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Editor's choice

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Editorial of this issue is 'Risk Factors of IUGR'. It is a very common problem in worldwide as well as in Bangladesh. Here causes and consequences of IUGR, diagnostic procedure, treatment protocol and preventive measures are discussed. Apart from that this issue also contains 6 original articles,1 review article and 2 case reports.

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Dr. G.M. Raihanul Islam
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Editorial

Risk Factors of IUGR

Intrauterine growth restriction(IUGR) is the second leading cause of perinatal morbidity and mortality[1,2]. IUGR is defined as fetal growth less than the normal growth of a specific infant because of genetic or environmental factors.IUGR is a clinical definition and applied to neonates with clinical evidences of malnutrition[3]. World wide, IUGR is observed in about 24% of newborns; approximately 30 million infants suffer from IUGR every year[4,5]. The burden of IUGR is concentrated mainly in Asia which accounts for nearly 75% of all affected infants. Africa and Latin America account for 20% and 5% cases respectively[5].

The causes of IUGR are broadly described under three main categories: maternal, fetal, and placental5.Several maternal demographic factors have been associated with IUGR. Women at extremes of reproductive age, especially young maternal age, are at increased risk for IUGR[5,6,7]. Similarly advanced maternal age has been associated with low birth weight[7,8]. Maternal race, lower socioeconomic status, and living in a developing country have been found to risk factors for IUGR[9]. Women with lower socioeconomic status and those living in developing countries commonly have poor nutritional status, maternal anemia, and poor prenatal care and substance abuse problem, which affect fetal growth. Maternal weight at birth, low pre-pregnancy weight, and poor weight gain during pregnancy are positively associated with increase in IUGR [9,10]. Exposure to various medications, such as warfarin, anticonvulsants, antineoplastic agents, and folic acid antagonists (such as trimethoprim-sulfamethoxazole, phenobarbital), can result in IUGR[11]. Maternal systemic conditions, such as chronic hypertension, preeclampsia, pregestational diabetes, chronic renal insufficiency, systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), can affect the fetal microcirculation and thereby decrease fetal perfusion, leading to hypoxia and IUGR[12]. Genetic causes can contribute to 5-20 % of IUGR, especially for early onset growth restricted fetuses. Beside this, congenital malformations, fetal infection, or other causes, including multiple pregnancies are responsible for IUGR. Abnormal implantation, such as placenta previa, can result in suboptimal nutrition to the fetus. Other common placental causes of IUGR include placental abruption, placenta accreta, placental infarction, fetal villous obliteration, circumvallate placenta, and placental hemangioma[13]. Confined placental mosaicism, single umbilical artery, and velamentous cord insertion also can result in growth restriction[14]. Rare placental tumor, such as chorioangioma, can decrease the uteroplacental flow, which can impair fetal growth.

With maternal or placental causes of IUGR, there is decreased placental transfer of nutrient (including oxygen) resulting in reduced fetal body stores of lipids and glycogen resulting in neonatal hypoglycemia; chronic hypoxemia stimulates erythropoietin production leading to polycythemia. These infants are also at increased risk for perinatal asphyxia. Other associated problems include hypocalcemia, pulmonary hemorrhage, hypothermia and IUGR associated with toxemia, thrombocytopenia and leukopenia. With fetal causes, decreased growth is constitutive (due to genetic factors) or secondary to infection. IUGR infants face multiple problems from birth to adolescence. They are more prone to immediate mortality and morbidities, apart from experiencing the long term growth deficits and abnormal neurodevelopment. They are also more likely to have poor school performance and childhood behavioral issues.

The major risk factors for IUGR include racial/ethnic origin, social and economic deprivation (as measured by education, occupation or financial classification), infant sex, poor gestational nutrition, low pre-pregnancy weight, short maternal stature, low paternal weight and height, parity, short birth intervals, history of prior low-birth weight infant, general morbidity and episodic illness, malaria, severe anemia, cigarette smoking or tobacco chewing[15,16].

Intrauterine growth restriction (IUGR) is a common diagnosis in obstetrics and carries an increased risk of perinatal mortality and morbidity. Identification of IUGR is crucial because proper evaluation and management can result in a favorable outcome. Certain pregnancies are at high risk for growth restriction, although a substantial percentage of cases occur in the general obstetric population. Accurate dating early in pregnancy is essential for a diagnosis of IUGR. Ultrasound biometry is the gold standard for assessment of fetal size and the amount of amniotic fluid. Growth restriction is classified as symmetric and asymmetric. A lag in fundal height of 4 cm or more suggests IUGR. Serial ultrasonograms are important for monitoring growth restriction.

The management of IUGR must be individualized for each patient. In addition to managing any maternal illness, a detailed sonogram should be performed to search for fetal anomalies, and karyotyping should be considered to rule out aneuploidy[17]. Symmetric restriction may be due to a fetal chromosomal disorder or infection. This possibility should be discussed with the patient, who may decide to undergo a diagnostic procedure such as amniocentesis. It should be remembered, however, that many infants with evidence of growth restriction are constitutionally small. Serial ultrasound examinations are important to determine the severity and progression of IUGR.A controversy involves the timing of delivery to prevent intrauterine demise because of chronic oxygen deprivation. Preterm delivery is indicated if the growth-restricted fetus demonstrates abnormal fetal function tests, and it is often advisable in the absence of demonstrable fetal growth. The risks of prematurity must be weighed against the complications unique to IUGR[18]. General management measures include treatment of maternal disease, cessation of substance abuse, good nutrition and bed rest. Although not of proven benefit, bed rest may maximize uterine blood flow. In any case, antenatal testing should be instituted. Options include the nonstress test, the biophysical profile and an oxytocin challenge test. The biophysical profile involves assessment of fetal well-being with a combination of the nonstress test and four ultrasonographic parameters (amniotic fluid volume, respiratory movements, body movements and muscle tone). The use of Doppler flow velocimetry, usually of the umbilical artery, identifies the growth-restricted fetus at greatest risk for neonatal morbidity and mortality.Because of the increased risk of intrapartum asphyxia, the fetus should be monitored carefully and continuously during labor[19,20]. Delivery should be in a hospital capable of dealing with the various

neonatal morbidities associated with growth restriction, including asphyxia, meconium aspiration, sepsis, hypoglycemia and malformations. Preterm induction of labor is often required. Amnioin fusion may be of benefit in the presence of a non reassuring fetal response during labor and a low amniotic fluid index or oligohydramnios. In the face of deteriorating fetal status, a cesarean section should be performed.

IUGR is one of the most common pregnancy complications and substantially increase the prospective risk of adverse outcome. Yet most instances of IUGR are not detected as such antenatally. Modern obstetric care needs to raise the level of awareness of the importance of this condition and establish evidence based protocols for improved surveillance. Accurate dating, preferably by routine ultrasound examination is the first step in the accurate diagnosis of IUGR. The routine use of single or serial ultrasound examinations in the third trimester of high risk pregnancies would detect the majority of the cases of IUGR .Because the only current treatment for IUGR is delivery, the main consideration needs to be appropriate timing, balancing the risk of potential iatrogenic morbidity and continued exposure to an unfavorable intrauterine environment.

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Original Article

Predication of Intrauterine Growth Retardation by Second Trimester Umbilical Artery Doppler Abnormalities

Biswas PR[1], Paul GK[2], Khatun M[3], Ullah MS[4]

Abstract:

Background: *Impaired fetoplacental perfusion is associated with intrauterine growth retardation (IUGR) and pregnancy induced hypertension. Both the pregnancy related complications make significant contribution to perinatal mortality and morbidity. Umbilical cord arterial Doppler imaging for assessing fetal health, controversy exists about its usefulness. Few studies have directly compared noninvasive tests and umbilical cord arterial Doppler imaging for predicting IUGR7-8. A pulsed Doppler apparatus may be used to assess the blood flow velocity profiles in the umbilical arteies at 16 to 22 weeks gestation to determine if complications associated with impaired trophpblastic invasion of the placental bed could be predicted by this measurement.*

Objective: *To determine the utility of Color Doppler sonography of the feto-placental circulation in predicting the outcome in middle part of pregnancies .To examine the diagnostic value of umbilical artery velocity wave forms for the early detection of IUGR*

Method: *This prospestive study was done on114 subjects were included in this study. This study was conducted in the Department of Obs & Gynae, SSMC & Mitford Hospital in Collaboration with radiology and imaging department of Dhaka Hospital , Mitford in 2008. Gestational age were 16 to 22 weeks. Blood flow through the uteroplacental circulation can be studied non invasively with the use of Doppler ultrasound.*

Result: *A total 114 subjects of 16 to 22 weeks of gestation were included in this study Mean age of the respondents was 23.74 years with a standard deviation of ± 4.15 years. All patients were within 17 to 35 years age range .19.3% respondents were nullipara ,36.8% were primipara and 43.9% were multipara. Weight of intrauterine growth retarded baby and normal baby was 2.34±0.75 and 3.01 ± 0.42 kg respecitively ($p<0.05$). Negative correlations were observed between birth weight and S/D ratio ($r=-0.336, p<0.001$) and birth weight and RI index ($r=-0.242, p<0.001$).Sensitivity of Doppler USG to diagnose IUGR was 77.8% ,specificity 96.2% ,positive predicictive value 63.6% ,Negative predictive value 98.1% and accuracy 94.7% at S/D cutoff level. Sensitivity ,specificity, positive predicictive value, negative predicictive value, accuracy was found 44.4% ,100.0%,100.0%,95.5%,and 95.6% respectively at 5.5 cutoff level. Diagnostic accuracy was determined as receiver operating Characteristic(ROC) curve, suggesting that the area under the curve (AUC) of Doppler USG at S/D cutoff level 5 and 5.5 was 0.87 and 0.72,respectively ,So S/D cut off level 5 was more appropriate to predict IUGR.*

Conclusion: *A close linear relationship between birth weight and umbilical artery Doppler velocity waveforms was observed .As umbilical artery Doppler is easy to perform and it is done in between 16 to 22 weeks of gestation can be done along with anomaly scan which is also done at 20-22 week of gestation . so ,UA Doppler does not cause additional USG scan . Along with anomaly scan UA Doppler will help to screen out high risk pregnancy who are going to develop IUGR.*

Keyword: *Intrauterine Growth Retardation, Second Trimester, Color Doppler sonography*

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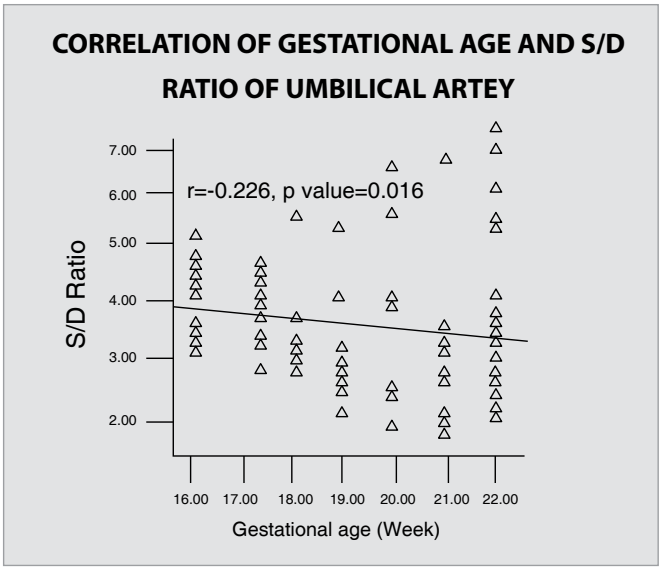
Introduction:

It has long been recognized that impaired fetoplacental perfusion is associated with intrauterine growth retardation (IUGR) and pregnancy induced hypertension. Both the pregnancy related complications make significant contribution to perinatal mortality and morbidity. The utroplcental arteries are formed as a result of conversion of the maternal spiral arteries by trophoblastic invasion. The normal pattern of trophoblastic invasion develops from as early as eight week gestation and is well established by 20-22 weeks gestation, a process that converts the spiral artery is low resistance, high conductancevessel. Blood flow through the uteroplacental circulation can be studied non invasively with the use of Doppler

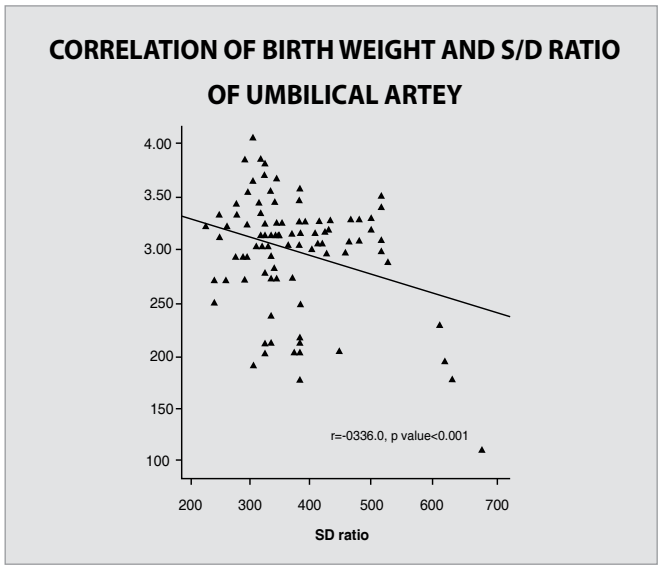
ultrasound. The impedance to flow in the uterine arteries progressively decreases during the first two trimesters of normal pregnancies. This observation has been attributed to a direct effect of trophoblastic invasion on the musculoelastic coat of uterine spiral arteries (Pijnenborg 1980). Placental pathology from pregnancies diagnosed with preeclamsia and intrauterine growth retardation shows failure of the normal transition of maternal placental arteries into low resistance vessels1. Pre-eclamptic pregnancies demonstrate high impedance in the fetoplacental circulation and reduction in the volume of flow, through to result from failed trophoblastic invasion of the spiral arteries in the early second trimester. Fetoplacental vascular resistant can be assessed by Doppler ultrasound and therefore impedance indices measured by Doppler ultrasound have been evaluated as an early screening test for IUGR2. Quantification of flow velocity wave forms of the umbilical artery obtained with Doppler examination has become recognized as potentially useful additional method of fetal assessment. In normal pregnancy there is a progressive increase in end-diastolic velocity and hence a steady fall in peripheral resistance in the umbilical placental circulation. Reduced, absent, or even reversed end-diastolic flow velocity may occur in pregnancies complicated by severe intrauterine growth retardation, and cause low APGAR scores. Various hypotheses have been proposed to explain these changes, such as an increase in fetal whole blood viscosity. In a study demonstrated that reduced mean small arteries vessel counts in placentas from pregnancies with abnormal flow velocity waveforms of the umbilical artery3. An increased in placental bed resistance caused by obliteration of these small vessels is the primary cause of the changes observed in flow velocity waveforms of the umbilical artery4. . IUGR is said to be present in those babies whose birth weight is below the 10 percentile of the gestational age. IUGR can occur in preterm or post term babies. In developed countries its overall incidence is about 2-8.0%5. The incidence among the term babies is about 5% and that among the post term babies is about 15.0%.Doppler resistance index (RI) was inversely related with the percentage of vessels demonstrationg trophoblastic invasion (Prefumo, Sebire, and Thilaganathan 2004) This observation appears to support that a relationship between trophoblastic invasions and RI can be demonstrated early in pregnancy, and gives credence to the possibility that this technique may prove useful predicting adverse obstetric outcome, specially IUGR, later in pregnancy. Doppler velocimetry of the umbilical artery is studied in pregnancies with complication. Increased PI means reduced diaslotic velocities and incasred placental vascular resistance (IUGR, Hypertension). Absence or reversal of end diastolic flow velocities in the umbilical artery is not an indication for immediate delivery. But it needs immediate and intensive fetal surveillance (Biophysical profile, biometry, and CTG)6. Doppler wave form abnormalities have been reported to be the most accurate predictor of poor neonatal outcome. Despite numerous reports demonstrating the usefulness of umbilical cord arterial Doppler imaging for assessing fetal health, controversy exists about its usefulness. Few studies have directly compared noninvasive tests and umbilical cord arterial Doppler imaging for predicting IUGR7-8. A pulsed Doppler apparatus may be used to assess the blood flow velocity profiles in the umbilical arteies at 16 to 22 weeks gestation to determine if complications associated with impaired trophpblastic invasion of the placental bed could be predicted by this measurement.



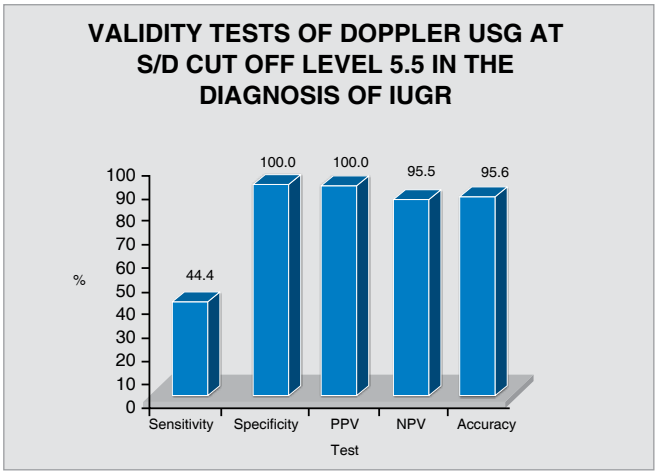
Method:

This prospective study was carried out in 114 randomly selected patients from 17-35 years of ages whose umbilical artery Doppler sonography was done between 16-22 weeks of gestation. Type of study: It was a prospective observational type of study. Place of study: This study was conducted in the Department of Obstetrics & Gynaecology, Sir Sallimullah Medical Collage & Mitford Hospital Dhaka in collaboration with radiology and imaging department of Dhaka hospital. Duration of study: The study was carried out from 1st July, 2006 to 30 June, 2008, a period of two years.

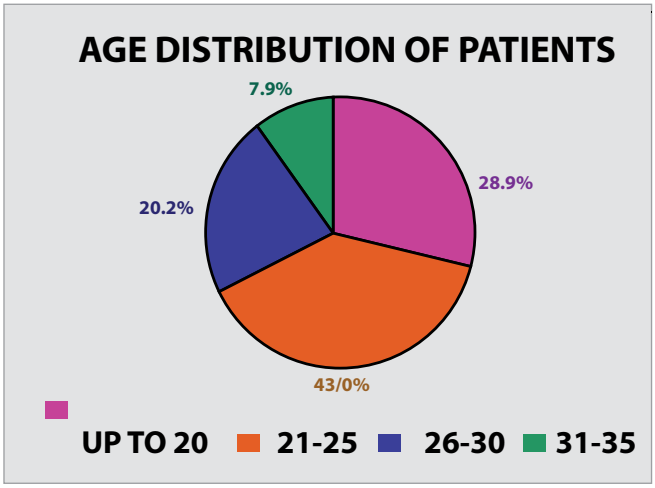
Scatter diagram shows that negative correlation between gestational Age and S/D ratio. Pearson correlation between-birth weight and S/D ratio was-0.226 and it was highly statistically significant. (p value = 0.016)



Scatter diagram shows that negative correlation between birth weight (KG) and S/D ratio. Pearson correlation between birth weight and S/D ratio was -0.336 and it was highly statistically significant. (p value < 0.001).

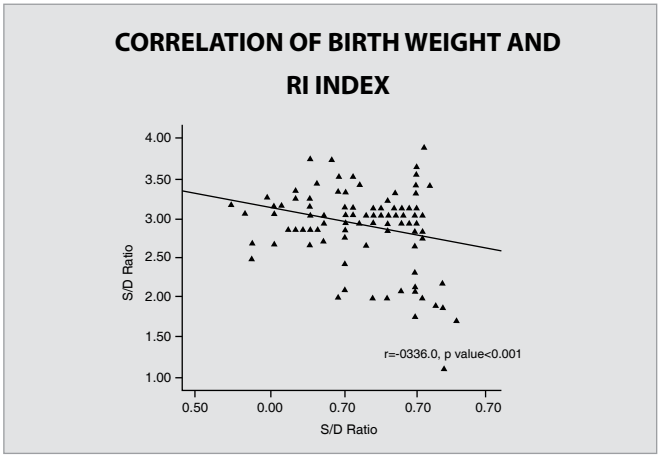


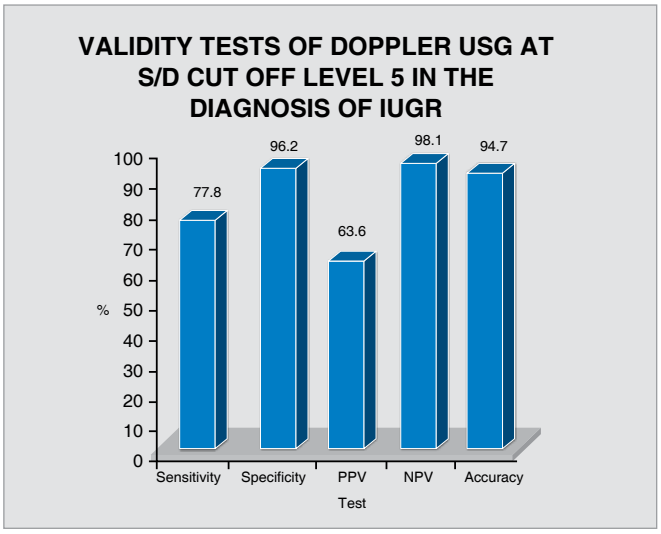
Scatter diagram shows that negative correlation between birth weight (KG) and RI index. Pearson correlation between birth weight and RIindex was-0.242 and it was highly statistically significant. (p value <0.001).

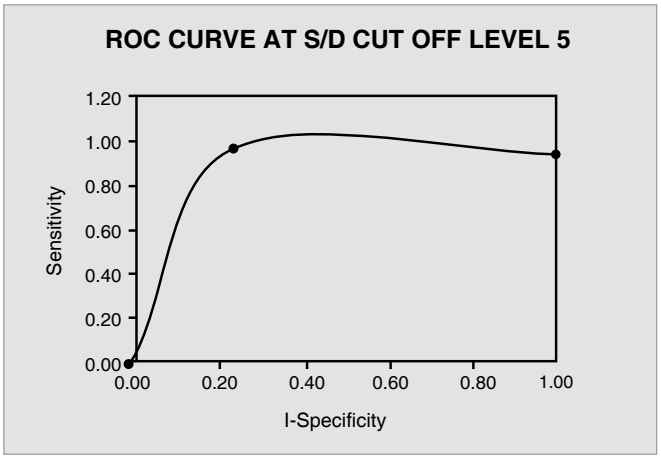


Result

A total 114 subject of 16 to 22 weeks of gestation were included in this series. Mean age of the respondents was 23.74 years with a standard deviation of + 4.15 years. All patients were within 17 to 35 years age range. Weight of intrauterine growth retarded baby and normal baby was 2.34 + 0.75 and 3.01 + 0.42 Kg respectively ($p < 0.05$). Negative correlation were observed between birth weight and S/D ratio ($r=-0.336$, $p< 0.001$) and birth weight and RI index ($r=-p.242$, $p< 0.001$).- Sensitivity, specificity, positive predictive value, negative predictive value accuracy was found 77.8%, 96.2%, 63.6 %, 98.1% and 94.7% at S/D cutoff level 5. Sensitivity, specificity, positive predictive value, negative predictive value accuracy was found 44.4%, 100.0%, 100.0%, 95.55 and 95.6 % respectively at 5.5 cutoff level. Diagnostic accuracy was determined as receiver operating characteristic (ROC) curve, suggesting that the area under the curve (AUC) of Doppler USG at S/D cutoff level 5 and 5.5 was 0.87 and 0.72 respectively, so S/D cutoff level 5 was more appropriate to predict IUGR. Out of all cases 7 were diagnosed as IUGR by Doppler USG (S/D 5 and above) and confirmed by birth weight after delivery. They were true positive.





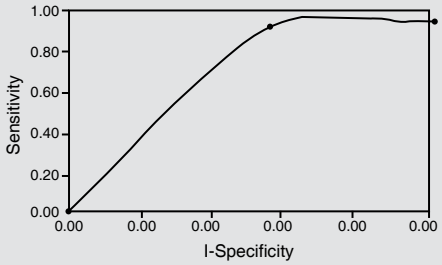


Discussion:

Intrauterine growth retardation (IUGR) is associated with significant perinatal mortality, perinatal morbidity, and long-term sequelae which include , impaired neurological development and cerebral palsy in childhood, and non-insulin-dependent diabetes mellitus and hypertension in adult life. Various studies have been done to investigate the value of Doppler ultrasonography of the umbilical artery and various foetal vessels in the diagnosis and management of IUGR[9]. Doppler velocimtry studies of placental and foetal circulation can provide important information regarding foetal well-being,

ROC curve revealed that in the diagnosis of IUGR by Doppler USG at 5 Cutoff level of S/D ratio. AUC was found 0.87

ROC CURVE AT S/D CUT OFF LEVEL 5.5



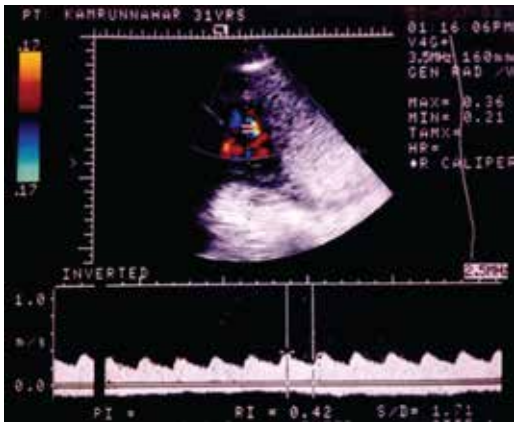
ROC curve revealed that in the diasnosis IUGR by doppler USG at 5.5 Cutoff level of S/D ratio. AUC was found 0.72

yielding an opportunity to improve foetal outcome[10]. The use of Doppler ultrasound in the evaluation of umbilical artery velocity waveforms in high risk pregnancies has been exhaustively assessed in different studies[3,11]. (Giles, Bigits and O' Callaghan et al 1993; Alfirevic et al, (1995). Doppler ultrasound in high risk pregnancies has been associated with significant reductions in perinatal mortality, the rate of stillbirths in normally formed infants, antepartum admission to hospital, induction of labour, elective delivery and caesarean section for fetal distress with an increased in deliveries <34 weeks of gestation[3].

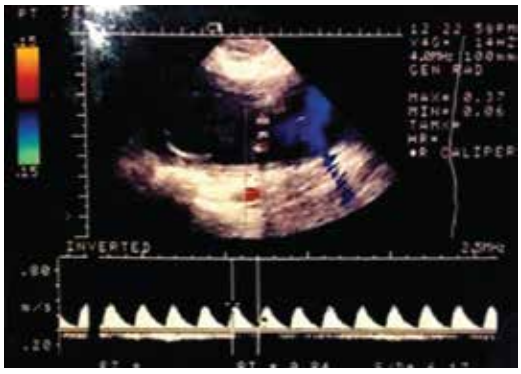
Doppler velocimetry of the umbilical artery is commonly used as a test for fetal surveillance in high-risk pregnancies. The presence of decreased, absent, or reversed diastolic flow in the umbilical artery has been correlated with fetal growth restriction and increased neonatal morbidity and mortality[12]. This study confirms the association of umbilical artery S/D ratio with IUGR. This prospective study was conducted in the Department of Obstetrics & Gyaecology, Sir Sallimullah Medical Collage & Mitford Hospital Dhaka with collaboration of radiology and imaging department of Dhaka hospital during the period of two years from July 2006 to June 2008. A total 114 subjects with 16 to 22 weeks of gestation were included in this study. In this study mean age of the respondents was 23.74 years with a standard deviation of + 4.15 years. All patients were within 17 to 35 years age range. Maximum respondents (43.0%) of the study group were belonged to 21 to 25 years followed by 28.9% within up to 20 years age group. In Acharya, Wilsgaard and Berntsen et al (2005) series maternal age (median, range) was 30 years with a range of 18 to 43 years. Mean para and gravid ware 1.4+ 0.99 and 2.23+ 1.03 respectively. 19.3% respondents of our series were nullipara, 36.8% were primipara and 43.9% were multipara. In Lakhkar, Rajagopal and Gourisankar series (2006) 60.3 % were primipara and 39.7% were is comparable with Acharya, Wilsgaard and Berntsen et al[13]. Mean pulse, systolic Bp and diastolic Bp of this study were, 76.82/ Minute, 115.4 mm of Hg and 72.4 mm of Hg respectively. Weight of intrauterine growth retarded baby and normal baby was 2.34+ 0.75 and 3.01+ 0.42 kg respectively. Statistically significant difference was observed interm of birth weight between IUGR and normal baby ($p<0.05$). In Lakhkar et al[14]. Birth weight (median, range) was 3665 g (1645-4590g). Acharya et al[13]. found a significant negative association between birth weight and gestational are-specific values of RI, and S:D ratio (p=0.011, 0.024, respectively). In our series negative correlations were observed between birth weight and S/D ratio (r=-0.336,$p<0.001$) and birth weight and RI index (r=-0.242,$p<0.001$) .Similar observation was made byBonnin et al[15].

Gradual declining trend in S/D ratio from 16 weeks to onward was also revealed in our series. Sensitivityof Doppler USG to diagnose IUGR in present series was 77.8%,specificity 96.2%,positive predictivevalue 63.6%,negative predictive value 98.1% and accuracy 94.7% at S/D cutoff level 5. But at 5.5 cutoff level sensitivity, specificity , positive predictive value ,negative predictive value ,accuracy was found 44.4%,100.0%,100.0%,95.5%and 95.6%respectively . The study by Barnett et al & Beattie et al [16,17] abnormal umbilical artery flow appeared to be a good predictor of adverse pregnancy outcome with a sensitivity 89% a specificity of 86%,a positive predictive value of 86% and a negative predictive value of 89%in preeclampsia and in pregnancies at risk for intrauterine growth retardation.In Lakhkar et al[14]. statistical analysis showed that umbilical artery S/D ratio was the most sensitive(66.6%)in predicting perinatal morbidity like IUGR. But the specificity of this index was the least among different parameter(45.4%).The accuracy of the umbilical artery S/D ratio was also less.In the same series it was also revealed that in predicting major adverse perinatal outcome umbilical artery

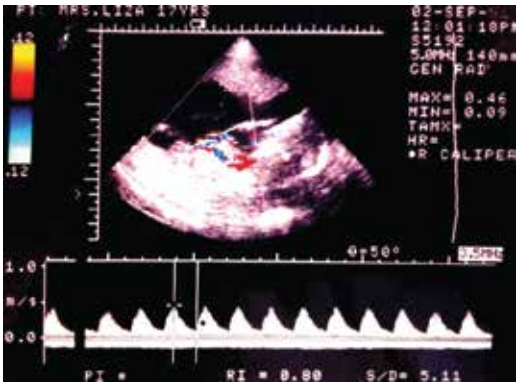
DOPPER USG UMBILICAL ARTERY SHOWING NORMAL FLOW PATTERN (S/D ratio=1.71)



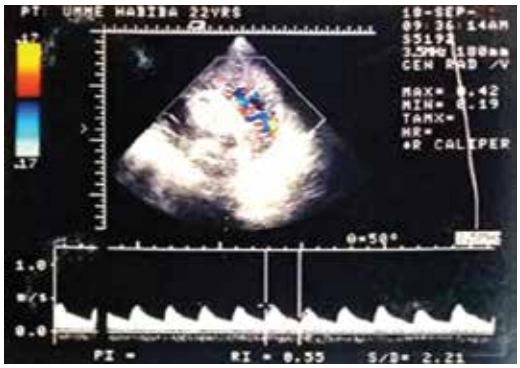
DOPPLER USG OF UMBILICAL ARTERY SHOWING ABNORMAL FLOW PATTERN RATIO (S/D RATIO =6.17).



DOPPER USG UMBILICAL ARTERY SHOWING NORMAL FLOW PATTERN (S/D ratio =5.11)



DOPPER USG UMBILICAL ARTERY SHOWING NORMAL FLOW PATTERN (S/D RATIO =2.21)



S/D ratio was 75.0% sensitive , 41.3% specific, NPV was 86.3% and accuracy was 48.0%. Diagnostic accuracy was determined as receiver operating characteristic (ROC) curve, suggesting that the area under the curve (AUC)of Doppler USG at S/D cutoff level 5% and 8.7 was and 0.72,respectively . In our series it was found that S/D cutoff level 5 was more appropriate to predict IUGR.

Conclusion and Recommendations:

A close linear relationship between birth weight and umbilical artery Doppler velocity waveforms has been described previously[15].The present data had confirmed that relationship . S/D ratio was found an important parameter to determine the IUGR .Receiver operating characteristic (ROC)curve revealed that the area under the curve (AUC)of Doppler USG at S/D cutoff level 5 and 5.5 was 0.87and 0.72,respectively . So, it was concluded that S/D cutoff level 5 was more appropriate to predict IUGR. As umbilical artery Doppler is easy to perform and it is done in between 16to 22weeks of gestations can be done along with anomaly scan which is also done at 20-22weeks of gestation. So, UA Doppler does not cause additional USG scan. Along with anomaly scan UA Doppler will help to screen out high risk pregnancy who are going to develop IUGR. In our country all district level hospitals and medical colleges are equipped by USG machine at present and in future USG machine with Doppler facilities can be provided in above mentioned hospitals ,so that patients of all social strata can avail of this opportunity.

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Original Article

Low Dose IV Ketamine Relieves Epigastric Discomfort, Chest burn, Nausea & Vomiting During Surgery in Peroperative Period under Spinal Anesthesia.

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ABSTRACT

Background: *Almost all patients feel epigastric discomport chest burn, Nausia & Vomiting when peritonial handeling (eg, peritonial toilating, closing peritonium)done in peroperative period under spinal anesthesia. Many drugs are used to minimize the symptoms. This study was done to find out the IV action of katamine to reliving the epigastric discomfort under spinal anesthesia during surgery when peritoneal handeling was done.*

Methods: *This prospective randomized double blind study was done in 250 bed district hospital attached in medical college. A total number of 100 patients age between 15 to 50 years under going caeserian section, abdominal hysterectony, Appendisectony and other lower abdominal surgeries ware radmonized going group A (No. 50) receiving IV Katamine dose 0.5 mg/per kg (0.5 ml) and group B (No. 50) receiving IV 0.5 ml distilled water 1 minute before peritonial handeling. Patients discomfort and adverse effect ware observed and analyzed.*

Result: *50 patients is each group was conscious, responds to vocal comments but group A patients are mildly sedated. It was observed that epigastric discomfort (eg chest burn Nausia, vomiting) decrease significantly in group A, It occurs 6% and group B it occurs 64%.*

Conclusion: *Use of low dose IV Katamine before peritonial handeling in peroperative period under spinal anesthesia decrease patients epigastric discomfort, chest burn and vomiting.*

Key words: *Katamine, Epigastric discomfort, Spinal anesthesia.*

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Introduction:

Intraoperative transient chest discomfort or chest burn is a common problem during lower abdominal surgery under spinal anaesthesia.

Acute pain consists of basal or background pain with spikes of more intense pain layered on top of this background. The basal or background pain that can fluctuate over time is called breakthrough pain[1]. Breakthrough pain, related to some specific activity is known as incidental pain. There is literature addressing treatment of incidental pain occurring on operating table immediately after lower abdominal surgery under spinal anaesthesia. Intravenous opioids are well studied for intra-operative or postoperative pain relief but limited availability of short acting opioids like fentanyl or alfentanil, especially in rural/remote areas of developing countries prevents their use. Ketamine is well known and popular in every place, including rural areas.

Ketamine is an anesthetic drug with non-competitive antagonist of the Nmethyl-D-aspartate receptor (NMDA-R) that inhibits central sensitization and has a preemptive analgesic effect to relieve postoperative pain[2-3]. In particular, even when ketamine is administered in low doses with no anesthesia effect, it suppresses facilitation of pain related to NMDA-R[4]. Reports regarding the preemptive analgesic effect of ketamine administered to patients undergoing cesarean section are inconsistent[5-9]. Ketamine administered during surgery reportedly has a preemptive analgesic effect, surgery under spinal anesthesia[6-7]. The contrasting results are considered to be due to differences in administration time and dosages of ketamine, anesthesia method, and in the method for controlling postoperative pain. The administered dose of ketamine may explain the preemptive analgesic effect of ketamine. Low-dose ketamine is defined as an IV injection or epidural administration of $\leq$ 1.0 mg/kg, or an IM injection of $\leq$ 2.0 mg/kg[8]. reported that the postoperative morphine requirement was not reduced in their study when 0.5 mg/kg ketamine was administered, but the postoperative analgesic requirement was reduced when 1.0 mg/kg was administered in a study by Ngan Kee et al[5]. They explained that this was because when a high dose of ketamine is administered, it can reach a relatively higher plasma concentration to suppress NMDA-R activation compared to that of low-dose administration. However, there are other reports in which 0.5 mg/kg of ketamine was helpful for relieving postoperative pain after abdominal surgery[10-12] and even that the analgesic requirement after cesarean section was reduced with administration of a low dose of 0.15 mg/kg.6-7 There is also a report that the morphine requirement was not different in three groups of cesarean section patients administered 0.25, 0.5, or 1.0 mg/kg of ketamine[13]; thus, it is possible that the preemptive analgesic effect of ketamine is not dose dependent. Moreover, a high dose of ketamine can cause psychomimetic effects.

Opioids are traditionally an integral part of therapy for acute post-operative pain. Unfortunately, possible hyperalgesia from opioids can result in increased analgesic requirements. However, ketamine can block these mechanisms; when administered at sub-anesthetic and repeated doses, ketamine has been shown to prevent the development of increased pain sensitivity and opioid tolerance[14]. Administering 0.5 mg/kg ketamine upon induction, followed by 10 μg·kg-1·h-1 until wound closure, decreases perioperative opiate requirements in opiate-dependent patients with chronic back pain undergoing back surgery[15]. Hasanein and colleagues[16] investigated the administration of low-dose intra-operative ketamine in laparoscopic Roux-en-Y gastric bypass (LRYGB) and demonstrated improved pain scores and reduced post-operative opioid requirements.

Atashkhoyi et al[17] concluded that the use of low-dose ketamine with propofol-fentanyl anesthesia in patients undergoing diagnostic laparoscopy for gynecological procedures was associated with less pain during propofol injection, a lower incidence of hemodynamic changes, lower total propofol requirements and improved post-operative analgesia.

Meer et al.[18] reported that ketamine in spinal anesthesia for lower abdominal surgery had lower side effects such as itching, urine suppression, hallucination, nausea and vomiting. Ketamine with sub anesthetic doses has analgesic effects which had been used for chronic pain relief. Several clinical trials have reported that ketamine can be administered during anesthesia to reduce opioids needs for postoperative pain relief. Cochrane review at 2006 reported that "Ketamine in subanesthetic doses is effective in reducing analgesic requirements in the first 24 hours after surgery"[19]. Ketamine, also decreases postoperative analgesic consumption due to prevention from opioids tolerance[20] This impact was also seen in using sub anesthetic dosage of ketamine (0.15 mg/kg) during spinal anesthesia for lower abdominal surgery[21-22]. We think that a single low dose of ketamine during spinal anesthesia in different type of lower abdominal surgery might decline the incidence of breakthrough pain in the first 24 hours postoperatively.

Method:

After approval from hospital ethical committee, and informed consent, 100 patients aged 15-50 years, of American Society of Anesthesiologist (ASA) grade I or II scheduled for caeserian section, abdominal hysterectony, appendisectomy and other different types of lower abdominal surgeries under spinal anesthesia, attended in 250 bed district hospital attached in a medical college were included in this prospective, randomized-controlled, double-blinded study. Patients with history of hypertension, ischemic heart disease, rheumatic heart disease, reflux esophagitis, disarranged hepatic or renal function, head trauma, psychiatric diseases, and sensitivity to studied drugs or contraindication to spinal anesthesia were excluded from the study.

All patients were randomly assigned to two equal groups. Randomization was done by an investigator involved in drug administration and data collection. Concealment was done via the sealed opaque envelope technique. Data analysis was carried out by another investigator blinded to group allocation. Patients complaining of chest discomfort or chest burn during surgery were included in the study.

Group A (No. 50) receiving IV Katamine dose 0.5 mg/per kg (0.5 ml) and group B (No. 50) receiving IV 0.5 ml distilled water 1 minute before peritoneal handeling. Duration of surgery, time of onset of pain, time required to relieve pain, hemodynamic parameters, adverse efects were observed.

On arrival to the operative room, monitors were placed and baseline parameters recorded. All patients were preloaded with lactated ringer solution (15 ml/kg) via 18 G peripheral

IV catheter. Before the commencement of spinal anesthesia, patients were explained about the chest discomfort/pain. In the sitting position under standard aseptic precautions, using a midline approach lumbar puncture was performed at L3-L4 or L4-L5 intervertebral space by 25 gauge Quincke spinal needle . Having confirmed the free flow of cerebrospinal fluid through the spinal needle, Bupivacaine (heavy) 2.5 ml solution was injected intrathecally over a period of 10–15 sec. and patients were turned to the supine position. Surgery was not allowed till bilateral sensory block reaches up to T18 to T8 level. Any episode of hypotension (systolic blood pressure < 90 mmHg or > 25% below baseline) was managed by ephedrine (5 mg) and an additional fluid bolus of ringer lactate solution. Bradycardia (< 50 beats/min) was managed by inj atropine 0.5 mg IV bolus.

Statistical Analysis:

Study data were entered into the SPSS 22.0 software and analyzed with chi-square test for qualitative and student t-test for quantitative variables between trial and control groups. Less than 0.05 calculated p-values were assumed as significant results.

Results:

All 100 patients completed the study successfully . The study groups were comparable in terms of demographic profile, baseline hemodynamic variables, ASA status and the duration of surgery **(Table 1).**

Table 1: Demographic profile and baseline parameter between two groups.

Parameter	Group A (n=50) Mean±SD	Group B (n=50) Mean±SD	p value
Age (year)	30.16 ± 2.32	31.24 ± 3.12	a0.052ns
Body weight(kg)	53.35 ± 10.0	53.30 ± 7.07	a0.977ns
Duration of surgery(min)	66.25 ± 14.94	66.50 ± 16.8	a0.938ns
ASA I/II	20/30	22/38	b0.720ns
94.12 ± 7.34	92.80 ± 8.65	a0.413ns	
Baseline systolic blood pressure (mmHg)	127.20 ± 11.13	128.16 ± 10.84	a0.605ns
Baseline diastolic blood pressure (mmHg)	84.63 ± 11.39	83.33 ± 12.21	a0.583ns

ns=not significant

ap value reached from unpaired t-test

bp value reached from chi-square t-test

Data are presented as mean ± SD. p value <0.05 considered as significant. ASA= American Society of Anesthesiologist, SD=Standard deviation

Maximum patients are female in both and maximum patients were in Caeserian section group.

Table 2: Types of Surgery and sex of the patients.

Parameter	Group A (n=50)		Group B (n=50)	
Male	18	36.0	17	34.0
Female	32	64.0	33	66.0
Types of surgery				
Caeserian section	22	44.0	23	46.0
Abdominal hysterectomy	10	20.0	9	18.0
Appendisectomy	6	12.0	6	12.0
Other lower abdominal surgeries	12	24.0	12	24.0

Table 3: No of patient felt Retrosternal chest discomfort or chest burn.

Timing of Pain	Group A (n=50)		Group B (n=50)	
	n	(%)	n	(%)
At peritoneal incision (PI)	4	8.0	5	10.0
Between PI and peritoneal closure	6	12.0	8	16.0
At time of peritoneal closure	3	6.0	32	64.0

Maximum number of patients developed chest discomfort/chest burn between peritoneal incision and peritoneal closure in both groups. (Table 3).

Data are presented as occurrences or percentage.

Table 4: Systolic blood pressure at different time intervals.

Timing of Pain	Group A (n=50) Mean±SD	Group B (n=50) Mean±SD	p value
	n(%)	n(%)	
Baseline	121.20 ± 11.13	122.16 ± 10.84	0.663ns
5 min after subarachnoid block	102.12 ± 8.12	103.27 ± 8.83	0.499ns
At onset of chest discomfort/chest burn	118.81 ± 10.13	120.31 ± 9.45	0.446ns
5 min after drug administration	130.45 ± 8.98	118.26 ± 9.12	0.001s
10 min after drug administration	125.12 ± 9.24	114.45 ± 8.86	0.001s
15min after drug administration	120.23 ± 8.54	116.37 ± 7.98	0.022s
Postoperative recovery room	118.65 ± 9.87	117.68 ± 10.12	0.692ns

Data are presented as mean ± SD. SD=Standard deviation.

At onset of chest discomfort/pain, there were transient decrease in heart rate and blood pressure from baseline value in both groups but intergroup comparison shows that means are equal **(Table 4)**.

Table 5: Mean Heart rate (per minute) at different time intervals and their comparison with baseline.

Timing of Pain	Group A (n=50) Mean±SD	Group B (n=50) Mean±SD	p value
	n(%)	n(%)	
Baseline	94.12 ± 7.34	92.80 ± 8.65	0.413ns
5 min after subarachnoid block	82.15 ± 8.65	79.60 ± 9.69	0.168ns
At onset of chest discomfort/pain	92.34 ± 8.45	90.23 ± 8.23	0.209ns
5 min after drug administration	118.62 ± 10.24	111.30 ± 8.22	0.001s
10 min after drug administration	99.46 ± 9.34	96.64 ± 8.24	0.113ns
15 min after drug administration	96.12 ± 8.42	95.12 ± 7.35	0.528ns
Postoperative recovery room	96.58 ± 8.11	94.34 ± 6.26	0.125ns

After intravenous distilled water there was no change in heart rate and mean arterial blood pressure but in ketamine group, heart rate and mean arterial blood pressure remain higher.

There was significant fall in heart rate and systolic blood pressure from baseline value after subarachnoid block in both groups but intergroup comparison shows that two means are equal **(Table 5)**.

Data are presented as mean ± SD. SD=Standard deviation.

Table 6: Side Effects.

Timing of Pain	Group A (n=50) Mean±SD		Group B (n=50) Mean±SD		p value
	n	(%)	n	(%)	
Hypotension	7	14.0	10	20.0	0.425ns
Bradycardia	1	2.0	8	16.0	0.014s
Tachycardia	6	12.0	2	4.0	0.140ns
Shivering	1	2.0	8	16.0	0.014s
Nausea/Vomiting	1	2.0	7	14.30	0.027s

Adverse efects eg. hypotension, bradycardia ,nausea and vomiting were more common in distilled water group while tachycardia ,and less nausea/vomiting were in ketamine group, but the difference was statistically significant between two groups **(Table 6)**.

Discussion:

Our study demonstrates that low dose ketamine can be used safely for relief of transient retrosternal chest discomfort or chest burn during lower abdominal surgery under spinal anaesthesia. We selected ketamine because of its easy availability in developing countries, short duration of action and proven analgesic effect at sub-anesthetic dose by various mechanisms[23-26]. In lower abdominal surgery, there are some studies which used ketamine in sub anesthetic dosage. Sen et al[27]. reported that patients who received ketamine (0.15 mg/kg) during spinal anesthesia had declined diclofenac recruitment in the first day postoperatively. Kwok et al[28] in laparoscopic gynecologic surgery reported that reduced requirement to paracetamol in the first week postoperatively in women who received ketamine (0.15 mg/kg).

Mismatch between oxygen supply and demand occurs due to combination of tachycardia, hypotension and coronary vasoconstriction that leads to myocardial ischemia and chest discomfort/pain[29-30] The patients develop chest discomfort/pain may be due to traction on peritoneum, reflux esophagitis or small venous micro embolism etc.

Ketamine causes sympathetic stimulation that lead to increase in heart rate and blood pressure while distilled water causes decrease in heart rate and blood pressure but statistically not significant and two means are equal.

Patients in this study of low dose ketamie had no considerable side effects and ketamine was tolerated well. Though Ketamine had some side effects such as urine suppression, hallucination, nausea and vomiting[31] Similar to our study, Meer et al.[32] reported that ketamine in anesthesia for lower abdominal surgery had lower side effects.

Limitation:

This study has three main limitations. First, patients and surgeons satisfaction was not checked. Second, we did not access the duration of postoperative analgesia. Third, sample size was small. These results may vary from investigations performed on other ethnic groups due to variations in pain or drug sensitivity.

Conclusion:

We conclude that low dose IV. Ketamine can be used as a good intervention for relief of transient intra-operative chest discomfort/pain during different types of lower abdominal surgery under spinal analgesia, without any significant adverse events.

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Conflict of Interest: None

Author contribution: All authors contributed in the conduct of study, literature search, data analysis and manuscript preparation and review.

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Original Article

Peptic Ulcer in Cirrhosis: an Endoscopic Study

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ABSTRACT

Background: *Liver cirrhosis results in portal hypertension, splenomegaly, esophageal varices and peptic ulcers. Fatal hemorrhage in patients of cirrhosis due to mainly variceal haemorrhage and some extend to peptic ulcers. Peptic ulcer bleeding is a serious complication with significant morbidity and mortality.*

Objective: To determine the frequency of peptic ulcers and pattern of peptic ulcer among patients of liver cirrhosis.

Method: *This is a hospital based observational study carried out in the Department of Hepatology, Shaheed Ziaur Rahman Medical College Hospital (SZMCH),Bogura over a period of 06 months, from January 2018 to June 2018. The study was approved by the Ethical Institutional Review Board (IRB) of SZMC, Bogura. Sixty three index patients of liver cirrhosis were enrolled in the study after the exclusion criteria. 8These patients were then subjected to upper gastrointestinal endoscopy after informed consent and the presence and pattern of peptic ulcers were noticed.*

Results: *Among 63, 73% were male (n=46) and mean age was 50.92 (±12.13) years with range from 22 to 78. Mean Child-Pughscore was 8.90 ± 2.22. Most common cause (49.3%) of liver cirrhosis was chronic hepatitis B. Peptic ulcers were present 41.3 % (26) among them GUD and DUD were 22.2% (14) and 14.3 % (09) respectively. Peptic ulcer was predominant in Child-Pugh C group 69.2 % (18).*

Conclusions: Peptic ulcer is common in liver cirrhosis and more especially in Child Pugh C. liver cirrhosis patient should be screened for the presence of peptic ulcer at the time of initial diagnosis, and at periodic intervals thereafter throughout life.

Keywords: *Peptic ulcer, Liver cirrhosis.*

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Introduction:

Cirrhosis results from the necrosis of liver cells followed by fibrosis and nodule formation. The liver architecture become diffusely abnormal and this interferes with liver blood flow and function. This derangement produces the clinical features of portal hypertension and impaired liver cell functions. Portal Hypertension, ascites, hepatic renal failure, encephalopathy, hepatocellular carcinoma and coagulopathy are the main complications[1]. Cirrhosis represents a growing burden of morbidity and mortality in United Kingdom, with an estimated 30,000 people living with cirrhosis and at least 7000 new cases being diagnosed each year. There was 45% increase in the incidence of cirrhosis during the decade 1992-2001 in the UK and 68% increase in prevalence[2]. In cirrhotic patients, gastrointestinal bleeding is usually attributed to esophageal varices; however it has now been observed that 5-15% [3] cirrhotic patients bleed from duodenal ulcer instead of varices. Peptic ulceration has been found in 11% of 324 patients with cirrhosis [4]. Seventy per cent were asymptomatic. Helicobacter pylori infection remains one of the most common chronic bacterial infections affecting humans and is usually acquired in childhood. The prevalence of Helicobacter pylori based on serology is significantly greater in patients with cirrhosis than those without liver disease (76 vs 42%)[5]. Bleeding from peptic ulcer disease is commoner in patients with cirrhosis and associated with increased mortality rates compared to patients without known liver disease [6].

The aim of this study was to determine the frequency of peptic ulcer in patients of liver cirrhosis. This study will help in

management of cirrhotic patients having peptic ulcers by knowing how frequently it is present and to help in decreasing morbidity and mortality.

Method:

Study Population

This is a hospital based observational study conducted in Hepatology department, Shaheed Ziaur Rahman Medical College Hospital (SZMCH), Bogura which was completed over a period of 06 months, from January to June 2018. The sample size was 63. Both male and female patients of ages between 18-80 years with cirrhosis were included. Patients having cerebrovascular disease, chronic obstructive pulmonary disease, MI, corrosive intake and chronic renal failure were excluded. Aims and objectives along with its procedure, risks and benefits of this study were explained to the patients and attendants in easily understandable local language (Bangla) and then informed written consent was taken from each participant. Prior to the commencement of the study, the research protocol was approved by the Institutional Review Board (IRB) of SZMC. Statistical Analysis

All data was recorded systematically in a preformed data collection sheet and quantitative data expressed as mean ± SD. Qualitative data analyzed by chi square test and quantitative data by student's T test or Mann Whitney's U test. Differences in laboratory parameters compared using one-way ANOVA.P value of ≤0.05 was considered to be statistically significant. All statistical computations were performed by using SPSS version 20 (Statistical Package for Social Science).

Results:

Demographic and laboratory characteristics

Most of the patients age belonged to ≤20 years in both groups, Table I demonstrated the demographic and laboratory parameters of the subjects in the study, including age, gender, occupation, educational status, monthly income, haemoglobin (Hb), ESR, Total count of WBC, platelet count(PLT), INR, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum bilirubin, serum albumin ,α-fetoprotein (AFP) and etiology of cirrhosis.

Table I. Baseline Demographics (n=63)

Age	
Mean ± SD	50.92 ± 12.13 Years
Range	22 to 78 years
Gender	
Male :Female	2.07:1
Occupation (%)	
Housewife	27
Service	33.3
Farmer	33.3
Business	4.8
Others	1.6
Monthly Income (%)	
< 10,000 TK/Month	15.3
10-20,000 TK/Month	54.7
20-50,000 TK/Month	20.7
>50,000 TK/Month	09.3
Education (%)	
Illiterate	44.4
< SSC	17.5
< BSC	17.5
Above	20.6
Parameter	Mean ± SD
Haemoglobin (g/dl)	10.46 ± 1.90
ESR (mm in 1st hour)	58.72 ± 29.07
Total Count of WBC	8825.32 ± 9722
Platelet count (109/L)	32.52 ± 56.58
INR	1.66 ± 0.36
Alanine aminotransferase (U/L)	67.13 ± 48.43
Aspartate aminotransferase (U/L)	91.88 ± 57.76
Serum bilirubin (mg/dL)	.67 ± 3.6
Serum albumin (g/dl)	2.80 ± 0.63
AFP (ng/ml)	05.89 ± 4.22
Child Pugh	
Score	8.90 ± 2.22
Grade A (%)	15.9
Grade B (%)	44.4
Grade C (%)	39.7
Eitiology of Cirrhosis (%)	
Chronic Hepatitic B	49.3
Chronic Hepatitic C	15.7
Non B & Non C	35.0

Distribution of the study population by age range

Table II shows distribution of the study population by age range. Maximum (50%) patients' ages were belonged to 41-60 years. The mean age was found 50.92 ±12.13 years with range from 22 to 78 years.

Table II: Distribution of the study population by age range (n = 63)

Age range	Frequency	Percent	Cumulative Percent
18 -30	03	04.8	04.8
31- 40	08	12.7	17.5
41- 50	16	25.4	42.9
51- 60	17	27	69.8
> 60	19	30.2	100.0
Total	63	100	100

Gender distribution of the study population

Figure 1: shows male gender was predominant 73% (46) of the study population. Male female ratio was 2.7:01.

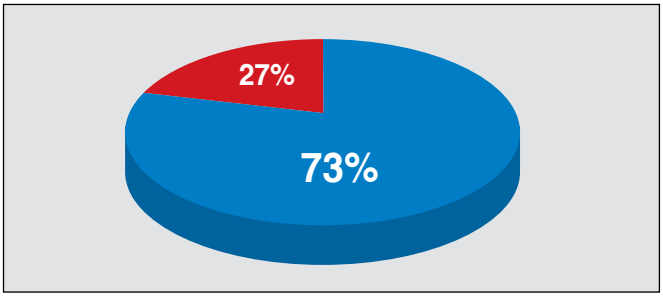

Figure 1: Gender distribution of the study population (n= 63).

Distribution of the study population according to Ulcer status

Table III shows the Peptic ulcers were present 41.3 % (26) among them GUD, DUD and both were 22.2% (14), 14.3 % (09) and 4.8 % (03) respectively.

Table III: Distribution of the study population according to ulcer status (n = 63)

Ulcer status	Frequency	Percent	Cumulative Percent
18 -30	03	04.8	04.8
31- 40	08	12.7	17.5
41- 50	16	25.4	42.9
51- 60	17	27	69.8
> 60	19	30.2	100.0
Total	**63**	**100**	**100**

DUD-Duodenal Ulcer Disease; GUD-Gastric Ulcer Disease

Distribution of peptic ulcer according to cirrhosis (Child-Pugh) status

Peptic ulcer was predominant in Child-Pugh C group 69.2 % (18) whereas non-ulcer was predominant in the Child-Pugh A & B group 81% (30). The difference was statistically significant (P=0.001).

Table IV: Distribution of peptic ulcer according to cirrhosis (Child-Pugh) status (n = 63)

ULCER	CIRRHOSIS STATUS (CHILD-PUGH)							
STATUS	CP A		CP B		CP C		Total	
	n	%	n	%	n	%		
No ulcer	09	14.3	21	33.3	07	11.1	37	
GUD	00	00	01	1.6	13	20.6	14	P value*
DUD	01	1.6	05	7.9	03	4.8	09	0.001[s]
Both	00	00	01	1.6	2	3.2	03	
Total	10	15.9	28	44.4	25	39.7	63	

s= significant, df=6, *Chi- square test was done to measure the level of significant; CP- Child Pugh

Discussion:

The aim of the study was to determine the frequency of peptic ulcers and pattern of peptic ulcer in patients of liver cirrhosis. Most of the patients included in our study were between 18 to 80 years of age. Similar mean age was found in most of other studies done on cirrhotic patients[7-8]. The reason may be that cirrhosis usually occurs as an end result of chronic hepatitis which usually takes one to two decades to lead to cirrhosis.

Gastrointestinal (GI) bleeding in the patients of liver cirrhosis is usually attributed to esophageal varices. However; peptic ulcer can be the cause of the upper GI bleeding instead of varices. Similarly dyspepsia in cirrhotic patients may be because of gastro duodenal ulcer in about 30 % and not due to cirrhosis itself[9]. Peptic ulcer bleeding is the most common cause of upper gastrointestinal bleeding, responsible for about 50% of all cases. Esophagitis and gastric erosions are 2nd and 3rd common causes respectively. Esophageal varices are the cause of bleeding in cirrhotic patients in up to 70% cases[10].

It was found in a study conducted by Svoboda P et al[11] that duodenal ulcer frequency is 11.1%. In our study, similar results are found. The frequency of duodenal ulcer in our study is 14.3% (09 out of 63 patients) and peptic ulcer 41.3%. In another study conducted by Svoboda P et al.gastroduodenal ulcers were found to be 25.8 %[12].

It has been reported that there is an increased incidence of duodenal ulcer in patients of liver cirrhosis with low incidence of Helicobacter pylori infection[13]. It has also been reported that there is higher prevalence of asymptomatic peptic ulcer in decompensated cirrhotic patients[14]. The pathogenesis of peptic ulcer in cirrhosis might be portal hypertension, which causes splanchnic congestion, interferes with formal reparative process of gastroduodenal mucosa, leading to increased susceptibility towards acid and pepsin secretion[15]. Changes in gastric microcirculation in cirrhosis, such as increased number of straight arterioles and dilated precapillaries and veins have been reported. These alterations might contribute to gastroduodenal ulcers and other putative acid peptic lesions[16]. Another factor potentially responsible for gastroduodenal lesions seen in cirrhosis might be hyper catabolic state of cirrhotic patients. This condition seems to occur independent of portal hypertension, but is more evident in patients with severe disease. It is most probably related to impaired reparative process[17]. Increased levels of histamine have been reported in cirrhotic patients which might increase gastric acid secretion leading to peptic ulceration[18]. It has also been reported that there is excess vagal drive in cirrhosis[13] and diminished prostaglandin content in gastric mucosa, which can cause peptic ulceration. H.pylori infection has been linked directly to duodenal ulcers, in general population[19]. However, duodenal ulcer in cirrhotic patint seems to be independent of Helicobacter pylori infection[20]. Duodenal ulcer in patients of cirrhosis tends to heal slowly and recur with higher frequency than in controls without cirrhosis. Seventy-nine percent of recurrences are asymptomatic with cirrhotic patients[14].

There are limitations of this study; firstly it is a hospital based observational study for more accurate data long term follow up and case control study will be needed, secondly etiology of peptic ulcer was not clearly done, thirdly single center and short duration study.

Conclusion:

Our study suggests that peptic ulcer is common in liver cirrhosis and more especially in Child Pugh C class. It has therefore been recommended that patients with liver cirrhosis should be screened for the presence of peptic ulcer at the time of initial diagnosis, and at periodic intervals thereafter throughout life.

Conflict of Interest Statement

No potential conflicts of interest are disclosed.

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Original Article

Validity of CT-Guided FNAC in Differentiating Malignant and Non-malignant Lung Lesion

Kabir MA [1], Zaman N [2], Yasmin D [3]

ABSTRACT:

Background: *Lung cancer is the most common cancer worldwide. Lung cancers are categorized as small cell carcinoma or non–small cell carcinoma (e.g., adenocarcinoma, squamous cell carcinoma, large cell carcinoma). These categories are used for treatment decisions and determining prognosis. Signs and symptoms may vary depending on tumor type and extent of metastases. The most common symptoms are cough, haemoptysis, weight loss, shortness of breath, and chest pain etc. Performing a chest radiograph is first investigative step if a person reports symptoms that may suggest lung cancer. But lung tumour often appears as a solitary pulmonary nodule on a chest radiograph. However, the differential diagnosis is wide. Many other diseases can also give this appearance, including tuberculosis, fungal infections, metastatic cancer or organizing pneumonia etc. Though the clinical symptoms and radiological findings are not confirmatory, CT-guided FNAC is valuable in confirmation of diagnosis of lung cancer and accurate diagnostic tool for clarification for all suspected cases.*

Objective: *Aim of this study was to observe the validity of CT guided FNAC in differentiating malignant and non-malignant lung lesion.*

Method: *This observational study was conducted in Gazi Medical College Hospital over a period two years from March 2016 to March 2018. Total sample size was 50. Patients present with clinical and radiological features of lung lesion were enrolled for study. Sample was selected from the population by convenient and purposive sampling technique. Detail demographic data were collected from the patients and recorded in structured case report form. Clinical examination and relevant investigations were done meticulously.*

Result: *Mean age of the patient was 53.72 ± 9.78 years. Male and female ratio was 2.84**:**1. Present study show that respiratory distress, cough, weight loss and chest pain were the commonest presentation (100%, 90%, 78% and 74% respectively) of the patients, and smoking was a prime risk factor. Primary diagnosis of lung lesion was done by evaluation of history, clinical examination and categorization was done on the basis of CXR finding. Among the clinically suspicious lung cancer, 45(90%) were diagnosed as bronchial carcinoma and remaining (10%) patients were non-specific inflammation. CT guided aspiration cytology showed that non-small cell carcinoma was predominant, present in total 37(74.0%) of patients. Correlation of cytological examination with clinical and radiological finding revealed that cytological examination was more precise, correlates with the suspected malignant lung cancer. Maximum malignant cases 44(97.7%) had proven in cytological examination as like. Present study shows that sensitivity of CT guided FNAC is higher than specificity. Sensitivity of CT guided FNAC in diagnosis of bronchial carcinoma is 93.61%. Specificity of CT guided FNAC in diagnosis of bronchial carcinoma is 66.6%.*

Conclusion: *CT-guided FNAC is an extremely valuable and fairly accurate diagnostic aid of pulmonary mass lesions, with a reasonable rate of complication.*

Key words: *Lung lesion, Bronchogenic carcinoma, CT guided FNAC.*

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Introduction:

Cancer is the sixth cause of mortality in Bangladesh and 60% of cancer patients die within five years of diagnosis[1]. Cancer registry report in Bangladesh revealed that lung cancer in males, cervical and breast cancer in females constitute 38% of all cancers in Bangladeshi patients. In registry report shows lung cancer was the leading cancer (17.3%), followed by cancers of breast (12.3%)[2], lymph nodes and lymphatics (8.4%) and cervix (8.4%) for sexes combined in all ages. Smoking is the single most preventable risk factor for lung cancer. In the registry about 60% of the male lung cancer patients were smokers whereas 5% female lung cancer

patients were smokers. Therefore their prevention warrants serious attention[2]. Early detection and accurate management can reduce the burden of cancer.

Lung carcinoma is the leading cause of cancer-related death worldwide. About 85% of cases are related to cigarette smoking. Symptoms can include cough, chest discomfort or pain, weight loss and hemoptysis; however, many patients present with metastatic disease without any clinical symptoms. The diagnosis is typically made by chest x-ray or CT and confirmed by biopsy[3]. As an overview, lung cancer and mouth-oropharynx cancer rank as the top two prevalent cancers in males. Leading cancers and the prevalence in last 5 years in males shows 13.1% were lung cancer prevalence[4]. The risk of lung cancer increases with combined exposure to toxins and cigarette smoking. Other possible risk factors include air pollution, exposure to cigar smoke and exposure to carcinogens (e.g, asbestos, radiation, radon, arsenic, etc.)

An early, accurate diagnosis is of paramount importance for initiating specific therapy for malignant lesions and for avoiding unnecessary procedures for benign conditions. Chest x-ray is often the initial imaging test. It may show clearly defined abnormalities, such as a single mass or multifocal masses or a solitary pulmonary nodule, an enlarged hilum, widened mediastinum, tracheobronchial narrowing, atelectasis, cavitary lesions, or unexplained pleural thickening or effusion. CT also can guide aspirated cytology of accessible lesions and is useful for confirmed diagnosis. Cytology is the method used to obtain cells or tissue for confirmation depends on the accessibility of tissue and the location of lesions[3].

Fine Needle Aspiration Cytology (FNAC) is a procedure to obtain material from organs that do not shed cells spontaneously. Fine needle aspiration with computed tomography (CT) guidance has accuracy and high sensitivity for the detection of malignancy in lung nodules. The modality selected to diagnose a suspected lung cancer is based on the size and the location of the primary tumors[5]. Fear of neoplastic implantation in the needle track may have initially inhibited its use but have proven groundless[6]. Thus, after clinical risk assessment tissue diagnosis is the next step in managing radiologically suspicious lung nodules.

Direct tissue sampling for diagnosis is essential in most patients for decisions regarding treatment and can be accomplished by fine needle aspiration. Most patients with lung cancer present with clinical advanced disease and therefore are not candidates for surgery with curative intent, but are rather treated with systemic therapies. In the age of personalized therapies, cytological material in the form of FNAC may be the only available diagnostic specimen, and the only material available for molecular studies, necessary for current therapeutic decision making[7]. Computerized tomography (CT) guided fine needle aspiration cytology (FNAC) of lung lesions has rapidly emerged as a less-invasive, cheap, rapid and fairly accurate diagnostic aid in lung lesions[8].

Fine needle aspiration cytology (FNAC) is a rapidly emerging diagnostic modality to assess the nature of radiologically demonstrated lung lesions[9]. Early initiation of specific therapy is possible as FNAC helps to differentiate between benign and malignant nature. Early detection means detecting cancer prior to the development of symptoms or as soon as is practicable after the development of symptoms. Its aim is to detect the cancer when it is localized to the body organ of origin, before it has time to spread to other parts of the body. It is one of the parts of a wider strategy including diagnosis, treatment and follow-up.

There are a variety of techniques to assist physicians in obtaining an accurate tissue diagnosis. Selecting the most appropriate test usually requires consultation with a pulmonologist, interventional radiologist, or thoracic surgeon. In patients with apparent early non–small cell carcinomas, who are surgical candidates, thoracotomy is the recommended test for tissue diagnosis and staging. Noninvasive radiographic imaging with chest CT and positron emission tomography (PET) scans is routinely performed in patients with suspected metastatic lung cancer. Transthoracic needle aspiration has been shown to be more sensitive than bronchoscopy in patients with peripheral lung tumors[10]. In a study shows, out of 127 cases selected for the study, 59.8% were males while the rest were females. Cough was the most common symptom present in 71.2% cases, followed by weight loss (62.4%). 21.2% cases were cytologically benign. Adenocarcinoma (54.2%) was the commonest malignant tumor. FNAC provided at least 96% sensitivity and 100% specificity in diagnosing lung tumors. Among the benign lesions, specific diagnoses were obtained in 48.1% cases[11].

Method:

This is observational study was conducted amongst patients having clinically suspicious and radiologically diagnosed peripheral pulmonary mass lesions that can be approachable through transthoracic FNAC with sputum samples negative for acid fast bacilli on three consecutive days were included in the study. Severe infection, terminally ill patients like respiratory disease, patients with pulmonary hypertension, preexisting haematological and coagulation disorder were excluded from this study. Patient were informed about the objectives of the study, risk and benefits, freedom for participating in the study and confidentiality. Informed consent was obtained accordingly. The pre-structured Case Record Form (CRF) filled up by the study physician. The case definition of operational variable had been described. Patient data such as age, sex, clinical presentation, investigation findings etc. were noted. Premedication with midazolam given prior to procedure. Before performing FNAC, a detailed history was taken and clinical examination was done. FNAC was performed in the presence of a pathologist, radiologist and clinician after explaining the risks and benefits to the patients. An axial scan of area of interest was carried out to accurately localize the lesion and to judge the best patient positioning, i.e., supine or prone was judged depending on the shortest distance from the lesion to the visceral surface of lungs, except the presence of overlying skeletal structures or large pulmonary vessels. FNAC was performed in the pulmonary lesions using a 22-gauge disposable lumbar puncture needle with needle length 90 mm, which was introduced during the suspended respiration directing the tip of needle towards the lesion. The aspirate was obtained by to

and fro and rotating movements of the needle within the lesions by the pathologist using aspiration with a 10 ml syringe. The aspirate was smeared on 5-6 slides and half of the slides were fixed. The patients were kept in the radiology department for follow-up for a period of 2 hours after fine needle aspiration to keep track of any complication and a chest X-ray was carried out after 24 h to rule out any subsequent development of pneumothorax. If there was no complication after 24 h of observation the patient was safely discharged from the hospital. All information and findings recorded in data collection sheet. Collected all questionnaire checked very carefully to identify the error in collecting data. Data processing work were consisting of registration of schedules, editing, coding and computerization, preparation of dummy tables, analysis and matching data. The technical mater of editing, encoding and computerization looked by researcher.

Result:

Table-I: Age distribution of the study population (n=50)

Age (years)	Frequency	Percentage (%)	Mean ± SD
<30	4	8.0	53.72 ± 9.78
31-45	13	26.0	
46-60	24	48.0	
>60	9	18.0	
Total	50	100%	

In this study, the maximum numbers of patients (48%) were between 46-60 years age groups, next (26%) were between the age group of 31-45 years. Mean age of the patient were 53.72 ± 9.78 years. (Table-I)

Table-II: Clinical manifestation of the pulmonary lesion

Clinical manifestation	Number of patients	Percentage (%)
Dyspnoea	50	100.0
Cough	45	90.0
Weight loss	39	78.0
Chest pain	37	74.0
Haemoptysis	32	64.0
Fever	32	64.0
Abdominal pain	16	32.0
Altered Conciousness	13	26.0
Anorexia	13	26.0
Vomiting	12	24.0

On evaluation of clinical manifestations, respiratory distress, cough, weight loss and chest pain was the commonest presentation (100%, 90%, 78% and 74% respectively) of the lung cancer patients, followed by haemoptysis (64%), fever (64%), anorexia (26%), and Abdominal pain (32%). (Table-II)

Table- III: Gender distribution of the study population (n=50)

Gender	Frequency	Percentage (%)	M:F ratio
Male	37	(74%)	2.84:1
Femal	13	(26%)	
Total	50	(100%)	

Out of 50 cases 37(74%) cases were male and 13(26%) were female. Male – female ratio was 2.84:1. (Table- III)

Table-IV: Clinical & radiological diagnosis of suspected pulmonary lesion (n=50)

Variable	Radiological diagnosis		p-value
	Male (n=37)	Female (n=13)	
Bronchial carcinoma	33(89.1)	12(92.3)	0.747
Non-specific inflammation	4(10.8)	1(7.6)	
Total	37	13	

All patients' radiological evaluation was performed. Among the clinically suspicious lung lesion, 45(90%) were diagnosed as bronchial carcinoma and remaining (10%) patients were non-specific inflammation. Among bronchial carcinoma (89.1%) cases of male patients and (92.3%) of female patients result were significant. Categorization was done on the basis of CXR finding. The p-value is 0.747. This result is not significant at $p < .05$. (Table-IV)

Table-V: CT-guided FNAC findings of pulmonary lesion (n=50)

Findings	CT Guided FNAC result		Total
	Male (n=37)	Female (n=13)	
Non-small cell carcinoma			
Squamous cell carcinoma	19(51.3%)	3(23.0%)	22
Adenocarcinoma	8(21.6%)	7(53.8%)	15
Small cell carcinoma	7(18.9%)	2(15.3%)	9
Metastatic hepatocellular carcinoma	1(2.7%)	0	1
Non-specific inflammation	2(5.4%)	1(7.6%)	3

CT guided aspiration cytology shows that non-small cell carcinoma was predominant lung cancer, present in total 37(74.0%) of patients. Result shows that male patients were had higher frequency of squamous cell carcinoma (51% versus 23%) and in female adenocarcinoma observed most common lung cancer, present in (54%) of patients. (Table-V)

Table VI: Frequency & pattern of lung lesion according to cytological examination (n=50)

Pattern of Lesion	Frequency	Total
Benign	3(6%)	50(100%)
Malignant	47(94%)	

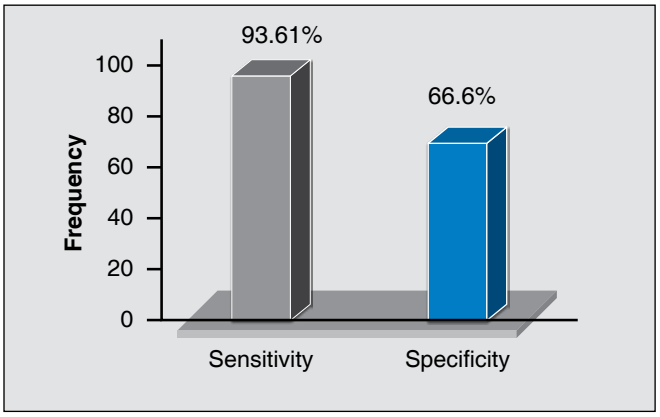
Overall cytological finding demonstrated that, total 94.0% of patients detected malignant lesion and 6% was benign lesion. (Table-VI)

Table-VII: Correlation of CT guided FNAC result with clinical & radiological finding (n=50)

Clinical and radiological finding	CT Guided FNAC result		p-value
	Malignancy	Benign lesion	
Malignant lesion (n=45)	44(97.7%)	1(2.2%)	0.00074
non-specific inflammation (n=5)	3(60.0%)	2(40.0%)	
Total	47	3	

In this study correlation had done on cytological examination with clinical and radiological finding. Cytological examination was more precise, correlates with the suspected malignant lung cancer. Maximum malignant cases 44(97.7%) had proven in cytological examination as like. On the other hand 3(60.0%) of non-specific inflammation also correlates with cytological examination. The p-value is .00074. This result is significant at $p < .05$. (Table-VII)

Table-VIII: Validity of CT guided FNAC in Differentiating Malignant and non-malignant Lung Lesion (n=50)



In diagnosis of bronchial carcinoma present study showed that sensitivity of CT guided FNAC was higher than specificity. Sensitivity of CT guided FNAC in diagnosis of bronchial carcinoma was 93.61%. Specificity of CT guided FNAC in diagnosis of bronchial carcinoma was 66.6%. (Table-VIII)

Discussion:

In this study, the maximum numbers of patients (48%) were between 46-60 years age groups, mean age of the patient were 53.72 ± 9.78 years. Male – female ratio was 2.84:1. Study also showed that large numbers of respondents came from urban area (58%), followed by rural area (30%) and sub-urban/slum area (12%).

All these result accordance with report of other study. Bangladesh hospital cancer registry showed that most of the cancer patient's age group is between 30-65 years, which is around 66%. These people are the main workforce structure of a country. It has gigantic economic impact. It has direct and indirect cost, which needed to be measure urgently. As an example we may look for the WHO study that revealed the annual cost of tobacco-related illnesses in Bangladesh as attributable to tobacco usage is estimated to be 45 billion taka considering that only a quarter of the patients with tobacco-related illnesses receive hospital care[1]. In a prospective study, the age of the patients ranged from 14 to 78 years with the mean age of 51.6 years, but the mean age in case of malignant lesions was 62.5 years[9].

Another report in Bangladesh tertiary level hospital showed, carcinoma of lung was the commonest cancer among the patients & who attended NICRH. A total of 3,209 lung cancer patients attended during these three years, of them 86% (2,763) were males. The number of lung cancer patients was increasing year by year; there were 902 lung cancer patients in 2005, 1,076 in 2006 and 1,231 in 2007. About 29% (934) of them belonged to 55-64 year age group and around 23% (744) belonged to both 45-54 and 65-74 years age groups. About 52% (1,678) had a history of smoking and almost all of them were male[2].

Present study showed that respiratory distress, cough, weight loss and chest pain was the commonest presentation (100%, 90%, 78% and 74% respectively) of the lung cancer patients. Radiological evidence suggested that most of the lesion were solitary mass lesion (64.0%). Collapse/consolidation was (28.0%) present. Among the clinically suspicious lung cancer, 45(90%) were diagnosed as bronchial carcinoma and remaining (10%) patients were non-specific inflammation. Among bronchial carcinoma (89.1%) cases of male patient and (92.3%) of female patient result was significant.

Findings consistent with result of other studies. In a prospective study showed cough was the most common respiratory symptoms (100%) followed by weight loss (91.9%) and fever (62.2%). Cytological diagnoses showed, benign (32.4%), suspicious of malignancy (8.1%), and malignancy (51.4%). Regarding the malignant categories, non-small cell carcinoma, not otherwise specified (NOS) (13.5%; 10 cases) was the most common malignancy followed by adenocarcinoma (10.8%; 8 cases), small cell carcinoma (8.1%; 6 cases) and squamous cell carcinoma (6.7%, 5 cases) respectively[9].

Transthoracic FNAC has been recognized since the 1970's as a critically important diagnostic technique and is particularly valuable in the diagnosis of space-occupying lesions located in the periphery of the lung and in the mediastinum that are inaccessible to the bronchoscope and do not desquamate cells into the bronchial tree. CT or, less commonly, ultrasound is used to guide the direction and depth of insertion of the needle. The technique is used with increasing frequency to investigate pulmonary infiltrates as well as more discrete masses in the lung. It is also considered the tool of choice for the morphological characterization of patients suspected of having small peripheral lung cancers (<2 cm)[12]. In this study CT guided aspiration cytology showed that non-small cell carcinoma was predominant lung cancer, present in total 37(74.0%) of patients. Result shows that male patients had higher frequency of squamous cell carcinoma (51% versus 23%) and in female adenocarcinoma observed as most common lung cancer, present in (54%) of patients.

Gangopadhyay et al[13] observed 96% sensitivity and 100% specificity in diagnosing lung tumors by CT-guided FNAC.

Adenocarcinoma (54.2%) was the most common malignant tumor in their study group. In our study, most common malignant tumor was non-small cell carcinoma. This difference is probably due to the smaller size of the sample. Mukherjee et al[13] carried out their study on solitary pulmonary nodules and found most of the patients of malignant lesions (76%) were in the age group of 40-70 years and most were males (85%). They noticed 97.7% sensitivity and 100% specificity for CT-guided FNAC as a diagnostic procedure. These findings are comparable with our study.

In this study correlation had done on cytological examination with clinical and radiological finding. Cytological examination was more precise, correlates with the suspected malignant lung cancer. Maximum malignant cases 44(97.7%) has proven in cytological examination as like. On the other hand 3(60.0%) of non-specific inflammation also correlates with cytological examination. The p-value is .00074. This result is significant at $p < .05$. In diagnosis of bronchial carcinoma present study shows that sensitivity of CT guided FNAC is higher than specificity. Sensitivity of CT guided FNAC in diagnosis of bronchial carcinoma is 93.61%. Specificity of CT guided FNAC in diagnosis of bronchial carcinoma is 66.6%.

Previous study reported that, more than 13,000 pulmonary fine needle aspiration (FNA) specimens showes the diagnostic sensitivity was 89% for the procedure itself and 99% for the pathologist's interpretation[14]. FNAC is of greatest benefit to patients for whom it spares a more invasive surgical procedure. Surgical intervention, in fact, can be avoided in up to 50% of patients with clinically suspected lung cancer[15]. With regard to the management of patients with primary lung cancer, the most important consideration is to discriminate between small cell and non-small cell carcinoma of the lung, which is possible in more than 95% of cases diagnosed by FNAC[16].

Conclusions:

The Lung cancer remains one of the health problems in Bangladesh and worldwide. Although we have many methods for the diagnosis of cancer, CT guided FNAC is minimally invasive and reliable procedure with good diagnostic accuracy. Cigarette smoking is the principal risk factor; passive exposure to tobacco smoke also can cause lung cancer. The main primary types are small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC). The most common symptoms are cough, haemoptysis, weight loss, shortness of breath, and chest pains etc. Though the clinical symptoms and radiological findings are not specific, CT-guided FNAC is valuable in confirmation of diagnosis of lung cancer. Present study demonstrated that cytological examination implies more precise, accurate with the suspected lesion. Sensitivity & specificity of CT guided FNAC is higher in differentiation of malignant lesion from other lung lesion.

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Original Article

Laparoscopic Appendectomy in Perforated Appendicitis in Children: is it Safe?

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ABSTRACT:

Background: *Laparoscopic appendectomy for uncomplicated appendicitis is associated with good outcomes but the role of laparoscopy in perforated appendicitis is more controversial because of high incidence of infectious complications. The aim of this current study is to evaluate the efficacy and safety of laparoscopic appendectomy in perforated appendicitis in children.*

Method: *From January 2013 to May 2018, 85 patients aged 3 to 15 years old underwent laparoscopic appendectomy for perforated acute appendicitis. The following variables were analyzed : age, sex, operative findings, operative time, return of bowel function, resumption of oral feeds, length of hospital stay, postoperative complications ,ileus, wound infection and intraabdominal abscess etc).*

Results: *The mean age of studied cases was 7.1 years. In 82 patients (96.4%) the procedure was completed laparoscopically. 3 (3.6%) patients required conversion to open appendectomy. The operative time was 83.5±25.8 minutes. Four patients (4.6%) had post-operative ileus. Seven patients (8.5%) developed superficial wound infection.Five patients (6%) developed intra-abdominal collections. Two (2.4%) patients were readmitted because of recurrent abdominal pain Two patients(2.4%) developed postoperative pyrexia due to pneumonitis and Three patients (3.6%) developed gastroenteritis. The mean length of hospital stay was 5.8±2.1 days. No mortality was recorded.*

Conclusion: *Laparoscopic appendectomy can be the first choice for cases of perforated appendicitis in children. It is a feasible, safe procedure and is associated with acceptable post-operative morbidity with rapid recovery and better cosmetic results.*

Keywords: *Children, Perforated appendicitis, Laparoscopic appendectomy*

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Introduction:

Childhood acute appendicitis is one of the most common conditions that pediatric general surgeons treat. About one third of appendicitis cases in children younger than 18 involve a perforated or ruptured appendix. That causes fluid to spill into the peritoneal cavity, increasing risk for infection and other complications. With a perforated appendix, the perforation isn't the problem. It's all the spillage that has spread around the peritoneal cavity. It is generally accepted that younger ages are more susceptible to complications[1]. The high frequency of complications (perforation, gangrene, abscess formation, pelvic abscess formation) is essentially due to recurrent delayed diagnosis in young children because of their inability to communicate and the high rate of benign pediatric digestive disorders[2].For a long time, open appendectomy (OA) was the conventional procedure for appendicitis but laparoscopic appendectomy (LA) has gained popularity among pediatric surgeons since its introduction in 1992[3]. Many published series have reported that LA is superior to OA in uncomplicated appendicitis,especially in terms of reduced postoperative pain, short hospital stay, rapid return to physical activity, better cosmetic results, and lesser incidence of wound complications[4–9].Several studies in the past have assessed the role of laparoscopy in complicated appendicitis but the results are controversial. Moreover, compared with OA, LA needs higher technical skills, longer operative time,and is associated with a higher incidence of intra-abdominal collections[10–13]. More recent studies have reported the safety and feasibility of this procedure in perforated appendicitis, with low incidence of infectious

complications[14-16].The aim of current study was to evaluate the efficacy and the safety of LA regarding postoperative morbidity in children age ranges from 3 to 15 years with complicated appendicitis.

Methods:

This study was carried out during the period from January 2013 to May 2018 in single medical institutions. (Holy Family red crescent Medical College Hospital)The study included 85 patients age ranges from 3 years to 15 years who were admitted to the paediatric surgery department and underwent LA for perforated acute appendicitis. Surgical consent was taken from all parents of patients before undergoingLA.Perforated appendicitis in this study was defined as acute appendicitis in which perforation and or gangrene formation with purulence or fecalith in the abdominal cavity or an intra-abdominal or pelvic abscess was needed. We identified the complicated cases on the basis of clinical and operative findings. Patients with noncomplicated appendicitis and appendiceal masses confirmed on imaging or peroperative findings were excluded from the study.All patients received preoperative intravenous antibiotics (cephalosporin,Metronidazole and amikacin). All cases made LA under general anesthesia, with endotraceal intubation. A Foley catheter and a nasogastric tube were used but not routinely in all childrens.LA was performed using a two-handed, three-trocar technique. The 10 mm umbilical port was introduced using the open technique. The CO2 insufflation was initiated at a pressure of 8–10 mmHg. Two 5-mm trocars were then placed in the lower-left quadrant and suprapubically under direct vision. The appendix was dissected and the mesoappendix cauterized using a bipolarpolar diathermy attached to either a hook or grasping forceps. The appendicular base was ligated using a pretied handmade Vicryl 2/0 suture in an extracorporeal or clipped by haemolock. The appendix was divided above the knot and extracted immediately through the port in the left quadrant. Interloop adhesions were released and the pus cavity was drained when encountered. Suction/irrigation was carried out using sufficient saline solution till the aspirate became clear.Closed tube drain was not routinely used and was placed only when deemed necessary. All appendix specimens were sent for histopathological examinations.After surgery, intravenous antibiotics (cefotaxime 100 mg/kg/24 h and metronidazole 30 mg/kg/24 h,amikacin 15 mg/kg/24 h) were given. Analgesia was achieved with intravenous/ rectal paracetamol for the first and second postoperative days. Oral intake was started as soon as patients could tolerate it and when the bowel function was restored .Patients were discharged after remaining afebrile for 24 hours after they could tolerated normal diet and exhibited a decrease in the white blood cell count to the normal level.The patients were followed up in the outpatient clinic at 1 week, 2 weeks, and at 1 month intervals for 3 months.Postoperative complications were recorded during hospitalization and the follow-up period. Post-operative ileus was defined as a delay in return of bowel function of more than 48 h. Surgical site infection, erythema, or localized wound collection were treated by antibiotics or surgical drainage. Intra-abdominal collections following appendectomy were diagnosed by using abdominal ultrasound. Patients with collections less than 3 cm were managed conservatively with intravenous antibiotics.The data were collected, organized, and tabulated,with particular reference to patients demographics,operative findings, operative time, return of bowel function, resumption of oral feeds, length of hospital stay, and postoperative complications such as ileus, wound infection, and intra-abdominal abscess etc.

Results:

During the period from May 2013 to May 2018, 85 patients with complicated acute appendicitis under went LA. Fourty five (52.9%) patients were boys and 40 patients(47.1%) were girls. Their ages ranged from 3 to 15 years(mean: 7.1 years).In 82 (96.4%) patients the procedure was completed laparoscopically; however, in three (3.6%) patients,conversion was mandatory because appendices were extremely friable upto its base and obscured anatomy. The operative time was 83.5±25.8 min. The children were able to resume oral intake within 2.1±0.5 days. Four (4.8%) patients experienced postoperative ileus.Seven (8.3%) patient developed superficial wound infection in port site incision,which was treated conservatively with dressing and antibiotics. Five (6%) patients developed intra-abdominal collections and were treated successfully with intravenous antibiotics only (third-generation cephalosporin).Two (2.4%) patients were readmitted because of recurrent abdominal pain.No relevant cause was detected and they were discharged and followed up in the outpatient clinic. Two patients(2.4%) developed postoperative pyrexia due to pneumonitis and Three patients (3.6%) developed gastroenteritis.All are treated conservatively with antibiotics and supportive therapy.In two(2.4%)patients urinary bladder wall was injured with leakage of urine from bladder during peroperative trocer incertion which were treated conservatively with catheterization of patients for upto seven postoperative day. All were doing well with no more symptoms.The mean length of hospital stay was 5.8±2.1 days. No mortality was recorded

Discussion:

The first report of LA in children goes back to 1991,when Ure et al[3] presented a small prospective series of 82 patients, concluding that it was a safe procedure. Then many reports published worldwide.Some studies suggested a lack of good evidence supporting laparoscopic approach for complicated appendicitis[10–13]. However,Many others concluded that LA for complicated appendicitis is better than is open OA[14–17]. They reported, in complicated appendicitis, especially in children, LA can benefit a patient compared with OA because it minimizes the tissues trauma, allows better visualization of abdominal spaces and meticulous peritoneal irrigation,avoids large wound incision and extension, improved cosmesis, shorter hospital stay, decreased rate of misdiagnosis,better pain control, earlier return to normal activities and is associated with less exposure of wound surface area to contaminated fluid[17]. Taking in consideration the above-mentioned debate, the aim of our study was to evaluate the efficacy and safety of LA in children with perforated appendicitis in our institutions.In their study, Wang et al[14] reported that the operative time in LA is significantly longer than that in OA. This longer duration is due to the fact that the manipulation of inflamed tissues with laparoscopic instruments is more difficult, making the dissection slower, to avoid the risk of visceral injury and operative time can be reduced with the increase of surgeon's experience [14].

The mean operative time in our study was 83.5±25.8 min. Other studies have reported a longer or shorter operative time[17–19]. This difference could be attributed to the difference in the level of laparoscopist's skills.In this study, the conversion rate was 3.6%, which nearly matches that reported in other studies . On the other hand, Vahdad et al[21] observed a higher conversion rate (24%), whereas Wang et al[14] reported no conversion in their study. We believe that the surgeon's experience plays an important role in determining the rate of conversion.

Forty five (52.9%) patients were boys and forty patients (47.1%) were girls. This male preponderance was also noted by other authors [6, 8, 9, 12, 15] . The high incidence in male is probably because males are more exposed to environmental and dietary changes than females. Our patients were able to start oral intake within2.1±0.5 days, and stayed in hospital for 5.8±2.1 days. These results are in agreement with the results of Wang et al[14] in their study the duration of restarting oral intake was 1.8±0.6 days and the length of hospital stay was 6.5±2.2 days.Several studies have shown that younger-aged children with appendicitis usually have higher rates of perforation and greater risk for developing complications because of delayed diagnosis[22]. This could be explained by the fact that many nonsurgical conditions such as constipation, gastroenteritis, and mesenteric adenitis may mimic appendicitis, as well as the lack of verbal communication skills [11].

Many studies found that LA markedly reduced the postoperative wound infection rate when compared with OA (1.3 vs. 12.5%)[21]. The rate of wound infection in our study was 8.3%. This low rate of postoperative wound infection could be explained by fact that in LA the incisions are small and limited to the trocar entry sites and the perforated appendix is extracted within a retrieval bag.

There is always a concern about the high risk for postoperative intra-abdominal collection in complicated appendicitis. In our study, the postoperative intra-abdominal collection was observed in three (6%) patients. Menezes et al[23] published a retrospective study of 118 children with complicated appendicitis:they stated that the incidence of intra-abdominal collection in LA was lower than that in OA (5.5 and 7.8%, respectively). Similarly, Kwok et al.[24] found a similar incidence (5.7 vs. 4.3%). This may be due to the fact that laparoscopy gives the surgeon the privilege to explore the whole intra-abdominal recesses and to irrigate with normal saline and aspirate any visible collection. The mortality rate was found to be zero percent in the present series, it has been stated that the risk of death from complicated appendicitis should be the risk of death from general anaesthesia. However, the mortality rate appears higher in newborn or premature infants who develop perforated appendicitis. Also, factors contributing to the death of children may include delay in diagnosis, inadequate fluid replacement, immunotheraphy and postoperative infection or vascular complications[17].

Conclusion:

The benefits of treating perforated acute appendicitis with LA include wide inspection of the peritoneal cavity, debridement, irrigation, and lavage under direct visualization, avoidance of large abdominal incisions, acceptable postoperative other morbidity, rapid recovery, shorter hospital stay better pain control, better cosmetic results, lower pulmonary and wound complications and ultimately earlier return to normal activities. Another benefit of LA is that diagnostic laparoscopy can be performed before the actual open appendectomy in doubtful cases and thus decreases rate of misdiagnosis.

Our study demonstrated that using LA to treat perforated acute appendicitis was not associated with additional surgical complications when compared with those who had open appendectomy for complicated acute appendicitis. Therefore, it seems feasible to use LA as the first-choice treatment for both uncomplicated and perforated acute appendicitis.

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Original Article

Early Outcome of Bortezomib,a Novel Therapy in Newly Diagnosed Cases of Multiple Myeloma in Tertiary Care Hospitals

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ABSTRACT

Background: *Multiple Myeloma is a the second most common haematological malignancy,with an estimated annual incidence of approximately 75,000 cases worldwide.1 This B-cell malignancy characterized by accumulation of terminally differentiated clonal plasma cells in the bone marrow, the production of a monoclonalimmunoglobulin detectable in the serum and/or urine and the presence of lytic bone lesions.Bortezomib, first in class proteasome inhibitor,induces apoptosis and growth arrest and reverse chemoresistence in Myeloma cell and has demonstrated no irreversible adverse effect on Haemopoietic stem cell.Thusbortizomib is a highly effective regimen for previously untreated Multiple myeloma cases and may represent the basis of future strands of care in multiple myeloma patients.The study will reflect theefficacy,safety and response of Bortezomib in newly diagnosed cases of Multiple Myeloma patient in two tertiary care hospitals.*

Method: *This descriptive cross-sectional study was conducted in Haematology department of two tertiary care hospitals of Dhaka city. A self administered questionnaire containing different set of questions regarding multiple myeloma were used for data collection.*

Result: *A total 25 adult multiple myeloma patients were included for the study. They were in age group from 42- 75 years. Among the 25 patients 60% were male and 40% were female; most of the patient businessman (40%), followed by housewife and service holder. Among the study population, 96% of patient had anaemia followed by bone pain (88%) and renal impairment (36%). At diagnosis, mean of S. creatinine, S. albumin, S. calcium and β2 microglobulin were 2.05,29.12, 9.95& 4.75 respectively. But at 12 week mean were 1.25, 35..36, 9.02 & 2.7 respeqtively. Mean ESR before chemotherapy was 90.76, where after treatment at 6 weeks and 12 weeks were 34 and 18.30 respectively. Before treatment mean Hb concentration was only 8.36 which was increase to 10.87 and 11.85 at 6 and 12 week. 19 patient (76%) had serum monoclonal protein. It is reduced to 48% at 6 week and 12% at 12 week of treatment. Only one patient (4%) had urinary Bence Jones protein which remained positive at 6 week but disappeared at 12 week of treatment. We found only 4 cases (16%) had bony lesion in skull and chest. Lytic lesion with fracture in spine was found in 1 cases (4%). During treatment 6 patient (24%) suffered from somnolence and 5 patient (20%) had Peripheral neuropathy. Three (12%) patient complained of constipation and we found 4% of suffered from hyperglyecaemia, rash, cardiac arrest electrolyte imbalance. Life threatening intracranial haemorrhage occurred in two patient (8%).Complete response achieved only 13 patient (52%) where 20% and 16% of patient belonged to partial and no respone respectively. Death occurred in 3 cases (12%). In this study,S. creatinine, β2 microglobulin and bony lesion variables showed significant association with treatment response.*

Conclusion: *Bortizomib is a highly effective regimen for previously untreated multiple myeloma patients due to its novel mechanism of action.It can be administered safely and effectively in the outpatient setting provided clinicians use in an appropriate stage in individual's management,have an understanding of its different mechanism of action and can manage toxicities appropriately.*

Key words: *Multiple myeloma, Bortezomib,Proteasome inhibitor.*

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Introduction:

Multiple Myeloma is a B-cell malignancy characterized by accumulation of terminally differentiated clonal plasma cells in the bone marrow, the production of a monoclonalimmunoglobulin detectable in the serum and/or urine and the presence of lytic bone lesions. The clinical manifestation of Myeloma are heterogeneous and include bone complications, symptoms of impaired haemopoiesis and hyperviscosity, renal dysfunction, infection, peripheral neuropathy and extra medullary disease. Myeloma constituting 1 % of all cancer but it is the second most common blood cancer after Lymphoma and account for 15 % of Haematological malignancies. The incidence of Multiple Myeloma has been reported to be increasing, but it probably reflects increasing diagnostic accuracy[1]. The median age at diagnosis is 65-75 yrs. Myeloma seems to be more common in men that women. The etiology of the disease is unknown but it is more common in certain racial groups such as those of Afro-Caribbean origin[2].

The Myeloma cell is a post germinal centre plasma cell that has undergone immunoglobulin class switching and somatic hypermutation and secretes the paraprotein i.e. present in serum[3]. M protein (M component, Myeloma protein or M spike) is a hallmark of disease.97% of Myeloma patient have an intact Immunoglobulin or a free light chain that can be detected by protein electrophoresis[4].

Diagnostic workup may reveal a normochromic normocytic or macrocytic anaemia, marked rouleaux formation, neutropenia and thrombocytopenia in advanced disease, high ESR and CRP, monoclonal protein in serum or urine or both, increased abnormal plasma cell > 20% in the bone marrow, bone lesion, hypercalcemia, hyperuricemia, low serum albumin, renal impairment, etc.Serum B2 microglobulin is often raised and is a useful indicator of prognosis.Sensitivity to drugs and clinical course vary widely among patients[5].

At the current time, the disease remains incurable except for those very few, mostly younger patient who may be cured by allogenic stem cell transplantation. Rest of the modalities of treatment is various combination of chemotherapy, among them MP(Melphalan and Prednisolone) was probably the first line treatment for many years. But it induces partial remission in 50 % patient, while CR is very rare.VAD (Vincristine, Adrimycine, Dexamethasone) has significant CR rate but its toxicities are sometimes intolerable. The response rate of VMCP (Vincristine, Melphalan, Cyclophosphamide, Prednisone) is not so much optimistic and above all resistance rate is high[2].

Another induction regimen, Thal-Dex had a higher response rate than VAD(76 % vs 50% respectively). Thal-Dex may be considered an effective and relatively well tolerated oral alternative to the more complex VAD regimen as front line therapy for Multiple Myeloma patient[8]. Randomized Phase-3 study [Eastern Cooperative Oncology Group(ECOG) 100] .In newly diagnosed patients with Myeloma reported that the combination of thalidomide 200mg/d and high dose dexamethasone achieved an overall response rate of 63% and 5% CR. Although an oral regimen may be more convenient, the ultimate choice of first line therapy will be balanced by efficacy, convenience, patient reference and clinical-trial result[6].

Another regimen Bortezomib, first in class proteasome inhibitor,induces apoptosis and growth arrest and reversechemo-resistance in Myeloma cell and hasdemonstrated no irreversible adverse effect on Haemopoietic stem cell.Importantly(the CR + nCR rate + PR) 88% with Bortezomib alone with undetectable paraprotein is 6% and detectable by immunofixation only in 19% nCR7. Another study showed 32 patients received single agent bortezomib for the 1st 2 cycles-13 patients(40%) responded with one CR,three(9%)nCR and nine(20%) PR.Twenty eight(88%) of the thirty two patient had confirmed response(CR+PR) to therapy with CR in two(6%),nCR in six(19%) and PR in twenty patients(63%).The adverse event profile for Bortezomib and Dexamethasone reported in one study were constipation(28%),myalgia (28%),sensor neuropathy (31%), fatique(25%), neutropenia(13%)[6].

Although, Bortezomib therapy is costly regimen for our general population but it is used as induction agent for its effectiveness and clinical trial results. It is usually given as a short intravenous infusion on days 1,4,8,11 of a 3 weekly cycle on an outpatient basis. The 72 hour gap between infusion is important to allow recovery of the proteasome inhibition in the normal cell. The ten day treatment free period allows cell recovery and prevents excessive side-effect. A total upto 4-6 cycle may be given depending on response and toxicities[7].

Unfortunately, in our country no such organized and structured clinical trial of response of Bortezomib in newly diagnosed cases of Multiple Myeloma have been carried out. The present clinical study will reflect the response of Bortezomib in newly diagnosed cases of Multiple Myeloma patient in Bangladesh.

Method:

A descriptive cross sectional study was conducted over the period of six months from January 2018 to June 2018 in Bangabandhu Sheikh Mujib Medical Universityand Dhaka Medical College Hospital.Actual sample size was 30 newly diagnosed case of multiple myeloma. Among them 5 patient discontinue treatment, so final sample size was 25. Diagnosis of all the patients based on S.protein electrophoresis, bone marrow examination with proper leishman staining and radiological findings. Fulfilling the criteria for entry into the study detailed clinical history, physical examinations & relevant investigations were recorded in data sheet. After taking written informed consent, these patients were enrolled in this study.

Inclusion criteria:

- Patient age 65-75 years/patients less than age 65 years who refused or were ineligible for high dose therapy
- Platelet count=100x 10^9/ L
- Absolute Neutrophil count = lxl0^9/L
- Corrected Serum Calcium = 14mg/dl
- Serum Hepatic Amino Tranferase level =2.5 x the upper limit of normal. Normal value- 7-56u/dl of serum
- Total Bilirubin =1.5 x upper limit of normal. Normal value-0.2-1.2mg/dl and Creatinine clearance = 30ml/min.
- Patient willingly given informed consent to take part in this study.

Exclusion criteria:

- Patient of attendant unwillingly to give informed consent to

take part in this study

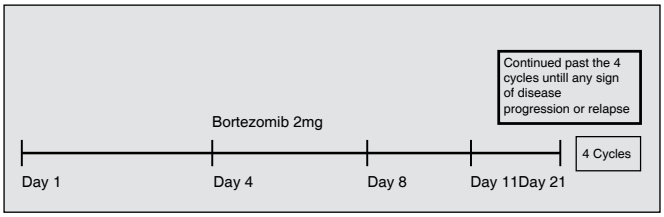
- Age >75 years of newly diagnosed case of Multiple Myeloma
- Relapsed or refractory Multiple Myeloma patient
- Confirmed Amyloidosis.
- HIV positivity
- History of other malignancy, uncontrolled Diabetes, Grade=2 Peripheral Neuropathy (National Cancer Institute)

Data were collected using a preformed data collection sheet (questionnaire) according to the above mentioned criteria.

Operational definitions:

Diagnosis of all the patients based on S.protein electrophoresis, bone marrow examination and radiological findings. After fulfilling the criteria for entry into this study Inj. Bortezomib (21 days x 4 cycles)

Figure 1. Bortezomib Treatment Regimen



Patients were treated with Bortezomib in indoor and same patients as day care basis in outpatients department. Anti-platelet drug (to prevent the risk of thromboembolism).antibiotic (for infection) and red cell concentrate transfusion (if hemoglobin less than 8gm/dl) were given as necessary. Most of the patients received variable number of zolendronic acid.

When to stop Bortezomib

- Hypersensitivity to bortezomib and discontinue therapy immediately.
- Cough and SOB
- Bloody Vomiting
- Bloody Diarrhoea
- Peripheral neuropathy

Follow-up time-

- Indicates, time between initiation of bortezomib and the date of last follow-up.

Follow-up Schedule-

- Every 21days interval for 6 months

Assessment of Response:

S.protein, electophoresis and bone marrow examination were done after 4 cycles of Bortezomib for final assessment of responses with the following criteria. In this study I use the European Group for Blood and Marrow Transplantation (EBMT) criteria or response to anti-myeloma was used.

Response to therapy- Indicate:

- ➔ Complete response (CR) or
- ➔ Partial response (PR) or
- ➔ Non- responder (NR)

Complete response was absence of M protein in serum or urine protein electrophoresis, the absence of plasmacytoma and <5% plasma cells in the bonemarrow.

Partial response was defined as >50%reduction o in bonemarrow plasma cells and absence of Mprotein in the serum and absence of urinary Bencejones protein.

No-response was defined as <50%reduction of plasma cells in the bonemarrow or presence of Mprotein in the serum or presence of urinary Bencejones protein.

Time to obtain response:

Indicates time between the initiation of Bortezomib and the date of completion of 4 cycle Bortezomib.

Statistical analysis:

Data were analyzed using the Package for the Social Science (version 19.0 for Windows; SPSS Inc, Chicago, IL)

A total 30 new diagnosed patient of Multiple Myeloma were taken for induction therapy with Bortezomib.Among them 5 patient discontinue treatment, so final sample size was 25. Base data were recorded before treatment and follow up were recorded at 6 and 12 week.

Discussion:

The mean age was 54.04 (SD±8.35) and median was 53 .Age ranged from 42-75 years. These findings are a little bit lower than study done by Rajkumar, blood, Vosle et al (2005), Lokhorst, Wolf and Sonneveld et al (2008), Dingli, Rajkumar, Nowakowski(2005). They found the median (range) age 65 (38-83), 57 (34-65) and 66 (36-78).[8,10,13,15-17] In the present study the number of male was 15 (60%) and female was 10 (40%) and male to female ratio was 1.5:1. Sex ratio of the patient vary widely, the male –female ratio in studies by Rajkumar, blood, Vosle et al (2005), Lokhorst, Wolf and Sonneveld et al (2008), Dingli, Rajkumar, Nowakowski(2005) are 1:1,2:1 and1:1 respectively[13,15,18-20].Most of the patient(40%) were business men by profession; other frequent occupation was house wife(28%), service holder (20%) and doctor, farmer & teacher were 1% each.

All of the patient (25) presented with weakness, followed by 88% patient had bone pain and 28% noticed weight loss. On examination, 96% of patient had anaemia, 40% had evidence of infection and renal impairment was found in 9 (36%) cases. Only 1(4%) patient suffered from neuropathy. Where Khan MA, Sarker S, Kabir A, Hasan M, Haque M D (2002) found 100% of patient had bone pain, 77% had anaemia, 41% had infection and 18% had renal impairment[21].

In this study population(25), mean ESR before chemotherapy was 90.76, where after treatment at 6 weeks and 12 weeks were 34 and 18.30 respectively. Before treatment mean Hb concentration was only 8.36 which was increase to 10.87 and 11.85 at 6 and 12 week. Where Khan MA, Sarker S, Kabir A, Hasan M, Haque M D (2002) showed 86.4% had high ESR (>85 mm in 1st hour) and 82% of patient had Hb<10gm/dl[22-25]. Among the study population, mean S. calcium before chemo-

therapy was 9.95 which gradually went down to 9.18 and 9.02 at 6 week & 12 week respectively. At diagnosis, mean of S. creatinine, S. albumin and β2 microglobulin were 2.05 mg/dl, 29.12 gm/l & 4.75 mg/dl, 9.95 mg/dl respectively. But at 12 week mean were 1.25 mg/dl, 35.36 gm/l & 2.7mg/dl, 9.02 mg/dl respectively. In our study only 2 patient (8%) had hypercalcaemia , where Khan MA, Sarker S, Kabir A, Hasan M, Haque M D (2002) found 18%[23-25.]

Bortezomib, a first-in-class proteasome inhibitor, induces apoptosis and growth arrest and reverses chemoresistance in myeloma cells and has demonstrated no irreversible adverse effect on haematopoietic stem cells[13]. During treatment 6 patient (24%) suffered from somnolence and 5(20%) had Peripheral neuropathy. Three (12%) patient complained of constipation and 4% suffered from hyperglyecaemia, rash, cardiac arrest electrolyte imbalance. Life threatening intracranial haemorrhage occurred in two patient (8%). Sundar Jagannath, Brian G. M. Durie, Jeffrey Wolf, Elber Camacho, David Irwin, Jose Lutzky, Marti McKinley et al. found the most common adverse events sensory neuropathy (31%), constipation (28%), myalgia (28%) and fatigue (25%)[23,25].

Out of 25 patient, 13 patient (52%) achieved complete response (20%), 5 patient achieved partial response and 4(16%) patient achieved no response.SundarJagannath, Brian G. M. Durie, Jeffrey Wolf, Elber Camacho, David Irwin, Jose Lutzky, Marti McKinley et al. study showed response rate (CR + PR) was 88%, with undetectable paraprotein (CR) in 6% and All 32 patients completed the first two cycles of bortezomib alone, of whom 3% achieved CR, 9% nCR, and 28% PR[23-25.] Three patient (12%) died during treatment, 2 patient due to intracranial haemorrhage and another from cardiac arrest.

In this study comparison of categorical variables was done by Chi-square test and P value <0.05 was considered significant. S. creatinine, β2 microglobulinand bony lesion variables showed significant association with treatment response, where other variables failed to show any significant association.

Conclusion:

Bortezomib, a novel therapy in multiplemyeloma represent a new treatment paradigm targeting both tumour and microenvironment, which has already markedly improved overall response, quality of response, Progression free survival and overall survivial across all risk groups, recognizing that poor prognosis patients remain a major challenge. The treatment of newly diagnosed multiple myeloma has dramatically changed since the emergence of proteasome inhibitors. Since the depth of response to treatment correlates with outcomes, both consolidation and maintenance therapies are now being employed to deepen the initial response and prevent relapse, respectively.

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Review Article

Male Infertility-A Global Overview & Bangladesh Perspective

Chowdhury SH[1]

Abstract:

Infertility in developing countries is an understudied concern in sexual and reproductive health, yet its impact can be staggering. An inability to conceive or bear children can result in being socially ostracized or divorced, and may have economic, mental or other health implications. Despite associations with serious negative health, social and economic outcomes, infertility in developing countries is a marginalized issue in sexual and reproductive health. Obtaining reliable, nationally representative prevalence estimates is critical to address the issue, but methodological and resource challenges have impeded this goal. Male infertility is a grave concern affecting couples including loss of status within the family and community. About 20% men could suffer worldwide from fertility problems and the rising level of male infertility has become a serious concern for public health. In developing countries, patterns of infertility are quite different from those in developed countries and the incidence of preventable infertility is much higher in developing country. Infertility as a socio medical problem can be considered in Bangladesh became male infertility adversely and negatively causes family unrest, multiple marriage, divorce and even sometimes suicide. Therefore, addressing the issue of male infertility appears to be one of the priority tasks of infertility programmers in the developing countries.

Key words: *Male infertility, Male factors, Global health, Worldwide*

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Introduction:

Male infertility refers to a male's inability to cause pregnancy in a fertile female. In human it accounts for 40–50% of infertility[1-3]. It affects approximately 7% of all men[4]. Male infertility is commonly due to deficiencies in the semen, and semen quality is used as a surrogate measure of male fecundity[5]. Inability to conceive after 1 year of unprotected sexual intercourse. 15% of couples. 40%: male; 40%: female; 20% both. At least 30 million men worldwide are infertile with the highest rates. A third challenge stems from the fact that male infertility has never been defined as a disease, which has resulted in sparse statistics6.

Leading factors to male infertility

Pre-testicular causes:

Pre-testicular factors refer to conditions that impede adequate support of the testes and include situations of poor hormonal support and poor general health including:

- **Hypogonadotropic hypogonadism due to various causes:** *Obesity increases the risk of hypogonadotropic hypogonadism[6]. Animal models indicate that obesity causes leptin insensitivity in the hypothalamus, leading to decreased Kiss1 expression, which, in turn, alters the release of gonadotropin-releasing hormone (GnRH)[7].*

- **Undiagnosed and untreated coeliac disease (CD).** Coeliac men may have reversible infertility. Nevertheless, CD can present with several non-gastrointestinal symptoms that can involve nearly any organ system, even in the absence of gastrointestinal symptoms. Thus, the diagnosis may be missed, leading to a risk of long-term complications8. In men, CD can reduce semen quality and cause immature secondary sex characteristics, hypogonadism and hyperprolactinaemia, which causes impotence and loss of libido[9]. The giving of gluten free diet and correction of deficient dietary elements can lead to a return of fertility[8,9]. It is likely that an effective evaluation for infertility would best include assessment for underlying celiac disease, both in men and women[10].

- Drugs, alcohol

- Strenuous riding (bicycle riding[11], horseback riding)

- Medications, including those that affect spermatogenesis such as chemotherapy, anabolic steroids, cimetidine, spironolactone; those that decrease FSH levels such as phenytoin; those that decrease sperm motility such as sulfasalazine and nitrofurantoin

- Genetic abnormalities such as a Robertsonian translocation

Testicular factors:

Testicular factors refer to conditions where the testes produce sperm of low quantity and/or poor quality despite adequate hormonal support and include:

Varicocele:

Varicocele, is a condition of swollen testicle veins. It is present in 15% of normal men and in about 40% of infertile men. It is present in up to 35% of cases of primary infertility and 69-81% of secondary infertility[12].

Others:

Immune infertility:

Antisperm antibodies (ASA) have been considered as infertility cause in around 10–30% of infertile couples[16]. ASA production are directed against surface antigens on sperm, which can interfere with sperm motility and transport through the female reproductive tract, inhibiting capacitation and acrosome reaction, impaired fertilization, influence on the implantation process, and impaired growth and development

of the embryo. Risk factors for the formation of antisperm antibodies in men include the breakdown of the blood testis barrier, trauma and surgery, orchitis, varicocele, infections, prostatitis, testicular cancer, failure of immunosuppression and unprotected receptive anal or oral sex with men[16,17].

Tobacco smoking:

There is increasing evidence that the harmful products of tobacco smoking may damage the testicles[18] and kill sperm[19,20], but their effect on male fertility is not clear[21]. Some governments require manufacturers to put warnings on packets. Smoking tobacco increases intake of cadmium, because the tobacco plant absorbs the metal. Cadmium, being chemically similar to zinc, may replace zinc in the DNA polymerase, which plays a critical role in sperm production. Zinc replaced by cadmium in DNA polymerase can be particularly damaging to the testes[22].

Updated WHO guidelines on semen analysis

In 2010, the WHO changed their guidelines for semen analysis for the diagnosis of the infertile male[23]. In doing so, they established reference values that were much lower than their previous ones, resulting in more men qualifying as "normal"[6]. Now, a man with reference values of greater than 15 million sperm, greater than 5% normal morphology, and 40% progressive motility would be considered normal[24]. With the new guidelines, more men would be considered fertile, while there may be an unnoticed rise in the number of infertile men. Therefore, a recent study involving our group advises caution when interpreting the new WHO reference values because they have not yet been accurately defined to discriminate fertile from infertile men[24].

Clinical Relevance of Oxidative Stress (OS) in Male Factor Infertility

Male factor has been considered a major contributory factor to infertility. Along with the conventional causes for male infertility such as varicocele, cryptorchidism, infections, obstructive lesions, cystic fibrosis, trauma, and tumors, a new, yet important cause has been identified: oxidative stress. Oxidative stress (OS) is a result of the imbalance between reactive oxygen species (ROS) and antioxidants in the body, which can lead to sperm damage, deformity and eventually male infertility.This involves peroxidative damage to sperm membrane and DNA fragmentation at both nuclear and mitochondrial levels. OS has been implicated as the major etiological factor leading to sperm DNA damage. OS-induced DNA damage can lead to abnormalities in the offspring including childhood cancer and achondroplasia. In this article, we discuss the need of ROS in normal sperm physiology, the mechanism of production of ROS and its pathophysiology in relation to male reproductive system[25].

Effects of OS:

All cellular components including lipids, proteins, nucleic acids, and sugars are potential targets of OS. The extent of OS-induced damage depends on the nature and amount of ROS involved and also on the duration of ROS exposure and extra-cellular factors such as temperature, oxygen tension and the composition of the surrounding environment (e.g. ions, proteins, and ROS scavengers)[26].

Oxidative Stress (OS) and conception:

Lipid peroxidation induced by H2O2 not only disrupts sperm motility but also impairs all the sperm functions, which are dependent on the integrity of plasma membrane, including sperm-oocyte fusion and ability to undergo acrosomal exocytosis[27]. Smoking, oxidative stress, and infertility Animal studies have indicated deleterious effects of cigarette smoke on sperm maturation and ability of sperm to establish a viable pregnancy[28]. Significant positive association has been reported between active smoking and sperm DNA fragmentation[29]. Assessment of ROS by chemiluminescence The most common method of measuring ROS is a chemiluminescence assay. Luminol (5-amino-2, 3, dihydro 1, 4, phthalazinedione) and lucigen probes can be used for quantification of redox activities of spermatozoa[30]. Luminol can measure both intracellular and extracellular ROS whereas lucigen can only measure the superoxide radical released extracellularly. ROS levels can be determined by a luminometer. The results are expressed as •106 counted photons per min (cpm) per 20•106 sperm. Normal ROS levels in washed sperm suspensions range from 0.10 to 1.0•106 cpm⁄20•106 sperm and 0.145•106 cpm per 20•106 sperm in unprocessed ejaculated samples[31]. Direct methods such as pulse radiolysis and electron-spin resonance spectroscopy are limited by problems of relatively low volume of seminal plasma, short life span of ROS, and the need to evaluate in fresh samples[8].

Management: Physical examination and laboratory test are the top requirement. Lastly the advent of ICSI (intracytoplasmic sperm injection) has revolutionized the management of couples suffering from severe male factor infertility. There has been a vast improvement in the management of infertility in the last 20 years. The rational use of different drugs, surgery and newer IVF techniques holds the promise of a solution for many infertile couples. But for clinicians, it is also a challenge to deploy these new techniques safely and effectively[32].

Aromatase inhibitors for obesity-related male infertility

Obesity is a risk factor for male infertility. Peripheral androgen aromatization is enhanced in men with elevated BMI. Obese men show increased plasma estradiol and low testosterone levels. Lowering estradiol levels, by administration of AI, increases LH and FSH levels by pituitary modulation, and increase testosterone levels. AI may stimulate sperm production; effects upon fertility are still to be determined.

Laboratory tests

- Urinalysis
- Semen analysis
- Semen collection: 48-72 hours of sexual abstinence.
- Seminal fructose and postejaculate urinalysis
- Fructose: derived from the seminal vesicle
- Hormone assessment
- FSH and testosterone

Adjunctive tests

- Semen leukocyte analysis;
- Antisperm antibody test;
- Hypoosmotic swelling test;
- Sperm penetration assay;
- Sperm chromatin structure;
- Chromosomal studies;
- Genetic analysis

Treatment of Male Infertility (Surgical treatments)

- Varicocele:
- Vasovasostomy or epididymovasostomy
- Ejaculatory duct obstruction: TURED
- Electroejaculation spinal cord injury; pelvic or retroperi toneal surgery injured the pelvic sympathetic nerves.
- Sperm aspiration: vas deferens, epididymis, or testicle.
- Orchidopexy: within two years of age
- Testicular torsion; the unaffected, contralateral testis can become infertile after torsion of its mate. Sympa thetic orchidopathia, immunologic in nature.
- Pituitary ablation
- Elevated serum prolactin levels stemming from a pituitary adenoma can be treated medically and surgically.

Treatment of Male Infertility (Nonsurgical treatments)

- Pyospermia: evaluate the patient for sexually transmitted diseases, penile discharge, prostatitis, or epididymitis
- Coital therapy
- Immunologic infertility
- Corticosteroid suppression, sperm washing, IUI, IVF, and ICSI.

Assisted reproductive technologies

- Intrauterine insemination (IUI): Cervical factors; low sperm quality, immunologic infertility, poor sperm delivery. At least 5-40 million motile sperm in the ejaculate.
- In Vitro Fertilization and Intracytoplasmic sperm injection
- IVF: controlled ovarian stimulation and ultrasound-guided transvaginal egg retrieval from the ovaries before normal ovulation. 500,000 to 5 million sperms are required
- ICSI: one viable sperm
- Eliminate many natural selection barriers that exist during natural fertilization, genetic defects that caused the infertility are expected to be passed on to offspring unabated.
- Preimplantation genetic diagnosis

Antioxidants and its implication

Studies have shown that antioxidants protect spermatozoa from ROS producing abnormal spermatozoa, scavenge ROS produced by leukocytes, prevent DNA fragmentation, improve semen quality in smokers, reduce cryodamage to spermatozoa, block premature sperm maturation and stimulate spermatozoa and improve ART outcome. Seminal plasma contains superoxide dismutase, catalase, and glutathione peroxidase/glutathione reductase in addition to non-enzymatic antioxidants such as ascorbate, urate, vitamin E, pyruvate, glutathione, albumin, vitamin A, ubiquitol, taurine, and hypotaurine[26].

Major antioxidants

Vitamin E

Vitamin E is a major chain-breaking antioxidant in the sperm membranes and appears to have a dose dependent effect[33]. It scavenges all the three types of free radicals, namely superoxide, H2O2, and hydroxyl radicals[34]. Administration of 100 mg of Vitamin E three times a day for 6 months in a group of asthenozoospermic patients with normal female partners showed a significant decrease in lipid peroxidation and increased motility and pregnancy rates[35].

Vitamin C

Vitamin C is important chain-breaking antioxidant. It neutralizes hydroxyl, superoxide, and hydrogen peroxide radicals and prevents sperm agglutination[34]. It prevents lipid peroxidation, recycles vitamin E and protects against DNA damage induced by H2O2 radical.

Administration of 200 mg of vitamin C orally along with vitamin E and glutathione for 2 months significantly reduced hydroxyguanine(8-OH-dG) levels in spermatozoa and also led to an increase in sperm count ($P < 0.05$)[36].

Coenzyme Q-10

Coenzyme Q-10 is a non-enzymatic antioxidant that is related to low density lipoproteins and protects against peroxidative damage[37]. It is an energy-promoting agent and enhances sperm motility[38]. It is present in the sperm mid-piece and recycles vitamin E and prevents its pro-oxidant activity[39]. Oral supplementation of 60 mg/day of coenzyme Q-10 was shown to improve fertilization rate using intracytoplasmic sperm injection (ICSI) in normospermic infertile males[38].

Role of antioxidants in preventing cryodamage

Sperm freezing and thawing procedures cause a significant and irreversible decrease in motility and metabolic activity of sperm along with disruption of plasma membrane[40]. Vitamin E (10 mmol/L) and Rebamipide (300 mmol/L) have been shown to decrease the cryodamage during freeze-thaw procedure and improves post thaw motility[41]. In vitro supplementation of 300 lmol/L of Rebamipide in semen sample during incubation (37_C) and cryopreservation 196_C, 3 days) showed significant decrease in ROS level[42].

Role of antioxidants in preventing DNA damage

Antioxidants have been demonstrated to decrease DNA fragmentation induced by OS. Daily oral supplementation of 1 g vitamins C & E for 2 months recommended.

Conclusion:

In the last decade, there has been a phenomenal growth in our knowledge of male reproduction, sperm function and development of diagnostic tools and treatment modalities. In addition, our understanding of OS has given rise to several new treatment modalities, which are now being investigated for improving male infertility.

Despite associations with serious negative health, social and economic outcomes, infertility in developing countries is a marginalized issue in sexual and reproductive health. Obtaining reliable, nationally representative prevalence estimates is critical to address the issue, but methodological and resource challenges have impeded this goal.

Future strategies:

Evaluation of OS status and use of antioxidants is not routine in clinical practice. The immediate need is to simplify and validate the evaluation of ROS and OS status so that it can be performed routinely without the use of sophisticated equipment.

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Case Report

Triple Malignancy, Sequential Development in One Patient in Different Times : A Case Report and Review of the Literature.

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ABSTRACT

During the long term follow-up of patients with breast cancer, the incidence of subsequent second primary malignancies increases with each passing year. The incidence of more than one second primary malignancy in these patients is very rare. We are presenting a case report where one of our patients developed metachronous malignancy with duct cell carcinoma of left breast, adenocarcinoma of ovary and adenocarcinoma of stomach.

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Introduction:

Cancer patients are at an increased risk for developing additional subsequent primary tumors. One recent study using Surveillance Epidemiology and End Results (SEER) data found that of the cancer patients alive as of January 1, 2001, nearly 8% were diagnosed with more than one primary malignant tumor between 1975 and 2001[1]. This statistics underscores the pervasive nature of multiple malignancies and raises important questions regarding aetiology, treatment decisions, demographics, and outcomes. The development of multiple malignancies in an individual has been reported after successful treatment of primary tumors[2]. In the follow-up of patients with successful treatment of kidney cancer, second malignancies have been reported. Most commonly involved sites with second primary malignancies include urothelial, lung, breast, ovary, colon, stomach and skin. We are presenting a case report in which one of our patients developed three malignancies metachronously, which involved left breast, ovary, and stomach with successful treatment she was in good control for last 22 years. The patient was died in December, 2017 at 5th post operative day.

Case Report:

A 70 years old Bangladeshi woman, normotensive, nondiabetic, nonsmoker and non betel nut user attended to us in 2016 with the complains of abdominal pain, loss of appetite and weight loss. After evaluation, she was diagnosed as a case of poorly differentiated adenocarcinoma of stomach by endoscopic biopsy without lymphadenopathy . She gave a history of duct cell carcinoma of left breast in 1996 without distal metastasis except axillary lymphnodes and adenocarcinoma of ovary in 2012 without distal metastasis or ascites. The patient was treated with modified radical mastectomy, 8 cycles chemotherapy (4cycles Adriamycin and cyclophosphamide followed by 4 cycles paclitaxel) and external beam radiotherapy of 45 Grays to left breast region including left axilla for breast cancer and was in follow up and remained in good control for 16years upto 2012. In 2012, she developed abdominal pain and by work up she was diagnosed as a case of ovarian cancer and was treated by surgery(total abdominal hysterectomy, bilateral oophorectomy and omentectomy) and 6 cycles chemotherapy with paclitaxel and carboplatin and was in follow up and remained in good control for 4 years upto 2016 . In 2017, she was diagnosed as a case of stomach cancer and was treated with neoadjuvent chemotherapy. She was given 3 cycles chemotherapy and felt better and improved her general condition. After 2 weeks, she again developed abdominal pain and she was underwent total gastrectomy on December 2017 but unfortunately she died on 5th post operative day.

Discussion:

Multiple primary malignant tumors are a well-known phenomenon. Breast cancer has been linked to numerous secondary malignancies. Reports have showed that other primary malignant tumors associated with breast cancer include cancer of the ovary[3,4] colorectal and renal cell carcinoma associated with urinary bladder and skin cancer.[5]

The aetiology of multiple primary malignant tumors is complex and includes environmental factors, genetic predisposition, previous medical treatment, gender-specific factors, hormonal factors, and interactions of these factors. Multiple malignancies most often involve two sites.

The occurrence of the third malignancy is exceedingly rare. In our patient, a common risk factor was genetic predisposition and chemotherapy agents. All cancers in the patient developed as metachronous lesions and were treated successfully. While several investigations have focused on assessing risk factors for developing subsequent primary malignancies,

long-term outcome data on patients with multiple malignancies are lacking. Multiple malignancies may have better overall prognosis as compared with their single malignancy counterparts.

It is well-known that cancer therapy may result in other primary cancers, but these usually appear after 10 years. As the standard treatment of breast cancer includes chemotherapy

or radiation, this is probably a major contributory cause to the increased risk of second primary

cancers. In our patient, the time gap for the occurrence of ovary cancer was 16 years and 21 years for stomach cancer from the onset of breast cancer. Both ovary and stomach were outside the treatment field of radiation for breast cancer.

Conclusion:

To conclude, we would recommend every patient of malignancy to be screened for second malignancy during follow-up.

Source of support: Nill

Conflict of interest: None

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Case Report

Intracranial Hemorrhage in Idiopathic Thrombocytopenic Purpura

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ABSTRACT

A rare and life threatening complication of idiopathic thrombocytopenic purpura is intracranial hemorrhage (ICH). It is rare among adults and is the leading cause of death. We report a 24 years old woman with ITP in whom spontaneous ICH developed. The eventual favorable outcome in this case despite severe initial neurological deficit makes this case unusual. It is essential to precede an early diagnosis, prompt and aggressive management in an ITP associated ICH.

Keywords: *Idiopathic thrombocytopenic purpura, intracranial hemorrhage.*

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Introduction:

Immune (idiopathic) thrombocytopenic purpura (ITP), an autoimmune disorder characterized by antibody mediated destruction of platelets, is generally a self-limiting benign disorder with a 60-80% chance of spontaneous recovery occurring usually within a few months after onset[1-4]. However, the risk of hemorrhagic manifestations, especially intracranial hemorrhage, prompts many physicians to consider some form of therapy. The risk of ICH is considered to dwindle after the first few days of presentation of the acute form and is exceptionally rare in chronic ITP[5-8]. Although relatively rare, intracranial hemorrhage (ICH) is the most serious complication of idiopathic thrombocytopenic purpura (ITP) and is the leading reported cause of death[9-11].

The occurrence of ICH in ITP, the location of the hemorrhage and the favorable neurological outcome in this patient makes this case unusual. Further, a plan of management is suggested based on our experiences and review of previous publications.

Case Report:

A 24 year old female presented with a 3 weeks history of bleeding gums, tarry stools, and easy bruising. No history of recent infections, myalgia, arthralgia, rash, fever, chills, photophobia or systemic lupus erythromatosus was obtained. She had not been taking any medications that could precipitate ITP. Five months prior to admission the patient delivered a normal male infant. There was no history of blood transfusion or thrombocytopenia at that time.

Examination revealed an acutely ill patient, who was afebrile with a blood pressure of 140/90 mmHg. There was diffuse purpura, ecchymosis and gum bleeding, but no rash. There were no retinal hemorrhages, splenomegaly or lymphadenopathy. Laboratory investigations revealed hemoglobin of 6.7 g/dl, white blood count of 14.5 x l09/l with a normal differential and a platelet count of 12.0 x 109/l, reticulocyte count was 4.2%. Peripheral blood film shows thrombocytopenia. The prothrombin time, partial thromboplastin time, thrombin time, fibrinogen, fibrin split products and chest x ray were all normal. The bone marrow aspirate and biopsy showed increased megakaryocytes consistent with peripheral platelet destruction, but no other abnormality. Platelet antibody levels were not performed because of the profound thrombocytopenia. The work up for the etiology of other thrombocytopenia including autoimmune and microbiological serology was completely negative and a diagnosis of acute ITP was made.

Considering the severity of the case and potential for fatal outcome, therapy was initiated with 4 units of platelet and 3 units of packed red cell transfusion over the first 48 hours. Thrombocytopenia and mucosal bleeding continued and treatment was started with intravenous hydrocortisone, 150 mg every 6 hours, intravenous gamma globulin, 30 g/day. The patient did not respond to this therapy, attaining a maximum platelet count of 16 x l09/l during the first 4 days of hospitalization. On hospital day 6, the patient developed a sudden onset of severe excruciating headache which is gradually increasing and associated with confusion and disorientation. Neurological examination revealed normal fundi, and there were no focal neurological deficits. New subconjunctival hemorrhages were present. The platelet count was 8 x l09/l. A clinical diagnosis of ICH was made. CT scan of the head showed bilateral basal ganglia hemorrhage. Treatment was started with intravenous dexamethasone 10mg every 6 hours and 20% mannitol 1 mg/kg to reduce cerebral edema and intracranial pressure.

The patient was transfused with 10 units of platelets, 3 units of packed red blood cells. Treatment continued with dexamethasone, 10mg every 6 hours, platelet transfusions and intravenous gamma globulin, 400 mg/kg/day. On hospital day 11, the patient developed a right sided focal seizure involving the head and arm which lasted about 5 minutes. An EEG showed a generalized dysrhythmia, delta grade II activity. A repeat CT scan showed no change. She was treated with phenytoin 300 mg/day intravenously and no further seizures occurred. At this point, the patient was semi-comatose and over the next week remained in this state. However, during this period her platelet counts began to rise. The dexamethasone and gamma globulin were slowly tapered over the next 2 weeks and eventually discontinued and no further bleeding episodes occurred. With improvement of her platelet counts, which rose to 85 x 109/l, the neurological status improved. four weeks later her platelet count reached 150 x 109/l and 8 weeks after admission 450 x 109/l. Follow-up has continued for one year and the platelet counts and neurological examination have remained normal without any bleeding episode.

Discussion:

Acute ITP is mainly a disease of childhood occurs in equal frequency in both sexes and chronic ITP occurs most commonly in adult typically under the age of 40 with female to male ratio 3:1 as observed worldwide[12]. A platelet count below 1,00,000/cmm is generally considered to constitute thrombocytopenia. However spontaneous bleeding does not become evident until platelet count falls to 20,000/cmm.[13]

The most serious and life threatening complication of ITP is ICH[9,14,15]. Fortunately ICH is rare in ITP and probably occurs in less than 1% of all cases of ITP[15,16-20]. The hemorrhages are usually found in the subarachnoid areas, but can occur in the intracranial spaces[14]. In this case hemorrhage in subdural space, posterior fossa hemorrhages are specially dangerous due to possibility of rapid cerebellar herniation and brain stem compression. Retinal hemorrhage often occurs at the time of ICH[21]. In our case purpura and hemorrhage occur spontaneously both in subdural space and subconjunctival hemorrhage.

Factors predisposing to development of ICH are not well understood. Although trauma has accounted for some cases, most ICH seem to be spontaneous.[16] ICH occurs most commonly in the early days after diagnosis, but can occur nearly anytime after onset[18,20]. It has been suggested that patients with platelet counts of less than 10 x 109/l are at a greater risk of ICH[16,18,20,22].

Previous authors have commented on the relative rarity and fatality of ICH in adults with ITP. For example, Difino et al[23]. reported three incidences of ICH in his series of 67 adult cases of ITP, all of which were fatal and Carpenter et al[24]. reported two cases of ICH in his series of 85 adults and both were fatal. However, they gave no specific details as to how the diagnosis of the ICH was made, the clinical course, or the treatment. Other reports also allude to adult cases of ITP complicated by ICH, but this diagnosis was uncertain because no investigational tests (e.g. CT scan) were performed to prove that hemorrhages had occurred[23-26] Further, with the current knowledge of the disease, it is questionable whether some of the older reports of ICH were truly examples of ITP or whether they represented other diseases which may have presented as thrombocytopenia. More recently, Nagler et al[21]. reported the occurrence of a subdural hematoma in a 32 year old man with chronic ITP. This is the only other documented case of an ICH occurring in an adult with ITP.

If a patient with ITP develops signs or symptoms of central nervous system bleeding such as retinal hemorrhages, convulsions, meningism, headache, personality changes or neurological signs, rapid and vigorous treatment must be initiated as this can be fatal. Therapy for ICH associated with ITP consist of controlling Intracranial pressure while also achieving a rapid rise in the platelet count to control bleeding with intravenous dexamethasone with 20% manitol can be implement to control cerebral edema[15]. Steroid and immunosuppressive therapy appear to increase platelet life span but no controlled studies show that this reduces the risk of ICH.[16,27-29]

If the neurological sign aggravate then neurosurgical intervention may be warranted but the decision to operate has to be taken considering the risk and benefit of the individual case. Hemorrhages into the posterior fossa should usually be treated with craniotomy due to the possibility of a rapid rise in intracranial pressure[16]. It has been stressed that splenectomy should be done prior to craniotomy to avoid further ICH during surgery although both procedures may be done together under one anaesthesia[22,30]. But in this study patient's intracranial hemorrhage managed conservatively and there was no residual effect.

Conclusion:

An intracranial hemorrhage is the most dreaded complication of ITP, it is essential to proceed on early diagnosis, prompt and aggressive management. Our case demonstrates that successful treatment of the ICH depends on early diagnosis and prompt, aggressive management of the bleeding. If central nervous system symptoms are present, the alert physician with use of the present diagnostic techniques, and medical and surgical management, may be able to prevent permanent neurological deficit in an effective manner.

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