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Editorial

"Kangaroo Mother Care"

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EDITORIAL

Kangaroo Mother Carer

Maksudur Rahman

Kangaroo Mother Care (KMC) was proposed in 1978 by Dr Edgar Rey and Dr Hector Martinez of the Instituto Materno Infantil in Bogota, Colombia.[1] Their Maternity Unit at the San Juan de Dios Hospital was very large with 11, 000 babies delivered annually, many of them are at high risk. KMC was proposed as a solution to the problems in the nursery of overcrowding, nosocomial infection, and high mortality and abandonment rates. The programme was aimed at infants who had overcome the difficulties of early neonatal life when most mortality occurs. There was some initial confusion around the excellent mortality rates of the programme which were related to infants eligible to enter the programme and not to the overall perinatal or neonatal mortality rates of the unit.[2] The issue of who is the study population and who is excluded remains important in evaluating studies on KMC as these can differ. UNICEF was quick to recognize its potential.[3] In the 40 years since its conception KMC has evolved in different directions and its evidence base has broadened. Firstly the components of KMC have been moreprecisely defined. Following a two-cohort study that raised questions about early weight gain and neurode-velopment in the KMC infants,[4] Charpak et al. modfied KMC for an open randomized controlled study.[5]

It had three components.

(i) **Kangaroo position**-mothers were used as 'incubators' with the infant kept 24 hours a day in strict upright position, in skin to skin contact, firmly attached to the mother's chest. Infants remained in the kangaroo position until they no longer accepted it by demonstrating discomfort, pushing out limbs, or crying and fussing when mothers tried to return them to the upright position.

(ii) **Kangaroo feeding**-infants were breastfed regularly. Pre-term formula supplements were adminis- tered to guarantee adequate weight gain (20 g per day) if necessary.

(iii) **Kangaroo discharge**-infants less than 2000 g at birth were discharged as soon as they overcame major adaptation problems to extra-uterine life, received proper treatment for infection or concomitant condi-tion, could suckle and swallow properly, and achieved a positive weight gain regardless of actual weight or gestational age.

Clearly access to the resources needed to fulfil this study definition is not available in many first-level facilities in countries with very limited resources. A position paper produced by the participants of an international workshop on KMC in 1996 and gives very helpful guidance on implementation of the intervention in first-, second-, and third-level facilities in countries with very limited resources.[6] The workshop participants produced a further consensus paper which clarified five critical requirements for the implementation of KMC irrespective of the setting and of the available resources.[7] These are:

- information and support to mothers, including the issues of consent, replacement of mothers by other family members and the need for support after discharge
- training of health personnel
- skin to skin contact and thermal control
- breastfeeding
- discharge when (a) the infant is suckling on the breast and swallowing adequately and is gaining weight; (b) there is temperature instability in the kangaroo position; and (c) adequate follow-up.

As KMC has evolved, different facets of the programme have attracted research in their own right. In particular, the skin to skin component has been adapted by high technology units in Europe and North America. Different outcomes have been measured:

- temperature control is at least as good as that provided by an incubator
- a reduction in apnoea and periodic respiration compared to control infants
- higher oxygenation levels and less oxygen desaturation
- no increase in oxygen consumption
- improved neurobehaviour
- no additional risk of infection
- increased production of breastmilk.

It is interesting that paternal kangaroo care can improve the neonate status as well as maternal care.[8]

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In an attempt to understand what dynamics underlie the premature infants' improved outcomes from skin to skin care Feldman and Eidelman suggest that the key may be the unique integration of the self-regulatory, minimal handling, tactile stimulation, and sensory enrichment perspectives within the setting of parent-infant physical contact.[9] Some research groups in resource-poor countries have evaluated the in-patient kangaroo position and kangaroo feeding, also called Hospital KMC. Bergman and Jurisoo reported an observational study with a historical control group from a rural Zimbabwean hospital. There was a reduction in mortality in infants of less than 1500 g from 90 to 50 per cent and in infants weighing 1500 to 1999 g from 30 to 10 per cent. [10] This is the only study to date to show a reduction in mortality. KMC infants had significantly less hypothermia and were significantly more likely to be breastfeeding at discharge, these differences were most marked in Merida. KMC infants had a higher mean daily weight gain and were discharged earlier. KMC was found to be at least as safe as conventional methods of care and was found to be feasible in different settings, acceptable to mothers of different cultures, and less expensive. [11] The Bogota research group alone have taken the complete KMC package and sought to evaluate its effect. An initial observational two cohort study was complicated by baseline differences between the cohorts. These were particularly apparent in socio-economic status and perinatal care. There was no statistical difference in mortality but the KMC group showed poorer growth in the first 3 months and more develop- mental delay at 1 year. 4 The confounding variables were addressed in the follow-up trial which was an open randomized controlled trial [5] with the KMC principles defined as above. This study showed no significant difference in mortality. The growth of the KMC infants was similar to the controls. The KMC group had fewer nosocomial infections and a shorter hospital stay. The early discharge did not increase the readmission rate due to apnoea, hypoglycaemia, or aspiration. This study reported follow-up to 40-41 weeks post-conception age only. Research on KMC has progressed rapidly since the strategy was first reported. It is important when reading the literature to be clear which aspect of KMC is being evaluated. The skin to skin facet investigated in the developed world has good evidence to show that it is physiologically safe. However, the long-term effects on neuropsychologic and emotional development need to be explored further. Hospital KMC or the use of kangaroo position and kangaroo feeding has a growing evidence base. It has only been shown to reduce mortality in one study with a historical control group, however it does not increase mortality either. It has been demonstrated to reduce hypothermia, improve weight gain, and breast-feeding rates at discharge. It also leads to early discharge, is cost effective, and acceptable to parents. The entire KMC package has been evaluated in one randomized controlled trial which was very encouraging but had a short follow-up period. The International Network on KMC (INK) established at the 1996 Trieste workshop has produced further research priorities. These include: (i) work on the effectiveness and safety of KMC as a means of stabilizing premature and low birthweight infants just after birth; (ii) further health system research on the application of KMC in different settings; (iii) KMC at birth for very low birthweight infants in first- and second-level maternity units in settings with very limited resources; and (iv) KMC for home deliveries not assisted by trained personnel.[7]

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SPECIAL ARTICLE

Personalized Medicine

Muhammad Tawfique

Introduction

Personalized medicine or precision medicine, is a medical model that separates people into different groups-with medical decisions, practices, interventions and/or products being tailored to the individual patient based on their predicted response or risk of disease.[1] The terms personalized medicine, precision medicine, stratified medicine and P4 medicine are used interchangeably to describe this concept.[1,2]

While the tailoring of treatment to patients dates back at least to the time of Hippocrates,[3] the term has risen in usage in recent years given the growth of new diagnostic and informatics approaches that provide understanding of the molecular basis of disease, particularly genomics. This provides a clear evidence base on which to stratify (group) related patients.[1,4,5]

Personalized Medicine

The emergence of the 'omics' platforms (genomics, proteomics, metabolomics, transcriptomics, and interactomics) now gives us a pipeline around which to develop the infrastructure required for personalized (precision, P4) medicine. While the concept of personalized medicine is not new (it was actually described in The Yellow Emperors Canon of Internal Medicine over 2000 years ago, the concept has gained momentum since the turn of this century. At the proteomics level this concept has been championed by Prof Lee Hood at the Institute of Systems Biology in Seattle who has coined the phrase P4 medicine: predictive, preventive, personalized and participatory.[6] He realized that a multidisciplinary systems biology approach was required, combining the concerted effort of specialists from a wide variety of disciplines (e.g. medicine, chemistry, biochemistry, physics, mathematics, computing, bioinformatics, and manufacturing), to bring together the multiple skills and technologies required.

Personalized medicine involves specifically tailoring treatment to the individual characteristics of the patient rather than the current approach of stratifying patients into treatment groups based on phenotype. It will address both health and disease and impact on predisposition, screening, diagnosis, prognosis, pharmacogenomics, and surveillance[7], based on a comprehensive understanding of an individual's own biology. Importantly the patient now defines his own normal levels, facilitating the correct interpretation of biomarker assays. Personalized medicine is predicted to significantly reduce global health budgets, both by reducing the need for hospitalization and associated costly procedures, and by minimizing the unnecessary/inappropriate use of drugs (the top ten highest-grossing drugs in the United States only help from 4% to 25% of the patients who take them).[8]

There is no doubt that a personalized approach to medicine is viable and effective as evidenced by the recent study by Chen et al[9] in which a comprehensive "omics" characterization (Integrative Personal Omics Profile (iPOP), an analysis that combines genomic, transcriptomic, proteomic, metabolomic, and autoantibody profiles) of an individual over a 14-month period revealed dynamic molecular and medical phenotypes including a risk for type 2 diabetes. This study alone generated more than 30 terabytes of data[10]highlighting the massive computing support that will be required for personalized medicine.

Concept of Personalization in Medicine:

The concept of 'personalized medicine' (PM) is generally used to describe interventions which seek "to improve stratification and timing of health care by utilizing biological information and biomarkers on the level of molecular disease pathways, genetics, proteomics as well as metabolomics" in addition to

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clinical patient characteristics.[11] The key emerging finding from research based discussions was that the basic principles and methods of economic evaluation are appropriate for PM, in general, and PM in oncology, specifically. There was a preference for model-based cost-effectiveness analyses to facilitate the evidence-based synthesis of multiple data sources and long-term patient-relevant outcomes in a structured decision-analytic framework.A second key emerging finding was that, taking an economic perspective, two distinct, but linked, interpretations of the concept of PM exist (hereafter termed 'concepts') which involve specific challenges for the design and conduct of economic evaluations: (1) using physiological biomarkers and/or (2) using individuals' preferences for 'personalizing' medicine.[12] The following sections will highlight the implications of the two distinct concepts of personalization for the design and conduct of methods of economic evaluation.

Physiology-based personalization

According to a recent systematic review and appraisal of published definitions of "personalized medicine", the term corresponds with detecting differences in the physiological characteristics of patients to target medical interventions.[11]

Preference-based personalization

PM involves better information about a patient's likelihood to respond to a treatment or to develop adverse effects. In addition to objective health benefit, such data adds to the information available to patients which could be used to better incorporate subjective preferences into treatment choices. Most cost-effectiveness (and cost-utility) analyses assess the mean incremental effects and costs associated with the available treatment options.[12] If PM is interpreted as better accounting for patient preferences (at a population level), this has a fundamental impact on the role and methods of economic evaluation as preferences can also be used to define what constitutes expected 'benefits' or 'harms' and thus determine the quantified expected effect from a treatment.[13]

Revealed Preferences: uptake, adherence, and impact on (non)adherence

The preferences of patients and clinicians can affect the decision to adhere, and continue to adhere, to a prescribed healthcare intervention. Understanding the reasons for non-adherence has been identified to be an important step to improve efficacy of treatment, minimize adverse drug events, and thus maximizing the benefit of patient's health.[14] In the context of PM, two different aspects of analyzing (non) adherence are relevant. First, the uptake of the test, as well as adherence to the treatment recommended on its basis, is typically uncertain. Evidence on the uptake parameters is of high importance to estimate the health gains and costs associated with the use of a biomarker.[15] Second, it has been claimed that PM, by providing patients with additional information that the prescribed treatment is more likely to provide benefit with fewer adverse events, increases adherence (compared with a non-personalized option which would also be available).[16]

Stated preferences

The role of preferences reaches beyond the use of PM and its impact on health gain and costs. The next sections describe some potential broader impacts.

Risk attitude

Strategies for PM can provide clinicians and patients with additional information on the relative risk of an adverse event occurring from a particular treatment. However, health care professionals, health care regulators and patients may be prepared to accept different levels of risk reduction and have different relative preferences for the trade-off between anticipated benefits, and the risk of adverse reactions from the same technology. Therefore, robust and reproducible methods of eliciting preferences for risk-benefit trade-offs need to be used to ensure the health valuations incorporated in the economic assessment are valid and sufficiently robust to provide a solid evidence for coverage decisions on PM. Stated preference methods, such as discrete choice experiments (DCEs), are now commonly used to measure preferences for healthcare treatments in terms of their constituent attributes.[17,18] They may also offer a solution to the quantification of risk-benefit trade-offs if they are cognizant of the challenge of including risk in a DCE.[19] This information in itself can provide useful standalone evidence for decision makers. However, the challenge remains on how to incorporate such identified stated preferences for the relative value of risk reduction and benefits and use them within a formal economic evaluation framework.

Methods of Personalized Medicine:

In order for physicians to know if a mutation is connected to a certain disease, researchers often do a study called a "Genome-Wide Association Study" (GWAS). A GWAS study will look at one disease, and then sequence the genome of many patients with that particular disease to look for shared mutations in the genome. Mutations that are determined to be related to a disease by a GWAS study can then be used to diagnose that disease in future patients, by looking at their genome sequence to find that same mutation. The first GWAS, conducted in 2005, studied patients with age-related macular degeneration (ARMD).[20] It found two different mutations, each containing only a variation in only one nucleotide (called aingle nucleotide polymorphisms or SNPs, which were associated with ARMD. GWAS studies like this have been very successful in identifying common genetic variations associated with diseases. As of early 2014, over 1,300 GWAS studies have been completed.[21]

Disease Risk Assessment

Multiple genes collectively influence the likelihood of developing many common and complex diseases.[22] Personalized medicine can also be used to predict a person's risk for a particular disease, based on one or even several genes. This approach uses the same sequencing technology to focus on the evaluation of disease risk, allowing the physician to initiate preventative treatment before the disease presents itself in their patient. For example, if it is found that a DNA mutation increases a person's risk of developing Type 2 Diabetes, this individual can begin lifestyle changes that will lessen their chances of developing Type 2 Diabetes later in life.[23]

Revolutionizing drug discovery and patient care

Advances in human genome research are opening the door to a new paradigm for practising medicine that promises to transform healthcare. Personalized medicine, the use of marker-assisted diagnosis and targeted therapies derived from an individual's molecular profile, will impact the way drugs are developed and medicine is practiced. Knowledge of the molecular basis of disease will lead to novel target identification, toxicogenomic markers to screen compounds and improved selection of clinical trial patients, which will fundamentally change the pharmaceutical industry. The traditional linear process of drug discovery and development will be replaced by an integrated and heuristic approach. In addition, patient care will be revolutionized through the use of novel molecular predisposition, screening, diagnostic, prognostic, pharmacogenomic and monitoring markers. Although numerous challenges will need to be met to make personalized medicine a reality, with time, this approach will replace the traditional trial-and-error practice of medicine.[24]

Discovery of the drug in future

The elucidation of the 3.2-gigabase human genome will have various impacts on drug discovery. The number of drug targets will increase by at least one order of magnitude and target validation will become a high-throughput process. To benefit from these opportunities, a theory-based integration of the vast amount of new biological data into models of biological systems is called for. The skills and knowledge required for genome-based drug discovery of the future go beyond the traditional competencies of the pharmaceutical industry. Cooperation with biotechnology firms and research institutions during drug discovery and development will become even more important.[25]

Drug Development in the Era of Precision Medicine

For the past three decades, the use of genomics to inform drug discovery and development pipelines has generated both excitement and scepticism. Although earlier efforts successfully identified some new drug targets, the overall clinical efficacy of developed drugs has remained unimpressive, owing in large part to the heterogeneous causes of disease. Recent technological and analytical advances in genomics, however, have now made it possible to rapidly identify and interpret the genetic variation underlying a single patient's disease, thereby providing a window into patient-specific mechanisms that cause or contribute to disease, which could ultimately enable the 'precise' targeting of these mechanisms. Prior efforts using genomics to inform drug discovery (that is, expressed sequencing tag profiling and genome-wide association studies) have yielded an array of potential targets but have encountered difficulty in translating these discoveries into clinically efficacious drugs. Precision medicine marks a new relationship between genomics and drug discovery, one that provides both insights into the mechanisms and potential treatment options of a single patient's disease.

Oncology has been the leader in the field of precision medicine, with a multitude of successful examples of targeted treatments and immunotherapies available for a wide range of cancers. Precision therapies for Mendelian diseases, such as those that replace deficient proteins, directly target the dysfunctional protein or disease-associated pathway or influence expression of disease-relevant genes, and are clinically available for a number of conditions, such as lysosomal storage disorders, cystic fibrosis, tuberous sclerosis and spinal muscular atrophy.[26]

With various reliable model systems and a multitude of drug screening platforms, epilepsy is well positioned to serve as a model for precision medicine in highly genetic conditions. Although it is currently uncertain how generalizable genomic precision medicine approaches will be for all diseases, we imagine that some therapeutics that were developed for defined genetic conditions will also be efficacious in individuals with mechanistically related disease that do not necessarily carry the same genetic drivers.[27]

From Proteomics to Personalized Medicine

Over the past decade, improvements in instrument sensitivity, speed, accuracy, and throughput, coupled with the development of technologies such as multiple reaction monitoring (MRM), Stable Isotope Standard Capture with Anti-Peptide Antibodies, Sequential Window Acquisition of all Theoretical Mass Spectra, cross-linking mass spectrometry, imaging mass spectrometry, imaging flow cytometry, and middle/top down proteomics, have led to significant advances in the field of proteomics.[28,29] Under the guidance of the Human Proteome Organisation (HUPO) over 80% of the proteins predicted by the human genome have now been identified using either mass spectrometric or antibody-based techniques, and the remaining 'missing proteins' are being steadily accounted for.[30,31] Resources such as the Human MRM Atlas, a comprehensive resource designed to enable scientists to perform quantitative analysis of all human proteins, are being developed to facilitate reproducible transfer of quantitative assays between laboratories. Such developments and initiatives now enable both in-depth discovery and targeted/quantitative workflows, opening the door to the clinical diagnostic arena. Coupled with this, the establishment of comprehensive databases and the development of powerful *in silico* techniques is enabling effective data mining. In particular this has enabled interactome studies allowing the identification of key signaling pathways leading to potential new drug targets, although to date it has been estimated that less than 20% of the protein interactions in humans, not counting dynamic, tissue- or disease-specific interactions, have been identified.[32]

Personalized Medicine and Cancer

Cancer is one of the leading causes of death in the United States, and more than 1.5 million new cases and more than 0.5 million deaths were reported during 2010 in the United States alone. Following completion of the sequencing of the human genome, substantial progress has been made in characterizing the human epigenome, proteome, and metabolome; a better understanding of pharmacogenomics has been developed, and the potential for customizing health care for the individual has grown tremendously. Recently, personalized medicine has mainly involved the systematic use of genetic or other information about an individual patient to select or optimize that patient's preventative and therapeutic care. Molecular profiling in healthy and cancer patient samples may allow for a greater degree of personalized medicine than is currently available. Information about a patient's proteinaceous, genetic, and metabolic profile could be used to tailor medical care to that individual's needs. A key attribute of this medical model is the development of companion diagnostics, whereby molecular assays that measure levels of proteins, genes, or specific mutations are used to provide a specific therapy for an individual's condition by stratifying disease status, selecting the proper medication, and tailoring dosages to that patient's specific needs. Additionally, such methods can be used to assess a patient's risk factors for a number of conditions and to tailor individual preventative treatments. Recent advances, challenges, and future perspectives of personalized medicine in cancer are discussed.[33]

Challenges and opportunities for translational bioinformatics

The Big Data problem

One of the major hurdles in realizing the goal of personalized medicine, and currently perhaps the major bottleneck, will be effectively handling and storing the enormous amounts of data that will be

generated (the big data problem). It has been estimated that the size of 'Big Data' in the US health-care system alone was around 150 exabytes in 2011, is increasing at a rate of between 1.2 and 2.4 exabytes per year, and will rise faster as additional new data intensive technologies are adopted (e.g. microarrays, whole genome sequencing, and imaging). This can be extrapolated to suggest that, before long, countries with large populations and emerging economies, such as China and India, will be generating zettabyte (10^{21}) to yottabyte (10^{24}) amounts of health-related data each year.[34] Although the actual levels that will need to be stored will depend on how the data is finally summarized and processed. Big Data has 6 key considerations, known as the 6 Vs: value, volume, velocity, variety, veracity, and variability[35] that must be taken into account when designing suitable solutions to 'Big Data' analysis. Consideration must include: What information is needed? How to handle the complexity of information? How to filter unnecessary data? How to integrate the data in various formats from very heterogeneous resources? What kind of principles or standards need be adopted? How will data integrity be monitored?

Clearly a first requisite is rapid and facile data deposition and retrieval. However, even for the raw MS data this has not proved trivial, and there has been a relatively poor uptake of this essential action by the proteomics community, possibly due to burdensome and unreliable data deposition and retrieval protocols used in some earlier attempts. This has now been largely resolved, and, importantly, a number of the proteomics journals are now making data deposition mandatory for publication.[36]

Robust tools will be required for depositing and accessing all the necessary data. Coupled with this, robust storage with automated backup is essential. To ensure uniformity of data, Standard Operating Procedures across platforms are necessary and general acceptance of best practices will be required. Acceptance of a 'common language' between both vendors and scientific communities will facilitate this. Cloud computing will provide rapid, cost-effective analysis of the enormous amounts of data generated. Interestingly, at ACMS 2015 two companies (SCIEX and Thermofisher) launched cloud-based applications aimed at integrating multiple platforms.[38]

Ethical concerns

Another major hurdle that needs to be addressed sooner rather than later is that of ethics. Numerous concerns have been expressed in this area. The most important probably being those of informed consent, privacy, ownership, and the difficulty of providing meaningful access rights to individual data subjects who lack the necessary resources. It is important to tackle this issue globally with all key parties having a seat at the table.[37]

The funding dilemma

How will funding for such enormous projects be addressed? It has been pointed out recently.that this will almost certainly face some difficulties, particularly with grants involving multidisciplinary, multi-institutional, and often multinational groups of the type required to support personalized medicine. For the proteomics community funding may face additional hurdles. Poste has noted that the current herd mentality that portrays genome sequencing as a panacea for understanding all aspects of disease pathogenesis is unrealistic. This was recently further reinforced in a presentation by Prof Ralph Bradshaw at the recent 'The Omics Revolution: Uncovering the Complexity of the Human Proteome' meeting held in Kingscliff, Australia (October 2015), where he proposed that genomics and metabolomics were currently 'picking the low hanging fruit' and monopolizing funding, possibly because the type of data they produce and the analyses required are far simpler than those of most large-scale proteomic experiments.[38]

The road ahead

Clearly the introduction of personalized medicine holds enormous promise and benefits for mankind. It has already established a foothold, with more than 25% of all new drugs approved by the US FDA in 2015 relating to personalized medicine.[39] However, we are currently only looking at the tip of the iceberg. The switch toward personalized medicine will require many changes in the way we think and the manner in which things are done. Aside from the hurdles mentioned above (the size of the data, ethical, and funding issues) suitable reimbursement policies will need to be introduced to cover the new technologies, drugs, and services to ensure patients have full access to personalized medicine. Alongside this, the education system must be updated to prepare the next generation of doctors and other

health care professionals for the road ahead. Now is the time to ensure that all aspects of this paradigm shift in health care are carefully thought through and the correct global infrastructure developed.

Future perspective

There is a need for new clinical care delivery models for personalized and genomic medicine, and translational research has the potential to facilitate such models. There are estimates, however, suggesting no more than 3% of translational research efforts aim to validate genomic discoveries for use in practice.[40] This has been a growing domain that shows great promise to fill the gaps in health care system. As we move to more personalized health careresearches will be necessary to address challenges to validating genetic marker–disease correlations and identifying actionability, returning study results to patients, insuring privacy of patient data, educating patients and healthcare providers on the use and limitations of personalized medicine, and incorporating decision support tools to support personalized medicine.

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ORIGINAL ARTICLE

Effect of Perinatal Asphyxia on TSH and FT4 Hormone Level at 18 to 24 Hours after Birth

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Abstract

Background: *Perinatal asphyxia is the commonest cause of neonatal morbidity and mortality. It can affect almost all the organ systems of body due to oxygen deficiency at tissue level. Thyroid is the second most vascular organ in the body. As a result, it cannot be escaped from such an oxygen related insult.*

Objective: *To evaluate how perinatal asphyxia impacts on thyroid function in term newborn.*

Methods: *It is a cross sectional study which was conducted in Department of Neonatology of Dhaka Shishu Hospital (DSH) from January2017 to December2017. The sample size was 50. Among them, 25 in each group namely study group (asphyxiated neonates) and control group (full term healthy neonates). Blood sample from all the neonates were collected at 18-24 hours after birth. A semi structured, interview based, peer-reviewed data collection sheet was prepared. Data regarding socio-demographic, clinical and biochemical outcome profile were recorded, compiled, edited and analyzed using SPSS version 23. The results were presented as tabular form.*

Results: *Mean birth weight in asphyxiated and control groups were 2920±276.8 gm and 3123±179.3 gm respectively. In the initial group, the mean gestational age of babies was 38.07±0.68 weeks which was exactly 38.3±0.69 weeks in the later group. Blood gas analysis of arterial blood expressed pH and PaO_2 had statistically significant differences (p = 0.35 and 0.003 respectively) though $PaCO_2$ and base deficit showed no statistically significant differences (p = 0.53 and p = 0.37 respectively). Statistically significant difference was found between asphyxiated and control neonats, thyroid status especially in FT4 and TSH (p= <0.0001 and 0.003 respectively).*

Conclusion: *Perinatal asphyxia shows significant impact in alteration of TSH and FT4 level at 18-24 hours after birth.*

Key words: *Perinatal Asphyxia, Thyroid Function test, Morbidity.*

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Introduction

Perinatal asphyxia is the commonest cause of neonatal morbidity and mortality. It can affect almost all the organ systems of body due to oxygen deficiency at tissue level.[1,2] Thyroid is the second most vascular organ in the body. As a result, it can not be escaped from such an oxygen related insult. The decreased tissue perfusion causes diving reflex that causes shunting of blood away from lung, kidney, GIT, skin to brain, adrenals and heart.[3]

Cellular dysfunction occurs as a result of diminished oxidative phosphorylation and ATP production. Impaired oxidative phosphorylation can occur during the primary hypoxic ischemic insults as well as during a secondary energy failure that usually occurs approximately 6 to 24 hours after the initiating insult. Cell death can be either immediate or delayed, and either necrotic or apoptotic.

This condition is also responsible for the alterations in the concentrations of different hormones as like as adrenal hormones, B-endorphins, APH, renin, ANP and insulin.[4,5]

It is still obscured the effect of perinatal asphyxia on fetal and neonatal thyroid indices. Thyroid hormones play a pivotal role in developing central nervous system. There are some evidences regarding alterations of these important thyroid hormones level after 48 hours of life in case of perinatal asphyxia.[6] Though it was not evident after 4 days of life in another previous study.[7]

The main aim of this study was to evaluate the effect of perinatal asphyxia on level of thyroid hormones (TSH and FT4) by comparing thyroid profile in arterial blood at 18-24 hour after birth in neonates with or without asphyxia.

Materials and Methods

It was a cross sectional study conducted in Dhaka Shishu(Children) Hospital from January 2017 to December 2017. The sample size was 50. Among them, 25 in each group namely study group (asphyxiated neonates) and control group (full term non asphyxiated neonates). The inclusion criteria of study group were APGAR score ≤3 and ≤5 at the first and fifth minutes. The neonates who required bag and mask ventilation for at least one minute immediately after birth and in control group APGAR score was ≥8 and ≥9 at the first and fifth minutes. The neonates whose mothers had any medical condition during pregnancy, whose mothers took antihypertensive and any hormonal treatment before and during pregnancy and any congenital anomaly of the neonate were excluded from the study.

All asphyxiated newborns were admitted to the intensive care unit. Diuresis was monitored in first 24 hours after birth. All neonates were provided parenteral hydration at 50 to 60ml/kg. Besides, they were neurologically evaluated according to Sarnat and Sarnat's classification.[8] None of the neonates was fed during the first 24h of life. Five patients with severe life threatening clinical condition required mechanical ventilation. Furosemide, heparin or iodine contrast was not used in any newborn infant. Controls received assistance in the same room as their mothers (rooming-in environment) and did not undergo any special care. All patients were given appropriate follow up.

We can't collect umbilical cord blood sample for initial assessment. Between 18 and 24hs after birth, an arterial blood sample was collected from each newborn in both groups for the same purposes. A blood sample was collected for determination of FT4, and TSH levels. Immediately after collection; the sample for hormone dosage was centrifuged and stored at -20^0C. The serum collected for determination of FT4, and TSH levels was stored at-20^0C. The determination of hormone levels in all samples was performed on the same occasion.

Radioimmuno assay was used for the determination of hormone levels. All dosages were performed by the same biochemist, which was blinded to the patients' data. FT4 was determined with the Coat-a-Count Free T4 kit (DPC, Los Angeles, USA; intra-assay variation approximately 5%, inter-assay variation 7% to 9%). TSH was determined with the Coat-a-Count TSH IRMA kit (DPC, Los Angeles, USA; intra-assay variation 1.5% to 3.6%, inter-assay variation 3.7% to 9.8%).

FT4 values were expressed in ng/dl and TSH values were expressed in mU/ml. The range of FT4 value was 0.6-2.0ng/dl and TSH was 1-15.5mIU/ml.[9]

Initially a case record form was prepared which was semi-structured, peer reviewed, interview and observation based. It was used to collect data regarding, socio-demographic, clinical and biochemical profile. Data were gathered, edited and tabulated in tabular and figure form.

Sample size was calculated considering a significance level of α-0.05 (type I error) and a statistical power of 90% (β-0.10) to detect a difference of 1.3 in the level of FT4 between both groups, based on data presented by Borges et al[6]. According to these calculations, each group should consist of at least 14 newborns.

Initially, sample frequency tables were obtained for all relevant variables, with the aim of obtaining an overview of the data and cleaning the database, in addition to testing presuppositions for the performance of statistical tests.

Continuous variables were expressed as means and standard deviation; categorical variables were expressed as frequency percentages. The χ^2or Fisher's exact test were used in the analysis of categorical variables.For the analysis of continuous variables, Student's t-test was used for paired samples.[10]

The difference between mean hormone levels in the arterial blood collected 18 to 24hs after birth was also calculated, and results from cases and controls were compared. Student's t-test was used for equality of paired means.[10]

For comparison of thyroid hormone levels in the arterial blood (collected 18 to 24hs after birth) of asphyxiated newborns with and without moderate/ severe encephalopathy and of control newborns,[10] the significance level was 0.05.

The overall data collection, edition and analysis were done by Statistical Package for Social Science (SPSS) software version 23 (Ilinois: Chicago; USA)

Results

Table I shows that the overall clinical characteristics of neonates and their mothers. Mean birth weight in asphyxiated and control groups were 2920±276.8 gm and 3123±179.3 gm respectively. In the initial group, the mean gestational age of babies was 38.07±0.68 weeks which was exactly 38.3±0.69 weeks in the later group. Among the 25 neonates in each group, male babies were greater in number in both asphyxiated (M vs F = 56% vs 44%) and control group (M vs F= 52% vs 48%). White skin colour was more evident in both the groups (76% and 88% respectively) than non-white neonates (24% and 12% respectively). Vaginal delivery was higher in asphyxiated group (Vaginal vs. Cesarean = 56% vs 44%) whereas Cesarean delivery was higher in control group (Vaginal vs. Cesarean = 40% vs 60%). 80% neonates were found appropriate for gestational age in asphyxiated group whereas 88% were found similar in the control group.

Table-I
Clinical characteristics of the studied population (N=50)

	Asphyxiated group (n=25)	Control group (n=25)
Birth weight (g)	2920±276.8	3123±179.3
Gestational age (wk)	38.07±0.68	38.3±0.69
Sex		
Female	11 (44%)	12 (48%)
Male	14 (56%)	13 (52%)
Skin color		
White	19 (76%)	22 (88%)
Non-white	6 (24%)	3 (12%)
Mode of delivery		
Vaginal	14 (56%)	10 (40%)
Cesarean	11 (44%)	15 (60%)
Size for gestational age		
Appropriate	20 (80%)	22 (88%)
Large	3 (12%)	3 (12%)
Small	2 (8%)	0 (0%)
APGAR Score in 1 minute		
0 – 1	1 (4%)	0 (0%)
2 – 5	24 (96%)	0 (0%)
6 – 7	0 (0%)	2 (8%)
8 – 10	0 (0%)	23 (92%)
APGAR score in 5 minute		
1 – 5	13 (52%)	0 (0%)
6 – 8	12 (48%)	0 (0%)
9 – 10	0 (0%)	25 (100%)

In case of 96% neonates APGAR score in 1 minute was found around 2-5 in Asphyxiated group. On the contrary, approximately 92% patients were recorded as APGAR score in 1 minute from 9-10 which was subsequently followed by 8% neonates in 6-8 in the same group. In the Asphyxiated group, 52% neonates got APGAR score in 5 minutes around 1-5 which was subsequently followed by 48% around 6-8. The same parameter was observed 9-10 in case of 100% neonates in the control group.

Table II

Gasometric data from arterial blood collected 18 to 24 h after birth (N=50)

	Blood collected 18 to 24 h after birth		
	Asphyxiated group (n=25)	Control group (n=25)	P-value
pH	7.12±0.09	7.35±0.04	0.035^{S}
$PaCO_2$	51.28±10.36	38.96±4.15	0.53^{NS}
Base deficit	13.96±1.57	6.4±2.08	0.37^{NS}
PaO_2	54.61±12.45	78.08±6.22	0.003^{S}

P-value was calculated by student's t test
P-value was significant at <0.005
NS: Not significant S: Significant

Table II shows that the blood gas analysis of arterial blood collected after 18 -24 hours of birth in both asphyxiated and control groups. pH and PaO_2 showed statistically significant differences (p = 0.035 and 0.003 respectively) though $PaCO_2$ and Base deficit showed no statistically significant differences (p = 0.53 and p = 0.37 respectively).

Table III

Serum levels of thyroid hormones and thyroid-stimulating hormone (TSH) in arterial blood collected 18 to 24 hs after birth(N=50)

	Blood collected 18 to 24 h after birth		
	Asphyxiated group (n=25)	Control group (n=25)	P-value
FT4 (ng/dl)	1.27±0.65	1.55±0.37	<0.001^{S}
TSH (mU/ml)	10.34±7.48	9.79±4.17	0.003^{S}

P-value was calculated by student's t test. P-value was significant at <0.005. NS: Not significant
S: Significant

Table III shows that there was statistically significant difference between asphyxiated and control neonats, thyroid status after 18-24 hours of birth specially in FT4 and TSH. (p= <0.001 and 0.003 respectively).

Figure-1 shows that total 15(60%) patients out of 25 showed involvement of single or multiple organ/organ system complications after asphyxia during birth process. Among these 15 patients 8(32%) and 5(20%) showed moderate and severe CNS involvement respectively whereas 1(4%) each had pulmonary and cardiac involvement. One out of 25 patients in asphyxiated group died due to delayed seeking of medical attention.

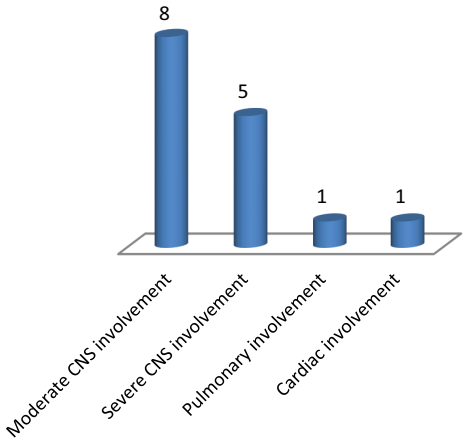

Fig 1 *Involvement of different organs/organ system in asphyxiated neonates (N=25)*

Discussion

Perinatal asphyxia continues to be an important cause of morbidity and mortality in newborn. Organ dysfunction depends in asphyxiated neonates on duration of asphyxia and early management. Because of diving reflex in newborn blood diverted from less vital organ to more vital organs like brain, heart and kidney. The present study included 50 neonates of which 25 were cases of perinatal asphyxia and 25 were healthy neonates as control.

Gestational age, weight, sex, mode of delivery, Eclampsia, APH, Birth Asphyxia, PROM, HIV status, maternal age and thyroid status and so on are the different factors that were studied for influence on neonatal blood T3, T4 and TSH.[4,11]

The mean weight in asphyxiated newborns was 2920±276.8 kg while in control group it was 3123±179.3kg in this study. Borges et al.[6] found mean birth weight in their study as 3.6kg and 3.3kg respectively. This deference in the mean weight of newborn observed in our study and other studies is may be due to ethnic and geographic variation.

Moshang et al compared alteration of thyroid function in acute versus chronic hypoxia in children around 2-16 years and found elevated serum rT3 and decreased serum T3 concentrations (indicating extra thyroid metabolism).[12] Warner S et al, they observed

that hypoxia leads to activation of deiodinase type 3 in turn inactivates the peripheral conversion of T4 to T3.[13] in turn inactivates the peripheral conversion of T4 to T3.[13]

According to Borges et al though there was maximal TSH surge, in asphyxiated newborns serum FT3 and FT4 levels failed to increase. They concluded that the alterations in the thyroid function observed in asphyxiated newborns may be caused by the low consumption of oxygen with low metabolic rate, suggesting that asphyxia plays an important role in thyroid metabolism.[6]

Procianoy et al[14]. suggested that decreased levels of T4 and T3 18-24 hours after birth in asphyxiated new-borns is due to a diminished TSH level.[14] Pareira DN and Procianoy RS found that serum concentration of TSH, T4, T3, and FT4 are lower in asphyxiated new-borns than in the normal newborns between 18 and 24 hours of life.[15]

Frank et al[4] reported that use of thyroxine as prenatal treatment and thyroid releasing hormone (TRH) that accelerates surfactant system maturation has opposite effect on the antioxidant enzyme in the lung.[16] Gupta et al observed that neonates with low APGAR at 1 minute resulted in significantly raised cord blood TSH ($p<0.01$).

Tahivoric et al[17] studied the serum concentration of thyroid hormone levels (T4, FT4 , rT3 , T3, TSH and TBG) in cord blood at birth and serum on 5th day of life he concluded that neither hypoxia nor the method of delivery had any influence on the peripheral metabolism of thyroid hormones.

In our study, we assessed FT4 and TSH levels in arterial blood in 18-24 hours period after birth among asphyxiated and control newborns in order to investigate the effect of asphyxia on those hormone concentrations. We observed that the single mortality case in our study had a FT4 level below cut off point.

In this blood samples, asphyxiated neonates had significantly lower FT4 level ($p=<0.001$) in comparison to that of control group and same significant difference has also observed in case of TSH level in both group ($p=<0.003$). On the contrary, TSH level was significantly higher in asphyxiated group than that of control group.

The pattern of alterations found in the arterial blood of our study patient group suggests the occurrence of thyroid gland dysfunction where TSH level significantly raised, and FT4 level was decreased, in comparison to our control group. We were unable to determine the duration and extension of such alterations in the metabolism of asphyxiated newborns, since this would have required several sample collections, over several days, in both asphyxiated and normal newborns, and we did not consider this to be ethically acceptable.

Conclusion

Perinatal asphyxia shows significant impact in alteration of TSH and FT4 level at 18-24 hours after birth. Though this study was based on arterial blood. The study with cord blood sample would be more precise which was the vital shortcoming of the study.

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ORIGINAL ARTICLE

Comparative Effect of Combined Desferioxamine and Deferiprone with Desferioxamine Alone in Iron Chelation Therapy of Beta-Thalassemia Patients

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Abstract

Background: *Efficacy of combined chelation therapy with Desferioxamine and Deferiprone is better than single chelation therapy with Desferioxamine due to synergistic effect of combination therapy in iron overloaded Beta-thalassemia patients.*

Objectives : *To compare the effectiveness of combination therapy with Desferioxamine and Deferiprone versus single Desferioxamine therapy in iron chelation of Beta-thalassemia patients.*

Methods:*Eighty patients of Beta-thalassemia were randomized to receive one of the treatment : Desferioxamine was given alone in group-1and Desferioxamine combination with deferiprone in group-2. Change of serum ferritin, SGPT, BUN, Serum creatinine were compared before and after treatment between two groups. Drug toxicity and clinical parametres were also compared between two groups.*

Results : *After one year the mean serum ferritin (±SD) in Desferioxamine alone group decreased from 3105 (±1070) ng/ml to 1650(±1050) ng/ml (p value <0.05).In the combination group treated with Desferioxamine and Deferiprone , decline was noticed from 3110 (±1070)ng/ml to 1050 (±1040) ng/ml (p value <0.001). Significant improvement was observed after 6 months of combination therapy. Qualities of life was better in combination group. The main side effects were skin reactions (Desferioxamine alone group), nausea and arthralgia (Combined group.)*

Conclusion: *Combination therapy is a practical and effective regimen to decrease severe iron overload in Bta-thalassemia patients than single therapy and also more effectve in reducing iron overload related complications.*

Key words*: Beta-Thalassemia , Desferioxamine, Deferiprone.*

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Introduction

Beta Thalassemia is a genetically inherited disorder characterized by reduced synthesis of the beta-globin chain which in turn results in reduced synthesis of hemoglobine A (HbA).[1,2] The main genetic variants in beta-Thalassemia are beta-Thalassemia Major (α^0), β-Thalassemia intermedia and E-beta Thalassemia.[3]

Iron overload is an inevitable problem in beta-Thalassemia patients. Iron overload can cause tissue damage such as heart failure ,liver disease , endrocrine disturbances ,which could cause eventual death.[4,5] There have been established evidence that iron chelator drugs reduce tissue damages and improve life expectancy in these patients.[6] The aim of iron chelation therapy in these patients are to reduce iron burden, reduce risk of tissue damage especially in specific key organs such as heart and liver, to improve quality of life and survival, to provide twenty four hour protection from the toxic effects of iron such as labile plasma iron and finally, to reduce gap free of iron chelator drugs.[7]

Desferoxamine (DFO) was the first clinically available iron chelating agent, introduced over 40 years ago and life expectancy in Thalassemia patients increased dramatically with its use.[8,9] However its beneficial effects are tampered by requirement of subcutaneous rout and failure to remove cardiac iron which lead to heart failure and cardiac death.[10]

Deferiprone(DFP) is an orally active chelator with a lower molecular weight that is uncharged at physiological pH , and which is both hydrophilic and lipophilic enabling it to readily penetrate myocardial cells. It has been shown to be superior to deferioxamine in removing iron from the different organs.[11-16]

Prior to the discovery of DFP, the only option for treatment of iron overload was desferioxamine, an iron chelator that is not orally absorbed and thus needed to be administered parenterally for 8 to12 hour nightly infusion,[5-7] nights a weeks (Thalassemia International Federation Guidelines 2000). While the use of DFO for about 2 decades prior to the introduction of DFP decreased morbidity and mortality among those who were able to comply with night –long infusions, but consistent proportion of patients refused therapy limiting the usefulness of this chelator, and a key factor for scientists to find an effective alternative chelator. Thus introduction of DFP was accompanied by much hope among hematologists and thalassemia patients alike.[17]

Materials and Methods

This Randomized control clinical trial was conducted in the Department of Paediatric Haematology and oncology in Dhaka Shishu Hospital from July 2013 to June 2014. A total of 40 diagnosed patients of Beta-Thalassemia by Hb electophoresis upto 18 years of age receiving regular blood transfusion having serum ferritin level >1000ng/ml were randomized in each group. In group-1 Desferioxamine was given at a dose of 40 mg/kg/day 6 days per week subcuteniously and in group-2 Combined chelation therapy was given with Desferioxamine subcutaneously at a dose of 40 mg/kg/day and Deferiprone orally given at a dose of 75mg/kg/day two to three times daily. During chelation therapy clinical parameters pulse rate, Respiratory rate were monitored three hourly. Hematological evaluation included Hb%, WBC count, absolute neutrophil count and platelet count measurements were done every two weeks in first two months and then monthly for next ten months. Serum ferritin level, liver function, renal function were done three monthly and complete physical examination was done six monthly and also compliance of the drugs were monitored by counting the drugs (DFP)in packets which were supplied to them.

Data was processed and analyzed using computer aided statistical software SPSS (Statistical Package for Social Science) version 20. Presentation was done by tables and graphs. Association between treatment and outcome was assessed by applying Chi-square (χ^2) test, To compare the quantitative variable in the same group paired t-test and between groups independent sample t-test were done. The cut- off value <0.05 was considered as significant.

Results

In this study, total 80 patients were included from outdoor of thalassemia centre who attended for blood transfusion or iron chelation. These patients were randomized to receive one of the treatments: Desferioxamine was given alone in group-1 and Desferioxamine and Deferiprone in group-2. Change of serum ferritin, ALT, BUN, Serum creatinine were compared before and after treatment between two groups three monthly. Level of serum ferritin was significantly changed in combined group than single group after 6,9,12 months of therapy (p value .048,.002,.001). But no significant difference in change of ALT, BUN, Serum creatinine between two groups (p value >0.05). The results are shown in different tables.

Table I
Base line characteristics of patients before treatment

	Group-1(DFO)	Group-2 (DFP+DFO)	P value
Number	40	40	
Age(mean±SD)in year	6.5±2.90	6.4±2.89	0 .412
Sex -Female (%)	18(45%)	19(47.5%)	0 .241
Hb g/dl (mean±SD)	6.9±10	6.8±10	0 .426
Mean age(in year) of starting iron chelation	6.5±2.90	6.4±2.89	0 .415
Mean age of diagnosis (in months)	7.8±3.28	8.2±3.30	0 .761
Age of onset of blood transfusion(in year)	5.5±5.2	5.6±5.1	0 .632

Independent t-test was done to measure the level of significance

There was no significant difference between two groups in base line characteristics like mean age, sex, Hb level, mean age of starting iron chelation therapy.

Table II
Biochemical parameters in both groups before treatment

Biochemical parametre	Group-1 (DFO)	Group-2 (DFP+DFO)	P value
Serum ferritin(mean±SD) (ng/ml)	3105±1076	3110±1050	0.182
ALT (IU)	39.90±10.35	40.15±8.89	0 .534
BUN (mg/ml)	10.96±1.02	10.98±1.03	0 .332
Serum creatinine (mg/ml)	.49±0.06	.49±0.08	0.243

Independent t-test was done to measure the level of significance.

There was no significant difference between two groups before treatment in biochemical parameters like serum ferritin, BUN, serum

Table III
Comparison of biochemical parameters after 6 months of treatment

Biochemical parametres	Group-1 Mean±SD	Group-2 Mean±SD	P value
Serum ferritin (ng/ml)	2515±870	2000±626	0.048
ALT (IU)	41±10.45	44±11.04	0.532
BUN (mg/ml)	12±1.23	13±1.30	0 .334
Serum creatinine (mg/ml)	.47±.06	.48±.08	0 .241

Independent test was done to measure p value

There was statistically significant difference of serum ferritin level in between two groups but no difference in ALT, BUN and Serum creatinine level after 6 months of treatment. creatinine , ALT.

Table IV
Comparison of biochemical parameters after 9 months of treatment

Biochemical parametres	Group-1 Mean±SD	Group-2 Mean±SD	P value
Serum ferritin (ng/ml)	1916±824	1256±424	0.002
ALT (IU)	40±10.35	41±11.05	0.523
BUN (mg/dl)	11.06±1.03	11.08±1.25	0 .341
Serum creatinine (mg/dl)	.50±.06	.49±.08	0.263

p value was generated by independent t-test
There was significant difference of serum ferritin level after 9 months of treatment but no difference in ALT, BUN, Serum creatinine level.

Table V
Comparison of biochemical parameters after 12 months of treatment

Biochemical parameters	Group-1 Mean±SD	Group-2 Mean±SD	P value
Serum ferritin(ng/ml)	1650±778	1050±245	0 .001
ALT (IU)	41±10.35	42±11.25	0 .502
BUN (Mg/dl)	10.96±1.02	10.48±1.04	0.341
Serum creatinine (mg/dl)	.49±.07	50±.08	0 .242

p value was generated by independent t-test

There was significant difference of serum ferritin level between two groups after 12 months of treatment but no difference in ALT, BUN and Serum creatinine.

Table VI
Change of serum ferritin in two groups after 12 months of treatment

	Group-1 (Mean±SD)	Group-2 (Mean±SD)
Before treatment	3105±1076	3110±1050
After treatment	1650±778	1050±245
P value	Within group 0.001	Between groups 0.001

P value was generated by paired t-test

There was significant improvement of serum ferritin level in both groups(p value <0.05) but more in combination group and the difference was significant (p value <0.001).

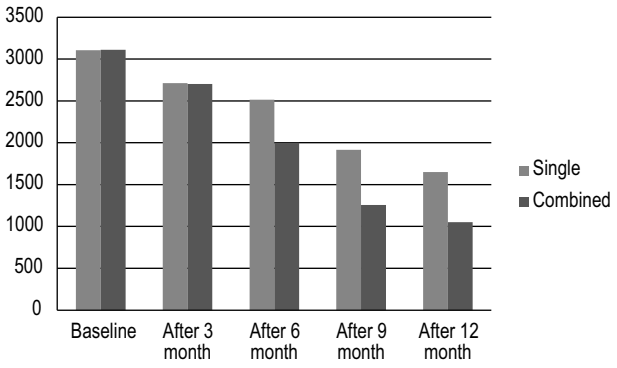

Fig 1 *Change of serum ferritin level during one year of treatment in single and combined groups*

Discussion

The combined treatment has advantages of targeting more iron pools and achieving a longer period of chelation coverage. Recent retrospective studies have

reported that oral deferiprone has a greater ability to reduce iron loading in the heart and a greater cardio protective effect than has subcutaneous desferioxamine.[17-19]

In this study there were no significant differences between Desferioxamine and combined Desferioxamine-Deferiprone group regarding age, sex, Hb%, Serum ferritin level, ALT, BUN, Serum creatinine and P value was >0.05. Level of serum ferritin ,BUN, ALT, Serum creatinine did not change significantly after 3 months of treatment. After 6months of treatment there was significant decreased of serum ferritin between two groups (P value was <0.05) but no significant difference regarding ALT, BUN, Serum creatinine (P value >0.05). The same results were found after 9 months and 12 months therapy with Desferioxamine in single group and Desferioxamine and Deferiprone in combined group.

A Tamaddoni et al. conducted a randomized clinical trial on 80 patients of Thalassemia major to see the comparative effect of single DFO versus combined DFO-DFP therapy. They showed that significant improvement of serum ferritin level after 6 months of therapy and there was significant difference between two groups regarding serum ferritine level (Pvalue<0.05).[20]

Zareifar S. et al. conducted a single blind radomized control trial to see the efficacy of combined desferioxamine and deferiprone versus single desferioxamine therapy in thalassemia major patients. They showed that after 6 and 12 months of therapy there was significant decrease of serum ferritin within the groups and between groups (P value <0.05). There was no significant difference between two groups regarding ALT, BUN and Serum creatinine level (P value >0.05). The result of their study is similar to our study.[21]

M.A. Tanner et al. performed a placebo-controlled, double-blind trial of the effect of combined therapy with desferioxamine and deferiprone on myocardial iron in thalassemia major using cardiovascular magnetic resonance. They showed that combination treatment with additional deferiprone reduce myocardial iron and improved the ejection fraction and endothelial function in thalassemia major patients with mild to moderate cardiac iron loading.[22]

Nancy F.et al .showed in their study on Iron - chelation therapy with oral deferiprone in thalassemia major patients, that deferiprone reduced hepatic iron in low level which was not efffectively reduced by previous desferioxamine theray which was associated with increased risk of cardiac disease and early death.[23]

In our study the combination treatment with desferioxamine and deferiprone was more affective and safer due to the ability of deferiprone to reduce more cardiac iron and reducing iron in safe level to reduce complications due to iron overload than desferioxamine alone therapy

Conclusion

Desferioxamine is effective in reducing iron overload of beta-thalassemia patients. But combination therapy with Desferioxamine and Deferiprone is more effective regarding reduction of iron overload and related complication.

Recommendation

After proper counseling Combination therapy should be started if possible. Combination therapy with desferioxamine and deferiprone is more effective than single Desferioxamine therapy in iron overload of beta- thalassemia patients.

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ORIGINAL ARTICLE

Rapid Standardized Enteral Feeding Strategy in Preterm Infants - Its Safety and Outcome

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Abstract

Background: *Optimal enteral feeding methods in preterm infants have not been well defined. A relatively more rapid advancement of enteral feedings in preterm infants may be well tolerated and improve their nutritional status and potentially shorten the length of hospitalization.*

Objective: *To evaluate the tolerance of rapid advancement of enteral feeding in preterm babies less than 34 weeks and find out its risk and benefits.*

Methods: *This Randomized Control Trial was carried out in preterm babies less than 34 weeks admitted in neonatal ward from January to December 2016. Sample subjects fulfilling inclusion criteria were assigned to either slow enteral feeding (20 mL/kg/day) or rapid enteral feeding group (30 mL/kg/day) through simple randomization and allocation was concealed by sealed envelopes, which was equal in number for each group.*

Results: *A total of 240 infants were enrolled, 120 infants in the intervention group and 120 in the control group. Enteral feeding advancements were well tolerated by the intervention group of stable preterm neonates than the control group (62.75% vs. 72.55%, p value > 0.05). Infants in the intervention group achieved full volume feedings sooner (9.4 days vs 13.6 days), regained birth weight earlier (8 days vs 11.4 days), and had fewer days of intravenous fluids (6.6 days vs 9.20 days) in comparison to slow feeding group. Ten infants in the intervention group and nine in control group died due to sepsis. There was no incidence of NEC. No statistical differences in the proportion of infants with feed interruption or feed intolerance.*

Conclusion: *Rapid enteral feeding with breast milk in preterm (34 wks) low birth weight infants was found to be well tolerated than the slow enteral feeding group. There was significant rapid weight gain and decrease duration of hospital stay in rapid enteral feeding group without any incidence of NEC.*

Key words: *Prematurity, entetal feeding, rapid standardized.*

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Introduction

The delivery of a preterm baby is a nutritional emergency. After stabilization of initial problems including respiratory status, nutrition is the major challenge in front of the treating neonatologist.

Optimal enteral feeding methods in preterm infants have not been well defined.[1] Controversy exists regarding when feedings should be started, whether minimal enteral feedings should be used routinely in small preterm infants, and how fast to advance enteral feedings.[2–5] Preterm infants can exhibit delayed gastric emptying and often have feeding residuals, although what constitutes a clinically significant gastric residual remains unclear.[6] However, recent evidence suggests that very low birth weight infants who develop necrotizing enterocolitis (NEC) have more gastric residuals than those who do not.[7] On the basis of these and other factors, enteral feedings are frequently advanced slowly in these neonates. This practice may compromise the precarious nutritional status of some of these infants and prolong the use of intravenous fluids. Increments of enteral feeding of 10 to 20 mL/kg per day have been reported as safe in a prospective study,[4] but several retrospective studies have suggested that advancing feedings rapidly is associated with an increased risk for NEC.[8,9] In 1 of these studies, feeding increments were as high as 40 to 50mL/kg per day.[8] Conversely, a relatively more rapid advancement of enteral feedings in preterm infants may improve their growth and nutritional status, decrease the need for and hazards of intravenous infusion solutions, and potentially shorten the length of hospitalization. Rayyiset al[5] reported no difference in the incidence of feeding intolerance or NEC in infants who received 35-mL versus 15-mL feeding advancements. Intermediate rates of advancement have not been studied. Therefore, we examined whether infants who were fed initially and advanced at 30 mL/kg per day take fewer days to get to full feedings than those who were fed initially and advanced at 20 mL/kg per day, without increases in their incidence of feeding complications and NEC. Also, we studied whether infants who were fed the higher volume regain birth weight earlier, have fewer days of intravenous fluids, and have a shorter hospital stay than those who were advanced at the slower rate.

Materials and Methods

This randomized controlled trial (RCT) was conducted from January to December 2016 at Neonatal ward in Dhaka Shishu (Children) Hospital. A total of 240 infants were enrolled, 120 infants in the intervention group and 120 in the control group. Preterm neonates with birth weight 1200gm to <2200gm, gestational age < 34 weeks, postnatal age <72 hours and hemodynamically stable babies were included in the study. Preterm neonates with major congenital abnormalities, severe perinatal asphyxia (Apgar score<3 at 5min), Infants with ventilator support and SAG (Small for gestational age) were excluded from the study.A RCT was carried out among the hospital admitted preterm low birth weight (wt 1200gm to <2200gm, gestational age < 34 weeks gestation) neonates. This randomized controlled trial was conducted in Dhaka shishu (Children) hospital (a tertiary hospital) over 12 months period. Both male and female were included in this study. Sample was selected by fulfilling the inclusion and exclution criteria and after obtaining consent from the parents for enrolment in the study. Sample subjects were assigned to either slow enteral feeding or rapid enteral feeding group through simple randomization and allocation was concealed by sealed envelop, which were equal in number for each group. Data was collected by using a structured questionnaire containing all the variables of interest. Interested Outcome variables were clinical outcomes are time taken for full enteral feed, duration of hospital stay, days to regain birth weight and duration of IV fluid. Feeding outcomes are no of infants with feed interruption, infants with vomiting, abdominal distention, infants with withheld of feeding, necrotizing enterocolities etc. A detailed history was taken from mother/caregiver and from the obstretic record and then entered in the structured questionnaire. Feeding was initiated as soon as the baby was stable. Expressed human milk was used eighter from mothers milk or from doners milk after taking consent from both side. In the intervention group, feeding was initiated with 30ml/kg per day and advanced by 30ml/kg per day until 170ml/kg per day was reached. Feeding in the control group was initiated with 20ml/kg per day and advanced by 20ml/kg per day until 170ml/kg per day was reached. Before starting enteral feeds, a test feed was given, when feed was tolerated, then feeding was continued. However, when there was evidence of feeding intolerence e.g. the infant had > 30-50% gastric residue of the previous feed or gastric residual 3ml/kg body weight, apnea, bilious vomiting, abdominal distention, gatrointestinal bleeding, paralytic ileus or NEC, then subsequent feeding was not being given. During that period the infant was investigated for sepsis and NEC (complete blood count, CRP, blood culture, abdominal X-ray, serum electrolytes, occult blood test). During the whole study period feeding was checked usually

before giving every 3rd feeding whether the previous feed was tolerated or not. Bolus feeding was given through nasogastric tube every 2 hours for 20 minutes by the action of gravity; when the infants become more accustomed to enteral feeding with improvement of coordinated sucking, swalling and breathing, gradually feeds was given by spoon or cup and fianally successful breast feeding. A total daily fluid intake of 170ml/kg was mainted by concomitent reduction in parenteral nutrition.when enteral intake was exceed 150ml/kg/day, parenteral nutrition was discontinued. The maximum enteral feeds of 170ml/kg/day was achieved. During hospital stay, both the groups was monitored for daily weight gain, nosocromial infection, feeding intolerence, necrotizing enterocolitis, physiologiacal parameters (heartrate, respiratory rate, temperature and oxygen saturation) and duration of hospital stay by a single observer at the same time every day. The criteria for hospital discharge was uniform among the study infants: satisfactory weight gain (i.e.weight gain 15-20gm/day) while receiving full oral feeding, maintenance of thermal stability and resolution of acute medical conditions, mother was confident to take care her baby.A statistical analysis was carried out by using the Statistical Package for Social Sciences version 19.0 for Windows. The results were reported as mean (±S.D) for slow enteral feeding and rapid enteral feeding. Student's independent 't' test was used for comparison between continuous variables. Pearson chi-square test and Fisher's exact test were used for comparison between categorical variables. Fisher's exact test was used if frequencies for categorical variables were <5. Pearson chi-square test was used for all other categorical variables. Statistical significance was set at 0.05 level of probability (i.e. p value <0.05 was considered as significant). Prior to the commencement of this study the research protocol were approved by the ethical review committee of Bangladesh institute of child health and Dhaka Sishu (Children) Hospital. The aim and objective of the study along with its procedure, methods, risks and benefits were explained to the respondent's parents in easily understandable local language and informed consent were taken from the guardian. No financial burden were given to the parents and no extra investigation were done except the routine one.

Results

This Randomized Control Trial (RCT) was conducted in Dhaka Shishu Hospital during January to December 2016; patients who fulfill the inclusion criteria were enrolled in this study. The various result of this study is shown in tabulated form according to the following groups:

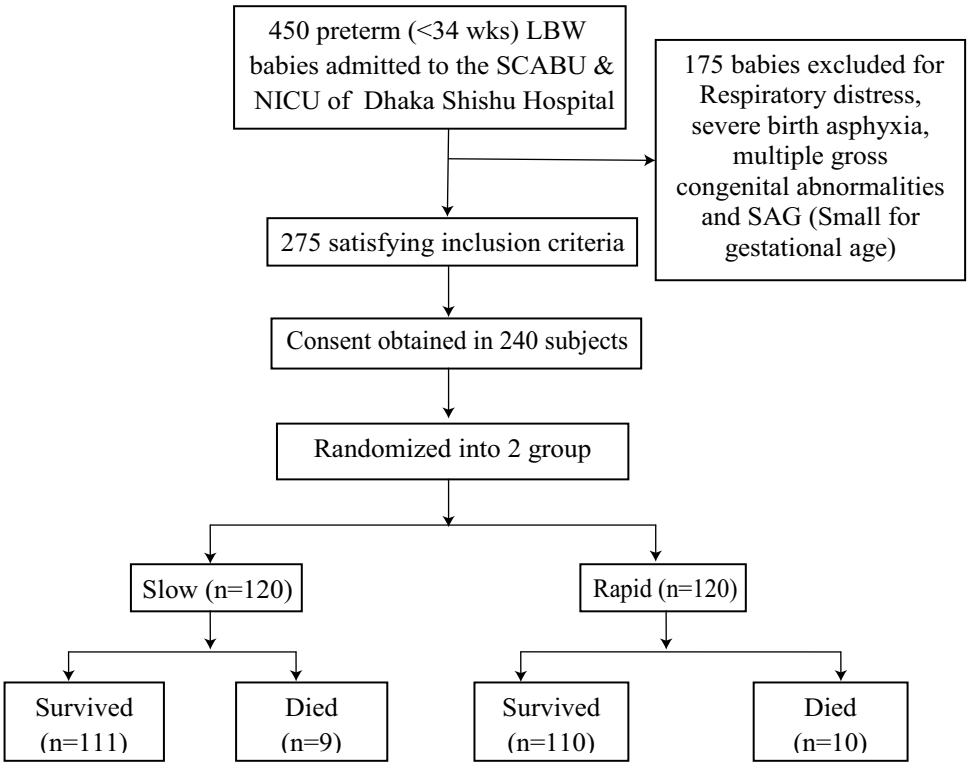

Fig.-1: *Grouping of Sampling Population*

A total of 240 infants were enrolled, 120 infants in the intervention group and 120 in the control group. Enteral feeding advancements were well tolerated by the intervention group of stable preterm neonates like the control group (62.50% vs. 72.50%, p value > 0.05). Infants in the intervention group achieved full volume feedings sooner (9.4 days vs 13.6 days), regained birth weight earlier (8.04 days vs 11.47 days), and had fewer days of intravenous fluids (6.60 days vs 9.20 days) in comparison to slow feeding group. Ten infants in the intervention group and nine in control group died due to sepsis which was statistically not significant. There was no incidence of NEC. No statistical differences in the proportion of infants with feed interruption or feed intolerance.

Table I
Demographic characteristics of the study population

Parameters	Slow Group (n=120)	Rapid Group (n=120)	p value
Gestational age (Wks)	32.76 (±1.94)	30.35(±2.01)	0.26
Weight on admission (gm)	1614.70(±361.85)	1730.58(±250.41)	0.06
Enrolment age (hours)	32.76(±1.94)	33.17(±1.77)	0.31
Sex			
· Male	85	64	0.42
· Female	35	56	

Table II
Feeding outcome of the study population

Characteristics	Slow Group (n=120)	Rapid Group (n=120)	p value
Feeding tolerance	87(72.50%)	75(62.50%)	0.29
Feeding intolerance	33(27.50%)	44(36.67%)	0.29
Abdominal Distention	30(25.00%)	35(29.10%)	0.56
Vomiting	51(42.50%)	42(35.00%)	0.41
Increase Gastric Residual/Gastric Aspirates >50%	05(4.16%)	14(11.67%)	0.26
Feeding Interruption	33(27.5%)	35(29.16%)	0.82
Necrotizing entero colitis (NEC)	00	00	—

Table III
Clinical outcome of the study population

Characteristics	Slow group (n=120)	Rapid group (n=120)	p value
Duration of IV fluid(days)	9.20 (±1.61)	6.60(±1.32)	<0.001
Time taken for full enteral feed (days)	13.60(±2.75)	9.40(±0.96)	<0.001
Duration of Hospital Stay (days)	16.56(±2.80)	12.75(±1.83)	<0.001
Days to regain birth weight	11.47(±3.07)	8.04(±1.41)	< 0.001

Table IV
Comparison of mortality of the study population

Parameters	Slow group (n=120)	Rapid group (n=120)	Total	p value
Discharged with Breast feeding	111(92.50%)	110(91.67%)	221	0.74
Died	09(7.50%)	10(8.33%)	19	
Total	120(100%)	120(100%)	240	

Discussion

There is still a lack of consensus among the neonatologist regarding when and how to start enteral feeding in preterm neonates. However, it is presumed that slow enteral feeding may be well-tolerated than rapid enteral feeding but rapid enteral feeding with breast milk will be cost-effective and promotes growth better than slow feeding. This randomized controlled trial was carried out to evaluate the tolerance of rapid advancement of enteral feed in preterm low birth weight babies. Besides this, benefits and risks between these two groups were also determined.

Total two hundred forty preterm low birth weight (1200 gm to 2200 gm) gestational age <34 weeks of gestation) neonates were enrolled in the study. One hundred twenty preterm neonates each were randomized into slow and rapid feeding volume advancement group respectively. Both groups were similar in respect to baseline demographic parameters.

Both slow and rapid enteral feeding groups were comparable in gestational age, weight on admission, age on admission and sex. There was no significant difference of these demographic characteristics of the study population between the two groups.

Enteral feeding advancements were well tolerated by the rapid feeding group of stable preterm neonates like the slow feeding group (62.50% vs. 72.50%, p value > 0.05). This finding is also consistent with previous studies done by Caple et al[10] and Krishnamurthy et al.[11]

Rapid enteral feeding group needed shorter duration of intravenous fluid than slow enteral feeding group {6.60(±1.32) days vs. 9.20(±1.61) days; p value <0.05}; which is statistically significant (Table IV). This is consistence with some previous studies done by Caple et al. Krishnamurthy et al., and Karagolet al.[14]

Rapid enteral feeding took significantly shorter duration to reach full enteral feeding than slow enteral feeding {9.40(±0.96) days vs. 13.60(±2.75) days; p value <0.05}; (Table III). This is also consistence with some previous studies done by Caple et al.[10] and Krishnamurthy et al.[11]

Rapid enteral feeding took significantly fewer days to regain weight than slow enteral feeding {8.04(±1.41) days vs. 11.47(±3.07) days; p value <0.05}. This finding is well supported by Cochrane review conducted by Opiyo et al.[13] In rapid enteral feeding group regained weight is earlier because calorie intake was high in comparison to slow feeding group. As it is not possible for us to provide TPN (Total Parenteral Nutrition) in preterm low birth weight babies because it is expensive and its administration procedure is not well established in our hospital setup.

Rapid enteral feeding took significantly shorter duration of hospital stay than slow enteral feeding {12.75(±1.83) days vs. 16.56(±2.80) days; p value <0.05}. This is consistence with some previous studies done by Krishnamurthy et al[11] and Karagol et al.[14] But there was no significant difference between the two groups in few other studies which were conducted by Caple et al[10], Rayyis et al[5], and Salhotra et al[12] In their studies, both the groups were kept in the hospital until they reached to the higher limit of the weight of their respective age group but the long-term clinical importance of these effects are unclear.

Feeding was interrupted in both slow and rapid enteral feeding groups which were 33 (27.50%) vs. 44 (36.67%); p value >0.05. There was no statistically significant difference between the two groups (Table II). This is also similar with few other related studies done by Caple et al[10] and Krishnamurthy et al.[11]

Frequency of feeding complication e.g. abdominal distention, feeding intolerance and increase gastric

residual were more in rapid enteral feeding than slow enteral feeding, but there were no significance difference between these two groups; p value for mentionedvariables were > 0.05. It also confirmed with all the mentioned previous studies. In case of vomiting the frequency was more in slow enteral feeding than rapid one, but again this is not statistically significant; p value > 0.05.

Regarding Necrotizing enterocolitis (NEC), there was none for both the groups in this study. Meticulous observation, proper sepsis screening and prophylactic antibiotic was given when necessary. Moreover, only breast milk was provided and no formula milk was added in this study. In all the previous mentioned studies, few incidents of NEC were present and it was similar for both the groups but not statistically significant.[9-14]

In this study, mortality was almost equal (9.80% vs. 11.76%; p value was > 0.05) for both in slow feeding and rapid feeding due to only sepsis which was statistically not significant. In all the previous mentioned studies, less mortality was found due to both NEC and sepsis; these incidents of NEC and sepsis were similar for both the groups but not statistically significant where the study was done by Capleet al.[10] and Krishnamurthy et al.[11]

Conclusion

Rapid enteral feeding with breast milk in preterm (<34 wks) low birth weight infants was found to be well tolerated than slow enteral feeding group. The duration of intravenous fluid was lower in rapid enteral feeding than slow enteral feeding. Rapid weight gain was significant and duration of hospital stay was less in rapid enteral feeding without any incidence of NEC.

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ORIGINAL ARTICLE

Electrolyte Status in Critically Ill Neonates to Predict Their Survival in Intensive Care Unit (ICU) of a Tertiary Care Paediatric Hospital

Mir Mohammad Yousuf[1], Md. Jahangir Alam[2], MAK Azad Chowdhury[3]

Abstract

Background*: Critically ill neonates who need intensive care are vulnerable to electrolyte derangement. Early and prompt recognition helpful to care and overall survival of these neonates.*

Objective*: To study electrolyte status in critically ill neonates admitted in ICU.*

Methods*: This observational prospective study was carried out at ICU of Dhaka Shishu (Children) Hospital (DSH) from January 2015 to July 2015. Total 121 neonates were enrolled according to inclusion criteria and analyzed their electrolyte status as part of proper management as well as to predict their survival.*

Results*: In critically ill neonate perinatal asphyxia was common disorder having electrolyte disruption with the highest mortality followed by sepsis. Lower sodium and higher potassium level were observed statistically significant in perinatal asphyxia. Significant association between mortality with lower potassium and lower sodium level was observed.*

Conclusion*: Early electrolyte status helpful to care and overall survival of critically ill neonate. Low sodium and low potassium level are predictor of mortality in this group of neonate.*

Keywords*: Electrolyte status, perinatal asphyxia, mortality.*

Introduction

Critically ill neonate commonly have electrolyte disorder, which is a valuable indicator to a paediatrician about patient assessment, therapeutic decision and prognosis of the patient.[1] These occur in a variety of conditions and may remain unrecognized leading to morbidity and mortality irrespective of the primary disease need more vigorous measures to reduce mortality in an emergency situation.[2] Sodium is the major cation of the extracellular compartment. It regulates the voltage of action potentials in skeletal muscles, nerves and myocardium. Sodium plays an important role in the maintenance of acid-base balance, and

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fluid balance in the ECF through maintenance of the osmotic pressure (osmolality). In the critically ill neonate hyponatremia may occur as the result of excess water retention in the ECF, or a combination of these two. Hyponatremia (<135 mmol/L) leads to a generation of cellular swelling or edema. Within the brain, where there is limited capacity for expansion, there development of cerebral edema can have catastrophic consequences (eg. cerebral herniation and death).[3] Potassium is the body's primary intracellular cation. Potassium has four major functions within the body: maintenance of cells electrical neutrality and osmolality, neuromascular transmission of nerve impulses, skeletal and cardiac muscle contraction and electrical conductivity and maintenance of acid-base balance. Maintenance of intracellular osmolality is accomplished through the sodium-potassium pump (active transport). Hypokalaemia (<3.5mmol/L) occurs as the result of loss of potassium or a shift of potassium out of the ECF (intravascular space) into the ICF. Bicarbonate (normal level 22-27 mmol/L) is an important electrolyte acts as a buffer to maintain the normal levels of acidity (p^H) in the blood and other fluids in the body.[3]

A buffer is a substance that preserves the original concentration of a fluid. Low level reflects the acid status of blood (eg. metabolic acidosis). When acids build up through the metabolic process or production of lactic acid in muscles, the kidneys release the bicarbonate (an alkaline solution into the body to counteract the increased acidity). If body is becoming more basic, the kidneys will lessen the amount of bicarbonate to increase acidity. Without this system, rapid changes is pH balance could cause severe problems in the body like damaging sensitive tissue around the central nervous system. The anion gap (8-12mEq/L) is used to aid in the differential diagnosis of metabolic acidosis.[4,5] In perinatal asphyxia and neonatal sepsis, syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a common problem where severe hyponatremia and hyperkalaemia can occur. Hyperkalaemia results from ischaemic insult reflected cellular changes leading to diminished oxidative phogphorylation and ATP production. This energy failure impairs ion pump function, resulting in accumulation of intracellular Na+ and extracellular K^+.[6] If inappropriate fluid and electrolytes are given, serious morbidity can result from fluid and electrolyte imbalance. Hyperkalaemia (>6 mmol/L) occurs in approximately 30% all newborns of birth weight low than 1000 gm, even in the absence of renal failure.[7] Excessive of sodium-bi-carbonate, improper preparation of formula feeds, increased insensible water less especially in premature babies kept under radiant warmers can cause hypernatremia in neonates.[8] A high index of suspicion, prompt recognition and a through understanding of common electrolyte abnormalities are necessary to ensure their correction.[9] So routine measurement of serum electrolyte is the best way to monitor the bodies electrolyte status and the adequacy or excess of electrolyte intake.[10] This study was carried out in neonates with various ailments attending ICU at a tertiary care hospital of Dhaka, Bangladesh. The objective was to study electrolyte status in critically ill neonates, association with primary illness and their impact on mortality.

Materials and Methods

This prospective observational study was conducted at ICU, Dhaka Shishu (Children) Hospital during the period of January 2015 to July 2015. For each neonate a detailed history from the mother or other care-giver was recorded in a preset questionnaire. Maternal history included antenatal care, prolonged rupture of membranes (>12 hours before delivery was considered), prolonged second stage of labour. Admission weight of the baby was recorded by electronic weighing scale. Gestational age was determined from maternal records, first day of last menstrual period, EDD of mother, Dubowiz scoring system and also by ultrasonography of the mother during pregnancy. Time of first cry or breathing immediately after birth, apnoea/cyanosis, convulsion, reluctant to feed and bleeding manifestation were recorded along with particulars of the patients. The presence of perinatal asphyxia was determined by history of no or delayed cry or breathing after birth. Total 161 neonates admitted during this period, among these 40 were excluded from this study due to any congenital anomaly, severely Jaundiced due to blood group incompatibilities or received LAMA (Left against medical advice). Before enrollment parent of each child was given a detail explanation about the nature and purpose of the study. The study was started after obtained ethical clearance by Bangladesh Institute of Child Health, Dhaka Shishu Hospital. 121 neonates were analyzed for electrolyte status, blood gas as well as baseline investigation.

With all aseptic precaution venous blood sample was collected for estimation of serum sodium, potassium. Electrolyte analyzer (Rapid lab 1265) based on the principle of potentiometry analyzed Na^+, K^+, CI^-. $HCO3^-$ was calculated by blood gas analyzer (Gastat-600). Anion gap was calculated from the following formula.[5]

$AG=[Na^+ + K^+]- [CI^- + HCO3^-]$.

Each case was thoroughly examined and followed up regularly. Definite newborn septicaemia was diagnosed by positive blood culture and probable septicaemia was diagnosed by a scoring system[11] and positive CRP. Relevant investigations for the diagnosis and follow up included complete blood count, blood culture, chest X-ray, serum electrolytes, blood gas analysis, blood grouping and serum bilirubin. Temperature maintenance, appropriate feeding, management of fluid and electrolytes, treatment of infection, mechanical ventilation for respiratory failure, management of acid-base disturbances, transfusion of fresh blood or fresh frozen plasma in case of bleeding manifestations and phototherapy in case of Jaundice were ensured. Strict aseptic measures were ensured followed to prevent infection.

Unpaired t-test was used to test the significance of difference of electrolyte status in major diagnosed pathological conditions (perinatal asphyxia and sepsis) among ill neonates and also the significance of difference of mortality among survivors and non-survivors.

Hyponatremia and hypernatremia were defined as serum sodium concentration <130mmol/L[12,13]and >150mmol/L[14,15] respectively. Hypokalaemia and hyperkalaemia were defined as serum potassium level <3.5 mmol/L[9,15] and >6 mmol/L [16,17] respectively.

Results

In this study, 121 neonates (0-28 days), median age was 7 days. Eighty four neonates were male and thirty seven were female, ratio was 2.27:1. Ninety one babies (75%) had electrolyte abnormalities (Table I). Of these 21(17%) had mixed electrolyte imbalance. Hyperkalaemia was seen in 44 (36%), hypokalaemia in 8 (6.6%), hyponatremia in 16 (13%) and hypernatremia in 2 (1.65%) of cases (Table I). Most of the neonate with electrolyte imbalance had perinatal asphyxia (Table II) hyponatremia (18.42%), hyperkalaemia (52.63%), hypokalaemia (2.63%) and mixed (26.3%) followed by sepsis (Table III).

Table I
Type of electrolyte abnormalities (n=121)

Abnormal electrolytes	Number	Percent
Hyperkalaemia	44	36.36
Hypokalaemia	8	6.61
Hyponatremia	16	13.22
Hypernatremia	2	1.65
Mixed		
Hyponatremia and hyperkalaemia	10	8.26
Hyponatremia and hypokalaemia	6	4.95
Hypernatremia and hyperkalaemia	5	4.13

Metabolic acidosis was present in 48.7% with hyperkalaemia, 12.8% with hypokalaemia and 38.4% with normal potassium level. Overall K^+ level was

Table II
Primary disease profile with electrolyte imbalance and % of their non-survival

Primary disease	No. of patient (%)	Electrolyte imbalance (%)	Non-survival among Electrolyte imbalance (%)
Perinatal asphyxia	43(35.54)	38(41.76)	18(36)
Neonatal sepsis	39(32.23)	26(28.57)	17(34)
Preterm LBW	19(15.70)	11(12.09)	8(16)
Others	20(16.53)	16(17.58)	7(14)
Total	121(100)	91 (100)	50(100)

found more, Na^+ level was less in perinatal asphyxia than sepsis which were statistically significant (Table IV) . On the other aspect, comparatively non-survivors had less sodium and less potassium level than survivors which were statistically significant (Table V).

Among these 91 patients with electrolyte imbalance, 42 (46.1%) died. Ten (23.8%) were from hyponatremia, one (2.38%) from hypernatremia, six (14.28%) from hypokalaemia and fifteen (35.7%) were from hyperkalaemia groups. Ten (23.86%) had mixed (combination) groups combination of hyponatremia and hyperkalaemia (11.9%), hyponatremia and hypokalaemia (4.76%), hypernatremia and hyperkalaemia (7.14%) (Table V) .

Case fatality rate was highest (75%) in those with hypokalaemia followed by hyponatremia (62.5%) and hypernatremia (50%). Mortality was lowest with hyperkalaemia (34%). Hypokalaemia was found to have a significantly higher mortality (p=.001) when compared to those with normal electrolyte values and similar underlying disorders (Table V) .

Table II- Shows a comparative observation of electrolyte status in major diagnosed pathological disease in critically ill neonates. Perinatal asphyxia was common disorder in this group of neonate having electrolyte imbalance with the highest mortality.

Table III
Electrolyte abnormalities in relation to their primary illness (n=121)

Primary disease	Hyponatremia	Hypernatremia	Hypokalaemia	Hyperkalaemia	Mixed	Total
	No (%)	No (%)	No (%)	No (%)	No (%)	No(%)
Perinatal asphyxia	7(18.42)	0(00)	1(2.63)	20(52.63)	10(26.72)	38(100)
Neonatal sepsis	5(19.23)	1(3.85)	3(11.54)	9(34.61)	8(30.71)	26(100)
LBW	2(18.18)	0(00)	1(9.09)	7(63.64)	1(9.09)	11(100)
Others	2(12.50)	1(6.25)	3(18.75)	8(50.00)	2(12.5)	16(100)
Total	16(17.58)	1(2.20)	8(8.79)	44(48.35)	21(23.08)	91(100)

Table IV
Electrolyte parameters (Mean ±SD) in perinatal asphyxia and sepsis (admission)

	PNA (n=43) Mean±SD	Sepsis (n=39) Mean ±SD	p value
Na^+ (mmol/L)	135.76 ±7.41	140.03 ±9.44	0.026^s
K^+ (mmol/L)	5.26 ±1.40	4.7 ±1.0	0.016^s
CI^- (mmol/L)	98.86 ±10.29	102.79 ±15.3	0.176^{ns}
HCO_3^- (mmol/L)	16.83 ±4.91	19.31 ±10.09	0.155^{ns}
Anion Gap (AG)	25.5 ±10.25	21.81 ±14.82	0.193^{ns}

p value reached from unpaired t-test

Table IV- Gives a comparative observation of electrolytes parameter in major diagnosed pathological conditions (perinatal asphyxia and sepsis) among neonate. Here K^+ level was found more: Na^+ level were found less in PNA patients than sepsis which were statistically significant.

Table V
Value of electrolytes at admission and mortality statistics (n=121)

Electrolyte status	Survival	Non-survival	Total	Case Fatality (%)	Statistics
Normal electrolyte	22	8	30	26.67	
Perinatal asphyxia	3	2	5	40.00	
Neonatal sepsis	9	4	13	30.76	
Preterm LBW	8	1	9	11.11	
Others	2	1	3	33.33	
Hyponatremia	6	10	16	62.50	P= .032
Perinatal asphyxia	1	6	7	85.71	
Neonatal sepsis	3	2	5	40.00	
Preterm LBW	0	2	2	100.00	
Others	2	0	2	00.00	
Hypernatremia	1	1	2	50	P= 0.744
Perinatal asphyxia	0	1	0	00	
Neonatal sepsis	0	1	1	100	
Preterm LBW	0	0	0	0	
Others	1	0	1	00	
Hypokalemia	2	6	8	75	P= .001
Perinatal asphyxia	0	1	1	100	
Neonatal sepsis	1	2	3	66.67	
Preterm LBW	0	1	1	100.00	
Others	1	2	3	66.67	
Hyperkalemia	29	15	44	34.09	P= 0.251
Perinatal asphyxia	14	6	20	30.00	
Neonatal sepsis	7	2	9	22.22	
Preterm LBW	4	3	7	42.86	
Others	4	4	8	50.00	
Mixed	11	10	21	47.62	
Perinatal asphyxia	7	3	10	30.00	
Neonatal sepsis	2	6	8	75.00	
Preterm LBW	0	1	1	100.00	
Others	2	0	2	00.00	

Discussion

Electrolyte abnormalities were observed in 75% of ill neonates getting admitted to Intensive Care Unit. Hyperkalaemia was the commonest, found in 36% cases. These finding are in contrast to those by Singhi et al.[18-20] and Rao et al[9] who found by hyperkalaemia in 5.4% and 14.4% respectively in ICU admitted neonates. This difference could be due to the fact that as we do not use central lines during venous blood collection, some tissue fluid could have been mixed with collected blood or blood drawn through a tiny needle may cause haemolysis leading to falsely elevated potassium level. In 48.7% neonates with hyperkalaemia there was concomitant metabolic acidosis, another important cause. The other possibilities of increased potassium release are tissue

destruction, trauma, cephalhaematoma, hypothermia, bleeding, intravascular or extra vascular haemolysis, asphyxia, ischaemia and IVH.[21] Most of these condition were present in our study subjects.

Yuan et al[17] have found hyperkalemia in 44% of sick neonates which is consistent with the present study. Hyponatremia was the second most common electrolyte abnormality (13%) noted in this study. In a study conducted in a paediatric ICU, 9.5% of total admissions had hyponatremia.[9] Since sick neonates with SIADH were included, this may explain the higher incidence of hyponatremia in the present study. Also these babies may be predisposed to excessive intravenous fluid, diuretics, necrotizing enterocolities and in VLBW preterm bodies there could be renal water and sodium wasting.[21] Hypokalaemia was less common (6.6%) electrolyte abnormality observed in the present study. However, a significantly lower (3.6%) [9] and two higher frequencies (13.9% & 14.8%)[18,22] were observed in three studies.

The risk of mortality in our study is significantly higher in patients with hypokalaemia (75%) in comparison to those with normal electrolyte values (26.6%). Higher risk of mortality was also observed in a prospective study of 727 sick children,[23] in contrast lowest mortality with hypokalaemia was reported by Rao et al.[9] Due to mixture of blood with tissue fluid or haemolysed sample actual serum potassium value could be even lower than that of the reported value and during correction of metabolic acidosis, a complication of perinatal asphyxia and neonatal sepsis iatrogenic hypokalaemia may be precipitated. In our study hyponatremia was found to have a significantly higher mortality rate (62.5%) after hypokalaemia which is consistent with other studies.[2,23,24] In very sick neonates SIADH is a common problem and severe hyponatremia can occur.

Case fatality rate (41.3%) in patients with hyperkalaemia was lower than other electrolyte abnormalities in sick neonate. This is in contrast to other studies[17] where it has been shown that hyperkalaemia is associated with higher mortality. This finding may be attributed to spurious hyperkalaemia in patients having normal potassium as our samples were collected from peripheral veins and sometimes with difficulty squeezing the tissue. Mortality rates in patients with mixed electrolyte abnormalities were higher when compared to these with most single electrolyte abnormality. Similar observations were made by others.[18,23]

Conclusion

Electrolyte abnormalities are common in sick neonates helpful in explaining of mortality admitted in ICU. Low potassium and low sodium are significantly correlate with the ultimate outcome of critically ill neonates requiring total ICU care to reduce their mortality.

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ORIGINAL ARTICLE

Dorsal Lumbotomy and Anterolateral Flank Incision for A-H Pyeloplasty - A Comparative Study

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Abstract

Background: *The most common cause of hydronephrosis in children is pelviureteric junction (PUJ) obstruction. The incidence is 1 in 1250. Most of them diagnosed antenatally by ultrasonography. Open pyeloplasty is considered as gold standard for the treatment of PUJ obstruction. Anderson Hynes (A-H) pyeloplasty is more acceptable. Dismembered Anderson Hynes (A-H) pyeloplasty has many approaches. This study is an attempt to compare the surgical outcome between dorsal lumbotomy (DL) and anterolateral flank incision in unilateral PUJ obstruction.*

Methods: *Total 54 patients of PUJ obstruction were included in this study after fulfillment of inclusion criteria from July 2015 to June 2017. They were randomly assigned to dorsal lumbotomy group (Group 1=27 children) and anterolateral flank incision group (Group 2=27 children). The comparative parameters between two groups were the length of incision, operation time, hospital stay and post operative complications. Wound infection, urinary tract infection and incisional hernia were assessed at the follow up evaluation at 6 months post operatively.*

Results: *The length of incision was significantly shorter in Group 1 (30.93±2.34 mm) than Group 2 (113.07±4.63 mm) ($p<0.0001$). Operation time was also significantly shorter in Group 1 (61.07±4.36 minutes) than Group 2 (89.33±3.77 minutes) ($p<0.0001$). Duration of hospital stay was also significantly shorter in Group 1 (5.67±1.18 days) than Group 2 (8.00±0.83 days) ($p<0.0001$). Incisional hernia developed in 1 patient in Group 2. None of the patient developed wound infection and 7 patients developed urinary tract infection.*

Conclusion: *Anterolateral flank incision for pediatric pyeloplasty requires large incision, long operation time, and long hospital stay as it cuts several muscles, but dorsal lumbotomy approach is advantageous in the form of small incision, short operating time, early recovery and short hospital stay.*

Key Words: *Anderson Hyneys Pyeloplasty, Dorsal Lumbotomy, Anterolateral flank incision.*

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Introduction

The most common cause of hydronephrosis in children is a pelvi-ureteric junction (PUJ) obstruction, it occurs due to developmental change during antenatal period and occurring in 1 in 1250. Pelvi-ureteric junction obstruction is also the most common cause of postnatal hydronephrosis.[1] Due to advances in radiology, most of the hydronephrosis diagnosed prenatally.[2] First description of reconstructive surgery was given by Trendelenburg in 1891 since then various modifications in techniques have been described by various authors. Open pyeloplasty is considered the gold-standard for the treatment of PUJ obstruction.[3] Dismembered pyeloplasty as described by Anderson Hynes in 1946 has become the gold standard in pyeloplasty.[4] The objective of pyeloplasty is to repair PUJ obstruction with the best functional results. There is a success rate of 90% to 99% with open pyeloplasty.[5]

In the last few decades, advanced urological instrumentation and techniques have revolutionized the management of PUJ obstruction toward using minimally invasive procedures.[6] These techniques offered the advantages of short operative time, minimal morbidity, decreased postoperative analgesic requirements, shorter hospitalization, and early recovery and convalescence.[7]

Since the past two decades have witnessed a rapid integration of minimally invasive surgery to pediatric surgical practice.[8] This study attempted to evaluate the current status of mini-incision pyelpolasty in pediatric urology and to compare its results with other different surgical techniques for pyeloplasty.

Renal surgery was started by Gustav Simon in 1870 through a posterior lumbotomy incision. Although this incision provides the quickest and anatomically straight access of upper urinary tract, flank incision has been the standard with most surgeons for reasons of wider access. Dorsal lumbotomy was popularized on the European continent by Gil-Vernet and Lurz in the sixties.[9]

Recent studies have further described the outcomes of minimally-invasive open renal surgery done with a fairly small incision, less hospital stay, and reduced postoperative pain.[10] In this regard, the dorsal lumbotomy (DL) approach offers a direct exposure to the pelviureteric junction and upper ureter through a muscle sparing incision that is associated with a short convalescence.[11] Besides, synchronous bilateral pyeloplasty can be performed without re draping or repositioning the patient in bilateral cases, which may constitute up to 20% of children with PUJ obstruction.[12]

Materials and Methods

This was a prospective comparative study. Total 54 patients of PUJ obstruction were included in this study after fulfillment of inclusion criteria from July 2015 to June 2017. Patients with bilateral PUJ obstruction and previous history of A-H pyeloplasty were excluded from this study. They were randomly assigned to dorsal lumbotomy group (Group 1=27 children) and anterolateral flank incision group (Group 2=27 children). The comparative parameters between two groups were the length of incision, operation time, hospital stay and post operative complications. Wound infection, urinary tract infection and incisional hernia were assessed at the follow up evaluation at 6 months post operatively.

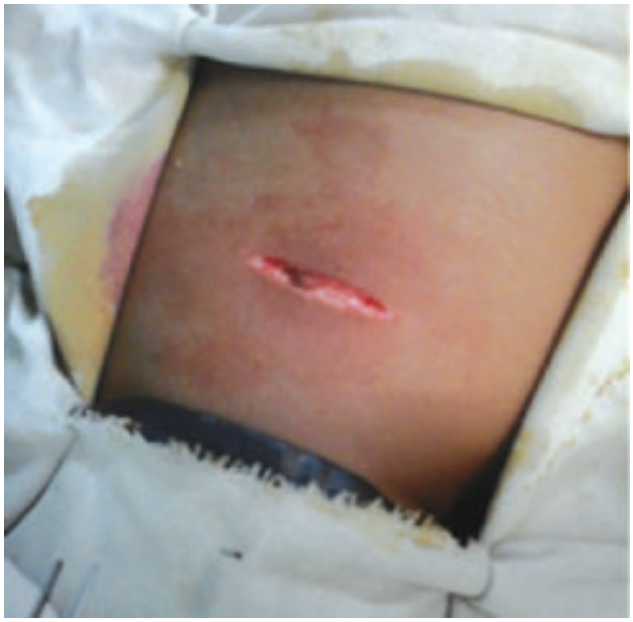

Fig 1 *Dorsal lumbotomy incision*

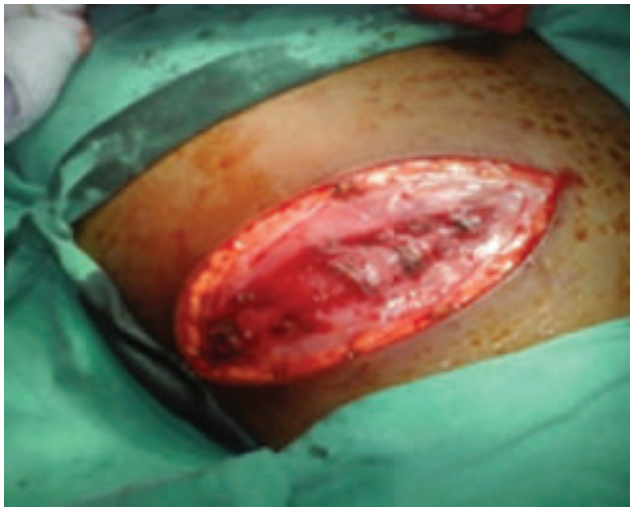

Fig 2 *Anterolateral flank incision*

Results

Among 54 patients 40 were male and 14 were female. The length of incision was significantly shorter in Group 1 (30.93±2.34 mm) than Group 2 (113.07±4.63 mm) (p<0.0001). Operation time was also significantly shorter in Group 1 (61.07±4.36 minutes) than Group 2 (89.33±3.77 minutes) (p<0.0001). Duration of hospital stay was also significantly shorter in Group 1 (5.67±1.18 days) than Group 2 (8.00±0.83 days) (p<0.0001). Incisional hernia developed in 1 patient in Group 2. None of the patient developed wound infection.

Table 1
Comparison of age of the participants between two groups

Age(in months)	Grou 1 (n=27)	Group 2 (n=27)	P value
Median	18.00	24.00	0.214
Minimum	3	4	
Maximum	120	96	

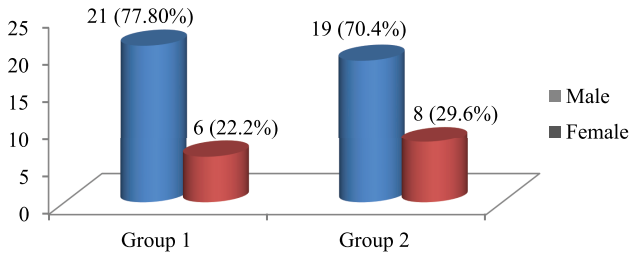

Fig 3 *Sex distribution of the participants in two groups*

Table II
Comparison of side involvement of PUJO between two groups

Side of PUJO	Group 1 (n=27) No. (%)	Group 2 (n=27) No. (%)	P value
Right	12(44.4%)	12(44.4%)	1.000
Left	15(55.6%)	15(55.6%)	

Table III
Comparison of length of incision between two groups

Length of incision(In mm)	Group 1 (n=27)	Group 2 (n=27)	P value
Mean±SD	30.932.34	113.074.63	0.0001

Table IV
Comparison of operation time between two groups

Operation time (In minutes)	Group 1 (n=27)	Group 2 (n=27)	P value
MeanSD	61.074.36	89.333.77	0.0001

Table V
Comparison of duration of hospital stays between two groups

Duration of (in days) hospital stays	Group 1 (n=27)	Group 2 (n=27)	p value
Mean SD	5.67 1.18	8.00 0.83	0.0001

Table VI
Post-operative complications within 6 months follow up between two groups

Post-operative complications	Group 1 No. (%) (n=27)	Group 2 No. (%) (n=27)	P value
Wound infection	0(0.0%)	0(0.0%)	
Incisional hernia	0(0.0%)	1(3.7%)	1.000
UTI	3(11.11%)	4(14.81%)	1.000

Discussion

Hydronephrosis is more common problem in Bangladesh and all over the world. The dismembered pyeloplasty (Anderson-Hynes pyeloplasty), is the most popular. It involves complete removal of the narrowed (dysfunctional) segment, tailoring of the renal pelvis (if necessary), and re approximation of the ureter to the renal pelvis in a dependent position. The Anderson-Hynes dismembered pyeloplasty can be performed through dorsal lumber or a flank incision. Posterior lumbotomy incision is anatomically the most straight forward approach to the kidney and the upper ureter. Although posterior lumbotomy incision provides the quickest and anatomically straight access to upper urinary tract, flank incision has been the standard with most surgeons for reasons of wider access provided by the later.

In the current study, pediatric age group were taken as the study population. In group 1, the minimum

age was 3 months and maximum age was 120 months. In group 2, where the minimum age was 4 months and maximum age was 96 months. There was no significant difference between ages of two groups.

PUJ obstruction is more commonly found in boys than in girls, especially in the newborn period, when the ratio exceeds 2:1.[13] This phenomenon was also found in this current study. In group-1, 77.8% participants were male and in group-2, 70.4% participants were male which meant that in both groups majority of the participants were male.

It has been mentioned in literature that there is a predilection for the left side in children (66%), whereas the reverse is true for PUJ obstruction of adults.[14] In both groups, 55.6% participants had PUJO on left side. This side involvement did not showed any statistical difference in the study.

Although often asymptomatic, children with PUJ obstruction may have variable symptoms such as episodic flank, abdominal pain, or less commonly a urinary tract infection.[14] In this study, the presenting complains of respondents were flank pain, abdominal lump, fever and UTI which did not show any statistical differences between the study groups.

Halder et al. performed Dorsal Lumbotomy approach for pediatric dismembered Pyeloplasty where the average length of incision was 3-4 cm and mean operating time was 50.6 minutes.[15] In the present study the mean length of incision of Dorsal Lumbotomy group was 30.932.34 mm with 61.074.36 minutes operation time. The mean length of incision matched in both study but the difference between operations times might be due to surgeon to surgeon variation.

The Dorsal Lumbotomy approach took on an average 61.074.36 minutes to perform whereas the anterolateral flank incision took on an average 89.333.77 minutes to perform. As the Dorsal Lumbotomy required small incision and did not cut any muscle it took less operation time than anterolateral flank incision which required large incision and several muscle cut. This difference of operation time showed strong statistical difference (p=0.0001). Wiener and Roth had done a research work to compare the outcome of surgical approaches for pediatric pyeloplasty: dorsal lumbar versus flank incision where they also found that in children older than 1 year pyeloplasty through a dorsal lumbar incision was statistically significantly faster than the flank approach (p=0.0205).

Wiener and Roth found that hospital stay was approximately 2 days shorter in infants who had a dorsal lumbotomy versus a flank incision and this difference did reach statistical significance.[16] Kumar and Smith also found that there was significant statistical difference between dorsal lumbar and a flank incision group regarding hospital stay ($p < 0.001$).[11] Similar result was found in the present study. In group 1, the mean duration of hospital stays was 5.67 1.18days and in group 2, the mean duration of hospital stays was 8.000. 83 days. The result showed that there was strong statistical difference in time of hospital stays between two groups as the.

There are many ways to divert urine, and different types of drainage methods have been described in the literature, including nephrostomy tube drainage, internal ureteral stents such as the double 'J' stent, external stent, and a combination of these modalities. The most common reasons to leave a stent in place after pyeloplasty are to ensure proper urinary diversion, maintain ureteral caliber, and ensure anastomotic alignment. In every patient, a DJ stent was used to prevent adhesion to the suture site by splinting the suture line, help to maintain an appropriate diameter and alignment of the ureter, and limit ureter kinking. DJ stent was removed with a brief cystoscopy under a short general anesthesia. In group 1 and group 2, the times of DJ stent removal were 6.48±0.80 weeks and 6.81±0.74 weeks after operation respectively which did not show any statistical difference.

Reis et al. suggested that if there was satisfactory diuretic renogram at 3 to 6 months after pyeloplasty with maintained renal function and stable hydronephrosis, no need for further follow-up.[17]

Conclusion

Flank incision requires large incision, long operation time, and long hospital stay as it cuts several muscles. On the other hand, dorsal lumbotomy approach for pediatric pyeloplasty is advantageous in the form of small incision, short operating time, early recovery to normal activity and short hospital stay.

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DS (Child) H J 2017; 33(2) : 119-123

ORIGINAL ARTICLE

Prenatal Diagnosis of Thalassaemia in a Tertiary Level Hospital by Amplification Refractory Mutation System (ARMS) Method

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Abstract

Background: *Thalassaemia and Haemoglobinopathies constitute the commonest recessive monogenic disorders. Beta thalassaemia major and Hb-E- Beta thalassaemia is common in Bangladesh. Treatment of the disease is expensive not affordable by majority of the patients. Prenatal diagnosis and option to abort the affected child has been shown very succesful prevention of birth of thalassaemic in many country of the world. Prenatal diagnosis should be approached for diagnosing the affected children of the couples at risk, so that they can be offered options to have healthy offsprings.*

Objective: *This study shows the result of DNA analysis of fetal tissue for thalassaemia mutations.*

Methods: *This study shows result of prenatal diagnosis of fetuses from chorionic villous and amniotic fluid for detection of mutation for thalassaemia. Pregnant mother of seventy six thalassaemic patients underwent chorionic villous sampling or amniocentesis for taking part in the study. Two fetus were lost after chorionic villous sampling and one fetus lost after amniocentesis. We could detect the absence or presence mutations of seventy two fetal samples by ARMS method. One of the sample not detected by ARMS method was referred for sequencing.*

Results: *DNA analysis of the collected samples of fetuses done by ARMS method showed, Twenty nine fetuses were Beta thalassaemia trait, twenty two fetuses were HB-E trait, twelve fetuses were HB-E-Beta thalassaemia, three fetuses were homozygous for beta thalassaemia. No thalassaemia mutation was detected in six fetuses.*

Conclusion: *From the results of our samples, it can be concluded that prenatal diagnosis of Beta-thalassaemia and HB-E thalassaemia can be done using ARMS method. ARMS method is a cheap, accurate, rapid and simple method for prenatal diagnosis in a resource limited country like Bangladesh.*

Key words: *Thalassaemia, dna analysis, prenatal diagnosis, ARMS method.*

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Introduction

Beta thalassemias and hemoglobinopaties are among the commonest autosomal recessive diseases with a high frequency in population of the Mediterranean area, the Middle East, the Indian subcontinent, the Far East, Tropical Africa and the Caribbean.[1]

Beta thalassaemia and Hb-E- Beta thalassaemia is common in our country. A conservative world health report has estimated that 3 percent are carriers of Beta thalassaemia and 4 percent are carriers HB-E-Beta thalassaemia (WHO, 1994).[2] In Bangladesh overall prevalence of Beta thalassaemia trait was 4.1 percent and Haemoglobin E trait was 6.1 percent.[3]

Awareness about the disease, detection of carrier and prenatal diagnosis of the couple at risk are prerequisite for success of prevention programme of thlassaemia and haemoglobinopathy. Prenatal diagnosis with an option for abortion of the affected fetus has been very successful to limit the births of thalassaemic children in Cyprus, Italy, Greece and UK led to the development of control programme in many other countries.[4-8] Iran has been very successful in diminishing the births of thalassaemic children after introduction of prenatal diagnosis and legally approved option for abortion of an affected child.[9]

There are some of ways of sampling procedures for prenatal diagnosis. Invasive procedures are Chorionic villous sampling, Amniocentesis and Fetal blood sampling. Non-Invasive procedures are on trial, which is Isolation of fetal cells from maternal blood. Pre-implantation genetic diagnosis (PGD) is another promising part for in vitro fertilization (IVF) or test tube baby.[10]

In this study molecular diagnosis of fetuses have been done both from amniotic fluid and from chorionic villous. Their mutations were detected by Amplification Refractory Mutation System. The amplification-refractory mutation system (ARMS) is a simple method for detecting any mutation involving single base changes or small deletions. ARMS is based on the use of sequence-specific PCR primers that allow amplification of test DNA only when the target allele is contained within the sample. Following an ARMS reaction the presence or absence of a PCR product is diagnostic for the presence or absence of the target allele.[11]

Materials and Method

This was a cross sectional study. Study period was from November 2013 to December 2016.

Pregnant mother of thalassaemic patients who came to Dhaka Shishu (Children) Hospital with their second or third pregnancy for prenatal diagnosis took part in the study by giving their fetal samples. Mutations of parent were detected by ARMS method from blood sample. Fetuses were diagnosed by the same method from amniotic fluid or from chorionic villous.

Before collection of amniotic fluid or chorionic villous, both parents were properly counseled. During chorionic villous sampling there is 0.5 to 1% chance of fetal loss.[12] Procedure related risk of amniocentesis is also 0.5 to 1%.The main disadvantage of amniocentesis is lateness of the diagnosis.[13] A consent from in local language which have detailed information about chorionic villous sampling and amniotic fluid collection were given to the parents and their consent was taken. Their blood samples were collected. Fractions of haemoglobins were detected by high performance liquid chromatography BIORAD VARIANT II â thalassemia short program and by capillary electrophoresis utilizing CAPILLARYS 2 SEBIA FLEX PIERCING. Tests were done according to procedures provided by manufactures. Their mutations were detected by Amplification Refractory Mutation System. Amniotic fluid was collected at 16 th weeks ofgestation.[14]Chorionic villous sample were taken from 12th weeks onward. Total three fetuses were lost after sampling procedure two after collection of Chorionic villous and one after collection of Amniotic fluid.

DNA were extracted from the parents blood using the Genomic DNA Mini Kit (Blood/Cultured Cell) protocol which provides an efficient method for purifying total DNA from whole fresh blood.[15] The purified DNA, with approximately 20-30 kb, was suitable for use in PCR. DNA were extracted from the fetal sample by using Genomic DNA Mini Kit (tissue) protocol.[15] After DNA extraction, beta globin chain was analysed by allele specific primers using Amplifiction Refractory Mutation System – Polymerase Chain Reaction (ARMS-PCR).[16]

Initially, DNA analysis was done with five mutations present in Indian sub-continent which accounted for

84.50%. These mutations were IVS-I-5 (G>C) (*HBB*: c.92+5G>C), codon 30 (G>C) (*HBB*: c.92G>C), FSC 8/9 (+G) (*HBB*: c.27_28insG), frameshift codons (FSC) 41/42 (–TTCT)(*HBB*: c.124_127delTTCT) and 619 bp deletion **(**NG_000007.3:g.71609_72227del619**)**.[17] DNA analysis was done with 7 less common mutations also found in Indian sub-continent which were Cd 16 (-C) (HBB:c.51delC), IVS 1-130 (G>C) (HBB:c.93-1G>C), IVS 1-130 (G>A) (HBB:c.93-1G>A), -90 (C-T) (HBB:c.-140C>T), Cd 15 (G>A) (HBB:c.48G>A), Cd 15 (-T) (HBB:c.46delT) and Cd 30 (G>A) (HBB:c.92G>A).[18] For haemoglobin E codon 26 (G>A) (*HBB*: c.79G>A) primer was used . Mutation of one sample could not be detected by ARMS method using these primers and was referred for sequencing..

Data were recorded in a computer using SPPS version 15.Simple descriptive analysis were done

Results

Seventy six fetal samples were collected through abdominal route as chorionic villous and Amniotic fluid (Table I).

Table I
Type of fetal sample

Fetal sample	Frequency	Percent
Chorionic villous	43	56.6
Amniotic fluid	33	43.4
Total	76	

Three of the fetuses were lost after sampling procedure.

We could diagnose seventy two fetal samples by ARMS method one sample was referred for sequencing. Our finding was Beta thalassaemia trait with a single mutation for beta globin gene, HB-E-Beta thalassaemia trait having a single muatation of codon 26, HB-E-Beta thalassaemia having a mutation of codon 26 and another mutation for beta globin gene, homozygous for Beta-thalassaemia with two mutations for beta globin gene and no thalassaemia mutation was detected in some fetuses Table-II.

Table II
Spectrum of diagnosis of the foetal samples

Diagnosis	Frequency	Percent
Beta thalalassaemia trait	29	40.3
Hb E trait	22	30.6
Haemoglobin E Beta Thalassaemia	12	16.7
Beta thalassaemia major	3	8.3
Normal	6	4.2
Total	72	100

Mutation detected were Cd 26 (G-A), followed by IVS 1-5 (G-C), these two mutation comprsises 84.73% of the mutations. Other less common mutation were Fr-41/42(TTCT) 5.06%, IVS 1-30(G-A) 2.53% , Cd 30 (G-C)1.26% ,Fr 8/9 (+G)1.26% ,Fr 16(-C) 1.26% ,-90(C-T) 1.26%,Cd15 (-T) 1.26%,Cd15(G-A) 1.26%.

We have to do sequencing for one sample which was not detected by ARMS method for rare mutation, the mutation detected was Cd -44(-C) (HBB: c.135delC).

Discussion

Developing countries like Bangladesh have improved a lot in health services, as a result of successful vaccination programme and better nutrition leading to fall of death rates from infectious diseases. Now genetic diseases like thalassaemia and haemoglobinopathies are becoming an increasing health problem.

Standard treatment of thalassaemia is costly which includes blood transfusion and iron chelating therapy to control the deleterious effects of progressive iron overload. In developing country like Bangladesh most of the patients cannot afford adequate treatment. Prevention of births of thaslassaemic children is to reduce the burden of thalassaemic patient in the family as well from the society has been found to be best option and cost effective. All over the world prenatal diagnosis with option for abortion has been found to be very successful. Other methods like discouraging the carriers not to marry has not been successful as seen in Saudi Arabia .[19] In Iran there is rapid fall of births of thalassaemic children after the introduction of prenatal diagnosis has been reported.[9]Prenatal diagnosis was therefore started in this hospital.

Prenatal diagnosis of Beta thalassemia was accomplished for the first time in the 1970s by globin chain synthesis analysis on fetal blood obtained by placental aspiration at 18–22 weeks gestation. Since then, the molecular definition of the beta globin gene pathology, the development of procedures of DNA analysis, and the introduction of chorionic villous sampling have dramatically improved prenatal diagnosis of this disease and of related disorders.[20]

In our study we have collected fetal sample from amniotic fluid on 16 th weeks preganancy[14] which was consisted with the study of Gajra Bani et al in 2003, [21] We have also collected fetal samples from chorionic villous on 12 th week onwards, Sujoy Dasgupta et al in 2015[22] collected fetal samples at 10 th to 13 th week of pregnancy in same type of study.

We have detected the mutations by using ARMS method, which is a well established method for detection of known mutation of thalassaemia. Same type of studies were conducted by Anwar Tazeen et al in 2014.[23] Agarwal S et al in 2003[24] used different techniques like Reverse Dot Blot (RDB) and Amplification refractory mutation system (ARMS).

Various methods was previously practiced for prenatal diagnosis of beta thalassaemia among them amplification of fetal DNA - obtained by chorionic villous biopsy is preferred now for detection of beta-thalassaemia mutation.[25]

Our study show that chorionic villous sampling done from 12th weeks of gestation and amniocentesis at 16 th weeks by transabdominal approach are simple and safe techniques. For early detection of disease chorionic villous sampling is a better option.[26] Tasleem Samina et all in 2007 did sampling at 10 th to 12 th week of gestation. [27]

Conclusion: Prevention of birth of thalassaemic child by prenatal diagnosis has been successful in many countries of the world. There are many methods for mutation analysis like Real Time PCR and Sequencing but they are expensive. ARMS method is an accurate, rapid, simpler and inexpensive method for prenatal diagnosis.[28]

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ORIGINAL ARTICLE

Complications of Colostomy in Anorectal Malformation (ARM) - 5 Years Experience at Dhaka Shishu (Children) Hospital

Md. Delwar Hossain[1], KMN Ferdous[2], Umama Huq[3], Ashrarur Rahman[4]

Abstract

Introduction: *Colostomy has long been a common preliminary treatment in the surgical management of many congenital and acquired conditions of gastrointestinal tract among children, and many are done on an emergent or urgent basis. The aim of this study was to characterize the complications of colostomy formation in newborn infants with anorectal malformations.*

Methods: *This prospective observational study analysed the complications of colostomy formation over a 5 years period during which 200 infants underwent colostomy formation as the initial management of high and intermediate variety of anorectal malformation at Dhaka Shishu (Children) Hospital.*

Results: *Out of 200 neonates, 75 underwent divided colostomy and 125 underwent loop colostomy. Among these colostomies, 138 were done on sigmoid colon and 62 were done on transverse colon. Patients with loop stomas were significantly more likely to develop complications (p=0.037). When comparing the rates of developing each individual complication, the rate of wound infection was found to be statistically higher in patients with divided stomas (p<0.001) and the rate of prolapse of colostomy was found to be statistically higher in patients with loop stomas (p=0.034). Mortality rate was very low and it was not statistically significant between groups.*

Conclusion*: Loop colostomies were found to be associated with a higher incidence of morbidities than divided sigmoid colostomies. Rate of mortality showed no significant difference between groups.*

Key words*: Anorectal Malformation, Colostomy, Transverse, Sigmoid, Complications.*

Introduction

Anorectal malformations (ARM) is one of the most common surgical conditions in pediatric surgical practice.[1] Colostomy for patients with anorectal malformations decompresses an obstructed colon, avoids fecal contamination of the urinary tract, and protects a future perineal operation.[2] By itself, creating a colostomy is a minor surgical procedure, but with potentially significant morbidity.[2,3,4] Complications include, but are not limited to,

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retraction, prolapse, parastomal hernia, bowel obstruction, skin excoriation, need for revision, and anastomotic leak and wound infections following stoma closure. The type of a diverting colostomy chosen depends on healthcare resources, surgeons' training, personal experience and preference.[5] The aim of this study was to characterize the complications of colostomy formation in newborn infants with anorectal malformations.

Materials and Methods

This prospective observational study was carried out in the Division of Pediatric Surgery, Dhaka Shishu (Children) Hospital, Dhaka, during the period of January 2013 to December 2017 in the management of neonates with high and intermediate variety of anorectal malformations who required colostomy. Variety of ARM was diagnosed by an X-ray prone cross table lateral view with elevated buttock after 24 hours of birth for those patients where no fistulous tract was identified. Patients' with Pouch colon syndrome, VACTERL association, Intestinal perforation, Septicemia and DIC or other gross congenital anomalies were excluded from the study. In some cases USG of KUB region, plain X-ray of abdomen in erect posture and Echo cardiogram was done. In each follow up patients were assessed clinically for the feeding history, color of stoma, wound infection, skin excoriation, prolapse of colostomy, retraction of colostomy and parastomal hernia. The statistical analysis was conducted using SPSS (statistical package for social science) version 20 statistical software. Categorical and continuous variables were analyzed with Chi-square test and t-test respectively. $p<0.05$ was considered significant and all p-values were two sided.

Results

Out of 200 neonates, 75 underwent divided colostomy and 125 underwent loop colostomy. Among these colostomies, 138 were done on sigmoid colon and 62 were done on transverse colon. Patients' characteristics were shown in table I. Statistically significant differences were not found between patients who had a loop and those who had a divided colostomy regarding sex, gestational age, age, birth weight, presence of fistula and associated anomalies. Highly statistically significant differences were found between patients who had a loop and those who had a divided colostomy regarding operation time (Table II). The types and rates of stoma related complications were summarized in Table III. Patients with loop stomas were significantly more likely to develop complications ($p=0.037$). When comparing the rates of developing each individual complication, the rate of wound infection (Fig.1) were found to be statistically higher in patients with divided stomas ($p<0.001$) and the rate of prolapse (Fig.2) of colostomy were found to be statistically higher in patients with loop stomas ($p=0.034$). Mortality rate was very low and it was not statistically significant between groups.

Table I
Patient's characteristics

Characteristics	Divided colostomy(n=75)	Loop colostomy(n=125)	P value
Sex			
Male	40(53.3%)	72(57.6%)	0.556
Gestational age			
Term	68(90.7%)	106(84.8%)	0.232
Age at colostomy (in days)			
Mean±SD	2.65±1.39	2.65±1.22	0.978
Birth weight(in kilograms)			
MeanSD	2.79±0.27	2.75±0.33	0.313
Fistula			
Absent	42(56.0%)	83(66.4%)	0.253
Retrovestibular fistula	17(22.7%)	28(22.4%)	
Retrourinary fistula	12(16.0%)	11(8.8%)	
Cloacal anomaly	4(5.3%)	3(2.4%)	
Associated anomaly			
Absent	43(57.3%)	86(67.8%)	0.101
Present	32(42.7%)	39(31.2%)	

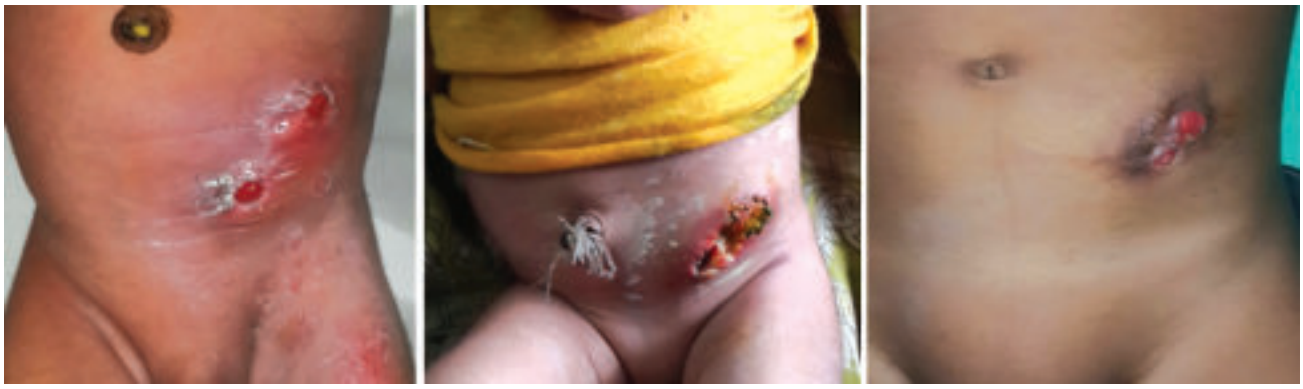
Table II
Comparison of operation time

Operation time (in minutes)	Divided colostomy (n=75)	Loop colostomy (n=125)	P value
MeanSD	46.92±3.24	39.40±6.07	<0.001

Table III
Comparison of stoma related complications

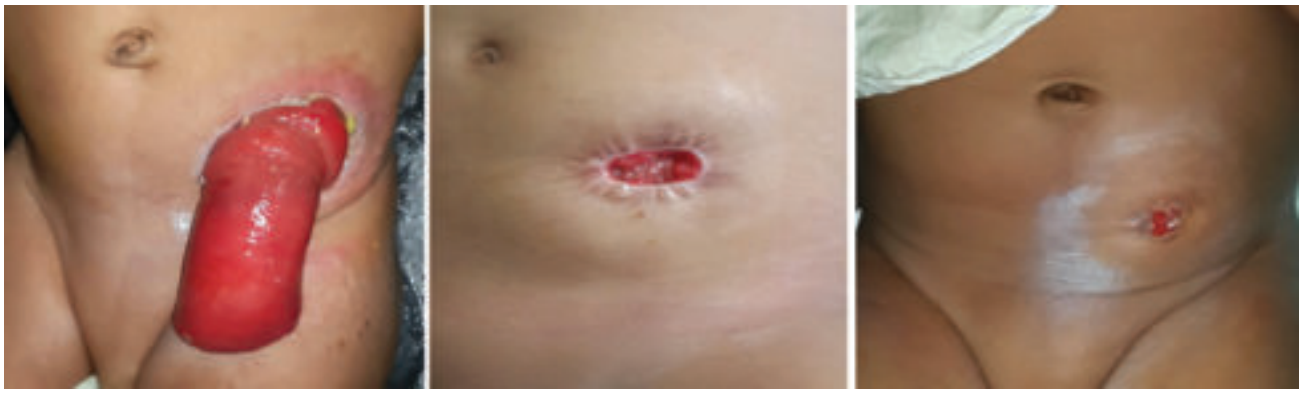
Stoma related complication	Divided colostomy (n=75)(%)	Loop colostomy (n=125)(%)	P value
Morbidity	23(30.7)	57(45.6)	0.037*
Skin excoriation	19(25.3)	35(28.0)	0.681
Wound infection	19(25.3)	3(2.4)	<0.001*
Prolapse of colostomy	7(9.3)	26(20.8)	0.034*
Retraction of colostomy	2(2.7)	9(7.2)	0.173
Stenosis	7(9.3)	8(6.4)	0.446
Mortality	1(1.3)	3(2.4)	0.602

**statistically significant value*



a) Skin excoriation b) Wound infection c) Stenosis of colostomy

Fig 1 *Complications of dividing colostomy*



a) Prolapse of colostomy b) Retraction of colostomy c) Stenosis of colostomy

Fig 2 *Complications of loop colostomy*

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Discussion

Colostomy has long been a common preliminary treatment in the surgical management of many congenital and acquired conditions of gastrointestinal tract among children, and many are done on an emergent or urgent basis. There are various surgical options for management of anorectal malformations. Colostomy is usually performed as a first stage in a new born with high and intermediate variety of anorectal malformations. In spite of various innovations in the understanding and management of congenital anomalies, complications of colostomy and its closure have remained substantially high.[3,6]

Loop colostomies are used by many surgeons perhaps because they can be opened and closed quickly. Occasionally some of these colostomies work well. However, many other loop colostomies did not work that way, particularly if they were partially retracted. They allow for passage of stool distally, which produced urinary tract infections and fecal impaction in the distal pouch of the colon. The fecal impaction in the distal colon produces megarectum, particularly when a patient spends a long time (months) between the opening of the colostomy and the main repair of the malformation. The presence of a megarectum correlates with the severity of constipation that this patient suffers after the repair of the malformation.[2] Many pediatric surgeons recommended a divided sigmoid colostomy in the left lower abdominal quadrant with a sufficient skin bridge between proximal stoma and distal mucous fistula. They believe that complete stool diversion will prevent the development of megarectum, UTI, and wound infection after anoplasty.[7]

In this study, majority of the participants were male. This result was consistent with other studies where they also found a slight male preponderance.[8]

Most babies (50% to 60%) with anorectal malformations have one or more abnormalities that affect other systems. Higher abnormalities are associated with more malformations. Many are incidental findings, but others, such as cardiovascular defects, may be life threatening.[8] Bhargava et al. had conducted a research work in India to study the hospital incidence of anorectal malformations (ARM), frequency of various types of defects, their sex distribution and the spectrum of anomalies associated with ARM. Associated defects seen were urogenital, cardiovascular, gastrointestinal, genital and limb defects.[9] In the present study, 42.7% patients who underwent divided colostomy and 31.2% patients who underwent loop colostomy had associated anomalies. Among the patients who had anomalies, almost one third of the patients had cardiovascular defects which include ASD, VSD and PDA. Urogenital malformation was seen in 22.6% patients which included hydronephrosis, renal agenesis, undescended testis and hypospadias. Cleft lip and palate were seen in two patients.

Following colostomy formation, colostomy-related complications have been reported in up to 80 percent of patients. These include peristomal skin excoriation, prolapse, stomal obstruction, stenosis, parastomal herniation, and stomal bleeding.[10] The present study found that rate of complications in divided and loop colostomy were 30.7% and 45.6% respectively and this difference was found statistically significant (p=0.037). The study of Oda et al also found significantly higher rate of complications in loop colostomy than divided colostomy (p=0.031).[7] Among the complications, skin excoriation was common in both groups. High incidence of skin excoriation in our study was due to poor compliance of our patients with colostomy appliance especially those from rural areas. Other studies also found high rate of excoriation after colostomy.[5,11] In the present study, significant statistical difference was found between groups regarding wound infection (p=0.002). As in divided colostomy, wound infection was more due to presence of a wound in between two stomas.

Prolapse is one the more common late complications after stoma creation. The estimated incidence is reported to be between 2 to 26%.[12] Stoma prolapse remains the most common complication, occurring in one-quarter of patients with a transverse loop colostomy; the divided and separated descending colostomy is only rarely complicated by this problem. Many previous reports have confirmed this high rate of stoma prolapse associated with transverse loop colostomies. Important contributory factors include shrinkage of the distal dilated obstructed bowel after stoma formation and the marked mobility of the transverse colon.[13] The current study found significantly higher rate of prolapse in loop colostomy (p=0.034) which was consistent with other study.[7]

In the current study, 2 (2.7%) patients developed retraction after divided colostomy whereas 9 (7.2%)

patients developed retraction after loop colostomy which was not statistically significant. This result was consistent with other study where retraction occurred in 1.4% cases of loop colostomy and 4.2% cases of divided colostomy which was also not statistically significant.[7] Retraction of colostomy was less in divided colostomy due to proper fixation of the colon with the peritoneum, muscle and skin and the distal mucous fistula small and flat. But in loop colostomy, distal stoma was dilated and it cannot be made small as it was continuous with the proximal stoma. When dilatation subsided stoma became retracted.

Though stenosis and mortality were present in each group, no significant difference was found regarding this issue.

Conclusion

Loop colostomies were found to be associated with a higher incidence of complications than divided sigmoid colostomies. The rate of prolapse of colostomy was found to be statistically higher in patients with loop stomas. Rate of mortality showed no significant difference between groups.

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ORIGINAL ARTICLE

Outcome of Children with Non-Convulsive Status Epilepticus after Treatment

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Abstract

Background: *Non convulsive status epilepticus (NCSE) is an electrical diagnosis and done on the basis of electroencephalogram (EEG) finding. Usually occurs in children with known epilepsy. It is difficult to diagnose clinically but some recent clinical change in behavior and seizure may arise suspicion of the condition.*

Objective: *To see the clinical co -relations, previous seizure type with AED used and immediate electro - clinical outcome at discharge after treatment of the condition.*

Methods: *This retrospective analysis was done from the records of the patients admitted in the Child Development & Neurology Unit, Dhaka Shishu (Children) Hospital during the period of 2006 to August 2009 who were diagnosed as non convulsive status epilepticus (NCSE). Diagnosis of the condition was based on EEG findings and children of all age group were included.*

Results: *Total 19 children were admitted and 17 (89%) had history of previous seizure.*

Recent change in clinical condition was present in 15 (80%) children. After treatment electrical (EEG) improvement to normal or near normal achieved in 11 (58%), partial improvement in 3(16%) and no improvement in 5 (26%) cases. Clinically - behavior problem was reduced in 8 (42%), seizure reduced or stopped in 8 (42%), fall or head drop reduced in 3 (16%) and overall mental function improved in 11 (58%) children. One child presented with chorea which stopped after treatment.

Conclusion: *Careful observation of recent clinical change and subsequent EEG can diagnose NCSE. Early treatment can improve mental functions and reduce behavioral abnormality and seizures.*

Key words : *Non-convulsive status epilepticus (NCSE), children, electro-encephalogram (EEG).*

Introduction

Nonconvulsive status epilepticus (NCSE) is an important status epilepticus (SE) type and is defined as a mental status changes from baseline of at least 30 to 60 minutes duration associated with continuous or near continuous ictal discharges on electroencephalogram (EEG).[1] The identification of NCSE is made by a combination of clinical suspicion and electrographic monitoring. Prolonged EEG monitoring is established as an important test in comatose adults and high-risk neonates.[2] It is estimated in adults to account for about 25% of all

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cases of status epilepticus.[3] It is often under-diagnosed in comatose patients and may conceivably be difficult to diagnose in pediatric patients in whom changes of behavior and consciousness may not be as quickly recognized as in adults.[4] The term NCSE encompasses several conditions that differ widely in their etiology, prognosis and management. They include absence SE, myoclonic SE, complex partial SE, simple partial SE, SE in coma, and SE in patients with learning difficulties.[5]

EEG evaluation is vital to confirm the diagnosis of NCSE and may also be useful to exclude other potential explanations for the clinical signs such as metabolic, infectious and ischemic events As there is no consensus regarding the definition and precise nature of NCSE, it is difficult to suggest guidelines for its treatment. The goals of treatment should be to obtain a cessation of EEG abnormalities in the short term with prevention of breakthrough NCSE in the long-term.[6] Benzodiazepines are first-line therapy for NCSE. Although intravenous benzodiazepines is preferred, oral administration is also effective and easier to administer.[7]

Objective of this study was to analyze clinical co relations, previous seizure type with AED used and electro-clinical outcome after treatment of the condition at discharge.

Materials and Methods

NCSE diagnosis was based on the specific EEG criteria of continous or near continuous epileptiform discharges.

NCSE is defined as a change in behaviour and/or mental processes from baseline associated with continuous epileptiform discharges in the EEG. It is important to note that as yet no universally accepted definition of NCSE exists.[8,9]

This was a retrospective study from the records of the patients admitted/attended in the Paediatric Neuroscience department, Dhaka Shishu Hospital dating from June 2006 to December 2009. Nineteen pediatric patients were diagnosed as non convulsive status epilepticus (NCSE). Diagnosis of the condition was based on EEG finding. Children of all age groups were included. EEG recordings were performed on 21 channel EEG instruments using the international 10–20 electrode placement system. EEG tracings were reviewed to determine the EEG background, discharge type, maximal frequency reached and location of discharges. Patient's clinical information was collected and included age, sex, preexisting medical and neurological conditions, seizure history, types of anticonvulsants used, neuroimaging findings (with computerized tomography or magnetic resonance imaging of the brain) and outcome at the time of discharge from hospital. Most of the children were treated with intravenous midazolam (MDZ) (0.15-0.3 mg/kg/hour) introduced for 8 hours on the first day followed by EEG on the next morning, if no change noticed, the infusion was continued for 12 hours and repeated up to maximum 10 infusions till EEG abnormalities cleared or becomes normal. Daily EEG recording for 30 minutes were performed to record the change of continuous discharges. Some of the patients were treated by Diazepam infusion and some with oral Clobazam and SodiumValproate.

Results

The 19 patients identified with NCSE ranged in age from 1 year to 15 years. A large proportion (42%) of these patients was of age from 5 to 10 years. There was a slight preponderance of males in the study population : 53% was male and 47% was female. 11(58%) patient were from rural area and eight patients (42%) were from urban area. (Table I).

Table I
Patient profile

Item	Number	%
Age		
Up to 1 year	1	5
>1 to 5 year	7	37
>5 to 10 yr	8	42
>10 yr	3	16
Total	19	100
Sex		
Male	10	53
Female	9	47
Total	19	100
Residence		
Urban	8	42
Rural	11	58
Total	19	100
H/O of perinatal insult		
Present	8	42
Absent	11	58
Total	19	100
Consanguinity		
Present	4	21
Absent	15	79
Total	19	100

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Recent change of behavior was presenting clinical condition in 11 (58%) cases and frequent fall or head drop found in 5 (26%) cases (Figure 1). Prior seizure type was generalized clonic in 9 (47%) cases, multiple types in 3 cases and no H/O seizure in 2 cases. Cognitive, motor and speech delay was present in 8 cases, cognitive and motor delay in 2 cases, motor and speech delay in 1 case, only speech delay in 2 cases, only motor delay in 1 case and developmental milestone was appropriate in 5 cases. Diagnosis on admission shows epilepsy in 4 cases, sequele of Encephalitis in 3 cases and Diplegic CP in 2 cases (Table II).

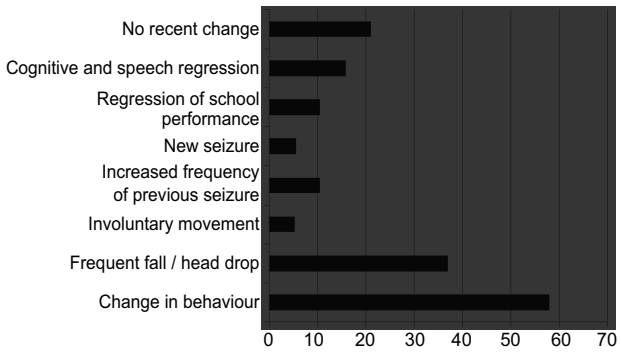

Fig 1 *Percentage distribution of study patents according to presenting clinical condition*

EEG findings of patients are presented in Table III. The EEG recordings of the patients revealed generalized near continuous spike wave discharge in 11 (58%), near continuous localized spike-wave discharge in 3 (16%) and near continuous spike-wave discharges involving posterior two thirds of brain in 3 (16%) patients (Table III)

Four patients were taking Carbamazepine (CBZ), 3 patients Valproic acid (VPA), 3 patients Herbal/ Kabiraji medicines, 4 patients in different combination of VPA, CBZ, Clonazepam (CZP) and in 3 patients the AED was uncertain prior to admission (Table III).

Twelve patients (63%) were treated with Midazolam infusion, 2 (11%) with diazepam infusion and 4(21%) with oral VPA and CLB (Table IV).

Four to six infusion courses given to 2 patients and 1 to 3 courses to 6 patients.7-10 courses given to 5 and more than 10 courses was required for 2 patients. Four patients didn't get infusion and treated with oral AED (Table IV).

Table II
Presenting clinical condition and diagnosis on admission

Prior seizure criteria	Number	%
Generalized clonic	9	47
Multiple type	3	16
Generalized tonic	2	10.5
Myoclonic	2	10.5
Atonic	1	5.5
No H/O of previous seizure	2	10.5
Total	19	100
Early milestone of development		
Age appropriate	5	26
Cognitive, motor & speech delay	8	42
Cognitive & motor delay	2	10.5
Motor & speech delay	1	5
Only motor delay	1	5
Only speech delay	2	10.5
Total	19	100
Diagnosis on admission		
Epilepsy	4	21
Seq. of encephalitis	3	15.5
Diplegic CP with epilepsy	2	10.5
Autistic features with epilepsy	1	5.3
Speech delay with epilepsy	1	5.3
Hypotonic CP with Epilepsy	1	5.3
Chromosomal disorder with epilepsy	1	5.3
Hemiplegic CP with epilepsy	1	5.3
Worster- Drought syn. With epilepsy	1	5.3
Cerebrovascular disorder	1	5.3
Lissencephaly	1	5.3
Wilsons disease	1	5.3
Suspected neurometabolic disorder	1	5.3
Total	19	100

Table III
EEG findings and AED used before admission

EEG criteria of diagnosis:	Number	%
Near continuous spike wave	11	58
Near continuous localized spike wave discharge (lat.)	3	16
Near continuous spike wave discharge involving frontal half of the brain	3	16
Frequent diffuse epileptiform discharge	1	5
Near continuous spike wave discharges involvingPosterior two-third of brain	1	5
Total=	19	100
Antiepileptic drug (AED) before admission		
Carbamazepine (CBZ)	4	20
Valproic acid (VPA)	3	16
Uncertain	3	16
Phenobarbitone (PHB)	2	11
VPA + CBZ	2	11
No h/o previous seizure & AED	2	11
VPA + Clonazepam (CLN)	1	5
CBZ + CLN + Lamotrigine (LMT)	1	5
Herbal by kabiraj	1	5
Total=	19	100

Table IV
Treatment provided

Drug used	Number	%
Midazolam infusion	11	58
Oral VPA + Clobazam (CLB)	5	26
Diazepam infusion	2	10.5
Diazepam followed by midazolam infusion	1	5
Total	19	100
Number of infusion courses given		
1 – 3 courses	6	32
7 – 10	5	26
No infusions	4	21
4 – 6	2	10.5
>10	2	10.5
Total	19	100
Hospital stay		
0 -2 weeks	9	47
>2 – 4	7	37
>4	3	16
Total=	19	100

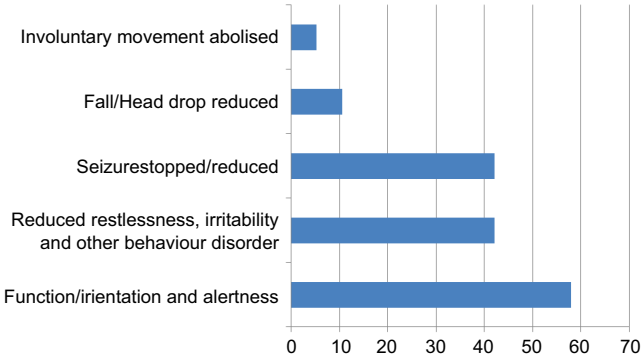

Fig 2 *Clinical outcome on discharge*

Table V
EEG outcome on discharge

EEG outcome on discharge	Number	%
Improvement	11	58
Partial improvement	5	26
No improvement	3	16
Total=19	100	

Clinical outcome shows Improvement of mental function achieved in11 patients, seizure reduced in 8 patients and behavior disorder also reduced in 8 patients (Figure 2).

Nine patients stayed in hospital upto 2 weeks and seven patient stayed 2-4 weeks.

Electrical (EEG) improvement to normal or near normal achieved in 11(58%), partial improvement in 3 (16%) and no significant improvement observed in 5 (26%) patients after treatment (Table V).

Discussion

The diagnosis of NCSE is difficult in some cases because there are no specific clinical features or laboratory test other than EEG examination. For the acute diagnosis, the presence of seizure activity on EEG in addition to variable clinical findings without convulsive movements should be demonstrated[10].

Nonconvulsive status epilepticus may be the first seizure in healthy children without a history of epilepsy; on the other hand epileptic children may present NCSE with or without any preceding factor.[11] Two of out nineteen patients had no history of previous seizure. In his study Yuksel found three of eight patients had no history of previous seizure.[12]

Eleven of our nineteen patients presented with recent change of behavior and seven with frequent fall, three presented with cognitive and speech regression and two with regression of school performance. Only one patient of eight presented with behavior problem and other seven patients were non-cooperative ranging from mild-moderate confusional state to coma.[13] The EEG findings of NCSE are heterogeneous; generalized or focal (temporal,temporo-frontal) spike-and-slow wave complexes, polyspike discharges, irregular sharp or slow waves may be seen.[14]

According to Kaplan NCSE may be classified as 1) localization-related NCSE, 2) generalized NCSE, and 3) indeterminate or intermediate NCSE.[15]

In our study generalized spike-wave discharge was found in 11 patients.

Randomized controlled trials of treatments for NCSE are lacking. A few small case series have reported success with valproate.[16] Most conventional antiepileptic drugs (AEDs) have been reported to be effective for some patients. Refractory NCSE has been reported to respond to midazolam, propofol or pentobabrbitona.[17] It will be appropriate to monitor the patients with continuous EEG monitoring. If NCSE is due to an acute medical illness treatment with pentobarbital, propofol, or midazolam to attain EEG background suppression, may be more effective than other strategies.[18]

In a systemic review of treatment of refractory status epilepticus, NCSE was most often treated with midazolam. Of the 16 patients with NCSE, only in one patient (6%) NCSE could not be ultimately controlled with midazolam.[19]

Return of the baseline electroclinical state needed single course in those with previously normal developmental milestone and apparently shorter duration of NCSE. This finding is supported by other studies.[20]

Several recent reports have shown intravenous MDZ as highly effective in controlling status epilepticus in children who remained in status despite adequate doses of diazepam, DPH (phenytoin sodium) & PHB (phenobarbitone).[21,22]

.Benzodiazepines are first-line therapy for NCSE. Although intravenous benzodiazepines is preferred, oral administration is also effective and easier to administer. A single dose of oral benzodiazepines was effective in terminating NCSE in a study report of Gastaut.[23]

In our series I.V. MDZ was given as the drug of first choice in 12 patients among 19 patients. Electro-clinical improvement occurred in most of the cases. Six cases improved after 1 – 3 courses of infusion. Five patients improved after giving 7 – 10 courses of infusion and two patients needed more than 10 courses. No infusion given to 4 patients and treated with oral VPA and CLB. The consequences of NCSE are far more poorly characterized and depend upon its clinical situation.

Conclusion

NCSE is not uncommon and should be suspected in children with recent change in behavior, school performance, cognition and speech. EEG is critically important for the diagnosis and also plays a vital role in monitoring responses to treatment. Early diagnosis and management is essential and can improve the behavioral abnormality, seizures and mental function.

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ORIGINAL ARTICLE

Prevalence of Different Types of Rheumatologic Diseases in Children at Department of Pediatric Rheumatology of Dhaka Shishu (Children) Hospital

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Abstract

Background: *Number of pediatric rheumatologic diseases (RD) are increasing globally as well as national level. Among these several diseases are responsible for long term morbidity and disability.*

Objective: *To see the prevalence of different types of rheumatologic diseases in Pediatric Rheumatology Department of Dhaka Shishu (Children) Hospital.*

Methods: *A retrospective observational study was done in the department of Pediatric Rheumatology unit from July 2016 to June 2017. Data were collected from the registry of Rheumatology Department of Dhaka Shishu (Children) Hospital.*

Results: *Total 43 cases were admitted in the department of Pediatric Rheumatology unit of Dhaka Shishu (Children) Hospital during this period of them female were 63%, mean age was 84.9 months and disease pattern were Polyarticular Juvenile Idiopathic Arthritis (JIA) 33%, Oligoarticular JIA 26%, Systemic onset JIA (SoJIA) 14%, Enthesitis Related Arthritis (ERA) 9%, Systemic Lupus Erythematosus (SLE) 9%, Post Infectious arthritis 2%, Septic arthritis 2%, Reactive arthritis 2% & Poly Arteritis Nodosa (PAN) 3%. Outcome of all the cases were satisfactory without mortality.*

Conclusion: *The prevalence of Polyarticular JIA is high followed by Oligoarticular JIA, SoJIA, ERA, SLE, Post Infectious, Septic arthritis, Reactive arthritis and PAN. Outcome of the children were satisfactory without any mortality and major disability.*

Key words: *Prevalence, Rheumatologic disease, Children.*

Introduction

Although the diseases that kill attract much of the public's attention, musculoskeletal conditions are the major cause of morbidity throughout the world, having a substantial influence on health and quality of life, and inflicting an enormous burden of cost on health systems. Critical advances in these conditions in understanding the nature of inflammation, the cells

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and the molecules that mediate it and the therapeutic possibilities of regulating the aberrant immune response have been seen in recent years.[1] Rheumatic diseases (RD) in children remain one of the chronic conditions which pose a long-term risk of disability if not recognized and treated properly. The dedicated and comprehensive pediatric rheumatology clinical programme was established at KK Women's and Children's Hospital (KKH) in Singapore in 2009. Their study reports the first pediatric rheumatology clinic population in Asia. They showed that almost half of the patients referred to their programme were non-rheumatic conditions which is the same issue faced in other developed countries. Systemic vasculitides were the most common encounters with HSP and Kawasaki Disease (KD) being the top two. ERA was the most common JIA subtype while uveitis related to JIA was rare.[2] However limited data are available for Southeast Asia (SEA), where the shortage of pediatric rheumatologists is severe and certain life-threatening RDs may be more prevalent, such as SLE and systemic vasculitis.[3] In Bangladesh a single center study over 5 years revealed highest number of patients had JIA (77%), which was followed by SLE (10%), Henoch Schonlein purpura (4.2%), Polyarteritis Nodosa (1.9%) and Kawasaki Disease (0.6%).[4] Epidemiological studies of chronic arthritis in childhood are meaningful to allow disease classification, description of the natural history and outcome in different disease entities, the identification of early prognostic factors, health care planning and, eventually, the identification of possible etiological factors.[5] Number of pediatric RD are increasing globally as well as national level.[6] The subspecialty of pediatric rheumatology (PR) is the newest discipline established at Dhaka Shishu (Children) Hospital. So this study was done to find the disease epidemiology, efficacy of treatment and outcomes of childhood RD in Bangladesh.

Materials and Methods

This is a retrospective observational study. All the cases are taken from the record of the rheumatology department of Dhaka Shishu (Children) Hospital from July 2016 to June 2017. Data were collected from the registry of Rheumatology Department of Dhaka Shishu (Children) Hospital. All the children fulfilling the ILAR classification criteria of Juvenile Idiopathic Arthritis (JIA),[7] revised ACR classification criteria 1997 for SLE,[8] EULAR-PReS classification criteria of childhood vasculitis,[9] Bohan A, Peter JB classification criteria for JDM[10] and preliminary criteria for the classification of Systemic Sclerosis (SS)[11] were enrolled in this study. A total of 43 patients were admitted with rheumatological diagnosis during one year period. Statistical analysis was done using Microsoft Excel 2016.

Results

Demographics showed female children dominated most of cases (63%) [Fig.-1]. Poly articular JIA outnumbered the most frequently encountered (33%), followed by Oligoarticular JIA (26%), Systemic Onset JIA (14%), SLE and ERA (both 9%). Less frequent rheumatological diagnosis were Post infectious arthritis, Poly Arteritis Nodosa, Septic arthritis and Reactive arthritis (each was 2%) [Fig.-2]. In our observation average age of onset of disease were as follows Oligoarticular JIA (80.5 months), Polyarticular JIA RF Positive (36 months), Polyarticular JIA Negative (110.4 months), Systemic Onset JIA (48.66 months), ERA (138 months) and Others (74.4 months) [Table-I].

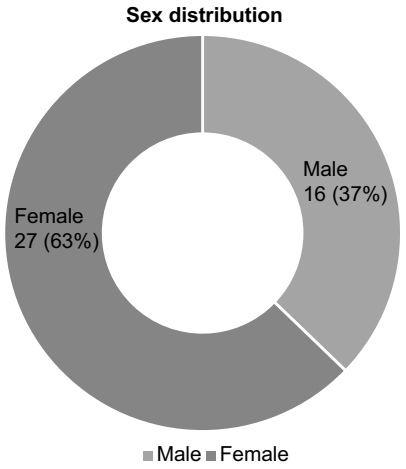

Fig 1 *Sex Distribution among the cases*

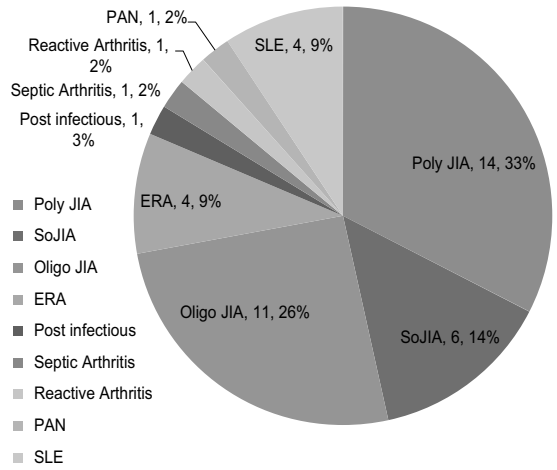

Fig 2 *Disease Pattern*

Table-I
Different pattern of Rheumatological diseases

Diseases	N = 43	Sex		Age distribution at diagnosis(months)		
	(%)	Male	Female	12 – 60	61- 120	121-192
Poly Articular JIA (Poly JIA)	14(33%)	4	10	4	7	3
Oligo Articular JIA (Oligo JIA)	11 (26%)	7	4	4	6	1
Systemic Onset JIA (S,JIA)	6(14%)	2	4	4	2	0
Systemic Lupus Erythromatosis (SLE)	4 (9%)	0	4	0	2	2
Enthesitis Related Arthritis (ERA)	4(9%)	4	0	0	3	1
Post Infectious Arthritis	1 (3%)	0	1	0	1	0
Poly Arteritis Nodosa (PAN)	1(2%)	1	0	0	1	0
Septic Arthritis	1(2%)	0	1	0	1	0
Reactive Arthritis	1 (2%)			0	1	0

Table-II
Comparison of demographic data of DSH with BSMMU study

Category	DSH study			BSMMU Study[4]		
	Frequency (%)	M:F	Average Onset age (months)	Frequency (%)	M:F	Average Onset age (months)
Oligoarticular JIA	11	7:4	80.5	31.1	2.25:1	106.2
Poly RF Positive	4	4:0	36	32.8	1.9:1	121.2
Poly RF Negative	10	10:0	110.4	5	1:4	146.4
S,JIA	6	1:5	48.66	14.1	2.4:1	74.4
ERA	4	4:0	138	10	8.75:1	168
Others	8	1:7	74.4	7	7:1	122.4

Discussion

In Bangladesh there is no Rheumatological disease registry for pediatric patients. In a previous study conducted in Bangabandhu Sheikh Mujib Medical University (BSMMU) tried to determine the prevalence and pattern of pediatric rheumatic diseases. But that doesn't reflect the scenario of the country. Islam et al[4] showed that the ratio of male and female in Oligoarticular JIA was 2.25:1, but interestingly our observation showed this ratio as 7:4. Again in case of RF negative Poly articular JIA, we found the ratio as high as 10:0 as all the cases were male. This might be due to smaller sample size obtained over a very short period of observation. Average onset of Oligoarticular JIA was 80.5 months i.e. significantly earlier than previous study. Earlier detected rheumatological disease was RF positive Polyarticular JIA i.e. 36 months. Age of onset of SLE was about 123 months.

Al-Hemairi et al[12] showed that systemic onset JIA was the most common JIA subtype 36.5% followed by polyarticular JIA subtype 29.26% and then oligoarticular JIA subtype 28%. In our study, polyarticular JIA is the most common type. Unlike most of previous similar studies where oligoarticular JIA was found to be the most common, mainly in Europe, USA, Canada, South America, and Turkey.[13-16] The data reported here will serve as basic information for researchers, government agencies and members of the public with regards to the unique burden of rheumatic diseases in Bangladesh. We also believe that a single center study may not reûect the correct distribution of

pediatric rheumatologic diseases (RD) in our country which needs multicenter and a population-based study.

Conclusion

The prevalence of Poly JIA is high followed by Oligo JIA, SoJIA, ERA, SLE, Post Infectious, Septic arthritis, Reactive arthritis and PAN. Outcome of the children were satisfactory without any disability.

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REVIEW ARTICLE

Congenital Anomalies: Facts, Care and Prevention

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Abstract

A congenital anomaly (CA) consists of a departure from normal anatomic architecture of an organ or system. Abnormalities may result from an intrinsically abnormal primordium or analge of an organ or from a normal primordium that is affected during development by extrinsic forces. CA affect approximately 2-3% of all live births every year and are a major cause of perinatal and neonatal deaths and affected children who survive infancy, often struggle with lifelong physical and mental disabilities. Congenital defects arise partly of genetic, some of environmental and other of multifactorial causes. Factors such as favorable prenatal environment and early treatment can prevent or reduce the phenotypic effects of some birth defects. Although many birth defects cannot be prevented, the probability of some conditions can be reduced through awareness of the effects of various prenatal factors including nutrients, teratogens and mutagens. Early detection and/or treatment of CA can sometimes reduce the long term impact of these conditions.

Key words: *Congenital; Anomaly; Prevention.*

Introduction

A congenital anomaly (CA) is an abnormality of structure, or body metabolism that is present at birth and results in physical or mental disability, or is fatal. Each year, eight million children are born worldwide with congenital anomalies of which 3.3 million die before the age of five; 3.2 million of survivors may be mentally and physically disabled.[1] As many infectious disease have been controlled by the use of vaccines and antibiotics, CA are increasingly playing a significant role in neonatal mortality and morbidity.[2-3] Treatment and rehabilitation of these morbid children is difficult and costly.[3-4] Congenital anomalies are either single isolated defects or present as multiple anomalies in a single individual. A syndrome is defined as a pattern of multiple abnormalities that are related by patho-physiology and result from common, defined etiology.

It is estimated that 1 in 40, or 20% of newborns, have recognizable malformation or malformations at birth. In about half the cases, a single malformation is found, while the other half display multiple malformations. About 10% of pediatric hospital admission have genetic conditions, 18% have congenital defects of unknown etiology. Forty percent of surgical admissions are patients with congenital malformations. About 20-30% of infant deaths and 30-50% of deaths after the neonatal period are due to congenital anomalies.[5] Despite perceptions to the contrary, cost effective approaches are available in low-income countries for the care of children with serious birth defects. The priorities for action

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proposed build on public health efforts by broadening the current scope of woman, maternal, newborn and child care services in primary health care and developing secondary and tertiary medical genetic services.[3-5]

Epidemiology

The birth prevalence of congenital anomalies (CA) in the developing world is underestimated by the deficiency in diagnostic capabilities and lack of reliability of medical records and health statistics. As a result, recorded diagnoses in vital statistics focus on overt acute illness, rather than on preexisting congenital conditions that increase vulnerability to infections and malnutritions.[6] More reliable estimates of the prevalence at birth of congenital anomalies come from registries of congenital malformations in newborns.[7] which show that the prevalence of recognizable malformations among newborn is between 2-3% that is similar to that found in the industrialized world[8]. Considerable variation in frequency in different populations has been reported from as low as 1.07% in Japan[9] to as high as 3% to Taiwan.[10]

However, the prevalence of birth defects is comparable all over the world, 3% in the United States[11], 2.5% in India[12] and 2 to 3% in the United Kingdom[13]. Several factors contribute to variarions in population between and within countries and across regions. Among the factors, the notable examples include: malaria, migration, consanguineous marriage, advanced maternal age, poverty and level of health care.[14] Compared with noncarriers, healthy carriers of recessive genes for hemoglobin disorders (sickle cell anemia and thalassemia) and glucose-6-phosphate delydrogenase (G6PD) deficiency have a well documented survival advantage against the lethal effects of malaria. As a result, carriers are more likely to reach reproductive age. Over time, this has lead to an increase in the population of these genes in tropical regions. Consequently, the birth prevalence of thalassemia, sickle cell disease, and G6PD deficiency is high in malaria endemic regions of the World such as Sub-Saharan Africa, the Eastern Mediterranean and North Africa, Southeast Asia, and the Western Pacific.[15,16,17] People moving to different countries and regions embed their single gene defect into the population they enter, for example, sickle cell anemia was spread from Africa to the Americas and the Carribean by the slave trade, and porphyria was introduced to South Africa by the emigration of the Dutch for trading purpose in the 17th century. In the instance of urbanization, the movement of people from rural regions and traditional life styles to towns and cities may put them at increased risk of defects due to combined genetic predisposition to teratogens, such as fetal alcohol syndrome.[18,19] The social custom, involving consanguineous marriage is accepted by at least 20 percent of world's population which increases the prevalence of autosomal recessive birth defects, almost doubling the risk of neonatal and childhood death from birth defects.[20]

Advance age (35 or older) is associated with an increased birth prevalence of chromosomal trisomies, particularly down syndrome. In middle- and low-income countries, a high percentage of women give birth over the age of 35 years without the availability of community education and universally available and accessible family planning services, genetic screening, prenatal diagnosis, or associated services. The birth prevalence of chromosomal aneuploidies is therefore, high in these countries.[19] Reduced socioeconomic circumstances are associated with an increased birth prevalence of birth defects. Mothers in poverty are more likely to be malnourished before and during pregnancy, and are at greater risk of exposure to environmental teratogens such as maternal infection.[14] The prevalence of birth defects is influenced by the national level of available and accessible health care, especially reproductive and maternal health services. These health services are capable of preventing Down syndrome, common single gene defects, neural tube defects and congenital malformations, fetal alcohol syndrome, congenital syphilis, iodine deficiency disorder and congenital rubella syndrome.[7]

Etiology

Congenital malformations have been known and recognized for centuries. It is a stimulating problem for research study because of the high frequency of their occurrence and the devastating effect they may have on the individual and family.[8-10] It was only in the 20th century that the causes of birth defects were delineated, allowing for their categorization into three broad groups: birth defects originating in the preconception period (due to primarily genetic and partly genetic cause), birth defects arising after the

conception but before birth, and birth defects of unknown cause.

Most birth defects originate before conception and are due to abnormalities of genetic material-chromosomes and genes. Partly genetic defects are due to a combination of genes that put the fetus at risk in the presence of specific fetal environmental factors. Genetic abnormalities include chromosomal abnormalities, single gene defects and multifactorial disorders caused by the interaction of genes and the environment. Chromosomal abnormalities are changes in the number or the structure of chromosomes that result in a gain or loss of genetic material. They account for approximately six percent of birth defects in industrialized countries. Down syndrome generally caused by an extra chromosome21(trisomy21)is the most common chromosomal abnormality.[21] Single gene defects are caused by alternations in gene structure (mutations) that result in abnormal cell functioning. More than 6000 single gene defects have been described.[22] Single gene defects account for an estimated 7.5 percent of all births in industrialized countries. The concept of multifactorial inheritance was proposed by Borris Ephrussi in 1953 and is now broadly accepted. Multifactorial birth defects, alternatively called congenital malformations, involve a single organ, or limbs, and include congenital heart diseases, neural tube defects, cleft lip and /or cleft palate, and club foot. Multifactorial inheritance is also the cause of many common diseases with a genetic predisposition that present later in life. These diseases are usually systemic and do not involve malformations. Example includes hypertension, diabetes, stroke, mental disorder and cancer[21]. Birth defects originating after conception are nongenetic in origin. The genetic material inherited by fetus is normal and the birth defect is caused by intrauterine environmental factors such as teratogens that interfere with normal growth and development of the embryo or fetus, mechanical forces that deform the fetus, or vascular accident that disrupts the normal growth of organs. Examples of these three categories include rubella and toxoplasma, maternal insulin-dependent diabetes mellitus and iodine deficiency, and alcohol and antiepileptic drugs, respectively.[23] Birth defects due to teratogens are more readily preventable, and pregnancies in middle- and low-income countries, compared to high-income countries are more likely to be at risk from potential pathogens for several reasons.[24] These include increased frequency of intrauterine infection, poor maternal nutrition, low socio-economic and educational levels, lack of environmental protection policies, and poorly regulated access to medication.[25] An estimated 5 percent to 10 percent of all birth defects in industrialized nations are of post-conception origin.[21] The estimate for low-income countries is 10 to 15 percent.[24] A specific cause cannot be designated in approximately 50 percent of all children born with birth defects. Some of these birth defects may be due to new autosomal dominant mutations, submicroscopic chromosome deletions, or unpaired disomy.[21] Causes for birth defects continue to be identified, so, the percentage of birth defects of unknown cause can be expected to decrease in the future.

Types/Classification

A congenital anomaly consists of a departure from normal anatomic architecture of an organ or system. Abnormalities may results from an intrinsically abnormal primordium or analge of an organ or from a normal primordium that is affected during development by extrinsic forces. Different anomalies may be classified as malformations, deformations and disruptions. Co-existent group of anomalies is described as polytopic field defect, sequence, syndrome and association. Other classification may be major and minor anomalies.

Major anomaly is one with a medical, surgical or cosmetic importance and will impact on morbidity and mortality; examples: VSD, cleft lip. Minor anomaly is one that does not have a serious surgical, medical or cosmetic significance and does not affect normal life expectancy or life style, e.g., periauricular pit, development variant/variation e.g.,fifth finger clinodoctyly.[26] Structural anomalies are considered overt when they are visible on inspection, otherwise they are considered occult.[27] The common disorders that account for approximately 25 percent of birth defects: Congenital heart defects, neural tube defects, hemoglobin disorders, sickle cell disorders and thalassemias, Down syndrome, G6PD deficiency leading to neonatal jaundice with kernicterus or significant hemolysis.[28] Common recessive disorders include: the hemoglobin disorders, G6PD deficiency, oculocutaneous albinism in Sub-Saharan Africa and cystic fibrosis.[29] The most common chromosomal

anomalies include Down syndrome which can be as high as 2 to 3 per 1000 live births in middle- and low-income countries. Multifactorial birth defects, which represent as congenital malformations of single systems organs, or limbs, are the most common type of birth defects.[30] Teratogen induced birth defects are more common in middle-and low-income countries. The four most common causes of teratogen induced birth defects are congenital syphilis, congenital rubella syndrome, congenital iodine deficiency disorder, and fetal alcohol syndrome.[14]

Congenital anomalies

Congenital anomalies can create long-term, permanent, serious health problems that can involve a lifelong need for medication therapy, medical interventions and procedures and medical care. Repeat surgical procedures, lifelong physical, speech, occupational, and behavioral therapy, and ongoing permanent care in a facility might also be needed. These anomalies can also lead to other physical reactions. In some cases, there is no chance of survival after birth for developing babies diagnosed with a disastrous birth defect in the womb, forcing parents to face devastating birth choice. In every case, the outcome creates untenable trauma and can lead to massive medical bills.[31] Birth defects are a global problem but their impact on infant and childhood death and disability is particularly severe in middle low-income countries where up to 94 percent of those born with birth defects and 95 percent of the children who die from birth defects occur.[28]

Diagnosis

Congenital anomalies if overt can be picked up easily at birth by trained pediatricians, anomalies like congenital defects of the heart are apparent in seven to ten days even if not apparent at or soon after birth. Sometimes patients are informed beforehand about the anomalies on a antenatal ultra sonogram, most common of these include hydrocephalus, renal anomalies, heart defects and anomalies of the lungs so that antenatal counseling can be done and necessary management plans can be laid out.[32] The history and physical findings should lead to an initial impression and differential diagnosis. These will guide selection of preliminary tests, the content of initial counseling of the family and development of an immediate plan for management, which can be modified as new information is developed and synthesized. Initial impressions should fit into one of three categories: single (isolated) malformation; multiple malformations, recognizable pattern (syndrome identification); multiple malformations, pattern not recognized.[27] Screening of fetal chromosomal anomalies is an essential part of antenatal care. Historically, maternal age was the determinant of risk.

Women older than 35 years at the time of delivery were offered genetic counseling and amniocentesis because of procedure related loss rates. However, only 20 percent of infants with Down syndrome (trisomy21) are born to women older than 35 years.[33] With the advent of maternal serum alpha-fetoprotein (AFP) testing in the mid-1980s, women younger than 30 years had an option for antenatal diagnosis.[34] In the past two decades, additional tests have been shown to increase the detection rate of chromosomal abnormalities. This gives pregnant women of all ages the opportunity to undergo screening or invasive diagnostic testing before 20 weeks' gestation which includes chorionic villous sampling (CVS) and amniocentesis.[35] Ultrasonography is one of the non-invasive tests which give a great amount of information about the structure and to some extent physiological aspects of the state of fetus. Some anomalies like anencephaly can be picked as early as 12 weeks.[36] Increased nuchal translucency (an ultrasonographic sonolucency) in the posterior fetal neck is associated with major congenital heart defects, defects of great vessels, fetal malformations, dysplasia, deformation, disruption and genetic syndromes.[37] Nuchal lucency testing should be combined with serum measurements of pregnancy-associated plasma protein A (PAPP-A) and human chorionic gonadotropin (hcG) to improve the detection rate of congenital anomalies.[38] After the introduction of maternal serum AFP, hCG and unconjugated estriol testing were added, resulting in the triple screen.[39] The addition of inhibin A testing to the triple screen yielded the quadruple screen.[40] Advantages of antenatal screening include increasing the odds of identifying an abnormal fetus and reducing the numbers of invasive diagnostic tests and procedure-related losses of normal fetuses. Based on these informations, all pregnant women specially at risk should be offered screening for anomalies. [35]

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Management

Management of people with birth defects includes diagnosis and treatment. The latter should include medical genetic counseling with psycho-social support.[19] As a general principle, as much care as possible should take place close to the patient's home and so should be undertaken in a primary health care setting. Referral for treatment should be contemplated only when a diagnosis is not possible or when further management such as pediatric surgery will improve the condition. Effective care depends on accurate diagnosis, which should be possible for most common birth defects. Accurate diagnosis allows practitioners to plan further care, taking care into account the circumstances of the family, community and medical services. Where a definitive diagnosis is not available, identifying the component disabilities and other clinical problems that constitute the disorder enables similar planning of treatment, therapeutic, surgical and neurodevelopmental therapies, and genetic counseling. Treatment for newborns and children with birth defects can be provided feasibly and effectively in low-income settings. For example, the treatment of children with thalassemia with blood transfusions and iron chelating agents begun in Iran in 1970s. While the success of the program led to higher treatment costs, it helped spur the government to establish a national thalassemia prevention program, thus demonstrating the synergy between care and prevention.[41]

Prevention

The WHO has recently made a number of recommendations to prevent congenital anomalies and genetic disorders, with particular attention to developing countries. There are two main types of programs for the prevention of congenital anomalies in the developing countries: (a) primary prevention and (b) secondary prevention based on prenatal diagnosis and selective interruption of affected pregnancies and tertiary prevention.[7,42] The goal of primary prevention is to reduce the incidence of congenital anomalies through the removal of causative factors. The majority of identified causes of congenital anomalies are non-hereditary and the main preventive measures recommended and being tried in developing countries are (i) expansion of rubella immunization, (ii) access to family planning programs that include the encouragement to complete reproduction before 35 years of age, (iii) periconceptional supplementation of folic acid, and (iv) access to adequate prenatal care, including nutrition, control of maternal infections and avoidance of teratogens.[43] Secondary prevention aims to reduce the number of children born with birth defects. This is achieved through medical genetic screening and prenatal diagnosis to detect birth defect and offers the couple genetic counseling and therapeutic options. To make informed decisions affecting the outcome of pregnancy, parents need the best information available about their specific set of circumstances. This includes the diagnosis, if possible, affecting their fetus; the cause; the consequences for the fetus; available options for the treatment and prognosis as far as this is available; and the risk for recurrence and whether this might be reduced. Secondary prevention requires prenatal diagnosis, which must be accompanied by genetic counseling that includes the description of the tests available, with their scope and attendant risk. Tertiary prevention is directed towards the early detection and care and amelioration of problems once a child with birth defect is born. Intervention include early recognition and diagnosis, including newborn screening if available; medical treatment of complications; surgical repair of congenital malformations such as cleft lip and palate, and congenital heart defects; and neurodevelopmental therapy programs to infants and children with disabilities.[44]

Conclusion and recommendation

Over 3.3 million children die from birth defects each year. When disability is considered, the global toll of birth defects reflects an even harsher reality. In Bangladesh where the social support system is virtually non-existent, bringing up a child with mental or physical handicap is major burden for the patients and family. In cases where primary prevention does not seem possible, prenatal diagnosis by ultrasound scan and other laboratory tests provide the next test alternative. Systematic clinical examination of newborns for congenital anomalies/ malformations can be a method of minimization of medical consequences through early detection of anomalies that may warrant medical or surgical intervention. A developing country of low income and scarce resources can accomplish goals of prevention and care of genetic diseases and birth defects by implementation of clear policies, potential will and an adequate organization of resources.

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CASE REPORT

Congenital Lobar Emphysema

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Introduction

Congenital lobar emphysema (CLE) is an uncommon and potentially life threatening abnormality affecting infants with an incidence of 1 per 20,000-30,000 birth.[1]Patients often present within the first 6 months of life with recurrent respiratory distress. [1] There is congenital defect in bronchial wall as well as in alveoli. So during expiration there is collapse of bronchial wall and that causes trapping of inspiratory air, resulting in hyper inflation of the lung lobe.[2] Causative factors of CLE could be found only in half of the cases which include: 1) partial bronchial obstruction, due to cartilage abnormalities such as completely absent, hypoplastic, flaccid, or immature cartilage; however, bronchomalacia is the most common abnormality; exuberant mucosal fold; extrinsic vascular or lymph node compression of bronchi, e.g. congenital avalvular pulmonary artery; bronchial distortion from an anterior mediastinal lung hernia; and retained secretions. 2) Intrinsic alveolar disease, including; tears in the alveolar walls or enlarged pores of Kohn; abnormal collagen deposition in the alveolar walls and the supporting stroma.[3-6]There are some case reports showing that congenital cytomegalovirus infection may play some role in the development of CLE.[3]

The clinical feature of CLE is usually respiratory distress which is progressive in nature. Symtoms most of the cases develop early neonatal age then in early infancy. There is recurrent cough, wheeze and respiratory distress seen in this disease. Respiratory tract infection is also associated with CLE.[3,5,7] Concomitant congenital heart disease may be associated with CLE (12 to 20%). [2] Chest X-ray and CT scan of chest are diagnostic and show the hyperlucent affected lobe with herniation of the lobe to the opposite side, shifting of the mediastinum to the opposite side and collapse of the remaining part of the ipsilateral lung.[2] The management of congenital lobar emphysema has traditionally been surgical which is followed by conservative management.[8]

Case Summary

Arafat, a 2-month-old male infant, weighing 4.200 kg, hailing from Bagerhat of a non consanguineous parents was admitted on 12/05/2017 in Dhaka Shishu (Children) Hospital with the complaints of cough and respiratory distress for 3 days. He had H/O recurrent cough and mild respiratory distress without cyanosis. Each episode persisted for 4-6 days treated by local doctors without doing chest x–ray. Baby was born normally at term with an average birth weight at home without any complications and he was on exclusive breast feed. The patient was active, afebrile, tachypneic (RR-54/min) with SpO2- 91% on

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room air. There was restricted movement of left chest with subcostal indrawing. Breath sound was diminished on left upper chest. Heart rate was 140/ min without murmur. Others systems revealed normal. Baby was diagnosed initially as left sided pnumothorax and treated with Oxygen by facemask 1L /min, i/v fluid, i/v antibiotics. Chest x-ray revealed emphysematous change in left upper, middle and part of lower zone. Subsequently diagnosis of congenital lobar emphysema of left upper lobe was confirmed by CT scan of chest. Clinically and Echocardiographicaly heart was normal. He was underwent left thoracotomy with left upper lobectomy. Left lung expansion was present in subsequent chest x-ray. On 7 days after operation he was discharged on breast feeding with normal respiration and his growth was normal in subsequent follow up.

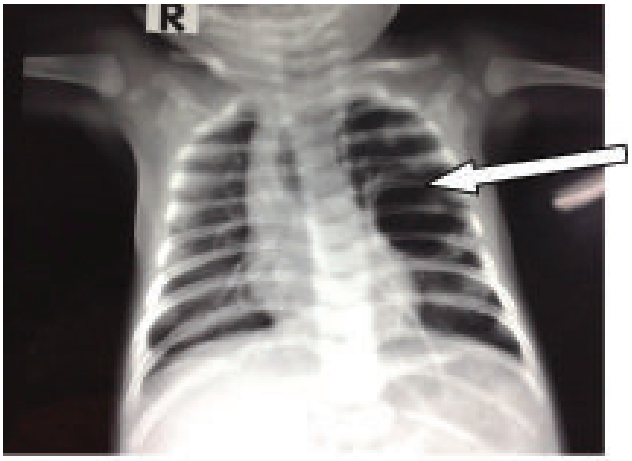

Fig 1 *Chest X-ray A/P view shows hyper lucent area in left upper, mid and part of lower zone (arrow) extending to right side of chest having few bronchovascular marking with mediastinum shifted to the right. Radiological diagnosis- Congenital lobar emphysema (left)*

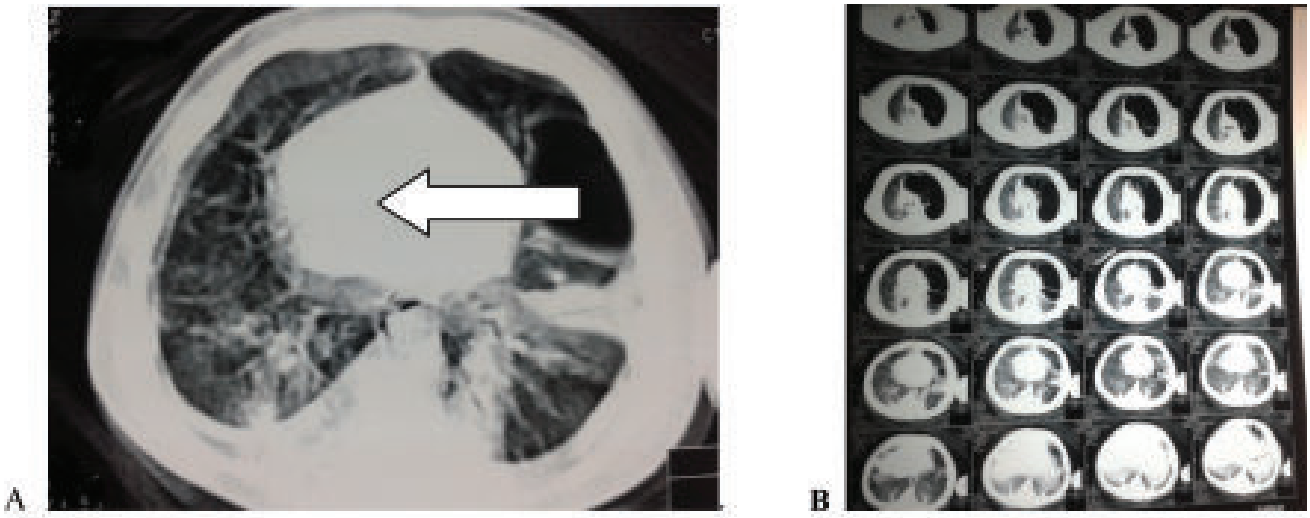

Fig 2 A. & B. *HRCT chest axial view shows hypodense area (arrow) in left lung field involving segment 1 to 7 having few bronchovascular marking causing mild mediestinum shifting towards right side of chest. Radiological diagnosis- Congenital lobar emphysema (left upper lobe)*

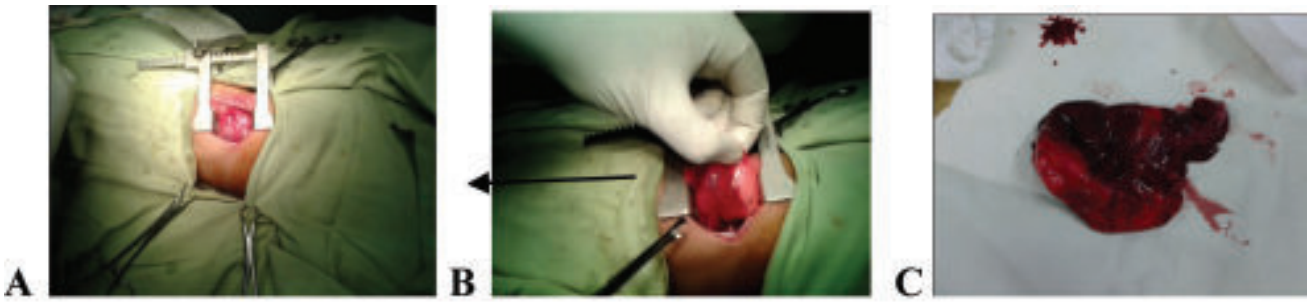

Fig 3 A & B. *Per operative picture shows emphysematous portion of left lung (Red) with remaining intact lung (pale pink, arrow) tissue. C. Resected emphysematous part of left lung*

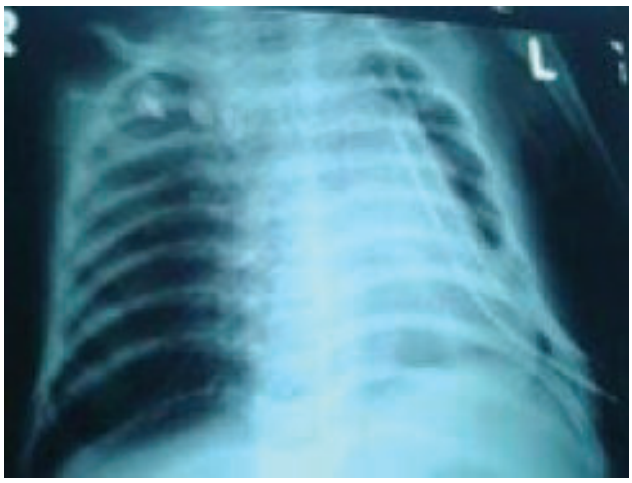

Fig 4 *X-ray chest A/P shows hyper inflation of right lung and small left lung volume with a tube in left chest with mediastinum shifted to the lift side*

Discussion

Congenital lobar emphysema is a rare variety of congenital malformation of lung and potentially life threatening abnormality affecting infants.[1] In this disease, recurrent respiratory distress often develops within the first 6 months of life.[1] This baby presented with cough and respiratory distress for 3 days at 2 months of age and was diagnosed as congenital lobar emphysema after doing X-ray and CT scan of chest. There was delayed diagnosis due to no chest x-ray was done previously inspite of occurrence of two episodes of respiratory complaints. Many case reports were published regarding CLE. Saedi et al., Dutta et al. and Minira et al. showed in their study that the time of diagnosis of CLE was at 21 days, 45 days and 27 days of infant age respectively.[2,9,10] Like our case, delayed diagnosis also occurred in other studies (Saedi et al. and Minira et al.) inspite of hospitalization of their babies.[9,10] The differential diagnosis of CLE are bronchial mucous plug with associated hyper aeration, extrinsic bronchial compression, agenesis/ hypo genesis of contra lateral lung, bronchial hypoplasia with air trapping peripherally, congenital cystic adenomatoid malformation and pneumothorax. Chest X-ray and CT scan of chest are diagnostic.[10] The management of congenital lobar emphysema is usually surgical along with conservative management. Few cases with mild respiratory distress may be managed only with conservative treatment but stringent follow up is necessary. CLE has a good prognosis after medical and surgical management.[10]

Conclusion

The early diagnosis of congenital lobar emphysema is very important. Chest x-ray should be the first investigation of a infant at the time of initial attack of respiratory distress.

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CASE REPORT

Kimura's Disease

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Introduction

Kimura's disease (KD) is a rare chronic angiolymphoid proliferative soft tissue disorder of unknown origin. It occurs most often in young and middle aged Asian malespecially Japanese and Chines.[1]It is a benign condition, but may be mistaken for a malignant disease. It is most common in head and neck region, with a predilection for pre-auricular area. Typical clinical presentations are painless subcutaneous masses, regional lymph node enlargement, blood and tissue hyper eosinophilia, and markedly elevated serum IgE levels.[2] According to the previous medical literatures, Kimura's disease has a high recurrence rate so early & definitive diagnosis of the disease is vital for effective treatment plan.[3] Renal involvement is its only systemic manifestation. Here we report a case of Kimura's disease.

Case report

Mehedi Hasan, a 10 years old boy immunized as per EPI schedule, was admitted into this Dhaka Shishu(Children) Hospital (DSH) with multiple swellings in the right side of neck for 6 months which was slowly increasing in size. He has no history of fever, cough, fatigue, loss of weight, contact with TB patient, bleeding manifestation, discharging sinus or bone and joint pain. He was on family diet. He belongs to a middle class family and no history of such type of illness in his family members. The child was co-operative, afebrile, mildly pale & anthropometrically age appropriate. His, Heart rate 84/min, Respiratory rate 16/min, normal Temperature, Blood pressure 90/60mm of Hg. BCG mark was present. There was no organomegaly or evidence of ascites. Lymph nodes were enlarged on right anterior cervical chain, largest one was 8x4cm, non- tender, firm, discrete, free from overlying skin & underlying structure, without discharging sinus. Other groups of lymph nodes were not enlarged. Other systemic examinations revealed normal findings. The child has normal Blood parameters except eosinophilia (Hg-12gm%. WBC count 9600/cmm (Neutrophil 32%. Lymphocytes 42%, Eosinophil 24%, Monocyte 2%) Platelets was adequate) and his peripheral blood film no malignant cells seen. CTscan and MRI of the chest excluded evidence of underlying

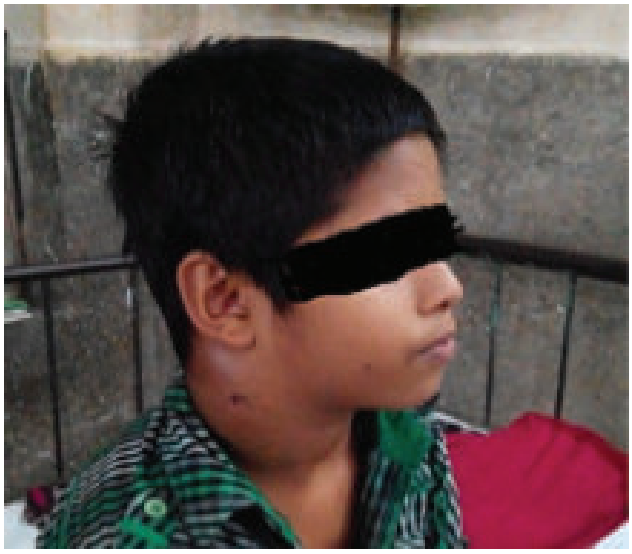

Fig 1 A large Mass shows in Neck

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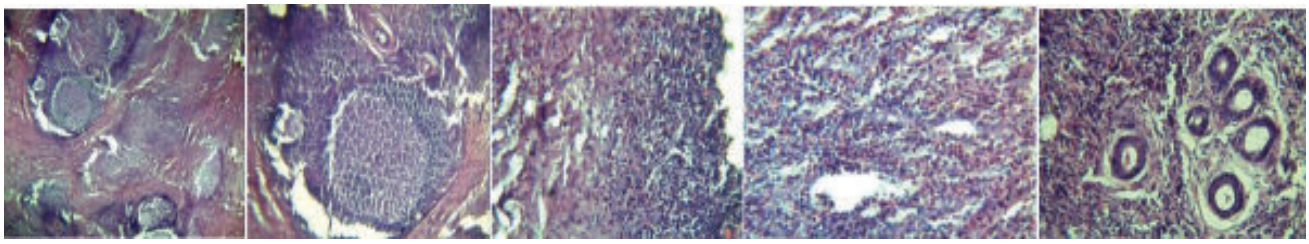

Fig 1a Lymphocytic infiltration with follicle formation and fibrosis. (4x), **1b** Well defined lymphoid follicle with prominent germinal center, (10x) **1c** Chronic Inflammatory cell infiltration with predominant eosinophils with micro abscesses (40x), **1d** Interfollicular areas showing mixed inflammation with prominent eosinophil and proliferation of venues (40x), **1e** Interfollicular areas showing increased number of venules with endothelial cell

malignancy or lymphadenopathy. Renal function was within normal limit. Serum immunoglobulin E level was high (500 IU/L).

Excisional biopsy findings reveals partial effacement of its architecture. There is extensive infiltration of eosinophils with focal eosinophilic micro abscess. Hyalinized vessel wall, interstitial fibrosis & deposition of proteinaceous material. Some aggregates of epithelioid cells & multinucleated giant cells are noted. No evidence of malignancy is seen. Features are consistent with Kimura disease.We have treated the patient with surgical excision, Broad spectrum antibiotics for 7 days and oral prednisolone 2mg/kg/day for 21 days with much improvement, then we discharge the patient with gradual tapering of oral prednisolone and follow up after 2 weeks. During follow up patient was well and we keep him for long follow up with advice.

Discussion

Kimura's disease(KD) first described in1937 in Chinese literature by H.T.Kimm and C.Szeto and they termed it as "eosinophilic hyperplastic lymphogranuloma".[4]The disease became widely known as Kimura's disease after Kimura and colleagues reported two cases of unusual granulation combined with hyperplastic changes of lymphoid tissue. The etiopathogenesis of KD remains unknown and it is considered now a days as an allergic disease and it seems to be a systemic immunological disorder. Eosinophilia and increased serum IgE levels make KD be considered a CD4 (+) T helper 2 (Th2) allergic reactions. Th2 cells would produce interleukins (IL) IL-4, IL-5 and IL-13, which, in turn, would act in B cells favoring the production of antigen-specific IgE. Th2 cell proliferation and the overexpression of cytokines would play an essential role in the development of the disease.[5]

It occurs predominantly as a unilateral manifestation in the head and neck and it is frequently associated with regional lymphadenopathy with or without involvement of salivary glands.[6]In the present case, e presence unilateral parotid gland swelling with regional lymphadenopathy led to the clinical diagnostic dilemma of other pathologic entities affecting salivary glands & lymph nodes. The differential diagnosis of Kimuras disease frequently in previous literatures are Lymphomas, salivary gland neoplasms, benign lymphoepithelial lesions (BLL / Mikulicz's disease), Angiolymphoid hyperplasia with eosinophilia (ALHE/ Epitheloid-hemangioma) and angioimmunoblastic lymphadenopathy (AIL). Constant classical features of KD include numerous lymphoid follicles, mixed inflammatory infiltrate composed mainly of eosinophils and increased amount of post capillary venules.[7]

Till date there is no definite treatment for KD is well established. However the treatment plan should aim at preservation of vital structures associated with the lesions & cosmetic rehabilitation, while preventing recurrences. Treatment options range from observation & follow-up of mild & symptomatic cases to conservative surgical approach, medication & radiotherapy in symptomatic & recurrent cases. If the lesion is primary, localized or present in young age then surgical approach is more preferable. Oral corticosteroids: Dose 1-2 mg/kg/day can be given with variable results but the disease frequently recur after cessation of therapy.Cyclosporine, azathioprine induce remission. Dose: 5mg/kg/day. Radiotherapy-in case of failure medical therapy or in recurrent or persistent Kimura's disease lesion. Oral pentoxifyllin & IV immunoglobulin.

According to previous literature, only surgical approach had high incidence of recurrence (25%).[8]If the lesion is recurrent with systemic involvement, application of medication like corticosteroid and immunosuppressive agents have been shown to decrease size of the lesion. Irradiation should be considered in patients resistant to the steroid or to prevent the patient from deleterious effect of long term use of steroid.[9]

Conclusion

Kimuras disease is a rare chronic inflammatory disease that mimics neoplastic conditions. If any patients presented with head & neck mass and painless unilateral cervical lymphadenopathy Kimuras disease should be kept in mind in differential diagnosis and investigate accordingly. Early diagnosis and appropriate management is crucial as this disease has good prognosis.

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ABSTRACT FROM CURRENT LITERATURE

Comparative evaluation of efficacy of leflunomide versus combination of methotrexate and hydroxychloroquine in patients of rheumatoid arthritis – an Indian experience

Rekha Mathur, Harpreet Singh, Suvrat Arya, Vikram Singh

Indian Journal of Rheumatology 11 (2016): 86-9 0

Introduction: Methotrexate (MTX) is most widely used both as monotherapy and in combination therapy for the treatment of rheumatoid arthritis (RA). Combinations of different disease modifying anti-rheumatic drug/s provide additional or even have potentiating effects and therefore have become widely used. Leflunomide (LEF) alone has been seen to improve both the subjective symptoms and the objective parameters in RA.

Material and methods: An open label, prospective, comparative clinical study was conducted with 100 patients, divided into two groups of 50 patients in each. Subjects in group-1 were given LEF (20 mg/day) and group-2 received a combination of MTX (initial dose of 7.5 mg/week escalated to 25 mg/week) and hydroxychloroquine (HCQ) (200 mg twice a day). The various scores and parameters of disease activity were compared every 4 weeks for 12 weeks using Disease Activity Score (DAS28) and Clinical Disease Activity Index (CDAI) scores.

Results: At 4 weeks, in group-1, DAS28 improved by 1.28 and CDAI improved by 16.82; while in group-2, DAS28 and CDAI improved by1.02 and 14.39 respectively. At 12 weeks, DAS28 and CDAI improved by 2.22 and 25.33 in group-1 and 2.35 and 26.53 in group-2 respectively. When DAS28 was compared in between groups, it was insignificant at baseline, 4 weeks, and 12 weeks with a p-value of 0.547, 0.960 and 0.182 respectively, which suggested that both groups were comparable throughout the study. The comparison of CDAI between the groups was insignificant at baseline, 4 weeks and 12 weeks with a p-value of 0.634, 0.893 and 0.333 respectively, which also suggested that disease activity in both group were comparable from baseline to 12 weeks.

Conclusion: LEF was found to have equal efficacy as the combination of MTX and HCQ in reducing DAS28 and CDAI score (i.e. from severe to moderate disease activity) and so may be considered as initial therapy in RA.

P-Glycoprotein Activity In Steroid-Responsive Vs. Steroid-Resistant Nephrotic Syndrome

Hassan S. Badr, Mahmoud A. El-Hawy & Mohammed A. Helwa

Indian J Pediatr, DOI 10.1007/s12098-016-2142-y.

Objectives: To explore the expression of P-glycoprotein (P-gp) in the peripheral blood nucleated cells (PBNCs) of children with nephrotic syndrome in relation to their clinical response to glucocorticoid treatment.

Methods: Thirty-six children with nephrotic syndrome (20 cases of steroid-responsive and 16 cases of steroid-resistant) were examined. All the participants were subjected to complete history taking, thorough clinical examination, laboratory investigations (24-h urinary protein, serum albumin, complete blood count with differential white blood cell count, serum cholesterol, serum urea, serum creatinine) and functional assay of P-gp using FACS Calibur flowcytometry. P-gp assay was done in both groups during remission.

Result: P-gp activity was significantly higher in steroid-resistant than steroid-sensitive cases.

Conclusion: P-gp can be used as a predictor of outcome, as a part of laboratory evaluation of the cases before starting steroid therapy, so as to determine whether to use alternative line of therapy or use one of the P-gp inhibitors with steroid therapy.

The Relationship Between Thrombocytopenia And Intraventricular Hemorrhage In Neonates With Gestational Age <35 Weeks

Idha Yulandari, Lily Rundjan, Muzal Kadim, Pustika Amalia, Harynti F. Wulandari, Setyo Handryastuti

Paediatr Indones. 2016;56:242-50.

Background: The prevalence of thrombocytopenia in neonates ranges from 22 to 35%, and one of the most feared complications is intraventricular hemorrhage (IVH). Previous research in Cipto

Mangunkusumo Hospital (CMH), Jakarta reported a high incidence of IVH (43.47%) in infants with a gestational age of <35 weeks. Intraventricular hemorrhage causes disturbances in neurological development and can be fatal. In Indonesia, research on the relationship between thrombocytopenia and IVH has been limited.

Objective: To study the relationship between thrombocytopenia and IVH in neonates with gestational age <35 weeks and assess for a correlation between the severity of thrombocytopenia and the severity of IVH.

Method: This cross-sectional study was performed by reviewing medical records in the Neonatology Division of the Child Health Department, University of Indonesia, CMH. Subjects were neonates hospitalized from January 2012 to December 2014 with IVH. Subjects were categorized into either mild to moderate IVH (grade d"2) or severe IVH (grade >2). Thrombocyte counts were recorded on the same day as the diagnosis of IVH.

Results: The risk of severe IVH was 28.2% in neonates with thrombocyte counts <100,000/uL, and 10.4% in neonates without thrombocytopenia (P=0.014). Multivariate analysis revealed that gestational age <32 weeks and the use of respiratory support (ventilator and high frequency oscillatory ventilation) had significant associations with severe IVH. However, multivariate analysis did not show a significant relationship between thrombocytopenia and severe IVH (correlation coefficient = 0.21).

Conclusion: Thrombocytopenia is not significantly associated with the incidence of severe IVH based on multivariate analysis. Also, the severity of thrombocytopenia has no correlation with the severity of IVH.

The 2015 Jones Criteria for Acute Rheumatic Fever – Need for a Critical Reappraisal

Pandiarajan Vignesh and Avinash Sharma

K C Chaudhuri Foundation

Indian J Pediatr 2016

Acute rheumatic fever (ARF), a non-suppurative complication of group A beta hemolytic streptococcus (GAS), continues to be an important cause of acquired heart diseases in children. Whilst the burden of rheumatic heart disease (RHD) has significantly reduced in developed countries, it still continues to be a major health problem in developing countries [2]. Prevalence of RHD in India is estimated to be 0.67/1000 children in a recent school based survey. Over past 50 y, significant developments have occurred in diagnosis and management of ARF. One of the major changes noted in the diagnosis of ARF is the utility of Echocardiogram and Doppler (E&D) studies for detection of clinically unrecognizable carditis for the diagnosis of ARF. Subclinical carditis (SC) is a condition where clinical cardiac examination is completely normal and only E&D studies pick up the valvular abnormalities. Diagnostic criteria for ARF was initially put forth by Dr. T. Duckett Jones in the year 1944. The criteria have been revised and updated several times, and the most recent update of the Jones Criteria have been released by the American Heart Association in May 2015. Main aim of these guidelines has been to have a uniform diagnostic criteria across the globe and to prevent over-diagnosis. However, even the most recent version has several shortcomings for clinical application in developing countries where the vast majority of patients with ARF are likely to be diagnosed and managed (Table I). Recent revision of Jones Criteria for diagnosis of ARF has suggested that echocardiography be performed in all cases of suspected ARF [6]. Subclinical carditis is now considered one of the major criteria for diagnosis of ARF. The addition of SC as the major criteria is based on large numbers of good quality evidence from both developed and developing countries around the globe, which suggested that E&D based screening is more sensitive than clinical examination for detection of carditis. However, it is prudent to note that long term outcome of subclinical carditis is not clearly known and it may well represent only a transient phenomenon. Robust data on long term follow-up of patients with subclinical carditis is lacking. This recommendation in the 2015 criteria is, therefore, open to debate and controversy. Existing data on follow-up studies indicate that subclinical carditis may worsen to RHD, may remain unchanged, or may also improve over time. Moreover, facilities for E&D based screening for carditis in patients with suspected ARF would not be easily available at the point of care in most developing countries. Interpretation of the E&D studies would also need an experienced cardiologist/echocardiographer, who may not be

Table 1 The 2015 revision of the Jones Criteria for the diagnosis of Acute Rheumatic Fever and its shortcomings for clinical application in the developing nations

2015 update of Jones Criteria for diagnosis of ARF		Shortcomings
A **For all patient populations with evidence of preceding GAS infection**[#]		Clinical symptoms and signs of GAS sore throat may not be always straightforward and laboratory confirmation is essential for diagnosis. Moreover, facilities for confirming the GAS sore throat may not be available in remote centres, especially in resource constraint settings.
Diagnosis of initial ARF: 2 major manifestations or 1 major plus 2 minor manifestations		
Diagnosis of recurrent ARF: 2 major or 1 major and 2 minor or 3 minor		
B **Major criteria for low-risk populations**	**Major criteria for moderate and high-risk populations**	
1. Carditis	1. Carditis	1. Long term outcome of subclinical carditis/ echocarditis is not well studied.
• Clinical and/or subclinical[$]	• Clinical and/or subclinical[$]	2. Utility of E&D studies for all cases of suspected ARF may not be applicable for resource limited settings, where cardiology expertise is not available everywhere.
2. Arthritis	2. Arthritis	1. Over-diagnosis of ARF is likely for all joint complaints.
• Polyarthritis only	• Monoarthritis or polyarthritis	2. Serious causes of monoarthritis such as septic or tubercular arthritis may be mislabelled as ARF.
	• Polyarthralgia (to be considered only when reactive, autoimmune, infective causes are ruled out)	
3. Chorea	3. Chorea	-
4. Erythema marginatum	4. Erythema marginatum	
5. Subcutaneous nodules	5. Subcutaneous nodules	
C **Minor criteria for low-risk populations**	**Minor criteria for moderate- and high-risk populations**	-
Polyarthralgia	Monoarthralgia	
Fever (≥ 38.5 °C)	Fever (≥38 °C)	
ESR ≥ 60 mm in the first hour and/ or CRP ≥ 3.0 mg/dl	ESR ≥60 mm in the first hour and/or CRP ≥ 3.0 mg/dl	
Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)	Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)	

ARF Acute Rheumatic Fever; *GAS* Group A beta hemolytic Streptococcus; *ESR* Erythrocyte Sedimentation Rate; *CRP* C Reactive Protein

[#] Evidence of preceding GAS infection- 1) Increased or rising anti-streptolysin O titer or other streptococcal antibodies (anti-DNASE B); 2) A positive throat culture for GAS; 3) A positive rapid group A streptococcal carbohydrate antigen test in a child whose clinical presentation suggests a high pretest probability of streptococcal pharyngitis

easily available in all centres. If the new criteria have to be accepted and implemented, then a seemingly large number of patients may need referral to higher centres where experts in cardiology are likely to be available. Table 1 The 2015 revision of the Jones Criteria for the diagnosis of Acute Rheumatic Fever and its shortcomings for clinical application in the developing nations 2015 update of Jones Criteria for diagnosis.

Acknowledgments

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Contributions PV, AS: Framing of initial draft, editing, and final approval of the manuscript. Dr. Surjit Singh will act as guarantor for the paper.

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DSH NEWS

Celebration of World Meningitis Day, 25 April 2017 with a rally started from Dhaka Shishu (Children) Hospital campus.

Celebration of International Nursing Day, 12 May, 2017 at the auditorium of Bangladesh Institute of Child Health (BICH).

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BICH NEWS

BICH is the academic wing of Dhaka Shishu Hospital. It was established in 30th January, 1983. It is affiliated with Dhaka University, Bangabandhu Sheikh Mujib Medical University (BSMMU) and Bangladesh College of Physicians and Surgeons (BCPS). It has been conducting different courses e.g. DCH, FCPS, MD Paediatrics, MS Paediatric surgery & B.Sc in Health technology. It also conducts different sub-specialty courses e.g. FCPS Neonatology, FCPS Haemato-oncology, FCPS Nephrology, MD Neonatology, MD Haemato-oncology and MD Nephrology. It conducts 3 months certificate course in Paediatrics and 15 days Intensive course for MCPS. It organizes IMCI training and Palli Shishu Rural Health Training. Apart from this, the Institute also runs its regular academic activities. It has established Basic Science Department since 2006.

Diploma course of paediatric nursing has been started from 1st January 2012 and Diploma in paediatric physiotherapy under process.

Library facilities

The library of BICH has a rich collection of updated medical texts and reference books and reputed Medical Journals of home and abroad. BICH has introduced Broad Band facilities which are open to all students, teachers/ consultants of hospital for 24 hours. Facilities of library are also improved by HINARI. Students can download 2230 Medical Journals & more than 50 Paediatric Journals.

Present News

A newly formed classroom in BICH has been named as Prof. Sultan Ahmed Chowdhury as a tribute to First Honarary Director of Dhaka Shishu Hospital.

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Postgraduate courses/training in paediatrics and child health

1. FCPS in paediatrics : Twice in a year, in the months of January and July.
2. Recognized center by BCPS for training in FCPS (Paeditric surgery) .
3. Recognized centre for course and training in different subspeciality as: Neonatology, Pediatric Nephrology, Paediatric Haematology and Onchology, Paediatric Pulmonology and Paediatric Neuroscience.
3. MD/MS in paediatrics : Part I: In the month of January every year; 2nd and 3rd parts twice every year.
4. DCH course : Once in a year in the month of July.
5. Three months certificate course : The institute every year runs 3 months certificate course on paediatrics for general practitioners & other post graduate candidates e.g. MCPS.
   (Ist August – 31st October)
6. Training programme on IMCI (Integrated management of childhood illness), Essential Newborn Care for doctors and nurses, KMC (Kangaroo Mother Care) traing, ETAT (Emmergency Triage, Assessment and Treatment) training.

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Students Qualified from Bangladesh Institute of Child Health

Undergoing Courses of BICH

Institution	Courses
Bangabandhu Sheikh Mujib Medical University	MD (Paediatrics) MD Paediatric s Nephrology (sub-specialty) MD Neonatology (sub-specialty) DCH MS (Paediatrics Surgery)
Bangladesh College of Physicians and Surgeons (BCPS)	FCPS Part II (Paediatrics)_ FCPS Neonatology FCPS Paediatric Nephrology FCPS Hematology & Oncology FCPS Paediatric Surgery FCPS Paediatric Neurology & Development FCPS Paediatric Pulmonology
Dhaka University	B.Sc in Health technology (Lab)
Bangladesh Nursing Council	Diploma in Paediatric Nursing

Student Qualified from BICH till June 2017

Course	Number
DCH	340
MD (Paediatrics)	110
MS (Paediatrics)	103
FCPS (Paediatrics)	28
MD (Neonatology)	13
MD (Paediatrics Nephrology)	5
Total	**599**

Foreign Student Qualified from BICH till January 2013

Country of origin	Course	Number
Nepal	DCH	23
	MS (Paed Surgery)	2
	MD (Paed)	1
India	MD (Paed)	1
Iran	DCH	1
Iraq	DCH	1
Somalia	DCH	1
Sudan	DCH	1
Total		**31**

Present Students July 2017 - December 2017

Name of Courses		Number of Students
DCH		13
MD (Paediatrics)	Phase-A	14
MD (Neonate)	Phase-A	3
MD (Paediatrics Nephrology)	Phase-A	2
MS (Paediatric Surgery)	Phase-A	10
FCPS (Paediatrics)	Part-II	2
MS (Paediatric)	Part-III	2
FCPS (Paediatrics)	Part-II	6
Total		

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Seminar/Symposium & CME/CPD programs held at BICH (July- December 2017)

Sl. No.	Topic	Medical Unit	Date
1	Neonate sepsis	(MU-IV)	30.07.2017
2	Childhood TB - An update	(MU-V)	27.08.2017
3	Chikungunya fever	(MU-VI)	24.09.2017
4	Management on childhood burn	(SU-I)	22.10.2017
5	Nocturnal enuresis	(MU- VII)	26.11.2017
6	Immune thrombocytopenic purpura - An update	(MU- VIII)	24.12.2017

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INSTRUCTIONS FOR AUTHORS

Dhaka Shishu Hospital Journal is the official organ of BICH which is the academic wing of DSH. It is published twice a year since 1984. The present editorial board has decided that the cover design will be in accordance with the subject of editorial in each issue. The editor welcome articles to be published in the journal as leading article, original article, review article, case report, current issues of child health, short report and junior's page where trainee doctors are encouraged to publish their topic of interest.

Original papers written in *english* will be considered for publication provided these have not been published previously and are not under consideration for publication elsewhere.

Conditions for manuscript submission:

- All manuscripts will be subjected to peer and editorial review.
- Accepted manuscripts become the property of the *Dhaka Shishu Hospital Journal*. Any reproduction in whole or part will require written permission from the editorial board of the journal.
- The author should obtain written permission from appropriate authority if the manuscript contains any table; data or illustration from previously published in other journals. The letter of permission should be submitted with the manuscript.
- If the photographs are not disguised, permission from the patient or parents/ guardians to print should accompany the manuscript. Otherwise identity will be blackened out.
- Rejected manuscripts/electronic copies/ illustrations/photographs will not be returned to the authors.
- Editors are not responsible for courier/postal failure.

Manuscript preparation: The format of the Dhaka Shishu Hospital Journal complies with *"Uniform Requirements for Manuscripts Submitted to Biomedical Journals"* published by the International Committee of Medical Journal Editors in Vancouver, British Columbia in 1979 (the widely accepted ***"Vancouver style"***)' published in the Annals of Internal Medicine 1982; 96: 766-71. All scientific units should be expressed in *System International (SI) units*. Authors are referred to Annals of Internal Medicine 1987; 106: 114-29 for guidance in the use of SI units. All drugs should be mentioned in their generic form.

- Should be typed in english and on one side of A4 (290 x 210cm) size white paper, using *Times New Roman* font size 12, with single space.
- There should be one original and two paper copies and one IBM compatible electronic copy. (CD or Pen drive)
- There should be a margin of 2.5 cm at top and bottom, and 1.2 cm left and right.
- Pages should be numbered in english numerical at the upper right hand, consecutively, beginning with the title page.
- Manuscripts should be submitted in the following order:
  - Title : should not exceed 100 characters (Font size 16, bold)
  - Name of authors, e.g. 1. Prof. Saiful Islam FCPS, FRCP, 2. Dr. Nurun Nahar MD, these two author's name will be written like this; S Islam[1], N Nahar[2], etc. (Font size 12) Author's designation and name of place of study will be written after the end of the abstract. (Font size 10).
  - ***Abstract with a specific format with five sections (about 350 words maximum): Background, Objective, Methodology, Results, Conclusion, address of correspondence. All these sections will be Times New Roman, Font size 12 and italic , bold but text will not be bold. No references are allowed in the abstract.***

- Text (Introduction, Materials & Methods, Results, Discussion, Conclusion).
- Acknowledgements
- References
- Photographs:
  - In CD/ Pen drive
  - With appropriate labeling (number in English numerical, title of photographs and title of manuscripts.) It should be placed in appropriate place of the article.
- Illustrations:
  - All illustrations should be cited in the text
  - Illustration should be numbered in English numerical and labeled properly, placed appropriately in relation to text of manuscript.
- Tables:
  - Should be appropriately titled.
  - Numbered with Roman numerical serially in order of text description.
  - Abbreviations if used, should be explained in footnotes.
  - Same table should not be repeated as chart.
- Figures:
  - Should be appropriately titled and title will be placed below the figure.
  - Numbered with English numerical serially in order of text description.
- Placement:
  - All photographs, illustrations, tables and figures should be placed in the text in their appropriate places where their description are given.
- References:
  - *References from journal* should be indicated by superscript numbers consecutively in the text and placed after full stop (e.g. ….has been reported.[1] or as shown by Akbar[2] .....) in the order in which they are first mentioned and should be listed in numerical order on a separate sheet at the end of the article.
  - References cited only in tables or legends or illustrations should be numbered in accordance with a sequence established by the first mention in the text.
  - Titles of journals should be abbreviated according to Index Medicus or given in full.
  - References must include: (i) all authors, surnames and initials (if there are 6 authors or fewer) or if there are more than 6 authors, the first six authors followed by et al; (ii) the full title of the paper; (iii) the abbreviated or full title of the journal in italic; (iv) the year of publication; (v) the volume no will be bold; (vi) the first and last page numbers followed by full stop. *Example*: Khan NZ. A study of mentally handicapped children: aetiology and associated factors. *Bangladesh Journal of Child Health* 1985; **9**(2):102-08.
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  - *Documents in electronic format* must include: (i) title, (ii) authors name, (iii) year of publication, (iv) web site address, (v) date of access. *Example*: United Nations Programme on HIV/AIDS. Children living in a world with AIDS. Geneva, 1978 (htpp://www.....), accessed on (dd/mm/year).

Manuscripts Submission: the manuscripts should be submitted to the editor/ associate editors with a covering letter, mentioning that the work has not been published or submitted for publication anywhere else.

Reprints for the authors: 2 copies of original journal and five copies of each article will be provided to the corresponding author free of cost.