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EDITORIAL

Palliative Care: We should begin to Think

The word 'palliative' comes from the Latin '*pallium*' meaning cloak. Palliative care affords relief, not cure, by concentrating on cloaking the severity of disease symptoms . World Health Organization defines Palliative Care [PC] as an approach of active total care, which focuses on the relief of physical, psycho- social and spiritual sufferings experienced by patients with life limiting illness and their families. The goal is to improve quality of life by offering comfort, promoting dignity and providing a support system in the face of incurability. PC attempts to celebrate life, even when time is limited.

Since the second half of the 20th century, world has witnessed important changes in medicine. Rapidly evolving development and high technology therapy has led to an increased emphasis to 'fight aggressively' against illness. Along with this change, there has been gradual shifting away from provision of symptom management, comfort and compassionate care[1]. This is particularly true when health professionals are required to care for the dying, in the face of incurability. Well-acclaimed SUPPORT study (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments) documented these 'high technology deaths' with a futile attempt to prevent it[2]. Another influential report by the Institute of Medicine (IOM), published in 1997, sought to strengthen popular and professional understanding of the need for good care towards the end of life. It observed that lack of formal and proper education in palliative care, beginning from the medical school to residency and beyond was a barrier in providing the appropriate care to these patients[3]. Similar observations were noted in a number of editorials of globally acclaimed journals during later part of 20th century [4,5,6,7].

The rise of PC in a modern approach took place against a backdrop of modest but growing clinical, educational and research interest [8]. In 1953, John Bonica published the first textbook on Pain Medicine. His groundbreaking work studied the problems of patients suffering from advanced diseases. The insights that emerged from this work strongly influenced the activities of palliative care[9]. This momentum continued in the early 1960s with studies on bereavement and terminal cancer at home followed by a number of publications in reputed journals. The St. Christopher Hospice was opened in 1967 in South London by Dame Cicely Saunders. Since then, the 'era of modern palliative care' began. In 1974 Balfour Mount in Canada, first coined the term 'Palliative care' in clinical practice[10]. By the year 1999, there appeared 6540 PC services in 84 countries, though mostly in developed part of the world. Whereas the number of palliative care services are increasing rapidly in affluent world, [11] the extent of establishment in developing countries remain at a poor level [12]. Nevertheless, according to 'The Quality of Death' report, published by the Economist Intelligence Unit, it is a right denied to all but only 8% of patients who are in need of this care worldwide every year [13].

All practicing doctors in any field of medical science have to look after their patients at times who have potentially life threatening illnesses. In 1998, the American college of Surgeons adopted a statement on principles guiding the surgeons at the end of life of their patients. This guideline incorporates almost all the principles of PC including provision of access to organized Palliative Care service. A group of surgeons was convened in 2001 to put these principles into operation and to introduce the percepts and techniques of PC into surgical practice and education.

A subset of surgical PC, palliative surgery has been recently defined which includes surgical procedures even with curative intent. In surgical oncology it plays an important role, e.g. in breast cancer requiring mastectomy, a bypass operation in inoperable colonic or biliary malignancies. Resections of hepatic or pulmonary secondaries, along with other 'therapies' are good examples of palliative procedures [14]

Principles of palliative care are within the larger primary goals of medicine. [15]

These are:

- to Restore function of patients as normally and for as long as possible,
- empathic listening and providing all honest informations,
- to ensure patient or patients' family know who to call if things go wrong,
- to appreciate that many choose home, but some hospitals for their care,
- to be aware of different cultural practices and religious beliefs,
- to be aware of how looking after seriously ill patients can affect heath care workers.

In developing countries, an estimated 27 million people would benefit from PC and this number is growing fast. Improving PC service would not require large money or restructuring of healthcare system. There are remarkable success stories of Palliative care in the developing world as in Kerala and Uganada [15].

Extent of the problems in Bangladesh: More than a million people die in Bangladesh every year. Approximately 0.6 million of them are estimated to be in need of PC service. More than 4% of the population are aged 65 and above and the number of elderly are on a steady rise. Most of these people are in need of care routinely offered by a palliative care services. While planning such services here, several factors like low income, limited academic link in health education, natural calamity, mismanagement of resources, and false belief etc. need special consideration. The positive side is our success stories of prophylaxis against common diseases, better health awareness, wide service delivery network even in villages, use of safe drinking water and many more.

To ensure that PC is available and accessible to the majority of the needy, a community-based approach should get appropriate consideration. It is essential that the doctors and other health care providers be educated with knowledge, technical skill and attitudinal motivation for dealing with these patients in a systemic manner. Opportunities for research in Palliative Medicine, like every subject, should be identified.

PC embodies the essential features of all good care to be attained through multidisciplinary or interdisciplinary approach. It is to be offered with all other medical treatments. Recently, Bangabandhu Sheikh Mujib Medical University has opened this chapter of Palliative Care, which is a step ahead in our country. The endeavor needs to be appreciated and acknowledged.

The authors do believe, '*let there be light'*.

(J Bangladesh Coll Phys Surg 2011; 29:)

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Study on the Effect of Total Intravenous Anesthesia (TIVA) on the Post-operative Respiratory Performance Regarding Early Extubation after Coronary Artery Bypass Graft (CABG) Surgery

AKMF HOQUE[a], Z RAHMAN[a], AH HABIB[b], A ALI[a], A ISLAM[b], AKMS RAHMAN[a]

Summary:

The outcome of anaesthesia in coronary artery surgery depends partly on the duration of invasive manipulations including endotracheal intubation. It is ideal to avoid prolonged mechanical ventilation and attempt early extubation. Depressant effect of some anaesthetic agents and narcotics makes it a common practice to ventilate the patients of coronary artery bypass graft (CABG) surgery overnight resulting in unsatisfactory respiratory and haemo-dynamic performance. This study was aimed at overcoming the effects of prolonged mechanical ventilation after CABG surgery by using Total Intravenous Anaesthesia (TIVA) and by extubating the patient early to achieve a better post-operative respiratory cardiovascular performance.

The study was conducted prospectively on 40 patients between 40 to 60 years, divided into two groups of 20 patients each. Gr.-A received infusions of Propofol 2-6 mg/kg/hr, Fentanyl 0.5-1.25 mg/kg/hr and Pancuronium bromide 0.01mg/kg. Postoperatively Propofol was continued in infusion for one hour while Inj. Diclofenac sodium was used as an analgesic.

Patients in group B received a typical conventional anaesthesia and were ventilated electively till next morning.

The study showed that in CABG surgery, TIVA produces non-significant depression of post-operative respiratory performance which helps in early extubation compared to those receiving conventional anaesthesia and electively ventilated overnight.

*Key words**: TIVA, CABG, Early extubation*[1]

(J Bangladesh Coll Phys Surg 2011; 29: 3--9)

Introduction:

The outcome of Cardiac surgery and anaesthesia depends on fast tracking which means early tracheal extubation, shorter stay in intensive care unit and minimization of complications [1].

Many randomized trials have found that early tracheal extubation can safely be achieved and may reduce the ICU stay measured by 'time to tracheal extubation' and a variety of haemo-dynamic endpoints [1-2]. However, some anaesthetic interventions may influence the outcome of cardiac surgery [3]. In the past, anaesthesia for CABG surgery was based on high dose opioids for haemodynamic stability which led to prolonged post operative mechanical ventilation. This practice has been questioned [4-5].

TIVA (Total Intravenous Anaesthesia) has been defined as 'a combination of hypnotic agent, short acting analgesic drug and muscle relaxant, excluding simultaneous administration of any inhaled agent'[6]. The development of new hypnotic and analgesic drugs has renewed interest in TIVA [7]. It enables the anesthesiologist to obtain a specific desired effect within a specific time frame. But there is considerable pharmacokinetic and pharmacodynamic variability even in matched patient populations[7].

TIVA is a standard procedure for day case surgery and other operations for shorter duration and to provide better haemodynamic stability and less neuro-humoral stress response to surgery,[8-9]. Some study concludes that

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TIVA represents an acceptable anaesthetic regimen for cardiac anaesthesia [10].

In cardiac anaesthesia it is a common practice to ventilate the patient mechanically overnight after CABG surgery to overcome the depressant effects of anaesthetic agents used intra-operatively. In this study, short acting analgesic (fentanyl) and anaesthetic agent (propofol) were used. Here, this regimen was applied to expedite early extubation without affecting the haemodynamics, pulmonary function, and other outcomes.

Materials and Methods:

In this prospective study, 40 patients between 40 to 70 years were divided into two groups of twenty patients each allocated by random selection of sealed envelope method. Group A was selected for TIVA by propofol, fentanyl and pancuronium bromide combination and group B received traditional balanced general anaesthesia (BGA)

for CABG surgery. Patients included in the study were of ASA grade I and II, ejection fraction 45% or above (Left ventricular function moderate to good.), and one/ two risk factors with Ischemic heart disease were allowed- e.g. - Diabetes Mellitus and/ or Hypertension. Exclusion criteria are detailed in Table- 1.

Both the groups were pre-medicated with oral midazolam 7.5 mg.

Group A patients were induced with propofol 1 to 2.5 mg/kg; Fentanyl 1-2 μg/kg and intubation was facilitated with pancuronium bromide 0.08 to 0.15 mg/ kg. Anaesthesia was continued with propofol infusion 2-6 mg/kg/hr, fentanyl: 0.5-1.25 g/kg/hr and pancuronium 0.04 mg/ kg followed by 0.01 mg/kg at 20-40 min. interval. Before transferring to the ICU, only propofol was continued and Inj. Diclofenac sodium 75 mg was given intramuscularly. Injection Pethidine was used as rescue analgesic.

Sleep was induced in Group B patients with thiopentone sodium 3-6 mg/kg; midazolam 0.1-0.4mg/kg; and morphine 0.01-0.5 mg/kg (not > 30mg) and intubation was facilitated by pancuronium (0.08 to 0.15 mg/ kg). Maintenance was done with nitrous oxide, halothane and intravenous morphine and pancuronium intermittently. Post-operative analgesia was maintained by inj. Morphine and followed by 75mg intramuscular diclofenac sodium. Patients were extubated the next morning.

Postoperative mechanical ventilation: Group patients were ventilated until they met the preset criteria for extubation, while those in group B were electively ventilated till next morning.

Rescue management for pain: Since we have deviated from usual analgesic therapy, it was not unexpected for some patient to have pain in the postoperative pain. If the patient complained of pain and found to have a score of more than 7 out of 10 VAS score, one would received injection pethidine 1.5 mg/kg intramuscularly. Such patients would also have dropped from the study.

Different intra operative data were collected in both the groups at 30 minutes interval which included pulse rate, intra-arterial blood pressure (IABP), pulse oxymetry (SPO2), electrocardiography (ECG), end tidal carbon-dioxide (ETCO2), central venous pressure (CVP), arterial blood gas (ABG), (PaO2, PaCO2) etc; were noted for further analysis

In group- A- in the post-operative period in the ICU, the propofol infusion was continued atat a rate of $\leq$ 2 mg/kg/hr for 1 hour and then gradually switched off after 2 hours approximately. Group- B patient received morphine 3 mg IV bolus and PCB 2 mg intermittently. They were ventilated mechanically to maintain PaCO2 between 35-40 mm of Hg and PaO2 > 90 mm of Hg. with FIO2 $\leq$ 45%. Patients were extubated when they fulfilled the extubation criteria. The time for extubation since the end of surgery was noted in both the groups. Injection diclofenac sodium 75mg was administered one hour before extubation and rescue analgesic was repeated at twelve hours interval.

Patients who did not meet the criteria for extubation (Table : 5) were excluded from the trial. Reversal of neuro-muscular blockade was done with neostigmine 2.5 mg with atropine 1.2 mg given intravenously.

After extubation, patients were monitored on an hourly basis for the next 3 hours. In addition, post-extubation data of respiratory parameters respiratory

rate, tidal volume, SPO2, ETCO2, PaO2, PaCO2), haemodynamic parameters (pulse, blood pressure, ECG for any arrhythmia, CVP, blood loss through drains, urine output); neuromuscular parameters , pain-parameters (grading of pain by visual analogue scale-VAS) and lastly the recovery Score by Aldrete and Kroulik's method was recorded.

Results and Observation :

The mean difference of all haemodynamic parameters before induction were statistically insignificant ($p>0.05$) between two group. Table 2 shows that the patients in the two groups were well matched.

On arrival in the ICU, when all patients were on ventilator, had no difference in resp parameters (table 3). However, they differed significantly at 30, 60 and 90 minutes after the surgery.

The mean difference of pain at extubation and subsequent 3 follow–up in each hour were statistically significant ($p<0.05$) between two groups. The mean difference of all neuro muscular parameters were statistically significant ($p<0.05$) between two groups (Table iii), except requirement of reintubation. Similarly mean recovery score of all follow-up were statistically significant ($p<0.05$) (Figure I).

Table-I

Exclusion criteria

Sl.	Criteria
1	Patient refusal
2	History of previous CABG surgery or heart valve surgery
3	Documented myocardial infraction within the previous six weeks
4	Overt congestive heart failure
5	Known history of respiratory illness like obstructive or restrictive lung disease or smoking
6	Known history of renal dysfunction with a creatinine level of > 150 mmol/1
7	Known history of seizure
8	History of allergy to propofol or its constituents
9	Renal dysfunction with a creatinine level of > 150 mmol/1
10	Anticipated ECC time (extra corporeal circulation time)- if prolonged & more than 4 hours and anticipated cross-clamp time- if more than 120 minutes

Table-II

Patient demography between groups.

Variables	TIVA (n=20)		Traditional (n=20)t value		t	Df	p value
	Mean±SEM	Range (min, max)	Mean± SEM	Range (min, max)			
Age	57.7±1.9	42 72	55.1±1.9	42 72	.962	38	0.342
Height	159.8±1.4	151 -170	151±1.7	150 173	.296	38	0.769
Ejection Fraction	55.3±1.1	48 62	55.7±1.3	51	60 -.238	38	0.813
Body surface area	1.7± .02	1.6 1.8	1.6± .03	1.4 1.9	1.34	38	0.189
Body weight	56.0± 1.1	53 60	57.2± 1.3	50 65	1.682	38	0.101

P value considered significant $p<0.05$

Table-III

Comparison of respiratory parameters between TIVA and Traditional group at arrival in ICU. (Patient in ventilator)

Parameters	TIVA(n=20)			Traditional (n=20)			t		P
	Mean±SEM	Min	Max	Mean±SEM	Min	Max	value	df	value
Respiratory rate	14±0.3	12	16	15±0.5	13	17	-1.98	38	0.123
Tidal volume	547.5±11.7	450	600	545.5±12.3	450	600	-1.38	38	0.176
SPO_2	99.6±0.3	98	100	100.0±0.2	98	100	1.85	38	0.102
$ETCO_2$	35.7±0.5	36	39	37.0±0.8	27	39	-1.39	38	0.171
PaO_2	345.9±19.9	227	500	327.2±9.6	312	452	0.85	38	0.402
$PaCO_2$	36.6±0.8	29	41	38.1±1.1	25	41	-1.13	38	0.265

P value considered significant p<0.05

Table-IV

Comparison of recovery score between TIVA and Traditional group.

	TIVA (n=20)		Traditional (n=20)		t value	df	p value
	Mean±SEM	Range (min, max)	Mean± SEM	Range (min, max)			
1 hour after	8.5±0.3	8 9	7.5±0.2	7 8	6.650	38	0.001
2 hours after	9.5±0.2	9 10	8.5±0.3	8 9	2.570	38	0.014
3 hours after	9.8±0.1	9 10	8.5±0.3	8 9	2.570	38	0.014

P value considered significant p<0.05
The above table show the mean difference of all follow-up were statistically significant (p<0.05) in unpaired t-test.

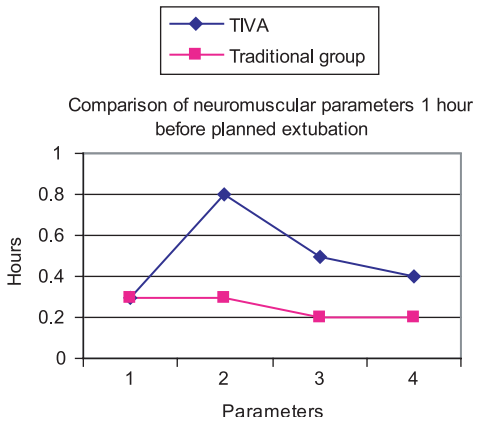

Fig.-1: *Comparison of neuro muscular parameters between TIVA and Traditional group 1 hours before planned extubation*

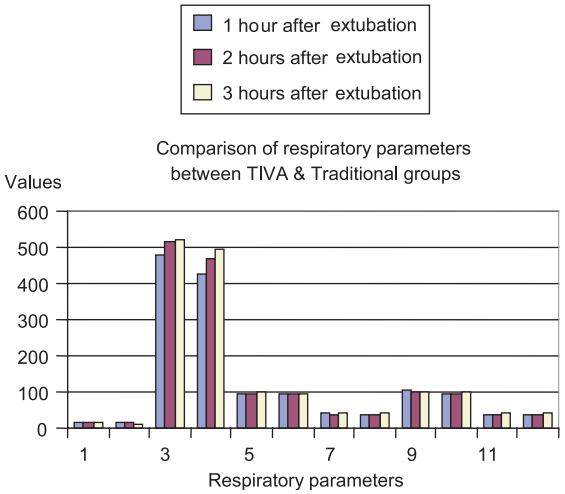

Fig.-2: *Comparison of respiratory parameters between TIVA and Traditional group*

Table-V

Extubation criteria

Parameters	Subclass	Extubation time	
Eye opening	1. Spontaneously	1. yes	1. Early extubation
	2. On command	2. yes	2. Delayed extubation
Muscle power	1. Hand grip	1. Strong- yes	1. Early extubation
	2. Leg raising	2. 15 seconds- yes	2. Early extubation
	3. Head lift	3. 5 sec - yes	3. Delayed extubation
TOF (Train of four) in Neuromuscular monitor	1. 75% of total muscle	1. yes	1. Early extubation
	2. 50% of total muscle	2. yes	2. Delayed extubation
Respiratory	1. Rate- 10-12/min	1. yes	1. Early extubation
	2. Tidal volume- 8-10 ml/kg	2. yes	2. Early extubation
	3. PaO2 >95mmhg in FIO2 60%	3. yes	3. Early extubation
Haemodynamic	1. Stable without inotrop support	1. yes	1. Early extubation
	2. Stable with inotrop support	2. yes	2. Early extubation
	3. Any mechanical device (IABP)	3. yes	3. Early extubation
	4. No new ECG change or myocardial infarction (ST segment > 2mm or T wave inversion in lead II).	4. yes	4. Early extubation
Pain	1. No pain	1. yes	1. Early extubaton
	2. Minimal pain	2. yes	2. Delayed extubation
Bleeding from chest drain	1. Minimal bleeding (< 50 ml/hr)	1. yes	1. Early extubation
	2. Greater blood loss (> 50ml/hr)	2. yes	2. Delayed extubation

Discussion:

Untill recent past , the traditional anaesthetic regimen for cardiac surgery was based on high dose opioids to afford a stable and safer recovery from surgery. But this has been challenged in favour of fast track anaesthesia to cut down the overall complications related to profound analgesia under elective postoperative ventilation for long hours.

The present study, based on this philosophy used short acting intravenous anaesthetic agent followed by a brief period of mechanical ventilation along with rapid emergence to full consciousness within very few hours of stopping anaesthetic drug.

At present what is commonly known as “fast track cardiac anaesthesia” (FTCA) which comprises early tracheal extubation to decrease length of intensive care unit stay, [11].

This randomised prospective study was carried out to see post-operative respiratory performance to help early extubation, early ambulation and to reduce length of stay in the post cardiac surgical ICU.

In a Turkish study, fast track protocol that is early extubation protocol under TIVA in patients older than 65 years was found suitable. In this study mean age of patients in both group was below 65 years but it is relatively higher in TIVA group, which showed better outcome [14].

Patients in both groups of our study were well matched and there were no significant difference in patient demography. No difference was observed in the respiratory parameters when they arrived in the ICU, except for respiratory rate which was higher in the traditional group.

The mean difference of all respiratory parameters 1 hour after arrival in ICU were statistically not significant ($p>0.05$).Similar significant results were also found in respiratory and haemodynamic parameters after 2 hours arrival in ICU.

In a study the influence of cardiopulmonary bypass (CPB) on respiratory performance was analyzed and proven that atelectasis lowers the partial oxygen tension in the arterial blood[15].

The mean difference of all respiratory parameter 1 hour after extubation were statistically significant ($p<0.05$) except SPO_2 and $PaCO_2$, which were insignificant and 2 hours and 3 hours after extubation were statistically significant ($p<0.05$) except $ETCO_2$ and $PaCO_2$, which were also insignificant.

Bedford RF and Wollman H found in their study that the respiratory rate was always higher postoperatively in patients who received halothane for coronary artery bypass disease, which closely agrees with the present study[16].

Fayez MK et al 2004 showed diclofenac alone or with paracetamol had a significant opioid–sparing effect after CABG producing rapid extubation and better oxygenation[17].

In an Indian study in 2009 , it was found that Rectal diclofenac suppository with tramadol provides adequate pain relief after cardiac surgery, and also reduces tramadol consumption and side effects commonly associated with tramadol [20].

All the neuro muscular parameters were significantly ($p<0.05$) higher in traditional group except requirement of reintubation. In the fast track setting, reversal of neuromuscular block should be done before weaning from mechanical ventilator[12]. Some author have found the pharmacokinetic profile of propofol favours earlier recovery from anaesthesia and sedation and thus earlier extubation[18-19]. In the present study the recovery score after 1, 2 and 3 hours were significantly ($p<0.05$) higher in TIVA group, which indicate that the mental function regain faster & titrated dose of muscle relaxant help recover neuromuscular function earlier [13].

The usefulness of TIVA on postoperative respiratory performance was analyzed in the present study. However efficiency of TIVA concerning cost effectiveness and complications- i.e. morbidity, mortality in distant future could not be verified in this small scale study. Though done on a small scale Bangladeshi population in a Bangladeshi setup (which in many ways are deficient) our study validates the findings of several studies done earlier in different centres.

Conclusion:

Present study suggests that CABG surgery under TIVA has an edge over traditional technique and results in marginally better respiratory performance after extubation than in anaesthesia with overnight mechanical ventilation on top of a stable haemodynamics with early neuromuscular recovery, early ambulation of the patient and shorter stay in the ICU. This study supports the concept of fast track anaesthesia for CABG under TIVA in our setup with favourable outcome.

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Implementing Skilled Midwifery Services in Dhaka City Urban Area: Experience from Community Based Safe Motherhood Project, Bangladesh

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Summary:

In Bangladesh majority of deliveries are attended by unskilled traditional birth attendants and maternal mortality is still quite high. Global evidence suggests that most critical intervention for reduction of maternal mortality is to ensure skilled attendance at birth.

The objective of this study was to explore the effect of strengthening obstetric care services through implementation of skilled Midwives at selected urban centres in terms of utilization of antenatal and delivery care in the community.

A quasi experimental community trial was conducted during January 2000 to June 2003. Ten health centers were selected from the maternity care centers of urban primary health care project in Dhaka city, matched into comparable pair and assigned randomly as intervention and control centers. The intervention consisted of deployment of 10 skilled midwives in pair to provide obstetric care services in five intervention centre and the community. Essential drugs and logistics were supplied to both intervention and control centers for optimizing the function.

A total of 6077 mothers having less than one year child were interviewed. There was significant improvement from baseline in the utilization of antenatal care services (6.1 vs. 2.1%, p<0.001), availing antenatal visits 5 times or more (13.4% vs. 8.1%, p<0.001), consultation with skilled health care providers for pregnancy complication (9.3% vs. 5.7 %, p<0.001), institutional delivery (7.3% vs. 4.1%, p<0.001) and delivery by skilled birth attendant (9.4% vs. 5.8%, p<0.001) between intervention and control area respectively.

The intervention of deployment of skilled midwives improved utilization of ANC, increased institutional delivery and delivery by skilled birth attendants. The program can be scaled up to see its impact on maternal health.

Key words: skilled midwife, emergency obstetric care, urban health care, antenatal care

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Introduction:

Every year 529,000 women die of pregnancy related complications throughout the world[1]. Ninety nine percent of such deaths occurs in developing countries[2]. South Asia has 22% of the world's population but 50% of the world's maternal death[3]. Majority of such deaths result from inappropriate management of pregnancy and childbirth. About 1.4 million newborn deaths within the first week and another 1.3 million stillbirths take place in South Asia[4].

In Bangladesh about 3.5 million deliveries take place annually, majority occur at home, attended by traditional birth attendants. Bangladesh health and demographic survey revealed that birth delivered in a facility was 4 % in 1993-94, 8% in 1999-2000, 9% in 2004 and 15% in 2007[5-8]. In urban area 21% births occur at health facilities[8]. Proportion of antenatal care from a trained person increased consistently and rose by 4 percent from 48 to 52 percent between 2004 and 2007 BDHS[7,8]. Maternal mortality and infant mortality was reported to be 320 and 580 per 100,000 live births respectively[9].

The health care in urban area is provided from 3 sources: Government, NGO and private. The public health care facilities are provided through general and specialized

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hospitals and dispensaries under ministry of Health and Family welfare. In metropolitan cities the City Corporation provide comprehensive Reproductive Health package with Emergency Obstetric Care in selected centers through its partner NGOs. However, the numbers of primary level maternity centers are inadequate in relation to the growing urban population of and there was also lack of sufficient number of professionally competent midwives[10].

The experience of different programs of global Safe Motherhood initiative since 1987, have identified that presence of a skilled attendant at the time of delivery is essential to detect and manage obstetric emergencies appropriately and thereby in saving lives[11]. Skilled Birth attendants refer to people with midwifery skill and defined as trained nurse, midwife or doctors who have completed set course and have necessary skill to manage normal deliveries safely, recognize complication, can manage and refer if needed[12]. It is acknowledged that the skilled attendants should live in and are part of the community they serve, so that they can cover home deliveries[12]. There is evidence that professionalisation of delivery care is a key to reducing maternal mortality. In developed countries decline in maternal mortality (between 1750 and 1850) was related both to an increasing proportion of midwives conducting deliveries and to a higher standard of midwifery[13] .

WHO recommends that for countries with high level of maternal mortality 60 percent of the deliveries should be conducted with skilled attendants by 2015[14]. Bangladesh National Maternal Health strategy has targeted to achieve 50 percent of all birth assisted by skilled birth attendant by 2010[15]. The objective of this study was to explore the effect of strengthening obstetric care services through implementation of skilled Midwives at selected urban centres in terms of utilization of antenatal care, delivery by skilled birth attendant, treatment for pregnancy complications and institutional delivery in the community.

Method:

This was a quasi experimental community trial conducted during January 2000 to June 2003. Ten health centers were selected systematically from about 105 primary care and 20 comprehensive reproductive health care centers under urban primary health care project in Dhaka city. They were matched into comparable pair and assigned randomly as intervention and control centers. The adjoining area containing approximately 20-25 thousand population constituted the study clusters.

The intervention consisted of training a group of diploma nurses (graduated from 3 years basic nursing with one year midwifery training) during January to December 2001 according to a competency based curriculum developed through national level workshop and expert meetings. The curriculum was standardized with WHO standards of Midwifery practice for Safe Motherhood, 1999[16]. It consisted of 11 modules viz General, Behaviour Change Communication (BCC), Antenatal, Postnatal, and Intranatal Care, Life saving, Breast Feeding, Family planning, Infection Prevention and Waste Disposal, Management and Computer module. The training was of one year duration with approximately 50 working weeks (2414 hours) and time distribution of theory 338 hours (14%) and practical 2076 hours (85%). Participatory training methodology was adopted and there was in course and end course assessments. After graduating from the training they were designated skilled midwives and deployed in 5 intervention centers in pair during January-December 2002 to serve both in the clinic and the community. Other health care providers like doctors, nurses and paramedics were similar among control and intervention centers.

For community mobilization in the intervention area the skilled midwives conducted about 100 group meeting with pregnant and lactating mothers, husbands and elder family members each lasting for 1-1.5 hours, distributed 25,000 leaflets , arranged 10 video show on obstetric emergency, provided a number of antenatal and delivery services at patient's home. Essential drugs (like iron, folic acid and calcium tablets, oxytocin and ampicillin injections etc) and instruments (like stethoscope, BP machine, spot light, scissor, forceps etc) were supplied to both control and intervention centers according to their requirements of use. Regular supervision and monitoring of the activities were done by the researchers and different registers were maintained to record the services.

Data was collected through home visits and interviewing women having less than one year child with pre-tested structured questionnaire during August to November 2001 and November 2002 to February 2003 for baseline

and post intervention respectively. A rapid survey of about 50,000 household were made to find out the eligible mothers and among them about 3000 were randomly selected each in baseline and post intervention survey. The data collectors were female graduates with experience in data collection and received specific training for 7 days. There were separate set of data collectors for baseline and post intervention survey and they were remained blinded regarding the intervention. The study was approved by ethical review committee of Institute of Child and Mother Health (ICMH) and informed written consent from respondents were obtained.

Data was analyzed in the IBM PC using EPI Info and SPSS software and validated with double data entry. Univariate and multivariate analysis was carried out and percent change of proportion between baseline and post intervention in relation to use of antenatal care, number of antenatal visits, use of skilled birth attendant for delivery and treatment of obstetric complications and number of institutional delivery were calculated at 95% confidence interval.

Results:

A total of 6077 mothers having less than one year child were interviewed. Over all sociodemographic characteristics were almost similar at baseline and post-intervention survey in both intervention and control area (Table-1). Performance of both types of study centers increased but it was significantly increased in intervention centers (Table-2)

Table-I

Socio-demographic characteristics

Elements/Indicators	Intervention (n=3049)			Control (n=3028)		
	Baseline	Post intervention	p value	Baseline	Post intervention	p value
Mean age of mothers (± SD)	24.5±5.2	24.7±5.2	0.21	24.8±5.0	24.5±4.9	.04
Mean age of menarche (± SD)	12.9±0.9	12.9±1.2	0.26	12.9±0.9	12.9±1.2	.97
Mean age of first marriage (± SD)	16.6±3.3	17.1±3.2	<0.01	16.8±3.3	17.0±3.3	.06
Mean age of first pregnancy (± SD)	18.4±3.2	18.9±3.3	<0.01	18.5±3.4	18.7±3.2	.17
Mother's Mean years of schooling (± SD)	5.4±4.7	5.4±4.6	.74	5.6±4.7	5.5±4.4	.90
Mean years of schooling of the husbands (± SD)	6.8±5.3	7.1±5.1	.15	7.0±5.1	6.8±5.0	.20
Average family income in BDT (± SD)	8988±10372	8615±9313	.29	10074±10300	9351±9310	.04
Average family expenditure in BDT (± SD)	7248±7260	7315±7218	.79	8055±7046	7950±7423	.69

Table-II

Clinic Performance of study centers

	Centre Type					
	Intervention			Control		
	Pre intervention*	Post intervention**	% change	Pre intervention*	Post intervention*	% change
Registration of pregnant women	376	858	+ 128.19	781	847	8.45
ANC Follow up	633	1339	+ 111.53	1020	1227	20.29
Normal Delivery	53	133	+ 150.94	109	140	28.44
PNC	102	403	+ 295.09	345	317	- 8.11
Family Planning	454	604	33.04	937	1175	25.40

* The month before intervention (Dec'2001)
** The last month of intervention (Dec'2002)

The utilization of antenatal care services was about 3 times more (6.1% vs. 2.1%, p<0.001) in the intervention area (Figure 1). The proportion of mothers who availed ANC visits 5 times or more during pregnancy were found significantly higher (13.4% vs. 8.1%, p<0.001) in intervention area than control (figure-2). Consultation with skilled health care providers for pregnancy complication was significantly higher (9.3% vs. 5.7%, p<0.001) in intervention area (figure 3).

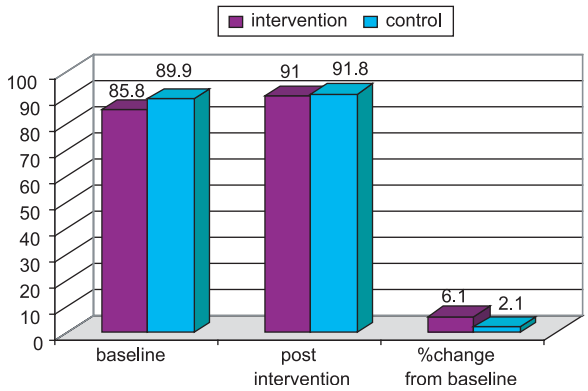

Fig.-1: *Impact of Skilled Midwifery service in utilization of Antenatal care*

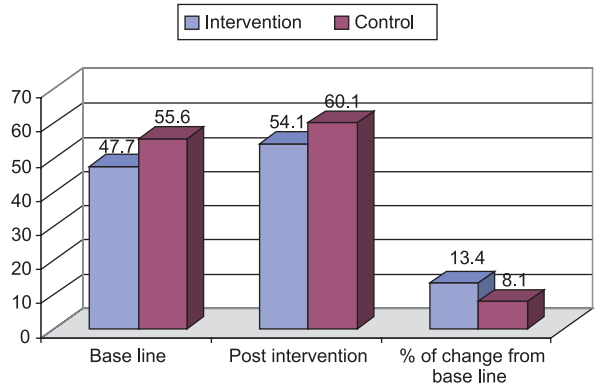

Fig.2: *Impact of Skilled midwives in utilization of ANC for 5 visits or more*

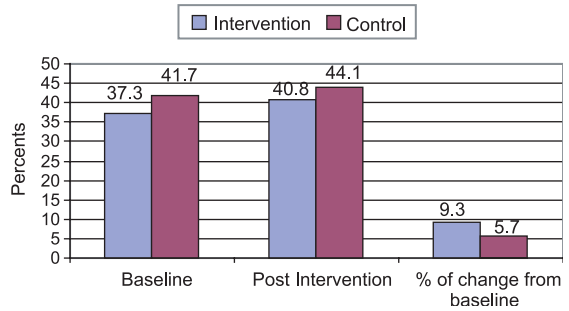

Fig.-3: *Impact of Skilled midwive on the consultation of skiiled birth attendant for pregnancy complication*

The increase in institutional delivery was almost double (7.3% vs. 4.1%, p<0.001) in intervention area than control (figure 4). The change in the utilization of skilled birth attendant for delivery was significantly higher (9.4% vs. 5.8%, p<0.001) in intervention and control area respectively (figure 5).

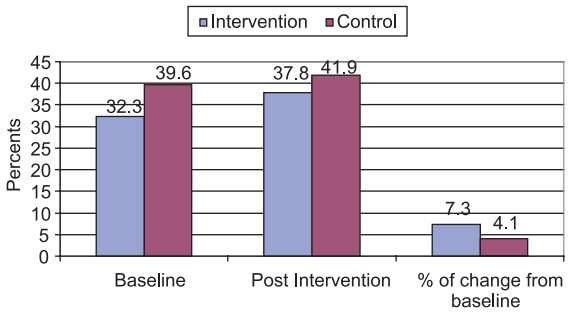

Fig.-4: *Impact of Skilled Midwives in proportion of Institutional Delivery.*

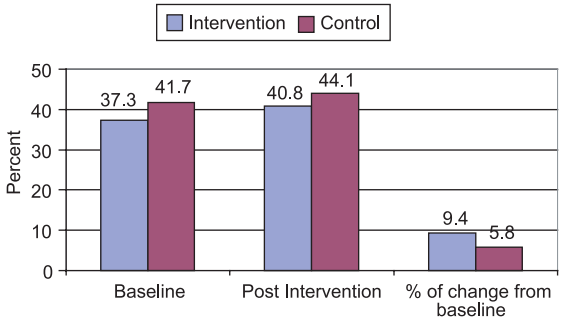

Fig.-5: *Effect of skilled midwives in increasing proportion of skilled birth attendants at delivery*

Limitation of the study

Measuring a change resulting from Safe Motherhood programs is a challenging issue and it is very difficult to infer certain effect explicitly to any specific intervention. To ascertain any change in mortality and morbidity would require large-scale program implementation over a sufficient length of time so impact evaluation is often discouraged and emphasis is given on process indicators for evaluation[17]. Different programs and services rendered by both government and non government organizations are potential confounders but they are applicable to both the control and intervention areas. Some of the changes could be reflection of natural progress with existing programs and services.

Discussion:

The current study has tried to gather evidence by comparing selected process indicators of obstetric care services in an urban setting. It has dealt with a huge sample size of about 50,000 households each during baseline and post intervention survey. Hospital registers showed that during the intervention phase about 14,661 pregnant women received antenatal care from the five intervention centers and 1469 had skilled attendance at delivery. This also reflects the social norm of delivering at home with traditional birth attendants as reported in Bangladesh health and Demographic survey that while antenatal care coverage was 48.8% the delivery conducted by skilled birth attendant was 13%[7].

Essential drugs were supplied to about 25,908 women while they were pregnant, at labour and lactating period at the centers and about 3000 pregnant and post natal women had iron and folic acid during social mobilization and home visits. Improved performance of study centers was also related to strict supervision and monitoring and well-structured documentation of activities with monitoring tool. This had a positive role to ensure quality of services. The performance of control centers also increased during study and that could be an effect of supply of essential drugs and logistics for obstetric services. This indicated the importance of ensuring an enabling environment along with the skilled manpower to optimize their function.

Population characteristics in terms of socio-demographic factors were similar at both pre and post intervention period between control and intervention area. However, in the intervention area mean age of first pregnancy was significantly higher (18.9 Vs 18.4 years) and this could be an incidental finding or the effect of strengthening family planning services through counseling and distribution of different methods by the midwives.

Bangladesh health and demographic survey (BDHS) shows an increasing trend of coverage on maternal health indicators. In urban area proportion of women receiving any antenatal care was 59% in 1999-2000 and in 2007 about 71% mothers received antenatal care from medical personnel[6, 8]. In urban area the use of health facility for delivery was 16% in 1999-2000, 21% in 2004 and 25% in 2007. Treatment sought for maternal complication from a medically trained person increased from 29% to 42% between 2004 and 2007[7, 8]. Proportion of women utilizing antenatal and delivery services in this study was consistent with other studies in urban area. Survey by urban primary health care project reported that antenatal care coverage was 73 percent in Dhaka division and almost all contacts were with trained health personnel[10].

Evidence shows that strengthening existing maternity services brings positive changes to safe motherhood indicators. Evaluation of impact of women's right to life and health (WRLH) project in northern part of the country showed that strengthening emergency obstetric care services at district hospitals and upazilla health complex the proportion of birth at the EmOC facilities increased 119% from 5.3% to 11.7% over 3 years[18]. Bangladesh Red Crescent Society, developed community midwives with four years of training and junior midwives with 18 months of training, following at least eight years of basic education, and deployed them to provide delivery services through 22 MCH centers. In the pilot project population maternal mortality declined from 410 to 230 per 100,000 live births[19]. The International Centre for Diarrhoeal Diseases Research, Bangladesh (ICDDR,B) developed and deployed trained midwives in the villages to provide maternity care and established referral centre. The intervention was reported to be successful in reducing direct obstetric mortality by 3% per year in the project areas[20]. However, recent analysis of their data showed that mortality declined by 68% in the ICDDRB service area and by 54% in the government served area over 30 years[21].

Developing countries that have gained success in safe motherhood like Malaysia, Sri Lanka had the experience that with greater coverage of skilled midwifery service there were improved utilization of the services, increments of institutional delivery and great dent to maternal and neonatal mortality was achieved[22] .

Conclusion:

Although in this study the intervention of skilled manpower (the midwives) was for a short time and covered a limited number of population the changes that occurred on utilization of routine ANC, consultation of trained health care provider for complication, number of institutional delivery and delivery by skilled persons were significantly greater than could be explained by

natural progress of existing programs. Further research is essential to scale up the program and evaluate its impact on maternal health.

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Tropical Sprue (TS); Experience in a Tertiary Care Hospital

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Summary:

Background: Tropical sprue (TS) is a common cause of malabsorption in the tropics. No report has yet been published on TS in Bangladesh. This report aimed to describe clinical picture of TS patients in a tertiary care hospital.

Methods : The data were collected from the admission and discharge registers and register of follow-up clinic of Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University during the period of 1981- 2004.

Results: A total of 23 patients with a mean age of 36.42 years were diagnosed to have TS (8 females and 15 males). Mean duration of their symptoms was eight months. Important presenting features were loose motions (82.6%) and progressive weight loss (73.91. Approximately 43.47% patients presented with abdominal discomfort or pain, 26.02% with fever and 26.03% with skin changes. Mean hemoglobin and serum albumin levels were 9.71gm/dl and 31.16 gm/dl respectively. Fecal fat was positive in only eight cases. Contrast X-ray showed dilatation of small intestinal loops in four cases and flocculation of dye in two cases. Duodenal biopsy showed partial (16cases) or subtotal (four cases) villous atrophy with chronic inflammatory cell infiltrate in lamina propria in 91.3 % cases. Patients treated with tetracycline or ciprofloxacin along with folic acid showed good initial response with improvement of bowel motions, weight gain and anemia. Only two patients presented with recurrent attacks.

In conclusion, TS is also prevalent in our country. A good number of TS patients presented with abdominal responses were pain and fever along with diarrhoea and weight loss. Small intestinal mucosal changes and treatment typical to TS.

Key Words: Tropical sprue, clinical profile

Key Message: The mal-absorptive disorder Tropical sprue is also prevalent in Bangladesh. Patients mostly presented with loose motions and progressive weight loss. A good number of TS patients' present with abdominal pain and fever along with diarrhoea and weight loss.

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Introduction:

Idiopathic chronic malabsorption in the tropics commonly referred to as 'Tropical sprue'; have been recognized for at least 250 years[1]. The condition continues to be surrounded by epidemiologic, clinical, and aetiogenetic controversies[2]. Hillary[3], has been credited with the first description of the disease and Manson[4] introduced the Dutch term "sprue" derives from the word "sprouw". The syndrome is defined as "malabsorption of two or more substance in people in the tropics when other known causes have been excluded"[5].

Little is known about prevalence and incidence of TS. Between 1943 and 1945, as many as 10% of British soldiers evacuated from China-Burma- India theatre were diagnosed with tropical sprue. Since the World War II, tropical sprue has been frequently recognized as a cause of persistent diarrhoea, weight loss, and malabsorption among residents and travellers in the tropics, usually Asia and rarely Africa.

Although the aetiology of "tropical sprue" remains unknown, overwhelming evidence now exists that "tropical sprue" has an infective basis[9, 10, 11, 12]; progression to the overt clinical syndrome –from an initial acute gastrointestinal infection— is probably

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under genetic control. Cook[6] has proposed that intestinal infection produces nonspecific mucosal injury, which leads to the elevated plasma levels of enteroglucagon, which is responsible for slowing of intestinal transit, thereby resulting in bacterial overgrowth. The importance of fat malabsorption, with respect to the "ileal brake", slowing intestinal transit and the effect of fatty acids on colonocyte function would appear to be possible mechanism in the pathogenetic cascade.

TS is a syndrome consisting of chronic diarrhoea often with clinical features of steatorrhoea, anorexia, abdominal cramps, bloating, and prominent bowel sounds[5,13,14]. Lactose intolerance is common in TS and may be associated with vitamin B_{12} and folic acid deficiency. A subclinical or latent variant was also described.

TS in many ways remain a diagnosis of exclusion. Likely pathogens should be sought. The gold standard however is jejunal biopsy; characteristically showing thickened and blunted villi, with plasma cells, histiocytes, lymphocytes, and eosinophils in the lamina propria. If diagnostic tests are consistent with tropical sprue rapid clinical response to folic acid and an antibiotic trial is considered strong confirmatory evidence of the diagnosis.

Being a tropical country TS is considered to be an important cause of Chronic Diarrhoea in Bangladesh. However no report has yet been published on TS. This descriptive report aimed to find out the clinical profile of TS in the admitted patients during the past 20 years in a tertiary care hospital.

Materials and Methods:

This retrospective data were collected from the admission and discharge register and register of follow-up clinic of Department of Gastroenterology, BSMMU during the period of 1981- 2004. Diagnosis of tropical sprue based on recognition of malabsorption in patients with persistent diarrhoea after exclusion of other specific causes. Distal duodenal biopsy was done in all cases to demonstrate villous changes along with infiltration of chronic inflammatory cells in the lamina propria. If diagnostic tests were consistent with tropical sprue rapid clinical response to folic acid and an antibiotic trial was considered strong confirmatory evidence of the diagnosis.

Patients with underlying immuno-suppressive disorders, or disorders predisposing to Small intestinal bacterial overgrowth (SIBO) were excluded from the study.

Qualitatative faecal fat analysis[15], haemoglobin and albumin levels were estimated in all cases to demonstrate malabsorption. Blood glucose level, thyroid function tests and HIV serology were done to exclude relevant diseases. Red cell folate and serum vitamin B12 level were estimated only in a few cases. Schilling test was once launched in INM of ex IPGMR. But the test was later abandoned. INM also failed to introduce D-xylose excretion test. For this reason dual labeled Schilling test was done in only 2 cases and D-xylose excretion test in only one case. Colonoscopy was done in more recently diagnosed cases, as the test is available now.

To exclude likely pathogens stool microscopy was done. Jejunal aspirate culture for small intestinal bacterial overgrowth and microscopic examination of duodenal contents ("touch preps" for giardiasis and other parasitic disease) were not done due to lack of feasibility. Similarly hydrogen breath test, serological test for anti-endomysial or anti-tissueglutaminase antibodies and many other tests were not feasible. The patients were not on elimination diet (gluten free diet).

Barium follow-through X-ray and multiple small intestinal biopsies by endoscopy were done to exclude structural abnormality, small intestinal lymphoma, intestinal tuberculosis, immunoproliferative small intestinal disease (IPSID) and other diseases.

Results:

A total of 23 patients were diagnosed to have TS, among these 8(34.21%) were females and 15 were males. Mean age of the patients was 36.42 $\pm$ 11.95 years (male 36.46 yrs, female 36.37yrs) with an age range of 14 to 52 years. Majority of the patients belong to third and fourth decade group.

Presentation

Mean duration of symptoms was 8 months. Loose motion was the most common presentation (82.6%) with a mean frequency of stool 4 motions/day. Weight loss was the second most common presentation (73.9%). Table-I describes the clinical presentation of the TS patients. A good number of patients presented with abdominal discomfort or pain (43.47%). Skin changes (including hyperpigmentation and desquamation of skin,

hair fall and Beau's line in the nails) were present in 26.03% cases.

Table I

Presentation of the patients with tropical sprue.

Symptom	Male	Female	Total	Percentage
Loose motion	14	5	19	82.6
Weight loss	10	7	17	73.91
Pain in abdomen	5	5	10	43.47
Fever	3	3	6	26.08
Anorexia	5	3	8	34.78
Nausea/ vomiting	3	3	6	26.08
Body swelling	4	1	5	21.73
Skin changes	2	4	6	26.08
Cheilitis/ glossitis	2	2	4	17.39
Anaenia	6	7	13	56.21
Oedema	3	1	4	17.39
hepatomegaly	2	2	4	17.39

Laboratory data

Mean haemoglobin level was 9.71gm/dl with a range of 4.8gm/dl to 15.25g/dl. A male patient presented with very low haemoglobin (4.8gm/dl). Investigations revealed associated beta thalassaemia major. Examination of stool showed presence of ova of AL in two cases. Faecal fat (> 60 droplets / HPF)[15] was positive in only 8 cases (male 4, female 4). Mean serum total protein (of 16 cases) was 60.64gm/dl with a range of 43- 105gm/dl and mean serum albumin(of 17 cases) was 31.16gm/dl(range 15-42gm/dl).

Imaging:

Chest X-Ray: Revealed cardiomegaly (one male, one female) in two cases and bilateral mild pleural effusion in one case (male).

Ultrasonography:

Ascites was detected in two cases (one male, one female) and fatty change in liver was found in one case (female).

Barium study of small intestine:

Barium follow through study was done in 12 cases. Dilatation of small intestinal loops and mucosal thickening were found in 4 cases, flocculaton of dye in two cases and areas of mucosal thickening in one case.

Endoscopy:

Endoscopy was done in all cases. Duodenal ulcers were found in 3 cases, antral gastritis in one case and Bilroth type II operation was found in one case.

Colonoscopy:

Colonoscopy was done in 4 cases. All were normal.

Dual label Schilling test was done in only 2 cases and malabsorption of intestinal origin was diagnosed.

D-xylose excretion study was done in one case and the finding was normal.

Distal duodenal biopsy showed chronic inflammatory cells (lymphocytes, plasma cells, histiocytes and eosinophils) infiltrate in lamina propria in 21 cases. Subtotal villous atrophy in four (4) cases and partial villous atrophy in 16 cases. One case had only chronic inflammatory cell infiltrate without villous abnormality.

Response to Therapy

Patients were treated with folic acid along with either tetracycline or another antibiotic. All patients showed good initial response with decrease in bowel frequency, weight gain, disappearance of oedema and raise of haemoglobin level. Only four(4) patients returned for follow up one month after discharge. Physical examination and laboratory data revealed continued improvement. Two patients presented with recurrent attack with good response to therapy during each attack.

Table-II

Laboratory data.

	Male	Female	Total / %
Mean Hb level	10.76 $\pm$ 2.57gm/dl	9.99 $\pm$1.57gm/dl	9.71$\pm$ 2.3 gm/dl
MeanWBC count	10.88X 10^9	8.7X10^9	9.96X10^9
Mean STP	61.0$\pm$ 8.6gm/dl	60.14$\pm$ 14.91gm/dl	60.64$\pm$ 11.18gm/dl
Mean serum albumin	33.75$\pm$ 8.24 gm/dl	26.71$\pm$ 10.84gm/dl	31.16$\pm$ 9.64gm/dl
Faecal fat	4	4	34.78%

Discussion:

Tropical sprue, a primary malabsorption syndrome affecting residents and visitors to several tropical regions occurs in India in epidemic and endemic form[16]. Epidemic tropical sprue has been best characterized in southern India but also in Burma, Bangladesh, and the Philippines, usually as a sequela to an outbreak of infectious diarrhoea[17]. Being a tropical country and in the regional territory of Indo-Pak subcontinent "tropical sprue" presumed to be prevalent in Bangladesh. Clinicians come across cases of tropical sprue in their daily practice. But no report has yet been published on tropical sprue in Bangladesh. This report aimed to give a description of tropical sprue in admitted patients in gastroenterology unit in Bangabandhu Sheikh Mujib Medical University, Dhaka in last 20 years.

The lower prevalence of TS (M: F = 1.9:1) in females may be related to lower access of females to health care facilities in Bangladesh. Like other previous reports[13, 14] patients mostly presented with loose motions (82.6%) and progressive weight loss (73.91%); only two presented with weight loss and anaemia without diarrhoea. In southern India, 1% of patients with endemic TS presents with nutritional deficiencies in the absence of diarrhoea[16]. Like other reports[17] a good no of TS patients presented with abdominal pain/cramp (26.02%) and fever (43.5%) with loose motion. Two patients presented with cardiomegaly and pleraral effusion and another two persons with ascites. Underlying disorders of congestive heart failure and cirrhosis were excluded in these patients. These patients improved significantly following treatment with transfusion, nutritional supplements and antibiotic therapy. A patient with Billroth type II operation presented with chronic diarrhoea and weight loss 8 years after surgery. This patient also responded to usual treatment of TS.

Laboratory data revealed low mean haemoglobin (9.71gm/dl) and albumin (30gm/l) suggesting malabsorption in these patients. Though quantitative faecal fat estimation is not available in our country, qualitative faecal fat analysis gave positive results in only 8 cases (34.78%) cases which may be related to low fat intake by our indigenous population[10] as described in previous reports. Due to lack of facilities, culture of jejunal aspirate and other malabsorption studies could not be done in these patients. The findings of partial or subtotals villous atrophy along with infiltration of chronic inflammatory cells in lamina propria in distal duodenal biopsies (91.3 % cases) are consistent with the other studies [5, 7].

Like previous reports [5, 8, 11] patients treated with either tetracycline or ciprofloxacin along with folic acid showed good initial response with improvement of bowel motions, weight gain and anemia. Clinical improvement of patients despite not on elimination diet (gluten free) provided strong evidence against coeliac disease. Only 4 patients returned for follow up and demonstrated continued improvement. Only two patients presented with recurrent attack with good response to treatment in each attack.

As this is a retrospective data the report has much inherent weakness. Patients were not randomly selected and the number of sample was small too. Much information is lacking, such as socio-economic status, food habit, general hygiene etc. Patients could not be appropriately investigated due lack of facility. Majority of the patients could not be followed up, as they did not return for follow up. Despite this report expected to provide preliminary information on tropical sprue in our country and likely to inspire researchers to carry out well designed studies on this subject.

Conclusion:

Present report suggests that as a cause of chronic diarrhoea and malabsorption, TS is also prevalent in our country. A good number of tropical sprue cases presents with abdominal pain and fever along with common features of loose motion, weight loss, anaemia, oedema and skin changes. Laboratory data revealed low mean hemoglobin and albumin levels and normal or increased faecal fat concentration in these patients. Villous changes along with chronic inflammatory cells infiltrate in mucosa were present in most of the cases. Al the patients showed good initial response to treatment with antibiotic and folic acid.

But much of the presentation and treatment of TS is not yet addressed in our country. The incidence and prevalence of TS in Bangladesh is also not known. Proper investigation facilities are to be available to exclude TS cases from Caeliac disease, SIBO and other common malabsorptive disorders. Further well-designed studies are needed involving a large number of random population and with appropriate investigations to find

out accurate prevalence, incidence, presentation and treatment response of TS.

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First Degree Relatives of Bangladeshi Prediabetic Subjects are at Increased Risk for Developing Glucose Intolerance

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Summary:

Background: The racial variation in genetic susceptibility of Type2 diabetes mellitus is well established. The stages of impaired fasting glucose (IFG) and/or Impaired glucose tolerance (IGT) (collectively known as 'prediabetic stages) are combined to be intermediate in the natural history of diabetes, but their genetic susceptibility are still a matter of investigation. Family study is the primary step to explore genetic susceptibility. In particular, there has been no study in Bangladesh related to genetics of prediabetes.

Objectives: The present study aimed to explore the genetic susceptibility of prediabetes in Bangladeshi population by observing the clustering of dysglycemia in first degree relatives of prediabetes.

Methodology: The study was designed as an experimental group comparison study. Newly detected prediabetic subjects (isolated IFG, IGT, IFG+IGT) were collected from BIRDEM OPD and reconfirmed by OGTT following WHO guidelines and sub grouped.

Relatives of the prediabetes, up to first generation, were included as cases and termed as R-IFG (first degree relatives of IFG), R-IGT (first degree relatives of IGT), R-IFG-IGT (first degree relatives of IFG-IGT) corresponding to the subgroups of prediabetes. Each relative underwent an OGTT following the same guideline.

Blood glucose was measured by glucose oxidase method.

Results: Different types of prediabetic subjects (IFG, IGT, IFG+IGT) and their first degree relatives (R_IFG, R_IGT, R_IFG+IGT) were studied. Among 41 first degree relatives of IFG (R_IFG), 2 (4.9%) had IFG, 4 (9.8%) had IGT, 1 (2.4%) had combined IFG+IGT, 5 (12.5%) had T2 DM and 29 (70.7%) had normoglycemia. Among 116 first degree relatives of IGT (R_IGT) none (0.00%) had IFG, 15 (12.9%) had IGT, 2 (1.7%) had combined IFG+IGT, 22 (19%) had diabetes and 77 (66.4%) having absolutely normal OGTT reports. Among 76 first degree relatives of IFG+IGT (R_IFG+IGT), 2 (2.6%) had IFG, 4 (5.3%) had IGT, 1 (1.3%) had combined IFG+IGT, 19 (25%) had diabetes and 50 (65.8%) were normoglycemic.

Conclusion: Clustering of pre-diabetes and diabetes is present in families of prediabetic subjects and they should be taken as a major target for primary prevention of these disorders.

Key words: Prediabetes, IFG, IGT, IFG+IGT, First degree relatives, Glucose intolerance.

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Introduction:

Diabetes is by far the commonest endocrine disorder in the wo-rld. The prevalence of diabetes (20-79 years) in South--East Asia in 2003 was 5.6% and predicted to be 7.5% in 2025 and in Bangladesh 3.9% in 2003 & predicted to be 4.8% in 2025[1].Asian Indians (like people from India, Pakistan, Bangladesh and Sri Lanka) have surprisingly high prevalence of type 2 diabetes compared to Caucasians. Excessive insulin resistance in Asian Indians compared to Caucasians may be one of the contributing factors. This difference in the degree of insulin resistance may be explained by either an environmental or genetic factors or by combination of both[2-9]. All forms of diabetes can pass through a stage

of IFG and/or IGT. In a study on Asian ethnicity, it was found that impaired glucose tolerance was more prevalent than impaired fasting glycemia in all Asian populations studied for all age-groups[10]. The rising prevalence rate of IGT may be mainly due to diabetogenic lifestyle factors that lead to obesity and increasing life expectancy. The rising prevalence of IGT is assumed to increase from 8.2 to 9.0% worldwide and 7.1 to 7.8% in Bangladesh from 2003 to 2025 in adults (20-79 yrs age groups)[1]. The crude prevalence of IFG was 12.4% in rural population of Bangladesh; the age-standardized prevalence of IFG was 13.0% [11]. Approximately 50% of people with IFG have IGT and 20-30% with IGT also has IFG[11]. About 25% of people with IGT progress to type 2 diabetes within 5 years, while the majority either remain within that category (50%) or revert to normal glucose tolerance (25%). Interestingly, there is a tendency for the prevalence rates of IGT to decline as those of type 2 diabetes mellitus (DM) rise, perhaps suggesting that areas with a high ratio of IGT:Type 2 DM are at an earlier stage of type 2 DM epidemic and thus a particular target for preventive strategies[12].

IFG and IGT are asymptomatic and unassociated with any manifested morbidity, but their sole significance lies in the fact that they predict future diabetes or cardiovascular diseases[13]. The main features of IFG/ IGT are: 1) a stage in the natural history of disordered glucose metabolism, 2) can lead to any type of diabetes, 3) increased risk of progression to diabetes, 4) some patients may revert to normoglycemia. Both IFG and IGT are similarly associated with an increased risk of DM. Risk is higher where IGT and IFG coexists[15]. IFG/ IGT is often associated with "Metabolic Syndrome", which includes obesity (specially abdominal or visceral obesity), dyslipidemia (high triglyceride level, low HDL level and smaller LDL particle diameter) and hypertension, along with glucose intolerance (type 2 diabetes mellitus, IGT or IFG) and hyperinsulinemia. Evidence is accumulating that insulin resistance may be the common etiological factor for the individual components of the metabolic syndrome. Both insulin resistance and impaired b-cell function are important pathophysiologic changes contributing to the onset and development of type 2 diabetes. It probably results from a genetically determined reduction in insulin sensitivity, compounded by exposure to the environmental factors, which further impair insulin action. A striking feature of type 2 diabetes is the strength of its genetic component. In a study suggest a more pronounced effect of a family history of diabetes on risk of type 2 diabetes in men and women. While both a family history of diabetes and lifestyle risk factors had effects on type 2 diabetes, irrespective of sex, these effects did not appear to interact[16].

Apart from genes, families share environments, culture and habits, yet familial aggregation of the disease is another source of evidence for a genetic contribution to the disease. Abnormal glucose tolerance is common in first-degree relatives of type 2 Diabetes Mellitus patients; but first degree relatives of prediabetes are not studied yet. Impairment of insulin secretory capacity and / or insulin sensitivity is present among prediabetes subjects. So the present study is designed to detect glycemic status of first degree relatives of prediabetes subjects in search of genetic linkage of T2DM.

Subject and methods

The study was conducted in the Dept of Endocrinology and Diabetology and Biomedical Research Group, Research Division, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), Dhaka, Bangladesh, during the period of March 2006 - April 2007. It was a cross sectional study. The subjects were selected purposively. Total 303 subjects were included in the study, 41 first degree relatives (RIFG group) of newly detected 14 isolated IFG cases, 116 first degree relatives (RIGT group) of newly detected 36 isolated IGT cases and 76 first degree relatives (RIFG-IGT group) of 20 newly detected combined IFG-IGT cases were included in the study. Subjects of extreme of age (<10 years & >65 years), those with serious comorbid diseases (infection, stroke, myocardial infarction, major surgery, malabsorption, CLD, renal failure etc.), with history of using drugs significantly affecting glucose metabolism (glucocorticoids, phenytoin, estrogen, progesterone, testosterone, thiazide diuretics etc.) or pre-existing diabetes, were excluded from the study.

Collection of the subjects

Subjects were selected from the Out-Patient Department (OPD) of BIRDEM who diagnosed as prediabetes first

time, (Newly detected IFG subjects (Fasting serum glucose 6.1- 6.9 mmol/L and serum glucose 2 hour after 75 gm oral glucose <7.8 mmol/L), newly detected IGT subjects (Fasting serum glucose <6.1 mmol/L and serum glucose 2 hour after 75 gm oral glucose 7.8-11.0 mmol/L), newly detected combined IFG-IGT subjects (Fasting serum glucose 6.1- 6.9 mmol/L and serum glucose 2 hour after 75 gm oral glucose 7.8-11 mmol/L).

After taking brief history, the purpose of the study was explained in details to each subject. They were advised to take unrestricted carbohydrate diet, to do normal physical activities and to avoid drugs that significantly interfere with blood glucose level (like Glucocorticoids, oral contraceptives containing Levonorgestrel or high-dose estrogen, Phenytoin, high-dose Thiazide diuretics, etc.) for 3 days. They were also advised to abandon the program if they became sick. Then they were requested to report to Biomedical Research Group, Research Division, BIRDEM after 3 days at morning following an overnight (8-14 hours) fasting. When the subjects reported, informed written consent was taken and OGTT was done to reconfirm prediabetic state. After reconfirmation the subject was requested to bring their first-degree relatives at least of two generation, mentioning all the above prerequisites. Then sample was collected and printed questionnaire was filled up.

The subjects were selected purposively. About 1200 patient were interviewed at OPD, BIRDEM detected as a new case of IGR (IFG, IGT and combined IFG-IGT). Among them 410 IGR subjects were enlisted their name to recheck their IGR status at BMRG laboratory according to WHO criteria, but only 160 was reported, and they were reconfirmed as 22 IFG, 76 IGT, 38 IFG-IGT, 12 DM and 12 normal OGTT subjects. The IGR subjects were requested to bring their first degree relatives, at least 3 in number and if possible from two generations among parent, sibling and offspring. Finally 41 first degree relatives (RIFG group) of 14 isolated IFG subjects, 116 first degree relatives (RIGT group) of 36 isolated IGT subjects and 76 first degree relatives (RIFG-IGT group) of 20 combined IFG-IGT subjects were included in this study.

Analytical methods and lab analysis

Serum glucose (fasting and 2 hours after 75g glucose) was measured by Glucose-Oxidase (GOD-PAP) method (Randox Laboratories Ltd., UK).

Statistical analysis

Statistical analysis was performed using SPSS (Statistical Package for Social Science) software for Windows version 10 (SPSS Inc., Chicago, Illinois, USA).

Results:

In this cross sectional study different types of newly diagnosed prediabetic subjects (IFG, IGT, IFG+IGT) and their first degree relatives (R_IFG, R_IGT, R_IFG+IGT) were studied. Total 303 subjects were included in the study, 41 first degree relatives (RIFG group) of 14 isolated IFG cases, 116 first degree relatives (RIGT group) of 36 isolated IGT cases and 76 first degree relatives (RIFG-IGT group) of 20 combined IFG-IGT cases. Among them 129 (42.57%) were male and 174 (57.43%) were female. Ages of prediabetes subjects (IFG, IGT, IFG+IGT) were with in 4^{th} decade and of their first degree relatives were (R_IFG, R_IGT, R_IFG+IGT) were in 3^{rd} decade. (Table I). Among the study population 213 (70.30%) resides in urban area, 35 (11.55%) in semi urban area and 55 (18.15%) in rural area. (Table I) Among 41 first degree relatives of IFG (R_IFG), 2 (4.9%) have IFG, 4 (9.8%) have IGT, 1 (2.4%) has combined IFG+IGT, 5 (12.5%) have diabetes and 29 (70.7%) having absolutely normal OGTT reports. Among 116 first degree relatives of IGT (R_IGT), none (0.00%) have IFG, 15 (12.9%) have IGT, 2 (1.7%) have combined IFG+IGT, 22 (19%) have diabetes and 77 (66.4%) having absolutely normal OGTT reports. Among 76 first degree relatives of IFG+IGT (R_IFG+IGT), 2 (2.6%) have IFG, 4 (5.3%) have IGT, 1 (1.3%) has combined IFG+IGT, 19 (25%) have diabetes and 50 (65.8%) having absolutely normal OGTT reports. (Table II). Considering IFG, IGT, IFG+IGT and Diabetes as abnormal OGTT group among the 303 study subjects including both prediabetes and their first degree relatives found that 66.7% of them were from urban residence, 14.3% from semi urban residence and 19% from rural communities (Table III).

Table I

Age, sex and residence status of the study subjects

Group	No.	Age, yrs	Sex		Residence		
			Male N (%)	Female N (%)	Urban No (%)	Semiurban No (%)	Rural No (%)
IFG	14	45±21	8 (57.1)	6 (42.9)	10 (71.4)	1 (7.1)	3 (21.4)
IGT	36	41±12	8 (22.1)	28 (77.8)	23 (63.9)	5 (13.9)	8 (22.2)
IFG+IGT	20	45±10	7 (35)	13 (65)	17 (85)	1 (5)	2 (10)
R_IFG	41	36±16	18 (43.9)	23 (56.1)	28 (68.3)	3 (7.3)	10 (24.4)
R_IGT	116	36±18	50 (43.1)	66 (56.9)	77 (66.4)	18 (15.5)	21 (18.1)
R_IFG+IGT	76	35±17	38 (50)	38 (50)	58 (76.3)	7 (9.2)	11 (14.5)
Total	303		129 (42.6)	174 (57.43)	213(70.30)	35 (11.55)	55 (18.15)

IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IFG+IGT, combined IFG & IGT; R_IFG, First degree relatives of IFG; R_IGT, First degree relatives of IGT; R_IFG+IGT, First degree relatives of IFG+IGT.

Table II

Pattern of Glycemic status among the first degree relatives of different prediabetic subjects

Group	Normal OGTT	Abnormal OGTT				
	Normal N (%)	IFG N (%)	IGT N (%)	IFG+IGT N (%)	DM N (%)	Total, N (%)
R_IFG, n=41	29 (70.7)	2 (4.9)	4 (9.8)	1 (2.4)	5 (12.2)	12 (29.3)
R_IGT, n=116	77 (66.4)	0	15 (12.9)	2 (1.7)	22 (19)	39 (33.6)
R_IFG-IGT, n=76	50 (65.8)	2 (2.6)	4 (5.3)	1 (1.3)	19 (25)	26 (34.2)

DM, diabetes mellitus; OGTT, oral glucose tolerance test.

Table-III

Area of residences of total study subjects characterized as having normal OGTT and abnormal OGTT

Group	Total, N (%)	Urban, N(%)	Semiurban, N(%)	Rural, N(%)
Abnormal OGTT	147 (100)	98 (66.7)	21 (14.3)	28 (19)
Normal OGTT	156 (100)	115 (73.7)	14 (9.0)	27 (17.3)

Discussion:

Diabetes mellitus is distributed world wide mostly type 2, without any sex difference. Risk of type 2 diabetes increases after 40 years of age but happened at earlier age due to change of life style and dietary habit, less physical activity and weight gain. In this study 129 (42.57%) were male and 174 (57.43%) were female subjects. Age of different prediabetes were in same decade (4th decade) and that of their relatives were match within their group (3rd decade). Among the study population 213 (70.30%) resides in urban area, 35 (11.55%) in semi urban area and 55 (18.15%) in rural area. Majority of the study subjects were from urban area with female preponderance and among the relatives, those had abnormal OGTT, majority were from urban residence. A distinguished number of first degree relatives found to have different form of glucose intolerance namely IFG, IGT, IFG+IGT and diabetes which were detected first time. We know prediabetes is a stage of natural history of any form of diabetes. Type 2 diabetes has a strong genetic susceptibility as evident by familial aggregation of this disease for decades, but

susceptible genetic locus had not been well established now. A study on Chinese population shows abnormal glucose tolerance is common in first-degree relatives of non-insulin-dependent Diabetes Mellitus patients; both insulin resistance and impaired beta cell function are associated with impaired glucose metabolism, which have existed before diagnosis of IFG, IGT and diabetes[17]. Both insulin resistance and impaired b-cell function are important pathophysiologic changes contributing to the onset and development of type 2 diabetes. These and changes in lipid profile have occurred before a patient is diagnosed with abnormal glucose tolerance[18]. No study was found among the first degree relatives of pre-diabetic subjects. In this study all form of glucose intolerance were found among the relatives, signifies that any types of pre diabetes state (IFG, IGT, IFG+IGT) can be the initial abnormal glucose tolerance among the first degree relatives of prediabetic subjects leads to clinical diabetes. Subjects those had abnormal OGTT reports among the total study subjects including both prediabetes and their first degree relatives showed that 66.7% of them were from urban residence, 14.3% from semi urban residence and 19% from rural communities. In this participation from urban area was greatest may be due to more convenience and awareness about diabetes. But most abnormal glucose reports were from urban communities that may be due to diabetogenic life style. Prediabetic subjects are at increased risk of developing diabetes. For primary prevention of type 2 diabetes among them several studies were carried out. Remarkable studies for primary prevention are Diabetes Prevention Program Study, Finnish Diabetes Prevention Study, STOP-NIDDM, TRIPOD, DREAM and XENDOS study [19-24]. Maintenance of ideal body weight, weight reduction if over weight or obese, practice of healthy diet of proper calorie, regular physical exercise are the tools identified as preventive measures. Intensive nutritional and exercise counseling along with or without drugs is the way of prevention. Drugs used in those different studies are Metformin, Rosiglitazone, Troglitazone, Acarbose, Orlistate and Ramipril. Promising result is found. So, from our study first degree relatives of prediabetes are at increase risk of developing any form of glucose intolerance (IFG, IGT, IFG+IGT, diabetes) and the target for prevention of type 2 diabetes.

Conclusion:

Clustering of pre-diabetes and diabetes is present in families of prediabetic subjects. So they should be taken as a major target for primary prevention of diabetes and prediabetes as like as first degree relatives of type 2 diabetic subjects.

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Biological Agents in the Treatment of Rheumatoid Arthritis

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Summary:

Rheumatoid arthritis (RA) is the commonest joint disease with considerable morbidity and mortality. Conventional disease modifying antirheumatic drugs like methotrexate form the cornerstone of therapy. These drugs have several limitations in terms of slow onset of action, adverse effects and modest remission rates. Several cytokines are involved in the pathogenesis of RA. Biological agents that specifically inhibit the effects of tumour necrosis factor-alpha (TNF-a) or interleukin-1 (IL-1) represent a major advancement in the treatment of RA. By targeting mediators that are directly involved in the pathogenesis of RA, these agents slow the radiological progression of bone and cartilage damage in joints, prevent or delay the onset of disability.

These are highly specific and better tolerated. The use of these biological agents needs careful monitoring for side effects, including the development of infection. Additional anti-cytokine agents for the treatment of RA are under further development.

Key words: Rheumatoid arthritis, biological agents, inflammatory cytokine.

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Introduction:

Rheumatoid arthritis is a chronic inflammatory disease. Established treatment is limited because of the unsatisfactory clinical response or the development of unexpected adverse events with the drugs used. In recent years intensive research into the pathogenesis of RA has yielded information which permits clear insights into the mechanism of the underlying disease. Inflammatory cells produce a number of cytokines, which play a role in inflammation leading to damage to the bone and cartilage. These findings finally led to the development of biological agents for the treatment of rheumatoid arthritis. These agents target cytokines such as tumour necrosis factor-alpha (TNF-a), interleukin-1 (IL-1), interleukin-6 (IL-6) or cell surface molecules such as (CD4, CD5, CD7, IL-2 receptor, CDw52 or CD54). New biological agents evaluated for treatment of RA have shown much success in different clinical trails[1]. RA is no longer considered a benign disease. Statistical analysis has shown increased mortality in patients with RA compared with average population[2].

Biological agents are recommended for the treatment of rheumatoid arthritis, juvenile chronic arthritis, still's disease, ankylosing spondylitis, psoriasis, psoriatic arthritis, castleman's disease, B-cell lymphoma, crohn's disease, vasculitis (refractory wegener's granulomatosis, life threatening Behcets disease)[3].

This review article will give a short overview on the various biological agents recommended in the therapy of rheumatoid arthritis (RA).

Pathogenesis of Rheumatoid Arthritis

Rheumatoid arthritis (RA) is characterised by persistent inflammatory synovitis. It predominantly affects the peripheral joints. Exact aetiology of RA is not known. Different research works suggest that RA is caused by an unidentified arthritogenic antgen[4]. The antigen could be either exogenous such as viral or bacterial protein or endogenous such as human cartilage glycoprotein 39 or heavy chain-binding protein[5].

Antigen-activated CD4+ T-cells stimulate monocytes, macrophages and synovial fibroblasts to produce various cytokines. Tumour necrosis factor - alpha (TNF-a), interleukin -1 (IL-1) and interleukin-6 (IL-6) are the key cytokines that drive inflammation in RA and cause

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joint damage. They are potent stimulators of synovial fibroblasts, osteoclasts and chondrocytes that release tissue destroying matrix metalloproteinases (MMP), which centribule to joint damage[6].

Activated CD4+ T-cells also stimulate B cells to produce immunoglobulins including rheumatoid factor (RF). RF may involve the activation of complement through the formation of immune complex. The products of activated macrophages, lymphocytes and fibroblasts stimulate angiogenesis[7]. Inflammatory cells are recruited into the joint by expression of adhesion molecules in endothelial cells in the synovium. This leads to the formation of hyperplastic, proliferating, inflammed synovium also called "Pannus"[7]. Activated macrophages and synovial fibroblasts are present in the interface between the Pannus and cartilage causing damage to the joint[8]. There occurs progressive erosion of subchondral bone with Juxta-articular osteopenia. Destruction of bone and cartilage occurs progressively leading to significant disability[9].

Radiological evidence of substantial joint damage is seen within 2 years of disease onset. Evidence of bone erosion is seen within first-few months by magnetic resonance imaging (MRI). Osteoporosis due to reduced bone mineral density increases the risk of bone fracture[11-12]. Recent study have shown that 80% of patients with RA are disabled within 10 years and survival is reduced[13].

Indications and clinical considerations of biological agents

Biological agents are used in the management of Rheumatoid Arthritis (RA). Juvenile idiopathic arthritis (JIA), still's disease, ankylosing spondylitis, psoriasis, Psoriatic arthritis, crohn's disease, vasculitis (Refractory wegener's granulomatosis and Behcet's disease).

The onset of action is rapid and occurs within 2 to 4 weeks. Infliximab can not be used as monotherapy and has to be combined with methotrexate. Other agents can be used alone or in combination with methotrexate[14,15]. Cytokine antagonists should be withdrawn in the face of adverse events or lack of adequate response. If one TNF-a blocker fails, substitution with another agent may be helpful[16]. Cardiovascular disease is the major cause of increased mortality in RA due to accelerated atherosclerosis [17,18]. Cytokine antagonists have shown a favourable response in endothelial cell dysfunction in these patients[19].

Classification and mode of action of biological agents

Functionally biological agents can be divided into three classes.

1. Interfere cytokine function
2. Inhibit the second signal required for T-cell activation so called co-stimulation blockade
3. B cell depletion.

Infliximab, etanercept, adalimumab and the interleukin-1 (IL-1) receptor antagonist anakinra were the first generation of biologics approved in the treatment of RA. Abatacept, rituximab and tocilizumab represent the next generation of biologics in RA[22].

1. Interfere cytokine function

   The anti-cytokine approaches include

   a) Anti-tumour necrosis factor-alpha (Anti-TNF-α)

      Infliximab, Etanerecpt, Adalimumab

   b) Anti-interleukin-1 (Anti-IL-1)
      Anakinra

   c) Anti-interleukin-6 (Anti-IL-6)
      Tocilizumab

There are three types of anti-cytokine molecules:

   i) Soluble receptor antagonist - Etanercept

   ii) Monoclonal antibodies (mAb) to cytokines or to their receptors

      Infliximab, Adalimumab, certalizumab

   iii) Cell surface receptor antagonist protein: Anakinra, Tocilizumab.

2. Inhibit the "Second signal" required for T-cell activation, the co-stimulation blocker, Abatacept.
3. B cell depletion – Rituximab[20,21,22].

Dosage, administration, side effects and contraindications of a few biological agents used in the treatment of rheumatoid arthritis

Infliximab (remicade)

3mg/kg i.v infusion at weeks 0, 2 and 6 followed by maintenance dose every 8 weeks. Has to be combined with methotrexate.

Side effects – Infusion reaction (Fever, chills, urticaria, chest pain, dyspnoea, hypotension), antibody formation,

infection, upper respiratory infection, reactivation of tuberculosis (TB), exacerbation of demyelinating disease,

contraindications – Active infection, uncontrolled diabetes mellitus, surgery (withhold for 2 weeks post-operatively)[23,24,25].

Etanercept (enbrel)

25 mg subcutaneonsly twice a week or 50mg once a week. May be given with MTX or as monotherapy.

Side effects – Injection site reactions, upper respiratory infection, development of anti-nuclear antibody (ANA), infection, reactivation of TB, exacerbation of demyelinating disease.

Contraindications – Active infection, uncontrolled DM, Surgery (withhold for 2 weeks post operatively)[26,27].

Adalimumab (humira)

40 mg subcutaneously every 2 weeks. May be given with MTX or as monotherapy.

Side effects – upper respiratory infection, injection site pain, rash, headache, sinusitis, infection, exacerbation of demyclinating disease.

Contraindications – Active infection [26,27].

Anakinra (kinaret)

100 mg subcutaneously once daily. May be given with MTX or as monotherapy.

Side effects – Injection site reaction, infection, neutropenia.

Contraindications – active infection[28].

Tocilizumab

8gm/kg subcutaneously every four weeks[29].

Safety Issues in Biological Agent Therapy

The cytokines play an important role in protective immunity. The risk of infection increases with the use of anti-cytokines[30]. Reactivation of tuberculosis occurs mostly with infliximab. Opportunistic infection and lymphoma has been reported with the use of TNF-a antagonists[31,32]. Demyelinating disorders may occur by therapy with all biological agents except anakinra[33]. Injection site reaction can occur[34]. Rarely bone marrow aplasia have been reported. Increased severity of heart failure, hepatotoxicity and drug induced lupus can occur. The side effects are mild, self limiting and seldom enough to warrant discontnuation of biologics. Severe adverse events are rare. Proper patient selection and preventive measures may limit the risks further[35].

Pre-Treatment Consideration in Biological Agent Therapy

Existance of any contraindications to the use of biological agents needs to be considered before commencement of therapy. Absolute contraindications for the use of TNF-a blockers are active infections (Including infected prosthesis, severe sepsis), recurrent or chronic infections (such as branchiectasis, untreated tuberculosis), moderate to severe congestive cardiac failure, Multiple sclerosis, optic neuritis, combined treatment with anakinra (IL-1 receptor antagonist). Active or recent history of malignancy except skin cancer. Relative contraindications are pregnancy, lactation, HIV, HBV and HCV infection[36].

Monitoring during therapy with biologics

Clinicians should be aware of potential treatment related adverse effects and monitor the patient accordingly. Most important adverse effects of anti TNF-a therapy is increased risk of severe infections due to blockade of pro-inflammatory cytokines. The half life of biological agents become relevant. Adalimumab has long half life of 2 weeks and produce a longer period of immunosuppresion with risk of infection per dose. Care should be taken for diabetic patients. Cutaneous injection site reaction consists of local erythema and swelling which usually subsides within 24 hours. It can be lessened by predosing with antihistamine. Intravenous infusion reactions are fever, chills and nausea. These can also be prevented by premedication[37].

Impact of biological agents in current clinical practice

Biological response modifiers represent advancement in the treatment of RA. Disease activity can be well controlled and joint function improves almost to normal. There are still some non-responders and newer agents address some of these needs[38].

Future trends of biological agents

Anti- TNF-a preparations that are given as monthly subcutaneous injections are currently being developed[38].

Conclusions:

The availability of biological agents that target specific cytokines involved in the joint destruction will raise the

new era in the treatment of RA. The major hindrance to the use of cytokine antagonists is their cost. Epidemiological studies will be needed to document the long term benefits and risks associated with the cytokines.

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Headache following Spinal Anaesthesia : A Review on Recent Update

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Summary:

Central neuraxial block is an extensively implemented technique in anaesthetic practice. Spinal dural punctures occur deliberately in spinal anaesthesia and inadvertently during attempting epidural blocks. The incidence of disabling headache following dural perforation ranges from 0.3 to 20% in spinal anaesthesia and may be upto 70% after accidental dural puncture in epidural anaesthesia. Decreased CSF volume causing reduced pressure and responsive cerebral venodilation due to CSF leakage are deduced as the prime reasons for this post-dural puncture headache (PDPH). The headache is self-limiting and 88% of it resolves without any interference, if not superimposed by any pre-existing or a de novo *complication. Anaesthesiologists have been perpetually active in reducing the incidence. Int'l and regional working groups have advocated the use of fine gauge pencil-point needles, delicate bevel orientation techniques, some new drug regimens and various useful and effective measures for the treatment and prevention of PDPH. This review considers some contentious aspects of pathogenesis, treatment and prevention of PDPH and summarises the recommendations incorporated with updated guidelines of American Society of Regional Anesthesia (ASRA) and Society for Obstetric Anesthesia & Perinatology (SOAP) for the management of PDPH.*

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Introduction:

Central neuraxial anaesthesia is the sensory neural transmission blockade using local anaesthetics and other additives. It is performed by putting the blocking agents in the vicinity of spinal neural tissues. For spinal anaesthesia (subarachnoid block, SAB) a deliberate lumber puncture (LP) occur below L_1 in adults (L_3 in child) to access the subarachnoid space avoiding the needle trauma to the cord.[1] Epidural or extradural anaesthesia offers a wider range of applications throughout the dorsal vertebral column.

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Historical Background

Early days of PDPH: In 1891, Wynter and Quincke aspirated cerebrospinal fluid (CSF) from subarachnoid space for treatment of intracranial hypertension in tubercular meningitis, and would certainly have led to PDPH. In 1898, Karl August Bier, a German surgeon, injected cocaine into subarachnoid space of seven patients, himself and his assistant, Hildebrandt. Bier, his assistant and four of his subjects all described the symptoms associated with PDPH.[2] Bier surmised correctly that the headache was attributable to loss of CSF.

Factors considered responsible for PDPH

Anatomical aspects of PDPH: Recent light and electron microscopic studies of human dura mater have contested the conventional concept of fibre direction that it is longitudinal. It described that there are several layers of both collagen and elastic fibres parallel to the surface and do not demonstrate specific orientation.[3] The outer or epidural surface may have longitudinal fibre direction, but this pattern is not repeated in successive layers. Recent studies have also projected that the posterior dura varies in thickness at different spinal levels within an individual and between individuals.[4] So, perforation in a thick area is less likely to lead to a CSF leak than in

a thin area, and may explain the unpredictable consequences.

Needle tip design: Patients who receive spinal anaesthesia with small gauge (24-30G) non-cutting needles generally have a reduced risk of PDPH.[5] Using smaller Gauge needle with an atraumatic spreading bevel tip can further reduce the incidence of PDPH. Green in 1926 showed that blunt-tipped spinal needles that separate dural fibres and allow recoil with minimal tearing significantly reduce CSF leak and PDPH.[6] The disadvantages of atraumatic needles include increased cost, lack of pop felt upon piercing the dura and difficulty in penetrating skin due to dull tip. Inadvertent dural perforation by Tuohy needles those are used for applying epidurals, whether the puncture is recognised by CSF visualisation or remained undiagnosed, have been considered as a potential factor to develope PDPH.

Patient factors: Patient-dependent factors of PDPH include age, gender, body mass index (BMI) (low BMI is a risk factor for PDPH), pregnancy and recurrent history of headaches. Race does not seem to be a risk factor for PDPH.[7]

The age group at highest risk is 18 to 40 years, being 3-4 times that at age of 65 years.[8] Children younger than 13 years rarely get PDPH due to their lower CSF pressure. There is decreased incidence after 60 years, which may also be related to reduced CSF pressure.[9] Also, older patients have lower sensitivity of vascular pain receptors and have narrowed route of CSF escape from the epidural space.

Female sex regardless of the age is also a risk factor for PDPH. Women have twice the likelihood compared to men. In general, headache is a common symptom, reported by more than 80% of women of child-bearing age. As many as 40 % of obstetric patients not receiving any neuraxial anaesthesia complain of headache during the peripartum period[10], emphasizing the need to rule out other causes of headache.

Obstetric patients are particularly vulnerable to PDPH. They are young, female, pregnant, and many receive epidural procedures for labour and delivery. Another possible predisposing factor to PDPH in pregnancy is lowering of intra-abdominal and epidural pressure after delivery, which promotes extra leakage of CSF.[11] Stress of labour, changing hormonal level and dehydration may also contribute to increased incidence of PDPH during pregnancy.

Operator factors: The incidence of inadvertent dural puncture during epidural anaesthesia is inversely related to operator experience.[12] However, sleep deprivation, operator fatigue and the effect of night work may be a confounding variable producing the higher incidence of accidental dural puncture by junior personnel performing epidural analgesia.

Pathogenesis of PDPH

Dural response to trauma: It is now claimed that the repair of a dural perforation is facilitated by the fibroblastic proliferation from surrounding tissues and promoted more by the damage to pia, arachnoid, the underlying neural structures and presence of blood clot.[13] So, a careful placement of spinal needle does not promote dural healing, as trauma to adjacent tissue is minimal in this instance. Indeed, it is now observed that bloody taps are less likely to lead to PDPH.[14]

Consequences after cutting tip puncture compared to spreading bevel: Insertion of needle with cutting bevel parallel to the long axis of the spine decreases the likelihood of PDPH as fewer fibres are cut compared with perpendicular orientation. Tearing of the dura may occur upon removal of the needle if it is rotated to a perpendicular orientation after insertion. Bevel orientation is not an issue with atraumatic needles as they separate the dural fibres rather than cutting them allowing them to return to their original position with decreased CSF leakage.[6]

Contact with bone during needle insertion of both cutting and spreading type may lead to tip deformation. Damaged tips could lead to an increase in size of subsequent dural perforation. Recent *in vivo* studies have demonstrated that mostly the beveled spinal needles get deformed after bony contact than the comparable sized pencil-point needles.[15]

Theories and mechanisms of PDPH: Puncture of dura has the potential to allow the excessive leakage of CSF which leads to intracranial hypotension due to reduction in CSF volume. After development of PDPH, a CSF leak has been confirmed with radionuclide cisternography (Figure-I), radionuclide myelography, manometric studies, epiduroscopy and direct visualization at laminectomy. The adult subarachnoid pressure of 5–15 cm H_2O is reduced to 4.0 cm H_2O or less. The rate of CSF loss through the perforation (0.084–4.5 ml s^{-1}) is generally greater than the rate of CSF production (0.35 ml min^{-1}), particularly with

needle sizes larger than 25G.[16] Gadolinium-enhanced MRI, in the presence of a PDPH, frequently demonstrates 'sagging' of the intracranial structures.

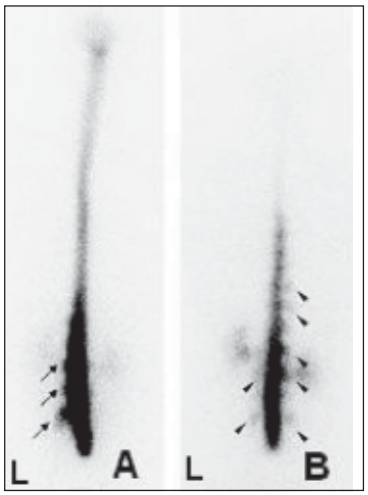

Fig.-1: *Radioisotope cisternography images in two patients of PDPH. A. Parathecal activity at lumbar level (arrows). B. Parathecal activity at both lumbar and thoracic levels (arrowheads). L: left side. (Reproduced from Takahashi K, Mima T. Cerebrospinal fluid leakage after radioisotope cisternography is not influenced by needle size at lumbar puncture in patients with intracranial hypotension. CSF Research 2009; 6:5)*

There are two possible mechanisms of headache. First, the lowering of CSF pressure causes traction on the intracranial structures in upright position. These structures are pain sensitive, leading to the characteristic headache. Secondly, the loss of CSF produces a compensatory venodilatation as per the Monro–Kellie doctrine.[17] The consequence of a decrease in CSF volume is a compensatory increase in blood volume. The venodilatation is then responsible for headache.

Incidence of PDPH

Concerning the needle tip design: The reported incidence of PDPH ranges from <3% to 75%, depending on various contributing factors.[9] This wide range is due to variable degrees of risk between different patient populations and dural puncture techniques. Reducing the size of spinal needle narrower to 31G has made a significant impact on incidence (Table-I).[18] However, technical difficulties leading to failure of the spinal anaesthetic are common with needles of 29G or narrower. Today the use of fine gauge pencil-point needles has largely reduced the incidence of PDPH (Figure - II).

Table I

Relationship between needle size and incidence of PDPH.[18]

Needle tip design	Needle gauge	Incidence of PDPH (%)
Quincke	22	36
Quincke	25	3–25
Quincke	26	0.3–20
Quincke	27	1.5–5.6
Quincke	29	0–2
Quincke	32	0.4
Sprotte	24	0–9.6
Whitacre	20	2–5
Whitacre	22	0.63–4
Whitacre	25	0–14.5
Whitacre	27	0
Atraucan	26	2.5–4
Tuohy	16	70

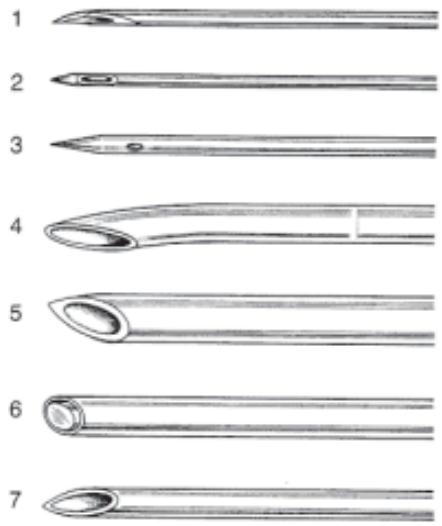

Fig.-2: *Graphical representations of needle used for central neuraxial blocks. 1. 26G Quincke® medium cutting bevel; 2. 26G Sprotte® pencil point; 3. 22G Whitacre pencil point; 4. 16G Tuohy needle; 5. 17G Barkers needle; 6. Large gauge spinal needle; 7. 18G Crawford needle. Needles 5, 6 and 7 are from the Sheffield Anaesthetic Museum and are an indication of the style of spinal needles used in the past. (Reproduced from Geurts JW, Haanschoten MC. Post-dural puncture headache in young patients. Acta Anaesthesiol Scand 1990; 34: 350–3).*

During applying epidurals, the incidence of accidental dural puncture (ADP) is in between 0.7 and 2.6%. The incidence of ADP with a Tuohy needle, unrecognized by CSF visualization, but subsequently diagnosed by onset of PDPH, is 1.8%. PDPH may also be even due to a scratch by the tip of a Tuohy needle on the dorsal dura.[19] The highest incidence of PDPH follows ADP during attempted epidural anaesthesia. An incidence of PDPH as high as 75% following an ADP using 17/18G Tuohy needles has been documented.[20] ADP occurs if the dura is perforated by the Tuohy needle or if the Tuohy needle damages the dura which is subsequently perforated by the epidural catheter.

Concerning patients and procedures: The parturients, scrupulously suffer from PDPH following spinal anaesthesia. They are also at particular risk of dural puncture and the subsequent headache because of their sex, young age, and the widespread application of epidural anaesthesia. As many as 26% of ADPs remain unrecognized at the time of the procedure and first present as PDPH in the early puerperium (Figure-III). Loss of resistance to air (LORA) confers a higher risk of dural puncture than loss of resistance to saline (LORS). The incidence of postpartum headache following epidural labour analgesia without clinically evident dural puncture is 12%. After a puncture with a 16G Tuohy needle, up to 70% of subjects reported symptoms related to low CSF pressure. Indeed, even up to 39%[21]of parturients who have not received neuraxial block report symptoms of a headache following delivery.

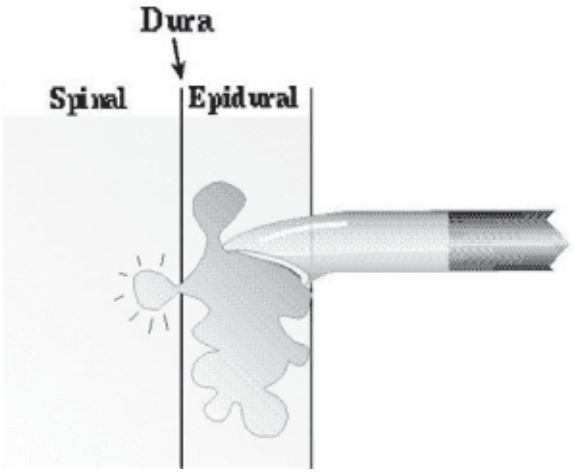

Fig.-3: *Unrecognised dural puncture by Tuohy needle. (Reproduced from Joseph Eldor, MD. Combined Spinal-Epidural Anesthesia. www.csen.com)*

Diagnostic Lumbar Puncture (LP): PDPH after diagnostic LP has an incidence of 6-40%, (the standard 20 or 22 G Quincke cutting bevel needle may be as high as 40%), however this number is reduced to about 5% when special measures are taken.[9] It should be acknowledged that the need for adequate CSF flow in diagnostic LPs limits the scope for reduction in needle size, but a needle with an atraumatic tip should be used.

Presentation of PDPH

Ninety per cent of headaches occur within 3 days of the procedure, and 66% start within the first 48 h. Rarely, the headache develops between 5 and 14 days after the procedure. Headache may present immediately after dural puncture.[22] However, this is rare and its occurrence should alert the physician to alternative causes.

Headache is described as severe, 'searing and spreading like hot metal', distributed over the frontal and occipital areas radiating to neck and shoulders. Neck stiffness may be present. Pain is exacerbated by head movement, and in upright posture, and relieved by lying down. An increase in severity of headache on standing is the hallmark of PDPH. Other symptoms include nausea, vomiting, hearing loss, tinnitus, vertigo, dizziness, paraesthesia of the scalp, upper and lower limb pain, visual disturbances and cranial nerve palsies.[23] Neurological symptoms may precede the onset of grand mal seizures.

Seventy two percent of headaches resolved within 7 days, and 87% had resolved in 6 months (Table-II).[24] In a minority of patients the headache can persist even for as long as 1–8 yr. It is interesting to note that even PDPHs of this duration have been successfully treated with an epidural blood patch.[25]

Table-II

Estimated rate of spontaneous recovery from post-dural puncture headache[24]

Duration (days)	Percentage recovery
1–2	24
3–4	29
5–7	19
8–14	8
3–6 weeks	5
3–6 months	2
7–12 months	4

Diagnosis and differential diagnosis: The history of deliberate or ADP, symptoms of postural headache, neckache and presence of neurological signs, usually guide the diagnosis. In case of doubt, additional tests may confirm the clinical findings. An MRI may demonstrate: diffuse dural enhancement with evidence of a sagging brain; descent of the brain, optic chiasm, and brain stem; obliteration of the basilar cisterns; and enlargement of the pituitary gland. A diagnostic LP may reveal a low CSF opening pressure or a 'dry tap', a slightly raised CSF protein and lymphocyte count. CT myelography or thin section MRI[26] can be used to locate the spinal source of the CSF leak. It is important to consider alternative diagnoses as serious intracranial pathology may pretend as a PDPH. Diagnoses that may masquerade as PDPH are shown in Table-III.[18]

Table-III

Differential diagnosis of post-dural puncture headache[18]

Viral, chemical or bacterial meningitis
Intracranial haemorrhage
Cerebral venous thrombosis
Intracranial tumour
Non-specific headache
Pituitary apoplexy
Cerebral infarction
Uncal herniation
Sinus headache
Migraine
Drugs (e.g. caffeine, amphetamine)
Pre-eclampsia

Approach to the problems and management principle

Over 85% of cases resolve with no treatment within 6 weeks (Table-III). However, a report identified 49 methods for treating PDPH.[27] There appears to be no limit to the imagination of physicians in treatments offered for it.

General measures

Reassurance appears as an effective remedy to the patients with PDPH. Patients may reveal a wide range of emotional responses from misery and tears to anger and panic. Obstetric patients are particularly unfortunate should they develop this complication, as they expect to feel well and happy and to be able to look after their new baby.[23] It is important to give the mother a thorough explanation of the reason for headache, the expected time course, and the therapeutic options available.

Supportive therapy such as bed rest, rehydration, acetaminophen, non-steroidal anti-inflammatory drugs, opioids, and antiemetics may control the symptoms and so reduce the need for more aggressive therapy, but may not provide complete relief.[28] But there is no point in administering fluids to a patient who is already appropriately hydrated.[59]

Posture that is comfortable is often identified by the patients without intervention of an anaesthetist and it is the supine position. The prone position has been advocated as it raises the intra-abdominal pressure, which is transmitted to epidural space and may alleviate the headache, although it is not comfortable for many as well as post-partum patients.[29]

Abdominal binders raise the intra-abdominal pressure which is transmitted to epidural space and may relieve the headache. Unfortunately, tight binders are uncomfortable and are seldom used in current practice.[30] There are few centres that would recommend this approach.

Theories that lead to different management

The main objective of the management of PDPH is interfering the CSF leakage. This can be achieved by the following specific approaches: (i) replacement of the lost CSF, (ii) sealing of the puncture and (iii) controlling the cerebral vasodilatation.

Caffeine is a CNS stimulant that produces cerebral vasoconstriction. It is available in an oral and i.v. form. Its enteral absorption is quick with a peak level within 30 min. The dose for PDPH now recommended is 300-500 mg of oral or i.v. caffeine once or twice daily.[31] One cup of coffee contains about 50-100 mg of caffeine and soft drinks contain 35-50 mg.

DDAVP (desmopressin acetate), i.m. before lumbar puncture is an option to reduce the incidence of PDPH. Its long-lasting antidiuretic and vesoconstricting action to restore CSF volume and pressure, and influence on increasing factor VIII and von Willebrand factor favouring quick sealing of dural perforation are thought to have role on relieving PDPH.[32]

ACTH (adrenocorticotrophic hormone)[33] has also been used as an infusion (1.5 μg kg^{-1}), but inadequate statistical analysis prevents assessment of the value of ACTH.

Sumatriptan is a 5-HT_{1D} receptor agonist that promotes cerebral vasoconstriction, in a similar way to caffeine. It is advocated for the management of migraine and recently, for PDPH.[34] Nanatriptan, zolmitriptan and rizatriptan are newer related drugs.

Theophylline administered orally or i.v. relieved symptoms of PDPH probably through its cerebral vasoconstrictive effects.[35]

Hydrocortisone i.v. has been used successfully after ADP by Tuohy needle. The outcome was good after failed conservative measures.[36]

Mirtazapine, a 5-HT_1 receptors (notably 5-$HT_{1B/1D}$) agonist has recently been tried to relief PDPH. It constricts dilated cerebral vessels and in addition, potentiates endogenous opioid systems.[37]

Gelatin powder (Gelfoam) and Fibrin glue has been proposed to repair spinal dural perforations. Cranial dural perforations are frequently repaired successfully with it. It may be placed blindly or using CT-guided percutaneous injection.[38] There is, however, a risk of development of aseptic meningitis with this procedure.

Epidural, intrathecal and parenteral opioids have been advocated by number of authors.[39] But a controlled trial of intrathecal fentanyl as prophylaxis found no evidence of reduction in incidence of PDPH after LP with a 25-gauge spinal needle.[40]

Intrathecal catheter placement through the ADP with a Tuohy needle may provoke an inflammatory reaction that will seal the hole. Evidence to support this claim is conflicting.[41] However, neurological complications preclude its usage.

Pregabalin, an anti-epileptic drug and a structural analogue of GABA have been tried recently and it caused a significant decrease in the difficult and severe PDPH's.[9]

Neural blockades of sphenopalentine ganglion and bilateral greater occipital nerves have been also applied recently for the minimal invasive and successful treatment of severe PDPH which does not respond to conservative treatment.[42]

Acupuncture is recognised as useful in the treatment of headaches of multiple aetiologies.[43] It is safe, has few risks and is minimally invasive in the hands of trained providers.

Surgical closures of dural perforation in instances of persistent CSF leaks, that are unresponsive to other therapies, have been reported with successful outcome.[44] This is clearly a last resort of treatment.

Special notes on EBP

After the observation that 'bloody taps' were associated with a reduced headache rate,[14] the concept of epidural blood patch (EBP) has developed.

Procedure is simple with the patient in lateral position; the epidural space is located with a Tuohy needle at the level of supposed dural puncture or an intervertebral space lower. The operator should be prepared for the presence of CSF within the epidural space. Twenty to 30 ml of blood is then taken from the patient's arm and injected slowly through the Tuohy needle. At conclusion, the patient is asked to lie still for one or, preferably, 2 h,[45] and is then allowed to walk. Contraindications are the presence of fever, infection on the back, coagulopathy, or patients' refusal and also include those that normally apply to epidurals.

The fate the blood patch has been assessed and reported by using either radiolabelled red cells or an MRI scan.[46] The mean spread of 14 ml of blood is 6 spinal segments cephalad and 3 segments caudad regardless of the bevel direction of Tuohy needle. After 7 days, a widespread fibroblastic activity and collagen formation have demonstrated in animal studies.[47] Fortunately, the presence of blood does not initiate an inflammatory process and no evidence of axonal oedema, necrosis or demyelination.

Outcome of EBP showed a success rate of 70–98%.[48] If an EBP fails to resolve the headache, repeating it has a similar success rate. Failure of the second patch and repeating a third or fourth one has been reported. However, in the presence of persistent severe headache, an alternative cause should be considered.

Prophylactic EBP is an attractive option where the known incidence of PDPH is high, such as in parturients. The blood patching is performed before the onset of symptoms. Controlled trials have confirmed the benefit of prophylactic patching.[49] A greater volume of blood

is needed to produce a successful patch compared with a late patch to avoid patch separation.

Epidural saline patch: Concerns have been expressed about the potential danger of an autologous EBP. As saline is relatively inert and sterile, and thought to have same mass effect, epidural saline appears to be an attractive alternative. There have been many regimens proposed for this therapy. One is to inject 40 ml of saline into the epidural space, and then an infusion of 40 ml/hr over next 12-24 hr.[50]

Epidural dextran: Some observers have considered the epidural administration of Dextran 40.[51] The studies conclude that the high molecular weight and viscosity of Dextran 40 slows its removal from the epidural space. The sustained tamponade around the dural perforation allows spontaneous closure.

Caudal epidural saline infusion has been used in PDPH which reduced the need for a blood patch or a saline epidural infusion.[52]

Prevention of PDPH

Needle tip design: The Quincke type is the standard tip-holed needle with a medium cutting bevel (needle-1, Figure-II). Then the 'pencil-point' or 'atraumatic' needles were developed, though in truth they are neither. Among those the Sprotte needle (needle 2, Figure-II) has a 'conical' tip and the tip of Whitacre needle (needle-3, Figure-II) is 'diamond' shaped. Clinical and laboratory[53] studies have confirmed that pencil-point tip-holed needles produce fewer PDPHs than medium bevel cutting needles. ASA guidelines 2007 have recommended that the pencil-point needles should be used instead of cutting-bevel needles to minimize the risk of PDPH.[54] However, these needles also have their limitations, such as obstruction of the delivery port by tissues affecting both cerebrospinal fluid flash back and drug delivery. In side-holed pencil-point needles, increasing the size of the lateral hole has led to mechanical complications, such as tip bending. A new spreading beveled tip-holed spinal needle has been designed by Jahangir SM to overcome the disadvantages of all the currently used spinal needles.[55]

Bevel orientation to dural fibres: There are many clinical, and laboratory,[56] studies that lend credence to the hypothesis that parallel bevel orientation to dural fibres of a spinal or epidural needle leads to a reduction in the incidence of PDPH. A delicate bevel orientation technique is postulated that it influences to produce a somewhat 'self-sealing' pattern of dural perforation (Figure-IV). But this technique is not yet accepted and recommended by any recognised authority of anaesthesiologists' professionals.

Limitations of fine bore spinal needles: Fine gauge spinal needles, 29G or narrower, are technically more difficult to use, and for SAB at least, are associated with a high failure rate. A balance has to be struck between the risks of PDPH and technical failure. 25G, 26G and 27G[57] needles probably represent the optimum needle sizes.

Conclusions:

Dural puncture procedures are commonly performed by various medical practitioners. The PDPH is a common complication resulting from intentional or accidental dural punctures. Patients who experience a PDPH should not be taken lightly. Data obtained from the ASA's closed claims analysis project showed that this is the third most common reason for litigation in obstetric anaesthesia.[58] Anyone being treated for a PDPH should receive reassurance as well as a full and frank discussion of treatment options.

The incidence of PDPH varies depending on various contributing factors which can be technical or patient dependant. Clinical diagnosis aided by history is the most important form of diagnosing PDPH; however, imaging may be done to exclude other causes of headache. The prime goal of treating PDPHs is restoring the CSF volume and pressure. Hydration and bed rest do little to prevent PDPH.

Analgesia plays a role in management of PDPHs, starting from mild analgesics initially, progressing to narcotics depending on severity of the headache. Other interventions include intravenous caffeine, intravenous theophylline, oral pregabalin, bilateral greater occipital nerve block, sphenopalentine ganglion block, caudal epidural saline infusions, epidural blood patch; however further randomised controlled trials are still needed to establish true roles of other treatment methods such as acupuncture, i.v. hydrocortisone, oral mirtazapine and caudal epidural saline infusions.

Using tip-holed spreading beveled spinal needle is mandatory to prevent the incidence of PDPH in intentional dural puncture procedures. Contacts of

needle tip with bones have to be avoided carefully. Development of operator skill in case of epidurals is also essential to reduce the incidence. Lose of resistance to saline technique is preferred to that of air during application of epidurals. Physicians have to consider the accidental unrecognized dural puncture during managing the post-procedural complications.

Epidural blood patch is the most effective form of managing severe headaches. Other therapies that have been offered have not always arisen through the application of logic or reasoning.[59] If PDPH persists untreated, may predispose to devastating complications such as subdural haematoma, herniation and even death, therefore prompt diagnosis and treatment is mandatory. It is wise to consider other causes of the headache before applying alternative and invasive therapeutic options.

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Non Hodgkin's Lymphoma Presenting with Urticarial Vasculitis – A Rare Association

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Summary:

Urticarial vasculitis (UV) has been described as a rare association with hematological malignancy. We report the case of a 52 year old patients of localized B-cell non-Hodgkin's lymphoma who presented with a recurrent non-painful urticarial type rash distributed around his face, arms, forearms, buttocks and lower legs since 1 year. The patient was managed by intensive combination chemotherapy (CHOP) regime for several cycles. The patient showed good response to treatment. The case is being reported because of the rare association of Non Hodgkin's lymphoma with urticarial vasculitis.

Key Words : Lymphoma; lymphadenopathy; chemotherapy; bone marrow; lymphoid; cutaneous; histology.

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Introduction:

Urticarial vasculitis (UV) has been described as a rare association with hematological and visceral malignancy. It is thought that tumour aassociated immune complexes might be involved in the pathogenesis of the vasculitis. Non-Hodgkin's lymphomas (NHLs) arise from the malignant, monoclonal transformation of lymphocytes. As a disease group they encompass a hodgepodge of histological types, cell lines and tumour grades. About 85% of NHLs derive from B cells, the rest from T cells. Low-grade disease predominantly occurs in elderly patients, with indolent courses and median survival times of 5–8 years. High-grade disease accounts for less than 5% of all NHLs and typically presents as rapidly progressive cancer in children and young adults. Intermediate-grade disease is the most common type, accounting for 65% of all NHLs and affecting any age group.[1]

Increased exposure to sunlight, with its resulting immunosuppressive effect, may be one of the factors for rise in incidence of Non Hodgkin's lymphoma.[2] Immunosuppression plays a role in the cause of some lymphomas. Transplant recipients are 35 times more likely than the general population to acquire NHL and the disease is a common manifestation of AIDS.

Numerous cutaneous manifestations can be associated with malignancies. About 50% of patients with lymphomas have cutaneous manifestations at some time during the course of disease. Epstein and MacEachenill divided cutaneous manifestations of lymphomas into specific malignant infiltrates and non-specific manifestations.[3] Specific malignant infiltrates are the ones which show characteristic malignant cells on histopathological examination. Non-specific lesions associated with lymphomas c be classified into infections, non-infective conditions and changes due to chemotherapy.[4] urticarial vasculitis is a cutaneous manifestation of visceral and haematological malignancy and is considered to be rare.[5]

Case Report

A 52-yr-old male presented with a 6 years of generalized arthralgia, myalgia and weight loss. On examination, he had a recurrent non-painful urticarial-type rash distributed around his face(Fig 1), arms, forearms, buttocks and lower legs since 1 year. The lesions persisted for 2–3 days and then subsided with residual pigmentation . The skin lesions developed three years after treatment of NHL. One month after the rash there was bilateral wrist and metacarpophalangeal joint synovitis. On systemic examination, the patient had right cervical, supraclavicular and bilateral inguinal lymphadenopathy .

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Investigations revealed an erythrocyte sedimentation rate (ESR) of 109 mm/h, C-reactive protein (CRP) concentration 157 mg/l, complement component C3 2.24 g/l (normal range 0.7–1.7 g/l) and C4 0.57 g/l (normal range 0.13–0.43 g/l). Screening for rheumatoid factor and autoantibody was negative. The peripheral blood film showed normocytic, normochromic RBC's showing little anisocytosis and poikilocytosis with eosinophilia. The platelet count of the patient was 1,80,000/cu mm and PTI (Prothrombin time index) was 80%. Lymph node biopsy showed an occasional lymphoid follicle with scanty mantle. The biopsy showed nodular architecture with replacement of parent tissue by sheets of small lymphoid cells having coarse chromatin scanty cytoplasm, cleaved nucleus with prominent indentations and infoldings. The cells were present diffusely in nodules. The medullary siniuses were congested and cords contained few plasma cells. The diagnosis of non hodgkins lymphoma (Monocytoid B cell type) was made. Bone marrow aspiration showed cellular marrow with normoblastic maturation with megaloblastic change. The megakaryocytes were normal in number and morphology. The marrow showed increased number of lymphoid and lymphoplasmacytoid cells constituting 20% of all nucleated cells. The myeloid:erythroid ratio was 1.6:1.

The ultrasound abdomen showed evidence of multiple enlarged hypoechoic abdominal lymph nodes seen involving paraortic, portocaval and coleliac axis groups with spleenomegaly. There was no free fluid in the abdomen. There was ultrasonographic evidence of cholelithiasis with splenomegaly with lymphadenopathy.

The skin biopsy showed following findings :- Epidermis was normal. Moderately dense mixed cellular infiltrate of lymphocytes, eosinophils and neutrophils was present in the papillary and upper dermis as well in betwen the dermal collagen fibres. Fibrinoid necrosis of vessel was absent but extravascated erythrocytes was noted (Fig 2). There was prominence of the endothelial cells lining the blood vessels with a chronic lymphocytic infiltrate around the dermal blood vessels.The pathology was consistent with urticarial vasculitis. A diagnosis of urticarial vasculitis was made and the patient was commenced on prednisolone 20 mg daily for recurring skin lesions and persistent synovitis. Two weeks later, there was a clear response to treatment, with resolution of the rash (with residual pigmentation) and no synovitis. ESR and CRP had also fallen and complement levels had normalized. His symptoms returned on reduction of the prednisolone dose, and methotrexate 10 mg weekly was commenced as a steroid-sparing agent. The patient was later put on intensive combination chemotherapy (CHOP) regime for several cycles. The patient showed good response to treatment.

Discussion:

People with NHL may be asymptomatic or may present with a range of features (e.g. painless lymphadenopathy, abdominal mass, weight loss or night sweats) or with symptoms specific to the tumour bulk in the involved sites, such as the tonsils, abdomen, thyroid or lung. [6,7] All patients require careful staging, which involves a thorough physical examination, CT scanning and bone marrow biopsy. Management is complex and requires referral to a cancer treatment centre. Patients with indolent lymphomas may undergo watchful waiting at first, but eventually they will require treatment with an alkylating agent such as chlorambucil, with or without steroid therapy. [8]The standard chemotherapy for intermediate-grade NHL is several cycles of CHOP (cyclophosphamide, doxirubicin, vincristine and prednisolone), administered intravenously and sometimes supplemented by radiotherapy. [9]Treatment of high-grade NHL is urgent, usually requiring intensive combination chemotherapy. Prognosis and response to therapy depends on the age of the patient and the tumour stage and subtype. Although UV is known to be associated with other connective tissue diseases, its association with malignancy is less well established. A review of the literature revealed five definite cases of UV associated with malignancy. [10] Two patients who had received therapy for Hodgkin's disease presented with UV. One case of UV associated with immunoglobulin A myeloma has been described[11] and two further cases have occurred in association with both metastatic adenocarcinoma of the colon[12] and metastatic malignant teratoma of the testes.[13]

To describe UV as a paraneoplastic phenomenon highlights the importance of excluding malignancy as an underlying cause. [14]While the histological appearances were not typical of a florid leucocytoclastic vasculitis in this case, in new-onset UV there may be little vessel wall disruption and only a minor degree of perivascular infiltration. [15]The exact pathogenesis of the

association with malignancy is unclear, but in malignancy immune defects occur which may give rise to complement fixation in vessel walls and subsequent development **of** a vasculitis.

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Heterotopic Pregnancy- Case Report

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Introduction:

Heterotopic pregnancy is the co- existence of an intrauterine and ectopic gestation. [1] In 1948, the spontaneous heterotopic pregnancy rate was calculated as 1 in 30 thousand pregnancies, based on an ectopic pregnancy incidence of 0.37% and dizygous twining rate of 0.8%. [2] In the 1980's, the number raised to 1 in 10 thousand due to an increased ectopic pregnancy rate. [3] Today, heterotopic pregnancies actually occur 1 in 3889 [4] to 1 in 6778 [5] pregnancies. In a review of 66 heterotopic pregnancies by Reece et al, [3] 93.9% were tubal and 6.1% ovaries.

Simultaneous existence of intra- and extra uterine pregnancies poses several diagnostic pitfalls. Heterotopic pregnancies are diagnosed in most cases after the development of symptoms and clinical diagnosis, and 50% of patients are admitted for emergency surgery following rupture.[1]

Similar to tubal ectopic pregnancies, the most common complaint is lower abdominal pain, occurring in 81.8% of patients. Peritoneal irritation occurs in 43.9% and vaginal spotting in 31.8%.[3] Routine Ultrasound detects only about 50% of tubal heterotopic pregnancies and the remainder is diagnosed at laparoscopy or laparotomy when patients become symptomic.[1] Serial levels of the â-subunit of human chronic gonadotropin (β-HCG) are not helpful due to the concomitant intrauterine pregnancy.

If patients are hemodynamically unstable, an exploratory laparotomy is warranted. If the diagnosis is suspected or the patient is symptomatic but hemodynamically stable, laparoscopy can be performed. Expectant management is not recommended, since β-HCG levels cannot be monitored adequately. Systemic methotrexate rate is contra indicated if a viable intrauterine pregnancy is present. Local injection of methotrexate with potassium chloride was not successful in a small case series.[6]

Case Report:

A 37 years old multigravid (G3P2) women came to a private clinic with 5 weeks of amenorrhoea with the complaints of severe lower abdominal pain, nausea and vomiting for the last 6 hours and with positive urine for pregnancy test. Her BP was 110/60 mmHg and pulse 85 beat per minute. On per abdominal examination abdomen was soft. A transabdominal Ultrasonography scan showed single early intrauterine pregnancy of 5.1 weeks duration with single fetal node. Fetal heart movement (FHM) and fetal movement (FM) not seen at scan. Fetal Biometry: GSD – 10.6 mm.

She was advised to do a repeat scan one week later. After 8 days again she had severe lower abdominal pain with passage of clotted blood and USG scan showed missed abortion, no mass of cyst could be seen in the abdominal region and dilatation and curettage was done. Histopathology report under microscopy showed: sheets of decidual tissue, blood clot and chorionic villi . Patient was discharged from hospital on the next day. Seven days later she had severe lower abdominal pain with fainting attack at home and BP was 80/50 mmHg, pulse was 120 bpm, Pervaginal examination was done and the result was cervix soft, OS 1.5 cm dilated, uterus was 10 weeks pregnancy size, fornices -right fornix full and tender. No palpable mass or cyst was felt in the left fornix. USG showed bulky uterus with mild PID, a well defined cystic area and thick wall seen in the right ovary measuring about 1.8*1.4 cm. A well defined fairly large mixed echogenic (Predominantly hypoechoic) focal lesion seen in the right adnexa, measuring about 6.1*3.8

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cm, left tubo-ovarian region appears to be normal. Serum â-HCG was 4539 mIU/ml, 60 laparotomy was done. Fallopian tube on right side was enlarged. Right sided salpingectomy and left sided tubal ligation was done. Patient and her husband gave consent for ligation. There was huge amount of blood and clots into the peritoneal cavity. After peritoneal toileting and haemostasis abdomen was closed in layers. She was transfused 2 units of blood. As Patient condition was stable, she was discharged on the next day.

Hispathology of the right fallopian tube showed marked oedema in the mucosa and serosa and lumen was dilated congested and contains chorionic villi and decidual changes along with blood clot in the fallopian tube. Diagnosis- ectopic tubal pregnancy.

Conclusion:

Diagnosis of ectopic pregnancy prior to rupture is an arduous task even with the availability of many new investigative methods and imaging modalities. A high index of suspicion is necessary when dealing with women who present in early pregnancy with abdominal pain and pervaginal bleeding. The use of transvaginal ultrasonography (TVS) and Sr. â HCG level will help in earlier diagnosis because of its advantages over transabdominal ultrasonography.[7]

This report should create the awareness of the possibility of heterotopic pregnancy in spontaneous cycles. With the increased use of ovulation induction agents, the probability of heterotopic pregnancy should be kept in mind.

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Successful Management of Massive Obstetric Haemorrhage due to Placenta Previa/Accreta – A Case Report

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Introduction:

Placenta accreta in association with placenta previa and previous caesarean delivery is a condition of increasing clinical significance[1]. Bleeding from placenta previa/ accreta of the lower uterine segment, during caesarean section operation or its immediate postpartum period portrays a difficult management problem in obstetrics. Approach to control such a bleeding depends upon the individual case and includes uterine packing, bilateral uterine artery ligation, bilateral internal illiac artery ligation, trans-catheter arterial embolization, and hysterectomy [2, 3]. One case of placenta previa/accreta with history of previous caesarean section with intractable postpartum bleeding is being reported here.

Keywords: Postpartum; Haemorrhage; Placenta previa/ accreta; Caesarean; Hysterectomy.

Case Report:

Mrs. Helena Khanam, a 35 years old, 2nd gravid patient, serving as senior staff nurse in General Hospital, Tangail, was admitted in labour ward of Dhaka medical college hospital on 1st of May, 2002 at 2:40am with the complaints of –

Severe per-vaginal bleeding following caesarean section and subtotal hysterectomy for 37 weeks of pregnancy with abdominal pain and gradual distension of abdomen for 9 hours. Indication of caesarean section was previous caesarean section with placenta previa.

She was a booked case of Gynae. out-patient department in Tangail General Hospital with regular antenatal check up. She delivered her first child by caesarean section 11 years back. During this pregnancy her antenatal period was uneventful, and she was non-diabetic, normotensive. Routine ultrasonography report revealed that placenta was in the lower uterine segment (placenta previa). According to her date of last menstrual period, her expected date of delivery would have been 17th of May 2002. So she was planned to deliver by caesarean section on 3rd May of that year.

On 30th April 2002, her labour pain started spontaneously. So she had undergone emergency caesarean section at 4:00 p.m. on the same day, and she delivered a mature healthy female baby. According to the operation note placenta was found morbidly adherent to the anterior wall of the lower uterine segment and also penetrated deeply through the uterine wall towards the urinary bladder. As the placenta was difficult to remove completely and uncontrollable bleeding started, so decision of subtotal hysterectomy was taken in the same sitting. The patient received 2 units of blood during her operation.

After half an hour following operation, she again started to bleed profusely per vaginally. Bleeding was so severe that she went to shock, and was managed by massive blood transfusion along with inj. Hydrocortisone, inj. Traxyl, inj. Adrenaline, inj. Caprolysin, and inj. Ergometrin. Condom catheterization was done in order to give compression over the remaining lower uterine segment. In the mean time, she received 23 units of blood and was referred to a renowned gynaecologist in a private clinic in Dhaka.

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On the way, she was unconscious, and was in shock, continuous blood transfusion and intravenous infusion was given via three intravenous channels. At the same time, she was also given inj. Hydrocortisone. Condom catheter was displaced there.

In the clinic, as the condom catheter was displaced, 3 mops were placed with an idea to pack the vagina. From there, she was immediately transferred to the labour emergency of Dhaka Medical College & Hospital, and was accompanied by the attending gynaecologist.

In DMCH, the patient was found in shock with cool and clammy skin, disoriented and restless. Patient was severely anaemic. Crepitations were present over both lung bases. Abdomen was tense and distended, and flanks were full. Patient was catheterized, and her urine output was satisfactory. A decision of laparotomy was taken.

Laparotomy was done with sufficient support of blood. Abdomen was opened through the previous incision. On opening the abdomen, abdominal cavity was found filled with blood clots, which were removed. Peritoneal toileting was done. Uterine stumps were ligated again. Remaining portion of lower uterine segment was removed. Abdomen was closed in layers after keeping a drain in situ. During the whole procedure, her blood pressure was maintained with inj. Adrenaline and blood transfusion. The indwelling catheter was kept in situ. A vaginal pack was given. From operation theatre, she was transferred to the Intensive Care Unit (ICU) of DMCH.

On the way to the ICU, she developed cardiac arrest, and was resuscitated successfully.

In ICU the patient was kept under positive pressure ventilation for 48 hours. There she developed focal convulsion, and was treated with anticonvulsant. After establishment of spontaneous respiration, endotracheal tube was removed, and subsequently she regained her consciousness fully.

When her general condition became stable, she was transferred to respective unit of Obstetrics department. Her basal parameters were monitored routinely from time to time. Her haemoglobin percentage was measured on every alternate day, and accordingly, she was given another several units of blood. Her general condition improved gradually. Laparotomy wound remained healthy. Stitches were removed on 10th POD. Throughout the whole event, the patient received a total 36 units of blood.

Discussion:

The successful management of massive obstetric haemorrhage demands speed skill and experience[4]. The essential management of major bleeding episodes is the same whatever the underlying causes of haemorrhage and involves –

1. Identifying the cause and treating it to stop blood loss as well as
2. Replacing the circulating blood volume and other blood constituents[5].

Placenta previa is more common in patients with a history of previous caesarean section with increasing incidence as the number of previous uterine scars increases[1]. Advancing age and parity are associated with the development of placenta previa, although the relative importance of these two factors is disputed[6]. Uterine scars, previous miscarriages, terminations, and dilatation and curettage are reported as predisposing factors, possibly due to endometrial damage[7]. There is an association between caesarean section scars and the subsequent development of placenta previa, which is reported as between 3% and 10% and increase with the number of previous caesarean section. This group of patients is also at risk of placenta accreta, which is stated at between 10% and 67%, again increasing with the number of previous caesarean section[6]. In our case patient had delivered her first child by caesarean section and in her second pregnancy she had placenta previa.

The morbid adherence of the placenta to the uterus is termed placenta accreta. The penetration of the placenta upto the myometrium is termed placenta increta, when it penetrates the myometrium to the serosa, the term placenta percreta is used[8]. In our patient it was not suspected that the myometrial invasion had taken place until portions of the placenta could not be separated evenly by digital dissection.

Because of the poorly contractile nature of the lower uterine segment, trophoblastic invasion may give rise to uncontrollable haemorrhage following placental removal, even without histological confirmation of placenta accreta[9]. In placenta accreta at emergency caesarean section attempts to remove the placenta are met with massive bleeding since no cleavage plane can be found[10].

The occurrence of an anterior placenta previa in a woman with a previous caesarean section scar should alert the obstetrician to the possibility of abnormal placental adherence. It is therefore prudent to warn the patient of the possibility of a caesarean hysterectomy in the event of uncontrollable haemorrhage[11]. There are several indications for emergency peripartum hysterectomy. The three most common reasons are uterine atony, placenta accreta and uterine rupture[12]. Majority clinicians in our country perform a subtotal or supracervical hysterectomy in most cases of emergency. As because there is a general belief that both operating time and blood loss are significantly lower with the subtotal technique. However even with this latter scenario, sometimes it is necessary to remove the cervix in case of placenta previa or placenta accreta involving the lower uterine segment. Somewhat surprisingly there is evidence that performance of a complete hysterectomy adds little to either operating time or blood loss[12].

Our patient had an emergency subtotal hysterectomy for severe haemorrhage secondary to placenta previa-accreta but continued to bleed profusely. So relaparotomy was needed and removal of the remaining portion of uterus ultimately controlled bleeding. The caesarean section for placenta previa is therefore the domain of a senior obstetrician, who is in a position to proceed to a hysterectomy without the need to defer. Total hysterectomy should be the goal, although subtotal hysterectomy may be the only possibility[11].

Conclusion:

In light of the increasing number of caesarean section, placenta previa and accreta will be more frequently encountered. In treating a patient who has had previous caesarean section and has a placenta previa, the clinician should consider the possible diagnosis of placenta accreta in advance which is a key to reduce maternal mortality. There should be a clear tested and tried protocol for dealing with massive obstetric haemorrhage. Adequate amount of blood must be in hand. Optimal management is a team work and requires the co-operation between obstetricians, anaesthetists, physicians, and haematologists.

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Vol. 29, No. 1, January 2011

Idiopathic Intracranial Hypertension Developing After Levothyroxine Replacement in a Patient with Acquired Primary Hypothyroidism- A Case Report

MA HAQUE [1], LS SHARMIN [2], QT ISLAM[3]

Summary:

Idiopathic intracranial hypertension (IIH) is the persistent increase in intracranial pressure in the absence of any intracranial lesions. Though termed idiopathic IIH is known to be associated with a wide variety of disease conditions and drugs i.e. SLE, adrenal insufficiency, Cushing disease, hypoparathyroidism, hypothyroidism, iron deficiency, vitamin A, tetracycline, nalidixic acid, steroid withdrawal and many others. IIH is a rare disease, but IIH developing after replacement of levothyroxine is even rarer. Only a handful of cases of IIH associated with levothyroxine therapy have been mentioned in the literature. We are reporting a case of IIH developing after starting levothyroxine replacement and then the literature is reviewed.

(J Bangladesh Coll Phys Surg 2011; 29: 49-51)

Introduction:

Idiopathic Intracranial Hypertension (IIH) is the persistent increase in intracranial pressure in the absence of any intracranial lesions: intracranial tumor, hydrocephalus, intracranial infections, dural sinus thrombosis or hypertensive encephalopathy[1]

Idiopathic intracranial hypertension corresponds partially to the old term of pseudotumor cerebri; the term benign intracranial hypertension is not used anymore because the

development of the disease can cause complications that are not benign at all. It was first described in the works of Quincke in the 19th century and later by Nonne in 1904, who used the term Pseudotumor Cerebri [2].

The term of "benign intracranial hypertension" was introduced by Foley in 1955 who defined the disease as "prolonged intracranial hypertension without ventricular

abnormality, focal neurological signs, or disturbance of awareness or intellect, the most important symptoms being headache of moderate degree, obscurations of vision, diplopia and sometimes tinnitus; marked papilloedema and abducens palsies are the only signs." In 1955 Foley advanced IIH as a diagnosis by exclusion, while in Dandy's diagnosis

criteria, modified by Wall, one of the elements of the diagnosis is the lack of a cause for the increase in intracranial pressure [3,4].

The IIH diagnosis is made only after measuring intracranial pressure and full neuroimaging exploration. The diagnosis criteria for IIH are-[5]

- CSF pressure is greater than 25 cm H_2O
- Normal CSF
- There are symptoms of increased intracranial pressure: papilloedema, headache, without any signs of neurological localization
- CT scanning or magnetic resonance imaging show a normal cranial-cerebral state, without any clinical or neuroimaging suspicion of venous sinus thrombosis

Because of chance association and to prevent biased reporting, Radhakrishnan et al insisted that, to be included in the list of causally related associations, the following criteria should be met-[6]

- At least 2 cases should have been described.
- The reported cases should have met all the criteria for the diagnosis of IIH.
- Intracranial dural sinus thrombosis should have been ruled out with reasonable certainty.

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Address of Correspondence: Dr. Md. Azizul Haque, Assistant Professor, Department of Medicine, Rajshahi Medical College, Rajshahi.

Receipted: 5 September, 2009 **Accepted:** 24 December, 2010

Case report:

A 23 year old non-obese lady presented to department of Medicine, Rajshahi medical College Hospital with the complaints of headache, and blurred vision for two months. The headache was diffuse, non-pulsatile, not associated with nausea or vomiting and only partially relieved by paracetamol. Her headache was persistent throughout the day and night. At first visit, fundus was found to be normal, so her headache was thought to be tension-type headache and amitryptyline was prescribed in a dose of 25 mg at night. She did not respond after 1 month of amitryptyline therapy. Moreover, she developed persistent blurred vision in both eyes. In the next visit, fundoscopy was done again and florid papilloedema was noted. She was not on oral contraceptives, nor did she give history of taking tetracycline, vitamin A, nalidixic acid, steroid or other drugs. MRI of brain with Magnetic Resonance Venography (MRV) was done, which was reported to be normal. CSF study was done which demonstrated increased CSF flow rate, but biochemical and microbiological examination was normal. Because of lack of facility, manometry of CSF to document exact CSF pressure could not be done. She was diagnosed as a case of primary hypothyroidism on the basis of serum T4 level 16.28 (normal 66-181 nmol/L), and TSH level > 100 (normal 0.27-4.2 micro IU/ml) 3 months back. Thyroxine replacement was started at a dose 50 mg per day and then gradually increased to 150 microgram per day. Her thyroid function test became normal after 2 months of thyroxine replacement. She had noted that her headache had started about one month after starting thyroxine replacement therapy. Idiopathic intracranial hypertension was diagnosed on the basis of diagnostic criteria and search for temporal association with thyroxine therapy was started. Hypothyroidism is a recognized association of IIH, but development of IIH after starting thyroxine therapy is documented in a few case reports. To avoid bias and chance association, we have followed the standard procedure advocated by Radhakrishnan et al [6] for linking IIH with other disease conditions. We found that; though very rare, there are more than 2 cases of IIH associated with thyroxine therapy have been described in the literature.

She was treated with acetazolamide 250 mg twice daily, prednisolone 60 mg for 2 weeks, and repeated therapeutic lumber puncture. Her headache subsided, and vision improved. She was discharged with acetazolamide and was asked to come to hospital for 2 weekly follow up. She was doing well when last seen.

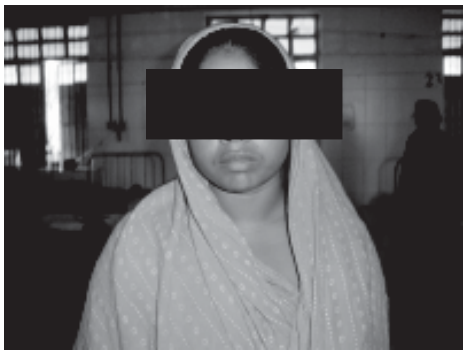

Fig.-1: *Patient (Printed with permission)*

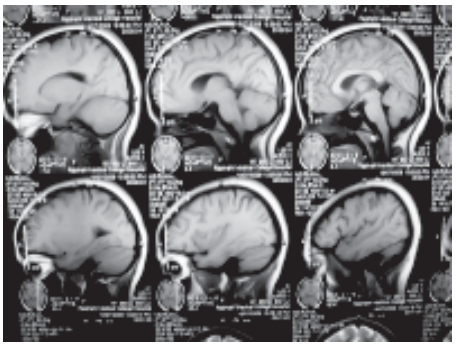

Fig.-2: *Normal MRI of brain*

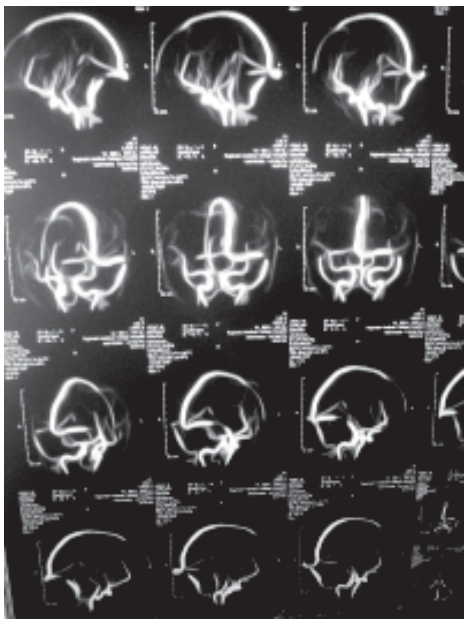

Fig.-3: *Normal MRV of brain*

Discussion:

The syndrome of increased intracranial pressure (ICP) without ventriculomegaly or mass lesion, and with normal cerebrospinal fluid (CSF) composition, was first

described more than a century ago, yet we still know little about its pathogenesis. It was once labeled as "Pseudotumor Cerebri" but now it is more appropriately called "Idiopathic Intracranial Hypertension" (IIH). It is a relatively common disorder that is commonly missed. In young overweight women, the annual incidence is as high as 20 per 100,000 persons[7]. Current theories include increased resistance to cerebrospinal fluid (CSF) outflow at the arachnoid granulations that line the dural venous sinuses and through which CSF reabsorption is thought to occur by bulk flow. Alternatively, occult cerebral venous outflow abnormalities may produce IIH. Farb and colleagues [8] have demonstrated that, in a series of 29 patients with IIH, narrowing of the transverse dural venous sinus was demonstrable on MR venography, while none of the 59 control subjects had this finding. These authors suggest that the narrowing is a consequence of elevated intracranial pressure, and, when the narrowing develops, it exacerbates the pressure elevation by increasing venous pressure in the superior sagittal sinus. Bateman has shown that some patients with IIH with normal dural venous drainage have increased arterial inflow suggesting that collateral venous drainage occurs in addition to that provided by the superior sagittal sinus and transverse sinuses [9].The same investigator measured MR venography and MR flow quantification in cerebral arteries and veins in a series of 40 patients with IIH, of which 21 patients had venous stenosis. The arterial inflow was 21% higher than normal and superior sagittal sinus outflow was normal, resulting in reduced percentage of venous outflow compared to inflow. The remainder of arterial inflow volume is presumed to have drained via collateral venous channels. With clinical remission of symptoms, the arterial inflow volumes returned to normal [10].

IIH developing after starting levothyroxine therapy has been reported by several authors. Patients who are euthyroid while taking thyroxine occasionally develop pseudotumour cerebri shortly after starting hormone replacement for hypothyroidism [11,12,13,14,15,16].

Interestingly, most of the patients who developed IIH after starting levothyroxine therapy were from paediatric age group. Our patient and another patient reported by Jacques S et al were adults. Number of total cases reported so far is still too few to comment whether this difference is significant.

It is not clear at all how starting thyroxine therapy might derange the CSF inflow or outflow and requires a lot more research. But, because of repeatedly reported cases over last few decades, it seems possible that the association has a genuine cause-effect basis, not merely a chance association. However, more questions remain unanswered than answered regarding association of IIH with levothyroxine therapy.

Conclusion:

IIH is a rare cause of headache, IIH developing after starting levothyroxine therapy is even rarer. But, because it is a treatable and potentially dangerous condition, patients with hypothyroidism should be closely monitored regarding development of IIH after starting levothyroxine therapy.

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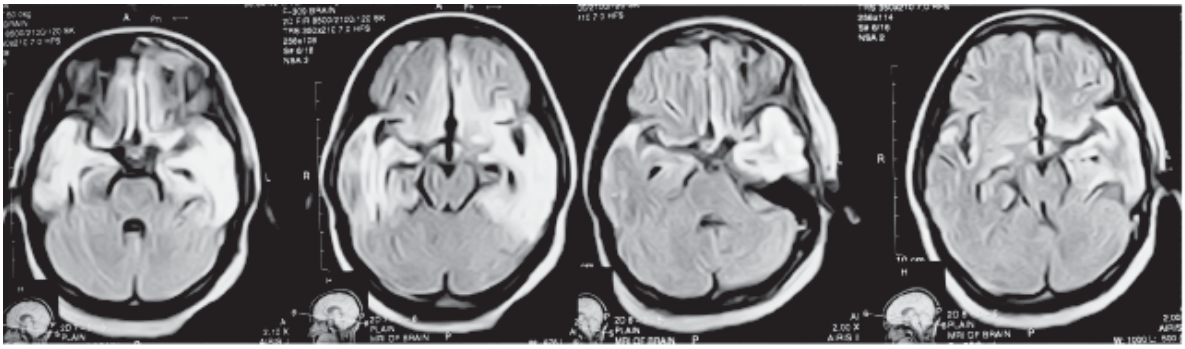
A Lady with Headache

MR SIDDIQUI[a], QT ISLAM[b], A HOSSAIN[c], YU RAHMAN[d], S SULTANA[e]

(J Bangladesh Coll Phys Surg 2011; 29: 52)



A 27-year-old previously healthy house wife who had fever and headache for 5 days, presented with unconsciousness and recurrent generalized motor seizure. She was comatose and had fever (102^0F). The Glasgow coma score (GCS) was 6. Pupils were equal but slow reactive to light and fundoscopy examination revealed bilateral papilloedema. The deep tendon reflexes were normal, with bilateral extensor planter reflexes. CSF analysis showed normal glucose and cell count but protein was slightly raised (65mg/dL). All other supporting investigations revealed normal findings. In these clinical backgrounds our diagnosis was viral encephalitis but we were looking for the site of lesion. Magnetic resonance imaging (MRI) of the brain revealed hypointense in T1 and hyperintense signal changes in T2, FLAIR (Fig.1) weighted images of the both temporal and part of the frontal lobe regions. This is a typical picture of Herpes simplex encephalitis. We started treatment with intravenous Acyclovir for 2 weeks followed by oral Valcyclovir for another 2 weeks. The consciousness of the patient recovered after 3 days of treatment and her temperature subsided at the fourth day of treatment. The patient was discharged with recovery after two weeks treatment. Follow up MRI showed significant improvement (Fig.2).

Herpes simplex encephalitis (HSE) is necrotizing focal encephalitis with typical localization involving the temporal and frontal lobes.[1] MRI of the brain provides the most sensitive method of detecting early lesions.[2] MRI findings corresponding to edematous changes in the temporal lobes, inferior frontal lobes, and insula with a predilection for the medial temporal lobes. Foci of hemorrhage occasionally can be observed on MRI.[2]

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a. Dr. Mahmudur Rahman Siddiqui, FCPS (Med) P-II Course student, Dept. of Medicine, DMC.

b. Prof. Quazi Tarikul Islam, Professor of Medicine, DMC.

c. Dr. Ahmed Hossain, Assistant professor of Medicine, DMC.

d. Dr. Yousuf Ur Rahman, Assistant registrar, Dept. of Medicine, DMC.

e. Dr. Sharmin Sultana, Postgraduate resident, Dept. of Medicine, DMC.

LETTER TO THE EDITOR

(J Bangladesh Coll Phys Surg 2011; 29: 53)

To
Editor in Chief
Journal of Bangladesh College of Physician and Surgeon,

Sir,
I had gone through the review article of your valuable journal (Vol.28 .No 3, Sep,2010) title with "Evaluation and management of Obscure Gastrointestinal Bleeding" by S Parvin et al and have few observation.

a. The review criteria were not mentioned. A systematic review with Pubmed , embase or Cochrane collaboration for specific duration of time would have been more informative in review process.

b. The content and illustration of the articles were very nice.

c. Less common causes of OGIB include hemosuccus pancreaticus [1], Strongyloides stercoralis infection, [2], pelvic radiotherapy, [3]pseudoxanthoma elasticum, [4] and Dieulafoy's lesions [5]. The first four are uncommon causes of OGIB but preferably can be included in the review article. One strongyloid stercoralis patient presented with haematemesis and melaena had been recently proven by Prof Quaz i Tarikul islam et al (on process of publication). Maunchausens syndrome patient can have taken animals and avians blood secretly and presented with OGIB.

d. The tabulated investigations are nice to look but it would have been more better if reraders came to know the sequentials steps of doing investigation.

e. The flow chart looks large. The visible bleeding if presented with no active bleeding, then routine endoscopy was advised for repetition but thereafter the steps are missing. The flow chart cab be repeat endoscopy, if negative capsule endoscopy, if it is positive , then enteroscopy and if it is negative then consider enteroscopy or other investigations including nuclear scan to angiography. A simple format of western Australia can be searched for.(www.imagingpathways.health.wa.gov.au/.../**gi_obscure**/**chart**.html)

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Dr. Robed Amin
Assistant Prof. of Medicine
DMC, Dhaka

Author's Reply

We are pleased and thankful for taking the pain and pleasure of reading the article and nice comments.As we have classified the causes of OGIB on the basis of site so Munchausen's syndrome may be included in serial no 7(no identified source). Other four causes pointed out are mentioned in the article. Hemosuccus pancreaticus is an extraintestinal site of OGIB discussed as haeobilia/Wirsungorrhagia, Strongyloides is mentioned under the head of colonic cause, pelvic radiotherapy under the head bleeding from any site as radiation damage and pseudoxanthoma elasticum under the head of physical examination,Sequential steps of tabulated investigations are discussed under 'investigations" though in short due to volume reduction before publication.Regarding the flow chart, steps following repeat routine endoscopy are not missing. It is given in the left as it continues "repeat routine endoscopy". Sorry for the misunderstanding.Perhaps an arrow pointing towards the middle would have explained it better.Criteria of the review is a mixed one and includes information upto 2008. We gladly accept your comments as source of inspiration.

Dr. Shaila Perveen
Classified Medical Specialist
CMH, Patenga, Chittagong

COLLEGE NEWS (CPD) PROGRAMME

(J Bangladesh Coll Phys Surg 2011; 29: 54)

Continuing Professional Development (CPD) Programme

Continuing Professional Development (CPD) is a multiprofessional educational activity that helps professional to keep their knowledge and skills upto date in response to the changing demands of the society and professions.

According to the suggestions given by the fellows, CPD committee of BCPS has decided to arrange the programme in different institutions instead of BCPS campus.

Accordingly, we have organized 1st CPD programme at DMC in April 2010, 2nd programme at SSMC in November 2010 and 3rd one at BIRDEM in December 2010. More than 300 undergraduate and postgraduate students attended each session.

Tow papers were presented at each session.

SSMC:

1. Kidney disease- an emerging global pandemic and its management. Speaker- Prof Md. Habibur Rahman, Dept of nephrology, BSSMU
2. Mono arthritis- How to approach? Speaker- Dr. Minhaj Rahim Chowdhury, Associate professor, Rheumatology, BSMMU

The programme was chaired by Prof. Md Mohsin, National Institute of Kidney Disease and Prof. Md. Abu Azhar, Principal & Prof. Medicine, SSMC. Dr. Anup kumer saha conducted the session as a moderator.

BIRDEM:

1. Vitamin D and non skeletal health. Role of Vit D beyond calcium metabolism and recent evidence of its association with cardiovascular disease, cancer and neurological disease. Speaker- Dr. Iftekhar Ullah, Assoct Prof, Internal Medicine, University of Mississippi, US
2. Dr. Sadeka Tamanna, Assist Prof. Internal Medicine, University of Mississippi, US

The programme was chaired by Maj. General (Prof) Md. Golam Rabbani, Ex Consultant Physician General and Prof. Khwaja Nazimuddin, Head of the Dept. of Medicine, BIRDEM respectively. Dr. Abdul Wadud Chowdhury, Assoct Prof, Cardiology, DMC acted as moderator.

Prof. Nazmun Nahar, President, BCPS was present on both occasion. Prof. Md. Azizul Kahhar, Chairman, CPD committee and Prof. Tahmina Begum, Member secretary, CPD committee were also there.

We have plan to arrange another programme at MMC in February 2011.

Prof. Tahmina Begum
Member secretary
CPD committee, BCPS

FROM THE DESK OF EDITOR in CHIEF

(J Bangladesh Coll Phys Surg 2011; 29: 55)

The editorial board meeting was held on 29th December, 2010 and chaired by Professor AKM Mahbubur Rahman. This meeting was the last formal board meeting of this editorial board (2009-2011).

In the meeting a decision has been taken that review & revise of guideline for the authors and also for reviewers are needed. A Committee will do this task as soon as possible.

A total of 5 web sites and 5 online indexing have been done so far for the journal.

This Journal Committee (2009-2011) has tried their best to do for the quality improvement of the Journal as well as international link with websites and online databases.

We always invite constructive criticism of our work so that we can improve and render more services for the journal.

Best wishes for all fellows.

Happy New Year 2011

Professor Quazi Tarikul Islam
Editor-in-Chief
JBCPS

NAME OF THE REVIEWER OF ARTICLES IN THIS ISSUE

(J Bangladesh Coll Phys Surg 2011; 29: 56)

Professor Selim Md. Jahangir, Dr. Manjarul Alam & Professor U.H. Shahera Khatun

Professor Farhana Dewan & Dr. Fatema Ashraf

Professor M A Masud & Dr. Nurul Alam

Professor M.A. Mannan & Dr. M.A. Hasnat

Professor Salim Md. Jahangir, Professor Wahiduddin Mahmood & Professor Md. Khalilur Rahman

Professor Sayed Atiqul Haq & Professor Abdullah Al Mamun

Professor Parveen Shahida Akhter & Dr. Salma Afrose

Professor Samsun Nahar Begum & Dr. Fatema Ashraf

Professor Latifa Samsuddin & Professor Saleha Begum Chowdhury

Professor Md. Azizul Kahhar & Professor A.R.M. Saifuddin Ekram

Obituary

(J Bangladesh Coll Phys Surg 2011; 29: 57)

The following Fellows who died between October 2010 to January 2011

Professor A.B.M. Badrur Rahman Khan

Professor A.B.M. Badrur Rahman Khan died on 19th November, 2010. He was awarded fellowship without examination in Pathology in 1994 from Bangladesh College of Physicians and Surgeons (BCPS). He was a Councillor of BCPS.

Professor S.I.M.G. Mannan

Professor S.I.M.G. Mannan died on 20th November, 2010. He was awarded fellowship without examination in Anatomy in 1985 from Bangladesh College of Physicians and Surgeons (BCPS). He was a paper setter, moderator & examiner in FCPS-I exam for long time. He also delivered lectures in basic science courses conducted by BCPS thorough out his life.

Professor Farida Huq

Professor Farida Huq died on 6th January,2011.She was awarded fellowship without examination in Microbiology in 1983 from Bangladesh College of Physicians and Surgeons (BCPS). She delivered lectures in basic science courses conducted by BCPS.