2017 / Vol. 5 (1&2) ISSN 2320 9208

CLINICAL COMMUNIQUES AND MEDICAL EDUCATION

A Peer-Reviewed (Refereed/Juried) International Journal

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ISSN 2320 9208

CLINICAL COMMUNIQUES AND MEDICAL EDUCATION

A Peer-Reviewed (Refereed/Juried) International Journal

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MMIMSR, MM (Deemed to be University),
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Tel : +91-1731-304551
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PUBLISHED BY

Maharishi Markandeshwar (Deemed to be University)
Mullana - Ambala (India)
Printed at: Crazy offset Printers, Kurukshetra

ISSN 2320 9208

From the desk of Editor-in-Chief

Positive Feedback For Clinical Competency

Postgraduate residency programme is very important period to acquire clinical competency.As of today the interns are mostly focused on preparing for qualifying the NEET(National Eligibility cum Entrance Test) examination to get admission to a postgraduate course. After joining as a resident in a clinical course the postgraduate student is exposed to an environment where he/she is expected to work as a competent doctor. Any deficiency at this stage is not viewed lightly and student has to face critical comments some of which can be demoralizing. Infact this is the period when the students are often receptive to any guidance. But all he/she has to handle is high expectations and criticism.

Giving feedback in a clinical environment can be very tricky. The mentor/faculty has to be careful about what is said in the bedside. At present the doctor patient relationship is at its low. Patients' well being is to a large extent dependent on faith and trust. The residents spend more time with patients than the faculty. The mentor/faculty has to be more careful and not to make comments which may be humiliating to the resident or any other staff. Any negative comment to the resident is unlikely to help anyone. A positive feedback is what is needed to improve the overall care of the patient. Lack of time is often cited for not giving a feedback. It may be true. But I feel it can be changed. First and foremost is acceptance on the part of faculty/teacher and resident/learner that feedback is a method to improve clinical competency. It need to be imbibed into the daily practice. For all it may take is spending a few minutes after the clinical round.in the corridors of the wards. The feedback should not be vague like 'you did well' or 'you need to improve" . Few specific points is required to be made. The positive points should be appreciated, strengthened, reinforced. The deficiency should be spelled out, at the same time how to go about those deficiencies or remedial measures should be suggested. The feedback can be given immediately after a clinical skill is evaluated/observed or delayed. To have an impact it probably should be early rather than late. Another important point is that any sensitive issue in the feedback are better conveyed one to one.

Any feedback to the articles published in CCME?! Write letter to editor -

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ISSN 2320 9208

CLINICAL COMMUNIQUES AND MEDICAL EDUCATION

A Peer-Reviewed (Refereed/Juried) International Journal

Jan-Dec. 2017 / Vol.5 / Issue 1&2

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ISSN 2320 9208

A study of suspected adverse drug reactions observed in a rural medical college & Hospital in North India

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ABSTRACT

The safety of prescribed medicine has become a highly visible topic in medicine, as a part to research suggesting that there are important ADRs caused by commonly used medicines. This observational, non interventional study was conducted in Bhagat Phool Singh Govt Medical College for women, Khanpur Kalan, Sonepat in Haryana which is a 500-bedded government medical hospital situated in rural area. Antibiotics (Cephalosporins), NSAIDS, etc were identified to precipitate most of the drug reactions. Polypharmacy, age, gender, etc were the reasons for development of adverse drug reactions. The causality assessment done showed that all suspect ADRs fell under possible or probable category.

Key words: Pharmacovigilance, ADR, PvPI, AMC

INTRODUCTION

The drug-related demage is currently one of the most important public health problem across all over the world. The safety of prescribed medicine has become a highly visible topic in medicine, as a part to research suggesting that there are important ADRs caused by commonly used medicines. It is well said by DJP Barker that a drug has three actions: The one you want, the one you don't want, and the one you don't know about.[1] Although medicines are generally given to treat and prevent illnesses as they have the ability to modify the altered physiological processes in the body, at the same time the drugs always carry certain amount of risk in the form of unwanted or unintended effects known as Adverse Drug Reactions(ADRs).

As per WHO, Adverse drug reaction (ADR) is ''any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiologic function'.[2]

Globally physicians are coming across problems of adverse drug reactions every day in their out patient departments. The 7th most common cause of death is adverse drug reactions and it was found that 6.5% of patient admissions is due to ADRs in National Health Service (NHS) hospitals.[3] A hospital has a burden of Rs.481/- per day in treating ADRs as studied by Arulmani R. [2] ADRs leaves a negative effect on both physical health and healthcare economics.

Variation in the pharmacokinetics and pharmacodynamics parameters in patients following drug administration leads to majority of ADRs. Patient related (age, gender, immune system), drug related (polypharmacy, drug-drug interaction) or socially related factors play a important role in the incidences of ADRs.[4]

Pharmacovigilance is the science that is related to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems[5]

In 2010, Central Drugs Standard Control Organization under the aegis of Govt. of India, Ministry of Health and Family welfare has come with new projects and started Adverse Drug Reaction (ADR) Monitoring Centres in various tertiary care hospitals in all over India (Pharmacovigilance Programme of India, 2010).

This study was conducted to assess the incidence of ADRs & analyze for causality and severity of adverse drug events reported to ADR Monitoring Centre, Department of Pharmacology, BPS GMC for women, Khanpur Kalan, Sonipat, Haryana, India.

METHODOLOGY

A observational and cross sectional, was conducted in BPS GMC for women, Khanpur Kalan, Sonepat, Haryana which is a 500-bedded government medical hospital situated in rural area. The Department of Pharmacology, BPS GMC for women, Khanpur Kalan, Sonepat, Haryana, India which is one of the ADR monitoring centre (AMC) under the Pharmacovigilance Program of India (PvPI) since Jan, 2014. Suspected adverse events due to drugs, vaccines and contrast media were collected from OPD and IPD of all clinical departments of hospital on regular basis.

The study was carried out for a period of 2 yrs from May, 2015 to April 2017 and was based on ADRs reported voluntarily by all the depts. to ADR Monitoring centre in the dept. of Pharmacology (reported by physicians, surgeons, nurses, pharmacists) & also by active surveillance of ADRs done by the staff of AMC from the hospital. It involved a multidisciplinary spontaneous & active surveillance reporting program that relies on both the prospective and concurrent detection of suspected adverse drug reactions and drug interactions. All patients of either sex and of any age who developed an ADRs during the above mentioned time period were included in the study and the exclusion criteria were considered as patients who developed an ADR due to intentional or accidental poisoning, ADRs due to the fresh blood/blood products, drug overdose and patients with drug abuse and intoxication were also excluded from the study.

Thus the main aim of this study was to detect and analyze Adverse Drug Reactions (ADRs) due to drugs of any class in patients coming to a tertiary care hospital.

RESULTS

Total 540 cases of adverse drug events were reported in rural tertiary care hospital from May, 2015 to April, 2017. Out of 540 cases reported, 436 (80.75%) cases were reported in IPD & 104 (19.25%) cases were reported in OPD setup at BPS GMC for women, Khanpur Kalan, Sonepat. 16 (3.00%) cases were serious and 554(97.00%) were non-16 serious (Fig. 1). 53.51% male cases and 46.48% female cases were reported. Patients aged between 31-45 years experienced maximum ADR cases (27.03%) (Table1). Maximum number of cases were reported from department of Surgery department (115) followed by Medicine (108), Skin & Venereology and Obstetrics & Gynaecology (45) (Fig.2). Almost all the ADRs (96%) were observed in patients receiving combination drug therapy (i.e. >2 medicines) when compared to patients receiving single drug therapy. The major group contributing to ADRs was antimicrobials (24.27%) followed by NSAIDS (7.34%), antiulcer (7.08%) and antiamoebics (6.95%) 9.58% cases were reported due to administration of vaccines followed by 0.78% cases due to contrast media. Among the antimicrobial agents (AMAs), ceftriaxone, augmentin, amoxicillin, ampicillin, ceftriaxone/sulbactam, cefotaxime (55.93%) were the most common culprits. Other medicines which were associated with ADRs were diclofenac, pantoprazole, ranitidine, metronidazole, aspirin, antitubercular drugs olanzapine, risperidone, phenytoin, metoprolol, hyoscine bromide, eldervit, ferrous sulphate, cyclophosphamide, doxorubicin, etc. (le 2). The most affected organ system was skin (43.84%) followed by the gastrointestinal system (26.63%) (Fig.3).

Most of the ADR were found to be 'Type A' reaction. Frequently observed types of ADRs were rashes (28.31%), erythema (20.03%), constipation (4.35%), nausea and vomiting (3.24%),

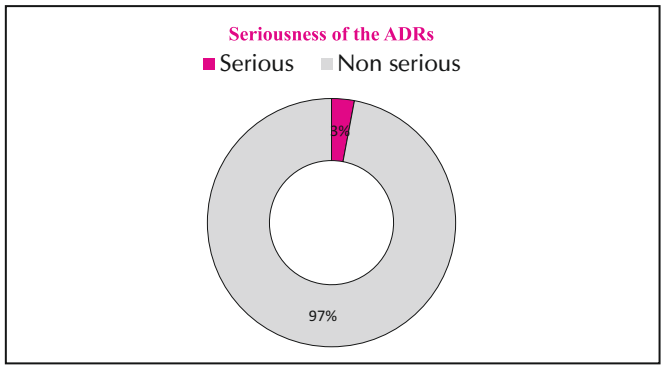

Fig. 1. Seriousness of suspected ADRs

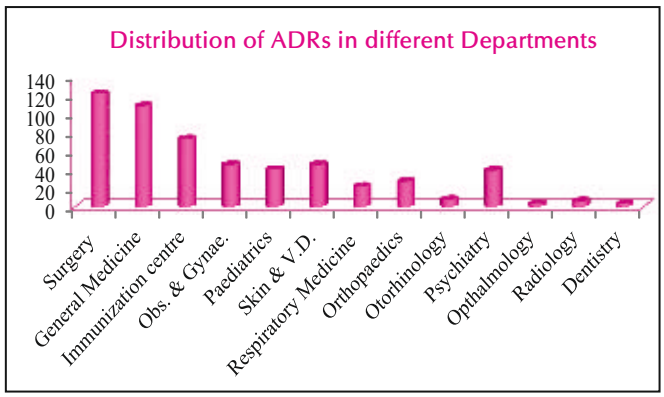

Fig. 2: Distribution of ADRs in Various Departments

Table 1: Age wise distribution of patients with ADRs

Age Interval (in years)	No. of patients
0-15	86
16-30	136
31-45	146
46-60	89
61-75	73
76-90	10

Table 2: Class of drugs implicated in suspected ADRs

Class of Drug		No. of cases reported	%age
Antimicrobial Agents (AMAs) (Ceftriaxone, Augmentin, Vancomycin, Metronidazole, Cyclophosphamide, Doxorubicin)	Antibiotics	185	24.27
	Anticancer	12	1.57
	Antiamoebic	53	6.95
	Antimalarial	9	1.18
	Antitubercular	18	2.96
	Antifungal	3	0.39
Drugs Acting on CNS (Olanzapine, Risperidone,Phenytoin, Diclofenac)	Antiepileptic	23	3.01
	Antidepressant	9	1.18
	Antipsychotic	16	2.09
	Antianxiety	23	3.01
	Steroids	2	0.26
	Analgesics (Opioids+ NSAIDS)	83	10.89
	Anaesthetics	2	0.26
Drugs Acting on CVS (Metoprolol, Aspirin,Furosemide)	Antihypertensive	26	3.41
	Diuretic	13	1.70
	Antiarrhythmic	1	0.13
Drugs Acting on GIT (Pantoprazole, ondansetron)	Antiulcer	42	5.51
	Antiemetic	12	1.57
	Antidiarrheal	1	0.13
Drugs Acting on Respiratory System (Chlorpheniramine, Salbutamol, Ambroxol Syrup)	Anti-asthmatic	6	0.78
	Cough relief	4	0.52
	Antihistaminic	54	7.08
Vaccine (Rabies Antiserum)		73	9.58
Others (Eldervit, Ferrous Sulphate, etc)		92	12.07

etc. The other ADRs that were observed included decreased appetite, hypoglycemia, hypokalemia, urinary retention, hypotension, insomnia, hepatitis, cough, neutropenia, steven johnson syndrome, seizure, facial puffiness, headache, fixed drug eruption, diarrhea, shivering, etc.

Rare and serious adverse events (SUSAR) reported was vancomycin induced seizure. The serious ADRs reported were propofol induced excessive myotonic contractions; antitubercular drugs induced hepatitis; sodium valproate, phenytoin, ciprofloxacin and diclopara induced steven johnson syndrome; metronidazole induced severe chest pain; methotrexate induced hepatotoxicity; meropenem and hydrocortisone induced hypokalemia; diclofenac transdermal

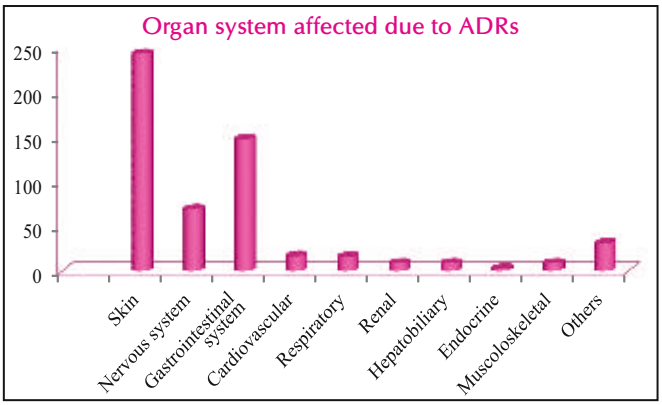

Fig. 3: Organ system affected due to ADRs

Table 3: Suspected serious ADRs & unexpected and serious ADR and implicated drugs with dose and route of administration

Serious ADRs and implicated drugs with dose and route of administration			
S. No.	Drug reaction	Drugs implicated with dose and route of administration	Condition Indicated for
1.	Steven Johnson Syndrome	Tab.Diclofenac/ Paracetamol (50 mg/ 500 mg, PO)	Fever
		Tab.Sodium valporoate (500mg, PO) Tab. Lamotrigine (50 mg, PO)	Epilepsy
		Syrup Phenytoin (6.5 ml, PO)	Epilepsy
		Inj. Ciprofloxacin (100 ml, IV) Inj, Metronidazole (100 ml, IV)	Acute gastro-enteritis
2.	Excessive Myotonic Contractions	Inj. Propofol (2 mg/kg, IV)	To induce general anaesthesia
3.	Hypokalemia	Inj. Meropenem (1g, IV)	
		Inj. Hydrocortisone (100 mg,IV) Inj. Meropenem (1g, IV)	
4.	Hypogly-caemia	Inj. Insulin Mixtard (14 units in morning and 10 units in evening, SC)	Diabetes mellitus
5.	Tachycardia and hypertension	Diclofenac transdermal patch (100 mg, transdermal)	Acute pain
6.	Tachycardia and rash	Inj. Rituximab (200 mg,IV) Inj. Cyclophosphamide (1100 mg,IV) Inj.Doxorubicin (70 mg, IV) Inj. Vincristine (200 mg,IV)	Non Hodgkin Lymphoma
7	Elevated liver enzymes	Inj. Methotrexate (50 mg, IV)	Breast cancer
		5 cases due to Antitubercular drugs	Respiratory Tuberculosis
Unexpected and Serious ADR and implicated drugs with dose and route of administration			
1.	Seizure	Inj. Vancomycin (200 mg,IV)	Pleural fluid effusion

patch induced tachycardia and hypertension; insulin mixtard induced hypoglycaemia and rituximab induced tachycardia (Table 3). These spontaneous ADRs were reported immediately to the department of pharmacology and to the regulatory body.

Out of 540 cases of ADR reported, 348 cases were reported between May, 2016 to April, 2017 and 192 cases were reported between May, 2015 to April, 2016. With the increasing awareness among healthcare professionals regarding ADRs in hospital, 28.88% increase in ADR reporting has been observed in a year (Fig. 4).

Number of cases reported in Causality assessment was done as per WHO scale of causality assessment. 29.00 % reported cases were found to Probably related to adverse events and 71.00% cases were found to be Possibly related to adverse events (. 5).

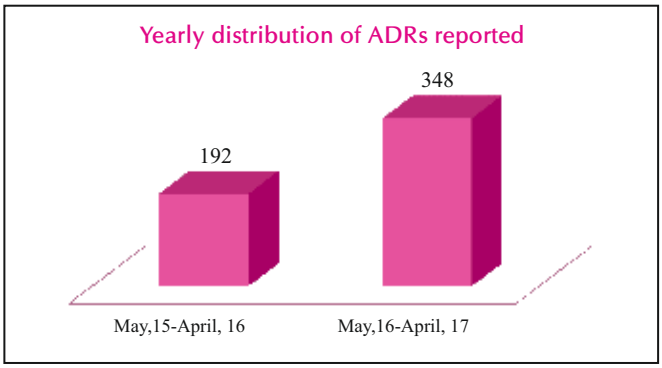

Fig. 4: ADRs cases reported every year

DISCUSSION:

It is the necessity of present era to have constant surveillance, collection and analysis of the adverse drug reactions along with severity in a proper manner for assessing the safety of drugs in a

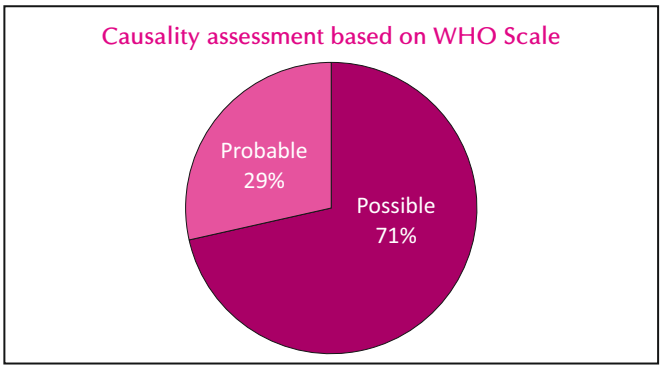

Fig. 5: Causality assessment of suspected ADRs

general population. However, many reactions are not documented and reported voluntarily. So, establishment of pharmacovigilance units (AMCs) in many hospitals has facilitated the reporting to a great extent. The ADR data is useful in future for better health care service within the country and even globally. Withdrawal of drugs like Rofecoxib, Terfenadine and Cerivastatin has been done on the basis of this reporting system.[6]

In the present study the reporting sources were doctors (consultants, senior residents, junior residents, interns), nurses, pharmacists and even patient himself. This study reveals the pattern of adverse drug reactions in outpatients (O.P.D.) and inpatients (I.P.D.) departments in a tertiary care hospital in rural setup with simultaneous impact of Pharmacovigilance activity.

The incidence of suspected ADRs was found to be 1.82%. Overall incidence of ADRs as per study conducted by Tiwari et al. was found to be 12% [7] which is in contrast to another study by Jose et al. which showed that the overall incidence of ADR was only 0.15%.[8] The reason behind such a wide variation was might be adoption of different methodology to collect ADR reports. Passive surveillance of ADR reporting (spontaneous reporting) results in low incidence when compared to active surveillance of ADR reporting.

The demographic details in the present study showed more ADRs in male gender as compared to female gender. This finding is concurrent to that of other studies reported in the literature.[9-11] The reason for such a result may be more number of admissions of male patient.

Maximum number of ADRs were reported in adult population (31-45 years) which is in linearity to that reported by the other studies.[12-14] It is likely due to more frequent visits of patient in outpatient department for their regular check-ups at this age. Also patient at this age are more vulnerable to co-morbid diseases like hypertension, diabetes, asthma and tuberculosis and so are often on multiple drug therapy.

ADR related hospital admissions were observed to be 2.96% as per our study. Various studies in past showed that 5-10% of the hospital admissions was due to ADRs.[15-16] It is a matter of great concern as on an average 8.36% hospital admissions are due to ADR, out of which 50% can be avoidable[17]

Occurrence of ADR is also observed to be affected by Polypharmacy (drug related factor as 79% of ADRs occurred in patients receiving 2 or more drugs. Patients with multiple diseases and on treatment due to infections were found to be taking more than two drugs. Age and polypharmacy was suggested as one of the factors for the risk of dementia as described in a study in Taiwan.[18] Another study showed incidence of acute renal failure due to polypharmacy with day.[19]Polypharmacy tends to increase the economic burden as well increases risk of occurrence of ADRs due to drug-drug interaction.

Almost all ADRs were found to be 'Type A' reaction. Any ADR which is related to dose of drug and to pharmacological action of the drug is termed as 'Type A' (augmented) reaction. Another study carried out by Tiwari et al. and Mjorndal et al gave the consistent finding as above result.[7,20]

Antimicrobials were observed to be the main culprit of ADRs as per our study. This finding is consistent with other studies.[7, 21] Amongst the antimicrobial agents cephalosporins and beta lactam antibiotics were responsible for the highest number of the ADR reports. The present study was similar to study conducted by Arulmani R et al. and Swamy S et al.[2,22]

Most commonly organ system affected by ADR in our study was skin, followed by gastrointestinal system. This result was comparable to many studies done in which skin was the most commonly affected organ due to ADR.[23-25]

Most of the ADRs belonged to “possible” followed by “probable” category when causality assessment of cases reported were done as per WHO-UMC scale for causality assessment. This is in linearity with that reported by other studies.[26,27]

Some of the limitations of our study is that our hospital is a government funded hospital with limited medicine supply. Multi specialty departments like Oncology, AIDS, Cardiology, etc are not available in our hospital. Work load on hospital staff including doctors, nurses, pharmacists, etc is also one of the limitations of our study.

CONCLUSION

The present study was carried out to estimate the incidence of ADRs, factors responsible and major causative agents involved in adverse drug reactions. Antibiotics (Cephalosporins), NSAIDS, etc were identified to precipitate most of the drug reactions. Polypharmacy, age, gender, etc were the reasons for development of adverse drug reactions. The causality assessment revealed that all suspect ADRs fell under possible or probable category. Although sensitization programmes are regularly conducted for healthcare professionals, there is a need for more awareness among healthcare professionals regarding polypharmacy, prescription errors and reporting of ADRs so that these ADRs can be avoided and quality of life of patient can be safeguarded.

CONFLICT OF INTEREST

None.

ACKNOWLEDGEMENTS

Authors would like to acknowledge National Coordination Centre-Pharmacovigilance Programme of India, Indian Pharmacopoeia Commission, Ministry of Health & Family Welfare, Govt. of India for their kind support to conduct this study.

REFERENCES

1. Gupta SK, Post marketing surveillance text book of Pharmacovigilance, (first ed.) Jaypee Brothers Medical Publishers(P) Ltd, 2011:75.
2. Arulmani R, Rajendran SD, Suresh B. Adverse drug reaction monitoring in a secondary care hospital in South India. Br J Clin Pharmacol. 2008;65(2):210-6.
3. Lukshmy M Hettihewa. et al. Casualty Assessment and the Severity of the Adverse Drug Reactions (ADR) actively detected in hospital-in Patients In Tertiary Care Hospital Sri Lanka: Prospective Observational Survey. Asian Journal of Research in Biological and Pharmaceutical Sciences. 2014;2(1):1–10.
4. Alomar MJ. Factors affecting the development of adverse drug reactions. Saudi Pharm J. 2014;22: 83-94.
5. WHO technical report. 2002.
6. Central Drugs Standard Control Organization. Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India.
7. Tiwari P, Anuradha, D'Cruz S and Sachdev A. Adverse Drug Reaction Monitoring in a North Indian Public Teaching Hospital. Journal of Pharmaceutical Care & Health Systems. 2016; 3(2).
8. Jose J, Rao PGM. Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital. Pharmacol Res. 2006;54: 226-233.
9. Sriram S, Ghasemi A, Ramasamy R, Devi M,etal. Prevalence of adverse drug reactions at a private tertiary care hospital in south India, J Res Med Sci. 2011;16(1): 16–25.
10. Gupta R, Sheikh A, Strachan D, Anderson HR. Increasing hospital admissions for systemic allergic disorders in England: analysis of national admissions data. BMJ. 2003;327(7424):1142–3.

11. Lobo MG, Pinheiro SM, Castro JG, Momente VG, Pranchevicius MC. Adverse drug reaction monitoring: support for pharmacovigilance at a tertiary care hospital in Northern Brazil. BMC Pharmacol Toxicol. 2013;14:2050-7.
12. Agouzal M, Benkirane R, Soulaymani A, Benjelloun R, Soulaymani-Bencheikh R, Quyou. Prevalence of Adverse drug events in the consultation centre of Ibn Sina. African Journal of Pharmacy and Pharmacology. 2009; 3:449-5.
13. Sharma H, Aqil M, Imam F, Alam MS, Kapur P, Pillai KK. A pharmacovigilance study in the department of medicine of a university teaching hospital. Pharmacy Practice. 2007; 5: 46-9.
14. Jha N, Bajracharya O, Namgyal T. Prevalence of adverse drug reactions with commonly prescribed drugs in different hospitals of Kathmandu valley. Kathmandu Univ Med J (KUMJ). 2007; 5: 504- 10.
15. Nelson KM, Talbert RM. Drug-related hospital admissions. Pharmacotherapy. 1996;16:701–707.
16. Sekhar SM, Mary AC, Anju PG, Hamsa AN. Study on drug related admissions in a tertiary care hospital in South India. Saudi Pharm. J. 2011;19:273–278.
17. Nivya K, Kiran VSS, Ragoo N, etal. Systemic review on drug related hospital admissions – A pubmed based search, Saudi Pharm J. 2015;23(1): 1–8.
18. Lai SW, Lin CH, Liao F etal. Association between polypharmacy and dementia in older people: a population-based case-control study in Taiwan. Geriatri. Gerontol. Int. 2012;12 (3): 491–498.
19. Chang Y, Huang SK, Tao P, Chien CW. Population-based study on the association between acute renal failure (ARF) and the duration of polypharmacy. BMC Nephrol. 2012;13:96.
20. Mjorndal T, Boman MD, Hagg S, Backstrom M, Wiholm BE, et al. Adverse drug reactions as a cause for admissions to a department of internal medicine. Pharmacoepidemiol Drug Saf. 2002; 11: 65-72.
21. Rehan HS, Chopra D , Sah RK, Mishra R. Adverse Drug Reactions: Trends in a Tertiary Care Hospital. Current Drug Safety.2012;7:384-8.
22. Swamy S, Bhanuprakash, Nadig P, Muralimohan, Shetty M. Profile of Suspect Adverse Drug Reactions in a Teaching Tertiary Care Hospital. J Pharmacol Clin Toxicol. 2012;1(1): 1005.
23. Jha N, Bajracharya O, Namgyal T. Prevalence of adverse drug reactions with commonly prescribed drugs in different hospitals of Kathmandu valley. Kathmandu Univ Med J. 2007; 5: 504- 10.
24. Baniasadi S, Fahimi F, Shalviri G. Developing an Adverse Drug Reaction Reporting System at a Teaching Hospital. Basic Clin Pharmacol Toxicol. 2008; 102(4) :408-11.
25. Jose J, Rao PG. Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital. Pharmacol Res. 2006; 54: 226-33.
26. Ghasemi A, Ramasamy R, Devi M, etal. Prevalence of adverse drug reactions at a private tertiary care hospital in south India. J Res Med Sciv.2011;16(1).
27. Davies EC, Green CF, Mottram DR, Pirmohamed M. Adverse drug reactions in hospital in-patients: a pilot study. J Clin Phar Ther. 2006;31(4):335–41.

ISSN 2320 9208

Emerging drug resistance in Citrobacter species: Study from a North Indian tertiary care hospital

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ABSTRACT

Citrobacter is a significant nosocomial pathogen, which has surfaced in recent years and is resistant to wide range of antibiotics. It causes various infections such asUTI, neonatal sepsis, wound infections, pulmonary infection and meningitis. This study was done to find the prevalence of antimicrobial resistance in Citrobacterspecies in our tertiary care hospital.Between Jan 2016 to Dec 2016, a total of 151Citrobacter species were isolated. All the isolates of Citrobacter species were tested for ESBL and Amp C production. Among the 151 Citrobacter isolates, 87 (57.6%) were ESBL producers. The percentage of Amp C producer among C. koseri was 51.9% (67/129).C. freundii was found to be more resistant to routinely tested antimicrobial agents as compared to C. koseri. Judicious use of antibiotics, infection control practices and antibiotic policy are the keys, which can help curb the upcoming drug resistance.

Keywords : Drug Resistance, Citrobacter Species.

INTRODUCTION

Citrobacter species has been increasingly implicated in various nosocomial infections. The genus has 11 different species of which *Citrobacter koseri*and *Citrobacter freundii*are significant pathogens. These bacteria are commonly found in water, soil, food and in gastrointestinal tract of humans and animals. However, these are known to cause serious infections in immunocompromised patients and neonates. They have been associated with wide spectrum of infections of respiratory tract, wound, urinary tract, bone, peritoneum, meninges and bloodstream.[1,2,3]

There is high degree of resistance to commonly used antimicrobial agents especially β- lactams. There is an increasing incidence of antibiotic resistant to *Citrobacter* isolates being reported from various health care settings throughout the world. *C. koseri* and *C.freundii* show inherent resistance to common antimicrobial agents.[4]

Among the acquired resistance is resistance to other β- lactams through the production of ESBL (Extended Spectrum β-lactamases) and Amp C. Organisms producing ESBLs are important to detect because they cause treatment failure with cephalosporins. The drug of choice for these ESBL positive isolates is β lactam / β lactamase inhibitor and carbapenem.[5] Due to inoculum effect seen during the treatment by β lactam / β lactamase inhibitor, carbapenems are left as last resort for ESBL associated infections. Amp C producing strains continue to be susceptible to advanced spectrum cephalosporin like cefepime and cefpirome, unlike ESBL positive strains.Therefore organisms producing Amp C are treated best with cefepime or with carbapenems.[5,6]

Simultaneous production of both ESBL and Amp C will be difficult to treat, limiting the treatment options and also increase health care cost. In addition most clinical diagnostic laboratories do not attempt to detect these enzymes i.e. ESBL and Amp C. Very limited data is available regarding the susceptibility of *Citrobacter* species to various antimicrobial agents and the prevalence of ESBL and Amp C in these bacteria. Therefore the objective of this study was to find the prevalence of antimicrobial resistance in *Citrobacter* species of our tertiary care hospital.

MATERIALS AND METHODS

Setting and Sampling techniques

Between Jan 2016 to Dec 2016, all consecutive non repeat strains of *Citrobacter* species isolated in the Department of Microbiology, Government Medical College Hospital, Chandigarh, from various clinical samples were evaluated. These samples were – wound swab, drain fluid, tracheal aspirate, and peritoneal fluid, pleural fluid and high vaginal swab.*C.koseri* and *C. freundii* were identified by characteristic growth on blood agar, Mac Conkey agar, Gram staining and various biochemical tests.[7]

Routine antimicrobial susceptibility testing by Kirby Bauer disc diffusion according to CLSI criteria was carried out on Mueller Hinton agar (Hi Media Mumbai). Antibiotics tested were amoxicillin (20μg), ceftazidime (30μg), ceftriaxone (30μg), cefepime (30μg), imipenem (10μg), piperacillin-tazobactam (100/10μg), amikacin (30μg), ciprofloxacin (5μg),tetracycline (30μg), and colistin(300μg) (Hi Media Mumbai).[8]

All the isolates of *Citrobacter* specieswere tested for ESBL and Amp C production. Detection was ESBL was according to CLSI-2016 criteria. Initial screening was done using ceftazidime and ceftriaxone disc and those with zone diameter ≤22mm (for ceftazidime) and ≤ 25mm (for ceftriaxone) was taken to be presumptive ESBL producer. Phenotypic confirmatory test was done using ceftazidime/ ceftazidime- clavulanate along with cefotaxime/ cefotaxime- clavulanate disc diffusion test. If there was ≥ 5mm increase in zone diameter for either antimicrobial agent tested in combination with clavulanic acid versus its zone when tested alone, then ESBL production was confirmed.[8]

All the strains of *C. koseri* were screenedfor Amp C using cefoxitin disc and zone diameter of ≤ 18 mm for cefoxitin was taken as presumptively positive for Amp C. The confirmatory test for Amp C β- lactamases production was done by Black Amp C disk test.[9]

RESULTS

During the study period, total of 151 strains of *Citrobacter* species were isolated from various samples. Among them *C. koseri* was more commonly isolated (129 strains) as compared to *C. freundii* (22 strains). High level of drug resistance was seen with almost all antimicrobial agents. Additionally C. *freundii* was more drug resistant than *C. koseri.*

Among the β- lactams, high level of resistance was seen for ceftriaxone (52.3%), ceftazidime (56.9%) and amoxicillin (87.3%). (Table-1) Among the Citrobacter strains resistance to amikacin was 67.5%, ciprofloxacin (73.4%), tetracycline (56.2%). The antimicrobial agents which showed less resistance to Citrobacter species were- cefepime (49.6%), imipenem (41%) and 26.4% resistance topiperacillin/tazobactum. None of the Citrobacter strains showed resistance to colistin.

Among the 151 *Citrobacter* isolates, 87 (57.6%) were ESBL producers. The production of ESBL was seen in 90% of *C. freundii* strains (20/22) and in 51.9% of *C. koseri* (67/129). The percentage of Amp C producer among *C. koseri* was 51.9% (67/129).

Table 1- Antibiotics resistance patternof Citrobacter isolates

Antimicrobial agent	Total *isolates (%)*	C. *koseri (%)*	C. *freundii (%)*
Amoxicillin	132/151 (87.3)	110/129(85.2)	22/22(100)
Ceftazidime	86/151(56.9)	66/129(51.1)	20/22(90.9)
ceftriaxone	80/151(52.3)	63/129(48.8)	17/22(77.2)
Cefepime	75/151(49.6)	57/129(44.1)	18/22(81.7)
Imipenem	62/151(41)	44/129(34.1)	18/22(81.7)
Piperacillin/ tazobactum	40/151(26.4)	25/129(19.3)	15/22(68.1)
Amikacin	102/151(67.5)	85/129(65.8)	17/22(77.1)
Ciprofloxacin	111/151(73.4)	92/129(71.3)	19/22(86.3)
Tetracycline	85/151(56.2)	70/129(54.2)	15/22(68.1)
Colistin	0/151(0)	0/129(0)	0/22(0)

DISCUSSION

Members belonging to genera *Citrobacter* species tend to cause serious nosocomial infections and they are increasingly being resistant to routinely used antimicrobial agents.

In our study *C. koseri* (85.4%) was more commonly isolated than *C. freundii* (14.6%). A prospective study by Mohanty S et al showed similar results i.e. the prevalence of *C. koseri* (90.2%) was more than *C. freundii* (9.8%). In Contrast Mohan S et al in another study from North India found the most common isolate in their hospital was *C. freundii* (49%) followed by *C. koseri* (28%). This highlights the importance of studying the epidemiology of *Citrobacter* infections, which varies from one health care setting to another.[10]

Resistance of *Citrobacter* species to different antimicrobial agents varied in this study. High degree of resistance was seen to amoxicillin (87.3%), ceftazidime (56.9%), ceftriaxone (52.3%), amikacin (67.5%), ciprofloxacin (73.4%)and tetracycline (56.2%). Whereas intermediate resistance was seen to imipenem (41%) and cefepime (49.6%). Among the antimicrobial agent piperacillin/ tazobactam was found to be an effective antimicrobial agent with resistance of only 26.4%. No isolates was found to be resistant to colistin. Thus, only colistin and piperacillin/tazobactum showed good activity against *Citrobacter* species. Whereas imipenem, cefepime and tetracycline showed moderate efficacy. This high level of antimicrobial resistance in our tertiary care hospital isolates could be because of selective pressure exerted on the microbes because of widespread use of broad spectrum antibiotics.

Mohanty S et al has shown similar results with ceftazidime (85.3%), cefotaxime (86.3%), piperacillin (80.5%) and ciprofloxacin (81.9%) having high resistance percentage.[10] Maraki S et al studied the resistance pattern of *Citrobacter* species and found colistin, carbapenem and β lactam/ β lactamase inhibitorcombinationsto most active antibiotics against these. This highlights the need to know the antibiogram pattern of one's own isolate so that correct empirical therapy can be started.[11]

On comparing the antibiogram of the two species of *Citrobacter*, *C. freundii* was found to be more resistant to routinely tested antimicrobial agents as compared to *C. koseri*. The resistance percentage of *C.freundii* to cefepime, imipenem, piperacillin/tazobactam,amikacin,ciprofloxacin and tetracycline was more than *C. freundii.*Maraki S et al studied the resistance phenotypes of Citrobacter isolates and found *C. freundii* more resistant than *C. koseri.C. freundii* is inherently resistant to amoxicillin, ampicillin, amoxicillin- clavulanate, ampicillin/sulbactum, first and second cephalosporins and cephamycins.*C.koseri* is inherently resistant to ampicillin, piperacillin and ticarcillin.[11]

The percentage of *Citrobacter* isolates producing ESBLs in our study is 57.6% (87/151). Nearly 90% of C. *freundii* strains and 51.9% of *C. koseri* were ESBL producers. Mohan S et al found similar results in a study from a tertiary care hospital of North India. Among the *Citrobacter* isolates from their set up approximately 54% were ESBL producers.[10]

In contrast the percentage of Amp C producer among *C. koseri* was 51.9% (67/129). Maraki S et al found 10.9% of Citrobacter isolates were Amp C producers.[11] Detection of Amp C in*C. koseri* is taken as plasmid mediated because they lack chromosomal Amp C. Additionally it is unnecessary to detect Amp C in *C. freundii* because they will produce inducible chromosomal Amp C. Very few studies have tried to find the prevalence of ESBL and Amp C in Citrobacter species. The detection of such hidden resistance is essential, to avoid spread of this multidrug resistant pathogen as well as restrict use of ineffective antibiotics, for better patient care.

Clinical Microbiology laboratories should look for the production of multiple beta lactamases in bacterial isolates. This would result in superior patient outcome in terms of avoiding inappropriate therapy and a decrease in antibiotic resistance through better infection control. Carbapenem therapy is usually successful in treating infections associated with Amp C-producing bacteria.

REFERENCES

1. Doran TI. The role of Citrobacter in clinical disease of

children: review. Clin Infect Dis 1999; 28:384-94.

2. Lipsky BA, Hook III EW, Smith AA, Plorde JJ. Citrobacter infections in humans: experience at the Seattle Veterans Administration Medical Centre and a review of literature. Rev Infect Dis 1980; 2:740-60.
3. Shih CC, Chen YC, Cahng SC, Luh KT, JHsieh WC. Bacteremia due to Citrobacter species: significance of primary intra-abdominal infection. Clin Infect Dis 1996; 23:543-9.
4. Orrett FA, Shurland SM. Prevalence of bacterial pathogens and susceptibility patterns from clinical sources in Trinidad. West Indian Med J. 2000; 49:205-9.
5. Kenneth S.T. (2010): Extended–Spectrum - β–Lactamases, Amp –C and Carbapenemase Issues. J Clin Microbiol, 48, 1019-1025.
6. Jacoby G A. (2009): Amp C β –Lactamases. Clin Micro Review, 22,161-182.
7. Collee JG, Miles RS, Watt B. Tests for the identification of bacteria. In: Collee JG, Fraser AG, Marmion BP, Simmons A (eds), Mackie & MacCartney practical medical microbiology, 14th ed., Churchill Livingstone, London 1996:151-79.
8. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility; twenty-fifth informational supplement. CLSI document M100-S25 Clinical and laboratory standards institute, Wayne, Pennsylvania, USA.2016 35:3
9. Black JA, Moland ES, Thomson KS, (2005): Amp C disk test for detection of plasmid-mediated Amp C- β lactamases in *Enterobacteriaceae* lacking chromosomal Amp C- β lactamases. J Clin Microbiol, 43, 3110-3113.
10. Mohanty S, Singhal R, Soos S, Dhawan B , Kapil A, Das BK. Citrobacter infections in a tertiary care hospital in Northern India. J of Infection 2007:54:58-64.
11. Maraki S, Vardakas KZ, Mavromanolaki VE, Kyriakidou M, Spais G, Kofteridis DP, Samonis G, Falagas ME.*In vitro* susceptibility and resistance phenotypes in contemporary *Citrobacter* isolates in a University Hospital in Crete, Greece. J infect Dis 2017; 49:532-9.

ISSN 2320 9208

Coagulation profile pre and post hemodialysis in chronic kidney failure

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ABSTRACT

Chronic kidney disease is a common ailment afflicting the mankind. Patients with end stage renal disease have abnormal haemostasis and they face the challenge of being prone both to thrombosis as well as bleeding. Haemodialysis is done to correct uremic bleeding. But situation may worsen in the immediate post dialysis period for various reasons. One reason being use of heparin during dialysis and secondly because of fall in platelet count after dialysis. In the present study fifty patients with end stage renal disease were evaluated in the post dialysis period. It was observed that activated partial thromboplastin time was significantly prolonged and there was a significant fall in platelet count. This knowledge is important if any invasive procedure is planned in a patient with chronic kidney disease requiring haemodialysis.

Keywords : Chronic Kidney Failure, Coagulation Profile.

INTRODUCTION

The National Kidney Foundation in India has found that kidney disease rank 3rd most common life threatening disease, after cancer and heart disease. It has stated that around 200,00 persons develop terminal kidney failure every year along with millions of other patients continuing to suffer from lesser forms of kidney disease[1]. Patients with end stage renal disease(ESRD)/uremia face the challenge of being prone both to thrombosis[2-5] as well as bleeding[6-9] complications.They have abnormal hemostasis with altered bleeding time, decreased activity of platelet factor 3,[10] abnormal platelet aggregation, adhesiveness,[11] renal loss of anticoagulation factor. There is paucity of studies available regarding prevention and treatment of uremic bleeding. Pathophysiology of the uremic bleeding remains elusive and appears to be multifactorial. The bleeding tendency is likely to improve after dialysis. But there is contradictions in the studies available i.e some showing improvement in platelet function while others showing worsening. Use of heparin during hemodialysis[12] may further aggravate the situation. Some postulate that removal of certain factor that is required for coagulation is also removed during dialysis.. With the improvement in health facility increasing number of people are surviving longer. They may also require surgical intervention for various comorbid indications. Dialysis is often considered to prevent uremic bleeding and it is done prior to surgery to improve the patients fitness as well. But with hemodialysis there is a risk of altered coagulation profile. Awareness about altered bleeding profile in the immediate post-dialysis period will make the clinician better prepared to manage the patients in such situations. This study was carried out to see the alteration of coagulation profile in the post dialysis period, if any, in patients in patients with ESRD undergoing hemodialysis.

MATERIAL AND METHOD

The study was conducted in the Department of Medicine of a tertiary care hospital. Fifty patients admitted in emergency (ED) or inpatient department (IPD) with diagnosis of end stage renal disease requiring hemodialysis were recruited. All subjects male and female aged above 16 yrs were included. In case of multiple admissions, subjects were considered on their first admission only. Patients who were on peritoneal dialysis were excluded from the study. Patients having known history of any bleeding diathesis or on anticoagulant therapy were also excluded. Approval was obtained from Institutional Ethics Committee before enrolling any patient. Informed consent in written was taken from each participant. Apart from getting demographic details, detailed history, symptoms, physical examination and detailed investigation were done.

Pre- hemodialysis samples were collected on presentation and post-hemodialysis blood samples were collected within 6hrs after hemodialysis session. Total platelet count, activated partial thromboplastin time (aPTT), prothrombin time(PT) and international normalised ratio(INR) were done pre and post hemodialysis. Platelet count was done by using SYSMEX XP 100 cell counter by taking patients sample and APTT and PT/INR by using automated coagulometer analyser using Liquicelin E reagent and thromboplastin reagent respectively.

RESULTS

In our study ESRD patients were of the age group between 20-72 yrs. Out of fifty patients twenty seven were male and twenty three were female patients. Their creatinine clearance was calculated taking their weight and gender into account by using Cockroft-Gault formula.

In our study the mean platelet count pre- hemodialysis is (2.0 lakh) and post- hemodialysis was (1.7 lakh) with a p- value <.001 which is significant. There was fall of platelet count in all the patients post- hemodialysis the range was (10,000 – 1.1 lac) with the mean fall of platelet count was 30,000.

Table 1 : Basic characteristics of the patients enrolled

Parameters		Statistics
Age(years)	Range	20 – 72
	Mean ± SD	49.7 ± 13.1
Gender	Male : Female	27: 23
Weight(Kg.)	Range	35 – 75
	Mean ± SD	56.4 ± 9.1
Creatnine clearance	Range	2.15 – 11.5
	Mean ± SD	7.3 ± 3.0
Platelet count(Lakhs)	Range	0.9 – 3.8
	Mean ± SD	2.0 ± 0.8
APTT(sec.)	Range	24.0 – 47.0
	Mean ± SD	33.7 ± 5.7
PT(sec.)	Range	10.0 – 20.0
	Mean ± SD	13.9 ± 2.1
INR	Range	1.0 – 2.9
	Mean ± SD	1.3 ± 0.3

Table 2 :Pre and Post- Hemodialysis parameters

	Pre-Hemodialysis (Mean)	Post-Hemodialysis (Mean)	p- value
Platelet Count (Lakhs)	2.0+/-0.8	1.7+/-0.7	<.001
APTT (Sec)	33.7+/-5.7	40.7+/-7.2	<.001
PT (Sec)	13.9+/-2.1	17.9+/-3.2	<.001

In our study the mean APTT pre- hemodialysis is 33.7(sec) and post- hemodialysis is 40.4 (sec) which showed p- value <.001 which is significant, the mean pre – hemodialysis PT(sec) is (13.9) sec and mean post- hemodialysis is (17.9) sec and the p-value being <.001 .

DISCUSSION & SUMMARY

Chronic kidney disease is term used for large spectrum of different pathophysiological mechanism which ultimately lead to decline in renal functions, depicted as gradual fall in glomerular filtration rate (GFR).Kidneys are responsible for performing various diverse body functions. Kidneys excrete nitrogenous waste products like urea and uric acid from the body, helps in protein and vitamin – D metabolism , produces hormones like erythropoietin , renin and prostaglandins. As the disease progresses normal homestasis along with functions of kidney start to decline. The most common causes of CKD are diabetes mellitus, glomerulonephritis, hypertension, autosomal dominant polycystic kidney disease and tubulointerstitial nephropathy.[13]

Patients with CKD ultimately require continuous renal replacement therapy. Renal dialysis refers to diffusion of small molecules down their concentration gradient across a semipermeable membrane. According to their concentration gradients small molecules like urea, potassium, phosphorus diffuse down from blood into the dialysate solution. Where as molecules like calcium and bicarbonate move from dialysate solution into blood according to their concentration gradient. Hemodialysis is one of the most commonly used renal replacement therapy worldwide it not only improves uremic symptoms of the patients but also correct electrolyte abnormalities, fluid overload state ultimately improving the quality of life and lowering the morbidity and mortality[14].

Bleeding due to uremia is a well known complication of chronic kidney failure. Various mechanisms like dysfunctional platelet, dysfunctional von Willebrand factor have been suggested to explain this bleeding tendency. One of the reason put forward is severe anaemia[15]. In patients with normal haemoglobin, because of the laminar flow of blood red blood cells(RBC) are more near the center of the vessel and platelets are displaced towards the

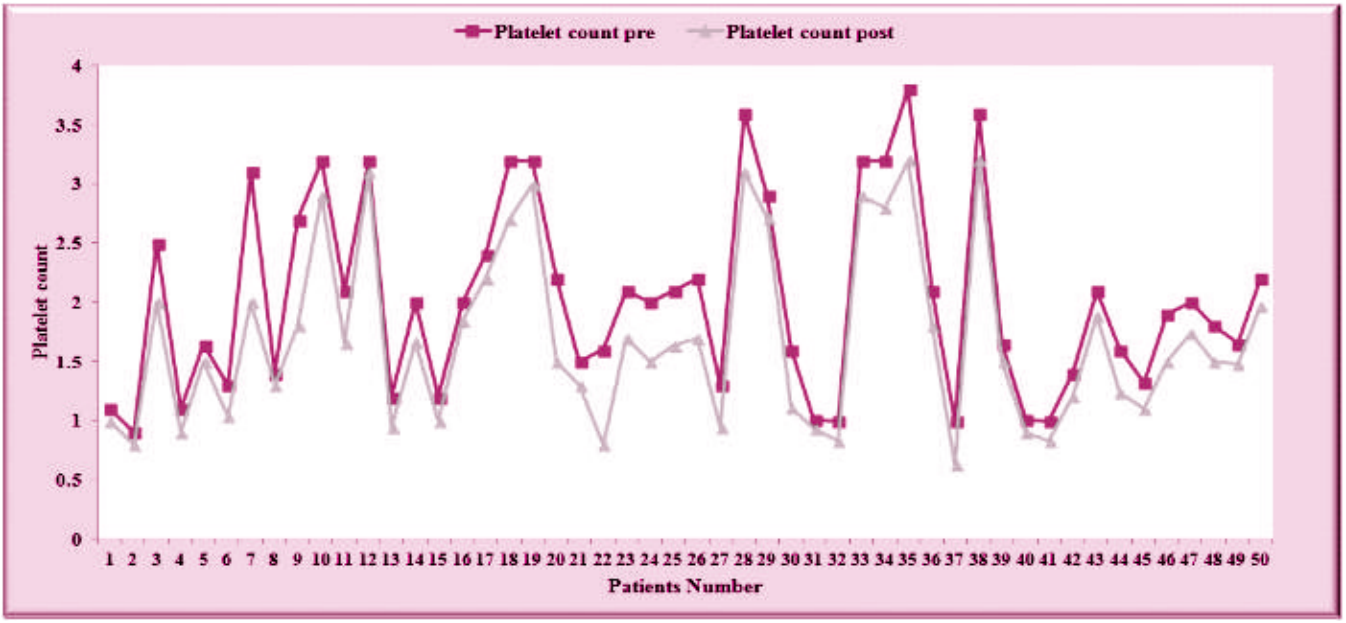

Figure 1: Pre post-hemodialysis platelet count among patients

endothelium of the vessel. In those who have low haemoglobin and RBC count, platelets move more towards the center and away from endothelium. In case of damage to the vessel platelets donot come in contact so efficiently[16-17]. The management of uremic bleeding involves dialysis, erythropoetin, tranexamic acid and cryoprecipitate or desmopressin if reqired. Erythropoetin not only improves anaemia and circulating red cells, it also appear to improve platelet function.

Present study shows a mean fall of platelet count of 30,000/cmm which is significant and is comparable to other studies ie Malik Zeb Khan et al[18] showing fall of(21,000), Abdullah Khader et al[19]. This decrease in platelet count is mainly because of exposure of blood in the extracorporeal circuit where platelets get activated and subsequently degraded and fragmented. Some of these platelets are also retained in the hemodialysis filters further causing fall in platelet count after hemodialysis. Further there is a possibility that thrombocytopenia may be due to heparin being used during hemodialysis. The incidence of heparin induced thrombocytopenia is less than 1% in those who receive therapeutic doses of heparin. It appears that heparin per se may not cause significant fall in platelet count but in such situations small decline may also be significant.

The study results showed the prolongation of APTT ,PT and INR of the patients post hemodialysis. The mean pre and post-hemodialysis APTT were 33.7 sec and 40.4sec respectively. This is comparable with other studies showing increase in mean APTT levels after hemodialysis. Malik Zeb Khan et al[18] study showed mean pre APTT (34.4sec) and post APTT (40.7sec), Abdullah Khader et all[19] study showed mean pre APTT (33.6sec) and post (64.6 sec) and Ali MSM et al[20] study showed mean pre APTT (30.2 sec) and post APTT (69.8sec).This increase in APTT may be due anticoagulant heparin being used during dialysis. There also occurs inactivation of proteinase involved in clotting[21].The mean values of PT and INR in study were mean pre PT/INR (13.9 sec/1.3)and post PT/INR (17.9 sec/1.5) which is comparable to Malik Zeb Khan et al[18] study which also showed significant increase in mean pre PT/INR (14.7sec/1.2) and post PT/INR (18.7/1.6) , Abdullah Khader et al[19] study showing mean pre PT/INR (12.9 sec/ 1.04) and post PT/INR (23.1 sec/1.97) values. This increase is due underlying reduced activity of various coagulation factor namely VII,IX,X,XII[22-23] along with regular usage of heparin.

There was a significant fall in platelet count post- hemodialysis. There are studies suggesting that heparin use during hemodialysis further leads to decrease platelet count but in our study we did not further evaluate for the same. Most of the patients showed increased post–hemodialysis APTT(in 92%) and PT/INR(in 90%). The present study suggests that there is alteration in coagulation parameters in patients undergoing hemodialysis. The clinician should be aware of the possibility so that they can be better prepared to manage such patients. This knowledge is more significant if any invasive investigational procedure or surgery is being planned in the immediate post hemodialysis period. Small sample size is a limitation of the study, further study with larger sample size is required to confirm the above observation.

REFERENCES

1. Natinal kidney foundation: K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease. Am J Kidney Dis. 2006;47(Suppl3):S33-S53.
2. Windus DW, Santoro S, Royal HD. The effects of hemodialysis on platelet deposition in prosthetic graft fistulas. Am J Kidney Dis 1995;26:614–21.
3. Porile JL, Richter M. Preservation of vascular access. J Am Soc Nephrol 1993;4:997–1003.
4. Goldwasser P, Michel MA, Collier J, et al. Prealbumin and lipoprotein (a) in hemodialysis: relationship with patient and vascular access survival. Am J Kidney Dis 1993;22:215–25.
5. Goldwasser P, Avram MM, Collier J, Michel MA, Gusik SA, Mittman N. Correlates of vascular access occlusion in hemodialysis. Am J Kidney Dis 1994;24:785–94
6. Santoro SA and Cowan JF (1982)Adsorption of von Willebrand factor by fibrillar collagen-implications concerning the adhesion of platelets to collagen.*Coll relat res* 2:31-43
7. Engvall E *et al.*(1978) Affinity of fibronectin to collagen of different genetic types and to fibrinogen.J Exp Med 147:1584-1595.
8. Mumby SM *et al*. (1984) interaction of thrombospondin with extracellular matrix proteins:selective binding to type V collagen.J Cell Biol 98:646-652.
9. Hartwig JH *ET AL. (1999)* The elegant platelet:signals controlling actin assembly.Thromb Haemost 82:392_398.
10. DeykinD. Uremic bleeding. Kidney Int 1983:24;698-705.
11. Escolar G, Cases A, Bastida E, *et al*. Uremic patelets have a functional defectaffectingthe interaction of von Willibrand factor with glycoprotein IIb-IIIa. Blood 1990:76;1336-40.
12. Salzman EW, Rosemberg RD, Smith MH, Lindon JN, FAVREAU L; Effect of heparin and heparin fractions on platelet aggregation. J Clin Invest 65;64,1980.
13. Kasper, Fauci, Hauser, Longo, Jameson, Loscalzo;Harrisons Internal Medicine19th edition. Chronic kidney Disease; chapter 335.
14. Caglar S: Coagulation, fibrinolysis inhibitors in hemodialysis patients;contribution of arteriovenous fistula. Nephrology. Dial. Transplant, 1996:11(7);1299-305.
15. Goldsmith HL(1971)Red cell motions and wall interactions in tube flow.Fed Prcc30:1578-1590.
16. CarvalhoAC. Acquirewd platelet dysfunction in patients with uremia.Hematol Oncol Clin North Am 1990:4;129-43.
17. Vigano G, Remuzzi G. Prevention and therapeutic management of bleeding in dialysis patients. In; Nissenson AR, Fine RN, editors..Dialysis therapy. 2nd ed. Philadelphia; Hanley and Belfus; 1993;124-8 .
18. Malik Zeb Khan , Sultan Zafar Akhtar, Shagufta Nasir Pervez, Muhammad Shoaib Khan, Asif Malik: KJMS January-June, 2014, Vol.7,no1.
19. Abdullah Khader Alghythan and Abbas H.Alsaeed; Scientific Research and Essay Vol 7(4),pp. 490-497,2012.
20. Abbas Babiker, Leena Babiker Merghani, Fadl Aljabbar Al Taib Ali, Mekki Hamad Abdulmajeed: Saudi J kidney Dis Transpl 2008;19(2):274-279.
21. Wardle EN(2002). Anticoagulation for hemodialysis and hemofiltration. Saudi J Kidney Dis Transpl., 13(1);40-4.

22. Naumnik B, Borawski J, Pawalak K, Mysliwiec M (2002). Effect of hemodialysis on plasma levels of vascular endothelial markers. Clin.Appl,Thromb.Hemost,8(3):245-250.

23. Gross R, Neith H, Mammen E. Blutungsbereitschaftund Gerinnungsstoerungen bei Uraemia. Klin Wschr. 1958:36;107-10.

ISSN 2320 9208

Refractive Errors among School Going Children of Ambala District of Northen India

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ABSTRACT

Around 153 million people over 5 years of age are visually impaired due to URE for the age group 5–15 years. Out of these 12.8 million are visually impaired from uncorrected or inadequately corrected refractive errors (RE), with a prevalence of 0.96%. Diagnosis and treatment of RE is one of the easiest way to reduce the impaired vision or even blindness.our study aimed to determine the Prevalence of Refractive Errors among the school children of 06–12 year age group and its various sociodemographic correlates and assess their compliance for wearing spectacle among those who needed.The study was school based prospective study conducted in government schools of Ambala District (Haryana, India) we found prevalence of refractive errors (RE) 8.9% in school children. Maximum prevalence was seen in the youngest age group of 6–8 years (11.1%). RE were more common in girls than boys and among students studying in urban area schools though results were not significant. Students with positive family history of RE had significantly higher prevalence of RE ($p<0.001$).Higher prevalence of RE in younger age group demands early screening of children for timely intervention. Children, teachers and parents must be educated to identify early signs of refractive errors and motivated for seeking treatment if needed.

Keywords: Refractive errors, compliance

INTRODUCTION

Globally uncorrected refractive error (URE) is the most common cause of vision impairment and is the second most common cause of blindness after trachoma. Visual impairment from URE has shown to cause early and delayed implications during childhood and adulthood which include loss of either educational or vocational capabilities or further leading to economic loss to individuals, families, communities and country. Thus uncorrected refractive errors during childhood are one of the key issues in the global initiative for the elimination of avoidable blindness. The Refractive Error Study in Children (RSEC) has been conducted under this initiative to estimate the problem of refractive errors in children which has highlighted the fact that for school children, poor vision can affect school performance and can lead to long term negative impact on future of children[1].

School going children years is considered as the wonder years in the person's life. School going years is also the formative year, which determines one's physical, intellectual and behavioral development. Any problem in the vision during the formative years can affect the intellectual development, maturity and performance of a person in future life Blindness is one of the main social problem in India. India alone has 12 million blind people[2]. Worldwide estimation has indicated that more than 1.5 million children are blind and developing countries are having 2/3rd of these affected children. India alone has 2,70,000 blind children accounting for more than 1/4th 0f the morbidity burden.[3]

RE is one of the most common causes of visual impairment around the world and the second leading cause of treatable blindness. Inclusion of URE will increase estimates of the worldwide prevalence of visual impairment by 61%[4]. It is estimated that 2.3 billion people worldwide have refractive errors, our of whom 1.8 billion have access to adequate eye examination and affordable corrections leaving behind 500 million people, mostly in developing countries with uncorrected error causing either blindness or impaired vision[5].

About 13% of Indian population is in the age group of 7-15 years and about 20% of population develop refractive error by the age of 16 years[7]. 6-7% of children in the age group of 10-15 years in India have refractive errors affecting their learning at school[6].

In view, of the importance of detecting eye defects in school children, this study is undertaken to know the prevalence of RE among school children of selected age group and also to assess their compliance after intervention.

AIMS AND OBJECTIVES

1. To determine the Prevalence of Refractive Errors among the school children of 06-12 year age group and its various sociodemographic corelates
2. To assess their compliance for wearing spectacle among those who needed.

MATERIAL AND METHODS

The study was conducted in Government schools of Ambala District from June2014 to May 2015

Study population: School children of age 06 - 12 years of selected urban and rural schools in the field practice area of Maharishi

Markendeshwar Institute of Medical Sciences and Research, Mullana, Ambala were included in the study. Those who were not willing to participate or children having impaired vision due to other reasons were excluded.

Study design:

❖ Cross sectional study to know the prevalence of refractive errors.

❖ Study was carried as prospective among those who were found to have refractive error and were prescribed glasses to know compliance for spectacle wearing.

Sample size: The Sample size was calculated by using expression $4pq/L^2$ where prevalence was taken as 10%[7] and relative error of 20% $4pq/L^2$ and taking 10% non response, total of 1000 students were included in the study.

Sampling Technique: - Considering the enrolment in rural and urban areas of 6435 and 4178 respectively. Taking an average of 100 students to be included from each school, total 10 schools were selected. Further on the basis of enrolment of 6425 in rural and 4178 in urban area, it was decided to include 06 schools in rural and 04 schools in urban area. Separate lists of schools for rural and urban area were prepared and required number of schools in both areas were selected randomly by lottery method. Permission from School Principals was sought. If any school didn't give permission, other school was selected from the list by lottery method.

Study Tools: Predesigned semi-structured Proforma was used which was pretested by Pilot study. Proforma was divided into three Sections : (a)Sociodemographic details, (b)Visual acuity testing, (c) compliance regarding wearing of spectacles. Details of various correlates like age, sex, family history of refractive errors was taken. History of already diagnosed RE was also noted if present. Then ophthalmological examination was done to assess the visual acuity and if RE was present, whether it was correctible or not (pin hole test was conducted to see whether the error was correctible or not). Due training was provided to the investigator before carrying out ophthalmic examination of the students. Further initial survey was carried out under the supervision of skilled optometrist to ensure investigator's competence to detect refractive errors. After three months follow up examination of the students with RE was done to assess their compliance for spectacle wearing.

Data Analysis: The data was entered in Microsoft XL spreadsheet and analysis was done using the Statistical Package for Social Sciences (SPSS version 20). Distribution of categorical variables was expressed as percentage and for quantitative variable like age, mean and SD were calculated. Chi-square test has been used to find the association on categorical scale between two or more groups. P value of less than .05 was considered significant at 95% confidence interval.

Ethics Considerations: The study was approved by Institutional Ethics Committee

RESULTS

Maximum No. of students (39.2%) were in the age group of 11 to 12 years, followed by students in the age group of 09-10 years (38.3%) and least No. of students (22.5%) were in the age group of 06-08 years. Majority of students i.e. 58.6% were boys and rest 41.4% were girls.

Prevalence of RE was found to be 8.9% (89 out of 1000), of whom 72 (80.9%) new cases of refractive error were found and 17 (19.1%) children were already wearing spectacles.

Prevalence of refractive error was maximum (11.1%) in age group of 6-8 year olds and least No. of students were 7.3% in 09-10 years age. Hence the association of age with prevalence of refractive errors showed no specific trend.

Prevalence of refractive error was higher in girls i.e. 10.87% as compared to Boys where it was 9.05%. The association was statistically insignificant (p=0.066). Further no specific reason could be cited for this sex preponderance.

Prevalence of refractive error was more in the Urban Areas (9.97%) compared to Rural Areas (8.23%). However, results were not statistically significant (p=0.639).

There was positive association of presence of refractive error with positive family history for refractive errors. It was seen that higher no. of students (65.79%) students with positive family history had refractive error as compared to students with no such positive family history (4.22%). This association was found to be statistically highly significant (p<.001). (Table-1)

Table 1: Sociodemographic correlates of refractive errors

Variable	Category	Refractive errors		Total	p-value
		Present	Absent		
AGE	6–8 Yrs	25 (11.1)	200 (88.9)	225 (100)	0.274
	9–10 Yrs	28 (7.3)	355 (92.7)	383 (100)	
	11–12 Yrs	36 (9.2)	356 (90.8)	392 (100)	
	Total	89 (8.9)	911 (91.1)	1000 (100)	
GENDER	Boys	44 (90.5)	542 (90.95)	586 (100)	0.066
	Girls	45 (10.87)	369 (89.13)	414 (100)	
	Total	89 (8.9)	911 (91.1)	1000 (100)	
REGION	Rural	51 (8.23)	568 (91.77)	619 (100)	0.639
	Urban	38 (9.97)	343 (90.03)	381 (100)	
	Total	89 (8.9)	911 (91.1)	1000 (100)	
FAMILY HISTORY	Present	50 (65.79)	26 (34.21)	76 (100)	<0.001
	Absent	39 (4.22)	889 (95.78)	924 (100)	
	Total	89 (8.9)	911 (91.1)	1000 (100)	

Figures in brackets indicate percentages

Among students who had refractive errors, it was observed that in 91.01% cases, error could be corrected by providing lenses of adequate power. However 8 students (8.99%) didn't show complete improvement even on prescribing glasses (Figure 1).

Reasons given by the children for non compliance with spectacle wearing at the time of follow up were that they didn't feel

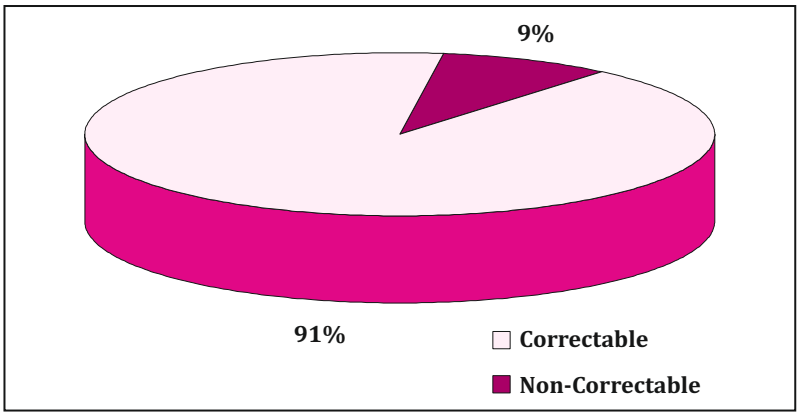

Figure 1:- Distribution of students with Correctable and Non Correctable refractive error

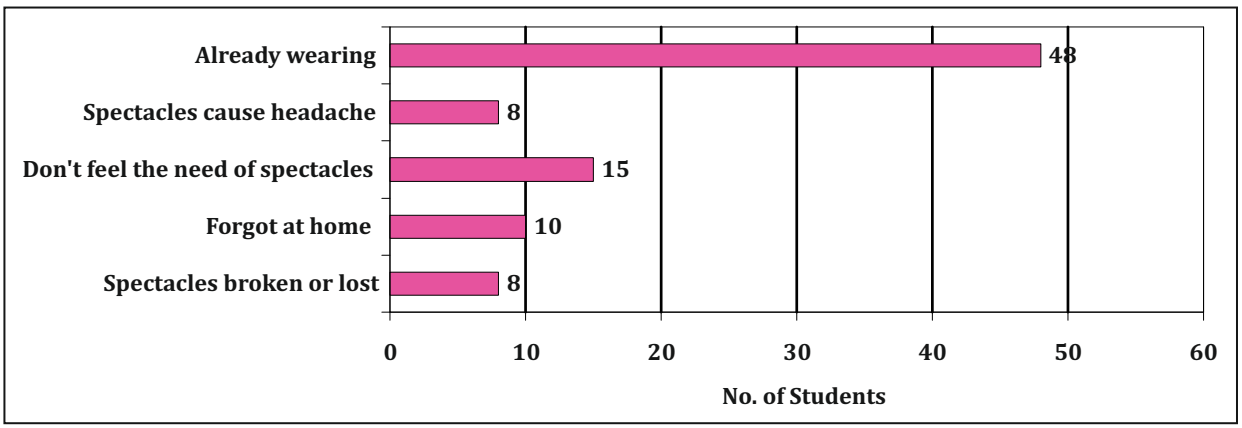

Figure 2:- Reasons for not wearing spectacles

spectacles are required. Other students had lost their spectacles or they forgot their spectacles at home. Some found that spectacles cause headache (Figure 2)

DISCUSSION

The present study revealed prevalence of refractive error as 8.9%. Seema et al found a high Prevalence (13.65%) refractive error in children of 06 – 15 years of age group. They conducted a study on 1265 students and found 172 children have defective vision[8,9].

Rahman et al confirmed 8.8% of the studied population of age 10-15 years attending the Government schools of Dibrugarh, Assam, had refractive error[10].

Study by Yingyong on refractive error survey in Primary School children (06-12 years) in 2 provinces Bangkok and Nakhonpathon revealed that the prevalence of refractive error was 12.7% in Bangkok and 5.7% in Nakhornpatho[11].

The prevalence of refractive errors was maximum in 06-08 years of age group i.e. 11.1% but there was no specific trend followed as the age increased. However some studies like Matta et al[12] found that with increase in age there was increase in prevalence of refractive errors.

The Refractive error were more prevalent in girls (10.87%) as compared to boys (9.05%) however this difference was statistically not significant. Female preponderance seen in various studies conducted by Dulani et al in Jaipur, Sewunet et al in Ethopia and Wadaani et al, though the percentage of prevalence varies from one study to another[13,14,15].However, In a study conducted by Niroula et al, in Nepal, and Rahman et al there is male preponderance of the refractive errors[16,10].

The relationship between the family History of Refractive error and the Refractive error in the children was found to be statistically significant. In this study, 65.79% of the children with refractive error had positive family History.

This is similar to the results obtained in a study conducted on Female primary school children in Saudi Arabia[1].Ali et al conducted a study on the prevalence of uncorrected refractive error among school children in Lahore and found that 61 out of 107 children with refractive errors have positive family History of Refractive error indicating a strong relationship between Refractive error and hereditary or family History[5].

Saw et al studied the factors contributing to the Epidemiology of Myopia on School Children in Singapore and found that most of the Myopics had a positive family History[17]

Among students who had refractive errors, it was observed that in 91.01% cases, error could be corrected by providing lenses of adequate power. However 8 students (8.99%) didn't show complete improvement even on prescribing glasses. The proportion of in correctible errors was higher when compared to study conducted by He et al who found that those 97.91% errors could be corrected[18].

After examining the school children spectacles were prescribed to all 89 students having Refractive error. On follow-up visit after 3 months, it was found that only 48 students were wearing

spectacles while the rest 41 students did not wear the spectacles even after the prescription.The results of the spectacle wear compliance after 3 months was found to be approximately similar to the results obtained by Pavithra et al[19].

In a study conducted by Dulani et al (2014), it was found that 33.33% of the children were not wearing spectacles at the time of visit even though they were advised to wear them[13].

Similarly in a study by Kumar et al (2014), 66.67% of the children were not wearing spectacles at the time of their visit for follow up[20].

Kandekar et al found while studying on the magnitude and determinants of Refractive error in Onami school children that 71.6% school children wore spectacle on the follow up visit[21].

As far as the reasons for the non-compliance with spectacle wear was concerned, leaving aside 53.93% students who were already wearing spectacles, it was found that 8.99% of the children reported about lost or broken specs, equal no. of students (8.99%) felt that specs caused headache, while 16.85% students didn't feel the need of specs and rest 11.23% of the children forgot their specs at home.

Aldebasi found main reasons for non compliance were parent's disapproval, not like to wear and don't feel the need of spectacles. Rest of the reasons for non compliance were broken spectacles, lost spectacles, forgot at home, headache on spectacle wearing etc[22].

CONCLUSION

High prevalence of refractive errors at young age demands early screening of children for timely intervention for correction of refractive errors to decrease morbidity among school children due to uncorrected refractive errors. Awareness must be created among students, teachers and parents regarding problems faced due to visual acuity problems. Regular screening of children by the health department authorities must be carried out to provide timely correction.

REFERENCES

1. Desouky DE, Nighat M, Khan T. Refractive error among a sample of female Primary school children in Taif city, KSA. International J. Public Health and Epidemiology 2014; 3 (10): 88 – 97.
2. WHO Data on blindness throughout the world. WHO chronicle 1979; 33(718): 275.
3. World Health Organization. Preventing blindness in children: report of WHO/IAPB scientific meeting. Programme for the Prevention of Blindness and Deafness, and International Agency for Prevention of Blindness. Geneva: WHO, 2000 (WHO/PBL/00.77).
4. Dandona R, Dandona L. Refractive error blindness. Bull World Health Organ. 2001; 79:237–243.
5. Ali A, Ahmad I, Ayub S. Prevalence of undetected refractive error among school children of Lahore. Biomedica 2007; 23:96-101.
6. Government of India (2004), Annual report 2003-2004, ministry of health and family welfare, New Delhi.
7. Sethi S, Kartha GP. Prevalence of refractive errors among school children (12- 17years) of Ahmedabad city. Ind Journal of Com Med, 2000; 25: 181-83.
8. Murthy GVS, Gupta SK, Ellwein LB, et al. Refractive error in children in an urban population in New Delhi. Invest OphthalmolVis Sci. 2002; 43:623–631.
9. Sharma S, Vashisht B M, Kalhan M, Goel M: Magnitude of Refractive Errors among school children in a rural block of Haryana. The Internet Journal of Epidemiology. 2009. 6(2).
10. Rahman M, Devi B, Kuli JJ, Gogoi G. A Study on the refractive status of school going children aged between 10 to 15 years in Dibrugarh Town, Assam. IOSR – JDMS 2015 JDMS 2015; 14(2) 827 – 833.
11. Yingyong P. Refractive error survey in Primary school children (06 – 12 years) in 02 provinces: Bangkok. Nakhonpatho M (one year result). Journal Medical Asso. Thai. 2010. 93 (10): 1205-1210.
12. Matta S, Matta P, Gupta V, Dev A. Refractive errors among adolescents attending Ophthalmic OPD; Ind J Comm Medicine. 2006-04 - 2005-06; 31(2).
13. Dulani N, Dulani H. Prevalence of refractive errors among school children in Jaipur, Rajasthan. International Journal scientific study 2014; 02 (05): 52 – 55.
14. Sewunet SA, Aredo KK, Gedefew M. uncorrected refractive error and associated factor among primary school children in Debre Markos district North West Ethopia. BMC Ophthalmology 2014; 14: 95.
15. Al Wadani Fa, Amin TT, Ali A, Khan AR. Prevalence and Pattern of Refractive error among Primary School children in Al Hassa, Saudi Arabia. Global J. Health Sci. 2013; 5(1): 125-134.
16. Niroula D R, Saha C G. Study on the refractive errors of school going children of Pokhara city in Nepal. Kathmandu University Medical Journal. 2009;7(25):67-72.
17. Saw SM, Hong RZ, Zhang MZ, Fu ZF, Ye M, Tan D, Chew SJ. Near-work activity and myopia in rural and urban schoolchildren in China. J Pediatr Ophthalmol Strabismus 2001; 38:149-55.
18. He J, Lu L, Zou H, et al. Prevalence and causes of visual impairment and rate of wearing spectacles in schools for children of migrant workers in Shanghai, China. *BMC Public Health*. 2014;14:1312. doi:10.1186/1471-2458-14-1312.
19. Pavithra MB, Maheshwaran R, Rani Sujata MA, A study on the prevalence of refractive errors among school-children of 07 – 15 years of age group in the field practice areas of Medical College in Bangalore. International Journal Medical Sci. & Public Health 2013; 2(3): 641-645.
20. Kumar P, Pore P, Dixit AK, Singh R. Prevalence demographic distribution of Refractive error in school children of Pune, India. International journal Research Health Sciences 2014; 2: 58-67.
21. Khandekar R, Al Harby S, Abdulmajeed T, Helmi SA, Shuaili IS. Validity of vision screening by school nurses in seven regions of Oman. East Mediterr Health J 2004; 10:528-36.
22. Al-Debase YH. A descriptive study on compliance of spectacle wears in children of primary schools at Qassim province, Saudi Arabia. International Journal Health Sciences 2013; 7(3): 291-299.

ISSN 2320 9208

Management of Hodgkin's Disease - A review

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ABSTRACT

Hodgkin's Lymphoma (HL) is one of the highly curable malignant disease. It is important to know the exact extent of disease for prognosis and treatment. Currently standard of care depends on disease stage and risk category. Hence clinical examination and staging investigations are of utmost importance. Combination chemotherapy and involved field radiation (IFRT) is standard of care for early disease while advanced disease is treated with combination chemotherapy alone. High dose combination chemotherapy followed by Autologus stem cell transplant (ASCT) is the standard of care for relapsed or refractory disease.

Targeted use of standardized therapies according to prognostic score has been the major advancement in treatment of HL, resulting in improved outcomes for patients.

Further improvement in efficacy and reduction of toxicity will depend on development of newer novel agents and their incorporation into individualized treatment for patients.

Keywords : Hodgkin's Lymphoma, Relapse.

INTRODUCTION

Thomas Hodgkin was the first physician to describe Hodgkin's lymphomain 1832. Its management is a medical success story, from being a nearly fatal disease in twentieth century to cure rates now approaching nearly 90%. Radiotherapy alone was initially used as a curative treatment. Survival rates improved with addition of multiagent chemotherapy in 60's and 70's. In the last three decades with the improvement in radiation techniques, development of more effective and less toxic chemotherapeutic agents, improvement in imaging technology and refinement in prognostic factors allows for better tailoring of treatment leading to better results.

NATURAL HISTORY & CLINICAL PRESENTATION

HL almost always develops in lymph nodes. Majority of patients (approximately 80%) present with painless cervical lymphadenopathy and around 50% have mediastinal lymph node involvement. In 20% cases, disease starts in lymph nodes below the diaphragm. Isolated involvement of the extra-lymphatic organ in absence of nodal disease is less than 1%. Contiguous spread of disease is known to occur in HL spreading from one lymph node station to the next. It has a bi-modal age distribution with early peak from 25 to 30 years and late peak from 75 to 80 years with slight male preponderance. Epstein Barr Virus (EBV) is known to be a risk factor for mixed cellularity variant of HL[1,2].

Common symptoms include unexplained fevers, drenching night sweats and significant weight loss (>10% of body weight in previous 6 months). These three are known as the B symptoms and predicts a poorer prognosis.

Other symptoms include generalized pruritis, fatigue, and alcohol-induced pain in tissues involved by HL. Visceral involvement is usually secondary to extension from adjacent group of lymph nodes.

World Health Organization (WHO) classification divides HL into 2 main types: Classical Hodgkin Lymphoma (CHL) and Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL).[3] CHL is further divided into Lymphocytic-rich CHL, Nodular Sclerosis CHL, Mixed Cellularity CHL and Lymphocytic-depleted CHL. CHL is characterized by Reed- Sternberg (RS) cell in an inflammatory background while NLPHL lacks RS cell but is characterised by lymphocyte-predominant cells, sometimes called popcorn cells.

WORK-UP

- History and Physical Examination including examination of all lymphnode areas on both sides of diaphragm and palpation of Spleen and liver..
- Routine Investigations:
- Blood Investigations: Complete Blood Count with differential, Anaemia is a common feature of Hodgkin lymphoma
- Kidney Function Test, Liver Function Test, Erythrocyte Sedimentation rate (ESR), S. Albumin.
- Chest X-ray Postero-anterior and lateral view to detect involvement of mediastinum.
- **Diagnostic and staging investigations:**
- Biopsy of Lymph Node is mandatory, Fine Needle Aspiration Cytology is not adequate as one must know the exact sub-type of disease which helps in determining prognosis.
- Computed tomographic (CT) scan of thorax, abdomen, and pelvis is required for staging. CT-Scan of head and neck ares can also be done, however, clinical examination alone is sufficient to assess extent of disease more so if neck irradiation is indicated.

- Positron emission tomography (PET) scan (preferred over CT, if available)
- Bone marrow, needle biopsy (if subdiaphragmatic disease or B symptoms are present)
- Cytologic examination of effusions, if present

STAGING

The Ann-Arbor staging system (Table I) was developed in 1971 to provide prognostic information and guide treatment[4].

TABLE I: Ann Arbor Staging Classification for Hodgkin's Lymphoma

STAGING	DEFINITION
STAGE I	Involvement of single lymph node region (I) or of single extralymphatic organ or site (IE)
STAGE II	Involvement of two or more lymph node regions on the same side of the diaphragm alone (II) or with involvement of limited, contiguous extralymphatic organ or tissue (IIE)
STAGE III	Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (IIIS) or limited, contiguous extralymphatic organ or site (IIIE), or both (IIISE)
STAGE IV	Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymphatic involvement
Presence of B symptoms are to be denoted by suffix "B" and their absence by suffix "A"	

However, some other important factors such as disease bulk and number of sites of involvement were not included in it for which Cotswolds modifications (Table II) were made to the Ann-Arbor system in 1988[5].

TABLE II: The Cotswolds Staging Classification for Hodgkin's Lymphoma

STAGING	DEFINITION
STAGE I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring) or involvement of a single extralymphatic site (IE)
STAGE II	Involvement of two or more lymph node regions on the same side of the diaphragm (hilar nodes, when involved on both sides, constitute stage II disease); localized contiguous involvement of only one extranodal organ or site and lymph node region(s) on the same side of the diaphragm (IIE). The number of anatomic regions involved should be indicated by a suffix (e.g., II3)
STAGE III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of the spleen (IIIS) or by localized contiguous involvement of only one extranodal organ site (IIIE) or both (IIISE)
III1:	With or without involvement of splenic, hilar, celiac, or portal nodes
III2:	With involvement of para-aortic, iliac, and mesenteric nodes
STAGE IV	Diffuse or disseminated involvement of one or more extranodal organs or tissues, with or without associated lymph node involvement

- o A or B suffix to be added for presence of absence of B symptoms.
- o X: Bulky disease (a widening of the mediastinum by more than one-third of the presence of a nodal mass with a maximal dimension >10 cm)
- o E:Involvement of a single extranodal site that is contiguous or proximal to the known nodal site
- o CS: Clinical Stage
- o PS: Pathologic stage (as determined by staging laparotomy)

PROGNOSTIC FACTORS

In order to provide appropriate treatment for HL, it is imperative to identify reliable prognostic factors and corresponding risk groups. For the purpose of treatment HL is divided into early (Stage I & II) and advanced disease (Stage III & IV). Early disease is further divided into favourable and unfavourable depending on absence or presence of risk factors respectively, as described in table III.

Table III: Risk factors in Early HL: European Organisation for Research and Treatment of Cancer (EORTC)[6] and German Hodgkin Lymphoma Study Group (GHSG)[7, 8] defined clinical criteria.

EORTC	GHSG
AGE ≥ 50 years	Extranodal disease/massive spleen
ESR ≥ 50 if B symptoms absent ESR ≥ 20 if B symptoms present	**ESR > 50 if B symptoms absent** ESR > 20 if B symptoms present
Involvement of >3 nodal areas	Involvement of >3 nodal areas
Mediastinum to thorax ratio ≥ 0.35	Large Mediastinal mass

For advanced HL there is a International Prognostic Score (IPS) based on risk factors which include age >45 years, stage IV, male sex, white cell count >15000/mm^3, lymphocyte count <600/mm3 or <8% of white cell count, albumin <4g/dL, and haemoglobin <10.5 g/dL[9]. With increase in each risk factor, failure free survival (FFS) is reduced by 7-8% and the IPS also reliably identifies a group of patients having IPS≥4 who have long-term FFS of approximately 50% or less.

TREATMENT

Cure of HL is success story of the 20th century. It is highly sensitive to both radiation and chemotherapy and both produce higher cure rates when used either singly or in combination. Role of surgery is limited to biopsy only.

Radiation Therapy

Use of Kilovoltage X-rays caused shrinkage of tumor and made way for its definitive treatment which was improved with use of Megavoltage radiation and subsequently Linear Accelerators. Initially localized field was used and all the lymph node groups were treated one by one and if new groups were involved, they were treated as and when involved and this technique was know as 'Chasing Technique' of radiation and it did significantly improve the survival. A radiation dose of 35-44 Gys produced complete and permanent regression of disease in the treated

area, however there were recurrences in untreated areas. Extended field radiation was thus introduced at Stanford,USA in 1968 where all the involved as well as uninvolved lymph node areas which were thought to be potentially involved areas, harboring micro metastasis, were treated together using one large field of radiation. All lymph node areas above the diaphragm were treated by extended field which was known as 'Mantle Field' and those below diaphragm were treated by 'Inverted Y' field. In stage IIIA , some time Total Nodal Irradiation was used. Extended field radiation increased 5 year survival of early stage favorable disease to 90-95% and was mainstay of treatment in 60's and 70's. However, increased morbidity and mortality was found to be associated with the use of large field of radiotherapy which exceeded the Hodgkin-related mortality after 10-15 years[10]. Combination chemotherapy developed In 70's and 80's gave comparable results with less toxicity and thus replaced extended field radiation as primary modality of treatment. Combination chemotherapy is now the treatment of choice and radiation is used as a boost to area of bulky disease, with smaller portals, to improve local control and survival without increasing the toxicity.

Chemotherapy

HL is sensitive to various chemotherapy drugs which include Vincristine, Vinblastine Cyclophosphamide, Nitrogen Mustard, Adriamycin, Dacarbazine, Bleomycin, Procarbazine and Prednisolone. Response rates and overall survival were low with single agent chemotherapy which led to introduction of combination chemotherapy. The first effective combination was given by Devita et al[11] in form of regimens including MOPP (nitrogen mustard, vincristine, procarbazine, and prednisone) or MVPP(Vincristine replaced with Vinblastine) in 1960s. These were effective combinations but concerns were late toxicity which included sterility and risk of secondary myelodysplastic syndrome or leukemia. The risk were more as the patients were younger. With the introduction of Adriamycin other combinations were investigated, most important among them was ABVD (Adriamycin, Bleomycin, Vinblastine and Dacarbazine) developed by Bonadona et al at Milan ,Italy which gave results similar to MOPP or MVPP however with lower toxicity. Since then ABVD has replaced MOPP as the gold standard of chemotherapy for Hodgkin lymphoma. This is based largely on the results of the intergroup trial that compared MOPP, ABVD, and MOPP/ABVD[12], where similar results were achieved with ABVD but with lesser toxicity as compared to MOPP. Most recently, in an effort to reduce toxicity or improve efficacy, new drug programs have been developed. These include Stanford V (Nitrogen Mustard, Doxorubicin, Vincristine, Vinblastine, Bleomycin, Etoposide and Prednisone) and BEACOPP (Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Vincristine, Procarbazine and Prednisone)

Combined Modality Therapy (CMT): CMT was introduced for reducing toxicity due to both Radiation and chemotherapy. Size of radiation portals were reduced in CMT, leading to concept of Involved Field Radiation Therapy (IFRT) along with reduction in number of chemotherapy cycles. It was logical to initiate treatment with chemotherapy as it had the advantages of treating all sites of disease at the outset (especially important in stage III or IV) and reducing bulky disease to facilitate subsequent irradiation with smaller portals (especially in the mediastinum). The irradiation dose of 20 to 36Gy was used in combined modality studies in adults. All patients with bulky disease in any area should be treated with CMT and must have radiation to the area of bulky disease after the chemotherapy using IFRT.

TREATMENT (as per risk group):

Early stage Favourable CHL:Current standard of care for early stage favourable CHL is 2 cycles of ABVD followed by 20Gy IFRT as per the GHSG HD10 trial[7]. The freedom-from progression is around 90% to 95%. Selected patients may be treated with chemotherapy alone if radiation therapy is contraindicated.

Early stage NLPHD: Long term disease free survival can be achieved by using IFRT to a dose of 30 to 36Gy. No additional benefit is achieved by addition of chemotherapy.

Early stage Unfavourable CHL: Combination of 4 cycles ABVD followed by 30Gy IFRT is thecurrent standard of treatment in this group of patients as per the GHSG HD11 trial[8]. This trial randomized patients into 4 cycles of chemotherapy (BEACOPP Vs ABVD) and radiotherapy to a dose of 20Gy Vs 30Gy. 4 cycles of ABVD with 20Gy IFRT had a significantly poorer tumor control while the rest were similar, thus bringing the current standard practice of using 4 cycles ABVD followed by 30Gy of IFRT.The expected freedom from progression is 80% to 90%.

Advanced Stage: Mainstay of treatment for patients with advanced-stage Hodgkin lymphoma is systemic chemotherapy. Cancer and Leukemia group B[12] conducted a landmark prospective, randomized clinical trial which proved that 6 to 8 cycles of ABVD were equivalent to ABVD/MOPP for 12 months and both were superior to MOPP alone, thus making them the standard of treatment.

CMT with addition of radiation was tried, however it was found in EORTC 20884[13] trial that addition of radiation is beneficial only in cases with partial response.

Escalated BEACOPP was also compared with ABVD in 4 subsequent trials, PFS was improved[14-17] but OS remained same with the exception of a borderline benefit in low International Prognostic Score (IPS) stage III/IV patients[17].

TREATMENT FOR RELAPSE: Depending on initial disease characteristics, initial treatment and response duration, relapse sites, and general condition of the patient, the treatmentmust be individualized for an effective secondary treatment program.

In general, patients who were treated initially with irradiation alone for stage I to II disease should receive chemotherapy as the primary treatment for relapse.

For patients with stage III to IV disease relapsing after achieving a complete response to chemotherapy or CMT, the standard salvage therapy is to use high-dose chemotherapy with autologous hematopoietic stem cell transplant (ASCT). The long-term progression-free survival rate for these patients is expected to be approximately 50%. Favorable prognostic factors in this group include a longer duration of response to primary therapy and absence of extranodal diseaseAnti-PD1 Antibodies. PD1 signaling regulates the immune .

Novel Newer Agents: Genomic advances in HL provided insights into deregulation of key nodal signaling pathways, including the PI3K, NF-κB, and JAK/STAT pathways, which are amenable to small-molecule targeting Novel therapies. Unique micro-environment of HL has very few malignant RS cells which are present among a large number of reactive and inflammatory cellular infiltrate[18]. This active immune micro-environment and inadequate immune response represents potential target for novel agents.

Anti-PD1 Antibodies. PD1 signaling regulates the immune The unique expression of CD30 on RS cells is an additional therapeutic opportunity.

New treatments have been developed that either directly target RS cells, target cells in the inflammatory infiltrate, or reverse the suppressed immune response[19].

- *Brentuximab Vedotin*. It is an antibody drug conjugate that specifically targets CD30.
- *Anti-PD1 Antibodies*. PD1 signaling regulates the immune response by decreasing T-cell activation and suppressing T-cell proliferation and cytokine production.
- *Everolimus*: It is an oral antineoplastic agent that specifically targets mTOR complex. It targets this pathway, specifically the mTOR complex 1 (mTORC1). Everolimus targets the signaling pathways within the Reed-Sternberg cells and also suppresses signaling within the immune infiltrate and production of cytokines present in the tumor microenvironment. It is useful for relapsed and/or refractory HL
- *Panobinostat and Mocetinostat:* These agents target histone deacetylase and have efficacy in patients with HL.
- JAK inhibitors, Anti PD-1 antobodies, Lenolidoamide have also shown activity in HL and are under investigation

CONCLUSION

HL is one of the highly curable malignant disease. Determination of exact extent of disease is most important to select appropriate treatment and also to predict prognosis The current standard of care of HL depends on disease stage and risk. Therefore complete clinical examination and staging investigations are of utmost importance. Combination chemotherapy with AVBD regimen with IFRT is standard of care for early disease HL while advanced disease is best treated with chemotherapy alone. High-dose therapy with ASCT is the standard of care for relapsed and refractory HL.

Targeted use of effective, standardised therapies according to reliable prognostic factors has been the major advancement in HL research resulting in the better outcome of the patients. Further improvements in efficacy and reduction in toxicity will rely on the development of the other promising novel agents and their incorporation into individualised combinations.

REFERENCES

1. Weiss LM, Movahed LA, Warnke RA, Sklar J. Detection of Epstein-Barr viral genomes in Reed-Sternberg cells of Hodgkin disease. N Engl J Med 1989;320:502-506.
2. Hjalgrim H, Askling J, Sorensen P, Madsen M, Rosdahl N, Storm HH et al. Risk of Hodgkin disease and other cancers after infectious mononucleosis. J Natl Cancer Inst 2000;92:1522-1528.
3. WHO classification of tumors of hematopoietic and lymphoid tissues. In: Swerdlow SH, Campo E, Harris NL, et al., eds (ed4). Lyon, France: IARC;2008.
4. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res. 1971 Nov;31(11):1860-1.
5. Lister TA 1, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol. 1989 Nov;7(11):1630-6.
6. Fermé C, Eghbali H, Meerwaldt JH et al. EORTC-GELA H8 trial: chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. N Engl J Med 2007; 357: 1916–1927.
7. Engert A, Pluetschow A, Eich HT et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. N Engl J Med 2010; 363: 640–652.
8. Eich HT, Diehl V, Görgen H et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. J Clin Oncol 2010; 28: 4199–4206
9. D. Hasenclever and V. Diehl, "A prognostic score for advanced Hodgkin's disease," NEJM, vol. 339, no. 21, pp. 1506–1514, 1998.
10. Horwich A, Specht L, Ashley S. Survival analysis of patients with clinical stages I or II Hodgkin's disease who have relapsed after initial treatment with radiotherapy alone. Eur J Cancer 1997;33:848-53.
11. De Vita VT, Hubbard SM, Longo DL. The chemotherapy of lymphomas: looking back, moving forward. The Richard and Hinda Rosenthal Foundation Award Lecture. Cancer Res 1987;47:4810.
12. Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin lymphoma with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 1992;327:1478-1484.
13. Aleman BM, Girinsky T, van der Maazen RW, Strijk S, Meijnders P, Bortolus R et al. Quality control of involved-field radiotherapy in patients with advanced Hodgkin's Lymphoma (EORTC 20884). Int J Radiat Oncol Biol Phys. 2005 Nov 15;63(4):1184-90.
14. Carde P, Karrasch M, Fortpied C, Brice P, Khaled HM, Caillot D, et al. ABVD (8 cycles) versus BEACOPP (4 escalated cycles => 4 baseline) in stage III-IV high risk Hodgkin lymphoma (HL): First results of EORTC 20012 Intergroup randomized phase III clinical trial. J Clin Oncol. 2012; 30 (Suppl): abstr 8002.
15. Merli F, Luminari S, Gobbi PG, Cascavilla N, Mammi C, Ilariucci F, et al. Long term results of the HD2000 trial comparing ABVD versus BEACOPP versus COPP-EBV-CAD in untreated patients with advanced Hodgkin lymphoma: A study by Fondazione Italiana Linfomi. J Clin Oncol. 2015 Dec 28. pii: JCO624817. [Epub ahead of print].
16. Viviani S, Zinzani PL, Rambaldi A, et al. ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned. N Engl J Med. 2011; 365: 203-212.
17. Mounier N, Brice P, Bologna S, Briere J, Gaillard I, Heczko M, et al. ABVD (8 cycles) versus BEACOPP (4 escalated cycles ≥4 baseline): final results in stage III-IV low-risk Hodgkin lymphoma (IPS 0-2) of the LYSA H34 randomized trial. Ann Oncol. 2014; 25: 1622-1628.
18. Montes-Moreno S. Hodgkin's Lymphomas: A Tumor Recognized by Its Microenvironment. Adv Hematol. 2011;2011:142395.
19. Anas Younes and Stephen M. Ansell, Novel agents in the treatment of hodgkin lymphoma: biological basis and clinical results, *Seminars in Hematology,* http://dx.doi.org/10.1053/j.seminhematol.2016.05.011

ISSN 2320 9208

Ecopharmacology: A New emerging discipline

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ABSTRACT

Ecopharmacology, this term describes the entry of drugs or different type of chemicals into the environment at any concentration by any route which brings changes in the balance of ecosystem. When a drug is taken by us or fed to animals it may not be fully absorbed and then some drug is excreted which enters into the environment. Due to the harmful effects of pharmacological chemicals found in different studies many researches are being done on personal care products which aim to answer many questions. The adverse effects by these chemicals and drugs on flora and fauna as reported by the researches make it necessary to take action by regulatory agencies like EU and FDA. Another aspect is that the use of pharmaceuticals products and products used for personal care is increasing day by day. These products upon getting added into the environment get accumulated and show their deleterious effects with passage of time. These effects may be in the form of effects on plants, animals and humans. These products also undergo biological magnification i.e. their concentration goes on increasing with passage from one species to another in the food chain. The harmful effects are not localized to particular to only some regions of the world but are increasing becoming visible all over the globe in one from or another. Hence to prevent the future generations from these effects concrete steps need to be taken.

Keywords : Ecopharmacology, Environment Contamination.

Ecopharmacology : A New Emerging Discipline

Ecopharmacology term describes-entry of drugs or different type of chemicals into the environment at any concentration by any route which brings changes in the balance of ecosystem.[1] It includes effect of Pharmaceutics and Personal Care Products (PPCPs) and Industrial and Chemical Pollutants (IACPs) on environment which in turn effect the ecology. 'Ecopharmacology' is a vast terminology and cannot be defined in a clear cut way.[2]

PPCPs includes a huge collection of group of chemical substances used for treatment and diagnostic purpose in humans and in animals, nutraceuticals i.e. bioactive food supplements and other cosmetics and sun protecting creams, biopharmaceuticals, dyes, pesticides,excipients-inert ingredients and many others.[3]

When a drug is taken by us or fed to animals it may not be fully absorbed and thensome drug is excreted which enters into the environment. As the new researches are done in ecology and environment studies, the harmful effects of these drugs come into light. The first study took place in 1976 at the Big Blue River sewage treatment plant in Kansas City that detected the concentration of drugs present in sewage.[4]Afterwards a large number of studies has been done measuring the level of drugs given therapeutically to humans and animals including antibiotics, hormones, analgesics, tranquilizers, anticancers, antiseizures in water – surface or ground.[4] The adverse effects by these drugs on flora and fauna reported by the researches make it necessaryto take action by regulatory agencies like EU and FDA.[5]

Sources of Pharmaceutical Contamination

There are different sources by which environment is contaminated that include

1. Drug manufacturing effluent
2. Hospital effluent
3. Agriculture run-off
4. Household effluent
5. Municipal STP effluent
6. Aquaculture

The use of pharmaceuticals products and products used for personal care is increasing day by day. An increase from 2 billion to 3.9 billion annual prescriptions between 1999 and 2009 was estimated to occur in the United States.[6]

In Europe, it has been estimated that domestic waste water contributes 80% and the hospitals contribute 20% to the pharmaceutical content into the environment[7]

In India, water samples of a stream at Patancheruin Hyderabad showed 21 different drugs including drugs used for treatment for hypertension, heart diseases, chronic liver ailments, depression and ulcers[8]

Unused drug is a major threat for Ecopharmacology. A study

found that 50% of medicines prescribed and purchased in Australia is not used[9] Dumping of these drugs in environment will affect human health.

Effect On Aquatic Life And Humans

Some research studies suggest that the size Tadpoles has decreased to 40% after exposure to water ofsewage treatment plants. Ethinyl estradiol used in OCP cause disruption in aquatic and amphibian life and has been linked to increased vitelliogenin production leading to feminization.[10] Propanolol has been implicated in causing reduction in egg production. Antidepressant drug like Fluxoetine shown to affect spawning in shellfish .[11] In South-East Asia vultures died after eating the carcasses of animals trated with diclofenac sodium.[12]

In 2006 a study found out that a combination of about 13 common drugs in drinking water stops the growth of human embryonic cells.[13]

Current Research

Due to the harmful effect found in different studies many researches are being done on personal care products which aim to answer many questions[14] such as the effects of exposure to these products over time, the effects on acute (short-term) or chronic (long-term) exposures and specific populations, like elderly, very young, or immuno-compromised and the effects on bacterial, fungal, and aquatic life. Also to find out the concentrations of antibiotics in the aquatic environment which may lead to development of antibiotic resistance and how exposure to steroid hormones affects animal and humans?

For assessing medicinal products in environment EU described two phases approach. Phase I calculate the medicinal product concentration in environment and Phase II includes the substance with specific mode of action like hormones irresepective of the exposure calculation.

Environmental Risk Assessment

It is an integral part of assessment of acute toxicity caused by medicines to environment and is based on the ratio between PEC (Predicted Environmental Concentration of the substance) and PNEC (Predicted No Effect Concentration of the substance). The ratio of PEC/PNEC ranges from 0.1 to 10 being insignificant to high respectively.[15]

These EMEA guidelines for environmental risk assessment is an approach to deal with the issues at hand but a more sophisticated approach is required.[16]

In U.S., the Federal Interagency Task Group on Pharmaceuticals and Personal Care Product was launched in September 2004 and had its first meeting in July 2005 to identify the concentration of these medicinal products concentration in waste water.

Another quantitative risk-based approach which is used for assessing the potential ecological and human health impacts of pharmaceuticals is by combining production estimate, attenuation and toxicity thresholds for multiple end-points[17] In a recent study - RANKVET - a ranking method was developed for comparing and prioritizing the environmental risk of veterinary pharmaceuticals to living organisms. In this method risk quotient (RQ) was calculated, which is the ratio of PEC to PNEC.If the RQ ≥ 1, a risk mitigation measure must be proposed for reducing the risk to a level that is acceptable. If the RQ continues to be ≥1, the environmental risk remains as such.[18]

DISCUSSION

As we are living in the surroundings which are polluted by metals, insecticides, drugs and drug related chemicals and these pollutants have so many adverse effects on health and ecosystem. To sort out these problems different approaches should be used like Green drug design, Development of biodegradable product, minimization of manufacturing emission, education on rational use, improved prescribing practice, management of unused drug. There are some pharmaceutical disposal and environmental standard guidelines which include Good Manufacturing Guidelines (GMP), EU Regulations, US EPA (Environmental Protection Agency), WHO Guidelines and Ecopharmacovigilance.

Conclusion

With growing pharma industry and new researches, there is cocktail of waste of pharmaceuticals products in the environment affecting the ecosystem. To minimize these harm effect proper waste management, proper disposal of drugs (unused and expired), green pharmacy the aim of which is zero pharmaceutical waste in ecosystem should be taken into account. It is mandatory to monitor and assess the effects of drugs to save the environment.

References

1. Valluri A. Ecopharmacology – In the Offing. International Journal of Scientific and Research Publications 2016;6(1):84-7.
2. Kummerer Klaus, Velo Giampaolo: Ecopharmacology: A New Topic of Importance in Pharmacovigilance. Drug Safety 2006; 29(5):371-3.
3. Daughton CG, Ternes TA: Pharmaceuticals and Personal Care Products in the Environment: Agents of Subtle Change? Environmental Health Perspectives 1999;107:907-38.
4. Hignite, C. and D. Azarnoff. Drugs and drug metabolites as environmental contaminants: Chlorophenoxyisobutyrate and salicylic acid in sewage water effluent. Life Sciences 1977;20(2): 337-41.
5. Rahman SZ, Khan RA, Kumar V, Misbahuddin M, Pharmaco-environmentology– A Component of Pharmacovigilance, BMC Environmental Health 2007; 6:20 http://www.ehjournal.net/content/6/1/20
6. Tong, A.Y., Peake B, Braund R. "Disposal practices for unused medications around the world". Environment International 2011;37: 292–8.
7. EU project report summary "Pharmaceutical Input and Elimination from Local Sources", 2012 http://www.pills-project.eu/PILLS_summary_english.pdf)
8. The Times of India: Kolkata, Section: Times Nation, Page: 7, Disaster zone: IskaVagu stream in Patancheru, near Hyderabad, Date: Jan 28, 2009.
9. Pándi C:3billion € spent on medicines. Around half of them end up in waste. Die Kronen Zeitung 2009.
10. Daughton, C.G. "Pharmaceuticals as Environmental Pollutants: The Ramifications for Human Exposure." International Encyclopedia of Public Health, 2008; 5: 66–102.

11. Rahman SZ, Khan RA: Environmental Pharmacology – A New Discipline. Indian J Pharmacol 2006; 34(4):1-2.

12. Shahid M, Khardori N, Tripathi T, Bergman S. Pharmaco-EcoMicrobiology: A newer component of medical sciences bridging pharmacovigilance, ecology and environmental microbiology. Journal of Infection and Public Health 2010;3:1-4.

13. Pomati F, Castiglioni S, Zuccato E, et al. Effects of a complex mixture of therapeutic drugs at environmental levels on human embryonic cells. Environ Sci Technol 2006;40(7):2442-7.

14. "Pharmaceuticals and Personal Care Products: An Emerging Issue (http://www.groundwater.org/gi/docs_pack/fa13.pdf)." The Ground water Foundation. Accessed 20 April 2009.

15. Environmentally classified Pharmaceuticals (2010), StockholmsIansLandsting,Stockholm County Council, January 2010 Ed.

16. Sumpter John P. Environmental Effects of Human Pharmaceuticals. Drug Information Journal. 2007;41:143–7.

17. Dong Z, Senn DB, Moran RE, Shine JP. Prioritizing environmental risk of prescription pharmaceuticals. RegulToxicolPharmacol. 2013;65:60–7.

18. Di Nica V, Menaballi L, Azimonti G, Finizio A. RANKVET: a new ranking method for comparing and prioritizing the environmental risk ofveterinary pharmaceuticals. Ecol Ind. 2015;52:270–6.

ISSN 2320 9208

Promoting Feedback seeking behavior in residents: cultivating a positive culture

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ABSTRACT

Feedback is a complex process influenced by number of factors. Role of receiver in effective feedback should be active one by asking teacher, how am I doing? This feedback-seeking behavior is affected by both learner and teacher attitude. Based upon literature review we have cited most common factors about feedback –seeking behavior in residents.

Key-words: Effective feedback, feedback-seeking, residents

Introduction

Most of the post-graduate learning occurs while participating in clinical work and Feedback plays an important role in this teaching- learning process. Both the teachers and residents agree that feedback is integral part of this reaching- learning process.[1] Without feedback learner couldn't make out about his/her performance, whether it was good or bad.[2] Learner during their residency are in crucial stage of learning, practices imbibed during this stage of learning last life –long just not in terms of clinical skills but also in terms of learning –seeking behavior, self-assessment etc. Many researchers have suggested that people should not wait around passively until they are given feed- back; instead, they proactively seek it. As many students find themselves in feedback vacuum because of insufficient feedback they received.

What are problems in Delivering Feedback?

Many studies have shown that both the medical students and the residents don't get sufficient or effective feedback during teaching-learning while teachers feel that feedback given by them generally go unrecognized.[3] Feedback has generally been viewed by teacher as information to be given to the learner without taking into account the learner's perspective. This type of feedback is teacher centered and there is no active role of learner in this type of feedback. While effective feedback requires active participation of learner in this whole process, including the feedback seeking attitude.[4] Feedback seeking behavior is a valuable resource for learning as it facilitates adaptation, learning and performance. Feedback-seeking behaviour can be defined as the conscious devotion of effort towards determining the correctness and adequacy of one's behaviours for attaining valued goals. So by seeking feedback learner wants to improve its skills to reach to desired goals.

Various Aspects of Feedback Seeking Behaviour

There are five key aspects of feedback seeking behaviour

i) Methods used to obtain feedback;

ii) (ii) Frequency of feedback-seeking behaviour;

iii) Timing of feedback seeking;

iv) the characteristics of the target of feedback seeking, and

v) the topic on which feedback is sought.

Various Factors Affecting Feedback Seeking Practice

There are multiple factors which affect residents feedback seeking behavior i.e teacher's receptivity to learners request, student- teacher relationship, teaching-learning environment, learners confidence in his/her ability etc.[5] Feedback helps learners to reflect on their own performance and to seek guidance that reinforce or correct their performance and guide their further learning. Seeking feedback from colleagues, seniors can help in professional growth. A number of factors influence the feedback seeking: relationship among colleagues and seniors, quality of feedback, culture of feedback, emotional response to feedback and time for feedback.

Usually tension appeared in both residents and faculty in response to feedback seeking practice. Residents perceived feedback as threat and at the same time both residents and teacher indicated that work-place culture strongly influence the feedback practice.[6] Residents want feedback to be at regular interval not at the end of summative assessment, where it is futile as at that time it doesn't help them in learning.[7] While teaches cite lack of institutional feedback culture regarding the feedback demotivates them to provide it. Both residents and teachers felt that lack of time is one of the major culprit in feedback seeking as residents avoid asking the busy teachers and teachers are busy in patient care and other departmental activities. Different tactics can be used like introduction of feedback at the end of rotation at the institutional level which will also encourage residents to seek feedback when they need it.

Relationship between teacher and residents also play a major role in feedback seeking. Residents seek feedback from those teachers, who want them to learn and spent time with them to directly observe their activities rather than those who only valued them for their services.[8] Level of comfort between residents and teachers strongly influences the feedback seeking,

residents seek feedback only from those teachers with whom they are comfortable. Even teachers felt uncomfortable when they don't get feedback back from the residents whether feedback given by them was helpful or not.

Both teachers and residents agreed that emotional response to feedback seeking is a huge barrier to feedback seeking activity. Many residents felt uncomfortable in receiving any feedback good or bad, but majority are afraid of getting any negative feedback and they feel their inability to handle emotional response to any negative feedback. Even teachers feel uncomfortable in providing corrective feedback and how to handle emotional response of residents to it.[9]

Conclusion

So to promote feedback seeking practice among residents:

1. Institutional feedback culture should be there. Feedback forms should be available in all wards.
2. Workshops on effective feedback should be done so that both teachers and residents can learn the different aspects of Feedback as well to manage their emotional responses.
3. To promote feedback seeking in residents we should incorporate feedback at undergraduate level so that they will be well acquainted with it when they need it most.

References

1. Archer JC. State of the science in health professional education: Effective feedback. Med Educ2010;44:101–108.
2. Rees C, Shepherd M. Students' and assessors' attitudes towardsstudents' self-assessmentof their personal and professional behaviours.Med Educ 2005;39:30–39.
3. Jensen AR, Wright AS, Kim S, Horvath KD, Calhoun KE. Educationalfeedback in the operating room: A gap between resident and faculty. perceptions. Am J Surgery 2012 204:248–255.
4. Milan FB, Dyche L, Fletcher J. ''How am I doing?'' Teaching medicalstudents to elicit feedback during their clerkships. Medical Teacher 2011;33:904–910.
5. Bindal T, Wall D, Goodyear HM. '''Trainee doctors'' views onworkplace-based assessments: Are they just a tick box exercise? MedTeacher 2011; 33:919–927.
6. Teunissen PW, Scheele F, Scherpbier AJ, van der Vleuten CP, Boor K,van Luijk SJ, et-al. How residents learn:Qualitative evidence for the pivotal role of clinical activities. Med Educ 2007;41:763–770.
7. VandeWalle D, Cummings LL. A test of the influence of goalorientation on the feedback-seeking process. J ApplPsychol1997;82:390–400.
8. Nussbaum AD, Dweck CS. Defensiveness versus remediation: Selftheoriesand modes of self-esteem maintenance. Personal SocPsycholBull 2008; 34:599–612.
9. Trope Y, Neter E. Reconciling competing motives in self-evaluation:The role of self-control in feedback seeking. J PersSocPsychol1994;66:646–657.

ISSN 2320 9208

Clival Chordoma: transnasal transsphenoidal endoscopic excision

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ABSTRACT

Chordomas are dysembyogenic bone tumors arising from the notochordal remnants. It may involve axial skeleton wherever from the base of skull to the coccyx, more commonly in the clivus and sacrococcygeal region. Intracranial chordomas mostly originate from the clivus and around it region and account for approximately one third of all chordomas. They are rare, slow growing but locally invasive tumors1. Primary therapy is complete surgical removal, but probability of recurrence is high inspite of thorough surgical excision. We are presenting a case of clival chordoma of a 47 year male who presented with complaint of headache and double vision since two months. After transnasal transsphenoidal endoscopic excision of the mass, patient showed relief from headache and double vision.

Keywords: Chordoma; clivus; endoscopic excision; transsphenoid approach.

INTRODUCTION

Chordomas are bone tumors arising from the notochordal remnants.[1] and intracranial chordomas account for approximately one third of all chordomas.[2] Chordomas are uncommon tumors with incidence of 0.1 cases per 100,000 of population and almost 1% of intracranial tumors[3]. 35% to 40% of the above mentioned, involve the clivus. The clivus is the ventral part of the skull base which comes between the nasopharynx and posterior cranial fossa, just inferior to the dorsum sella. It has the neurovascular structures of the brainstem lying closely. Clival chordoma grow into and invade the cranial nerves and nearby brain stem structures to become symptomatic.

CASE REPORT

A 47 year male, presented to neurosurgery out-patient department with complaint of headache and double vision. The patient had no complaint of nasal blockage, decreased vision, nasal discharge or bleed. Headache was spontaneous onset, continuous, dull in character and slowly progressive. There was no history of vomiting or vertigo.

On examination nasal cavity, oral cavity and oropharynx were normal. Cranial nerve examination revealed left sixth nerve palsy. Bilateral fundus was normal.

A computed tomography scan revealed approximately 3cmX3cmX2cm indistinct, heterogenous enhancing soft tissue mass causing erosion of clivus and occupying whole of sphenoid sinus.

The MRI showed destruction of clivus, by heterogenous mass (Figure 1). The T1 images showed the mass to be hypointense while it was predominantly hyperintense on T2 with heterogenous post contrast enhancement. Mass was involving basisphenoid with spread into the sphenoid sinus. Sellar floor was eroded with pituitary gland elevated posterosuperiorly. Cavernous sinus and Bilateral Internal carotid artery were spared.

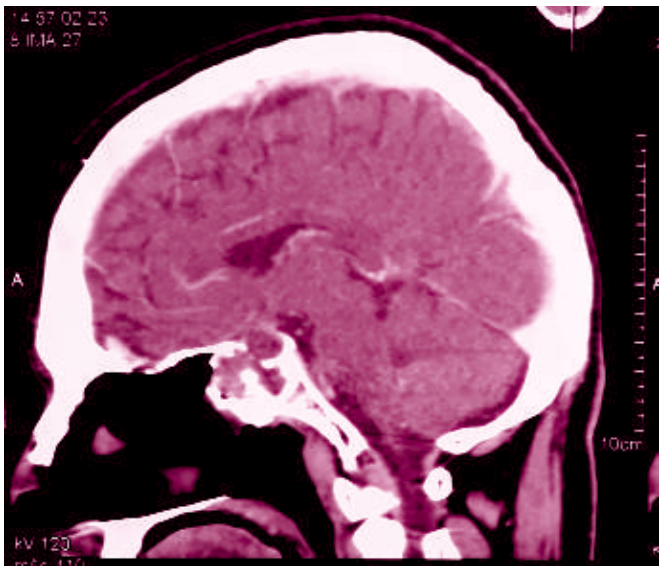
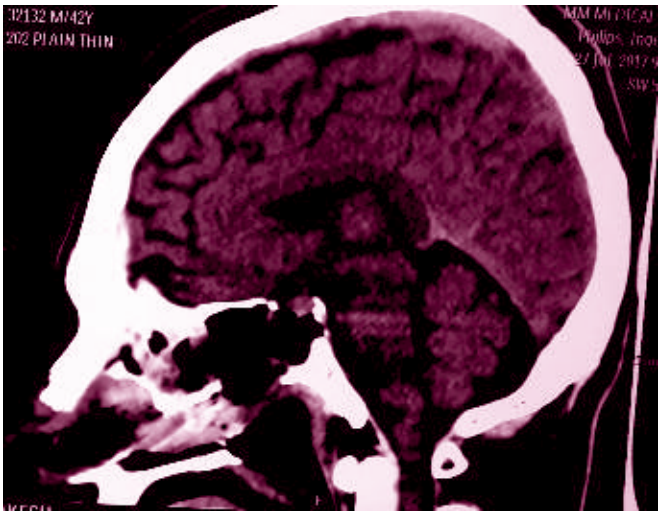


Figure 1. Preoperative sagittal section of Magnetic Resonance Imaging showing showing heterogenous mass and destruction of clivus.

Transnasal transsphenoidal (TNTS) endoscopic removal of the mass was done with patient in general anaesthesia. Posterior septectomy gave good exposure to undertake a 'two nostrils- four hands' technique for tumor excision. The tumor was soft, blue-grey in color and gelatinous consistency with lobulations, and was removed totally piecemeal by curette and Cavitron Ultrasonic Surgical Aspirator (CUSA). Dura exposed was found to be normal. The defect was closed by filling with surgicel, since there was no active cerebrospinal fluid (CSF) leak.

Postoperatively, the patient was asymptomatic and clinically better with no neurological deficits. Postoperative MRI showed no abnormality (Figure 2). The histopathological report was physaliferous cells separated by fibrous and myxoid stroma,

suggestive of chordoma (Figure 3).



Postoperative sagittal section of Magnetic Resonance Imaging showing the clival defect with no residual or recurrent mass.

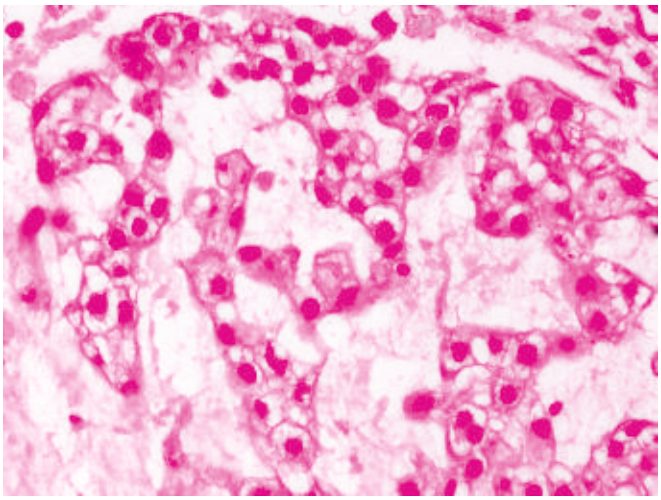


Figure 3. Photomicrograph showing physaliferous tumor cells with eosinophilic and vacuolated cytoplasm, creating a soap bubble appearance. The background is myxoid (H&E, x400).

DISCUSSION

The first description of chordoma was given by Virchow in 1857. He identified them to be tumors consisting of vacuolated or physaliferous cells, originating from rests of embryonic notochord along the midline central nervous system axis.[4] Clival chordomas are more common in males than in females (2:1), and is found mainly in adults[1]. Although slow growing, they are classified as tumors of low to intermediate malignancy with a tendency for local aggression and rare metastasis, usually after recurrence.[5]

Most patients of clival chordomas complain of headache, diplopia following VI cranial nerve involvement and decreased or blurrred vision due to pressure on optic chiasma. Symptoms are due to the mass effect on adjacent structures.[5] The multiple lower cranial nerve palsy may occur, presenting with facial paraesthesia, facial asymmetry, hoarseness, difficulty swallowing food and speech problem. Cerebrospinal fluid (CSF) rhinorrhoea may be the presenting complaint unusually.[6] Tumors large in size may compress brain stem and cause long tract signs and ataxia.[7]

The CT scan and MRI have a valuable contribution in the diagnosis and evaluation of the clival chordoma. CT scan helps to detect any bone erosion by the tumor and the degree of ossification within the tumor. The MRI helps in analyzing the brainstem involvement better than CT and its typical hypointense T1 weighted image and hyperintense T2 weighted, with heterogeneous enhancement, distinguishes it from meningiomas and schwannomas.[8] MRI also defines the position of optic chiasma, cavernous sinus and internal carotids in relation to the tumor.

Chordomas on histopathology may show any of the three types: classic, chondroid and dedifferentiated.[5] Classic chordomas appear as soft, grey-white, lobulated tumors composed of group of cells having round nuclei and an abundant vacuolated cytoplasm (Physaliferous cells). They also show mucoid substance with hemorrhagic and necrotic areas within the tumor. In some cases, calcification and bone sequestrations can also be found.[9]They show immunoreactivity for S-100 protein and MUC1 and cytokeratins the epithelial markers.

The optimal treatment is gross total resection.[5] But, because of their critical location and tendency for recurrence, these tumors are difficult to treat. Although various surgical approaches to the clivus are known but no single method has developed as a definitive mode for excision of these tumors. Traditional surgical approaches include transcranial, transoropharyngeal, transsphenoidal and maxillary osteotomy approaches. Transcranial approach involves brain retraction with increased risk of cerebral edema and hematoma, besides individual risk of carotid, basilar artery and optic nerve injury.[10] These complications are avoided with anterior (transnasal, transoral and transfacial) approaches. Endoscopic transnasal surgery not only gives direct access, but also excellent visualization of the clivus and surrounding structures, thus reduces morbidity.[10] Considering its safety, reliability and minimally invasive nature, TNTS is considered as a preferential approach to resect clival chordoma.

Chordomas are resistant to radiation and because of proximity to vital structures like brain, spinal cord, high dose of radiation cannot be given. Still radiotherapy is desirable in certain cases as may avoid recurrence postoperatively and thus prolong disease free survival Also, the patients who refuse or are unfit for surgery, radiotherapy may be considered as the primary treatment.[11]

Prognosis of the tumor is typically poor, due to the locally aggressive nature of these tumors, with the 10 year survival approximately 40%.[12] Besides high risk of local recurrence, there is high propensity to metastasize to lymph node, lung, liver and bone, which literature approximates to be ranging from 10% to 43%.[13]

REFERENCES

1. Gardner WJ, Tuner O. cranial chordoma: A clinical and pathologic study. JAMA Surgery 1941;42:411-425.
2. Yadav JS, Kumar V, Selvaraj S, Bhan C, Pandey M. Endoscopic removal of clival chordoma. Clin Rhinol An Int J 2017;10(1):28-31.
3. Al-Mefty O, Borba LA. Skull base chordomas: a management challenge. J Neurosurg 1997;86(2):182-189.

4. Soo MY. Chordoma review of clinicoradiological features and factors affecting survival. Australas Radiol 2001;45:427-434.

5. Fernandez-Miranda JC, Garner PA, Snyderman CH, Devaney KO, Mendenhall WM, Suarez C, Rinaldo A, Ferlito A. Clival chordomas: A pathological, surgical and radiotherapeutic review. Head Neck 2014;36(6):892-906.

6. Macdonald RL, Cusimano MD, Deck JH, Gullane PJ, Dolan EJ. Cerebrospinal fluid fistula secondary to ecchordosis physaliphora. Neurosurgery 1990;26:515-519.

7. Menezes AH, Gantz BJ, Traynelis VC, McCulloch TM. Cranial base chordomas. Clinical neurosurgery 1997;44:491-509.

8. Oot RF, Melville GE, New PF, Austin-Seymour M, Munzenrider J, Pile-Spellman J, Spagnoli M, Shoukimas GM, Momose KJ, Carroll et al. The role of MR and CT in evaluating clival chordomas and chondrosarcomas. AJR Am J Roentgenol 1988;151(3):567-575.

9. O'Connell JX, Renard LG, Liebsch NJ, Efird JT, Munzenrider JE, Rosenberg AE. Base of skull chordoma. A correlative study of histologic and clinical features of 62 cases. Cancer 1994;74(8):2261-2267.

10. Jiang WH, Zhao SP, Xie ZH, Zhang H, Zhang JY, Xiao JY. Endoscopic resection of chordomas in different clival regions. Acta Otolaryngologica 2009;129:71-83.

11. Raffel C, Wright DC, Gutin PH, Wilson CB. Cranial chordomas: clinical presentation and results of operative and radiation therapy in twenty-six patients. Neurosurgery 1985;17(5):703-10.

12. Carrabba G, Dehdashti AR, Gentili F. Surgery for clival lesions: open resection versus the expanded endoscopic endonasal approach. Neurosurg Focus 2008;25(6):E7.

13. Chambers PW, Schwinn CP. Chordoma: a clinicopathologic study of metastasis. Am J Clin Pathol 1979;72:765-776.

ISSN 2320 9208

Heterotopic pregnancy after ovulation induction by clomiphene citrate

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ABSTRACT

Heterotopic pregnancy is rare and is mostly seen in those conceived on assisted reproductive techniques. With advanced technologies heterotopic pregnancies can be diagnosed at early gestation and mostly have a good outcome. We are reporting a case of primigravida at 7+5 weeks with heterotopic pregnancy. Salpingectomy of the affected fallopian tube was done. Presently the patient is in third trimester of pregnancy.

Keywords : Hetrotopic Pregnancy, Clomiphene Citrate

Introduction

Heterotopic pregnancy is the coexistence of intrauterine and extra uterine pregnancy[1]. It is also known as multiple sited pregnancy, combined ectopic pregnancy, or coincident pregnancy. Its incidence is reported to be 1 in 30,000 in general population while 1 in 8,000 in those conceived on assisted reproductive techniques(ART)[2,3]. But it can occur in spontaneous conception too. The risk factors for heterotopic pregnancy include PID, ART, previous tubal surgery and other risk factors for ectopic pregnancy. First case of heterotopic pregnancy was reported as an autopsy finding in 1708[4] though with the advances in medical sciences not only can it be diagnosed earlier but successful outcome has also been reported for the intrauterine pregnancy. We are reporting a case of heterotopic pregnancy which was referred as ruptured ectopic pregnancy and on evaluation was found to be heterotopic pregnancy.

Case Report

26 yrs old primigravida at 7 weeks and 5 days period of gestation had complaints of pain in lower abdomen and dizziness since morning. She had a single episode of fainting attack. Patient consulted private practitioner from where she was referred to us as case of ruptured ectopic pregnancy. She was married since 1 year and 6 months and was under treatment for infertility since 2 months. Patient had conceived on ovulation induction with clomiphene citrate. Her menstrual, past and family history were unremarkable. On admission patient was conscious. Her pulse rate was 120 per minute, blood pressure was 100/70 mm of Hg and respiratory rate was 18 per minute. Abdomen was distended and tender on palpation. On per speculum examination cervix and vagina were healthy. No bleeding or discharge per vaginum was seen. On per vaginal examination uterus was anteverted, 8 weeks in size, mobile with right forniceal fullness present. Cervical motion tenderness was present. Ultra-sonography was suggestive of single intrauterine gestational sac of 7 weeks and 2 days period of gestation with right adnexal mass with free fluid present in abdomen and pelvis. (Figure1) Investigations sent at the time of admission revealed her haemoglobin 5.4 g/dl, platelet count 1.2 lac/dl, TLC 14,600 per cumm, DLC N88L10B1M1E0, PTI 74%. Keeping the differential diagnosis of ruptured corpus luteum with pregnancy or heterotopic pregnancy, patient was taken for exploratory laparotomy and proceeded. Intra-operatively note was made of right sided ruptured ectopic pregnancy at isthmic region along with haemoperitoneum of 1.5 litres and 350cc of clots. Uterus was 8 weeks in size. Left tube, left ovary and right ovary were normal looking.(Figure 2) Right sided salpingectomy followed by peritoneal lavage was done. Right tube was sent for histopathology. Patient was transfused 3 units of packed red blood cells and 4 units of fresh frozen plasma. Fetal well being was confirmed on ultrasonography and progesterone support was given postoperatively. She was discharged in satisfactory condition on post operative day 4. Histopathology report showed right tubal ectopic hence, the diagnosis of heterotopic pregnancy was confirmed.

Discussion

Heterotopic pregnancy is very dangerous and life threatening condition and is difficult to diagnose. Usually patients are missed in early pregnancy as after confirmation of intrauterine pregnancy on USG, adnexa are underlooked and thus coexistent extauterine pregnancy is missed. Such patients present to hospital with symptoms of ruptured ectopic pregnancy like in our case. Extrauterine site can be anywhere like tubal, ovarian, cervical or abdominal but most common is tubal pregnancy. Most of the heterotopic pregnancies are diagnosed between 5-8 weeks of gestation (70%) and rarely at or beyond 11 weeks (10%)[5]. Our case presented as right sided ruptured tubal pregnancy at 7 weeks and 5 days of gestation.

Patients undergoing ART are at increased risk for heterotopic pregnancy because of higher incidence of multiple ovulation[6], tubal malformation and/or tubal damage, and technical factors in embryo transfer. So these patients should be counselled about the possibility of heterotopic pregnancy though the overall incidence is low and this differential should always be kept in mind while performing first trimester ultrasonography in these patients.

Differential diagnosis of first trimester collapse include a) Heterotopic pregnancy with ruptured ectopic pregnancy b) Intrauterine gestation with hemorrhagic corpus luteum c) Bicornuate uterus with gestation in both cavities with ruptured horn c) Other surgical conditions of acute abdomen with

intrauterine pregnancy[7].

The management options include minimal invasive surgical procedure i.e laparoscopy or laparotomy, depending upon the available facilities and surgeon expertise as well as the patient's presentation although non-surgical forms of treatment like injection of potassium chloride for selective reduction of ectopic pregnancy are also reported[8]. Many cases are reported in literature in which surgical management was done in such cases for ectopic pregnancy and intrauterine pregnancy went well with patient delivering healthy baby at term[9,10] though in some cases spontaneous abortion was reported either prior to surgery or within a week of the surgical management. Our patient presented at 7 weeks and 5 days period of gestation and she is in second trimester at the time of reporting this case and is doing well with intrauterine pregnancy till date. Thus it requires a high index of suspicious for early and timely diagnosis of heterotopic pregnancy with good obstetric outcome.

Conclusion

Heterotopic pregnancy though very rare should always be kept in the differential diagnosis especially in those conceived on ART as timely intervention can result in successful outcome of the intrauterine fetus and prevent grave maternal morbidity.

References

1. Hassani KI, Bouazzaoui AE, Khatouf M, Mazaz K. Heterotopic pregnancy: A diagnosis we should suspect more often. J Emerg Trauma Shock 2010;3:304.
2. Reece EA, Petrie RH, Sirmans MF, Finster M, Todd WD. Combined intrauterine and extrauterine gestations: a review. Am J Obstet Gynecol 1983;146:323-330.
3. Devoe RW, Pratt JH. Simultaneous intrauterine and extrauterine pregnancy. Am J Obstet Gynecol 1948;56:1119-1126.
4. Bright DA, Craupp FB. Heterotopic pregnancy: a re-evaluation. J Am Board Fam Pract. 1990;3:125-128.
5. Tal J, Haddad S, Gordon N, Timor-Tritsch I. Heterotopic pregnancy after ovulation induction and assisted reproductive technologies: a literature review from 1971 to 1993. Fertil Sertil 1996;66:1-12.
6. Wang PH, Chao HT, Tseng JY, Yang TS, Chang SP et al. Laparoscopic surgery for heterotopic pregnancies: a case report and a brief review. Obstetrics & Gynecology and Reproductive Biology 1998;80:267-271.
7. Sohail S. Haemorrhagic corpus luteum mimicking heterotopic pregnancy. J Coll Physicians Surg Pak.2005;15:180–181.
8. Scheiber MD, Cedarus MI. Successful non-surgical management of a heterotopic abdominal pregnancy following embryo transfer with cryopreserved-thawed embryos. Hum Reprod 1999;14:1375-1377.
9. Russman C, MGruner C, Jiang X, Schnatz PF. Spontaneous Heterotopic Pregnancy: A Case Report. Gynecol Obstet (Sunnyvale) 2015;5:318. doi:10.4172/2161-0932.1000318
10. Espinosa PM, Alcantar Mendoza MA. Heterotopic pregnancy: Report of a case and review of literature. Ginecol Obstet Mex. 1997;65:482–486.

ISSN 2320 9208

Acute Pancreatitis as primary presentation of Systemic lupus erythematosus

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ABSTRACT

Pancreatitis is a rare manifestation of Systemic Lupus erythematosus (SLE). During the last 40 years only 90 cases of SLE patients with pancreatitis are reported and only 10 cases as primary presentation of SLE. We report the case of a 43-year-old woman, who presented with fever, abdominal pain and vomiting, photosensitive rash over face on examination and elevated levels of pancreatic enzymes. Further investigation led to a diagnosis of SLE: The treatment of SLE pancreatitis is steroids. Management of patient with steroids or azathioprine is associated with decrease in mortality. Pancreatitis may a rare but initial manifestation of SLE and should be suspected in case presenting with complaints of pain in abdomen, vomiting and unexplained fever with skin manifestation.

Key Words: Systemic lupus erythematosus, SLE, Acute and Chronic Pancreatitis.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder presenting with wide range of multi-systemic manifestations. The disease is characterized by antibodies in the blood directed against one or more components of cell nuclei[1]. Pancreatitis is an extremely rare manifestation of SLE. During the last 40 years only 90 cases of SLE patients with pancreatitis are reported and only 10 cases as primary presentation of SLE[2,3]. Younger females after the onset of puberty are more predispose compared to males. However, occurrence of the disease has been reported in children as young as 3 years of age[4]. Most patients present with involvement are the joint and cutaneous system, with associated nonspecific complaints of fever, malaise and fatigue, and renal disease[5]. Primary manifestation, however, can involve any organ system either singly or in combination, making the diagnosis difficult.

In 35% to 40% of patient of SLE develop gastrointestinal manifestations at some stage of their illness[6]. SLE is a rare etiology for pancreatic disease. Till date only about 5 cases of chronic pancreatitis associated with SLE have been reported in adults.

We present a report of a 43-year-old female who presented with fever, abdominal pain, vomiting and photosensitive rash over face on examination with elevated pancreatic enzyme levels. Our patient fulfilled the criteria's for diagnosis of SLE and illustrated a rare primary initial manifestation as acute pancreatitis. No other identifiable etiology for pancreatitis was found.

Case Report

A middle aged woman presented with complaints of persistent low grade fever since 4 months, with pain in upper abdomen and nausea since last 6-7 days. Patient also gave history of loss of hair loss, appetite and weight. History of occasional pain and stiffness in the small joints of the hand was present, which had subsided after taking analgesics. No history of alcoholism. Her past history was insignificant. Her family history was unremarkable for any auto-immune disorders. On examination patient was febrile, had tachycardia, tachypnoea with blood pressure of 130/90 mmHg. Erythmatous macular rash was present over face with sparing of nasolabial folds. Rash was also present over chest and back. Per Abdomen examination showed presence of tenderness in the epigastrium and around the umbilicus. However, there was no guarding or rigidity. Presence of ascitis could be appreciated clinically. Rest of the systemic examination was normal.

Patient was investigated peritoneal and pleural tapping analysis showed exudative nature of fluid. Her Serum Amylase and lipase levels were 466U/L and 938 U/L respectively. Her serum calcium level was 6.0 mg/dl. Her other biochemical reports like electrolytes, blood urea, creatinine, glucose, serum proteins and liver enzymes were normal. Her lipid profile was also obtained which was normal. Ultrasonography of abdomen was done which showed hypo echoic and bulky pancreas with minimal peri-pancreatic fluid collection s/o Acute pancreatitis with ascitis with right sided pleural effusion. Pancreatic duct was normal in course and caliber. Gall stones and pancreatic duct stones were absent.

A complete blood count (CBC) showed a white cell count of 15.5 x 10^3/µl with 92.2% neutrophils, 4.7% lymphocytes, 3.1% monocytes. Hemoglobin was 9.9 g/L, and platelets 163 ×10^3/µL. Blood culture was negative. Her serology for HIV was negative. Urine albumin was 3 (+) by dip stick assay. The erythrocyte sedimentation rate was 105. Electrocardiogram, 2 D ECHO were normal. X-ray chest revealed blunting of right CP angles. No evidence of old or active Koch's could be appreciated.

She was evaluated for autoimmune disease and was found to be positive for Antinuclear Antibody (ANA) titer with negative anti-double-stranded DNA (dsDNA) antibody titer.

As per The American College of Rheumatology (ACR) criteria[7] patient was diagnosed to have SLE with pancreatitis in view of presence of photosensitive rash, positive ANA, serositis and significant proteinuria. Other supportive findings were history of

arthralgia and hematological manifestation. Patient was started on steroids under cover of antibiotic, to which she responded. Fever, nausea, vomiting and pain in abdomen subsided but rash persisted. Patient was discharged on oral steroids (presdnisolone) and antibiotics.

After 15 days of first admission she presented back with complaints of pain in abdomen, nausea and vomiting with high grade fever. Repeat serum amylase and lipase levels were obtained and were found to be elevated (436U/L and 890 U/L) respectively. Repeat abdominal USG showed collection of free fluid in the right iliac fossa. Patient continued to have high grade fever inspite of adequate antibiotics and inject able steroids in the form of methylprednisolone. CT abdomen was planned but could not be done in view of poor general condition of the patient. Patient latter developed ARDS, septicemia and died.

Discussion

The American Rheumatism Association[8] recommends 4 of the following 11 revised criteria for the diagnosis of SLE:

i. Malar rash

ii. Discoid rash

iii. Photosensitivity

iv. Oral ulcers

v. Arthritis

vi. Serositis

vii. Renal disorder

viii. Neurologic disorder

ix. Hematologic disorder

x. Immunologic disorder on serologic testing

xi. Antinuclear antibodies

Our patient fulfilled the criteria. However, a diagnosis of SLE pancreatitis can be made only after excluding the commoner causes of acute pancreatitis, such as alcoholism and gallstones. Viral causes such as in HIV and AIDS may be considered in immunocompromisedpatient.

Reifenstein[9] in 1939 first documented the association SLE with pancreatitis. Detailed review of articles in English literature[10] over a period of last 3 decades, only 74 SLE patients with pancreatitis have been documented. The annual incidence of pancreatitis in SLE patients as documented by Saab and coworkers has been 1/1000[11]. They found only 8 cases of pancreatitis among 891 discharged patients of SLE over a period of 9 years. Derk and DeHoratius[2] found even lower incidence of 0.4/1000 patients over a period of 20 years. However, no gender differences have been noted in the incidence.

Acute pancreatitis usually occurs several months to years after the diagnosis of SLE. The median time between SLE diagnosis and occurrence of pancreatitis ranges between 2 to 25 yrs and the median period is around 2 years[10]. Pancreatitis presenting as initial manifestation is extremely rare. In an analysis of all the reported cases of SLE with pancreatitis done by Gideon Nesher et al, they showed pancreatitis as presenting symptom in only 15 cases of the 69 cases analyzed[10].

SLE patients may develop pancreatitis as a result common etiologies like choledocholithiasis, toxic-metabolites like alcohol intake, drugs, hypercalcemia, or hypertriglyceridemia but in majority of cases the cause remains "idiopathic". No etiology other than SLE can be identified. Multiple etiological mechanisms have been proposed like autoimmune pancreatitis, vasculitis, noninflammatory vasculopathy, or APLA-related thrombosis[10].

In patients of SLE, abdominal pain as reported by 88%patients, has been the most frequent pancreatitis-related symptom, followed by nausea, vomiting, fever and diarrhea[10]. Literature shows that the diagnosis of pancreatitis is mostly based on clinical findings along with laboratory evidence of elevated serum amylase or lipase. Imaging studies (Ultrasonography & CT) might not show any evidences of pancreatitis.

There has been debate as to the origin of pancreatitis in SLE, namely, steroid vs SLE itself as the primary cause. It has been noticed that most cases of pancreatitis in lupus have been in patients with long-standing disease who have multiorgan involvement and who are already on steroids, diuretics, or immunosuppressive therapy, all of which have been implicated as the etiological factors for pancreatitis. However recent studies have shown, treatment with steroids or azathioprine was associated with decreased mortality when treated after the onset of pancreatitis. Gideon Nesher et al showed mortality rate of 20% in patients who were treated with steroids following the diagnosis of pancreatitis compared with 61% among those who were not treated with steroids for pancreatitis[10].

Mortality rate of 27% have been shown in patients having SLE associated with pancreatitis[10]. Active lupus has been significantly associated with increased mortality. Literature shows a trend toward higher mortality rate in patients who presented with pancreatitis as the initial manifestation of SLE, possibly due to the delay in initiating appropriate immunosuppressive therapy. Hypocalcemia and raised serum amylase levels have been implicated as poor prognostic indicators.

In conclusion, pancreatitis may be the initial manifestation of SLE and should be suspected in case presenting with complaints of pain in abdomen, nausea, vomiting and unexplained fever with skin manifestation.

References

1. Mills JA. Systemic lupus erythematosus. N Engl J Med 1994; 330: 1871–9. (2)
2. Derk CT, DeHoratius RJ. Systemic lupus erythematosus and acute pancreatitis: a case series. Clin Rheumatol. 2004; 23(2):147–151.
3. Makol A, Petri M. Pancreatitis in systemic lupus erythematosus: frequency and associated factors—a review of the Hopkins Lupus Cohort. J Rheumatol. 2010; 37(2):341–345.
4. Block SR, Winfield JB, Lockshin MD, D'Angelo WA, Christian CL. Studies of twins with systemic lupus erythematosus. A review of the literature and presentation of 12 additional sets. Am J Med 1975; 59: 533–55.
5. Wallace DJ. The clinical presentation of systemic lupus erythematosus. In: Wallace DJ, Hahn BH, editors. Dubois' lupus erythematosus. 5th ed. Baltimore: Lippincott Wilkins & Wilkins: 1997; 627.
6. Watts RA, Isenberg DA. Pancreatic disease in the autoimmune rheumatic disorders. Semin Arthritis Rheum. 1989;19: 158-165.

7. American College of Rheumatology. 1997 Update of the 1982 American College of Rheumatology revised criteria for classification of systemic lupus erythematosus.
8. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25: 1271–7.
9. Reifenstein EC, Reifenstein Jr, EC Reifenstein GH. A variable symptom complex of undetermined etiology with fatal determination. Arch Intern Med. 1939; 63:552–574. (7)
10. Nesher G, Breuer GS, et al. Lupus – associated Pancreatitis. Seminars in Arthritis and Rheumatism 2006; 35(4): 260 – 267.
11. Saab S, Corr MP, Weisman MH. Corticosteroids and systemic lupus erythematosus pancreatitis a case series, J Rheumatol1998;25: 801–806.

ISSN 2320 9208

Side effects of β2-Agonists delivered through metered dose inhaler in 42 year old male patient suffering from seasonal bronchial asthma: whose responsibility?

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ABSTRACT

Background: Inhaler β2–Agonist therapy plays a critical role in the management of patient suffering from asthma and copd, but concerns have been raised time to time regarding their safety. Hereby we describe a case of toxicity due to inhaled β2–Agonist in 42 year old male patient suffering from seasonal asthma. Conclusion: inhaled β2–Agonist are commonly used along with inhaled steroids in asthma patients but unlike tablets or syrups chances of incorrect dose–administration is more with inhalers. This case report reinforces the importance of imparting education to patients regarding inhalation devices.

Key-words: β2–Agonist, metered dose inhaler, asthma, adverse effects

Introduction

For past many decades β-inhaled agonists have been integral part of management of Asthma.[1] Short-acting β2 -specific agonists (SABAs) have a rapid onset of action and short duration of action. several studies implicated that regular use of SABA in asthma lead to increase in number of deaths and near-death emergencies[2]; 18,19

Long-acting β2 agonists(LABA) were designed to have longer duration of action and less of such kinds of incidence.[3] Soon after their introduction in 1990 concerns were raised about their safety.[4] A case in which variety of side effects of LABA i.e. Formoterol metered dose inhaler(MDI) in a patient with seasonal allergic asthmatic patient is reported herein.

Case -history

A 42-Year-old male patient started showing shortness of breath with change in season at this age. His doctor prescribed him salbutamol MDI for this. He was taking two puffs of 200 g Salbutamol in the morning. His shortness of breath used to aggravate by exercise in the morning in winters, for which he was prescribed budesonide 200 mcg, formoterol fumarate 6 mcg (Budamate Transhaler) MDI 1 puff in the morning.

Patient took 2 puffs of salbutamol MDI before exercise and after coming back from exercise he still had shortness of breath so he himself again took two puffs of prescribed budesonide 200 mcg, formoterol fumarate 6 mcg MDI instead of one as prescribed. After taking it patient came to his workplace but soon after he started feeling palpitations, tremors, nervousness, severe headache, dizziness that he has to come back to home. Only after consulting the doctor he came to know that it was because the inhalation drug.

Discussion

Formoterol is a LABA which causes bronchial smooth muscle relaxation. and is used in treatment of asthma and chronic obstructive pulmonary disease (COPD), which includes chronic bronchitis, emphysema, and other lung diseases.[5] For safety reason, it is not used alone but given in combination with an inhalational corticosteroids(ICS) e.g., fluticasone.[6]

The patient probably has exercise-induced Bronchoconstriction (EIB), which is caused by the loss of heat, water or both from the lungs during exercise. Apart from general measures like covering of mouth and nose, warm up with light exercises pharmacotherapy of EIB include;

- SABA 15-30 min before exercise and are effective for 2-4 hours and
- LABA along with ICS to prevent bronco-constriction and are effective for 12 hours and should be taken only once in 12-hour time period[7]

Here patient took salbutamol as prescribed previously and again took LABA and ICS using his own judgment. Salbutamol and Formoterol are both β2 -specific agonists, are associated with side effects with increase in dose i.e. chest pain, syncope, tachycardia, bradycardia or irregular heartbeat, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, upset stomach, dizziness, excessive tiredness, difficulty in falling asleep or staying asleep, thirst, tiredness, flushing, dry skin, frequent urination, loss of appetite, trouble in breathing.[8] These side effects usually do not pose significant clinical problems but cardiac symptoms can lead to fatal condition especially when patient is suffering from some cardiac disease or is taking other medication.[9,10] As in this case patient got panicked, miss his work for a day. This situation could have been avoided by imparting sufficient knowledge regarding usage of inhalers. Although generally every MDI inhaler user receives a printed explanation of the key steps in correct use in the manufacturer's patient information leaflet (PIL), which by law must be included in every inhaler pack. The majority of PILs use both pictures and written

information regarding usage of MDI. It was also there in the preparation patient used, but still there are lacunas regarding their proper usage which can only be filled by more elaborate healthcare professional -patient talk. Health care -professional can play significant role in achieving initial therapeutic benefit as well as long term maintenance by providing verbal instruction and demonstration. This can be achieved by imparting education to health care professionals as well patient so that they can also actively seek it when required.

References:

1. G. Crompton, A brief history of inhaled asthma therapy over the last fifty years, Prim. Care Respir. J. 2006;15(6): 326-331.
2. J. Crane, N. Pearce, A. Flatt, C Burgess, R Jackson, T Kwong et al., Prescribed fenoterol and death from asthma in New Zealand, 1981-83: case-control study. Lancet. 1989; 333(8644):917-922.
3. Global Initiative for Asthma. NHLBI/WHO Workshop Report: Global Strategy for Asthma Management and Prevention (revised 2009).
4. Nelson HS, Weiss ST, Bleecker ER, Yendey SW, Dorinsky PM. The Salmeterol Multicentre Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest. 2006;129(1):15-26.
5. B. Lipworth, S. Tan, M. Devlin, T. Aiken, R. Baker, D. Hendrick. Effects of treatment with formoterol on bronchoprotection against methacholine. Am J Med, 104 (1998), 431-438.
6. A. Wallin, T. Sandstrom, M. Soderberg, HOWARTH P, B Lundback,G Della-Cioppa et al.The effects of regular inhaled formoterol, budesonide, and placebo on mucosal inflammation and clinical indices in mild asthma. Am J Respir Crit Care Med. 1999 Jan;159(1):79-86.
7. Parsons JP, Hallstrand TS, Mastronarde JG, Kaminsky DA, Rundell KW, Hull JH, et al. An Official American Thoracic Society Clinical Practice Guideline: Exercise-induced Bronchoconstriction. Am J Respir Crit Care Med. 2013 May 1. 187(9):1016-27
8. Formoterol Inhalation-solution. Drugs.com; 2017(Last accessed on 28th Nov. 2017)
9. M. Cazzola, C.P. Page, L. Calzetta, M.G. Matera, Pharmacology and therapeutics of bronchodilators, Pharmacol. Rev. 2012, 64 (3) 450-504.
10. Macie C, Wooldrage K, Manfreda J, Anthonisen N. Cardiovascular morbidity and the use of inhaled bronchodilators. International Journal of Chronic Obstructive Pulmonary Disease. 2008;3(1):163-169.