p<0.05$. There was no severe pain recorded in any groups.

Conclusion: It can be concluded that pre-treatment with 150 mg oral pregabalin two hours before induction of general anesthesia, effectively reduces incidence and severity of pain on propofol injection.

Key words: Pregabalin, propofol, pre-treatment, pain on propofol injection (POPI).

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Introduction:

Propofol, a widely used induction agent in anesthesia, has the main drawback of pain on injection that ranged 24-70%. Several interventions have been advocated to alleviate the pain associated with propofol injection, which include addition of lidocaine, cooling of propofol, dilution of propofol, injection of propofol into a large vein, and prior administration of ephedrine, ondansetron, granisetron, metoclopramide, opioids, thiopental, ketamine, acetaminophen, tramadol, different doses of lidocaine, different concentrations of propofol topical nitroglycerin, dexme - detomidine, dexamethasone, gabapentin and pregabalin.[1-20]

Pregabalin and its predecessor, gabapentin, are analogues of the inhibitory neurotransmitter gammaaminobutyric acid (GABA).Both the drugs bind to the alpha 2 -delta subunit of the presynaptic, voltage -gated calcium channels that are widely distributed throughout the peripheral and central nervous system. The probable mechanism of action of pregabalin is to reduce the release of several excitatory neurotransmitters (e.g. glutamate, substance P, noradrenaline, calcitonin gene -related peptide) by inhibiting calcium influx via the calcium channels.[21-23]

Pregabalin has been used for management of central neuropathic pain,[24] to relieve perioperative anxiety[25] and also used as a multidimensional analgesia for postoperative pain in various surgeries including dental, laparoscopic cholecystectomy, and spine surgery.[26-28]

The present study was conducted to determine the efficacy of oral pregabalin 150 mg, in comparison with placebo on incidence and severity of pain on propofol injection (POPI).

Method:

The present double-blinded study was conducted on 80 patients undergoing elective ENT surgery at National Institute of ENT Dhaka during August to November 2018 after obtaining informed consent. Inclusion criteria were age 20-50 years, both male and female, Class I and II American Society of Anesthesiologists (ASA), no history of known skin disease, lack of diabetes or heart, liver and kidney disorders. The patients were randomly divided into two groups of 40 after enrolment in the study. Group I (pregabalin group) was scheduled for taking 150 mg pregabalin orally 2 hours before induction of anesthesia and group II (placebo group) was scheduled for taking one placebo tablet 2 hours before induction. Prior to surgery, the patients had thorough pre-anesthetic check-up and required investigations. All patients were kept fasting for 8 hours.

On arrival to the operating room, standard monitoring was applied to all patients including pulse oximeter, electrocardiogram and noninvasive arterial blood pressure. A 20-gauge intravenous cannula was placed on the dorsum of non-dominant hand of the patient and lactated Ringer's solution was started before anesthesia. Before surgery, patients were educated about grading of pain as per McCrirrick and Hunter29 pain scale. Then first one-fourth of induction dose (2 mg/kg) of propofol was injected over 5 seconds. The pain intensity was measured according to the McCrirrick and Hunter scale. After the assessment of pain, induction of anesthesia was completed with the remaining dose of propofol, and tracheal intubation was facilitated with the injection of succinylcholine. Anesthesia was maintained with injection of fentanyl, vecuronium, oxygen, nitrous oxide (66%) and halothane. When surgery was completed general anesthesia was reversed as usual. Data were entered and analyzed using Statistical Package for Social science version 16.

Result:

There was no significant demographic difference between the groups (Table I). Basal mean arterial pressure (MAP) and heart rate (HR) were comparable in both groups. There was no significant difference of MAP and HR between pregabalin and placebo groups during pre-intubation or three minutes post-intubation period ($p>0.05$) (Table II). The incidence of pain experienced in (group I) pregabalin group was 45% patients and in group II (placebo group) was 75% patients, which was statistically significant $p<0.05$ (Table III). The severity of POPI was also lower in pregabalin group than the placebo group ($p<0.05$) (Table IV). The incidence of mild and moderate pain in groups I versus group II was 25% versus 45% and 20% versus 30% respectively $p<0.05$. There was no severe pain recorded in any groups.

Table I: Comparison of demographic data between the two groups

Parameter	Group I (Pregabalin group) n=40	Group II (Placebo group) n=40	p value
Age in years (mean±SD)	38.22±8.76	36.57±9.48	p>0.05
Weight in kg (mean±SD)	68.32±9.24	66.26±9.72	p>0.05
Sex (male/female)	24/16	25/15	p>0.05
ASA Physical status I/II	34/6	33/7	p>0.05

Table II: Changes of mean arterial pressure and heart rate between two groups

Hemodynamic parameter	Basal Group I / Group II	Pre intubation Group I / Group II	Post intubation Group I / Group II
Mean arterial pressure (MAP) mm Hg	91/97	85/92	102/106
Heart rate per minute	75/76	70/73	92/96

Table III: Incidence of pain following propofol injection between two groups

Characteristics of pain	Group I (Pregabalin group) n=40. Number and %	Group II (Placebo group) n=40. Number and %	p value
No pain	22 (55%)	10 (25%)	p <0.05
Pain	18 (45%)	30 (75%)	p <0.05

Table IV: Severity of pain following propofol injection between two groups

Characteristics of pain	Group I (Pregabalin group) n=18. Number and %	Group II (Placebo group) n=30. Number and %	p value
Mild pain	10 (25%)	18 (45%)	p <0.05
Moderate pain	8 (20%)	12 (30%)	p <0.05
Severe pain	0	0	-

Discussion:

Propofol consists of a phenol ring substituted with two isopropyl groups. All phenols irritate skin, mucous membrane and vascular intima. Pain on propofol injection (POPI) is immediate and delayed after 10-20 seconds.[30] The immediate pain is due to irritation of vascular endothelium whereas delayed pain is due to release of

mediators such as kininogen from kinin cascade.[31] According to recent study, the nonselective ligand-gated cation channels such as transient receptor potential (TRP) ankyrin 1 (TRPA 1) and TRP vanilloid 1 (TRPV 1) which are located in venous endothelium, are stimulated by injection of propofol releasing neuropeptides including calcitonin gene related peptide (CGRP). These mediators induce vascular leakage, dilatation and pain; this is the mechanism of delayed pain caused by propofol injection.[32,33]

Several medications have been advocated to alleviate the pain associated with propofol injection including pregabalin. In present study, the overall incidence of pain on propofol injection experienced in group I (pregabalin group) was 45% patients and in group II (placebo group) was 75% patients, which was statistically significant $p<0.05$. The severity of POPI was also lower in pregabalin group than the placebo group ($p<0.05$). The incidence of mild and moderate pain in groups I versus group II was 25% versus 45% and 20% versus 30% respectively $p<0.05$. There was no severe pain recorded in any groups.

The study done by Choi et al.[20] on alleviation of pain on propofol injection by comparing between two different doses of pregabalin and lignocaine. They used 150 mg and 75 mg oral pregabalin 2 hours before induction and 40 mg IV lignocaine 1 minute before induction in 3 groups of patients. The incidence of pain following propofol injection in 150 mg pregabalin group was 50%, 75 mg pregabalin group was 92.5% and in lignocaine group 55%. In present study, pain following propfol injection was observed in 45% patients nearly similar to the study done by Choi et al.[20] where 50% patients experienced pain.

Conclusion:

Pretreatment with a dose of 150 mg pregabalin orally administered 120 minutes before induction of general anesthesia can reduce the incidence and severity of pain on propofol injection without significant adverse effect.

References:

1. Fuji Y, Itakura M. Comparison of lidocaine, metoclopramide, and axetil for reducing pain on injection of propofolin Japanese adult surgical patient: A prospective, randomized, double blind, parallel-group, placebo-controlled study. ClinTher2008; 30:280-6.
2. Picard P, Tramèr MR. Prevention of pain on injection with propofol: A quantitative systematic review. Anesth Analg 2000; 90:963-9.
3. Singh D, Jagannath S, PriyeS, Shivaprakash, Kadli C. Prevention of propofol injection pain: Comparison between lidocaine and ramosetron. J Anaesthesiol ClinPharmacol. 2014: 213–6.
4. Yew WS et al, The effect of intravenous Lignocaine on pain during injection of medium and long chain triglyceride Propofol emulsion; Aanesthesia Analgesia Jun 2005;100 (6); 1693-5.
5. Ambesh SP, Dubey PK, Sinha PK. Ondansetron pretreatment to alleviate pain on propofol injection: A randomized, controlled, double-blinded study. Anesth Analg. 1999; 89:197–9.
6. Dubey PK, Prasad SS. Pain on injection of propofol: The effect of granisetron pretreatment. Clin J Pain. 2003; 19:121–4.
7. Scott RP, Saunders DA, Norman J. Propofol: Clinical strategies for prevention of pain of injection. Anesthesia 1988; 43:492-494.
8. Vijayant GA, Tej KK, Avtar S, Anju G. Analgesic effect of lignocaine, tramadol, ketorolac, and ketoprofen in ameliorating propofol induced pain. J Anesthesiol Clin Pharmacol. 2005; 21:389–93.
9. Aouad MT, Siddik-Sayyid SM, Ai-Amin AA, Baraka AS. Multimodal analgesia to prevent propofol-induced pain: Pretreatment with remifentanil and lidocaine versus remifentanil or lidocaine alone. AnesthAnalg. 2007; 104:1540-1544.
10. Agarwal A, Ansary MF, Gupta D, Pandey R, Reza M, Sing PK et al. Pretreatment with thiopental for prevention of pain associated with propofol injection. AnesthAnalg. 2004; 98:683-86.
11. Koo SW, Cho SJ, Kim YK, Ham KD, Hwang JH. Small-dose ketamine reduces the pain of propofol injection. Anesth Analg 2006; 103:1444-7.
12. Canbay O, Celebi N, Arun O, Karagöz AH, Saricaoğlu F, Ozgen S. Efficacy of intravenous acetaminophen and lidocaine on propofol injection pain. Br J Anaesth 2008; 100:95-8.
13. Pang WW, Huang PY, Chang DP, Huang MH. The peripheral analgesic effect of tramadol in reducing propofol injection pain: A comparison with lidocaine. Effect of mixed versus unmixed lidocaine with propofol. Reg Anesth Pain Med 1999; 24:246-9.
14. Tsubokura H, Inagaki Y, Adachi H, OtsukiA, Harada T, Hirosawa J, et al. Efficacy of simultaneous bolus injection of lidocaine with propofol on pain caused by propofol injection. Masui 2001; 50:1196-200.
15. Sen H, Sizlan A, Yanarates O, Dogru S, Mutlu M, Ozkan S, Dagli G et al. The effects of propofol concentration on propofol injection pain. Anatol J ClinInvestig 2009; 3:127-30.

16. O'Hara JR Jr, Sprung J, Laseter JT, Maurer WG, Carpenter T, Beven M, et al. Effects of topical nitroglycerin and intravenous lidocaine onpropofol-induced pain on injection. Anesth Analg 1997; 84:865-9.
17. Yan-bin He , Du-yu Li, Zhong Tan. Comparison of lidocaine versus dexmedetomidine in preventing propofol induced injection pain during induction of general anaesthesia in Chinese patient undergoing gynaecologic surgery: real world evidence. Biomedical Research 2017; 28 (4): 1890-93
18. Sing M, Mahota M, Sethi AK, Tyagi A. Efficacy of dexamethasone pretreatment for alleviation of propofol injection pain. Eur J Anesthesiol. 2005; 22:888-90.
19. Çakırgöz MY, Demirel I, Duran E, Özer AB, Türkmen UA, Ersoy A, et al. Gabapentin pretreatment for propofol and rocuronium injection pain: A randomized, double-blind, placebo-controlled study. Niger J Clin Pract 2018; 21:43-8.
20. Choi E, Kim D, Jeon Y. Comparative study between 2 different doses of pregabalin and lidocaine on pain following propofol injection: A double-blind, randomized clinical consort study. Medicine (Baltimore) 2016; 95:51(e5153).
21. Rose MA, Kam PC. Gabapentin: pharmacology and its use in pain management. Anaesthesia 2002; 57:451-62.
22. Gee NS, Brown JP, Dissanayake VU, et al. The novel anticonvulsant drug gabapentin (Neurontin), binds to the alpha 2 delta subunit of a calcium channel. J Biol Chem 1996; 271:5768-76.
23. Taylor CP. The biology and pharmacology of calcium channel alpha -2 -delta proteins. CNS Drug Rev 2004; 10:183-8.
24. Finnerup NB, Jensen TS. Clinical use of pregabalin in the management of central neuropathic pain. Neuropsychiatr Dis Treat 2007;3:885–91.
25. White PF, Tufanogullari B, Taylor J, et al. The effect of pregabalin on preoperative anxiety and sedation levels: a dose-ranging study. Anesth Analg 2009; 108:1140–5.
26. Hill CM, Balkenohl M, Thomas DW, et al. Pregabalin in patients with postoperative dental pain. Eur J Pain 2001; 5:119–24.
27. Esmat IM, Farag HM. Comparative study between paracetamol and two different doses of pregabalin on postoperative pain in laparoscopic cholecystectomy. Saudi J Anaesth 2015; 9:376–80.
28. Kim JC, Choi YS, Kim KN, et al. Effective dose of peri-operative oral pregabalin as an adjunct to multimodal analgesic regimen in lumbar spinal fusion surgery. Spine (Phila Pa 1976) 2011;36:428–33.
29. McCrirrick A, Hunter S. Pain on injection of propofol: the effect of injectate temperature. Anaesthesia 1990; 45: 443–4.
30. Briggs LP, Clarke RS, Dundee JW, Moore J, Bahar M, Wright PJ. Use of di-isopropyl phenol as main agent for short procedure.Br J Ansth. 1981; 53:1197-202.
31. Tan CH, Onsiong MK. Pain on injection of propofol. Anesthesia. 1998; 53:468-76.
32. Matta JA, Cornett PM, Mayares RL, Abe K, Sahibjada N, Ahern GP. General anesthetics activate a nociceptive ion channel to enhance pain and inflammation. Proc Natl AcadSci USA. 2008; 105:8784-89.
33. Fischer MJ, Leffler A, Niedermirtl F, Kistner K, Eberhardt M, Reeh PW, et al. The general anesthetic propofol excites nociceptors by activating TRPV 1 and TRPA1 rather than GABA receptors. J Biol Chem. 2010; 285:34781-92.

Original Article

Histopathological Evaluation of Lymphadenopathy in Children: A Laboratory Based Study of 179 Cases

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Abstract

Background: Lymphadenopathy in children (< 18 years) is common. Although a vast majority of cases are self-limiting, but a large spectrum of entities may give rise to benign, malignant & metastatic lesions. Sometimes they may represent a serious problem or a diagnostic dilemma. A thorough clinical history and physical examination, careful observation and appropriate investigations such as imaging studies with a biopsy will help the child to establish a correct diagnosis & provide an appropriate treatment recommendation by the clinicians. Biopsy following by histopathological evaluation plays an important role in establishing the cause of lymphadenopathy. Sometimes knowledge of the characteristic histopathological findings and causes of lymphadenopathy may spare patients from unnecessary investigations and management.

Objectives: To evaluate the most frequent causes of enlarged lymph node in our set up and to assess the spectrum of lymphadenopathy in pediatric age group.

Method: A retrospective observational study was conducted in the "The Alpha Laboratory" Kandirpar, Cumilla, Bangladesh. Clinical samples were collected from different medical college & hospital (Government and Private), Clinics and Physicians chambers.Total 179 numbers of patients from January 2017 to December 2017 were recruited. All autolyzed specimens and diagnosed cases were excluded. Diagnosis was made on the basis of gross morphology and light microscopic features (H & E Stain), Ziehl- Neelsen stain. Immunohistochemistry (IHC) were done in all malignant cases from higher center (Dhaka)

Result: This study revealed more male cases. Most frequently affected age group was between 6-15 years. Majority cases were benign lesions and it was about 84.91 % (152 cases), among them chronic nonspecific lymphadenitis (CNL) (105 cases, 69.07%) and tuberculous lymphadenitis (TB) (37 cases, 24.34%) are predominant involving age were 6-15 years and 15-20 years respectively. Cervical lymph nodes group were mostly involving group of all lesions and age group and it was about 100 cases (55.86%). Malignant cases (primary) were 15 (8.37%) and most cases were lymphoma like Non-Hodgkin Lymphoma (NHL) 4 cases (2.2%), Follicular lymphoma 4 cases (2.2%) and Hodgkin Lymphoma (HL) 7 cases (3.9%). Metastatic cases were 05 (2.80%) & others were 07 (3.91%).

Conclusion: Enlarged lymph node and tissue excisional biopsy & histopathological examination combined with immunohistochemistry remain most valuable diagnostic tool as it allows for the architecture of the gland to be viewed thereby given an accurate and concise diagnosis with minimal risk to the patient.

Key words: Lymphadenopathy (LAP), Chronic nonspecific lymphadenitis (CNL), Non-Hodgkin Lymphoma (NHL) and Hodgkin Lymphoma (HL), Immunohistochemistry (IHC).

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Introduction:

Lymphadenopathy means enlargement of the lymph nodes or glands. Palpable lymph nodes are common in pediatrics & nearly all children may experience lymphadenopathy at some time. As lymphatic system is the part of the immune system, it has to fight against the infection or disease. Lymph node enlargement is caused by proliferation of normal lymphoid elements or by infiltration with malignant or phagocytic cells.[1] In most patients, a careful history and a complete physical examination suggest the proper diagnosis.[2] Lymph nodes are not usually palpable in the newborn as well as in children. But if the nodes get bigger than usual, the child may have an infection or other problem. With antigenic exposure, lymphoid tissue increases in volume.[3]They are not considered enlarged until their diameter exceeds 1 cm for cervical and axillary nodes and 1.5 cm for inguinal nodes. As childhood lymphaden - opathy represent a large heterogeneous group

of lesions including inflammatory, reactive, benign & malignant or metastatic, they require proper histopathological evaluation. Usually intraabdominal & intrathoracic lymph nodes are not palpable, but visualized with imaging techniques such as USG, CT scan or MRI. Evaluation and treatment of lymphadenopathy are guided by the probable etiologic factors, as determined from the clinical history and physical examination[4]. Many patients with cervical lymphadenopathy have a history compatible with viral infection and need no intervention. If bacterial infection is suspected, antibiotic treatment covering at least streptococci and staphylococci is indicated.[5-8]

Those who do not respond to oral antibiotics, as demonstrated by persistent swelling and fever, require IV anti-staphylococcal antibiotics.[10] If there is no response in 1-2 days, or if there are signs of airway obstruction or significant toxicity, ultrasound, CT, or MRI of the neck should be obtained. If pus is present, it may be aspirated, with CT or ultrasound guidance, or if it is extensive, may require incision and drainage.[11-14] Gram stain and culture of the pus should be obtained. The sizes of involved nodes should be documented before treatment. Failure to decrease in size within 10-14 days also suggests the need for further evaluation.[15] This may include a complete blood cell count with differential; Epstein-Barr virus, cytomegalovirus, Toxoplasma, and cat-scratch disease titers; anti-streptolysin O or anti-DNAse serologic tests; tuberculin skin test; and chest radiograph.[16-18] If these are not diagnostic, consultation with an infectious disease or oncology specialist may be helpful.[19] Biopsy should be considered if there is persistent or unexplained fever, weight loss, night sweats, supraclavicular location, mediastinal mass, hard nodes, or fixation of the nodes to surrounding tissues.[20-23] Biopsy may also be indicated if there is an increase in size over baseline in 2 weeks, no decrease in size in 4-6 wk., no regression to "normal" in 8-12 weeks, or if new signs and symptoms develop.[24] Differentiating benign disorders from a malignancy may initially be difficult. Hard, nontender, non-erythematous nodes involving multiple regions (including mediastinum and abdomen), hepatic or splenic enlargement, fever, night sweats, and weight loss suggest malignancy or a granulomatous process.[25] Persistence of symptoms and lymphadenopathy greater than 2 weeks and certain locations (supraclavicular, mediastinal, and abdomen) also suggest malignancy. Cytopenias and elevated blood lactate dehydrogenase are associated with malignancy and certain inflammatory disorders. CT imaging is helpful in identifying other affected nodes and organs; CT or ultrasonographic guided needle biopsy is helpful in determining the etiology. Fine needle aspiration biopsy or excisional biopsy may be needed for superficial nodes to determine a diagnosis.[26]

Lymphadenopathy (LAP) in children is a common clinical diagnostic dilemma. The condition has multiple etiologies, but the vast majority is caused by benign disease. However, since LAP can be the first symptom of an underlying malignant disease, it often causes concern. The cervical region is the most common site for LAP.[27] Many methods are used to diagnose LAP, but the issue of how best to manage LAP in children remains unclear. Fine needle aspiration biopsy (FNAB) is performed routinely in the evaluation of cervical LAP in the adult population. In the Pediatric population, however, the use of FNAB is not always used as a routine diagnostic procedure and it is not well-described in the literature.[28]In children with LAP the clinical symptoms, physical evaluation and ultrasonography (USG) are often used for assessment. The surgical excisional biopsy is the golden standard to diagnose malignancy in cervical LAP.[29] This procedure, however, requires general or local anesthesia and involves a risk of nerve lesion, infection, hematoma and other operative complications. The aim of our study was to analyze the histopathology and location predominant types of childhood lymphadenopathy in various locations on the body to distinguish them requiring excisional biopsy.

Method: This retrospective observational study was carried out in "The Alpha Laboratory" Kandirpar, Cumilla, Bangladesh. Specimens were collected from different Government and Private medical colleges, clinics and physicians chamber. Cumilla is a city in the Chittagong Division of Bangladesh, located along the Dhaka-Chittagong Highway. It is the administrative center of the Cumilla District, part of the Chittagong Division. Cumilla is the second-largest city of eastern Bangladesh after Chittagong and is one of the three oldest cities in Bangladesh. This study was conducted considering the medical records of the patients less than 18 years of age during a period of one year from January 2017 to December 2017.Total 179 patients were recruited. All excised lymph nodes specimens having proper labeling received in the laboratory constituted the study material. The specimens were preserved in 10% buffered formalin immediately after operation before sending to the laboratory & processed for histopathological examination. Routine Haematoxylin & Eosin (H&E) stains sections were examined. Special stain like Ziehl-Neelsen stain was done for identification of acid fast bacilli. But immunohistochemistry (IHC) was employed for further confirmation of primary lymphoid neoplasms & metastatic lesions. All the lymph nodes studies were grouped into the regions from which they were collected (excised sites). All the lymph nodes biopsied,

which were found, damaged (autolyzed) specimens and known cases were excluded from this study. All surgically resected and biopsied specimens of lymph node received only less than 18 years old population both male and female. Histopathology slides of all cases were examined under microscope & reviewed in some cases. Clinical demographic data regarding age, sex, anatomical sites of nodal biopsy and clinical information were obtained from histopathology requisition forms and registered properly. Data were analyzed by IBM-SPSS-23 software using cross tabulation, figure and chart.

Result:

The present study was conducted in ``The Alpha Laboratory`` in Cumilla district of Bangladesh by histopathologists to find out the commonest cause of enlarged lymph nodes in our set up & to assess the spectrum of lymphadenopathy in child age groups. We found that out of 179 cases, 13.4 % (24) were below 5 years of age, 30.2%(54) in the 6-10 years age group, 34.6%(62) in the 11-15 years age group, 21.8% (39) in the 16-20 years age group(Table-I, Figure-I). We observed that out of 179 cases, 65.4% (117) were males and 34.6% (62) were females. Male to Female ratio was approximately 2:1. The present study includes patients of all pediatrics age groups. The peak incidence of age group suffering from the disease was 11-15 years (34.6%) followed by cases which are 6-10 years of age (30.2%)(Table-I,Table-II,Figure-I).

Table I: Age in years and gender

Age in years		Gender		Total
		Male	Female	
1-5	Count	16	8	24
	% within age in years	66.7%	33.3%	100.0%
	% within gender	13.7%	12.9%	13.4%
	% of Total	8.9%	4.5%	13.4%
6-10	Count	45	9	54
	% within age in years	83.3%	16.7%	100.0%
	% within gender	38.5%	14.5%	30.2%
	% of Total	25.1%	5.0%	30.2%
11-15	Count	31	31	62
	% within age in years	50.0%	50.0%	100.0%
	% within gender	26.5%	50.0%	34.6%
	% of Total	17.3%	17.3%	34.6%
16-18	Count	25	14	39
	% within age in years	64.1%	35.9%	100.0%
	% within gender	21.4%	22.6%	21.8%
	% of Total	14.0%	7.8%	21.8%
Total	Count	117	62	179
	% within age in years	65.4%	34.6%	100.0%
	% within gender	100.0%	100.0%	100.0%
	% of Total	65.4%	34.6%	100.0%

Majority cases were benign lesions and it was about (84.91%) (152 cases) among them chronic nonspecific lymphadenitis (CNL) (105 cases, 69.07%) (Table-III, Figure-II), tuberculous lymphadenitis (TB) (37 cases, 24.34%), histiocytic necrotizing lymphadenitis (KFD) 5 cases (3.28%), suppurative lymphadenitis 5 cases (3.28%) (Table-III & Figure-II). CNL & tuberculous lymphadenitis (TB) are predominant involving agewere 6-15 years and 15-20 years respectively (Figure-I,II). Cervical lymph node group were mostly involving group of all lesions and age group and it was about 100 cases (55.86%) (Table-II, Figure-I)

Out of all (179 cases) primary lymphoid malignant lesions were 15 cases (8.37%) and diagnosed as Non-Hodgkin Lymphoma (NHL) 4 cases (2.23%), Follicular lymphoma 4 cases (2.23%) & Hodgkin Lymphoma (HL) 7 cases (3.91%) and Metastatic lesions were 05 cases (2.80%) including Metastatic papillary carcinoma, Metastatic nephroblastoma (WT), Metastatic nasopharyngeal carcinoma, Metastatic malignant fibrous histiocytoma (MFH) & Metastatic embryonal rhabdomyosarcoma were single in number. Others (soft tissue) lesions were 7 cases (3.91%) & diagnosed as Lipoma 2 cases, Branchial cleft cyst, Neurofibroma, Chronic sialadenitis and Accessory axillary breast tissue were single in number (Figure-I & II), which were initially & clinically diagnosed as enlarged lymph nodes as in anatomical locations. But after biopsy & histopathological examination they revealed soft tissue masses & gland origin masses (salivary & mammary glands) other than lymphoid tissue (Table- III)

Table II: Age in years and groups of lymph node

Age in years	Group of lymph node							Total
	cervical	mesenteric	axillary	inguinal	submental	submandibular	supraclavicular	
1-5	8	4	5	4	1	2	0	24
6-10	36	5	2	7	0	4	0	54
11-15	34	11	8	6	0	2	1	62
16-18	22	1	5	5	0	5	1	39
Total	100	21	20	22	1	13	2	179

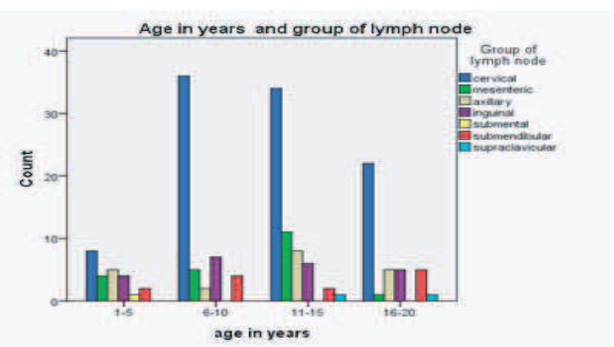

Figure-I: Age in years and groups of lymph nodes

Table III: Histopathological distribution of diseases pattern

Benign(lymphoid) lesions	Primary malignant lymphoid lesions	Metastatic lesions	Others (soft tissue) lesions
1. Chronic nonspecific lymphadenitis (CNL)(105)	1. Non-Hodgkin Lymphoma (NHL)(4)	1. Metastatic papillary carcinoma (1)	1. Branchial cleft cyst (1)
2. Tuberculous lymphadenitis (TB) (37)	2. Hodgkin Lymphoma (HL)(7)	2. Metastatic nasopharyngeal carcinoma (1)	2.Lipoma (2)
3 Histiocytic necrotizing lymphadenitis (KFD)(5)	3. Follicular lymphoma(4)	3. Metastatic nephroblastoma (1)	3. Neurofibroma (1)
4. Suppurative lymphadenitis (inflammation)(5)		4.Metastatic rhabdomyosarcoma(1)	4. Chronic Sialadenitis (2)
		5. Metastatic malignant fibrous histiocytoma (MFH) (1)	5. Accessory axillary breast tissue (1)
Total (152) (84.91%)	**Total (15) (8.37%)**	**Total (5) (2.80%)**	**Total (7) (3.91%)**
Total 179			

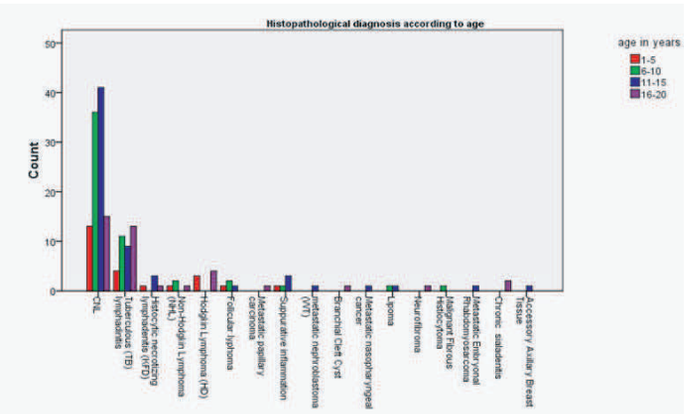

Figure II: Histopathological diagnosis according to age

Discussion:

Lymphadenopathy is common in children. It is usually not clinically important in and of itself. However, it can represent serious underlying disease. The challenge for clinicians is to avoid aggressive evaluation and biopsy of most children, while making timely, specific diagnosis in children with serious underlying disease. In studies conducted by Henry et al,[27] YeuTsu N et al[28] and in India by Kamat et al,[29] it has been found that benign lesions are much more common than malignant lesions. Rao M N et al[30] reported that, lymphadenopathy due to malignancy were 22 (44%), non-malignant causes were 28 (56%).In the present study, lymphadenopathy due to benign cases were (84.91%) (152 cases) and due to malignant & metastatic involvement were 15 cases (8.37%) & 05 cases (2.80%) respectively. In present study, 105 cases (69.07%) were chronic nonspecific lymphadenitis (CNL) and 37 cases (24.34%) were granulomatous lymphadenitis. According to Vacchani et al,[31] reactive hyperplasia (CNL) was 51% and granulomatous lymphadenitis was 24%. Tiwari et al[32] reported reactive hyperplasia to be 36% and granulomatous lymphadenitis to be 49 %. Kamat et al[29] reported reactive hyperplasia to be 30.73 % and granulomatous lymphadenitis to be 58.19%. Tuberculosis has also been reported by several authors as the predominant lesion in young adults in the tropics. Rahman et al[33] in his study found that tuberculosis was the commonest cause of lymphadenopathy accounting for 33.5% of cases. In the present study primary lymphoid malignancies accounted for 15 cases (8.37%) and metastatic lymph nodes accounted for 05 cases (2.8%). In the present study, lymphoma accounted for 8.37% of cases out of which Non-Hodgkin lymphoma & follicular lymphoma constituted 26.66% & 26.66 % respectively and Hodgkin lymphoma constituted 46.66% of total lymphoma cases. In study conducted in Nigeria by Akinde et al[34] lymphoma cases constituted 16.85 % of cases. In study conducted in India (Karnataka) by Kamat et al[29] and in Nepal by Tiwari et al[35] and in Gujarat by Vachhani et al[31] frequency of lymphoma cases are 3.7%, 2% and 2% respectively. In the Western world non-Hodgkin's lymphoma is reported to be 3 to 4 times more common than Hodgkin's lymphoma[34-39]. In our study we found 5 cases (2.80%) of metastatic lymph nodes & 7 cases (3.91%) of other lesions (soft tissue masses, salivary & mammary gland origin masses which were clinically wrongly diagnosed as lymphadenopathy before biopsy)

Conclusion:

Lymphadenopathy is an important finding in the diagnosis of many diseases. The histopathological examination helps us in assessing the architecture of the tissue. Combined with immunohistochemistry, it can be a useful tool in clinching a diagnosis. The history, blood examination and cytological correlation are required. The major limitation of our study was the small number of cases owing to the short duration of the study. Many cases were lost to follow up, some of the cases expired owing to malignant disease. Another limitation was that some of the specimens were badly preserved due to poor fixation by formalin before sending to the laboratory. We are planning to increase the number of cases in the years to come and maintain proper records of the patients so that they are not lost to follow up.

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References:

1. Friedmann AM. Evaluation and management of lymphadenopathy in children. Pediatr Rev2008; 29:53–60.
2. Goins MR, Beasley MS. Pediatric neck masses. Oral Maxillofac Surg Clin North Am2012;24: 457–468.
3. Ichikawa K, Sugimoto K, Isobe Y, et al. Usefulness of systemic computedtomography (CT) scanning in the detection of malignant lymphadenopathy.Medicine (Baltimore) 2011;90(6): 396–403.
4. Ludwig BJ, Wang J, Nadgir RN, et al. Imaging of cervical lymphadenopathy in children and young adults.AJR Am J Roentgenol2012;199:1105–1113.
5. Moffett KS. Pediatric infectious disease: unusual head and neck infections. Oral Maxillofac Surg Clin North Am2012;24:469–486.
6. Restrepo R, Oneto J, Lopez K, et al. Head and neck lymph nodes in children: the spectrum from normal to abnormal.PediatrRadiol2009;39:836–846.
7. Sinha IP, Stickland A, John CM. A child with neck swelling.BMJ 2012; 344:42–43.
8. Tanphaichitr A,Bhushan B, Maddalozzo J, et al. Ultrasonography in the treatment of pediatric midline neck mass.Arch Otolaryngol Head Neck Surg 2012;138(9):823– 827.
9. Twist CJ, Link MP. Assessment of lymphadenopathy in children. PediatrClin North Am 2002;49:1009–1025.
10. Chuang CH, Yan DC, Chiu CH, et al. Clinical and laboratory manifestations of Kikuchi's disease in children and differences between patients with and without prolonged fever. Pediatr Infect Dis J 2005;24:551–554.
11. Gosche JR, Vick L. Acute, subacute, and chronic cervical lymphadenitis in children, Semin Pediatr Surg 2006;15:99–106.
12. Hutchinson CB, Wang E. Kikuchi-Fujimoto disease. Arch Pathol Lab Med 2010; 134:289–293.
13. Jun-Fen F, Chun-Lin W, Li L, et al. Kikuchi-Fujimoto disease manifesting as recurrent thrombocytopenia and Mobitz type II atrioventricular block in a 7-year-old girl: a case report.ActaPaediatr2007; 96:1844–1847.
14. Lazzareschi I, Barone G, Ruggiero A, et al.Paediatric Kikuchi-Fujimoto disease: a benign cause of fever and lymphadenopathy. Pediatr Blood Cancer2008; 50:119–123.
15. Lee HY, Huang YC, Lin TY, etal. Primary Epstein-Barr virus infection associated with Kikuchi's disease and hemophagocytic lymphohistiocytosis: a case report. J Microbiol Immunol Infect2012; 43:253–257.
16. Lee BC, Patel R: Kikuchi-Fujimoto disease: a 15-year analysis at a children's hospital in the United States.ClinPediatr (Phila) 2013;52(1):92–95.
17. Monaco SE, Khalbuss WE, Pantanowitz L. Benign non-infectious causes of lymphadenopathy: a review of cytomorphology and differential diagnosis. Diagn Cytopathol2012; 40:925–938.
18. Mrowka-Kata K, Kata D, Kyrcz-Krzemien S, Helbig G. Kikuchi-Fujimoto and Kimura diseases: the selected, rare causes of neck lymphadenopathy.Eur ArchOtorhinolaryngol 2010;267:5–11.
19. Wong VK, Campion-Smith J, Khan M, et al. Kikuchi disease in association with Pasteurellamultocidainfection. Pediatrics 2010; 125: 679–682.
20. Connolly AA, MacKenzie K. Paediatric neck masses: a diagnostic dilemma. J LaryngolOtol 1997;111:541-5.
21. Oguz A, Karadeniz C, Temel EA et al. Evaluation of peripheral lymphadenopathy in children. PediatrHematolOncol 2006;23:549-61.
22. Wakely PE Jr, Kardos TF, Frable WJ. Application of fine needle aspiration biopsy of pediatrics. Human Pathology 1988; 19:1383-6.
23. Moore SW, Schneider JW, Schaaf HS. Diagnostic aspects of cervical lymphadenopathy in children in the developing world: a study of 1,877 surgical specimens. PediatrSurgInt 2003; 19:240-4.
24. Papadopouli E, Michailidi E, Papadopoulou E et al. Cervical lymphadenopathy in childhood epidemiology and management. PediatrHematolOncol 2009; 26:454-60.
25. Niedzielska G, Kotowski M, NiedzielskiA et al. Cervical lymphadenopathy in children: incidence and diagnostic management. Int J PediatrOtorhinolaryngol 2007; 71:51-6.
26. Hjalgrim H, Engels EA. Infectious aetiology of Hodgkin and non-Hodgkin lymphomas: a review of the epidemiological evidence. J Int Med 2008; 264:537-48.
27. 13 Henry P, Longo D. Enlargement of lymph nodes and spleen. In: Kasper D, Braunwald E, Fauci A, Hauser S, Longo D, Jameson L. Harrison's principles of internal medicine 2005;16:343-348.
28. Lee Y, Terry R, Lukes R. Lymph node biopsy for diagnosis: a statistical study. Journal of Surgical Oncology 1980; 14(1):53-60.
29. Kamat GC. A ten-year histopathological study of generalized lymphadenopathy in India. S AfrFamPract 2011:53(3):267-270.
30. Rao M, Raju Y, Prasad A. Evaluation of lymphadenopathy at a referral centre. JAPI 2002;50:1488-1489.

31. Vachhani A, Bhuva K, Jasani J, Patel D, Savjiani N, Patel K, et al. Histopathological study of lymph node biopsy. IJBAR 2013; 4(11):790-795.
32. Tiwari M, Aryal G, Shrestha R, Rauniyar SK, Shrestha HG, et al. Histopathologic diagnosis of lymph node biopsies.Nepal Med Coll J. 2007;9(4):259-261.
33. Rahman MA, Biswas MA, Siddika ST, Sikder AM. Histopathological Evaluation of Lymph Node Biopsies: A Hospital Based Study. J Enam Med Col 2012; 2(1):8-14.
34. Akinde OR, Anunobi CC, Abudu EK, Daramola AO, Banjo AA, Abdulkareem FB, et al. Pattern of lymph node pathology in Lagos. Nig Q J Hosp Med. 2011; 21(2):154- 158.
35. Sibanda EN, Stanczuk G. Lymph node pathology in Zimbabwe: a review of 2194 specimens. Q J Med.1993; 86(12):811-817.
36. Anunobi CC, Banjo AA, Abdulkareem FB, Daramola AO, Abudu EK. Review of the histopathologic patterns of superficial lymph node diseases in Lagos (1991-2004). Niger Postgrad Med J. 2008; 15(4):243-246.
37. Thomas JO, Ladipo JK, Yawe T. Histopathology of lymphadenopathy in a tropical country. East Afr Med J1995; 72(11):703-705.
38. Moore SW, Schneider JW, Schaaf HS. Diagnosticaspects of cervical lymphadenopathy in children in the developing world: a study of 1877 surgical specimens. PediatrSurgInt2003; 19(4):2040-2044.
39. Ochicha O, Edino ST, Mohammed AZ, Umar AB, Atanda AT. Pathology of peripheral lymph node biopsies in Kano: Northern Nigeria. Ann Afr Med 2007; 6:104-8.

Original Article

A Study on Usefulness of Neuro-electrophysiological Examination in Polyneuropathy

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Abstract

Background: : Polyneuropathy has many different causes. It is often very difficult to find out the cause. Knowing neuropathy as axonal or demyelinating may direct the search for cause. **Method:** Purposively selected 80 patients from the department of Neurology Dhaka Medical College during the period of January 2009 to June 2010 were taken for electrophysiological examination whose were compatible with polyneuropathy by history and clinical examination, axonal or demyelinating variety were find out. **Result:** Mean age of the patients was 34.5 ±6.8 and M: F was 1.8:1. Students, laborer and cultivators were the most affected people. 55% patients were acute cases and 35% patients were chronic Cases. 30% patient had no known risk factor for neuropathy 25% patient had antecedent infection, 15% had diabetes mellitus, 7.5% were exposed to drugs/toxins or solvents and 5% had family history of neuropathy. In clinical examination 37.5% patients were in motor type, 10% pure sensory type and 52.5% mixed sensorimotor type. In electrophysiological assessment 47.5% were motor, 7.5% pure sensory 45% mixed sensorimotor type. Electrophysiological axonal were 47.5%, demyelinating 27.5% and 25% as mixed axonal and demyelinating type. **Conclusion:** In clinical examination polyneuropathy cannot be classified as axonal or demyelinating variety whereas electrophysiological examination can do it.

Key words: Polyneuropathy, neuro-electrophysiology

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Introduction:

Polyneuropathy is the disorder in which the functions of numerous peripheral nerves are affected at the same time and leads to distal and symmetrical deficit with loss of tendon reflexes.[1] It is a relatively common syndrome which is often distressing and sometime disabling or even fatal.[2] Polyneuropathy has an estimated incidence of 25-200/100,000 persons per year and a prevalence of about 5%.[3]

Peripheral nerves have motor, sensory and autonomic component. Nerve fibers (axons) can be classified as either small fibers or long fibers. Large nerve fibers: - are long nerve fibers that are myelinated and enable very fast conduction of impulses to the brain. They carry non-nociceptive information and are not normally associated with pain. Lesions or injury to large fibers can affect many functions including - motor function, vibration perception, position sense, perception of temperature. Symptoms associated with large fibers neuropathy includes -numbness, tingling, weakness, pain, loss of deep reflexes. Small nerve fibers: - some are myelinated and some are not myelinated and each type involves different sensation. They contain nociceptors which are highly sensitive to pain and paresthesia. Symptoms of small fiber neuropathy are many and includes-pain describes as burning, stabbing, prickling, jabbing or lancinating (piercing), sensation of broken glass, burning sands, or ice pick in the bone, tight band like pressure, insensitivity to heat or cold and autonomic dysfunctions related to the organs.

Sensory nerves damage produce symptoms such as pain, numbness, tingling, burning or loss of sensation or feeling. Lack of sensation can produce cuts or burns unnoticed and ulcer or poor wound healing. Motor nerves damage results in decreased movement and muscle wasting. Symptoms usually begin as weakness or heaviness of the hands and or feet and may deteriorate over time.[4]

Polyneuropathy (PN) as a syndrome has many different causes and worldwide diabetes mellitus is the commonest cause other being are hereditary neuropathy, deficiency of vitamins, B1, B12, uremia, autoimmune neuropathies, infections including leprosy and HIV, drugs and toxins, porphyria, paraneoplastic state and 25% cases are idiopathic.[5, 6] About 80% of polyneuropathies are axonal and the remaining 20% are demyelinating. Most of the axonal polyneuropathies are either purely sensory or mixed sensory motor type.[2]

Electrophysiological studies play a critical rule firstly to confirm the diagnosis of PN and then to classify it as axonal or demyelinating variety and thereby directing the search for cause.[5,7] Furthermore electrophysiology is quite sensitive to detect sub clinical involvement of either motor or sensory component of apparently pure sensory or pure motor PN giving further clue to the aetiology.[8,9]

PN are also classified into acute and chronic form. Acute forms PN are those that have relatively dramatic onset and usually recovers within six weeks. The classical and commonest example of that group is Guillaine Barre Syndrome (GBS). The other less common causes of acute PN are vasculitic, drugs and toxins, porphyria diphtheria, acute idiopathic sensory neuropathies. Chronic PN are those which usually develop over several months. Most of the classical chronic PN which presents with signs symptoms of distal symmetrical way falls into this category. The causes of chronic PN are diabetes mellitus, uremia, alcoholism and other toxins, drugs, underlying neoplasm, hereditary (Charcot Marie tooth disease) and idiopathic.[10, 11, 12] After exclusion of common causes of PN routine and specific investigations is the first stage of screening, neurophysiological studies in the form of nerve conduction study (NCS) and electromyogram (EMG) becomes the vital and important way of approach to the underlying cause in the second stage. The subsequent investigation in the third stage depends on the findings of NCS which distinguishes demyelinating from axonal polyneuropathies and divides axonal type into purely sensory, pure motor and mixed sensory motor groups. Chronic axonal PN has many causes. After NCS confirmation further approach in the third stage should includes investigations to identify cases of diabetes mellitus that were not detected by the screening 1st stage tests and to show the less common medical condition. Even after extensive investigations about 25% of cases remain idiopathic, which occur mostly in elderly and is often indolent, predominantly sensory and unlikely to become severely disabling.[13. 14]

Method:

This cross sectional observational study was carried out in the Department of Neurology, Dhaka Medical College and Hospital, Dhaka From January 2009 to June 2010 Sample Size: A total of 80(eighty) subjects were included purposively in this study. Patients aged 18yrs to 60yrs of age with symptoms and signs of polyneuropathy were included and undergone electrophysiological investigation. Patients with mononeuropathy, traumatic or entrapment neuropathy, Conditions such as confusional state, pregnancy, skin diseases, oedema, prosthetic device that interfere with electrophysiological investigations, Neuropathy symptoms mimicking specific disease like motor neuron disease, myopathy, muscular dystrophy, spinal muscular atrophy or neuromuscular junction disorder were excluded. And patient who were not willing to participate in the study also excluded.

All the study cases were underwent meticulous history and asked for neuropathy symptoms and risk factors of polyneuropathy and physical examination were done by standard methods. Patients who presented with weakness, wasting and cramps were categorized clinically into motor type and those with tingling, numbness or paresthesias were categorized into sensory type and combination of sensory and motor features were classified into mixed type. Michigan neuropathy screening instrument questionnaire were used for quantitive assessment.

Electrophysiological study and relevant other investigations were done to find out the cause. Nerve conduction study was carried out using standard techniques by Neuro pack II of 'Nihon Kohden' MEB 9200 machine (Japan). Skin temperature was maintained between 32^0C to 34^0C. The studies included motor and sensory nerve conduction in at least cross limbs or one arm and two legs. Electrophysiological study was set as a gold standard test for neuropathy assessment.

Data Collection and Data Analysis:

Data was collected by semi-structured questionnaire by the investigator. Face to face interview, medical history and clinical examination and subsequent laboratory investigations were done. Proper permission was taken from the concern departments. All the patients (cases) were

informed about the about the nature of the study and their informed written consent were taken in a consent form before collecting data. Data was analyzed with the help of computer SPSS program version 16.0 software facility. The chi-square test and Fisher's exact test were used to evaluate the proportion. A p-value of less then 0.05 was considered as statistically significant. Agreement tests (reliability) were done to see clinical and electrophysiological relation.

Result:

A total of eighty patients of polyneuropathy (acute, subacute and chronic) were included in the study. Meticulous history and clinical examination was undertaken before neurophysiological investigation. The findings of study obtained from data analysis are presented below.

Table-I: Patients Characteristics (n=80)

	No of patients	Percentage (%)
Men	52	65
Women	28	35
Age in years		
18 – 30	32	40
31 – 40	28	35
41 – 50	8	9
51 – 60	12	16
Mean age ±SD=34.4±6.8		
Range of age = 18- 60		
Occupation		
Service	12	15
Business	6	7.5
Student	10	12.5
Labourer	14	17.5
Cultivator	10	12.5
House wife	8	10
Unemployed	10	12.5
Retired	4	5
Others	6	7.5
Mode of onset/Duration		
Acute/upto 4 weeks	44	55
Subacute / 4 to 8 weeks	08	10
Chronic / > 8 weeks	28	35
Risk factor distribution		
Diabetes	12	15
Connective tissue disease	2	2.5
Hypothyroidism	4	5
Hereditary/ Family history	4	5
Preceding illness- diarrhea or RTI	20	25
Drugs/Toxins/Solvents exposure	6	7.5
Deficiency (vitamin)	4	5
Malignancy	2	2.5
Heavy metal(lead)	2	2.5
Not known (Idiopathic)	24	30

SD= standard deviation, RTI= respiratory tract infection

Table-1 shows the age distribution of the patient in to four groups. Ages of the patient ranged from 18 – 60 years. Most of the patient fell into 18 – 30 and 31- 40 years age group and are 32 (40%) and 28 (35%) respectively. Lowest 8 (9%) was in 41 – 50 years age group. The mean age was 34.4 years with a standard deviation of 6.8. Patients were divided into male and female gender. Out of them 52 (65%) were male and 28 (35%) were female patients. M: F=1.8: 1. In occupation distribution service category comprised 15%(12), in business category 7.5%(6), student 12.5%(10), laborer 17.5%(14) which was the highest category, cultivator 12.5%(10), house wife 10%(8), unemployed comprises 12.5%(10), and retired 5%(4) which was lowest category and other not specified were 7.5%(6). Distribution of the patients according to the duration of illness i.e. mode of onset most of patient presented acutely which were 44(55%), chronic onset were 28(35%) and rests 8(10%) were in sub-acute category. Risk factors distribution of disorder causes polyneuropathy, highest number of patient were in not known or idiopathic group which comprises 30%(24), next in preceding illness of diarrhea or respiratory tract infection were 25%(20), history of diabetes were present in 15%(12), drugs/toxins/solvents in 7.5%(6), hypothyroidism in 5%(4), hereditary or family history of neuropathy also in 5%(4).

Table II: Clinical features of the study population (n=80)

Clinical feature		No of Patient affected	Percentage (%)
Symptoms			
	Paresthesia	70	87.5
	Tingling	72	90
	Numbness	24	30
	Lack of feeling	20	25
	Weakness	60	75
	Wasting	20	25
	Cramps	24	30
Signs			
	Cranial nerve palsy	26	32.5
	Loss of muscle power	60	75
	Loss of Pinprick	20	25
	Loss of Vibration sense	10	12.5
	Deep tendon reflex hypo/areflexia	70	87.5
	Autonomic dysfunction (any level)	10	12.5
	Gait abnormality (any level)	70	87.5
	Nerve thickening	2	2.5
Weakness Distribution			
Proximal and distal		40	50
Distal to proximal		20	25
No weakness		20	25
Clinical type of Polyneuropathy			
Motor		30	37.5
Sensory		8	10
Mixed		42	52.5

The multiple response table 2 shows that most of the patient had tingling, paresthesia and weakness which ranges from 75% to 90%, numbness in 30% patient, wasting in 25% patient, loss of muscle power were observed in 75%, deep tendon hypo or areflexia were in 87.5%, cranial nerve palsy in 32.5%, pinprick loss in 25%, loss of vibration in 12.5%, autonomic dysfunction at any level in only 12.5% and nerve thickening in only two patients. Distribution of weakness in study subject, 50% patient there were both simultaneous proximal and distal weakness, distal to proximal weakness were in 25% patient, and 25% patient were with no weakness at all. Clinical types of polyneuropathy among study population. Out of 80 patients, 42(52.5%) had mixed sensory motor neuropathy, followed by 30 (37.5%) had motor neuropathy and only 10% had sensory neuropathy.

Table III: Electrophysiological classification of neuropathy in study population (n=80)

Type	No of patients	Percentage (%)
Axonal	38	47.5
Demyelinating	22	27.5
Mixed axonal & demyelinating	20	25
Total	80	100
Motor	38	47.5
Sensory	6	7.5
Mixed sensorimotor	36	45
Total	80	100

The above table no. 3 shows the electrophysiological category of polyneuropathy in study population. Axonal varieties were highest and comprised 47.5 %(38), mixed variety were lowest 25 %(20) and demyelinating category were 27.5 %(22). Types determined by electrophysiological examination into motor, sensory and mixed sensorimotor polyneuropathy were 47.5 %(38), 7.5% (6) and 45% (36) respectively.

Table IV: Statistical analysis of Clinical and electrophysiological relationship of polyneuropathy

	Chi-square value	p value	Agreement test, k value
Motor polyeuropathy	9.59	0.0019	0.5 (fair agreement)
Sensory polyneuropathy		0.1597 (Fisher's exact)	0.19 (poor agreement)
Mixed sensorimotor polyneuropathy	5.681	0.0032	0.44 (fair agreement)
Weakness distribution of demyelinating type	1.726	0.1892	0.06(poor agreement)
Weakness distribution of axonal type	2.678	0.1018	0.14 (poor agreement)

The above table no 4 shows the statistical analysis of clinical and electrophysiological relationship. For motor type of polyneuropathy, statistical analysis shows there is significant relation as the p value is < 0.05 and k value = 0.5 (fair agreement). For sensory type of polyneuropathy, statistical analysis shows there is no relation as the p value is > 0.05 and k value = 0.19 (poor agreement). For mixed sensorimotor type of polyneuropathy, statistical analysis shows there is significant relation as the p value is < 0.05 and k value = 0.44 (fair agreement). Association of weakness distribution of proximal and distal with demyelinating category, statistical analysis shows that the association is not significant as the p value is >0.05 and k value = 0.06 (poor agreement). Association of weakness distribution of distal to proximal with axonal category, statistical analysis shows that the association is not significant as the p value is >0.05 and k value = 0.14 (poor agreement).

Discussion:

Polyneuropathy is relatively common and often a distressing chronic condition. It has many diverse underlying causes and in different diseases the incidence of PN varies considerably.[15]This cross sectional study was designed to see the clinical and electrophysiological features of polyneuropathy patients. This study also addressed the clinical and electrophysiological pattern of polyneuropathy patient.

In this study patients of all age group ranging from 18-60 years were included. Majority of the patients 32 (40%) were in 18 to 30 years of age with mean ±SD = 34.4 ±6.8. In this study 65 % were male and 35 % were female with M: F = 1.8: 1. In one local study[15] the M: F was 1.88: 1 and in another local study[16] the M: F ratio was 1.9:1 which resembles with the present study and it is observed that polyneuropathy is about two times more common in male. McLeod et al.[17] also found an overall predilection for men (3:1). In this study polyneuropathy were widely distributed in different occupations, labourers, cultivator and students were affected more. In this regard there are a few studies elsewhere. In the study of Chistee, [18] more or less similar findings were observed but in his series cultivators were less affected but housewives were more affected as well as labourer and students.

It was observed in this study that 55% patients presented acutely and 35% had chronic onset and 10% patients had sub-acute onset. Study on polyneuropathy patients comprising acute, sub-acute and chronic cases are few. Local study Chistee[18] of 50 polyneuropathy cases GBS cases were 50% and the findings were similar with the present study. In this study majority (30%) patients had no known history of risk factors i.e. idiopathic, antecedent infections (preceding illness either diarrhoea or RTI) was the next common risk factors (25%), next was diabetes mellitus (15%), followed by combined

drugs & toxins (7.5%). In a study of chronic polyneuropathy by Vrancken et al[3] idiopathic were 43%, diabetes mellitus 32%, alcohol abuse 14%, paraproeinaemia 9%, deficiency of vitamin 6% and autoimmune or systemic disease 4% were observed. In a Dutch study on chronic polyneuropathy, Rosenberg NR et al[6] observed 60(57.1%) patients of diabetes mellitus, followed by HIV infection in 21(20%) patients, alcoholism in 11(10.5%) patients; drug induced in 7(6.7%) patients and renal failure in 6(5.8%) patients in a study of 105 chronic polyneuropathy cases. In Lubec et al[19] frequency of causal factors in 124 cases were : - diabetes mellitus in 26(21%) cases, alcohol in 20(16.1%) cases, vitamin deficiency in 13(10.5%) cases, GBS in 9(7.3%) cases, paraproteinamias in 6(4.8%) cases, hypothyroidism in 5(4.03%) cases, borreliosis in 6(4.8%) cases, paraneoplasia in 4(3.2%) cases, CIDP in 5(4.03%) cases, hereditary in 3(2.4%) cases, hyperthyroidism in 3(2.4%) cases, critical illness in 2(1.6%) cases, vasculitis in 3(2.4%) cases, and each one(0.8%) case of sarcoidosis, vincristine, azathioprine, Refsum's disease, Sneddon's syndrome, Ehlers-Danlos syndrome, crohn's disease inflammatory polyarthritis and solvent. In an Asian study of 124 cases of chronic polyneuropathy Habib and Ferdousi[15] observed diabetes were 45.2%, idiopathic 45.2%, hereditary 5.7% and CIDP in 3% cases. So the distribution of polyneuropathy in different diseases varies worldwide. In this study less diabetic and infectious cases were observed as because major bulk of diabetes mellitus are cared by internationally reputed separate diabetic hospital and infectious disease hospitals.[16]

The features of polyneuropathy may be exclusively motor, sensory, autonomic or combined. Most PN present with mixed sensory motor symptoms. Sensory symptoms were usually the presenting features. These were tingling, pins and needles, burning sensation, pain and numbness in the extremities. Motor symptoms were usually those of weakness and wasting. [20] This is reflected in the present study where paresthesias were present in 87.5 %, tingling in 90%, numbness in 30% cases. Weakness in this study was in 75% cases, deep tendon reflex hypo/areflexia in 87.5% and abnormality of gate at any level were also 87.5%. Similarity was observed in the study of Habib and Ferdousi[15] also. A relative lack of muscle wasting in relation to the degree of weakness, weakness of proximal muscle as well as distal muscle, disproportionate loss of joint position and vibration sensation compared to relative preservation of pain and temperature are suggestive of demyelinating neuropathy.[21] In this present study proximal and distal weakness was in 50% cases and distal to proximal weakness was observed in 45% cases.

One of the most important aims of the study was to detect the clinical and neurophysiological type of polyneuropathy. In Rosenberg et al[6] 77.5% were mixed sensorimotor type, 13.75% were pure sensory type and 8.75% were pure motor type. In Konig et al[22] 42% were mixed sensory motor, 30% sensory, no case of motor type. In the study of Konig et al[22] cases of mononeuropathy and mononeuritis multiplex were included. In Macleod et al[17] 64% were mixed sensory motor type and 27% pure sensory type and 9% were pure motor type. In our present study mixed sensory motor types were 52.5%, motor types were 37.5% and pure sensory types were only 10%. Though in this present series mixed sensory motor type was the most common, the high motor type reflects the inclusion of significant acute polyneuropathy cases.

In this study of 80 polyneuropathy cases either cross limbs or both the lower limbs and an upper limb nerves were examined electrophysiologically. 80 median nerves, 80 ulnar nerves, 120 tibial nerves, 130 common peroneal nerves and 140 sural nerves were studied. In this study electrophysiological types of polyneuropathy were axonal type 47.5%, demyelinating type 27.5% and mixed type 25% which were near similar with Vrancken3 et al. Where axonal type was 57%, demyelinating type 13% and not specified were 31%. In another European study[6] (Rosenberg NR et al) of 56 chronic polyneuropathy cases, axonal types were 87.5% and demyelinating type were 12.5% and the findings resembles the present study. In a Bangladehi study by Habib and Ferdousi[15] 26.6% were axonal, 16.1% demyelinating and 31.5% were mixed axonal and demyelinating. The above mentioned local study does not match with our study due to the fact that 25.8% patient were not labeled in any particular pathological type.

It is important to know neuropathy as axonal or demyelinating as it helps proper management. Highly significant association was seen in motor and mixed sonsorimotor type of clinical and electrophysiological classification. In sensory polyneuropathy distribution in clinical and electrophysiological types varies. Comparison of the severity of polyneuropathy in clinical and electrophysiological grade there were poor relation among them. The weakness distribution such as distal to proximal with axonal and distal and proximal with demyelinating polyneuropathy, statistically significant association were not found. To determine the relation between neurophysiological data and clinical examination Lefaucheur[23] et al. observed that clinical and neurophysiological classifications and severity scores were correlated whatever the type of neuropathy. These differences with the present study might be due to that Lefaucheur23 et al studied the sensory neuropathy according to fiber type involvement. Latov[24] et al observed that the number and type of demyelinating abnormalities in patients with polyneuropathy vary with the clinical phenotype. Rajabally et al[25] in their studied patients with CIDP demonstrated the predominance of demyelination in upper limbs nerves, of axonal loss in lower limbs nerves and presence of about 50% of

demyelinating– range abnormalities in clinically unaffected territories. Vittadini[26] et al found significant correlation between alcoholic polyneuropathy, the duration of alcoholism and the type of alcoholic beverage consumed.

Conclusion:

In this present study there are some variations and there are some relations among the clinical and electrophysiological spectrums of polyneuropathy. Motor and mixed sensorimotor type of Clinical and electrophysiological classification of polyneuropathy are related but the sensory types of polyneuropathy are not related. So as it is immensely needed to know neuropathy as axonal or demyelinating, neurophysiological examination should always be done in polyneuropathy.

References:

1. Greenberg DA, Aminoff MJ, Simon RP Disorder of somatic sensation In. Clinical Neurology 5th edn. Newyork: Lange Medical Books/ McGraw-Hill 2002 ; 6: 208-12
2. Hughes RAC Peripheral Neuropathy. BMJ 2002; 324: 466-69
3. Vrancken AFJE, Kalmijn S, Busken E, Frannsen H, Vermeulen M, Wokke JHJ et al. Feasibility and cost efficiency of a diagnostic guideline for chronic polyneuropathy a prospective implementation study. J Neurol Neurosurg Psychiatry 2006; 77:397-401.
4. Jacob E Medifocus Guide book on Peripheral neuropathy (Updated in September 15, 2009 https/www.medifocus.com/ 2009 : 8-18
5. Notermans NC, Wokke JHJ, Jennekens FGI Clinical work-up of the patient with polyneuropathy. In Jong JMBV de, Vinken PJ, Bruyn GW (eds). Handbook of Clinical Neurogoloy. Amsterdum: Elsvier Science 1991; 2: 30-70.
6. Rosernberg NR, Poregies P, Visser M de, Vermulen M Diagnostic investigation of patient's with chronic polyneuropathy, evaluation of a clinical guideline. J Neurol Neurosurg Psychiatry 2001; 71:205-9.
7. Donofrio PD, Albers JW. AAEM minomonograph 34: polyneuropathy classification by nerve conduction studies and electromyography. Muscle Nerve 1990; 13: 889-903.
8. Wokke JHJ, Van dijk Gw Sensory neuropathies including painful and toxic neuropathies. J Neurol Neurosurg Psychiatry 1997 ; 244:209-221.
9. Van Diljk Gw, Notermans NC, Kater L Sjogren's syndrome in chronic idiopathic axonal polyneuro- pathy J Neurol Neurosurg Psychiatry 1997; 63: 376-8.
10. Davie L, Spies JM, Pollard JD, McLeod LG Vasculitis confined to peripheral nerves. Brain 1996; 19: 1441-8.
11. Dyck PJ, Bersted TJ, Conn DL, Stevens JC, Winderbank AJ, Low PA Nonsystemic vasculitic neuropathy. Brain 1997; 110: 843-54.
12. Dyck PJB, Norell JE, Dyck PJ Microvasculitis and ischaemia in diabetic lumbosacral radiculoplexus neuropathy. Neurology 2000; 53: 2113-21.
13. Saperstein DS, Katz JS, Amato AA, Barohn RJ Clinical spectrum of chronic acquired demyeliating polyneuropathies. Muscle Nerve 2001; 24: 311-24.
14. Russel JW, Feldmen EL Impaired glucose tolerance-does it cause neuropathy? Muscle Nerve 2001; 24: 1109-12.
15. Habib M and Ferdousi RS Electrophysio logical pattern of polyneuropathy in Bangladesh. Study of 124 cases. In Bangladesh Journal of Neuroscience 2004; 20 (1) 1-8.
16. Rizvi AN, Khan MRK, Ullah AKMA, Haque A Peripheral Neuropathy: A two years study. Bangladesh Journal of Neuroscience 2007; 23 (1): 23-27.
17. MacLeod JW, Prineas JW and Walsh JC The relationship of conduction velocities to pathology in peripheral nerves In. Desmeedt E ed. New developments in electromyography and clinical neurophysiology 1993; 2: 248-58.
18. Chistee SMSA Clinico-aetiological pattern of peripheral neuropathy In. Dissertation. Bangladesh College of Physician and Surgeon, Mohakhali, Dhaka. 2009
19. Lubec D, Mullbacher W, Finsterer J, Mamoli B (1999) Diagnostic workup in peripheral neuropathy: an analysis of 171 cases Postgrad Med J 1999; 75:723-727
20. Duska M and Danistic M Peripheral neuropathy In 6th internet world congress for Biomedical Science presentation # 171. www.uclm.es/inabis 2000. symposia /files171/ session /2004
21. Donaghy M Polyneuropathy In Donaghy M ed. Brains diseases of the Nervous system 12th edn. Oxford New York: Oxford University Press 2009; 21: 542-43.
22. Konig F, Neundorfer B, Kompf D, Polyneuropathien hoheren lebensalter Deutsch Med Wschr 1984; 109: 765-7
23. Lefaucheur JP and Creange A Neurophysiological testing correlates with clinical examination according to fiber type involvement and severity in sensory neuropathy J Neurol Neurosurg Psychiatry 2004; 75: 417-422
24. Latov N, Adina R, Goldfarb AR, Brannagan Th, Chin RL, DeSousa EA et al Correlation of demyelinating and clinical features in patients with neuropathy of otherwise unknown etiology. Neurology, Neurophy- siology and Neuroscience 2006; 7: 1-9
25. Rajablly YA and Narasimhan N Distribution, clinical correlates and significance of axonal loss and demyelination in chronic inflammatory demyelinating polyneuropathy European Journal of Neurology 2010: in press
26. Vittadini G, Buonocore M, Colle G, Terzi M, Fonte R, and Biscaldi G Alcoholic polyneuropathy: a clinical and epidemiological study Alcohol & Alcoholism 2001; 36(5): 393-400

Original Article

HER2 Expression is an Independent Predictor of Nodal Metastasis in Primary Breast Cancer

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Abstract

Background: Breast cancer is still the most frequent malignant tumor in women worldwide. Identification of metastatic potential of breast cancer cells is necessary for proper management of this disease.The purpose of the study isto estimate likelihood of axillary lymph node (ALN) involvement in breast cancer patients based onhuman epidermal growth factor receptor 2 (HER2) expression. **Method:** In CMH Dhaka this cross-sectional study included primary tumors of 177 breast cancer patients were evaluated for estrogen receptor (ER), progesterone receptor (PR) and HER2 expression by immunohistochemistry. The validity of these molecules to predict ALN metastasis was measured statistically and compared to predictive effect of other clinicopathological parameters. All the information's recorded through the pre-structured data collection sheet. Data analyzed by Statistical Program & Service Solution (SPSS) version 22. **Result:** ER, PR and HER2 expression was detected in 48.33%, 36.67% and 27.5% of tumors respectively. Although increased tumor size and grade, ER and PR negativity and HER2 positivity were strong indicators of ALN metastasis on univariate analyses. Only tumor size and HER2 expression were independent predictors of ALN involvement on multivariate analysis($p<0.05$). luminal A, luminal B, HER2-rich and triple negative tumors had 65.7%, 79.16%,81.81% & 66.67% increased risk of ALN metastasis compared to tumorsrespectively. HER2 expression in pT1 and pT2 tumors raised the risk of ALN metastasis by 2.7 times ($\chi 2 = 4.338$, $p= 0.01$) and 1.3 times ($\chi 2, = 3.841$, $p< 0.05$) respectively and grade I and II tumors that expressed HER2 were 8.0 times ($\chi 2 = 13.333$, p< 0,001) and 2.8 times ($\chi 2 =6.494$, $p<0.01$) more likely to have ALN metastasis respectively. **Conclusion:** Identification of metastatic potential of breast cancer cells is necessary for proper management of this disease. HER2 expression is associated with a significant rise of metastatic potential of breast cancer cells and could be an indicator of regional metastasis of breast cancer.

Key words: Breast cancer, Prediction of metastasis, Immunohistochemistry, Hormone receptors, Estrogen receptor (ER), Progesterone receptor (PR), Human epidermal growth factor receptor 2(HER2)

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Introduction:

Breast cancer is the most common cancer type among women. The mortality rate has been significantly reduced in recent years because of its early diagnosis and the advanced methods of treatment; however, it is still the second leading cause of death from cancer in women in European and Western countries, preceded only by lung cancer[1]. Factors including tumors size, histologic grade, lymph node metastasis and hormonereceptor status used to estimate prognosis[2]. Evaluation of prognostic factors including biomarkers is highly recommended for the best management and therapeutic decision of breast cancer patients[3].

Early diagnosis and appropriate treatment can prolong the survival of patients diagnosed with breast cancer. The normal treatment protocol is surgery followed by chemotherapy and radiotherapy, followed by adjuvant therapy. The kind of adjuvant therapy that can be given greatly influences survival and is determined by the expression of estrogen receptor (ER), Progesterone receptor (PR) and a transmembrane protein called HER2/neu expression on the cancer cells. ER / PR positive tumors are treated by Tamoxifen in pre-menopausal women and Aromatase

inhibitors in post-menopausal women. HER2/neu positive tumors are treated by a monoclonal antibody known as Trastuzumab (Herceptin). No adjuvant therapy is available for ER/PR HER2/neu negative (triple negative) tumors[4].

Breast cancer is no longer seen as a single disease but rather a multifaceted disease comprised of distinct biological subtypes with diverse natural history, presenting a varied spectrum of clinical, pathologic and molecular features with different prognostic and therapeutic implications. Consensus regarding the definitive prognostic/predictive analysis has yet to be reached, but significant progress continues to be made in the ongoing search for a specific, rigorous and reproducible method of identifying successful treatment algorithms utilizing biological markers[4].

Excision of the primary tumor with ALN dissection has been the standard surgical treatment of breast cancer. However, dissection of ALN is commonly associated with local complication of the related upper limb including lymphedema, impaired shoulder movement, pain and numbness[5]. The need for ALN dissection has been constantly reduced because of the introduction of sentinel lymph node biopsy. However; sentinel lymph node biopsy is still an invasive procedure and could be associated with a risk of missed nodal involvement and low sensitivity particularly in cases with micro-metastasis[3].

Several studies have been conducted to predict ALN metastasis in order to select patients unlikely to get benefit from ALN dissection. Size, grade and micro-vessel density of the primary tumors were stated to be independent predictors to signify ALN metastasis[5]. In addition, several molecules including estrogen receptor (ER), progesterone receptor (PR) and Ki-67 had been shown to have a predictive validity of nodal metastasis of breast cancer[6].

Among molecules that raised much attention as a possible prognostic marker is epidermal growth factor receptor 2; also known as HER2/neu or c-erbB-2. HER2 is a proto-oncogene that encodes a transmembrane receptor with a constitutive tyrosine kinase activity involved in cellular proliferation, differentiation, migration, and apoptosis. It is overexpressed due to gene amplification in 15–30% of human breast cancers[7]. In his review, Ross et al8 reported that HER2 amplification or overexpression was associated with poor outcome in patients with ALN metastases, but not in patients with tumor-negative lymphnodes. In this study, the validity of HER2 to predict ALN metastasis of breast cancer was evaluated and compared to other established predictive clinical and pathological parameters.

Method:

All primary breast cancer cases treated surgically at Combined Military Hospital during January 2015 to December 2016 were included in this study. The main inclusion criterion was surgical treatment by either radical mastectomy or conservative breast surgery with complete ALN dissection. Patients were excluded from the study if the primary tumor was previously excised, if the tumor was advanced (stage 4), if the patient underwent only ALN sampling, if they had distantmetastasis at time of diagnosis and if they received preoperative neo-adjuvant therapy. The patients were treated with modified radical mastectomy (n = 171) or conservative breast surgery (n = 6) with complete dissection of ALNs. All the information recorded through the pre-structured data collection sheet tumors and ALNs were reviewed for evaluation of histopathological findings.The commercially available statistical Program & service solution (SPSS) version 22 for windows was used for data analysis. A p-value of less than 0.05 was considered as statistically significant. Chi-square test ($\chi 2$) was performed to compare the rates of ALN metastasis between different study groups. Univariate binary logistic regression analysis was performed to assess risk factors for ALN metastasis and to calculate odds ratio and p-value of ALN metastasis.

Result:

One hundred and seventy-five women with primary breast cancer were included in this study. The age ranged between 23 and 72 years with a mean (±SD) of 43.23 (±9.53) years and a median of 43.5 years. 113 (64.57%) cases were premenopausal and 62 (35.42%) cases were postmenopausal. The tumor size ranged between 1.2- 12.0 cm with mean (±SD) and median values of 4.05 (±1.92) cm and 4 cm, respectively. Based on their sizes, the tumors were classified as pT1, pT2 and pT3 in 12(8.21%), 96(65.75%) & 38(26.03%) cases respectively. 98.28% of the investigated tumors (n = 172) were invasive duct carcinoma, not otherwise specified (IDCC, NOS) while others (mucinous,tubular) were recorded 3(1.71%) cases. The majority of tumors were grade II, representing 86(71.67%) while grade I and III occurred in 3(2.5%) and 31(25.83%) respectively. ALN metastasis was confirmed histologically & N0 50(28.33%), N1 55(30.83%), N2 38(21.67%), N3 34(19.17%) and the number of involved lymph nodes ranged between 1 and 23 with a mean 4.31 & median 4(figure 1). Expression of ER and PR was detected in 84 (47.5%) and 65 (38.67%) tumors respectively and over expression of HER2 protein (score 3+) was evident in 49 (27.5%) of the investigated cases. Based on combined expression of ER, PR and HER2 molecules, 52(29.41%) of the tumors were classified as luminal type A while luminal type B, HER2-rich and triple negative tumors were recorded in 34(19.32%), 33(18.49%) and 58(32.77%) cases, respectively. Among the luminal B tumors; 18 were luminal/HER2- negative and 16 were luminal/HER2-positive cases (Table 1) .

Among different investigated parameters of breast cancer - increase of tumor size and grade and positive expression of HER2 were strongly associated with ALN metastasis. According to combined expression of steroid and HER2 receptors, breast cancer would fall into one of eight possible categories: ER+/PR+/HER2+, ER+/PR+/HER2-, ER +/PR -/HER2+, ER+/PR -/HER2-, ER -/PR+/HER2-, ER-/PR-/HER2+ ER-,PR+,HER2+and ER -/PR - / HER2 - . These eight categories were presented in this study in 8(6.67%), 35(29.17%),3(2.5%), 12(9.17%),2 (.83%), 22(18.33%), 0(0%) & 39(32.5%) cases, respectively. Among these categories ER /PR -/HER2+ breast cancer subtypes had frequent ALN metastasis while ER+/PR+/HER2 - breast cancer was the least likely tometastasize (Table 2). In the same context, luminal B and HER2-rich breast cancer; both of which showed frequent over- expression of HER2 had 2.34 and 3.65 times increase risk of ALN metastasis; respectively compared to luminal A breast cancer which is HER2 negative while triple negative tumors had only 1.13 times increased risk of metastasis (Table 2).

Table I: Correlation of clinical & pathological parameters with axillary lymph node status

Variable	total	LN +ve	LN -ve	P value
Age (23-72 yr)	mean±SD 43.23±9.53 median 43.5			
Premenopausal	113(64.57%)	77 (70%)	33(30%)	0.1
Postmenopausal	62(35.42%)	30(65.47%)	16(38.78%)	
Pathology				
IDCC	172(98.28%)	128(74.42%)	44(25.58%)	
Other types	3(1.71%)	1(33.33%)	2(66.66%)	
Tumour size (1.2-12cm)	mean(SD)4.04±1.92 median 4cm			
pT1	12(8.21%)	6(50%)	6(50%)	0.001*
pT2	96(65.75%)	65(67.70%)	31(32.29%)	
pT3	38(26.03%)	33(86.84%)	5(13.15%)	
Grade				
GI	3(2.5%)	2(66.67%)	1(33.33%)	0.1
GII	86(71.67%)	77(70.64%)	32(29.35%)	
GIII	31(25.83%)	23(69.69%)	10(30.30%)	
ER				
ER+ve	58(48.33%)	41(70.69%)	17(29.31%)	0.1
ER-ve	62(51.67%)	45(72.58%)	17(27.41%)	
PR				
PR+ve	44(36.67%)	32(72.72%)	12(27.27%)	0.1
PR-ve	76(63.33%)	54(71.05%)	22(28.94%)	
HER2				
HER2+ve	33(27.5%)	27(81.81%)	6(18.18%)	0.05*
HER2-ve	87(72.5%)	59(67.81%)	28(32.18%)	
Molecular subtype				
Luminal A	35(29.16%)	23(65.7%)	12(34.28%)	0.01*
Luminal B	24(20%)	19(79.16%)	5(20.83%)	
HER2 rich	22(18.33%)	18(81.81%)	4(18.18%)	
Triple negative	39(32.5%)	26(66.67%)	13(33.33%)	

Table II: Risk of axillary lymph node metastasis in carcinoma breast subtypes defined by ER,PR, & HER2 expression:

Breast cancer subtype	Total no(%)	No(%) of LN+ve	No(%) of LN-ve	p value	Odds ratio
ER+/PR+/HER2-	35(29.17)	23(65.71%)	12(34.28%)		Referrence
ER+/PR+/HER2+	8(6.67%)	7(87.5%)	1(12.5%)	0.001	2.342
ER+/PR-/HER2-	12(9.17%)	9(81.81%)	3(27.27%)	0.1	1.565
ER-/PR+/HER2-	2(1.83%)	1(50%)	1(50%)	0.001	9.352
ER+/PR-/HER2+	3(2.5%)	2(66.67%)	1(33.33%)	0.1	1.0434
ER-/PR-/HER2+	22(18.33%)	18(81.81%)	4(18.18%)	0.01	3.652
ER-/PR-/HER2-	39(32.5%)	26(66.67%)	13(33.33%)	0.1	1.1304

There were significant associations of HER2 expression and ALN metastasis in early stages and low grades breast cancer. Among pT1 tumors, HER2-positivity was associated with Luminal A breast cancer nodal metastasis ($\chi 2$= 4.338, p = 0.01) [figure 2] and among pT2 tumors, HER2 expression raised risk of ALN metastasis ($\chi 2$ = 3.841, p < 0.05)[figure 3]. Similarly, grade I tumors that expressed HER2 were more likely to have ALN metastasis ($\chi 2$= 13.333, p = 0.001)[figure 4] and grade 2 tumors that expressed HER2 were more likely to have nodal metastasis ($\chi 2$= 6.494, p < 0.01)[figure 5].

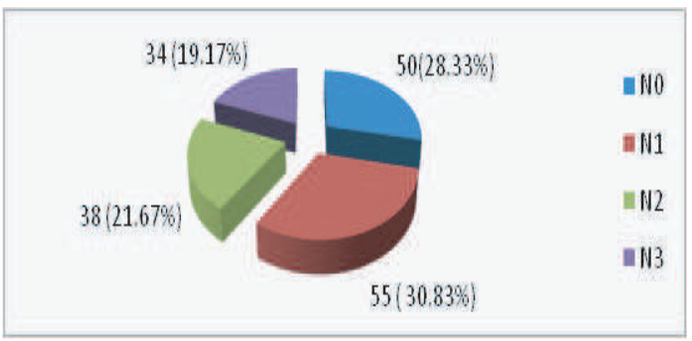

Figure 1 : ALN metastasis N0 28.33%, N1 30.83%, N2 21.67%, N3 19.17%,

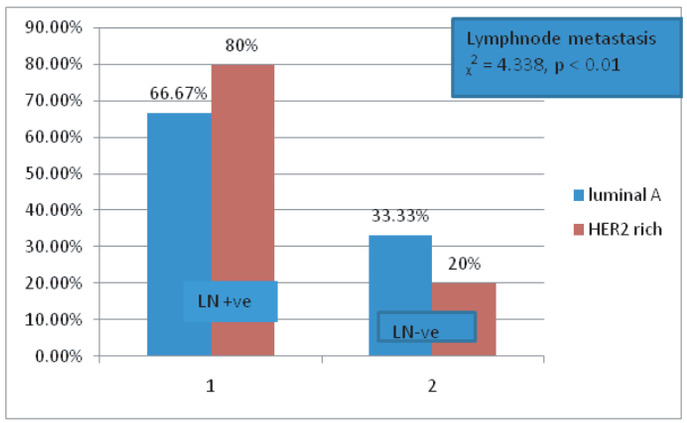

Figure 2: Association of HER2 expression with axillary lymphnode metastasis in pT1.

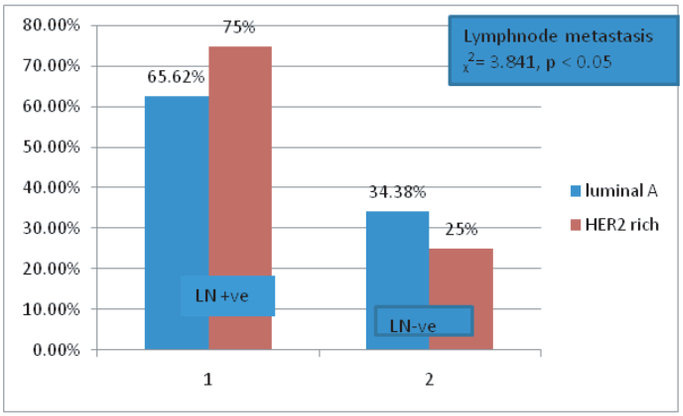

Figure 3: Association of HER2 expression with axillary lymphnode metastasis in pT2

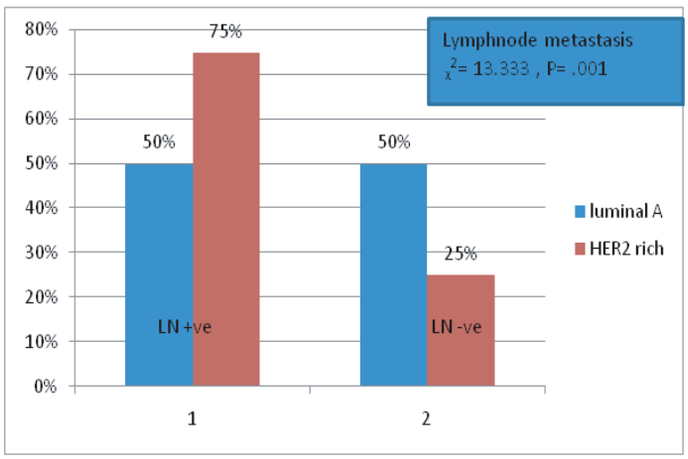

Figure 4: Association of HER2 expression with axillary lymphnode metastasis in G-I.

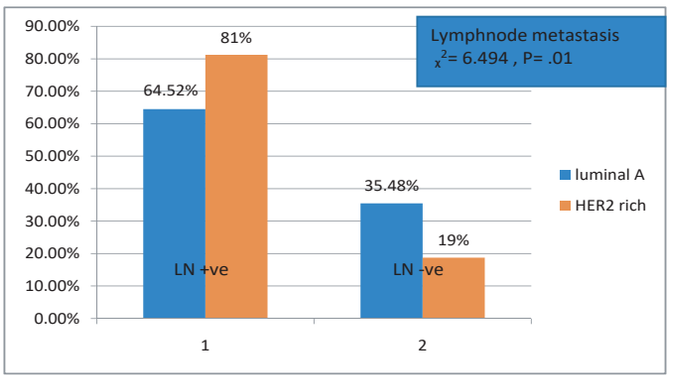

Figure 5: Association of HER2 expression with axillary lymphnode metastasis in G-II.

Discussion

While molecular and genetic testing is very elegant, prognostic and predictive, it is expensive and not yet widely available. Also, despite theprognostic information provided by the molecular test, current reports of assay results Breast cancer are a heterogeneous disease with different molecular subtypes, cellular composition, clinical behavior and response to treatment. Hence, pathological features such as tumor size, tumor grade, nodal involvement and hormone receptor status are essential for management and prognosis of this disease. Axillary lymph node (ALN) status is the best independent prognostic factor and is essential for treatment planning of breast cancer patients. Selection of type and intensity of neo-adjuvant and adjuvant chemotherapy of breast cancer is based mainly on ALN status and number of involved lymph nodes[9].

In this study; the validity of ER, PR and HER2 expression to predict metastatic potential of breast cancer in Bangladeshi women was evaluated and compared to other clinical and pathological parameters. Categorization of breast cancer according to ER, PR and HER2 expression was also provided.Thirty eight of the investigated cases (26.03%) had pT3 tumor stage and ALN metastasis was detected in 37(30.83%),26(21.67%) and 23(19.17%) were classified as pN1, pN2 and pN3 nodal stage, respectively. The rates of ER, PR and HER2 expression in study and the rates of intrinsic subtypes of breast cancer based on expression of these three molecules are comparable to records of previous literature [10,11].

According to this study; increased tumor size, high tumor grade, negative expression of hormone receptors and positive expression of HER2 were strongly associated with ALN metastasis. There is a consensus that tumor size, grade and lymphovascular invasion are strong predictors of ALN metastasis, disease free survival and overall survival of breast cancer[12]. Although ER and PR are well established strong predictors of hormonal therapy of breast cancer patients; their validity to predict ALN metastasis is controversial. Few reports referred to a negative association of hormone receptor expression and ALN metastasis[13] while others reported that expression of ER and PR was associated with a relative increased risk of metastasis [14]. Still other studies showed no relationship of ER or PR to ALN metastasis[15,16]. In this study, the expression of both ER and PR was predictive of absent nodal metastasis on univariate but not multivariate models which suggests a weak validity of both molecules in comparison to other parameters.

HER2 expression was a strong predictive factor of ALN metastasis on univariate regression analysis and it was the second strongest factor after tumor size in multivariate analysis. In the same context, HER2-rich breast cancer sub- type had the highest risk of ALN metastasis compared to luminal A tumors (Table 2) followed by luminal B subtype which included a considerable number of HER2-positive cases. Among luminal B cases; HER2-positive cases showed a significant association with ALN metastasis compared to HER2-negative cases (Chi-square = 13.664, p = 0.001). Moreover; HER2 expression was strongly associated with ALN metastasis in early stages and low grades breast cancer cases (Fig. 1-4).

Taken together; these data imply that whenever expressed, HER 2 is associated with a significant higher risk of AL Nmetastasis ofbreast cancer regardless of tumor size, grade, hormonal status or intrinsic subtype. In separate large studies; luminal/HER2 and HER2-enriched intrinsic subtypes had higher tumor and nodal stage, frequent regional recurrence, early relapse rates and worse overall survival compared to other subtypes[17,18]. In the same context, several studies showed that triple negative breast cancer which is a distinctive subtype with aggressive clinical course and poor outcome had significantly lower rates of ALN positivity compared to HER2-positive breast cancer subtypes [19]. Among the eight possible combinations of ER, PR and HER2 expression status; the triple positive and ER -/PR - /HER2+ breast cancer subtypes had 1.130 and 3.652 times increased risk of ALN metastasis; respectively compared to ER+/PR+/HER2- tumors which was the most frequent subtype in this study and the least likely to have ALN metastasis. Accordingly, expression status of HER2 could be valuable to predict metastatic potential ofbreast cancer cells. Multivariate regression analysis of different clinical and pathological characteristics of breast cancer showed that combination of tumor size and HER2 expression status had the best performance to predict ALN metastasis. This prediction scheme could be valuable to reduce the need for complete ALN dissection and to properly select patients with high risk of distant metastasis for subsequent targeted therapy.

The main limitation of this study was sub typing of luminal breast cancer into A and B subtypes based on expression status of PR but not on expression status of the proliferation marker; Ki-67. However; recent studies have reported that absence of PR expression is associated with poor prognosis of breast cancer and proposed that PR-negative breast cancer should be classified as luminal B subtype[20].

Conclusion:

Breast cancer is no longer a single but rather a heterogeneous disease with diverse clinical, biological, pathological and molecular features. Risk assessment of metastatic potential of this disease is important for therapeutic and prognostic implications. HER2 but not ER or PR expression was strongly associated with increased risk of breast cancer metastasis irrespective to tumor stage and grade and it had a strong validity to predict ALN metastasis in both univariate and multivariate regression analyses. Identification of these factors will eventually help in better treatment of breast cancers and improve patient survival.

References:

1. American Cancer Society [2015], Breast Cancer, Key Statistic for Breast Cancer.
2. McLaughlin SA, Wright MJ, Morris KT, Giron GL, Sampson MR, Brockway JP, et al. Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: objective measurements. J Clin Oncol 2014;26(32):5213–9.
3. Harigopal M, Berger AJ, Camp RL, Rimm DL, Kluger HM. Automated quantitative analysis of E-cad-herin expression in lymph node metastases is predictive of survival in invasive ductal breast cancer. Clin Cancer Res 2015;11(11):4083-9.
4. Fadda GM, Santeufemia DA, Basso SM, Tozzoli R, Falcomer F, et al.(2016) Adjuvant Treatment of Early Breast Cancer in the Elderly. Med Chem 12: 280-284.
5. Azizun-Nisa, Bhurgri Y, Reza F, Kayani N. Comparision of ER,PR and HER-2/neu (C-erb B2) reactivity pattern with histologic grade, tumor size and lymphnode status in breast cancer. Asian Pac J Cancer Prev 2013;9(4):553-6.
6. Onoda T, Yamauchi H, Yagata H, Tsugawa K, Hayas-hi N, Yoshida A, et al.The value of progesterone receptor expression in predicting the recurrence score for hormone-receptor positive invasive breast cancer patients. Breast Cancer 2013;1.
7. Dittrich A, Gautrey H, Browell D, Tyson-Capper A. The HER2 signaling network in breast cancer-like a spider in its web. J Mammary Gland Biol Neoplasia 2014;19(3–4):253–70.
8. Ross JS, Fletcher JA, Linette GP, Stec J, Clark E, Ayers M, et al. The Her-2/neu gene and protein in breast cancer 2003: biomarker and target of therapy. Oncologist 2013;8(4):307–25.
9. Gupta D, Gupta V, Marwah N, Gill M, Gupta S, et al. (2015) Correlation of Hormone Receptor Expression with Histologic Parameters in Benign and Malignant Breast Tumors. Iranian Journal of Pathology 10: 23-34.
10. Ellis IO, Cornelisse CJ, Schnitt SJ, Sasco AJ, Sastre-Garau Z, Kaaks R, et al. Tumours of the breast. In: Tavassoli FA, Devilee P, editors. World Health Organization classification of tumours; pathology and genetics of tumours of the breast and female genital organs. Lyon: IARC Press; 2003. p. 10–112.
11. Nadji M, Gomez-Fernandez C, Ganjei-Azar P, Morales AR. Immunohistochemistry of estrogen and progesterone receptors reconsidered: experience with 5,993 breast cancers. Am J Clin Pathol 2015;123(1):21–7.
12. Patani NR, Dwek MV, Douek M. Predictors of axillary lymph node metastasis in breast cancer: a systematic review. Eur J Surg Oncol 2014;33(4):409–19.

13. Li JW, Mo M, Yu KD, Chen CM, Hu Z, Hou YF, et al. ER- poor and HER2-positive: a potential subtype of breast cancer to avoid axillary dissection in node positive patients after neoadjuvant chemo-trastuzumab therapy. PLoS ONE 2014;9 (12):e114646.
14. He ZY, Wu SG, Yang Q, Sun JY, Li FY, Lin Q, et al. Breast cancer subtype is associated with axillary lymph node metastasis: a retrospective cohort study. Medicine 2015;94(48): e2213.
15. Chua B, Ung O, Taylor R, Boyages J. Frequency and predictors of axillary lymph node metastases in invasive breast cancer. ANZ J Surg 2011;71(12):723–8.
16. Lee JH, Kim SH, Suh YJ, Shim BY, Kim HK. Predictors of axillary lymph node metastases (ALNM) in a Korean population with T1-2 breast carcinoma: triple negative breast cancer has a high incidence of ALNM irrespective of the tumor size. Cancer Res Treat 2010;42(1):30–6.
17. Voduc KD, Cheang MC, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H. Breast cancer subtypes and the risk of local and regional relapse. J Clin Oncol 2010;28(10):1684–91.
18. Cheang MC, Chia SK, Voduc D, Gao D, Leung S, Snider J, et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. J Natl Cancer Inst 2014;101 (10):736–50.
19. Holm-Rasmussen EV, Jensen MB, Balslev E, Kroman N, Tvedskov TF. Reduced risk of axillary lymphatic spread in triple-negative breast cancer. Breast Cancer Res Treat 2015;149 (1):229–36. 226 A.R.H. Ahmed
20. Feeley LP, Mulligan AM, Pinnaduwage D, Bull SB, Andrulis IL. Distinguishing luminal breast cancer subtypes by Ki67, progesterone receptor or TP53 status provides prognostic information. Mod Pathol 2014;27(4):554–61.

Case Report

Dextrocardia with Situs Inversus Totalis in a 2-month-old boy A Case Report

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Abstract

Background: Dextrocardia with situs inversus totalis is a rare congenital recessively inherited condition in which there occurs transposition of all viscera with right sided heart (dextrocardia) in a mirror image form. It may be isolated or associated with malformations, especially cardiac and/or alimentary. Generally individuals with situs inversus totalis are asymptomatic and have a normal life expectancy. Many people with situs inversus totalis are unaware of their anatomical variation, which may be detected when subjects seek medical attention for some other condition.

We shall report a 2-month-old boy found to have dextrocardia with situs inversus totalis while presenting with cough for 7 days, fever for 2 days and respiratory distress for 1 day. This incidental finding of dextrocardia with situs inversus totalis was detected by physical examination and was confirmed later by Chest X-ray, ehocardiography and Ultrasonography of whole abdomen.This report underscores the need for proper and complete physical examination with special emphasis on cardiovascular system examination for all healthy and sick children after delivery before discharge to enable early diagnosis of congenital anomalies and for appropriate referral.

Key words: Situs inversus totalis, Dextrocardia.

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Introduction:

Dextrocardia is an abnormal congenital positioning of the heart: instead of the heart forming in the fetus on the left side, it flips over and forms on the right side. Situs inversus totalis is a congenital condition in which the major visceral organs are reversed or mirrored from their normal positions.[1] This condition, generally is an autosomal recessive genetic condition. The incidence of situs inversus totalis is about 1:10,000 live people.[2] Many people with situs inversus totalis are unaware of their unusual anatomy until they seek medical attention for an unrelated condition.[3] Dextrocardia is frequently diagnosed in a routine prenatal sonogram, although not every sonologist will identify it, particularly if there are no cardiac structural abnormalities.[4] Diagnostic modalities like a chest radiograph and an electrocardiogram are sufficient to make a diagnosis of dextrocardia, while more recent imaging modalities like echocardiography and magnetic resonance imaging puts the diagnosis beyond doubt.[1] A few cases of situs inversus totalis have been described in the literature.[5] We shall report a case of dextrocardia with situs inversus presented with cough, fever and respiratory distress in a 2-month-old boy.

Case Report:

A 2 month-old-boy, second issue of consanguineous parents was admitted in our hospital with the complaints of cough for 7 days, fever for 2 days and respiratory distress

for 1 day. Mother was on irregular antenatal check up and the baby was born at term at home by normal vaginal delivery. He had an H/O perinatal asphyxia and was treated in a hospital during his neonatal period. After that during the last one month he often developed cough and respiratory distress. On examination, patient was dyspnoeic (R/R-62), febrile (temp-101˚F), having chest indrawing, breath sound was vesicular with bilateral crepitations all over both lung fields. Apex beat was situated in right 4th intercostals space medial to the mid-clavicular line, heart rate was 144beats/min and there was no murmur. There was no organomegaly but umbilical hernia was present and other systems examination revealed no abnormality. With these findings diagnosis of Bronchopneumonia with Dextrocardia with Umbilical hernia was thought and investigations done for confirmation. Chest X-ray showed the apex of heart is on the right side and a few patchy opacities all over both lung fields (Figure 1). For evaluation of the heart, echocardiography showed dextrocardia with good ventricular systolic and diastolic function. Further, abdominal ultrasound revealed that the liver and gallbladder were located in the left hypochondrium, the spleen was located in the right hypochondrium (Figure 2). Both the kidneys were normal. There was a gap (1.7cm) in the subcutaneous area in the umbilical region, within which intestinal loops were noted; i.e; umbilical hernia.

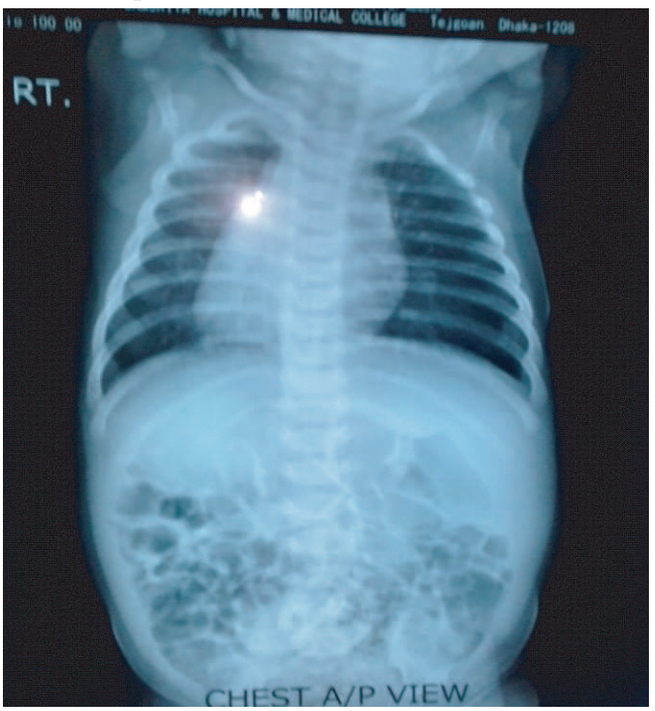

Figure 1: Chest radiograph showing the apex of heart on the right side and a few patchy opacities all over both lung fields.

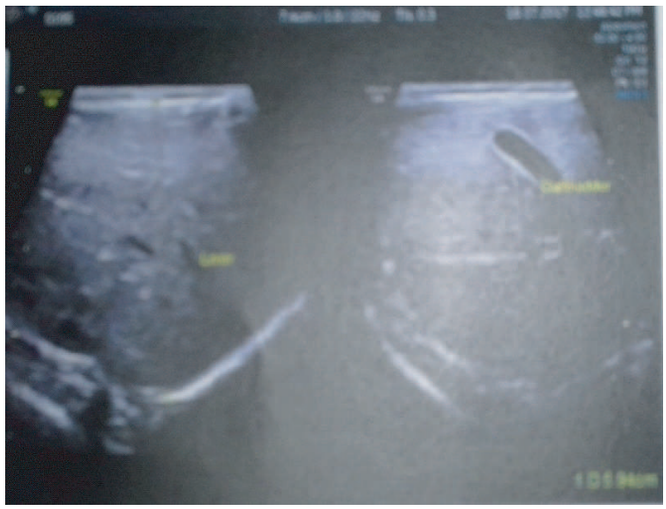

Figure 2: Abdominal ultrasound revealed that the liver and gallbladder were located in the left hypochondrium

Discussion:

Situs inversus is a rare congenital anomaly reported to occur in 1 in 8000 to 1 in 25,000 patients.[6] No racial predilection exists for situs inversus. The male-to-female incidence is 1:1.1 The arrangements of the position of the abdominal viscera in dextrocardia may be normal (situs solitus), reversed (situs inversus), or indeterminate (situs ambiguous or isomerism) in 32 to 35%, 35 to 39%, and 26 to 28% of cases, respectively.[7]

In our patient, situs inversus was associated with dextrocardia. No cardiac anomalies were identified on echocardiography. Both the kidneys were normal. Dextrocardia with a normal abdominal situs has a high incidence of associated congenital cardiac anomalies including transposition of the great vessels and ASDs and VSDs in 90 to 95% of cases, among others.[1] However, dextrocardia with situs inversus is associated with a lower incidence of congenital heart disease (0 to 10%), as was the case in our patient. Situs inversus may be associated with other congenital anomalies such as duodenal atresia, asplenism, multiple spleens, ectopic kidney, horseshoe kidney, and various pulmonary and vascular abnormalities.[5] Situs inversus totalis associated with primary ciliary dyskinesia is known as Kartagener syndrome.[8,9] Patients with primary ciliary dyskinesia have repeated sinus and pulmonary infections.[8,10] Typically, persons having situs inversus with dextrocardia without other congenital anomalies have a normal life expectancy and have a similar risk of acquiring disease as that of other persons of the same age and sex group.[1] In rare instances of cardiac anomalies, life expectancy is reduced; depending on the severity of the defect.[11] The recognition of situs inversus is also important for preventing surgical mishaps that result from the failure to recognize reversed

anatomy or an atypical history.[5] For example, in a patient with situs inversus, cholecystitis typically causes left upper quadrant pain, and appendicitis causes left lower quadrant pain. Cardiac situs is determined by the atrial location. In situs inversus, the morphologic right atrium is on the left, and the morphologic left atrium is on the right. The normal pulmonary anatomy is also reversed so that the left lung has three lobes and the right lung has two lobes. In addition, the liver and gallbladder are located on the left, whereas the spleen and stomach are located on the right. The remaining internal structures are also a mirror image of the normal. Although the exact cause is unknown, dextrocardia has been linked with several factors including an autosomal recessive gene with incomplete penetrance, maternal diabetes, cocaine use, and conjoined twinning.[12,13,14] Diagnosis of dextrocardia is usually confirmed by several modalities, which include chest radiography, ECG, echocardiography, computed tomography, magnetic resonance imaging, and abdominal ultrasonography.[1] This case is reported because of the situs inversus with dextrocardia discovered in a 2-month-old boy presented with cough and respiratory distress, and all physicians have to do proper and complete physical examination with special emphasis on cardiovascular system examination for all healthy and sick children after delivery before discharge and seen in their clinic.

Conclusion:

Dextrocardia with situs inversus, though rare, is a condition that demands attention and high index of suspicion. This is necessary as it will help in further management of other illnesses. Doctors should encourage routine medical examination for their patients which could help identify this anomaly, thereby preventing wrong diagnosis and possibly death due to delay in management.

References:

1. Saleh A. Dextrocardia with situs inversus totalis in a boy: a case report. Int J Contemp Pediatr. 2016 Aug; 3(3):1096-1098.
2. Das DK, Shukla S. Situs Inversus- Report of Twins. IOSR Journal of Dental and Medical Sciences. 2015 Jan; 14(1): 69-71.
3. Abdur - Rahman LO, Adeniran JO, Taiwo JO. Concurrent dextrogastria, reverse midgut rotation and intestinal atresia in a neonate. J Indian Assoc. Paediatr. Surg. 2007; 12(4):228-30.
4. Ofusori DA, Okwuonu CU, Ude RA, Adesanya OA. Dex-trocardia and situs inversus totalis in a Nigerian cadaver: A case report of rare anomaly. Int J Morphol. 2009; 27(3):837-40.
5. Kumar A, Singh MK, Yadav N. Dextrocardia and asplenia in situs inversus totalis in a baby: a case report. Journal of Medical Case Reports. 2014; 8: 408-409.
6. Madan Kumar K, Babu C, Chander S, Kumar A, Balchander J, Nachipaan M. Complete A-V canal defect with dextrocardia with CCTGA – A case Report. IJTCVS. 2003; 19:55.
7. Iino K, Watanabe G, Ishikawa N, Tomita S. Total endoscopic robotic atrial septal defect repair in a patient with dextrocardia and situs inversus totalis. Interact CardioVasc Thorac Surg. 2012; 14(4):476-7.
8. Ortega HA, Vega Nde A, Santos BQ, Maia GT. Primary ciliary dyskinesia: considerations regarding six cases of Kartagener syndrome. J Bras Pneumol. 2007; 33(5):602-8.
9. Holzmann D, Ott PM, Felix H. Diagnostic Approach to Primary Ciliary Dyskinesia: a review. Eur J Pediatr. 2000; 159(1-2):95-8.
10. Kennedy MP, Omran H, Leigh MW, Dell S, Morgan L, Molina PL, et al. Congenital Heart Disease and Other Heterotaxic Defects in a Large Cohort of Patients with Primary Ciliary Dyskinesia. Circulation. 2007; 115(22):2814-21.
11. Bohun CM, Potts JE, Casey BM, Sandor GG. A population-based study of cardiac malformations and outcomes associated with dextrocardia. Am J Cardiol. 2007; 100(2):305-9.
12. Olbrich H, Haffner K, Kispert A, Volkel A, Volz A, Sasmez G, et al. Mutation in DNAH5 causes primary dyskinesia and randomisation of left-right asymmetry. Nat Gente. 2002; 30:143-4.
13. Agirbashi M, Hamid R, Jennings HS, Tiller GE. Situs Inversus and Hypertrophic Cardiomyopathy in Identical Twins. Am J Genetics. 2000; 91:327-30.
14. Distefano G, Romeo MG, Grasso S, Mazonne D, Sciacca P, Mollica F. Dextrocardia with and without Situs Viscerum in Two Siblings. Am J Med. 1987; 27:929-34.

Case report

Choledochal Cyst -Trteatment of Three Cases by Roux-en-Y Hepaticojejonostomy.

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M SharifulAlam[5,] Riaz Ahmed Sakil[6]

Abstract

Background: Bile duct cysts (BDC) are rare congenital anomalies of the biliary tree that are characterized by cystic dilatation of the extrahepatic and/or intrahepatic bile ducts. Choledocal cyst (CDC) is an idiopathic disease, presence of an anomalous bilio-pancreatic junction allowing pancreatic juice to reflux into the biliary tree is the most widely aetiopathogenic concept currently accepted. BDC are associated with biliary stasis and lithiasis & the whole biliary epithelium is considered at risk of malignant transformation. Magnetic resonance cholangio - pancreatography (MRCP) is currently the most accurate preoperative imaging study to assess cyst anatomy and classify the disease according to the standard Todani classification. Complete cyst excision with cholecystectomy followed by biliary reconstruction using a Roux-en-Y hepatico - jejunostomy (RYHJ) is the treatment of choice for the extrahepatic component of the disease like type I cyst. The operation can be performed with open, laparoscopic & robotic technique and most crucial part of the operation is complete excision of the cyst, jejunal division & enterobiliary bypass.We have operated three cases at Comilla medical centre Pvt. Ltd. hospital from July'2015 to June'2018 and all the cases have got uneventful recovery.

Key words: Choledochal Cyst, MRCP, RYHJ.

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Introduction:

Choledochal malformation (CDM) is a pathological condition characterized by varying degree of congenital dilatation of the biliary system including the common, intrahepatic, and intrapancreatic bile duct[1].CDC are focal or diffuse dilatations of the biliary tree that are believed to be congenital abnormalities[2], first described by Vater and Ezler in 17233.However, the first full clinical description was produced by Douglas, 18233.The aetiology remains unknown.The most widely accepted hypothesis is that cystic dilatation of the bile ducts is related to an anomalous arrangement of the pancreaticobilliary ductal junction.An anomalous pancreaticobilliary junction is often associated with a long common channel that predisposes to reflux of pancreatic juice into the biliary tree, leading to inflammation, ectasia and ultimately to dilatation[3]. In 1977, Todani classified of the bile duct cysts into Type IA - Cystic dilatation of the extrahepatic bile ducts, Type IB-Extrahepatic distal focal-segmental biliary dilatation,Type IC-Extrahepatic fusiform biliary dilatation, Type II-Extrahepatic biliary diverticula, Type III-Intraduodenal portion of the common bile duct dilatation (Choledococele), Type IVA-Multiple cystic dilatation of the intrahepatic and extrahepatic bile duct, Type IVB-Multiple cystic dilatation of the only extrahepatic bile duct, Type V- Cystic dilatation of the intrahepatic bile ducts (Caroli's disease)[4].The incidence of choledochal cyst is high in Asia may be as high as 1 in

1000,with reports from Japan comprising more than half of the documented cases[2].The disorder more commonly in females than males,with a ratio of approximately [3-4]:1[2]. Common mode of presentation are cholestatic jaundice, abdominal mass & upper abdominal pain[5]. The most common complication was cystolithiasis (49%) followed by cholangitis (32%), acute pancreatitis (10%), hepatolithiasis (7%), malignancy (3%), portal hypertension (2%) and chronic pancreatitis (2%)[6]. Diagnosis can be concluded by ultrasonography, CT scan or MRCP. Treatment depends upon the type of cyst & for Type 1B CDC Roux-en Y hepaticojejunostomy (RYHJ) is the treatment of choice. The predecessor of hepaticoje - junostomy (HJ), made in 1921 by Reid[7]. The first report with the term hepaticojejunostomy (HJ) was made in the literature in 1949 by Sanders in a case of hemihepatectomy with HJ for irreparable defects of the bile ducts[8] . In 1987, Bismuth et al. announced the first application of RYHJ in the liver transplant setting as a safe and feasible approach to perform biliary anastomosis[3].

Here we have presented three cases of choledochal Type-I cyst which were managed by cyst excision along with removal of gall bladder & enterobiliary bypass. All the patients have got uneventful recovery in our three years follow up.

Case report:

Case – 1 :

Nazma-12-years aged girl form Chawddagram,Cumilla presented with colicky epigastric pain , nausea & mild jaundice for 1 year on 12/07/2015. On examination she was mildly icteric, there was an intraabdominal lump in the epigastrium which was 5/5 cm.Her investigation profile was Hb% - 9.5 gm/dl,ESR-11 mm in 1st hour, total count of WBC – 8000/cu mm of blood, RBS – 4.2 mmol/dl, S.creatinine – 1.1 mg/dl, S.bilirubin – 2.5 mg/dl, SGPT – 60 U/L , S. Alkaline phosphatase -156 U/L , S.Prothrombin time – 12 Sec,INR -1.1, Blood group – O +ve.USG revealed a cystic mass 6/5 cm originating from the common bile duct, CT scan revealed the mass as a choledochal cyst (6/5/4 cm).Her CXR was normal.

Case – 2 :

Mrs. Fatema Begum-42-years aged female form Laksham, Cumilla presented with severe upper abdominal pain for 4 hours on 07/05/2017 which was colicky in nature & radiating to the back. She also gave the H/o fluctuating jaundice with occasional fever, chills & rigor. She also had H/O old myocardial infarction. On examination she was obese, anaemic, there was epigastric tenderness. Her investigation profile was Hb% - 8.5 gm/dl, ESR-21 mm in 1st hour, total count of WBC – 9500/cu mm of blood, RBS – 5.5 mmol/dl, S.creatinine – 1.0 mg/dl, S.bilirubin – 1.7 mg/dl, SGPT – 70 U/L , S. Alkaline phosphatase -200 U/L , S.Prothrombin time – 14 Sec,INR -1.2, Blood group – A +ve.USG revealed a cystic mass 7/5 cm originating from the common bile duct,CT scan revealed the mass as a choledochal cyst (7/5/3 cm).Her CXR was normal. ECG showed pathological Q in chest leads & in echocardiogram report there was evidence of anterior wall hypokinesia , EF-53% & mild aortic flutter were also noted.

Case – 3 :

Miss Khadiza Akter-21-years aged lady from Muradnagor, Cumilla presented with recurrent attack of upper abdominal pain for 2 years on 23/06/2018 which was colicky in nature & radiating to the back. She had also vomiting & severe anorexia. She gave the H/o fluctuating jaundice & occasional fever with rigor. On examination she was anaemic, dehydrated & emaciated, there was epigastric tenderness & a lump was palpated. Her investigation profile was Hb% - 8 gm/dl, ESR-16 mm in 1st hour, total count of WBC – 7500/cu mm of blood, RBS – 5.7mmol/dl, S.creatinine – 1.2 mg/dl, S.bilirubin – 1.7 mg/dl, SGPT – 80 U/L , S. Alkaline phosphatase -170 U/L , S.Prothrombin time–14 Sec,INR-1.2, S.albumin – 3.2 gm/dl,S. electrolytes (Na+-125,K+-2.9,Cl—104,HCO3--24 mmol/L), Blood group – A +ve.USG revealed a cystic mass 6/5 cm originating from the common bile duct,CT scan revealed the mass as a choledochal cyst (7/5/4 cm).Her CXR & ECG were normal.

Fig 1: USG-Bile duct cyst (BDC: Case-1).

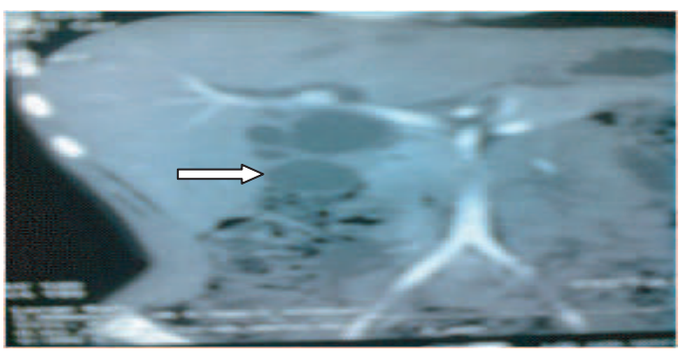

Fig 2: CT Scan- Choldochal cyst (Case-2).

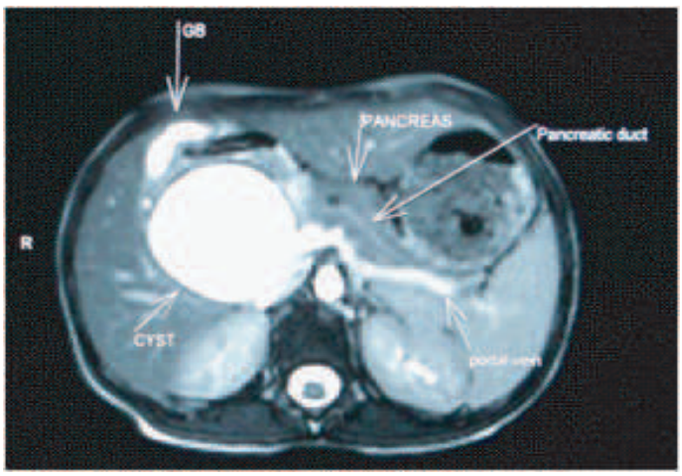

Fig 3: MRCP-Cystic lesion (Case-3).

After preoperative assessment & correction of electrolytes and dehydration, the patients party were counseled & they were admitted for laparotomy with a diagnosis of choledochal cyst and informed written consent were taken.

The abdomen was opened by suitable incision according to the body habitus of patient under general anaesthesia. Laparotomy revealed extrahepatic choledochal cyst. After cholecystectomy the cyst was separated from the portal vein, excised above the opening of cystic duct & below the upper border of duodenum. Distal CBD was closed by continued vicryl 3/0 suture after checking no stones left. The jejunal stump was divided 25 cm distal to Ligament of Treitz in a relatively avascular plane. Distal jejunal stump was anastomosed with the cut end of CHD by posterior continuous & anterior interrupted 3/0 vicryl suture. Then jejunojejunostomy was performed. Abdomen was closed in layers with two drains (subhepatic, pelvic) were kept in situ. In all the cases we have sent the excised cyst for histopathological examination to see any malignant transformation, but chronic inflammatory changes only revealed.

In postoperative period patient was NPO for 4 days,1 unit bood was transfused, (prophylactic and therapeutic I/V antibiotic was used during this time) postoperative analgesic I/M pathedine was used for 3 days. Drain & stitches were removed on 5th & 8th POD respectively. All patients were recovered uneventfully. Perioperative prophylactic antibiotic was maintained for 10 gas

Discussion:

Choledochal malformation (CDM) is characterized by dilatation of the biliary tract in the absence of acute obstruction to the bile flow. We found three female cases of bile duct cyst & the mean age were 25 years (12-42 years). Olival CLD et al, told in their study that it is recognized more frequently in children & incidence comes increasingly in adults, representing 20% of the cases[9]. Machado NO et al, treated ten patients for choledochal cyst, of whom eight were women with the mean age of 31 years (16-38 years), two were men with the mean age of 36 years (26-48 years)[1]. Purvi YP & Keith DL et al, told that biliary cysts are four times more common in women compared with men[2].

The common mode of presentation of our patient were colicky epigastric pain, lump & fluctuating jaundice. Md Kassem et al, mentioned in their series that classical triad of jaundice, right upper quadrant mass, abdominal pain is present in only minority of patients(0-17%), it is more commonly seen in cases with onset in childhood rather than in adults and 85% of children have at least two features of the triad at presentation, compared with only 25% of adults[10].

For proper diagnosis we used ultrasonography as a first imaging tool, CT scan in two cases & MRCP in one case for further evaluation.We couldn't take the facility of MRI in all cases due to unavailability. Sacher VY et al, described in their series that diagnostic accuracy of MRCP have improved in diagnosing choledochal cyst & their associated anatomic variants[11]. Purvi YP & Keith DL, told that MRCP is superior to CT scan for defining pancreaticobiliary maljunction but less sensitive for examining intrahepatic biliary anatomy[2].

We have were found all the cases as Type – IB according to Todani's classification of choledochal cyst. Mabrut JYet al, mentioned in their series that type I BDC is the more frequent cyst type encountered (70–90%), followed by type IV-A (10–20%), choledochocele (4%), type II (2-5%) and type V (1%)[12].

We done cholecystectomy along with complete resection of the cyst & Roux-en Y hepaticojejunostomy (RYHJ) in all cases for the treatment of choledochal cyst. Martínez CA et al & Kelly R et al, told in their series that Patients with biliary cysts type IA, IB, IC and II had a resection, cholecystectomy and reconstruction with Roux-en-Y anastomosis[13,14].

RYHJ is a versatile surgical procedure which is commonly used for various hepatobiliary and gastrointestinal diseases.We used posterior continuous & anterior interrupted suture with 3/0 vicryl for hepaticojejonostomy. Kirschner HJ et al, performed 6 cases of laparoscopic RYHJ & found one anastomotic leak[15]. Moris D et al, were used both anterior & posterior interrupted stitches for hepaticojejonostomy[3]. In 2004,

the first robotically assisted laparoscopic RYHJ was performed in experimental setting and a feasibility study between the latter and pure laparoscopic and open approach took place. The procedure was found feasible and safe but more time-consuming than the open approach[16].

The complication associated with RYHJ can be divided into early and late. Soares kc et al, mentioned early complications include biliary-enteric anastomosistic dehiscence with biliary fistula, bilioma or abscess formation, acute peritonitis, pancreatic leakage and fistula, acute cholangitis, acute pancreatitis, bowel obstruction due to kinking or adhesions, wound infection and dehiscence, gastrointestinal bleed, and hepatic failure[17] which were also recommended by Anan CKU[18]. Long-term complications include biliary-enteric anastomotic stricture, peptic ulcer disease, cholangitis, biliary and intrahepatic stones, pancreatitis, liver failure, and biliary cancer[3].

We operated three cases of type-I choledochal cyst with RYHJ & all the patients maintain a normal life in our three years postoperative follow up period.

Conclusion:

Biliary cysts require an accurate diagnosis and surgical treatment in order to decrease the risk of malignant transformation and progression of the disease. Most of the patients with dilatation or cysts can be treated with surgical resection and bilioenteric reconstruction. Precise surgical treatment is needed for biliary cysts to achieve complete resection and a long term postoperative follow up is mandatory for these patients because of the risk of developing malignant transformation.

Referrence:

1. Machado NO, Chopra JP, Al-Zadjali A and Younas S. Choledochal Cyst in Adults: Etiopathogenesis, Presentation, Management and Outcome—Case Series and Review. Gastroenterology Research and Practice. 2015; 60 : p 10.
2. Zinner MJ, Ashley WS. Choledochal cyst and benign biliary strictures. In. Purvi YP & Keith DL. Maingot's abdominal operations.12th ed.USA. The Mcgraw-Hill's Companies; 2012: p 1029-1037.
3. Moris D, Papalampros A, Vailas M, Petrou A, Kontos M, Felekouras E. The Hepaticojejunostomy Technique with Intra-Anastomotic Stent in Biliary Diseases and Its Evolution throughout the Years: A Technical Analysis. Gastroenterol Res Pract.2016 Apr;13:p11.
4. Jarangin WR,Jacqes B, Markus WB, William CC, Michael IDA, Ronald PD, Lucy EH et al. Bile duct cysts in adults. In: Saboor K & David MN. Blumgert's Surgery of the Liver,Billiary Tract,and Pancreas. 5th ed.Philadelphia. Elsevier; 2012: p 707-718.
5. Altıntoprak F, Uzunoğlu MY, Dikicier E, Zengin I. Choledochal cysts- Classification, physiopathology, and clinical course. Integr Cancer Sci Therap. 2016; 3: p 10.
6. Saluja SS, Nayeem M, Sharma BC, Bora G, Mishra PK.Management of choledochal cysts and their complications. Am Surg. 2012; 78(3): p 284-90.
7. Reid MR. Drainage of the common bile duct through the cystic duct: cystic- choledochostomy. Ann Surg. 1921 Apr; 73(4): p 458-69.
8. Sanders RL. Hemihepatectomy with hepaticoje junostomy for irreparable defects of the bile ducts. Archives of Surgery. 1949; 58(6): p 752–761.
9. Olival CLD, Fonseca N, Moacir CAN,Antonio LDM. Surgical management of cystic dilatation bile ducts in adults .ABCD, arq.bras.cir.dig.2015; 1:p 28.
10. Kassem MI, El-Haddad HM, Elriwini MT. Surgical outcome of choledochal cysts in adults: a prospective cohort study. Egypt J Surg. 2017; 36: 3 : p 274-282.
11. Sacher VY, Davis JS, Sleeman and Casillas J. Role of magnetic resonance cholangiopancreatography in diagnosing choledochal cysts: Case series and review.World J Radiol. 2013; 28: 5(8): p 304–312.
12. Mabrut JY, Bozio G,Hubert C,Gigot JF. Management of Cong congenital Bile Duct Cysts. Dig Surg. 2010; 27: p 12–18.
13. Martínez CA, López MJ, Franco SS. Biliary cysts in adults. 26 years experience at a single center. Ann Med Surg (Lond).2016: 11: p 29-31.
14. Kelly R, Sean M, Soares, Kevin C, Ejaz, Aslam, Pawlik,Timothy. M. Management of choledochal cysts. Current Opinion in Gastroenterology. 2016: 32: 3: p 225–231.
15. Kirschner HJ, Szavay PO, Schaefer JF, Fuchs J. Laparoscopic Roux-en-Y hepaticojejunostomy in children with long common pancreaticobiliary channel: surgical technique and functional outcome.J Laparoendosc Adv Surg Tech A.2010 Jun; 20(5): p 485-8.
16. Villegas L, Lagoo S, Schwartz T, Athar N, Greene R, Eubanks WS. Robotically assisted laparoscopic Roux-en-Y hepaticojejunostomy. JSLS, 2004; 8(3): p 239–244.
17. Soares kc, Arnaoutakis DJ, Kamel I, Rastegar N, Anders R, Maithel S and Pawlik TM. Choledochal Cysts: Presentation, Clinical Differentiation, and Management. J Am Coll Surg. 2014 Dec; 219(6): p 1167–1180.
18. Anan CKU, Rajeev BK, Priyadarshi N. Diagnosis and Management of Choledochal Cysts. Indian Journal of Surgery. February 2012; 74 : 1: p 29–34.

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