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EDITORIAL

CANCER PAIN AND PALLIATIVE CARE

Pain is among the most common problems in the field of medicine and its allied disciplines. Pain has long been considered to be a symptom of acute injury or some underlying pathology demanding attention. However, chronic pain from various causes often becomes a syndrome in its own right that poses considerable challenge of management. Persistent unrelenting pain, especially intractable cancer pain, not only prevents a person from functioning in his daily routine pattern of life but also impacts adversely on his/her family and the society at large. The cost of total national loss of work-hours from pain, the cost of prolonged treatment and the investment of time of family members; runs into billions of rupees that affects negatively upon national economy due to interrupted gross productivity. The deleterious psychological effects on the whole family is unfathomable in terms of value in money.^{4,5}

Unfortunately, the apparent state of despair among the public is because of the wide spread lack of awareness not only among the masses but also to a large extent among the care givers. Recent 'World Congress on Pain' has provided exciting evidence that great strides have been made in pain therapy during the last two decades in the amelioration of even the worst of pain of cancer. Various interventional modalities including oral drugs, local infiltration, nerve blocks, epidural injection, physiotherapy and psychotherapeutic treatment protocols are available today, which provide palliation / complete relief from pain for medium to long term periods. This positive impact is the result of advancement in research and multidisciplinary approach to pain management.²

A notable feature of management of pain syndrome is the establishment and spread of Pain Clinics in major cities of Pakistan, primarily initiated by anesthesiologists. The discipline of Pain Treatment has come of age by recognition by CPSP for Membership, after the graduation of hundreds of Pain Specialists obtaining Masters Degree. The message is spreading far and wide, evidenced by recruitment of more and more students in MSc Pain management. Many specialists of other disciplines are joining the group for relieving their patients from the agony of pain besides providing specific treatment. It is hoped that in the next five years or so pain management clinics will be established in all districts of Pakistan.

Another veritable development is the establishment of research in the discipline of pain management in collaboration with International Association for Study of Pain (IASP). Higher Education Commission (HEC) has also joined in this noble endeavour by publishing a text book on pain management; and is co-operating in advancement of research and development.⁵

The next step in advancement of the discipline of pain management is the development of Palliative Care Centers in all major cities, offering multidisciplinary services to patients of chronic intractable pain especially for untreatable cancer patients. At present only two centers for palliative care are functioning in Pakistan namely Palliative Care Programs at SKMC & RC and AKU. New programs are planned in Hyderabad, Karachi & Lahore. Palliative care is an urgent humanitarian need in Pakistan for people with cancer and other chronic fatal diseases. Palliative care patient requires three categories of support by: pain specialist, treating physician/surgeon and a psychiatrist/psychologist. A fourth dimension of spiritual support can be mustered by a religious person.^{1,3}

Cancer is becoming one of the major health problems in Pakistan. There is no national population-based cancer registry, and precise incidence, the mortality rates and the number of new cancer cases/deaths annually for Pakistan are not known. WHO fact sheets (N.297 updated Feb 2015) reported cancer figure: 14 million new cases and 8.2 million deaths in year 2012. Number of new cases is expected to rise by about 70% over the next two decades.

It is paradoxical to mention that alarm bells went off when AIDS made its appearance. But no alarm was raised when John J. Bonica and other experts in the field of pain management told the World that tens of millions of people are suffering from terrible pain, that their lives and their families are devastated; that the cost to society is in billions of dollars. It is unfortunate that there is huge grant for research on cancer, but there is little money for research on cancer pain.⁶

We have a mission – all of us – to rectify the existing situation, for cancer pain as well as non-malignant chronic pain, in adults and in children, and for all varieties of acute pain. We should have a program to promote education in the treatment of pain for physicians, for medical students, for nurses and for

paramedics. We must also create awareness among patients that they have a right to freedom from pain, that each suffering human being deserves the best that modern medical science can offer.

We must also get our message to those in the government that pain is a major affliction that saps the strength of society, that funds for research and therapy are urgently needed, that regulations regarding supply of special drugs must be modified and made convenient, to meet the urgent needs of people in pain.

Meanwhile it is desirable to re-emphasize the importance of dissemination of information far and wide, among public as well as all care givers, that unnecessary suffering of pain is avoidable and a spectrum of treatment modalities is available for the benefit of patients. This message of spreading awareness falls in our direct responsibilities and we should do it for the sake of humanity suffering from pain; and for the sake of our duty to society. If we can pursue these goals together – as scientists and therapists, as members of the full range of the scientific and health profession – we can hope to meet the goal we all strive for: to help our fellow human beings who needlessly suffer from chronic pain.

Pain management is a fundamental human right as declared by WHO. It is a fifth vital sign and should be recorded in patients chart as we record TPR & BP (Temperature, Pulse, Respiration and Blood pressure).

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EVALUATION AND ASSOCIATION OF DENGUE NON-STRUCTURAL PROTEIN-1 ANTIGEN, IgM, IgG AND PLATELET COUNT AS MARKER OF DENGUE INFECTION

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ABSTRACT

Objective:

This study was done to evaluate the efficacy of non-structural protein 1 (NS1) antigen, IgM, IgG, assay and platelet count as an early marker for diagnosis of dengue virus (DV) infection.

Place of study:

The study was conducted at Rawal Institute of Health Sciences Islamabad from August 2015 to Nov 2015.

Material and Methods:

A total of 61 clinically suspected cases of dengue were recruited in the study. 5cc Blood was obtained from antecubital vein under aseptic measures. This blood was transferred to serum gel separator tubes after labeling for further processing and testing for NS1, IgM and IgG by immunochromatography-based test. Platelet count was obtained by differential analyzer.

Results:

A total of 61 suspected cases of dengue fever were selected, out of which 42 (68.9%) were found positive for NS1, 14 (22.9%) for IgM, while 11 (18%) were found IgG positive only. Only 03 samples were positive for IgM, IgG and NS1. Thrombocytopenia $<100 \times 10^9/L$ was detected in 24 (39.3%) cases and were more consistently associated with IgG, and IgM compared to NS1 detection (P value <0.001). A significant positive correlation was found between platelet count and IgM ($r=0.358$, $p=0.005$) and IgG ($r=0.369$, $p=0.003$) as well as between IgM and IgG ($r=0.811$; $p=0.000$).

Conclusion:

Inclusion of NS1 in the diagnosis of dengue increases the detection rate significantly. In cases of fever, thrombocytopenia is more consistently found in dengue positive rather than dengue negative subjects. It correlates well when IgM is detected.

Keywords:

Dengue, IgM, IgG, NS1, Thrombocytopenia

INTRODUCTION

Dengue is considered to be an acute, febrile arboviral disease transmitted by mosquitoes affecting tropical and subtropical regions of the world.¹ The incidence of this disease has increased over the last 50 years with 2.5 billion people living in areas where dengue is endemic. It affects up to 100 million people each year, with 500,000 cases of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) and around 30,000 deaths,

mostly amongst children.²

It is one of the major health concerns since 2005. Dengue was detected for the first time in Pakistan in Karachi in 1994. Total of 48910 cases reported with 556 deaths reported till 2014.³

In 2011, Pakistan had the worst strike of dengue in which more than 20,000 cases and 300 deaths were reported officially which according to experts reflected under reporting. Lahore was the epicenter with maximum number of cases followed by Faisalabad, Rawalpindi and Sargodha. In Pakistan the number of dengue cases are gradually increasing from 500 in year 2000 to 2000 in year 2015.

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Significant constituents of the Asia-Pacific Dengue Strategic Plan by WHO (2008–2015) are to support collaboration, cooperation and biregional solidarity for effective and sustained prevention and control of dengue in countries of the Asia-Pacific Region. It uses prevailing policy agendas and infrastructure as integral parts of dengue prevention and control programmes, and integrates disease surveillance within the umbrella of basic health services. It also uses national, multicountry, biregional and global partnerships to support country activities.⁴

It is caused by four serotypes of dengue virus belonging to genus *Flavivirus* and family *Flaviviridae*. It is spread through the bite of infected *Aedes aegypti* mosquito. The infection can culminate into dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).⁵

The virus usually gives lifelong immunity to that type, but only short-term immunity to the others. Subsequent infection with a different type increases the risk of severe complications like DHF and DSS and their early diagnosis with supportive therapy reduces morbidity and mortality.⁶

Identification of dengue infections (DI) can be done by detection of specific virus, viral antigen, genomic sequence, and/or antibodies. Three basic methods are being practiced by most laboratories for the diagnosis of dengue virus infection, viral isolation and characterization, detection of the genomic sequence by a nucleic acid amplification technology assay and detection of dengue virus-specific antibodies. Molecular diagnosis based on reverse transcription (RT)-PCR, such as one-step or nested RT-PCR, nucleic acid sequence-based amplification (NASBA), or real-time RT-PCR, has gradually replaced the virus isolation method as the new standard for the detection of dengue virus in acute-phase serum samples.^{7,8}

Concurrent assays for dengue virus non-structural protein 1 (NS1), anti-dengue IgM, anti-dengue IgG along with platelet enumeration in the 'Dengue Package' is beneficial for diagnosis, management and prevention from complication.^{9,10}

A combination of NS1 and dengue specific IgM/IgG detection during the first few days of illness increases overall dengue diagnostic sensitivity. The NS1 is reported to be sensitive as well as highly specific. NS1 is a highly conserved

glycoprotein that is essential for the viability of DV and is produced both in membrane-associated and secretory forms by the virus. However, as antibody detection is an indirect method of diagnosis so there is chance of false positive and false negative results. The platelet count by microscope supports the diagnosis of DHF or DSS and platelet therapy is a standard clinical practice for dengue patients with severe thrombocytopenia.¹¹

As dengue created an alarming situation in Pakistan so the aim of our study is to evaluate the efficacy of non-structural protein 1 (NS1) antigen, IgM, IgG, assay and platelet count as an early marker for diagnosis of dengue virus (DV) infection.

MATERIALS & METHODS

The study was conducted at RIHS during the period August to November 2015, and a total of 61 suspected dengue patients were selected for testing assays for NS1, IgM, IgG and automated platelet enumeration. Blood samples were collected by venipuncture in the hospital laboratory under aseptic technique into ethylene diaminetetraacetic acid (EDTA) coated tubes. Samples were tested for antibody assays employing the single-step immunochromatographic method according to the manufacturer's instructions. The platelet enumeration was done in 3-differential analyzers, (BC-3000^{Plus} Mindary, Shenzhen, China). The reports were available within 1–2 hours. Apart from the in-built controls in the One-step dengue NS1 Ag (Healgen Scientific Limited Liability Company US; Sensitivity 95.7%, specificity 98.3%) and IgG (Standard Diagnostics, Inc., St. Ingbert, Germany, Sensitivity 90%, specificity 95%, IgM (Standard Diagnostics, Inc., St. Ingbert, Germany, Sensitivity 95.7%, specificity 98.3%) test, no independent controls from NS1 antigen, IgM and IgG were used.

The haemagglutination inhibition assay (HIA) has been considered the gold standard for detecting dengue-specific antibodies in serum samples. HIA can be used to identify past infection and to differentiate between primary and secondary dengue infections. HIA requires paired acute and convalescent serum samples to detect changes in antibody levels.¹² Other gold standard include Cell culture (using mosquito cell lines, such as C6/36 and AP61 or mammalian cell lines, such as Vero and LLC-MK2 cells) and Dengue viral RNA can be

detected using a nucleic acid amplification test (NAAT) on tissues, whole blood or sera in the acute phase of the disease.¹³

Data were entered and analyzed using the Statistical Package for Social Sciences (SPSS Inc, Chicago, IL, USA, Version 16). Non-parametric testing was carried out. $p < 0.05$ was considered significant.

The performance of this study was approved by the Ethical Committee of the RIHS hospital.

RESULTS

A total number of 61 patients were included in the study with an age of 29.24 ± 16.17 years.

Table 1: Distribution of various dengue specific parameters

| Variables | Number (%) | OR | CI | p value |
|---------------|------------|-------|--------------|---------|
| Myalgia | 48 (78.7%) | 0.943 | 0.718 –1.239 | 0.669 |
| Vomiting | 28 (45.9%) | 0.576 | 0.303 –1.094 | 0.069 |
| Skin rash | 10 (16.1%) | 3.360 | 0.960 –11.75 | 0.041 |
| Fever | 60 (98.4%) | 0.960 | 0.886 –1.040 | 0.226 |
| Platelet <100 | 37 (60.7%) | 0.720 | 0.365 –1.419 | 0.328 |
| IgG | 11 (18%) | 0.823 | 0.269 –2.516 | 0.731 |
| IgM | 14 (23%) | 1.080 | 0.427 –2.730 | 0.871 |
| NSI | 42 (68.9%) | 0.720 | 0.488 –1.602 | 0.071 |

Of the 61 most of the patients presented with fever (98%, OR 0.960; CI 0.886 – 1.040; $p=0.226$) and with muscle pains (78.7%, OR 0.943; CI 0.718 – 1.239; $p=0.669$) and were found to be statistically non-significant, while vomiting (45.9%, OR 0.567; CI 0.303 – 1.094; $P=0.069$) and skin rashes (16.1%, OR 03.360; CI 0.960 – 11.75; $P=0.041$) though less in percentage but were significant. Platelet count less than 1,00,000/ml was noticed in 24 cases (39.3%), however, bleeding tendency was not detected in any case.

Table 2: Comparison between various diagnostic variables

| Category | Cases (%) | OR | CI | p value |
|----------------------------|------------|-------|---------------|---------|
| IgG positive, IgM positive | 11 (18%) | 0.062 | 0.026 –0.144 | 0.000 |
| IgG negative, IgM negative | 47 (77.0%) | 4.667 | 1.712 –12.724 | 0.000 |
| IgM positive, NSI positive | 12 (19.6%) | 0.745 | 0.550 –1.009 | 0.121 |
| IgM negative, NSI negative | 17 (27.8%) | 2.532 | 0.664 –9.651 | 0.221 |

| | | | | |
|-----------------------------|------------|-------|---------------|-------|
| IgG negative, NSI negative | 19 (31.1%) | 0.603 | 0.533 –0.744 | 0.014 |
| IgG positive, NSI positive | 11(18.0%) | 0.620 | 0.499 –0.770 | 0.035 |
| Platelet <100, IgM positive | 10 (16.3%) | 3.854 | 1.363 –10.899 | 0.005 |
| Platelet <100, IgM negative | 14 (22.9%) | 0.654 | 0.458 –0.934 | 0.013 |
| Platelet <100, IgG positive | 09 (14.7%) | 6.938 | 1.638 –29.384 | 0.001 |
| Platelet <100, IgG negative | 15 (24.5%) | 0.661 | 0.480 –0.909 | 0.004 |
| Platelet <100, NSI positive | 21 (34.4%) | 1.542 | 1.120 –2.122 | 0.011 |
| Platelet <100, NSI negative | 03 (4.9%) | 0.289 | 0.094 –0.887 | 0.024 |

The serum samples of all cases were found positive for either one or more of the three markers (NSI, IgM and IgG). It was also revealed that 42 patients (68.8%) were positive for only NSI, 14 (23%) positive for only IgM, while 11 patients (18%) had only IgG positive. Collectively all three markers NSI, IgG, and IgM were detected only in 11 patients (18%). There were only 2 cases who were IgM positive but IgG and NSI negative. Only 24 (39.3%) patients were found to have a platelet count less than $100 \times 10^9/L$. Out of 60 patients having fever showed thrombocytopenia in 24 (39.3%) cases ($p=0.417$)

Table 3: Correlations between diagnostic variables

| | | platelet | IgM | IgG | NSI |
|----------|---------------------|----------|--------|--------|------|
| Platelet | Pearson Correlation | 1 | .358** | .369** | .042 |
| | p value | | .005 | .003 | .748 |
| IgM | Pearson Correlation | .358** | 1 | .811** | .145 |
| | p value | .005 | | .000 | .266 |
| IgG | Pearson Correlation | .369** | .811** | 1 | .151 |
| | p value | .003 | .000 | | .245 |
| NSI | Pearson Correlation | .042 | .145 | .151 | 1 |
| | p value | .748 | .266 | .245 | |

**Correlation is significant at the 0.01 level (2-tailed).

A statistically significant positive correlation was found between platelet count and IgM ($r=0.358$, $p=0.005$) and IgG ($r=0.369$, $p=0.003$) while non-significant correlation was found to be with NSI ($r=0.042$, $p=0.748$). Similarly a significant positive correlation was noticed between IgM and IgG ($r=0.811$; $p=0.000$) but with NSI it was found to be non-significant ($r=0.145$, $p=0.266$). NSI also showed a non-significant correlation with IgG ($r=0.151$, $p=0.245$).

DISCUSSION

The distribution of various dengue specific parameters is shown in Table 1. Our results showed that out of 61 cases, 42 were positive for only NSI antigen and are in consistence with Datta et al¹⁴ and

Shrivastava et al¹⁵ showing that NS1 was positive in 140 out of 600 (23.3%) and 15 out of 91 (16%) cases respectively in their studies. This is supported by the fact that a large number of cases would be missed if NS1 is not included in the test panel.

Among 61 cases there were 42 NS1 positive and 14 IgM positive patients as shown in Table 2. They were suffering from a primary infection in the early phase of illness and were also viremic, i.e. they could transmit the virus if bitten by a mosquito. The 11 patients who were exclusively IgG positives, with a secondary viral infection, would have also been overlooked. Without NS1 screening they been labeled as "dengue negative". They could have been infectious for mosquitoes during the earlier phase of illness. The concurrent NS1-positive and IgM-positive status of 17 patients (Table 2) reinforced the utility of antigen detection during the earlier phase of illness. Furthermore, 11 patients who were positive for NS1, IgM and IgG (triple-positives) were in the late stage of either a primary or a secondary infection and might have been infectious for mosquitoes. The NS1 test helped in diagnosing otherwise IgM negative cases. The NS1 negatives included 2 IgM positives that had a primary infection presenting a later phase of illness. They were IgG negative. It is unlikely that dengue IgG antibody levels became undetectable in the convalescent phase of illness. Furthermore, there were 11 cases that were positive only for IgG who might have presented themselves for 'Dengue Package' fairly early during a secondary infection.

A total of 11 cases were positive for both IgM and IgG (Table 2). Such patients with a primary or secondary infection had presented in a later stage of illness. Dengue viruses are generally extruded from the host when IgM antibodies are present.

For a long time detection of dengue-specific IgG/IgM has been the pillar of diagnosis of dengue infection. The dengue-specific antibodies begin to appear only around fifth day of fever in primary infection. Even in most secondary infections, both the IgM and IgG type antibodies cannot be recorded before third day. Therefore, there is always a window period, both in primary and secondary dengue infection when only antibodies are tested. The new parameter, the NS1 antigen, is detectable from day 1 of fever both in primary and secondary

infections. It is important to note that NS1 is shown to be highly specific viral marker making it extremely reliable parameter for the diagnosis of dengue infection from day 1 of the fever.^{17,18}

NS1 in combination with either IgM or IgG was positive in 12 and 11 respectively in our study. Among two antibodies, IgG is a less reliable marker in the diagnosis of DI.¹⁹ Both clinical and sub-clinical infections can produce IgG which may persist for several years affecting the interpretation of test results. It is highly likely that IgG levels could be higher in endemic areas because of bites from infected mosquitoes. However, dengue-specific IgM is a very good indicator of recent infection. It may also be detectable in secondary DI. Utility of antibody in the diagnosis of infections relies mainly on rising titres, especially in the endemic areas. When NS1 is positive, there is no need of repeat testing as it is a highly specific marker of DI.^{20,21}

We tried to rule out the association of dengue specific parameters with thrombocytopenia which is shown in Table 2 of results. Of the 61 cases, 24 showed thrombocytopenia. In 42 cases that were positive for NS1, thrombocytopenia was evident in 21 cases. The role of antibody in the pathogenesis of dengue fever is well-known. Therefore, better association of platelet count with detection of antibody is reliable.

Platelet counts are decreased in several other conditions like some viral infections other than dengue, drug induced thrombocytopenia, collagen vascular diseases, idiopathic thrombocytopenia.²⁸ In 61 cases of fever, thrombocytopenia was noted in 24 cases ($p=0.417$). A strong significant association ($p<0.05$) of thrombocytopenia and dengue parameter including IgG and IgM was noticed.

This study has been carried out at a tertiary care teaching hospital and most hospitals lack in viral culture setup. Dengue infection is present in urban, semi-urban and rural areas. Our healthcare system is extremely resource poor. It is important to conduct studies in the peripheral centers where the laboratory has to function without great technological backup and still is expected to provide reasonable opinion to the clinician in the management of infections like dengue.

CONCLUSION

IgG, IgM and NS1 Ag assays hold promise in early diagnosis of dengue infection. In cases of fever, thrombocytopenia is more consistently found in dengue positive rather than dengue negative subjects. It correlates well when IgM is detected.

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RUBELLA INFECTION: AWARENESS, VACCINATION AND SEROLOGY STATUS OF FEMALE MEDICAL STUDENTS OF A PRIVATE MEDICAL COLLEGE OF ISLAMABAD

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ABSTRACT

Objective:

To assess awareness and to determine vaccination and serology status of Rubella infection among female medical students of Foundation University Medical College Islamabad.

Methods:

A Cross sectional descriptive study was conducted by enrolling 366 female medical students from March to October 2012. After taking consent from the respondents, data was collected on a pre tested structured coded self administered questionnaire on variables of age, MBBS year, awareness of diseases and its prevention, sources of information, vaccination and serology status, reasons for not getting vaccinated etc and analyzed by using SPSS version 20. Chi square test was applied to see the association between awareness and the vaccination status.

Results:

The study showed that 198(68.3%) female medical students were fully aware and 92(31.5%) were unaware, whereas 56 (19.3%) were vaccinated against Rubella Infection while 139(48.4%) were not and 95(32.8%) were not sure of their vaccination status, reason given by 120 (51%) of the non vaccinated respondents was lack of time and there was no history of seroanalysis of all the respondents whether vaccinated or not. Statistically significant association was found at $p < 0.05$ between awareness level and vaccination status of the respondents..

Conclusion:

Awareness on Rubella infection was good but a significant number of students were not aware of its vaccination. Besides only one fifth of the female medical students were vaccinated against Rubella infection and none of them had undergone serology irrespective of their vaccination status. All opportunities should be availed by the educational institutes for awareness, vaccination and serology of their female students.

Keywords:

Infection, Serology, Vaccine , Congenital Rubella Syndrome

INTRODUCTION

Rubella is a key public health problem characterized by a mild rash sickness in children and adults. However, its gravity and public health significance originates from its transplacental infection of fetal tissue, which may lead to congenital rubella syndrome (CRS).^{1,2} It is a vaccine preventable viral disease which can easily be controlled by vaccination. The most vulnerable high risk group is the seronegative women of child

bearing age (15-49 years). Health professionals are constantly exposed to the infective health environment. A research was conducted in 2009 at Rawalpindi on surveillance of Rubella in female medical students, 80% of 1st year MBBS students were seronegative while 90% were seropositive in final year after 2-3 years of exposure to the hospital environment.³

Also known as "German measles" as first defined by a German physician. It is caused by one antigenic type of Rubella virus (Toga virus).³ It has a characteristic acute onset indiscriminate pinkish maculopopular rash and that is why the name "Rubella" which means "Little Red" is given. It is associated with a fever less than 37.2°C and sub-

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occipital or post-auricular lymphadenopathy and arthritis /joint pains.⁴ It has an incubation period of 12-14 days and can spread directly from infected individual to healthy individual via respiratory aerosols and from infected mother to fetus, 7 days before and after the onset of rash. Rubella has no specific treatment, only symptomatic treatment is given.

Though it is a mild self limiting disease but the virus is highly teratogenic if infection is acquired during first trimester of pregnancy which causes serious congenital diseases which comprise a syndrome known as Congenital Rubella Syndrome (CRS). Rubella is clinically diagnosed and confirmed by laboratory investigations. IgM antibodies against rubella are detected after isolation of virus from cerebrospinal fluid, nasal and throat secretions. ELISA is the most common serological test.⁵

The risk is higher (up to 90% cases) in the period from just before conception and during the first 8–10 weeks of conception. After 16th week of pregnancy there are fewer chances of fetal defects due to maternal rubella.⁶ CRS is a triad which constitutes congenital heart diseases especially Patent Ductus Arteriosus (PDA), congenital cataract, Microphthalmia and Sensorineural deafness. Other manifestations may include microcephaly, low birth weight (LBW) mental retardation, bone-marrow spleen, and liver problems.⁷ Developmental disabilities are faced by the surviving infants. Up to eighteen months of age, the infected infants keep on shedding the virus. It is one of the most significant causes of infant mortality rate.⁸ Rubella vaccinations is done in children and women of child bearing age (WCBA) by combination of a triple vaccine known as Measles Mumps and Rubella vaccine (MMR), passive immunization is also done.⁹ Long term protection is given by Rubella vaccine which is effective and safe as well.

A population of more than 22,064 (less than 5 years of age) and 45,622 (female 15-49 years of age) is at risk in Pakistan.¹⁰ As per WHO strategy, to decrease the risk of CRS, adolescent girls and WCBA are to be immunized at priority.¹⁰ However, women were difficult to access in many settings which resulted in low vaccine coverage and the circulation of rubella virus continues. Also when there is low coverage of routine childhood immunization, the children remain susceptible into adulthood. The focus is now

on interrupting transmission of rubella virus with the view to eliminate rubella as well as CRS over the long term.¹¹

In United States, before the introduction of the rubella vaccine in 1969, epidemics of rubella occurred in six to nine year cycles usually in the late winter and early spring. In 1964, a major global pandemic occurred which involved United States in which approximately 12.5 million cases of rubella, 11,000 fetal deaths, and 20,000 cases of CRS were reported. But with immunization, Rubella and CRS have mostly been eliminated in the United States.¹² The incidence of rubella has declined from 0.45 per 100,000 in 1990 to 0.1 per 100,000 in 1999.¹³ However, outbreaks of rubella continue to take place in other parts of the world. WHO estimates that in 1996, 22,000 children were born with CRS in Africa, 46,000 in Southeast Asia and almost 13,000 in the Western Pacific.¹³ RA27/3 rubella vaccine was first licensed in USA in 1979 and until now it is the only Rubella vaccine which is available other than the combination vaccines. Vaccination leads to production of IgG antibodies in more than 98% of vaccine recipients, a single dose gives long-term immunity.^{12,13} The first dose is given at 12 to 15 months of age, usually as a combination of Measles Mumps and Rubella vaccines (MMR) and one or two doses to susceptible WCBA.¹⁴ MMR vaccination is not included in Pakistan Expanded Programme of Immunization (EPI) but this vaccine is available in addition to Rubella vaccine Rubevac.¹⁵ Two doses of MMR Vaccine are also recommended for all travelers to Pakistan 4-8 weeks before departure.¹⁶

In 2011, Pakistan reported 189 cases of Rubella to WHO and no data was available for CRS while in the same year neighboring country Afghanistan reported 750 cases with 3 CRS cases.¹⁰ A study was conducted in 2004 at one of the children hospitals of Pakistan. During one year study period, 3 cases of CRS/100 live births were identified which is an alarming figure. Serological diagnosis of rubella in these infants was confirmed by the presence of rubella virus specific IgM in serum.¹⁷

This study is designed to assess the awareness regarding Rubella infection among the female medical students who are WCBA and the future health care providers and it is expected that they are having enough knowledge to protect themselves and their patients. The study itself will generate

awareness and motivation on such an issue in which the actual burden of disease especially CRS is not known. The susceptibility of these students of acquiring this viral infection cannot be denied. The study will highlight the ground realities of rubella vaccination status of this high risk population as vaccination of WCBA can prevent CRS and other teratogenic affects in future pregnancies which will otherwise be a distress to the family, society and the health system. The educational institutes have the opportunity of accessibility to this vulnerable population. The findings can be used to further establish their susceptibility by seroanalysis for this disease and future interventions can be undertaken.

OBJECTIVES

1. To assess the awareness regarding Rubella infection among female medical students of Foundation University Medical College (FUMC) Islamabad.
2. To determine Rubella vaccination and serology status of these students.

METHODOLOGY

A descriptive cross sectional study was conducted at Foundation University Medical College Islamabad, from March to October 2012 by enrolling 366 female medical students with their consent by homogenous purposive sampling. A self structured pretested questionnaire was administered and data was collected on the variables like age, MBBS year, awareness of Rubella disease and it's prevention, source of information, vaccination status, reasons for not getting vaccinated, willingness for vaccination and seroanalysis etc. Interviews with the Pathologist, Gynaecologist, Pediatrician, Cardiologist and Ophthalmologist were also conducted. In this study those who had the knowledge of vulnerable age group, cause and mode of spread, complications, teratogenic complications, and vaccination of Rubella were considered as fully aware and those who didn't know the disease and its vaccination were taken as unaware. Respondents who did not receive any vaccination or didn't know about their vaccination status were taken as not vaccinated. Data was analyzed on SPSS version 20. p-value of <0.05 was taken as significant. Chi square test was applied to determine the association between awareness and vaccination status of the respondents.

RESULTS

A cross sectional study was conducted on a study population of 366 female medical students out of which 290 responded with a response rate of 79.2%. Mean age was computed as 20.92 years \pm 1.71. 198 (68.5%) respondents were fully aware and 92 (31.5%) were unaware of the Rubella infection. The main source of information was print media 84 (42.4%) while in 33 (16.7%), the source was family doctors/ health care workers. (Table I). Only 56 (19.3%) were vaccinated and the 234 (80.7%) were either not vaccinated or not sure of their vaccination status and the main reason given by 169 (72.2%) of the non vaccinated respondents was lack of time and 38(16.2%) attributed to non availability of vaccine. (Table II). However, 196 (83.7%) out of non vaccinated respondents were willing to go for vaccination and 229 (79%) of the respondents irrespective of their vaccination status were willing for seroanalysis to assess their susceptibility level. (Table III).

Table I: Demographic profile, awareness status of the respondents and sources of information

| Variables | |
|--------------------------------------|------------------|
| Age in years | |
| Mean age \pm _SD | 20.92 \pm 1.71 |
| Mode | 20 |
| MBBS year wise distribution | n (%) |
| 1 st year | 75 (25.8%) |
| 2 nd year | 57 (19.6%) |
| 3 rd year | 56 (19.3%) |
| 4 th year | 42 (14.5%) |
| Final year | 60 (20.7%) |
| Marital Status | |
| Married | Nil |
| Unmarried | 290 (100%) |
| Nationality | |
| Pakistani | 281 (97%) |
| Foreigner | 9 (3%) |
| Awareness status | |
| Aware | 198 (68.5%) |
| Unaware | 92 (31.5%) |
| Source of information (n=198) | |
| Electronic media | 18 (9%) |
| Print media | 84 (42.4%) |
| Friends/ relatives | 29 (14.7%) |
| Family doctors/ Health care workers | 33 (16.7%) |
| Others | 34 (17.2%) |

Table II: Vaccination status and reasons for not getting vaccinated

| Vaccination status: | n (%) |
|---------------------------------------------------|--------------|
| • Vaccinated | 56 (19.3 %) |
| • Not Vaccinated | 142 (49%) |
| • Don't know | 92 (32%) |
| Reasons for not getting vaccinated. n=234: | |
| • Don't have time | 169 (72.2 %) |
| • Financial constraints | 8 (3.4%) |
| • Not willing | 19 (8%) |
| • Vaccine not available | 38 (16.2%) |

Table III: Future prospects for the prevention of Rubella among the respondents

| Vaccination status | n | Willingness status | Yes n(%) | No n(%) |
|----------------------------------------|-----|----------------------------------------------------------|-------------|------------|
| Non vaccinated | 234 | For Vaccination | 196 (83.7%) | 38 (16.3%) |
| All irrespective of vaccination status | 290 | For assessment of susceptibility by serological analysis | 229 (79%) | 61 (21%) |

DISCUSSION

Rubella is a viral infection which has a minor morbidity but the area of concern is its serious complication of CRS in the pregnant women who are exposed to this infection especially in the first trimester. Female medical students were purposively included in this study as they are in the child bearing age and also in the premarital stage as well. Being the future health care providers, they are also assumed to be fully aware of this disease and its prevention and vaccination. Awareness regarding Rubella infection among female medical students of FUMC was good which was assessed on the basis of their knowledge regarding the disease, vulnerable age group, mode of spread, complication for the fetus, vaccination etc. Awareness on vaccination was lacking and therefore who did not know about the vaccination was considered unaware. In a study conducted in Pakistan, 77.3% of the women were immune to rubella and 17.5% women were non-immune.¹⁸ Results are not comparable to this study as in our study none of the students knew about their seronegativity irrespective of their immunization status. In another study it was revealed that almost half of the women were seronegative for Rubella.¹⁹ Our results pertaining to awareness and vaccination status are

consistent with another study in which the awareness about rubella was high (94.1%) but only 42.1% were vaccinated.²⁰ The reasons given for not getting vaccinated showed their non-seriousness about the problem which is also supporting our findings as majority of the students couldn't find time for vaccination. Sources of information for rubella vaccination in the reference study were their gynaecologist/doctor (62.3%) or medical books or literature (36.5%) and not any mass media where as in our study print media was the commonest source and only a little contribution by the electronic media was there. In developing countries like Pakistan where literacy rate is quite low, general public awareness on prevention of Rubella disease and CRS is expected to be low, electronic media can play a positive role in awareness campaigns. WHO recommends that priority in preventing CRS should be given in order to protect susceptible WCBA from maternal rubella. Data was deficient on this public health issue and therefore burden of CRS cannot be assessed. In a study conducted in Pakistan, CRS cases as high as 3/100 newborns in a year were documented.¹⁷ Moreover during interviews of clinicians and pathologists, it was also conveyed that cases of CRS are occurring but reporting is deficient.

The burden of CRS In developing countries has been assessed by surveillance of CRS, by age-stratified serosurveys; by surveillance of acquired rubella and documenting the serosurveys for rubella susceptibility of WCBA.²¹

The encouraging finding of the study was that majority of the female students were willing for their seroanalysis to ascertain their susceptibility and eligibility for vaccination accordingly. There was limitation of not conducting seroanalysis of the study population due to resource constraints which can be overcome in future researches.

CONCLUSION

Awareness on Rubella infection was good but a significant number of students were not aware of its vaccination. Besides only one fifth of the female medical students were vaccinated against Rubella infection and none of them had undergone serology irrespective of their vaccination status. Majority of non vaccinated were willing for future vaccination and a large percentage of the respondents were willing for serology to ascertain their susceptibility.

RECOMMENDATIONS

More focus is required for developing awareness programmes and educating providers regarding the likely increased risk for rubella and ensuring that providers advise vaccine for susceptible persons. Assessment of seronegativity of our study population should be done before carrying out any vaccination programme. There is a dire need to evaluate the susceptibility of WCBA to rubella infection whether vaccinated or not in order to prevent CRS in future pregnancies by vaccinating seronegative women. CRS has a cumulative effect both on the family, society and the health system. MMR vaccine should be made available, accessible and affordable. All the opportunities for vaccinating women of child bearing age should be looked into and the educational institutes can also take this initiative. It's vaccination should be included in our national immunization programme. In Pakistan, actual burden of this disease and specially CRS can only be ascertained if there is surveillance and national reporting.

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PREVENTION OF CORONARY ARTERY DISEASE BY NIACIN AND GREEN CARDAMOM (ILAICHI)

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ABSTRACT

Objective:

Atherosclerosis is a complication of dyslipidemia causing coronary artery disease leading to mortality due to Myocardial Infarction. There are various drugs which reduce plasma lipids but with potential side effects. Herbal medication like Green Cardamom has potential to lower bad cholesterol, i.e. LDL-cholesterol and raise good cholesterol, i.e. HDL-cholesterol.

Objectives: To compare hypolipidemic effects of Niacin with Cardamom.

Methodology:

It was single blind placebo-controlled study carried out at Jinnah Hospital Lahore from July to November 2015. Seventy five hyperlipidemic patients were selected for research work. They were divided in three groups. Group-I was on placebo, group-II was given 1.5 grams Niacin, and group-III was advised to use powdered Cardamom thrice daily for the period of two months. Their base line lipid profile was determined by Freidewald Method. Total-cholesterol, LDL-cholesterol and HDL-cholesterol were main parameters we required for further calculation of any change. All patients were advised to visit clinic fortnightly for their follow up.

Results:

After two months therapy group-II patients reduced total cholesterol to 30.8 mg/dl and LDL cholesterol 12.1 mg/dl and increased HDL cholesterol to 5.6 mg/dl. In group-III Cardamom decreased total cholesterol 7.2 mg/dl and LDL cholesterol 8.8 mg/dl. HDL cholesterol in this group increased to 4.9 mg/dl. When results were compiled and analyzed statistically, these changes were significant.

Conclusion:

We concluded that Niacin had more effects on total cholesterol but effects of both drugs on LDL cholesterol reduction were almost the same.

Keywords:

Coronary artery syndrome, Green cardamom, Niacin, HDL cholesterol

INTRODUCTION

Atherosclerosis is the result of the oxidative changes of low density lipoproteins (LDL) in the arterial wall by reactive oxygen species i.e. free radicals.^{1,2,3} Free radicals have remarkable potential for development of atherosclerosis/coronary artery disease (CAD) leading to morbidity and mortality due to myocardial infarction (MI).⁴ Obese patients with high plasma lipids levels, patients with type 2 diabetes, patients with history of smoking, alcohol consumption, old age and with problem of nitrate intolerance are more prone to the consequences of

oxidative stress.⁵ It has been proved in many research trials that allopathic drugs or medicinal herbs with hypolipidemic potential can reduce overall oxidative stress in human body, making body less vulnerable to cause coronary artery disease and its consequences like MI.^{6,7} Hypolipidemic drugs reduce low density lipoprotein cholesterol (LDL-c) in plasma and thus lower the chance of developing atherogenesis leading to increased risk of hypercholesterolemic patients to be victimized by coronary artery disease, and myocardial infarction.⁸ Conventionally, drugs used in hyperlipidemia are statins, nicotinic acid, bile acid binding resins and fibrates, but all have potential for low compliance due to wide range of pharmacological and adverse effects.⁹ Vitamin B-3 (Niacin), if given in large

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doses inhibits lipolysis in adipose tissue which is main source of plasma free fatty acids. In liver due to lack of these free fatty acids, no triglycerides or lipoproteins carrying these lipid forms (VLDL) will be synthesized. Low density lipoproteins (LDL) are synthesized from VLDL. Thus no availability of very low density lipoproteins (VLDL) causes reduced synthesis of LDL in plasma. Niacin also decreases clearance of apoprotein A-1 in plasma, so high density lipoproteins (HDL) which are concerned with these apoproteins are also increased.^{10,11} To get good compliance, many health personals and researchers have started to put their healing potential for developing alternatives drugs used in primary or secondary hyperlipidemia. Cardamom or in Urdu ILAICHI is one of the hypolipidemic herb, widely encouraged by cardiologists to be used for prevention of atherogenesis, and coronary artery disease.¹² Cardamom contains some phenolic compounds and flavonoids which act as free radical scavengers.¹³ Green Ilaichi contains some chemical compounds which act as antioxidant at myocardial cells and hepatocytes. This medicinal herb also contain glutathione which acts as protective compound for normal visceral cells from damage due to formation of free radicals in various metabolic processes in human body.¹⁴ Cardamom is also rich in powerful anti-oxidant mineral, manganese and immune improving element zinc. Its magnesium and potassium contents keep heart cells healthy and normalize systolic/diastolic blood pressure, preventing risk of developing coronary artery disease.¹⁵

PATIENTS & METHODS

It was single blind placebo-controlled study conducted in Jinnah Hospital Lahore from July to November 2015. Seventy five hyperlipidemic patients were selected and enrolled for the study. Written, already explained and approved consent was taken from all patients. Inclusion criteria were age limit from 18 to 70 years of both gender primary or secondary hyperlipidemic patients. Patients suffering from any severe vital organ disease or their impaired function were excluded from the

study. Alcoholics, cigarette smokers and patients taking regular medicine for their any physical or mental disease were also excluded. Seventy five patients were divided in three groups, comprising 25 patients in each group. Group-I was on placebo therapy. The patients were provided capsules containing grinded rice and mixed wheat. They were advised to take one capsule before meal, thrice daily for two months. Group-II patients were advised to take half tablet niacin 250 mg, thrice daily after each meal. They were advised to raise dose of niacin tablets gradually after two days, until they tolerate dose of niacin up to two tablets of 250 mg, thrice daily after each meal for the period of two months, counting their day-0 from maximum tolerated dose of the drug. This titration of dose of drug was necessary because niacin can cause flushing if taken in high doses at start. Group-III was advised to take one gram grinded green cardamom powder mixed in black tea, thrice daily after each meal for the period of two months. Their base line lipid profile was determined by Freidewald method.¹⁵ Total-cholesterol, LDL-cholesterol and HDL-cholesterol were main parameters we required for further calculation of change in these parameters. All patients were advised to visit clinic fortnightly for their follow up. After two months therapy their lipid profile was measured again by same Freidewald method. Data were expressed as the mean \pm Standard Deviation and "t" test was applied to determine statistical significance as the difference. A probability value of > 0.05 was considered as non-significant and p value < 0.001 was considered as highly significant change in the results when pre and post-treatment values were compared.

RESULTS

After two months therapy with Niacin and Cardamom three patients withdrew to take niacin due to its unwanted effects like flushing and urticaria and one patient stopped to take cardamom due to its personal reasons. After completion of research, mean values were expressed in SD \pm SEM and paired t-test was applied to analyze result's significance biostatistically. Following changes were observed in total, LDL, and HDL cholesterol with their statistical significance.

Table I: Pre and Post treatment values with SD±SEM and their statistical significance

| GROUP | Parameter | At day-0 | At day-60 | Change | % change | p-value |
|------------|-----------|------------|------------|--------|----------|---------|
| G-I n=25 | TC | 228.2±1.99 | 226.4±1.23 | 1.8 | 0.8 | >0.05 |
| | LDL-C | 178.4±1.67 | 176.5±1.09 | 1.9 | 1.1 | >0.05 |
| | HDL-C | 40.7±1.90 | 40.9±2.98 | 0.2 | 0.5 | >0.05 |
| G-II n=22 | TC | 235.4±1.11 | 204.6±1.99 | 30.8 | 13.1 | <0.001 |
| | LDL-C | 181.1±2.87 | 169.0±2.22 | 12.1 | 6.7 | <0.01 |
| | HDL-C | 43.5±1.99 | 49.1±1.04 | 5.6 | 11.4 | <0.01 |
| G-III n=24 | TC | 239.0±2.32 | 231.8±1.33 | 7.2 | 3.0 | <0.01 |
| | LDL-C | 188.8±2.45 | 180.0±1.95 | 8.8 | 4.7 | <0.01 |
| | HDL-C | 39.6±1.11 | 44.5±1.55 | 4.9 | 11.0 | <0.01 |

KEY: G stands for group, G-I is for placebo group, G-II is for Niacin group, G-III is for Cardamom group, n stands for sample size, pre and post treatment changes are measured in mg/dl, ± stands for standard error of mean, p-values >0.05 indicates non-significant changes, p-values <0.01 indicates significant changes, and p-values <0.001 indicates highly significant changes in mean values.

DISCUSSION

Dyslipidemia in human beings may play cordial role in progression of atherogenesis leading to development of coronary artery disease, co sequencing mortality and morbidity due to MI. Niacin is major drug to treat primary or secondary hyperlipidemia. Regarding low compliance of niacin, it is usually advised patients to take drug in low dose and gradually increasing to its therapeutic dose. In our results two months therapy with niacin decreased total and LDL cholesterol.¹³ 1 and 6.7 % respectively. Statistically decrease in total cholesterol is highly significant while change in LDL-cholesterol is significant biostatistically. These results match with results of study conducted by Cantarella et al¹⁶ who observed about same changes in lipid profile of 107 patients. Our results of change in HDL cholesterol also match with results of Capuzzi et al¹⁷ who observed 14% increase in HDL cholesterol of 55 hyperlipidemic patients. Mittal et al¹⁸ explained that hypolipidemic effects of Vitamin B-3 (Niacin) can be achieved in doses that can damage liver. Soga et al¹⁹ conducted research and proved that one gram of niacin per day lowered total cholesterol maximum up to

9.11 mg/dl and LDL cholesterol up to 6.90%. These results are in contrast with our results. This difference in two results can be due to low dose of the drug used in their research work. Bruckert et al²⁰ has warned researchers that vulnerability of hepatic damage can not be avoidable in anti hyperlipidemic doses of this vitamin B-3 (niacin). To avoid frequent adverse effects and economic cost of conventional hypolipidemic agents like niacin or fibrates or even statins, alternative anti hyperlipidemic therapy by herbal medications are going to get popularity in different ethnic groups in developing countries. Green cardamom is used generally in many cocktail food preparations in India, Pakistan, Bangladesh and Srilanka.²¹ Our research study proved significant changes in total and LDL cholesterol in 24 hyperlipidemic patients, i.e. 7.2 mg/dl reduction in total cholesterol and 8.8 mg/dl decrease in LDL cholesterol. Changes in both parameters are biostatistically significant. Almost same results were observed by Babu et al²² in LDL-cholesterol, but they proved lesser reduction in total cholesterol, i.e. only 1.9% decrease in total cholesterol in four hyperlipidemic patients when they used one gram of green cardamom for three months. This difference may be due to small sample size, though they used same amount of cardamom as we used in our study. Goto et al²³ proved same increase in HDL cholesterol as we observed in our work. Galleano et al²⁴ agree with Alam et al²⁵ who wrote that wide variety of pharmacological effects by green Cardamom may cause metabolic processes of human body to affect carbohydrates, proteins and lipid metabolism beneficially but negligible adverse effects are not being evaluated which needs meta analysis and research on these herbs.

CONCLUSION

It was concluded from the research work that green cardamom herb is as hypolipidemic as Vitamin B-3 (niacin), regarding its effects on LDL and HDL cholesterol, but this herb's potential for reduction of total cholesterol is lower than niacin.

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ASSESSMENT OF KNOWLEDGE AND ATTITUDE REGARDING RABIES AND ITS POST EXPOSURE PROPHYLAXIS - A DESCRIPTIVE STUDY

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ABSTRACT

Objective:

Rabies is a fatal disease and is endemic in the developing countries of the world including Pakistan. Despite the existence of effective human & animal rabies vaccination, a large number of deaths due to rabies occur annually. This calls for the need of conducting a study to assess the knowledge and attitude of people regarding rabies and its post exposure prophylaxis in order to illuminate gaps in knowledge that potentially have bearing on disease control.

Objectives and Aim:

To assess the knowledge and attitude regarding rabies and its post exposure prophylaxis among general public.

Methods:

Descriptive cross-sectional study carried out from January 2015 to September, 2015, at Fauji Foundation Hospital, Islamabad. Three hundred and forty six attendants accompanying patients in General OPD of Fauji Foundation Hospital were conveniently selected to complete a self-administered questionnaire translated in urdu language for this descriptive cross sectional study.

Results:

Out of total 346 study subjects a good majority (89.3%) were aware of the disease by name and 61% knew the characteristic symptoms, 46.6% knew that rabies is caused by a virus. About 56.4% were unaware of the fact that rabies could be transmitted by other species of animals too. About 85.8% were aware that the post exposure prophylaxis of rabies in man included vaccination but knowledge of pet vaccination was present in 38.7% only.

Majority (97.7%) of the respondents said that they would consult a doctor in case of dog bite, and 66.2% were of the idea that pet dogs should be given vaccine if available to prevent rabies in them, while 88.2% were of the opinion that a rabid dog should be killed.

Conclusion:

The research concluded that majority of people had good knowledge about rabies disease and its symptoms as well as knowledge regarding the indications of post exposure prophylaxis, but almost half of them were unaware of the causative organism and rabies transmission by animals other than dogs.

Keywords:

Endemic, Post exposure prophylaxis, Rabies, Vaccination

INTRODUCTION

Rabies is a zoonotic disease caused by Raba virus (RABV) & other members of genus Lyssavirus. The majority of the cases of rabies (about 95%) are due to bites or scratches from rabid dogs, and a very few cases by bites from other animals like bats, foxes, raccoons and other wild carnivore species.¹

Early symptoms of the disease include fever & tingling at the site of exposure, followed by one or more of these symptoms: violent movements, uncontrolled excitement, hydrophobia, confusion & loss of consciousness. In the final stage, patient experiences lethargy, mania, coma and death due to respiratory failure. Rabies is endemic in developing countries of Asia and Africa & results in heavy losses in both human and livestock population in these regions. The case fatality rate of rabies infection is almost 99.9%.² Approximately 55,000 deaths are reported every year worldwide

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due to rabies, out of which 32,000 are in Asia.³ According to a report of World Health Organization (WHO) in 2012, dog rabies potentially threatens over 3 billion people in Asia and Africa.⁴ Among these the high risk population lives in rural areas where human vaccines and immunoglobulins are not readily available or accessible.

In our country there are very few national programmes for rabies control & prevention and it is taken as a disease of low public health priority which is also a reason for its endemicity in our area. Its incidence is grossly under reported in Pakistan. There were more than 97,000 recorded cases of dogbites in basic health units alone, in 2010. While those cases that were managed by secondary or tertiary care hospitals, private practitioners, spiritual healers and hakeems are not recorded.⁵ In Karachi alone, although no population based studies are available, incidence of rabies was estimated at 7 to 9.8 cases per million population annually.⁶ Majority of rabies victims are children, as they lack awareness and don't take precautions while playing with stray or pet dogs, and only 15% schools are educating children about rabies in South East Asia.⁷ Apart from disease burden, there is economic burden of rabies which constitutes the direct medical costs in humans from post exposure treatment, indirect patient costs, costs to control rabies in dogs, livestock losses incurred due to rabies and the surveillance costs.

Canine rabies is a socio-economic & public health problem in our country that needs our attention now. Hence assessment of the awareness of general public regarding rabies becomes mandatory since not many studies are conducted in our country.

Moreover, there are many myths and false beliefs associated with dog bite wound management around the world that need to be tackled. Apart from seeking doctors advice, people also consult other systems of medicine like hakeems, spiritual healers etc. This post exposure management includes application of oils, herbs, and red chillies on the wounds inflicted by rabid animals. People still have faith in indigenous medicines that are of unproven efficacy and a practice of not washing the wound properly because of fear that it would get infected.⁸

For effective control of rabies it is necessary to do prophylactic vaccination of dogs both pet and stray, on larger scale via certain vaccination campaigns.

Strict quarantine measures should be taken along with rabies control in wild life as well. Treatment after exposure is known as post exposure prophylaxis(PEP). Human rabies death is entirely preventable via prompt delivery of vaccine to victims within 10 days of infection. Thoroughly washing the wound with soap & water for approximately 5 minutes is effective in reducing the number of viral particles. Followed by administration of modern cell culture vaccines used in combination with rabies immunoglobulins that are virtually 100% effective in preventing human rabies deaths.⁹ The motivation behind this study was to assess the knowledge and attitude about rabies and its vaccine-preventable aspect in post exposure prophylaxis, as this can result into better practices for control and prevention, and save many precious lives.

Significance: Theoretical contribution: This study is a theoretical contribution to the body of knowledge regarding rabies and its post exposure prophylaxis, among general public, as no such study has been performed in this area of Pakistan before.

Applied aspect: This study identifies the gaps in knowledge regarding pet vaccine among general public, thus highlighting the aspects of disease control and paving the path for further studies, and helping the healthcare personnel and policy makers to devise intervention strategies for the prevention and control.

METHODS

A descriptive cross-sectional study was conducted in General OPD of Fauji Foundation Hospital, Islamabad, affiliated with Foundation University Medical College, from January 2015 to September 2015 after pre-testing a closed-ended, self made, structured questionnaire translated in Urdu. It was filled in by a convenient sample of 346 consenting adult male and female attendants aged > 18 years. The respondents were self interviewed by the research group students of fourth year MBBS. Only currently non-diseased adults who were willing to participate were subjects of our study. All subjects less than 18 year old were excluded, as well as patients, hospital staff and doctors were excluded from study. The tool was self made after consulting previous KAP studies on rabies done by Serebe S G in Gondar town, Ethiopia(in 2014); and Guadu T in

Bahir Dar Town done in 2014. The respondents were inquired about their knowledge of the disease and its symptoms as well as knowledge regarding the post exposure prophylaxis, and their attitudes towards rabies were assessed regardless of their dog ownership, to get a general idea about their community. After collection of data it was checked on the spot for omissions and mistakes and all questionnaires were found to be complete so data was entered in SPSS 17. Data analysis results for this study were mainly done in frequencies and percentages.

Ethics Statement

The study protocol was approved by the ethical review committee of Foundation University Medical College. Written informed consent was taken from all the study participants at the time of data collection. They were also verbally informed about the purpose of the study, by the research group students, emphasizing that their participation was voluntary and that confidentiality would be maintained by the researcher, and they could withdraw from the study at any time.

RESULTS

DEMOGRAPHIC DETAILS OF THE RESPONDENTS

Among 346 respondents 55.8 % (193) were males. Majority of respondents were in the age group range of 39 to 45 years, among which 19.7% were illiterate and a major portion attended middle school (25.4%) and secondary school (28.6%). About 42.5% (147) resided in rural areas whereas the remaining in urban (43.1%) and sub urban areas (14.5%).

KNOWLEDGE

Among the respondents 89.3% (309) were familiar with the disease by name and 61% (211) had knowledge about the characteristic symptoms of the disease. A majority, 90.2% (312) knew that rabies is transmitted through dog bites. About 45.1% (156) were unaware of the cause of the disease in dogs ,46.8%(162) had knowledge that it is caused by a virus while a few respondents said starvation 3.5% (12) and thirst 4.6% (16) were the cause. Out of 346 ,only 35% (121) were aware that rabies can be transmitted by bites from animals other than dogs. Out of all the interviewed, 43.9% said that rabies is

transmitted by bites only, & 22% said by scratches and contact with saliva only, and 11.6% mentioned bite and saliva contact with open wound and scratches. The awareness that post exposure prophylaxis of rabies included vaccination was present in 85.8% of the respondents. Majority (82.9%) knew that if rabies is not treated it will cause death. Among all, 39.6% (137) had knowledge that there is no need to take rabies vaccination if bitten by a vaccinated dog, and knowledge about pet vaccine was present in only 38.7% (134).

ATTITUDE

The study shows that 97.7% (338) of the respondents would consult a doctor in case of a dog bite, 0.3 % will consult Hakeem and 2% will consult a spiritual healer. A majority of them (88.2%) were of the view that a rabid dog should be killed and only 4% were of the opinion to report about a rabid dog to the authorities, while 7.8% (27) were of the view that a rabid dog should be observed for 10 days for symptoms.

A total of 310 (89.6%) respondents showed willingness to take vaccination in case of dog bite. Among all the respondents 66.2% were of the view that pet dogs should also be vaccinated if it was available. Almost 40.8% didn't know whether vaccine was available in the nearby hospital or not.

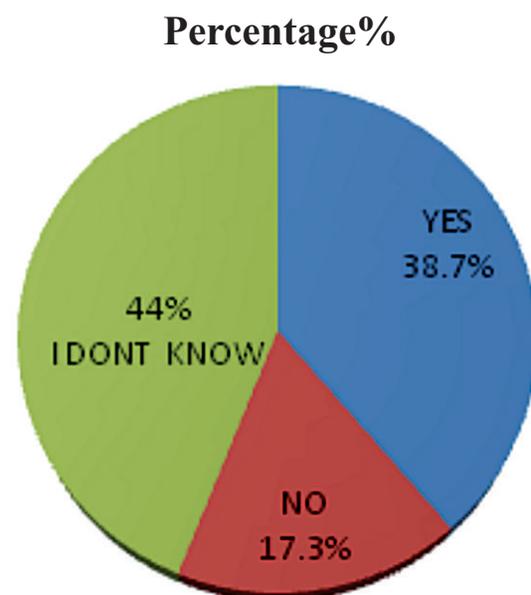


Figure I: Pie chart representing knowledge of pet vaccination against rabies (n= 346)

Table I: Demographic profile of subject above 18 years age at FFH General OPD (n= 346)

| GENDER | FREQUENCY | PERCENTAGE % |
|---------------|-----------|--------------|
| Male | 193 | 55.8 |
| Female | 153 | 44.2 |
| | | |
| AGE GROUP | FREQUENCY | PERCENTAGE |
| 18 - 24 years | 51 | 14.7 |
| 25 - 31 years | 58 | 16.8 |
| 32 - 38 years | 51 | 14.7 |
| 39 - 45 years | 64 | 18.5 |
| 46 - 52 years | 61 | 17.6 |
| 53-59 years | 37 | 10.7 |
| 60 and above | 24 | 6.9 |
| OCCUPATION | FREQUENCY | PERCENTAGE |
| UNEMPLOYED | 171 | 49.4 |
| EMPLOYED | 175 | 50.57 |
| EDUCATION | FREQUENCY | PERCENTAGE |
| illiterate | 68 | 19.7 |
| literate | 278 | 80.3 |
| RESIDENCE | FREQUENCY | PERCENTAGE |
| URBAN | 149 | 43.1 |
| RURAL | 197 | 56.9 |

Table II: Attitude about rabies and its Post exposure prophylaxis (PEP) among respondents (n=346)

| WHO TO CONSULT IN CASE OF DOG BITE | FREQUENCY | PERCENTAGE % |
|----------------------------------------------------------|-----------|--------------|
| Would consult doctor | 338 | 97.7 |
| Would consult hakeem | 1 | .3 |
| Would consult spiritual healer | 7 | 2.0 |
| ACTION THAT WOULD BE TAKEN AGAINST A RABID DOG | FREQUENCY | PERCENTAGE % |
| Would Kill it | 305 | 88.2 |
| Would report to the authorities | 14 | 4.0 |
| Would observe the dog for ten days for symptoms | 27 | 7.8 |
| ATTITUDE ABOUT VACCINATION OF PERSON BITTEN BY RABID DOG | FREQUENCY | PERCENTAGE % |
| Vaccination should be done | 310 | 89.6 |
| Vaccination shouldn't be done | 0 | 0 |
| I don't know | 36 | 10.4 |
| ATTITUDE ABOUT PET VACCINATION IF AVAILABLE | FREQUENCY | PERCENTAGE % |
| Vaccinate the pet | 229 | 66.2 |
| Don't vaccinate the pet | 55 | 15.9 |
| I don't know | 62 | 17.9 |

DISCUSSION

Rabies is a deadly disease on earth with a 99.9% fatality rate, but it is vaccine – preventable, as timely post exposure prophylaxis through vaccine stops the virus before clinical symptoms appear⁹. But the number of deaths occurring annually worldwide, make it necessary to check the knowledge of general public about this disease and its vaccination. As no such study was previously done in this region hence this study was planned which eventually revealed that only 46.8% people knew that virus is the causative agent of rabies in dogs, 3.5% blamed starvation, and 4.6% thirst, while 45.1% people had no idea about it. In a similar study done in Ethiopia¹⁰, 46.9% individuals considered starvation and thirst as causative factors for rabies in dogs while only 25% said that virus can be a cause. Hence this aspect needs attention. The causative organism is actually the virus, but people mostly relate the disease to some problem in the dog only.

According to our study 89.3% population had knowledge about rabies while 10.7% were ignorant. If we compare it to other studies in the world similar findings are observed. One done in USA in Texas¹¹ showed that 98% people knew about the disease. A study done in Sri-Lanka¹² showed 89.6% awareness while a KAP study done in Tanzania¹³ showed greater than 95% awareness and in Ethiopia,¹⁴ it was 96%. A multicentric study done in neighbour country India¹⁵ on general population of Delhi, Hyderabad, Raipur etc showed 68.7% population awareness about disease while in Indian Gujrat¹⁶, 100% awareness was revealed. In a previous study done in Karachi, it was 58%.¹⁷ Hence it depicts that awareness stands high round the globe regardless of development of country.

Surprisingly, in our study 85.8% population knew that its post exposure prophylaxis included vaccination, which is in accordance with the study in USA where it stands 85%, and 88% in the Srilankan study and 86.4% in the Indian study. In our study 82.9% people knew that the disease is fatal if untreated and in the study done in USA it was 59%. Thus awareness regarding rabies vaccine, and fatality due to disease also stands at an acceptably good level.

Our research revealed 97.7% population showed

willingness to consult doctor in case of dog bite which is very close to the study done in Sri Lanka where it was 96%, and 80% in Tanzania. On the contrary, in the multicentric study of India only 1.56% people agreed to consult doctor while others indicated that they will prefer home remedies like use of chillies, lime and turmeric as a treatment. Another similar study done in Indian Gujarat showed 36.4% willingness for doctor consultation. In the Ethiopian study, 46% said that they will prefer traditional medicines and 41.7% said that they will go to doctor for vaccination. This shows the level of misconceptions and malpractices in case of post exposure prophylaxis in these two developing countries, while our study reflects positive health seeking behavior.

Although knowledge of a vaccine for pet was present in only 38.7%, but 66.2% people in our study showed positive attitude towards pet vaccination if a vaccine was available, 15.9% said that there is no need to vaccinate the pets while 17.9% said they had no information about this. This shows that our study population shows a strong potential towards a positive health behavior that can be utilized in achieving our aim.

In study of Srilanka 76% people said that their pets were vaccinated, while in Tanzania this rate was 51% and in Ethiopia only 35.8%. In study of Sri-Lanka this was the answer by 87% out of total non pet-owners while 93% of the total pet owners. About 42.2% knew that a vaccine was available in the nearby hospital. This low level of awareness regarding pet vaccine in our study and its availability in nearby hospital potentiates the need to increase awareness of masses regarding pet vaccination and access to vaccine in health care institutes, and precautions regarding stray dog bites. Our study is limited by the small sample size taken and the mode of sampling that is convenience sampling which unavoidably introduces bias as compared to probability sampling. Hence results cannot be generalized for a larger population. Further population-based studies are required.

CONCLUSION

The research concluded that majority of people had good knowledge about rabies disease and its symptoms as well as knowledge regarding the indications of post exposure prophylaxis, but almost half of them were unaware of the causative

organism and rabies transmission by animals other than dogs

RECOMMENDATIONS

The study should be conducted on a larger sample size in order to have an exact idea about rabies awareness level in our country, and the results should be based on probability sampling avoiding bias. Keeping in view findings and results of this study it is recommended that health authorities of Pakistan chalk out a comprehensive campaign including print and electronic media to generate higher level of awareness regarding rabies pet vaccination among the masses of Pakistan, highlighting the avoidable aspect of disease and its timely reporting and positive health seeking behaviour. Simple messages regarding vaccination of dogs should be channeled through government and community networks. There is dire need to keep a check on stray dogs as well. This is going to be an additional measure to uplift the general health of the nation by decreasing the number of preventable deaths.

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COMPARISON OF INTRAVENOUS BOLUS VS INTRAVENOUS INFUSION OF HYDRALAZINE IN THE ACUTE CONTROL OF BLOOD PRESSURE IN PRE-ECLAMPSIA

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ABSTRACT

Objective:

To compare the time taken and amount of drug used in intermittent bolus injections of hydralazine versus continuous infusion of hydralazine for acute control of blood pressure in severe pre-eclampsia.

Setting:

The study was conducted in Obstetrics and Gynecology Department, Benazir Bhutto hospital (Rawalpindi General Hospital).

Duration of Study:

The study was conducted from 1 Feb 2009 till 30 June 2011

Study Design: Randomized controlled trial

Subjects and Methods:

90 patients were selected of severe preeclampsia which were divided into two groups with 45 patients in each group. The average age in group A was 32.14(\pm 5.06) years while in group B was 33.68(\pm 4.63). In group A the blood pressure was controlled using Bolus I/V dose of hydralazine while in group B it was controlled using infusion of hydralazine.

Results:

The mean time to reduce blood pressure in group A was 35.68 (\pm 14.442) minutes vs 54.55 (\pm 30.036) minutes taken in infusion regime ($p < 0.002$). While the amount used was 8.918 (\pm 3.751) mg in bolus while 9.618 (\pm 4.023) mg was used in infusion ($p < 0.503$). Conclusion: The time difference between the bolus group and Infusion group is significant. While there is no statistical difference in the amount of drug used.

Keywords:

Preeclampsia, Bolus dose, Hydralazine

INTRODUCTION

Severe pre-eclampsia is a rare but serious complications of pregnancy. It has been estimated by the World Health Organization (WHO) that worldwide approximately 60,000 women will die each year from pre-eclampsia.^{1,2} In the United Kingdom fewer than ten women will die each year from pre-eclampsia but this remains a relatively common cause of death in pregnancy in the developing world.³ The main cause of morbidity and mortality associated with pre-eclampsia is due

to its progression to eclampsia which is associated with, impaired renal circulation, hepatic failure, platelet dysfunction and impaired neurology. In Pakistan the maternal mortality is 500/100,000 live births and out of which the percentage attributed to eclampsia is 14.4.⁴

There is no effective management of pre-eclampsia other than to deliver the fetus as soon as possible.⁵

The principle objectives of management of pregnancy complicated with pre-eclampsia include^{1,5-7}

1. Termination of pregnancy with the least possible trauma to mother and fetus
2. Birth of an infant who subsequently thrives
3. Complete restoration of health to the mother

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Severe pre-eclampsia (blood pressure > 160/110mmHg, proteinuria greater than 5g/24 hours and presence of markers of severe pre-eclampsia), requires high dependency unit with strict observation. Antihypertensive drugs are administered parentally in severe pre-eclampsia to bring the blood pressure down in a controlled manner and to decrease the risk of morbidity and mortality to the mother and the fetus both. The drugs mainly used for the control of hypertension in severe pre-eclampsia include hydralazine, nifedipine and labetalol. Hydralazine is one of the most commonly used drugs. Although extensively used there is still no agreed consensus to the maximum amount to be used though some recommend a cycle treatment to be 30 mg.⁸ There are two commonly used regimes:-

1. 5mg Hydralazine as i/v bolus to be repeated at 20 min intervals until the blood pressure comes within the desired range i.e. systolic of 130 to 150 mmHg and diastolic of 90 to 100 mmHg.
2. A bolus of 5 mg given i/v over 2 min followed by infusion with 80µg/ml of hydralazine (i.e. 40mg hydralazine to 500ml hartmann's solution) started at 30 ml/h (40 µg/min), increasing by 30ml/h every 20 min to a maximum of 120 ml/h (160 µg/min) or until the BP is controlled.⁸

The aim of this study was to investigate the effectiveness of both these regimens for immediate lowering of blood pressure and to develop future protocols for management of pre-eclampsia in our institution.

OBJECTIVE

To compare the time taken and amount of drug used between intermittent bolus injections of hydralazine vs continuous infusion of hydralazine for control of blood pressure in severe preeclampsia.

MATERIALS AND METHODS

This was a randomized open labelled clinical trial carried out in the emergency department of Benazir Bhutto Hospital from 1 Feb 2009 to 30 Jun 2011. Patients reporting to emergency department with severe pre-eclampsia were managed and monitored till the blood pressure was stable before transferring them to high dependency unit.

Pregnant patients with systolic blood pressure of greater than 160 mmHg or diastolic BP of greater than 110 mmHg, having a proteinuria of 2+ or more

and hypertension occurring after 20 weeks of gestation were included in the study. Patients having hypertension prior to pregnancy, non-reliable record of blood pressure during pregnancy or those who were suffering from cardiac or renal diseases were excluded from the study.

After completing hospital formalities for documentation patients were randomly allocated to either group A or group B. Group A patients were administered IV bolus doses of 5 mg Hydralazine at 20 minutes interval until the blood pressure was within the desired range. Group B patients were given iv loading dose of 5mg hydralazine followed by hydralazine in infusion form i.e. 80µg/ml of hydralazine (40mg hydralazine to 500ml hartmann's solution) started at 30 ml/h (40 µg/min), increasing by 30ml/h every 20 min to a maximum of 120 ml/h (160 µg/min) or until the BP was controlled. The blood pressure was recorded at regular intervals of 10 minutes till patient's systolic blood pressure was less than 150 mmHg and diastolic was less than 100 mmHg. Monitoring was then done at 20 minutes intervals for next 6 hours

The time and the amount of drug used was recorded. Throughout this period maternal heart rate and fetal heart rate were also recorded.

DATA ANALYSIS

Data was analyzed using SPSS version 12. Mean SD will be calculated for age, systolic blood pressure, diastolic blood pressure, time taken to reduce the blood pressure and amount of drug used. Independent t test was used to see the significance of difference in the two groups, cases given hydralazine as bolus(Group A) and hydralazine given as infusion (Group B), separately for the time taken by the drug and the amount of drug used. A p value of less than 0.05 will be taken as significant.

RESULTS

There were 90 cases of pre-eclampsia who reported to Obstetrics and Gynecology department, BBH from 1 Feb 2009 till 30 June 2011 and satisfied the inclusion and exclusion criteria.

Age: The mean age in Group A (Bolus) was 32.24(±4.858) years. The range was 18 – 40 years; the mean age in Group B (Infusion) was 33.47(±5.097) years. The range was 18 – 40 years. The difference in the mean ages between the two groups was not significant (p value was 0.833).

Blood Pressure control: Blood pressure control is summarized in Table I.

Table I: Blood Pressure Control (n=90)

| | Group | Mean (mmHg) | Standard Deviation | Minimum (mmHg) | Maximum (mmHg) | p value |
|------------------------------|-------|-------------|--------------------|----------------|----------------|---------|
| Systolic BP On presentation | A | 173.33 | 15.521 | 160 | 230 | 0.325 |
| | B | 176.89 | 18.442 | 160 | 220 | |
| Diastolic BP On presentation | A | 114.22 | 7.534 | 110 | 140 | 0.288 |
| | B | 115.78 | 6.212 | 110 | 130 | |
| Systolic BP On control | A | 152.22 | 9.508 | 140 | 180 | 0.911 |
| | B | 152.00 | 9.195 | 140 | 180 | |
| Diastolic BP On control | A | 95.78 | 4.955 | 90 | 100 | 0.528 |
| | B | 96.67 | 7.977 | 80 | 120 | |
| Systolic BP after 6 hours | A | 149.56 | 10.435 | 130 | 170 | 0.108 |
| | B | 146.00 | 10.313 | 130 | 170 | |
| Diastolic BP After 6 hours | A | 94.44 | 6.236 | 80 | 100 | 0.134 |
| | B | 96.56 | 6.976 | 80 | 110 | |

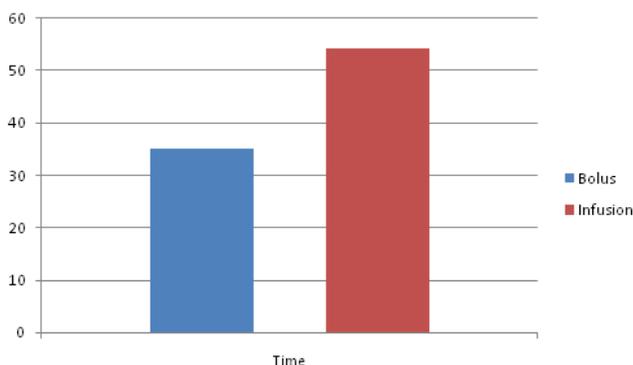


Figure 1: Comparison of time taken for control in minutes in each group (n = 90)

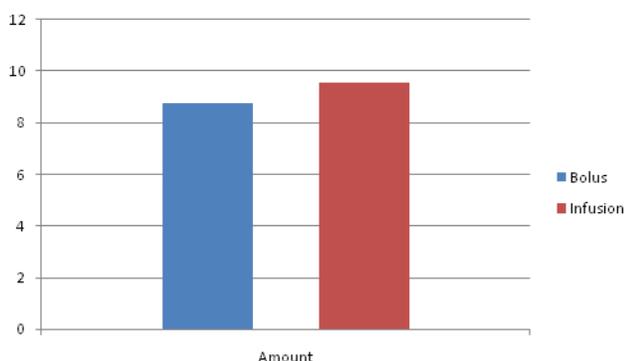


Figure 2: Comparison of amount used in each group (n = 90)

Failures In group A 2 cases required change in regime to control blood pressure, while in group B 3 cases required additional drugs to lower blood pressure upto the desired range.

Time The mean time taken for blood pressure control in group A was 35.11 (±14.400) minutes and the range was 20 – 80 minutes. While in group B mean time was 54.22 (±29.348) minutes and the range was 20 – 120 minutes. The **p value was <0.001** which is highly significant. These results are shown in figure I.

Amount of drug used The average amount of drug used in group A was 8.777 (±3.716) mg, the range was 5 – 20 mg. While in group B the average amount used was 9.580 (±3.950) mg, the range was 5.79 – 22.95 mg. The p value was 0.324 which is insignificant.

DISCUSSION

The corner stone of management of severe pre-eclampsia is reduction of blood pressure. A number of parenteral drugs may be used for lowering blood pressure in hypertensive pregnant patients. Each has its own merits and demerits.⁹ Treatment reduces the likelihood of cerebral hemorrhage and left ventricular failure and may also be a contributing factor in seizure prevention. Hydralazine is a well-accepted drug for management of hypertensive

emergencies during pregnancy. Hydralazine is used commonly and is considered safe for acute control of blood pressure in pregnancy.¹⁰⁻¹⁴ It is administered in either bolus injections or in continuous infusion form. In our study, the analysis of results revealed that both forms are equally effective in controlling the blood pressure however the hydralazine controls the BP much quicker. There was no significant difference between the blood pressure at control and at six hours, moreover the amount of drug used was also comparable in both regimens.

Begum, M.R.¹⁵ and co worker reported that bolus form of hydralazine achieves blood pressure control much quicker than hydralazine in infusion form. They reported that bolus dose achieved the therapeutic blood pressure goal within 65.23 ± 23.38 minutes (mean \pm SD) as compared with 186.36 ± 79.77 minutes in those who received hydralazine drip (group B) ($p < 0.001$). Similar findings were observed in our study, with time taken for BP control being much less when hydralazine was administered in bolus form. This observation was statistically significant (p value less than 0.001). Moreover, in our study the time taken to achieve blood pressure control was much shorter than that reported by Begum, M.R. This may be due to the fact that the starting blood pressures in our group were slightly lower. Also, dosing regimens used in our study were using larger amount of drug. A 5 mg bolus was administered to all patients in our study, even in those of the group B as loading dose of the drug before starting the infusion. Moreover, the incremental doses were higher in our study. On the other hand, the regimens used by Begum, M.R. involve drug administration in lower doses. They used a dosage regime of a bolus of 5 mg followed by a mini bolus of 2 mg every 15 min, and in the infusion they started without initial bolus. The author therefore recommended standard 5 mg bolus dose as loading dose in infusion regime as well. The mean time taken by bolus is $35.11 (\pm 14.40)$ min and by infusion it took $54.22 (\pm 29.348)$ min. ($p < 0.001$) which was significant.

The intravenous infusion had been showed to be an effective method of administering hydralazine reported by Aali et al¹⁶ and Bolte.¹⁷ The commonest side effect reported in literature of hydralazine in infusion form is sudden maternal hypotension.^{18,19} In our study we observed that there were no

instances of sudden falls in maternal blood pressure after giving drug in infusion form and the fall in blood pressure was comparable in both groups. The sudden maternal hypotension noted in meta-analysis by Magee, L.A.⁸ and coworkers is probably due to infusion given in high dosages i.e. 10mg/hr. In our study, much lower dose infusion was used initially gradually incrementing until the desired response was achieved, starting with $40\mu\text{g}/\text{min}$ which is equivalent to 2.4mg/hr. The increased occurrence of persistent severe hypertension noted by Magee, L.A.⁸ with hydralazine infusion when compared with bolus was also not observed in our study. This inability of blood pressure control was attributed to use of low dose infusion of 1mg/hr. Since we used 2.4mg/hr as starting dose of hydralazine infusion, the incidence of persistent severe hypertension in our study was not statistically significant.

Hydralazine was advocated to be administered as bolus instead of the earlier regimes of infusion by Mabie²⁰ because it is difficult to determine the cumulative dosage the patient has received. In resource poor setting especially in the developing world like ours where either trained staff is not available or is over burdened, bolus regime may be beneficial.

The amount of drug used in bolus regime in our study was almost similar to that used in infusion form. On the other hand, the other workers including Mabie²⁰ and Begum, M.R. and colleagues¹⁵ reported a much larger amount of drug required when infusion form was used. Moreover, in our study we used a much lower amount of drug as compared to that used by Begum, M.R. and coworkers, where it was $20.07 (\pm 11.38)$ mg where as in our study we used $9.580 (\pm 3.950)$ mg. This can be explained on the basis that the starting blood pressures were slightly lower in our study than their initial blood pressures.

CONCLUSION

There is a significant difference in the amount of time taken to reduce the blood pressure in bolus versus infusion regime and bolus regime controls the blood pressure much quicker than infusion form without causing maternal hypotension. There is no statistical difference between the amount of drug used in bolus and infusion regimes.

RECOMMENDATIONS

The sample size in our study was small, and we did not document the complications arising after 6 hour of control of hypertension. Therefore we recommend that a trial with larger size and longer follow-up may be undertaken.

Since both bolus dose and infusion form of hydralazine are equally effective in lowering BP it is recommended that bolus dose is preferably used because of convenience of administration and quicker control of blood pressure. Moreover, bolus administration does not require adept staff or complex equipment like infusion pumps.

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SUSCEPTIBILITY PATTERN OF METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS INFECTIONS IN CLINICAL ISOLATES OF A TERTIARY CARE HOSPITAL

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ABSTRACT

Background:

The importance of infections caused by Methicillin resistant *Staphylococcus aureus* (MRSA) cannot be denied in antimicrobial era. Reduced treatment options and burden of disease posed by these infections have been a problem for past half century.

Objectives:

The objective of this study was to find local susceptibility pattern of Methicillin resistant *Staphylococcus aureus*.

Methods:

Specimens received for culture and sensitivity during Jan 2015-June 2015 to Microbiology Laboratory, Fauji Foundation Hospital were processed, identified and susceptibility pattern was studied against commonly used antimicrobials using modified Kirby-Bauer disc diffusion method, as per the guidelines of Clinical and Laboratory Standards Institute (CLSI). Data was compiled and analyzed by SPSS (version 21).

Results:

Of total 162 MRSA isolates, susceptibility to erythromycin turned out to be (6.17%), to ciprofloxacin (17.28%), gentamicin (27.7%), chloramphenicol (75.92%), trimethoprim-sulfamethoxazole (37.03%), doxycycline (74.6%), vancomycin (100%) and linezolid (100%). Frequency of Multi Drug resistant (MDR) Methicillin resistant *Staphylococcus aureus* was calculated to be 74.6%.

Conclusion:

MRSA in this study was found susceptible to linezolid, vancomycin, doxycycline and chloramphenicol whereas, not many isolates were found susceptible to erythromycin, ciprofloxacin or gentamicin.

Keywords:

Antibiotic susceptibility, Kirby-Bauer disc diffusion method, Methicillin resistant *Staphylococcus aureus*

INTRODUCTION

Staphylococcus aureus is among the most common human pathogens causing a variety of infections including skin, soft tissue, bone, endocarditis and sepsis, toxic shock syndrome etc.¹ Methicillin introduced in 1960 was the first line of treatment against beta-lactamase producing *Staphylococcus aureus*.² No matter how humans have equipped themselves the resistance to this major antimicrobial was revealed in UK in 1961 and first case of Methicillin resistant *Staphylococcus aureus* (MRSA) infection was reported in 1965.^{3,4} Nasal carriers of Methicillin resistant

Staphylococcus aureus (MRSA) are at risk for infection by this pathogen.⁵ Glycopeptides are now the mainstay therapy of MRSA infections.⁶ Since 1990s even vancomycin resistant *Staphylococcus aureus* has also emerged.⁷ Linezolid is another addition to drugs other than glycopeptides against MRSA.⁸ Resistance to other antimicrobials is variable and depend on local set-up, hospitalization period, presence of patients colonized with MRSA in the same hospital, past antimicrobial use and central venous catheter use are independent risk factors in the intensive care unit acquired MRSA infections.⁹ The study was planned to find the susceptibility pattern of methicillin resistant *Staphylococcus aureus*.

MATERIAL & METHODS

This was a cross sectional study was carried out at Department of Microbiology, Fauji Foundation

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Hospital, Rawalpindi after formal approval of ethics and review committee of the institute. Clinical samples of the patients received in Microbiology department were processed for growth of *Staphylococcus aureus*. Clinical samples included pus, blood, urine, tracheal tube aspirates, cerebrospinal fluid, sputum, tissue fluid, nasal and aural swabs. Isolates were identified on the basis of colony morphology, Gram staining, catalase, coagulase and DNase test. For presumptive identification of *Staphylococcus aureus* as MRSA, according to Clinical Lab and Standard Institute (CLSI), isolates were tested for methicillin resistance by using 30 µg cefoxitin disc (oxid, Basingstone, UK). The plates were incubated at 35°C for 24 hours. Susceptibility to cefoxitin were interpreted as per CLSI criteria. A zone diameter of ≥ 21 mm was considered susceptible.¹⁰ Antimicrobial susceptibility was performed on Muller Hinton agar using standard technique for disk diffusion.¹⁰ The antimicrobial discs used were ciprofloxacin (5 µg), gentamicin (10 µg), chloramphenicol (30 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg), doxycycline (30 µg), linezolid (30 µg) and erythromycin (15 µg) (oxid Ltd, Basingstoke, Hampshire, England).¹⁰ Vancomycin susceptibility was determined using E-strip method as recommended by CLSI. Multi drug resistance was defined as resistance to least three classes of antimicrobials.⁸ Data were compiled and analyzed using SPSS software (version 21).

RESULTS

One hundred eighty-five isolates were identified as MRSA during a period of six months. MRSA was isolated from various clinical samples of pus (70.37%), urine (6.17%) and blood (7.4%). Distribution of Methicillin resistant *Staphylococcus aureus* from various clinical specimens is given in Table I.

The mean age of MRSA infected patients was 37.48 \pm 2 years. Age distribution is given in the Figure I.

There was marked peak of infections recorded in age group 11-20 years. Least number of infections by MRSA was recorded in age group less than one year. MRSA was most susceptible to vancomycin (100%) and linezolid (100%), followed by chloramphenicol (75.9%) and doxycycline (74.6%). Susceptibility pattern of antimicrobials is shown in

Table II.

Frequency of Multidrug resistant (MDR)-MRSA was calculated to be 74.6% (n=121).

Table I: Distribution of Methicillin resistant *Staphylococcus aureus* in various clinical specimens (n=162):

| Clinical specimen | n(%) |
|-----------------------|-------------|
| Pus | 114(70.37%) |
| Blood | 12(7.4%) |
| Urine | 10(6.173%) |
| Tracheal tube/Cannula | 10(6.173%) |
| Sputum | 7(4.32%) |
| CSF/Tissue fluid | 7(4.32%) |
| Ear/Nasal Swab | 2(1.2%) |

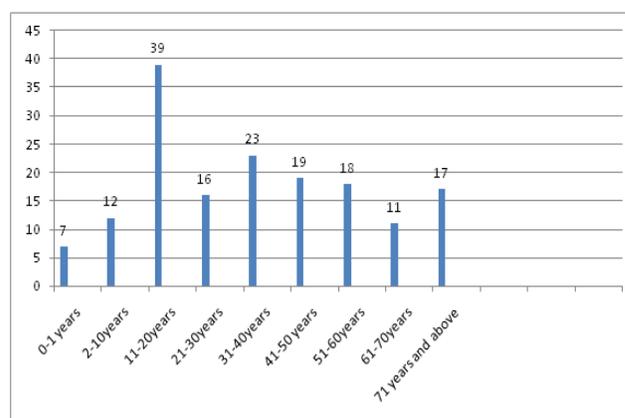


Figure 1: Age distribution of patients

Table II: Antimicrobial susceptibility pattern of MRSA (n=162):

| Antimicrobial agent | Susceptibility % (n) |
|-------------------------------|----------------------|
| Linezolid | 100% (162) |
| Vancomycin | 100% (162) |
| Chloramphenicol | 75.92% (123) |
| Doxycycline | 74.69% (121) |
| Trimethoprim-sulfamethoxazole | 37.03% (60) |
| Gentamicin | 27.7% (45) |
| Ciprofloxacin | 17.28% (28) |
| Erythromycin | 6.17% (10) |

DISCUSSION

The clinical importance of MRSA cannot be denied, since 1960s there have been many outbreaks of MRSA in hospitals and community.^{11,12,13} Many studies have been conducted to establish relationship between MRSA infections and carriage of MRSA in health care workers.¹⁴ The prevalence of MRSA is different in different countries geographical regions of the world. In Pakistan the prevalence varies from 2% reported from Sukkur to 46% reported from Islamabad and 61% reported from Lahore.¹⁵ The frequency of MRSA among all nosocomial isolates of *Staphylococcus aureus* increased from 39% in 1996 to 51% in 2003 as determined by a study conducted in Rawalpindi.¹⁶ Joshi et al, has reported 41% overall prevalence from India, with maximum isolation from Intensive care units.¹⁷ The percentage of Multi Drug resistance among MRSA was found to be 58.1%, which was defined as resistance to at least three classes of antimicrobials tested in the study.⁶ In this study, most common specimen for isolation of MRSA was pus. Kaleem et al, has also found pus as the most frequent sample for isolation of MRSA.¹⁸ However, Parveen et al, has found urine as the most common specimen where urine samples have contributed 25.14 % of MRSA isolates among all samples.⁶ In our study, urine samples have contributed only 6.17% of MRSA burden in all samples.

All isolates were found susceptible to linezolid and vancomycin re-endorsing the role of these agents in the treatment of MRSA infections. This is consistent with findings of Kaleem et al, who reported 100% susceptibility to these drugs. In another study from Rawalpindi, 98.5% susceptibility of MRSA to linezolid has been reported.¹⁹ Arora from India has also concluded 100% susceptibility of MRSA to vancomycin. However, susceptibility of MRSA to linezolid was 98.7% in this study.²⁰ A report from Libya has concluded 82.3 % susceptibility to vancomycin.²¹ About 75.9% isolates were susceptible to chloramphenicol in our study. Previous studies have also concluded a high percentage of MRSA susceptible to chloramphenicol. Parveen et al, reported 81.76% susceptibility of MRSA to chloramphenicol. However, Idrees et al, found a higher susceptibility of MRSA to chloramphenicol, 90% from Karachi.²² Kaleem et al, also reported

much higher chloramphenicol susceptibility (93%) from Rawalpindi.¹⁸ Kaur et al, reported 58.3% susceptibility to chloramphenicol.²³ Among tetracyclines group of antimicrobials, doxycycline was used, to which about 74.6% of isolates were found susceptible. Kaleem and colleagues have previously recorded 64% susceptibility of MRSA to tetracycline which is relatively lower percentage than our findings.¹⁸ Parveen has also reported about 40% isolates susceptible to tetracycline.⁶ Kaur, anyhow reported 78% susceptibility to doxycycline which is near to our study.²³ Low percentage of MRSA was found susceptible to trimethoprim-sulfamethoxazole. Kaur DC from India have concluded different result regarding trimethoprim-sulfamethoxazole, where 75% susceptibility of MRSA against this agent was noted.²³ In one study 67% isolates were found susceptible to trimethoprim-sulfamethoxazole.¹⁸ However, in another report only about 14% susceptibility to this antimicrobial has been found.⁶ Butt et al, reported statistically significant increase in susceptibility to doxycycline and trimethoprim-sulfamethoxazole in a period of seven years.¹⁶ Among gentamicin, erythromycin and ciprofloxacin none has shown reasonably good efficacy against MRSA. Kaur, has reported 0% susceptibility of MRSA to these drugs. Sharma has however, reported 45.6% susceptibility to erythromycin and 82.7% to gentamicin.²⁴ MDR-MRSA was taken as isolates resistant to three or more classes of antimicrobials tested other than beta-lactam. By this criteria 75% isolates were calculated as MDR. This much more than found by Parveen, who reported 58% MDR-MRSA.⁶ However, considerable difference in antimicrobials tested in this study can explain this difference. Pandey has concluded 75.86% of MDR-MRSA from Nepal.²⁵ However, a report from Uganda has reported MDR-MRSA as low as 19.22%.²⁶ The emergence of MDR-MRSA is worrisome among nosocomial infections. Importance of rational use of antimicrobials guided by standard testing of samples in Microbiology Lab can hardly be exaggerated.

CONCLUSION

MRSA in this study was found susceptible to linezolid, vancomycin, doxycycline and chloramphenicol whereas, not many isolates were found susceptible to erythromycin, ciprofloxacin or gentamicin.

RECOMMENDATIONS

The indiscriminate use of these agents may lead to positive selection of resistant strains so, vancomycin and linezolid should be only used in critically ill patients. For outdoor patients or infections not potentially life threatening can be empirically treated with doxycycline and chloramphenicol. However, side effects of all these agents should be kept in mind and appropriately managed by physicians.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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IMPACT OF IMMUNITY ON RESPONSE TO CHLOROQUINE TREATMENT IN PLASMODIUM FALCIPARUM MALARIA

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ABSTRACT

Objectives:

Host immunity to malaria plays a modulating role and selection of drug-resistant strains of the parasite is facilitated in the absence of adequate immunity. These factors have not been evaluated in Pakistan.

Place of study:

The study was conducted among adult Pakistani individuals of either sex living in urban areas of Rawalpindi/Islamabad district who reported the Military Hospital, Rawalpindi and diagnosed as a case of Plasmodium falciparum malaria.

Materials & Methods :

It was a hospital based prospective study. Seventy nine cases of Plasmodium falciparum infection were investigated for their immune response to the disease. The malarial antibodies were detected and estimated quantitatively by ELISA kit for detection of malaria IgG.

Results:

The immune response to falciparum malaria was not better than that in the healthy control subjects showing an overall inadequacy of immunity to Plasmodium falciparum infection in our patients.

Intensity of the parasitaemia was found to augment the humoral response. The mean IgG titres against Plasmodium falciparum were greater than the cut-off points in the patients in whom the parasitaemia exceeded 3000 parasites per cmm of the blood. The study also highlighted the modulatory role of immunity in relation to chemotherapy of the disease. In 77.27 % cases of chloroquine-resistance found in our study, the humoral response to the disease was inadequate. The incidence of chloroquine-resistance was double (34.0 %) in the patients showing a negative immune response to malaria as compared to that (17.24 %) in those who had adequate immunity. It was further noted that the patients showing RI and RII grades of chloroquine resistance were generally deficient in immunity.

Conclusion:

The failure of these cases to respond to chloroquine could therefore, be attributed to low levels of immunity in them. Therefore, it can be concluded that inadequate humoral immunity to malaria is an important factor in development of chloroquine-resistance in our scenario..

Keywords:

Plasmodium Falciparum Malaria, Chloroquine-Resistance, Malaria IgG, Humoral Immunity

INTRODUCTION

The global malaria situation is serious and becoming worse, each year infecting about three billion people¹, killing 1 to 2 million and profoundly declining economic development.² Pakistan, a moderately endemic country for malaria, reports 1.6 million cases annually.³

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Regardless of the availability of tools for the control and prevention, Plasmodium falciparum malaria persists and thrives, emphasizing the significance of the role of immunity. Host immunity is a vital but poorly understood determinant of antimalarial drug efficacy, influencing the outcome of prevention and treatment trials.⁴ Malaria immunity may be defined as the state of resistance to the infection brought about by all those processes which are involved in destroying the plasmodia or by limiting their multiplication.⁵

In populations long exposed to Plasmodium

falciparum, some resistance may occur due to natural selection. Children carrying sickle cell trait show a certain degree of resistance to Plasmodium falciparum which may be related to deficiency of Glucose-6 phosphate dehydrogenase in them. There is good epidemiological evidence to suggest that thalassaemia also protects against malaria.⁶

Acquired immunity to malaria is provoked by the asexual erythrocytic stages of malaria parasites and is directed against the mature schizonts and free merozoites of the parasite.⁷ Malarial IgG, chromatographically separated from the serum of apparently immune adults has been shown to produce clinical improvement in the children suffering from Plasmodium falciparum malaria reducing the parasite counts to below 1% within four days. The level of humoral immunity depends on the frequency of antigenic stimulation. The antibody titres tend to rise with age and number of episodes of malaria in children. Thymus-dependent immunity mediated by binding of macrophages or natural killer cells to the surface of parasitized red cells may lead to degeneration of parasites inside these cells.⁸

T cells are essential for both acquisition and regulation of malaria immunity. The frequencies and absolute numbers of peripheral T cell subsets have been shown to decrease during the acute stage of the disease. T Cell Receptor cells are intimately associated with protection against malaria.⁹ T cells from patients with acute falciparum malaria have been shown to stimulate T-dependent IgG secretion from B cells in vitro. The antibodies were directed to the intracellular forms of the parasite demonstrating cell-mediated immunity through the specifically sensitised T cells have a role in protection against Plasmodium falciparum infection in man.¹⁰

Humoral immunity operates mainly against the intra-erythrocytic mature asexual forms of malaria parasite and the extra-cellular merozoites by phagocytosis of parasites, with the co-operation of specific opsonizing antibodies. The Fab fragment of the specific IgG antibodies is actively antiparasitic in a dose-dependent manner. These antibodies might be directly lethal to the parasite i.e. destroy them by lysis, or may require the cooperation of a primed phagocytic system.¹¹ Antibodies induced after natural infection with Plasmodium falciparum bind specifically to the immuno-dominant

repetitive NANP epitope of the parasite.¹²

The patients suffering from acute Plasmodium falciparum infection generally show high titres of anti-sporozoite antibodies that may contribute to immune protection against malaria. The factors that determine the immune response to sporozoites include frequency of mosquito bites, exposure to infection and genetic factor of the host. The duration of such response varies with the length of exposure to infection. The titres rapidly decline after chemotherapy of clinical infection.¹³ The apparent antibody half-life was estimated at 27 days, which is comparable to the half-life of circulating IgG in humans.

Studies of parasite-induced changes on the surface of infected erythrocytes have revealed that with the maturation of erythrocytic stage of plasmodia, new membrane antigens appear on the surface of infected erythrocytes.¹⁴ Blocking effect of IgG obtained from donor clinically immune to Plasmodium falciparum malaria, on merozoite invasion of human is reported. It is due to an antibody directed against Pf155/RESA. Researchers found that adults having high antibody concentrations to RESA 1 were less likely to be parasitaemic.¹⁵

Permunitia in malaria may be defined as the clinical immunity associated with continued low-grade infection. There is evidence to suggest that recrudescences may arise from pre-existing systemic infection, which has been explained on the basis of soluble immune complexes or free antigens blocking the action of antibody. One significant mechanism of parasite survival is related to the ability of the organism to undergo antigenic transformation. Certain antibodies such as Schizont Infected red Cell Agglutinating (SICA) antibodies may induce antigenic transformation of the parasite and thus promote their survival in the immunized host.¹⁶

Chemoprophylaxis, by reducing parasitaemia, has been shown to produce a fall in malaria antibody levels. However this is not associated with reduced protective immunity to malaria. It is widely recognised that chloroquine-resistance in Plasmodium falciparum first became evident in non-immune subjects. The response to malaria chemotherapy in non-immunes is slower and incomplete as compared to that in partially immune subjects. Thus the interactions of malaria

chemotherapy with immunity to the disease are complex, the former impairing development of the latter. On the other hand, immunity assists the action of chemotherapy and inadequacy of the former may help in selection of resistant strains of the parasite.¹⁷ In view of these implications, this parameter of the study was designed to estimate the IgG titres against *Plasmodium falciparum* in local patients of malaria and to evaluate their influence on the clinical response of the infection to chloroquine.

MATERIAL AND METHODS:

A hospital based, prospective study was planned and conducted in the medical ward of Military Hospital, Rawalpindi for one year duration. The approval for the study was sought from the Ethics committee of "Centre for Research in Experimental and applied Medicine (CREAM)" Army Medical College.

SUBJECTS & THEIR TREATMENT:

Ninety nine cases of acute febrile illness of either sex were selected out of the patients attending Out Patients Medical Department by screening through thick and thin blood smears stained with Giemsa stain. Their ages ranged from 21 to 62 (Mean 34.56 10.33) years and body weights from 57 to 71 (Mean 64.29 3.05) Kg.

The following inclusion criteria were used for selection of the cases.

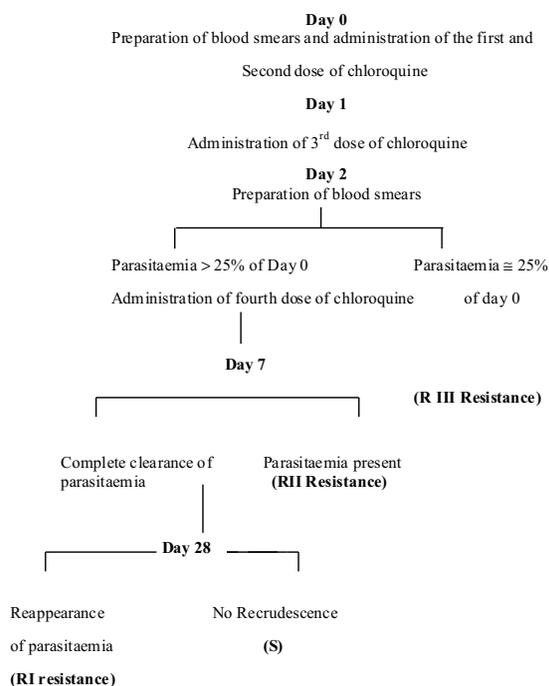
- (1) Parasite density between 1000 and 10000 asexual forms per mm³ blood.
- (2) Single species infection with *Plasmodium falciparum*.
- (3) Negative history of taking antimalarial drugs or tetracyclines during previous 14 days.
- (4) Patients admitted in the hospital for treatment were selected so that non-compliance in taking the drug could be ruled out.
- (5) Informed consent of the patient to participate in the study.

Ten healthy adult males, living in the same area as the subjects, with no history of suffering from malaria in the recent past, acted as the control for the study.

Patients were administered the standard dosage

regimen of chloroquine, 25 mg base per kilogram of body weight, given in four divided doses over 3 days. A total of 79 patients who completed the treatment successfully were investigated for their immune response to the disease and its influence on the outcome of treatment with chloroquine.

Scheme for interpretation of results of drug-sensitivity monitoring *in vivo*



PROCEDURE:

The initial sample of venous blood from the cases was collected and allowed to clot. Serum was separated by centrifugation at 1000 G and stored at -70°C until analysed.

The malarial antibodies were detected and estimated quantitatively by Enzyme-Linked Immunosorbent Assay (ELISA). It has been applied extensively in malaria research and commercially available kits of ELISA have been used by various research workers^{18,10} Our study was based on the indirect or sandwich ELISA principle.

ELISA kit for detection of malaria IgG, CELISA (CeLLabs Pty Ltd, Brook vale, Australia) was used in the study.

The kit was stored at 2-8°C in a refrigerator. The opened foil bags were resealed and all reagents were returned to the refrigerator immediately after use. Distilled water was used for diluting PBS-Tween and the substrate. For each of the two micro strips used in ELISA, 100 ml of PBS-Tween was prepared

by adding 5ml of the 20 x PBS-Tween concentrate to 95 ml of distilled water in a clean container. Separate pipette tips were used for each sample. Manufacturer's instructions were followed in storage and performing the assay.

The readings were made on ELISA-reader (Wellcozyme ELISA reader, Model MR 7000, Dynatech Laboratories). As per information contained in the supplier's manual, the reference positive serum should give a value of 0.8 and the reference negative serum should read under 0.15. The cut-off level was determined by the following formula.

$$\begin{aligned} \text{Cut off level} &= \text{Mean Reference negative} \\ &\text{absorbance} + 0.1 \text{ OD} \\ &= 0.0905 + 0.1 = 0.1905 \text{ OD.} \end{aligned}$$

The serum samples, which gave values above the cut-off point, were considered as positive for malaria antibodies. The titres of antibodies have been expressed in Optical Density (OD).

The IgG titres have been grouped according to the age of patients, intensity of parasitaemia and the response of disease to chloroquine. The statistical analysis of the data was done on computer using the programme Microsoft Excel.

RESULTS:

The Anti-Plasmodium falciparum IgG titres in the control subjects ranged from 0.029 to 0.306 with a mean \pm SD of 0.116 ± 0.105 OD, 30% of them showing positive IgG response.

A positive immune response to the disease was found only in 29 (36.71%) patients of acute malaria; not much different from controls. The results are summarized in table 1.

DISCUSSION:

These results indicate an inadequate immune response to malaria in majority of the patients in our study. In an area hypo-endemic for Plasmodium falciparum in Pakistani Punjab, Iqbal et al. found all the individuals positive for the antibodies to the parasite crude antigens, but only 29.5% had high titres of the antibodies.¹⁹ This is significantly greater immune response than that in our subjects. However, the study of these workers was carried out during the peak transmission period of malaria, which could have contributed to the higher level of immunity. Continued exposure to malarial parasite

for several months has been reported to augment the immune response to the disease as compared to the recent exposure.²⁰ The control subjects could have had a prolonged exposure to the parasite through sub-clinical infections, which failed to produce disease due to the good immunity protection available to them.

The data of present work indicate a rather poor immune response to malaria in our subjects, which could be conducive to the selection and propagation of resistant parasites in our society.

The highest mean IgG titres (0.151 0.107 OD) were recorded in the group of patients 31 to 40 years of age (Figure 2 & 3). Age-dependent increase in the malaria antibody levels has been described in the young children. However, such relationship with age in the adult patients of malaria has not been reported. In fact, Brown et al., failed to establish a correlation between the age of the patient and the antibody titres in acute malaria.²¹ We observed a downward trend of immune response in the group of patients above 50 years of age. The number of patients showing a positive antibody response also decreased in this group to 37.5 %. It is evident from these results that there was an age-dependent increase in the immunity to malaria in our patients up to 50 years. The decline of response in the elderly group may be related to the decreased activity of immune system in that age. In a sero-epidemiological survey conducted in Venezuelan Amazon, Sanchez et al., found comparable serological response among the subjects of ages ranging from 11 to 40 years.²²

Intensity of parasitaemia is an important factor that determines the level of immune response in a patient. Higher grades of parasitaemia produce greater antigenic stimulation leading to increased humoral reaction. This fact is illustrated by the results of this study (Figure-1) where a positive correlation ($r = 0.6531$) is visible between the level of parasitaemia and the IgG titres of the patients. All patients with parasitaemia more than 5000 parasites per cmm of blood were positive in their immune response to the disease. This correlation is in agreement with the reports from other parts of the world.^{23,24}

All the 22 cases of chloroquine-resistance in vivo in this study had IgG levels below 0.30 OD. 77.27% of these cases did not show an adequate antibody response to malaria (Table 1). The total incidence of

chloroquine-resistance noted in the subjects with a negative antibody reaction was almost double as compared to that in the patients who had adequate immunity to malaria.

Among the 42 patients, whose infection was found to be completely sensitive to chloroquine, 19 (45.24%) had adequate immunity to the disease.

The patients showing Sensitive/RI grade of response had IgG titres slightly lower, but not significantly different, from the sensitive group. Only 27.2% of the cases showing RI and 12.5% of the cases showing RII grades of resistance had adequate immunity to malaria. The response to chloroquine in these intermediate grades of resistance is modulated by immune status of the individuals. Draper et al. noted that in Tanzania, the

MIC for chloroquine in Plasmodium falciparum rose progressively over the years but there were no corresponding changes in the findings of the in vivo tests.²⁵ They attributed it to the immunity of the individuals in that region. Low level of immunity in our patients could have been a cause of treatment failure in these cases.

We conclude that the overall immune status of the majority of the patients of falciparum malaria in this region is not adequate. However, in patients showing sensitivity to chloroquine, presence of adequate IgG levels to malarial parasite might have assisted the drug in overcoming the infection. Thus, the humoral immunity to falciparum malaria appears an important factor modulating the drug response.

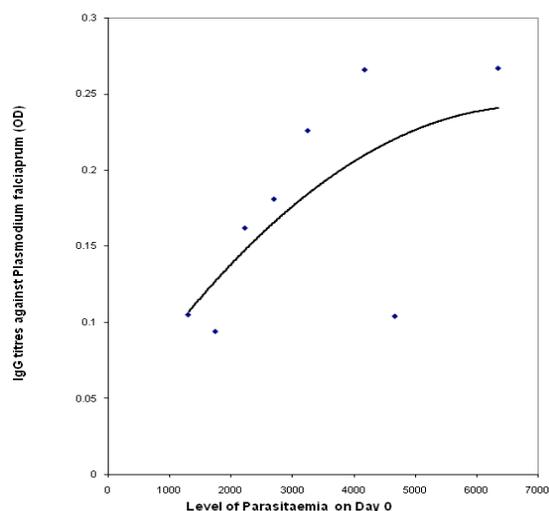


Figure 1: Graph showing relationship between initial parasitaemia in patients of Plasmodium falciparum malaria and antimalarial IgG titres (r=0.6531)

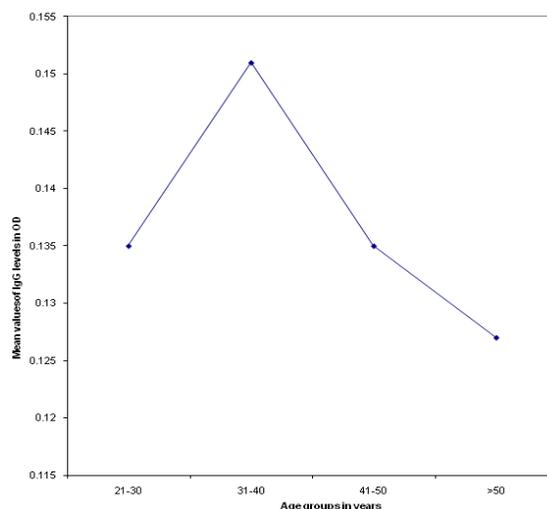


Figure 2: Graph showing relationship between age of malaria patients and antimalarial IgG titres

Table 1: Relationship between anti-Plasmodium falciparum IgG titres and the clinical response to chloroquine in vivo

| IgG titres (OD) | No of Patients showing IgG response | Response to Chloroquine <i>in vivo</i> | | | | | Incidence of chloroquine Resistance |
|-----------------|-------------------------------------|----------------------------------------|-------------|-------------|------------|------------|-------------------------------------|
| | | S | S/RI | RI | RII | RIII | |
| <0.1 | 38 (48.10 %) | 22 (57.89 %) | 8 (21.05 %) | 4 (10.53 %) | 3 (7.9 %) | 1 (2.63 %) | 8/38 (21.05 %) |
| 0.1-0.1905 | 12 (15.19 %) | 1 (8.33 %) | 2 (16.67 %) | 4 (33.33%) | 4 (33.33%) | 1 (8.33 %) | 9/12 (75.0 %) |
| 0.1906-0.3 | 16 (20.25 %) | 10 (62.5 %) | 1 (6.25 %) | 3 (18.75 %) | 1 (6.25 %) | 1 (6.25 %) | 5/16 (31.25 %) |
| > 0.3 | 13 (16.46 %) | 9 (69.23 %) | 4 (30.77 %) | Nil | Nil | Nil | Nil |

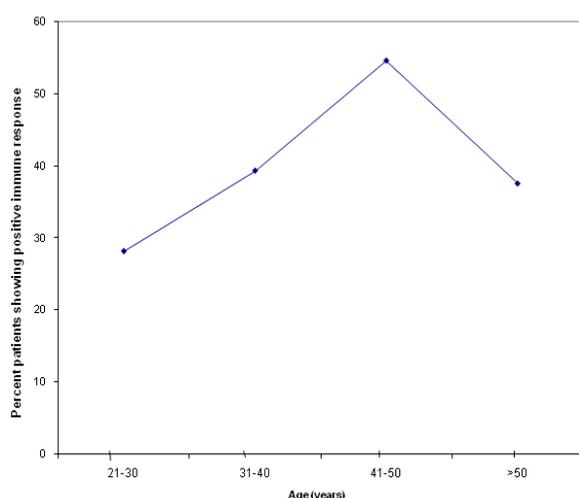


Figure 3: Graph showing relationship between age and percentage malaria patients showing positive immune response to Plasmodium falciparum ($r=0.511$)

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ASSESSMENT OF KNOWLEDGE, ATTITUDE AND PRACTICES REGARDING SKIN CANCER AND ITS PREVENTION AMONG THE STUDENTS OF FUMC

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ABSTRACT

Objectives:

To determine the knowledge and to identify the attitude and practices regarding skin cancer and its prevention amongst students of Foundation University Medical College.

Duration & Place of study:

The study was carried from January to September 2014 at Foundation University Medical College.

Methods :

A Descriptive Cross-Sectional Study among 200 students of first four academic years of FUMC was done; data was collected by Non Random Convenient Sampling through Structured Questionnaire and was analyzed using SPSS version 17.

Results:

Results showed that 76% were aware of the fact that the sun exposure can cause skin cancer. Regarding practices of protective measures 45.5% were using shades, 30.5% were wearing clothing covering most of their body and 24% were using sunscreen lotions. The attitude was positive among many students regarding the prevention towards skin cancer but the practices towards prevention were relatively low.

Conclusion:

Skin cancer development and progression can be prevented through heroic efforts by Health Care Professionals and the general public therefore it is needed to encourage practices among future Health Professionals.

Despite the knowledge adequate precautionary measures were not undertaken.

Keywords:

Sunburn, Radiation, Protection, Sunscreen

INTRODUCTION

Skin is the largest organ of the body and protects the body from injury and infection. Cancer of Skin is the 19th most common cancer worldwide.¹

Depletion of ozone layer leads to increase amount of ultra violet radiation which has harmful effects on human health. Among UV radiations, human skin is most sensitive to UV-B which can cause Sunburn, Skin Cancer and Skin Aging. It is widely accepted that a major etiological factor in the pathogenesis of skin cancer is excess exposure to ultraviolet (UV) radiation.² People, who have had at least one severe blistering sunburn, are at increased risk. Although people who burn easily

are more likely to have had sunburns as a child, sunburns during adulthood also increase the risk.³

Even single sunburn increases risk of developing melanoma, which is the third most common skin cancer and is more dangerous, especially among young people. Approximately 65%–90% of melanomas are caused by exposure to ultraviolet (UV) light or sunlight.⁴ More than one-third of the U.S. population reported sunburn in the previous years, with rates higher among men and the non-Hispanic white population.⁵

Skin cancer incidence can be reduced by adopting certain protected measures like seeking shade, wearing full clothing and most importantly using sunscreen lotion. One of the studies conducted by US Department of Health and Human Services states that, only 56% of adults practiced at least one of the three sun-protective behaviors (use

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sunscreen, wear sun-protective clothing, or seek shade).⁶

In Pakistan, incidence of skin cancer is comparatively lower. Studies on the population of Northern Pakistan, comprising Northern Punjab, Northern Baluchistan, KPK and FATA indicate that skin cancer is among the top three causes of cancer in these regions. In KPK skin cancer was the commonest cancer in males, accounting for 8.9% of all cancers and the second most common cancer in females.⁷ The Armed Forces Institute of Pathology (AFIP), Rawalpindi, reports skin cancer to be the fourth (6.68% of all cancers) and second (5.63 of all cancers) leading cause of cancer in males and females respectively in Northern Pakistan. The frequency of skin cancer reported from the South is not high.⁸

It is need of time to make serious efforts to reduce the morbidity and mortality from skin cancer. It is imperative to understand the knowledge, attitude and practices in our population about a condition that is life threatening. This includes diverse activities such as educating people to wear hats and long-sleeved clothes, stay in the shade, create shade by planting trees or constructing other canopies, reschedule work practices and sporting times, and other activities.

Skin cancer treats well and responds well to drugs. It is also easier to prevent, if proper measures are taken in the right direction. This requires thorough knowledge of the disease itself, which is the main goal of our research. Another reason to conduct research is to raise knowledge in medical students who as future doctors play a crucial role in prevention of skin cancer.

OBJECTIVES

- 1) To determine the knowledge regarding skin cancer and its prevention amongst students of FUMC
- 2) To identify the attitude and practices regarding prevention among students of FUMC

MATERIALS & METHODS

It was a descriptive study conducted among 200 students of FUMC through convenient sampling technique in the months of January to September 2014 by self administered questionnaire using SPSS version 17 for data analysis.

RESULTS

KNOWLEDGE OF SKIN CANCER:

99.5% of the students believed that skin cancer is more common in light haired and light skinned people. Statistics showed that 73% of the students know that change in mole size is an important indicator of developing skin cancer. 69% were with the knowledge that severe sunburn in childhood increase chances of skin cancer.

Table 1: Knowledge regarding effect of sun on skin

| | Yes | No | Total |
|-------------------------------------|-----|----|-------|
| Sun Exposure Cause Skin Cancer | 170 | 30 | 200 |
| Sunburn cause skin cancer | 185 | 15 | 200 |
| Sunscreen protect from UV radiation | 168 | 32 | 200 |
| Sunscreen SPF <15 is not protective | 142 | 58 | 200 |

ATTITUDE AND PRACTICES:

Table 2: Measures taken by students to protect themselves from skin cancer

| Measures of protection | Frequency | Percent |
|----------------------------------------|-----------|---------|
| Stay in the shade | 91 | 45.5 |
| Wear clothing covering most of my body | 61 | 30.5 |
| Use high protection sunscreen lotion | 48 | 24.0 |
| Total | 200 | 100.0 |

Table 3: SPF of sunscreen used by students

| | Frequency | Percent |
|-----------------------|-----------|---------|
| Less than 15 | 36 | 18 |
| Equal or more than 15 | 97 | 48.5 |
| I don't Know | 67 | 33.5 |
| Total | 200 | 100 |

DISCUSSION

According to our study conducted at FUMC Islamabad among medical students 76% were concerned that exposure to sun may give them skin cancer while 24% were not concerned. These results are consistent with the results of an Armenian⁹ research study. Study results showed

positive attitude towards sunscreen use as preventive measure. 70% of the sample agreed that sunscreen provides protection against harmful rays while 30% disagreed. These results were consistent with another U.S (10) study in which 63% sample showed positive attitude.

Our statistics showed that 73% of the students knew that change in mole size is an important indicator of developing skin cancer. The results are consistent with a pilot-study carried out at the Melanoma Centre, University Hospital Spedali Civili Brescia, Italy, which observed that eighty-seven melanoma had been Self-Detected and 44 Relative-Detected. Patients report most commonly signs/symptoms such as dark color (58%) and changing in size (47%).¹⁰ But the results were contrary with study conducted in Agha Khan Pakistan where study population were largely unaware that appearance of a new mole is a risk factor for MM (56% responded incorrect). This difference may be due to difference in study population, because respondents at Agha Khan were pre-clinical students.¹¹

Sixty-nine percent of students had knowledge that severe sunburns in childhood increases chances of skin cancer. This result is supported by another study done by Center for Disease Control and Prevention in US stating that just a few serious sunburns in childhood can increase skin cancer risk later on.¹² Extended sun exposure during childhood supposedly increases the probability of skin cancer later in life¹³ and has been identified as key period in the etiology of melanoma in adulthood.¹⁴

Among the most popular protective practices was shade seeking shade, covering entire body and sunscreen. Shade seeking was also popular among other studies, such as Turkish¹⁵ studies i.e. 44% and 23% respectively. According to our study sample 45.5% always used shade as protective measure 30.5% wore clothing covering most of the body and 24 % used high protection sunscreen protection. Another study in UK states that those aged 16–30 years were shown to be significantly less likely to avoid the midday sun, wear sunscreen, or cover up with additional clothing when in the sun.¹⁶

The Centers for Disease Control and Prevention (CDC) provides leadership for nationwide efforts to reduce illness and death caused by skin cancer, which is likely the most common form of cancer in the United States. The message of CDC's Skin Cancer Primary Prevention and Education Initiative is clear: When in the sun, seek shade, cover up, get a hat, wear sunglasses, and use sunscreen.

56% of adults practiced at least one of the three sun-protective behaviors (use sunscreen, wear sun-protective clothing, or seek shade),⁶ 30% reported usually applying sunscreen. 7% applied sunscreen with an SPF of 15 or higher 18% reported usually wearing some type of fully sun-protective clothing. 33% usually sought shade only 9% of high school students reported that they routinely used a sunscreen with an SPF of 15 or higher.¹⁷

A study conducted data from NHANES 2003–2006, restricted to adult whites (n = 3,052) to evaluate how Americans protect themselves from the sun. The most common sun protective behavior used by white adult Americans is sunscreen, with over 30% of individuals reporting frequently using sunscreen when in the sun for more than 1 h. While 25% of Americans frequently stay in the shade, only 16% regularly wear a hat, and 6% reported frequently wearing long sleeves. Over half of white Americans reported at least one sunburn, and 26% reported two or more sunburns in the past year.¹⁸ Another study conducted at medical students of University of Miami Miller School of Medicine (UMMSM) show that greater sun-protection knowledge was associated significantly with better sun-protective attitudes and behaviors. Students with good sun-protective attitudes were more likely to engage in sun-protective behaviors.¹⁹

According to our study 48.5% of sample wore sunscreen of SPF 15 and higher, 18% used SPF less than 15 while 33.5% were unaware of their sunscreen SPF.

Data on behaviors related to skin cancer risk among the U.S. population are collected by CDC through the national YRBS and NHIS. The national YRBS is a cross-sectional, school-based, biennial survey that monitors the prevalence of health risk behaviors among high school students. According to this, sunscreen use is low among U.S. high school students, with only 10.1% using sunscreen with an SPF of 15 or higher always or most of the time when outside for more than 1 hour on a sunny day.²⁰ This difference may be due to their desire to be tanned.

CONCLUSION

The number of positive responses towards skin cancer knowledge and prevention increased with corresponding academic year of study of students increased showing that senior students had more knowledge. However despite the knowledge precautionary methods were not taken. Our research also concludes that regardless of having knowledge, high number of respondents was aware of exposure to sun being a risk factor for skin cancer.

This shows that spreading awareness about the risk factors for skin cancer and the harmful effects of exposure to the sun may be fruitful but practical steps to encourage people to actively participate in protecting themselves against it is required.

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KNOWLEDGE AND COMPLIANCE TO METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS INFECTION CONTROL GUIDELINES AT TWO TERTIARY CARE HOSPITALS IN RAWALPINDI, PAKISTAN

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ABSTRACT

Methicillin resistant Staphylococcus aureus is a major cause of nosocomial infections increasing patient morbidity and mortality with massive expenditure on its control and treatment.

Objectives:

Our objective was to evaluate the knowledge and compliance of healthcare workers about infection control guidelines at two tertiary care hospitals in Rawalpindi, Pakistan.

Method:

A self-reported questionnaire was used to evaluate the knowledge and compliance of doctors, nurses and nursing assistants at Combined Military Hospital (CMH) and Military Hospital (MH) Rawalpindi, Pakistan.

Results:

A total of 600 healthcare workers were questioned out of which 27% were not even aware of the existence of MRSA infection control guidelines. Healthcare workers had gaps in their knowledge about patient transferring protocol and contact precautions. Many, although aware of the guidelines, were not practicing MRSA screening and decolonization techniques. Most healthcare workers were aware of the infection control practices but did not realize the importance of its execution. A revision and then concerted implementation of these guidelines is required in these health care institutions.

Keywords

Compliance, Infection Control, Knowledge, MRSA

INTRODUCTION

The first strain of MRSA was detected in United Kingdom in 1961 and in the subsequent decades it has spread rapidly throughout the world in most of the health care institutions.¹ In the United Kingdom, 4,935 MRSA isolates were reported between April to December 2006.² However the incidence of MRSA, seems to vary by region and country; during the last 20 years the proportion of isolates resistant to methicillin have ranged from <1% in The Netherlands to more than 30% in Spain, France, Italy and India; and 58% in USA.^{3,4}

Hospital personnel can serve as reservoirs for MRSA and their non-compliance to the infection control guidelines, have been implicated as a link for transmission between colonized or infected patients.^{2,5} Some authors have reported their experience in successfully reducing the

nosocomial spread of MRSA and even complete eradication of MRSA was possible with an aggressive approach using a sustained and consistent infection control strategy.^{4,6-9}

In Pakistan, nosocomial infections have remained one of the most demanding areas of concern for physicians, nursing staff and administration and yet a previous study conducted at Armed Forces Institute of Pathology reported as high as 51% of Staphylococcus aureus isolates as methicillin resistant.¹⁰ The Aim of our study was to evaluate the knowledge and compliance of healthcare workers about infection control guidelines at military institutions in Rawalpindi, Pakistan.

MATERIALS & METHODS

Medical personnel deputed at general surgical and medical wards, and Intensive Care Unit at Combined Military Hospital (CMH) and Military Hospital (MH) Rawalpindi participated in the study. These are 1,500 bedded tertiary care hospitals catering to most of the population in Rawalpindi.

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In order to assess the knowledge and compliance of health care workers regarding MRSA infection control, a questionnaire was used, based on the hospital's current infection control guidelines of the hospital. The study participants included doctors, nurses and nursing assistants appointed in the general surgical and medical wards, and intensive care units at CMH and MH. Informed consent was taken from each participant and the questionnaire was filled by the healthcare worker him/herself. The questionnaires were provided in both English and Urdu languages.

Each question was divided into two parts, the first assessed the knowledge of the healthcare worker and the later simply asked whether the mentioned practice was being performed, in order to assess the compliance. In case a study participant gave an incorrect answer to the knowledge based question, it was automatically assumed that compliance to that infection control guideline was not being maintained. The study participants were explained the importance of the study and ensured that

complete anonymity will be kept to make sure that they responded as truthfully as possible.

All data was analyzed using SPSS ver 17.

RESULTS

A total of 600 health care workers participated in the study during the study time period. All the health care workers were divided in to three groups. Group I comprised of Nursing assistants, Group II had nursing staff and group III comprised of Doctors. Nurses comprised the maximum percentage of the total sample (53%). Fifty-eight health care workers, all nursing assistants, were not even aware of the existence of MRSA and were hence not asked to fill the questionnaire. 25% of the healthcare staff was not aware of the presence of infection control guidelines for MRSA.

Most doctors had adequate knowledge about the infection control guidelines, though compliance in areas such as hand hygiene, patient transferring guidelines and MRSA eradication protocol was sadly lacking. (Table I)

Table I: Knowledge and Compliance of Healthcare workers

| Knowledge based question | Correct answer | | | Compliance to the infection control guideline | | |
|-----------------------------------------------------------------------------------------|----------------|-----|-------|-----------------------------------------------|-----|------|
| | I | II | III | I | II | III |
| Management of an MRSA patient | | | | | | |
| A patient is found to be MRSA positive what do you do? | 10% | 45 | 97.5% | 3% | 23% | 66.5 |
| Who do you take permission from when transferring an MRSA patient to another ward? | 3.5% | 12% | 19% | 1.3% | 10 | 14% |
| What do you do before entering a room of an MRSA patient? | 13 | 17 | 19% | 7% | 10 | 13 |
| What do you when leaving the room of an MRSA patient? | 63 | 76 | 81% | 25% | 45 | 57 |
| What instructions do you give to a visitor before entering the room of an MRSA patient? | 51 | 55 | 63% | 49% | 73 | 80 |
| What do you do to the patient file of an MRSA patient? | 21 | 47 | 95% | 64% | 83 | 89 |
| Staphylococcal eradication protocol | | | | | | |
| Treatment of culture positive MRSA from hair? | - | 1.4 | 86.5% | - | - | 36 |
| Treatment of culture positive MRSA from nasal swab? | - | | 84% | - | - | 42 |
| Treatment of culture positive MRSA from skin? | - | | 85.5% | - | - | 44 |
| Changing of MRSA infected bed linen? | 11 | 49 | | 46% | - | - |
| Changing of MRSA infected clothes? | 12 | 52 | | 43% | - | - |

Questioning the staff about transferring an MRSA positive patient from one ward to another raised much confusion and showed the least percentage of compliance to the infection control guideline. According to the hospital guidelines the staff is required to take permission for the Head of the Infection Control team before transferring an MRSA positive patient. Staff responsible to transfer a patient had no knowledge about whom to contact for further orders and protocols. When asked about hand hygiene practices while entering or leaving the room of an MRSA patient, most of the staff was using alcoholic hand rub as a mean of decontamination (61.7%). As the infection control guideline requires the staff to wash their hands with soap and water before entering majority of the staff was not complying with the hospital infection control guideline. Details are presented in table I.

Discussion

Hand Hygiene

Healthcare workers continue to turn a blind eye towards important yet simple practices like hand hygiene and barrier precautions.¹¹ Our results sadly reiterated the issue. Compliance with hand washing with soap and water before entering the room of an MRSA positive patient, as per MRSA infection control guidelines, was only 3% among nursing assistants and 23 % among nursing staff. 97.5 % doctors were having appropriate knowledge about importance of hand washing but unfortunately only 66% were compliant. This result was based on the infection control guideline, "Alcoholic chlorhexidine hand rub should be used after leaving the cubicle. This must not be used instead of hand washing before entering the cubicle".

Studies have shown that alcoholic hand rubs have equal efficacy as compared to soap and water in reducing contamination during routine patient care.^{12, 13} Soap and water is only indicated when the hands are visibly soiled or contaminated with blood or body fluid.²⁰ Alcoholic hand rubs increase compliance with hand hygiene by having the advantage of being less time consuming, less irritating to the skin and according to a study even more cost-effective than soap and water.¹⁴

Contact and Barrier Precautions:

According to both Centers for Disease Control and Prevention (CDC) and Cambridge University

Hospitals NHS guidelines, an MRSA patient needs to be isolated and the staff are required to wear both gloves and gowns when entering the patient's room.¹⁵ The MRSA infection control guidelines at our Military institutes only requires the staff to wash their hands before entering a room, wearing gloves or gowns are not part of the infection control protocol. This is a major break in the infection control as studies have shown up to 156 fold reductions in MRSA transmission using barrier precautions for colonized and infected patients as compared with Standard Precautions.^{16,17} The cost-effectiveness of such precautions is often an issue. Many believe that the reduction in MRSA rates, these precautions might bring, are not cost-effective. A recent study showed otherwise, claiming an 18 to 27 fold less expenditure than that required for controlling MRSA bacteremia.¹⁶

The infection control guidelines at military institutes also require the healthcare workers to take permission from the Head of the infection Control Committee before transferring a patient to another ward. Most healthcare workers were not aware of this guideline, showing a compliance rate of only 10.5%. Most international infection control guidelines require the healthcare staff to pre-inform the person in-charge of the unit, where the patient needs to be transferred, so that a particular area can be designated for the patient and if a procedure needs to be performed the patient can possibly be kept last on the list.¹⁷

Environmental Cleaning and Decontamination:

According to the Association for Professionals in Infection Control and Epidemiology (APIC), MRSA can survive up to 56 days on environmental surfaces, making it important to have cleaning and disinfection protocol for the patient's environment.¹⁸ Our infection control protocol at present does not have a detailed guideline addressing this important infection control intervention, making it a possible cause of high MRSA prevalence rates.

Our hospital's Infection control guideline for treatment of infected linen and patient's clothes in accordance with the international infection control guidelines require the healthcare workers to change these items on a daily basis and treat them as infected linen. The compliance with this guideline at our institutes was sadly lacking. Since most of the

healthcare workers were aware of this infection control guideline, a possible cause can be lack of funds and proper laundering services available for daily cleaning or simply underestimation of the importance of this guideline. According to a recent review the most common sites for MRSA, eradication of which could be the key factor in reducing MRSA infection rates include, Bed linen (41%) and Patient gown (40.5%).^{15,18}

Screening:

According to the MRSA infection control guidelines at our hospital, screening cultures need to be sent from nose, hairline, axillae, groin and any other wounds for a suspected MRSA patient. 9% of group I, 32% of group II and 84 % of Group III were aware of these guidelines, however only 2%, 31% and 48% in group I, II and III respectively were complying with it. One of the reasons for low compliance could be that, getting screening swabs from multiple sites can be cumbersome, time consuming and costly. According to the latest APIC guidelines and University College London guidelines, swabs from the anterior nares and areas of active skin breakdown and draining wounds for screening purposes is sufficient.^{10,13,15,18} Swabbing only anterior nares can detect up to 80% MRSA carriers and swabbing additional sites can increase it up to 92%.^{13,18} Hence, although swabbing of all possible carrier sites will definitely have a higher yield, reducing the screening sites to only anterior nares and skin and draining wounds, could be a more cost-effective and less time-consuming option leading to better compliance.

Decolonization and Eradication:

In 1988 The Netherlands adopted a new, “search and destroy” policy to cope with high MRSA prevalence rates. Needless to say, a prevalence rate of less than 1% currently, shows how effective this strategy turned out to be. The basic principle was intense implementation of all known infection control practices, while monitoring the compliance of the healthcare workers involved. These included screening patients at risk for MRSA colonization, as well as hygienic measures, strict isolation of colonized or infected patients, decolonization of patients, and identification and decolonization of MRSA-positive hospital staff.^{11,13,16,18} A recent study confirmed the effectiveness of this strategy when an MRSA epidemic in a large teaching hospital was

successfully controlled.¹⁰

Although the recent APIC guidelines do not recommend routine MRSA decolonization of patients, for fear of higher MRSA-resistance rates, the success gained by The Netherlands by adopting this strategy has lead us to believe that strict decolonization of all MRSA colonized patients and healthcare workers could be an important infection control practice in reducing our currently high MRSA prevalence rates. Our infection control guidelines for MRSA control currently do not specify the exact approach that needs to be taken when an MRSA patient is admitted in a ward till he is found to be MRSA negative.²⁰ We believe that this unclear and sketchy information could be an important factor, reducing applicability and comprehensibility of the guidelines for the healthcare workers leading to a decrease in compliance. Compliance with the decolonization protocol is one of the examples where although the healthcare workers were aware of the proper practice for performing and confirming MRSA eradication (80%) the compliance rates were only 45.5%.

LIMITATIONS

The compliance in our study was calculated based on self-reported behavior using a questionnaire. There is a potential for information bias with such a study pattern, however, due to lack of man power; we felt this was the only practical way to assess compliance. Having mentioned that, it is also possible that since the compliance is self-reported it might just be giving a more optimistic picture to the actual situation.

The healthcare workers at these medical institutes are constantly being reappointed from one department to another. So even though our study sample comprised of healthcare workers in surgical and medical wards, we had no way of knowing how long the healthcare worker had been working in that particular setting.

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DENTAL CARIES RISK ASSESSMENT

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ABSTRACT

Objective:

A study was conducted to find the caries status of patients and identify the risk factors predisposing to caries. The objectives were to find the general health contributing conditions which promote the development of caries and to determine the co-morbidities which are present in patients having caries.

Study Design:

Descriptive Cross Sectional

Material and Methods:

120 Patients were screened at Medical Camp and 80 patients were identified as having caries by using "Caries Risk Assessment (age<6) Form by American Dental Association" to study oral health related behavior. The questionnaire was filled in after informed consent. Demographic details were also recorded.

Results:

A total of 120 patient attended the OPD and 80 consented to participate and fill the questionnaire.

The age-wise oral hygiene status was fair in 28 individuals whereas it was poor in 52 patients. Highest prevalence of caries was seen in age group 21-40 years.

When the Contributing Conditions predisposing to caries were analyzed, it was found that fluoride exposure was in 21 (26.5%) patients, consumption of sugary food in 52 (65%) patients and presence of dental caries in 32 (40%) patients. None of the patients had previous record of dental treatment.

In terms of General Health Conditions, Special Healthcare Needs were reported by 3 (3.7%) patients, presence of Eating disorders by 15 (18.75%) patients, use of Medications that reduce salivary flow by 12 (15%) patients and Drug/alcohol abuse by 17 (21.25%) patients.

Analysis of the Clinical conditions of these patients revealed Cavitated or non Cavitated carious lesions in 80 patients (100%), Teeth missing due to caries in 32 (40%) patients, Visible plaque in 37 (46.25%) patients, Unusual tooth morphology in 21 (26.25%) patients, Interproximal restorations in 10 (12.5%) patients, Exposed root surfaces in 15 (18.75%) patients, Restorations with overhangs in 8 (10%) patients, Dental/Orthodontic appliance use in 12 (15%) patients and Severe dry mouth in 09 (11.25%) patients.

When the overall risk for further development of caries was assessed by the questionnaire, it was found that 19% had low risk, 33% had moderate risk and 47.5% had high risk of developing caries.

Conclusion:

Caries prevalence in this sample of patients was high. Most caries were untreated, being more common in patients who consumed sweets daily and had poor oral hygiene. Dental caries is a health hazard and is related to age, dietary habits, nutritional status, fluoride exposure, salivary flow and oral hygiene. Our population is highly prone to dental caries due to these risk factors. Dental health is as important as general health for a good quality life.

Keywords:

Dental caries, Oral hygiene, Tooth morphology, Caries risk

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INTRODUCTION

Dental caries or tooth decay is most important oral health problem in both developed and developing countries, affecting 60-90% of school children and vast majority of adults.¹ It starts as tiny area of

demineralized softened enamel at the surface of tooth, in the fissure of teeth or in between teeth, it then spreads to involve dentine which collapses to form a cavity and this destroys tooth.² It can also damage roots of teeth. Carious lesion occurs due to effect of acid on enamel surface, the acid is generated when carbohydrate present in foods or drinks interact with microorganisms present in dental biofilm or (plaque) which then causes loss of calcium and phosphate from the dentine.³ The microorganisms identified to be cariogenic are *Streptococcus mutans* and *Streptococcus sobrinus*.^{4,5}

In the initial phase, caries is recognized as dull white demineralized enamel⁶, occurring mostly on occlusal surface of teeth and in some cases on multiple surfaces.⁷ When decay progresses, the lesion becomes yellow or brown and cavitated.

Dental caries commonly occur at age 2-5 years in deciduous teeth and in early adolescence for permanent teeth, whereas in more developed countries it occurs at later ages because recession of gums along the roots of teeth occurs in old age.⁸ Carbohydrates are major factor in causing caries. Small size of sugar molecules facilitate salivary amylase to split the molecule into components that are quickly metabolized by bacteria in the plaque.⁹ This process produces acid which leads to demineralization of teeth.^{10,11} Various substances can prevent caries; these include use of fluorides and vitamins, decreased consumption of sugars and drinks. Use of fluoride decreases the incidence of carious lesion even in the presence of high consumption of sugary food.¹² Nutritional conditions have an important role especially deficiency of vitamin D, vitamin A and protein energy malnutrition leads to enamel dysplasia and this then leads to caries.

Vitamin deficiencies also contribute to salivary gland atrophy which in turn decreases mouth defense against infections and also the capacity of saliva to neutralize plaque acid. It was reported by Navia et al that deficiency of vitamin, zinc, iron and fluorides alter the quantity and composition of saliva and decreases its protective effect.¹³ Thus caries have a multifactorial origin and diet plays a pivotal role

along with host defence and microbial flora, these all interact over a period of time and promote demineralization of tooth enamel with resultant caries formation. Caries vary with age, gender, medical problems, oral hygiene status and tooth morphology and all the surfaces of tooth are not equally vulnerable.

A study was conducted at the dental OPD of Mohammad Medical College (MMC) Mirpurkhas, to find the caries status of patients attending the OPD and also to find whether eating habits, tooth morphology and co morbidities have any role to play in the development of caries.

METHODOLOGY

This was a descriptive cross sectional study conducted from Jan 2015 to June 2015 in collaboration with staff of MMC. The study was approved by ethical committee

A medical camp was held at MMC, from where patients were screened for medical and dental diseases. 80 patients were identified as having caries. Oral Examination was done using dental mirrors. Caries were measured according to DMFT (Decayed, Missing, Filled Teeth) index. Oral hygiene status was recorded according to VPI (Visible Plaque Index).

Caries Risk Assessment (Age>6) Form by American Dental Association²⁸ was used to study oral health related behavior. The questionnaire was filled in after informed consent. Demographic details were also recorded.

INCLUSION CRITERIA

1. Patient giving consent for participation
2. Patient of either gender
3. Age 10-70 years

EXCLUSION CRITERIA

1. Smokers
2. Patients consuming pan/gutka
3. Patients having growth or suspicious lesion in the mouth.
4. Patients taking antibiotics

RESULTS

Data collected was analyzed by SPSS version 22. Gender and age, were expressed in percentages. Chi square test was used to examine the statistical significance of differences observed. P value of <0.05 was considered significant.

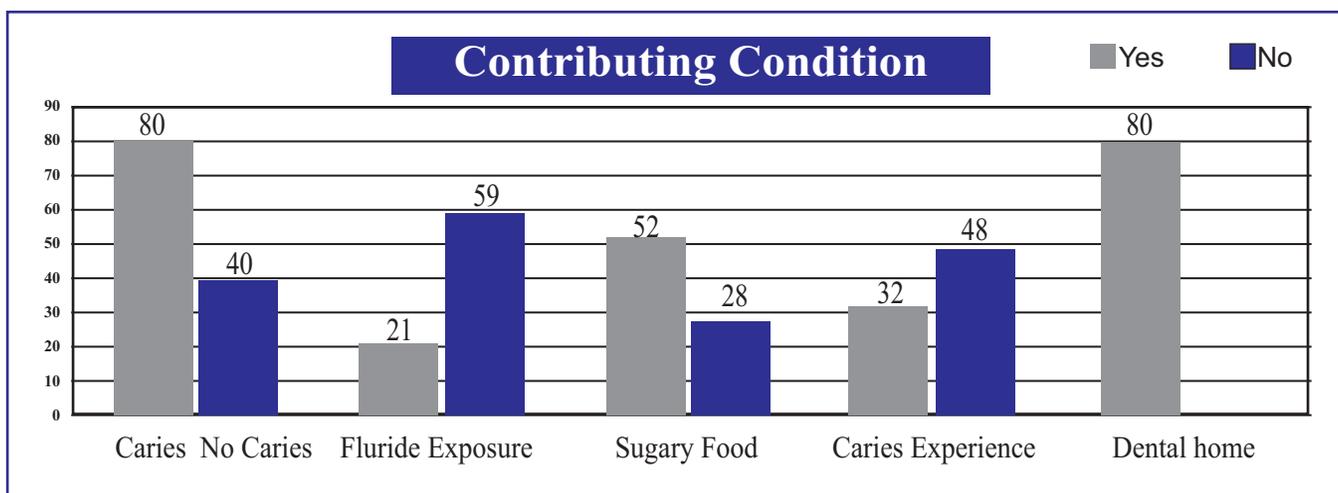
A total of 120 patient attended the OPD and 80 consented to participate and fill the questionnaire.

The age-wise oral hygiene status was fair in 28 individuals whereas it was poor in 52 patients. Highest prevalence of caries was seen in age group 21-40 years, as shown in Table-I.

Table 1: Oral Hygiene Status and Caries prevalence

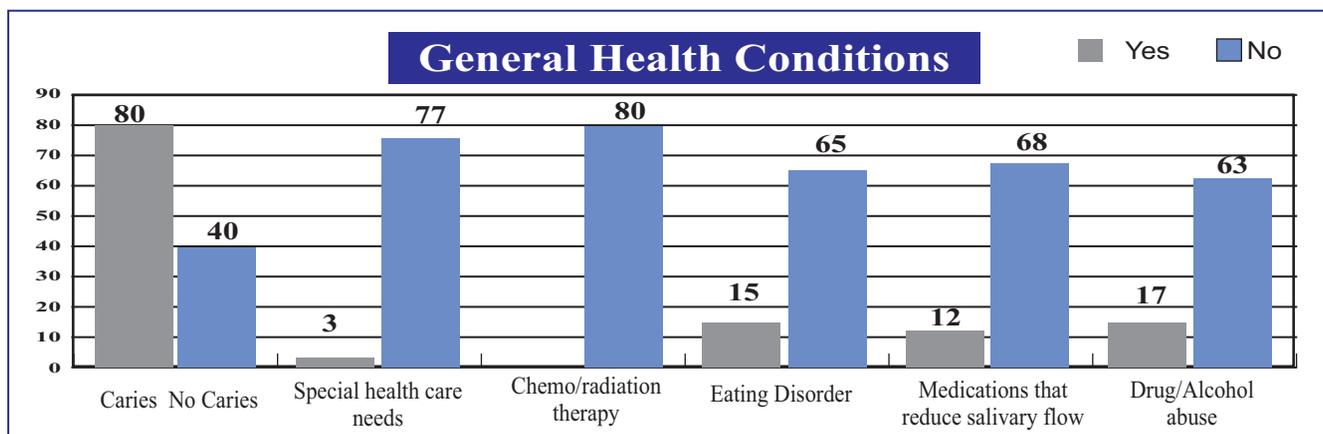
| Oral Hygiene (VPI) | Age (years) | Caries (DMFT) |
|--------------------|-------------|---------------|
| Fair | 10-20 | 6 |
| | 21-40 | 10 |
| | 41-60 | 7 |
| | 60-70 | 5 |
| Poor | Age (years) | Caries |
| | 10-20 | 13 |
| | 21-40 | 29 |
| | 41-60 | 07 |
| | 60-70 | 08 |

When the Contributing Conditions predisposing to caries were analyzed (Graph-I), it was found that fluoride exposure was in 21 (26.5%) patients, consumption of sugary food in 52 (65%) patients and presence of dental caries in 32 (40%) patients. None of the patients had previous record of dental treatment.



Graph I: Contributing Conditions in patients having caries

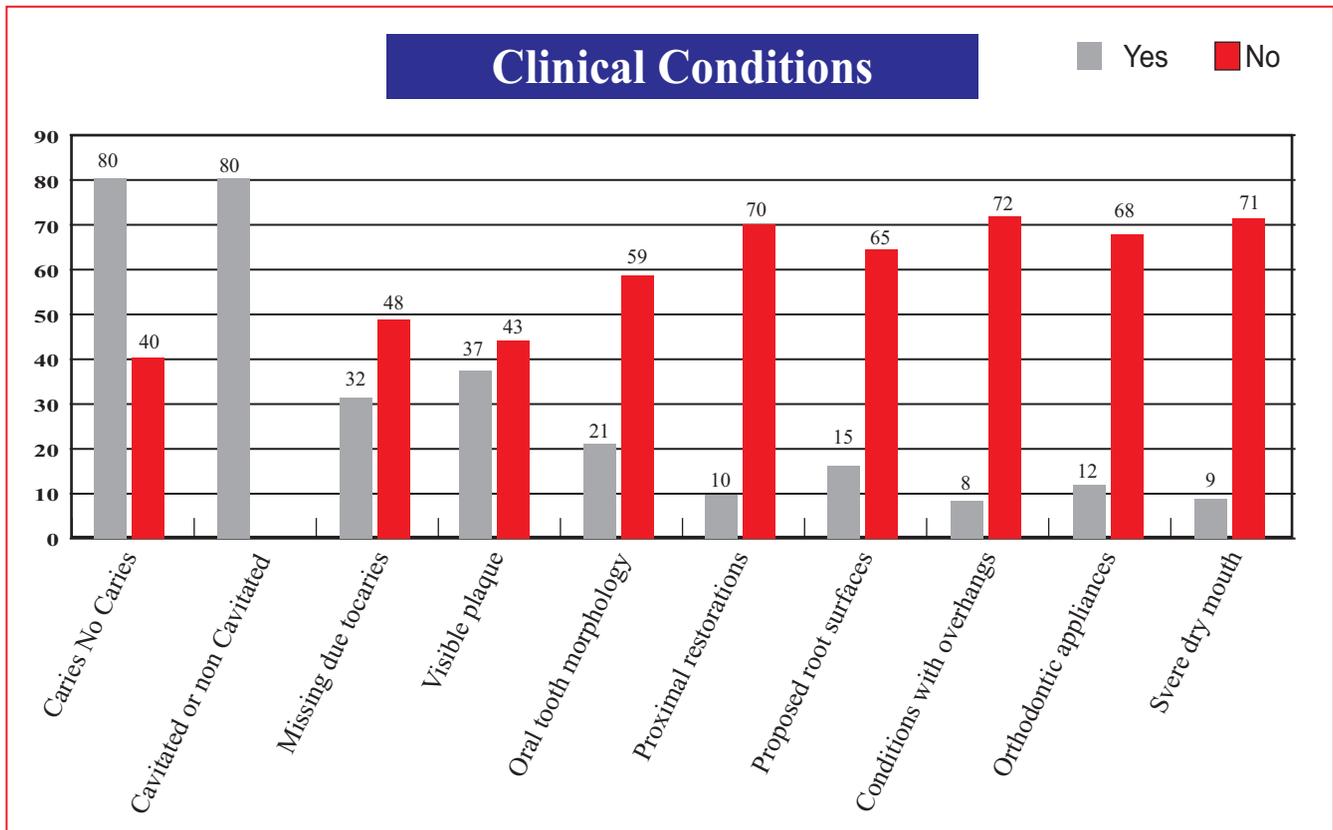
In terms of General Health Conditions (Graph-II), Special Healthcare Needs were reported by 3 (3.7%) patients, presence of Eating disorders by 15 (18.75%) patients, use of Medications that reduce salivary flow by 12 (15%) patients and Drug/alcohol abuse by 17 (21.25%) patients.



Graph II: General health conditions in patients having caries

Analysis of the Clinical conditions (Graph-III) of these patients revealed Cavitated or non Cavitated carious lesions in 80 patients (100%), Teeth missing due to caries in 32 (40%) patients, Visible plaque in 37 (46.25%) patients, Unusual tooth morphology in 21 (26.25%) patients, Interproximal restorations in

10 (12.5%) patients, Exposed root surfaces in 15 (18.75%) patients, Restorations with overhangs in 8 (10%) patients, Dental/Orthodontic appliance use in 12 (15%) patients and Severe dry mouth in 09 (11.25%) patients.



Graph III: Clinical conditions in patients having caries

When the overall risk for further development of caries was assessed by the questionnaire (Table-2), it was found that 19% had low risk, 33% had moderate risk and 47.5% had high risk of developing caries.

Table 2: Risk for development of caries.

| Degree of risk | Number & percentage of patients |
|----------------|---------------------------------|
| Low risk | 15 (19%) |
| Moderate risk | 27(33.5%) |
| High risk | 38(47.5%) |

DISCUSSION

Dental caries exist worldwide.¹ It leads to pain, difficulty in mastication and may produce local and systemic infections¹⁴ The Federation Dental International (FDI/World Dental Federations, Oral Health Atlas demonstrates that untreated dental caries affects more than 50% of children in most South East Asian countries.¹⁵

Oral health is an integral part of general health. Caries presence is highly related with snacking habits and maintenance of oral hygiene and general health. Dental caries is preventable, provided predisposing factors are controlled.¹⁶ Care must be given to diet as well as change of behavior and knowledge that healthy primary teeth are essential for permanent teeth.¹⁷ Nine (11%) of our patients had dry mouth, thereby

increasing their chance for Caries because absence of saliva increases the pH of the oral environment and promotes the growth of bacteria due to the lack of lubrication action of saliva. Therefore when acid produced by bacteria or food is not neutralized due to lack of saliva, loss of minerals from tooth surface occurs and these minerals are not replaced. Decreased saliva could be due to drugs. In our study population²¹ (25%) patients reported intake of drug like antihypertensives, thereby predisposing them to caries, because saliva forms a dental pellicle and hence prevents mineral loss and also restores calcium and phosphate. Saliva has antibacterial activity and buffering actions in addition, which facilitates mechanical disposal of residual food particles.¹⁸ In the oral cavity saliva has a protective role and if amount of saliva decreases, the risk for oral diseases rises. One in five persons complain of dry mouth, especially elderly people.¹⁹ Xerostomia or dry mouth leads to halitosis, sore mouth, difficulty in swallowing and speech.²⁰ Its prevalence varies from 10-45%, more in women.²¹ It is a risk factor for dental caries common in patients taking anti depressants, and some drugs for cardiovascular disorders.¹⁹ Some drugs decrease salivary flow which lowers buffering of plaque acids and demineralization occurs more rapidly than remineralization.²¹ Caries are common in patients with dry mouth. Decrease saliva could also be due to radiation of head and neck, psychological problems, diabetes, HIV, autoimmune disorders, Sjogren's syndrome.²⁰

Caries occurs in 1 in 5 dental patients and increased prevalence is seen in elderly and women. In a National Health and Nutrition Survey of 1999-2004, dental caries prevalence in adults aged 20-64 years was 92 %.²² 26% of adults had untreated decay. Many dietary factors are related with caries like fat and sugar in all ages.²³ Caries prevalence increases with age.²⁴ In a recent study, poor diet is related with tooth loss due to caries in adults. Dental erosion and severe tooth decay occurs on chewing sweets, soft drinks possess acid and sugars which have acidogenic and cariogenic properties several studies reported this correlation between caries and soft drinks²⁵ and our findings are also in accordance with it. It has also been reported by Majewski RF 2001 that carbonated drinks could reduce surface hardness of enamel, dentures and

dental restorations containing micro-filled composite and resin-modified glass ionomers. Tooth brushing is the best way to keep oral hygiene.²⁶ Non fluoride toothpaste could increase tooth loss compared with drinks alone²⁷ Whereas fluoride-containing and remineralizing toothpastes containing NaF, -Ca phosphate and fluoride ions are effective in inhibiting enamel erosion.

CONCLUSIONS

Caries prevalence in this sample of patients was high. Most caries were untreated, being more common in patients who consumed sweets daily and had poor oral hygiene. Dental caries is a health hazard and is related to age, dietary habits, nutritional status, fluoride exposure, salivary flow and oral hygiene. Our population is highly prone to dental caries due to these risk factors. Dental health is as important as general health for a good quality life.

Oral health is lot more than just healthy teeth. It affects one's appearance, socialization, physical and psychological well being. Advanced caries lead to premature loss of teeth and orthodontic problems, caries risk could be minimized by avoiding sharing of utensils, drinks, toothbrushes. Minimize bacteria predisposing to tooth decay by using mouth rinses, mouth gels and dentifrices. Oral health education promoting to use fluoridated toothpaste and fluoridated water consumption and avoiding carbohydrates diet and promoting fibre diet rich in fruits and vegetables.

Epidemiological studies can be of value in assessing the prevalence of disease and in finding trends in disease development and analyzing predisposing factors for the development of caries.

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MATERNAL DEPRESSION DURING PREGNANCY – RISK, CONSEQUENCES AND INTERVENTIONS - A REVIEW

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ABSTRACT

Maternal depression during pregnancy is a serious public health problem. The morbidity that is associated with antenatal depression has a number of potential consequences for the expectant mother and at the same time for the new born and other family members. This review offers a comprehensive discussion on prevalence, etiology of antenatal depression, effect on mother and family and cost effective interventions to decrease the burden and adverse effects of antenatal depression

ANTENATAL DEPRESSION

Depression has been described by mankind for several millennia. It manifests with either low self-worth or feeling of guilt, depressed mood, loss of interest or pleasure, poor appetite, low energy, sleep disturbance and poor concentration.^{1,2} Depression is one of the most common mental health problems occurring in women during their childbearing years.³ Since pregnancy has been traditionally viewed as a time period that protects women against development of depression. Therefore consequences of maternal depression during pregnancy has not received much attention in mental health, psychiatric, family medical or in obstetrical practice.^{4,5} In fact this period in a female's life is associated with exacerbation of several mental disorders as many physical as well as emotional changes, are taking place. It not only has deleterious effects on pregnant mother and her new born but also there is increased risk of development of postpartum depression.⁶ The prevalence in most studies has hovered between 30% and 40%, for example 31% in England⁸, 30% in Italy⁹ and to 38% in the U.S.¹⁰. Prevalence of both antenatal depression & postnatal depression is more common and higher in Asian countries as compared to western countries.³ The reported rates are as follow as 37% in Hong Kong¹¹ 27.5% in Turkey¹² 30.0% in Indonesia¹³ & 42 % in Pakistan.¹⁴ In Pakistan about 505 of the

expectant mothers from rural mountain area were found depressed whereas in southern villages it was reported to be 36%.¹⁵ The risk factors for antenatal depression are common both in Asian & Western countries except for some of the factors related specially to Asian culture.¹⁶ Most Recently healthcare professionals and researchers have started to think that there is a possibility that a continuum exists between postnatal and antenatal depression. Some studies have found that more than 50% mothers with postpartum depression had its origin either before pregnancy or during antenatal period.¹⁷ Pregnancy is associated with psychological and physical changes unique to all three trimesters of pregnancy. The risk factors for antenatal depression in different trimesters suggest that pathogenesis of clinical problems arising in different pregnancy trimester is different.¹¹ Therefore an understanding of antenatal depression during each of the three trimester is crucial so that number of contradictory findings reported in literature can be clarified and to focus the treatment towards the right direction in each trimester of pregnancy.^{18,19} In 1st trimester of pregnancy, a higher prevalence of depressive disorders was found to be independently associated with unwanted or unplanned pregnancy, literacy level, history of past depression, high neuroticism. Whereas in the 2nd trimester with unwanted or/ an unplanned pregnancy and in the 3rd trimester with high neuroticism, unplanned or unwanted pregnancy, and any psychosocial stressor in past year.²⁰ In a study, 46% of depressive symptoms variance in last trimester of pregnancy was due to lack of social support and low marital satisfaction.¹⁰ A U-shaped curve characterized the prevalence of depression as

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it decreases in second trimester as compared to the first trimester and then again increases in the third trimester.¹¹

RISK FACTORS FOR ANTENATAL DEPRESSION

Mostly studies for evaluation of risk factors for depression during pregnancy are conducted in Western countries mostly. Based upon these studies risk factors for depression include primarily a previous history of depression, low level of social support, marital difficulties and recent major life events.²¹ Despite that culture plays a vital role in the way women express their distress²² but many factors associated with antenatal depression seem similar in Asian countries to ones found in studies carried out in western countries e.g. stressful life events, marital difficulties, financial difficulties, low social support²¹, unplanned pregnancy, uneducated/unemployed husband and young age.^{13,23} However some factors are unique to Asian culture like conflict with their in-laws (in particular mother in-law, related to infant gender, most of the time a female baby) history of previous abortions.¹⁶

Mostly pregnancy is a happy time for the family mostly, but at the same time it increases expenses of the families that includes expenses for medical care (medical care during pregnancy & child birth) and of new family member. Especially in low-income families or in nuclear family where male is the sole earning member. Financial difficulties as a matter of fact are found to be associated with antenatal depression in both western as well as in Asian countries.²³ In the obstetric risk factors that reached statistical significance were complications in previous pregnancy, past history of miscarriages and stillbirths.¹⁴ Among psychological factors low self-esteem in pregnant mothers is considered a predictive factor for depression during pregnancy. Pregnant mothers with low self-esteem during pregnancy are not ready to face stressors and challenges of pregnancy and are therefore more likely to be depressed during pregnancy. Interventions should be done for enhancement of self-esteem of pregnant mother. Marital satisfaction, social & moral support can protect females from depression during pregnancy.^{7,24} Bowen found that significance of social support vary in different trimesters of pregnancy. Social support during third trimester protects against depression. Unwanted pregnancy six times

increases the risk of depression in pregnant mother.⁷ In literature marital satisfaction and perceived social support have been identified as protective factors for antenatal depression.^{7,24}

EFFECT ON MOTHER, NEW BORN AND FAMILY

It is presumed that pregnancy is a period of heightened emotionality and frequent mood swings are expected. Mood fluctuations are not always normal. This may be due to irritability, increase in emotional distress & comorbidity of psychiatric problems.⁷ Depression during the antenatal period is related to poor maternal health, negative outcomes for children harmful effects on the mother, the child, the family and marital dissatisfaction.^{25,26} Depression during pregnancy can not only affect women but their family also. Depression during pregnancy can effect maternal attachment to her fetus and intra uterine growth of fetus as well.²⁷ Poor maternal emotional state has been associated with poor attendance to antenatal care and with unhealthy behavior of mother towards antenatal care.^{11,27} This can have many consequences on mother and also have a negative impact on antenatal care.²⁸ Particularly in following instructions from the doctor or midwife, coping social stresses²², in areas of sleep habits, nutrition & exercise.^{29,30} Study confirms, self-harm thoughts and suicidality have been found to be related to maternal depression.³¹ Sleep disturbances were found to be significantly related to depression both in second and third trimester of pregnancy. It is believed that high norepinephrine trigger depression in pregnant mothers.^{12,32} There are also some other factors that we commonly think of as risks for prenatal depression such as a higher risk of suicide.³³

In addition to that antenatal depression increases the risk of obstetrical complications,²⁷ when compared to non-depressed mothers, depressed mothers were found to have decreased breastfeeding duration and more breastfeeding difficulties. Depressed mothers are more likely to combine breastfeeding with bottle feeding.³⁴ Depressed patients are more prone to develop cardiovascular disease³⁵, migraine with aura³⁷, Preeclampsia³⁶ and type 2 Diabetes.³⁵ Moreover depression and anxiety in early pregnancy may be associated with subsequent maternal Preeclampsia. Social support during pregnancy plays crucial role during pregnancy in

emotional coping.

At present, pathogenesis of antenatal depression is not known presently but a progress has been made towards an understanding of a complex interplay of estrogen & progesterone (the reproductive steroids) with other neuroregulatory systems like Hypothalamus, Pituitary and Adrenal axis in antenatal depression. Understanding of changes that occur in HPA axis during pregnancy & in postnatal period can give a better insight about the pathophysiology of antenatal depression.³⁸ Altered regulation of hypothalamic-pituitary-adrenocortical (HPA axis) has been the subject of investigative efforts in depression research. Scientists are exploring all of these potential connections and how the cyclical rise and fall of estrogen and other hormones may affect a woman's brain chemistry. As it has been Depressive symptoms contributing to unfavorable patterns of health care seeking for women and their children.³⁹

INTERVENTIONS

Treatment of antenatal depression can not be overemphasized due to its high prevalence and association with multiple long & short term health problems of new born & young children. Mothers play a very crucial role in almost all societies to provide care and nutrition to their children. This by all means is a very demanding task. Only mothers with good mental & physical health can take good care of nutrition, psychological & physical health of their children. Women with the stigma attached to mental health problems, usually are reluctant to seek health services usually. Literature suggests that 41% of depressed women are too embarrassed to seek help.¹¹

High risk mothers during regular antenatal visit can be identified by simple screening procedure by an obstetrician or primary care provider. This would provide an opportunity for timely interventions in antenatally depressed mothers. By awareness of personal and epidemiologic factors of antenatal depression by the Practitioners can help them in providing better care.⁴⁰ A women with a past history of depression specially during pregnancy or in postpartum period and/ or wit history of depression in family are at high risk for antenatal depression.^{21,40} Social conflict & low perceived social support by women increase risk of depression during pregnancy. Therefore primary care providers and

obstetricians must address these problems routinely and encourage pregnant mothers to strengthen their support networks. As low social support & social conflict is a significant risk factor for depression. Screening for social conflict during clinical interviews of pregnant mothers by asking if she feels tense from arguing, feel unloved & let down and how frequent are social interactions that are distressing & unpleasant would help identify women that can be benefitted from interventions by clinicians.⁴¹ Randomized trials from low-income and middle-income countries confirms that cognitive psycho therapeutic approaches, such as counselling and interpersonal psycho therapy are effective modalities to treat depression.⁴² Major hindrance however in these countries remains the dearth of mental-health specialities to deliver such interventions to non privileged communities .The need is to adapt and deliver these interventions by community health workers.

Moreover, it is essential that policy makers in recourse poor countries are convinced of integrating cognitive behavior therapy into the present health system.²³ By frequent visits health workers can provide health education to depressed mother, can do her psychotherapy and observe if she is taking her medication regularly and make her take an active role in her care.⁴³ Mothers can be motivated and empowered to take charge of their own & their children health measures. Such cost-effective interventions in resource-poor countries can be scaled up by empowerment of mothers which in turn will be a consonant for their good mental health.

All preventive strategies like counselling, health education, hygiene promotion, immunization, breastfeeding, infant weaning and health seeking behaviors depend on the functional capacity mother. The success of these programmes largely rely on how receptive & cooperative is the mother & are directed towards her ability to follow the intervention offered. In short, success of all interventions will depend on the mental health of the mother. All efforts for better maternal mental health can be integrated in programmes like IMNCH. Recognition of maternal depression during pregnancy by health workers is the first component second will be to develop interventions that can be delivered to target population by MCH and community health workers. Their objective

should be to involve, empower, and provide advice help and support on development of child in a psycho therapeutic manner. These interventions should be relevant culturally, evidenced based and are evaluated and refined regularly.

FUTURE OUTLOOK

Pregnancy is a time when a mother faces both physical as well as psychological challenges, specific for each trimester. An increase in awareness of the frequency and sequel of maternal depression during pregnancy can promote primary prevention in pregnant mother and its effects on new born. Pregnancy and child birth is a time of increased contact of a woman with health services. Routine antenatal check ups provide an opportunity for early detection and treatment of antenatal depression. Reliable diagnosis of depression can be done at primary health care setting. As both antidepressants and psychotherapy can both be delivered in primary care settings. By this barriers such as shortage of resources in terms of trained health care provider can be overcome. Another barrier that prevents women to seek help is the social stigma attached to mental health disorders. By increasing awareness about the cause and sequel of depression during pregnancy among policy - makers, health care professionals and community can help to reduce the guilt, stigma and shame associated with it.

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MACROPHAGE ACTIVATION SYNDROME AS FIRST PRESENTATION OF UNDIAGNOSED SYSTEMIC LUPUS ERYTHEMATOSUS CASE REPORT

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ABSTRACT

Macrophage activation syndrome (MAS) is an uncommon but potentially life threatening complication of rheumatic diseases. It belongs to a group of disorders known as Haemophagocytic Lymphohistiocytosis (HLH). MAS has a rare association with SLE, however it is rather frequently associated with systemic juvenile idiopathic arthritis, Adult onset Still's disease, rheumatoid arthritis and kawasaki syndrome. We are reporting a case of a young Asian woman, with a new onset of SLE presenting as MAS. The purpose of this case report is to increase the awareness of uncommon presentation of SLE.

Keywords:

Macrophage Activation Syndrome (MAS), Systemic Lupus Erthyematosus (SLE)

INTRODUCTION

Macrophage activation syndrome (MAS) belong to the group of Haemophagocytic Lymphohistiocytosis (HLH), which is further classified into Primary and Secondary types. Primary is the familial type which is a rare genetic disorder, while Secondary HLH is "triggered" by infections, malignancies, drugs and autoimmune disorders. The term MAS is used extensively by rheumatologists to describe secondary HLH associated with rheumatic diseases¹.

MAS frequently presents with recurrent fever, pancytopenia, malar rash, hepatosplenomegaly, lymphadenopathy, gastrointestinal and neuropsychiatric symptoms, and infections due to resultant leukopenia.

MAS is treated with high dose Prednisolone and Cyclosporine A. Early recognition and treatment improves outcome. We report a case of an Asian woman of 23 years of age, diagnosed with MAS at presentation as an onset of SLE.

CASE REPORT

A previously healthy 23 year old Asian woman was admitted with 4 weeks history of lethargy, recurrent high grade fever, vomiting, weight loss, malar rash

and cervical lymphadenopathy.

On admission she was febrile with temperature of 102F, blood pressure 130/80 mmHg, heart rate of 108/min, respiratory rate of 19/min. Her general physical examination revealed maculopapular rash on face (as shown in figure 1) as well as on ears, scalp, back of neck and hands. She was pale and had cervical lymphadenopathy and hepatosplenomegaly. Cardiovascular and respiratory examination was normal. Laboratory tests were done to rule out infections or lymphoproliferative disorders. Blood culture, urine culture, Hepatitis and TB screening test were negative and there was no serological evidence of recent infections. She had pancytopenia and her peripheral blood smear revealed poikilocytosis and rouleaux formation. Serum Ferritin, lactate dehydrogenase, alanine aminotransferase and fasting triglyceride levels were raised. ESR levels were normal, Albumin levels were low and her autoimmune profile revealed she was positive for Anti ds DNA and ANA.

Bone marrow aspiration and biopsy revealed hypercellularity and presence of histiocytes with hemophagocytosis. Lymph node biopsy showed features typical of hemophagocytosis: prominent large lymphoid follicles with active germinal centre, dilated sinuses filled with active histiocytes; phagocytosing blood cells.

She was diagnosed as SLE on the basis of presence of pancytopenia, acute cutaneous rash, non-

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scarring alopecia, positive titers of ANA and anti-dsDNA. According to the SLICC criteria.²

Apart from this the fulfilled criteria for MAS as well according to HLH criteria as give below:

HLH 2004 criteria^[3]

1. Recurrent Temperature (>38.5 C)
2. Spleen enlargement
3. Cytopenias (two or more cell lines)
4. Haemophagocytic cell in bone marrow, spleen or LN
5. Hyperferritinemia
6. Hypertriglycemia
7. Soluble CD25 >2400 U/ml
8. Decreased or absent NK cells

(At least 5 of them should be present)

The patient fulfilled the Systemic Lupus International Collaborating Clinics (SLICC) and HLH 2004 criteria for SLE and MAS.

So, after confirmation of diagnosis we treated her with intravenous methylprednisolone pulse therapy for three days followed by high dose oral prednisolone (1mg/kg body weight) and cyclosporine A (2mg/kg body weight).

Patient improved clinically. She was afebrile, no lymph nodes could be palpated, malar rash subsequently faded and her laboratory parameters improved significantly (Table 1)

Patient was discharged on oral prednisolone and cyclosporine A and is now on follow up in outpatient department.



Figure 1. Malar rash on cheeks and nose

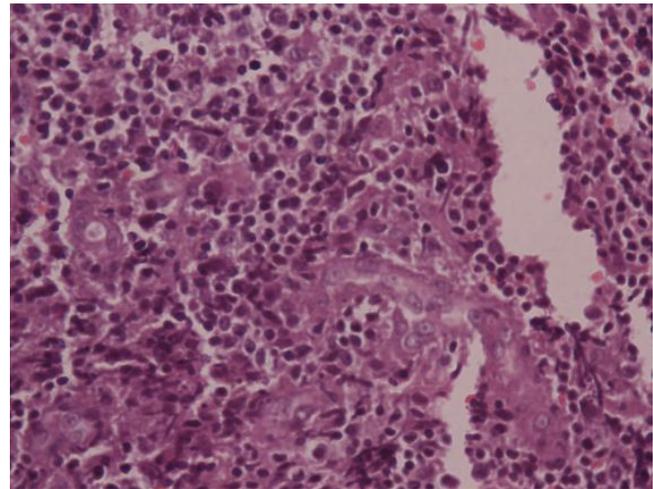


Figure 2. Lymph node biopsy (H&E stain 40 x objective)

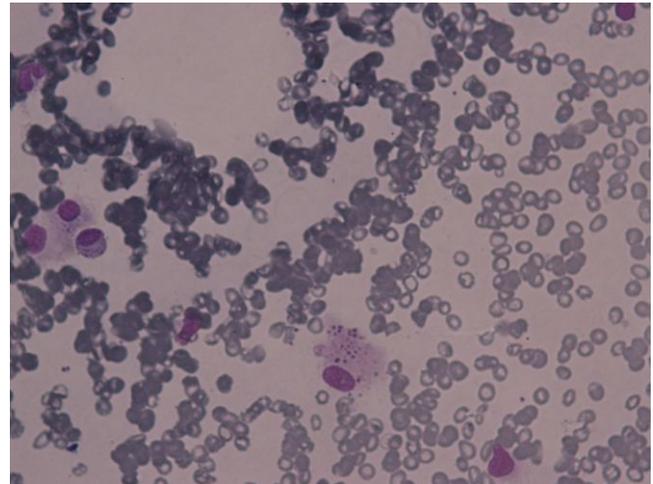


Figure 3: Bone marrow aspiration showing prominent histiocytes (H & E stain 40 x objective)

Table 1: Lab parameters before and after treatment

| Parameter | Before Treatment | After Treatment | Reference Range |
|------------------|--------------------------|-------------------------|-----------------------------|
| WBC Count | 0.92 x 10 ⁹ L | 3.7 x 10 ⁹ L | 3.8-9.8 x 10 ⁹ L |
| Hemoglobin | 84g/L | 97g/L | 140-175g/L |
| Platelets | 59 x10 ⁹ L | 139x 10 ⁹ L | 140- 450 x10 ⁹ L |
| Neutrophil Count | 0.47 x 10 ⁹ L | 2.1 x 10 ⁹ L | 1.8-7.8 x 10 ⁹ L |

DISCUSSION

The diagnosis of MAS is quite perplexing, as the clinical features of MAS mimics' features of active

SLE, infections and lymphoproliferative disorders; such as fever, lymphadenopathy and cytopenias.

Incidence of MAS concomitant with SLE is rare; about 0.9–4.6%.⁴ There were numerous other cases of MAS due to SLE that have been reported, but they were related to SLE flare-up or its complication.

Several other cases have been reported similar to this case, short standing history of fever, fatigue, weight loss and lymphadenopathy and diagnosed after ruling out all other infections, lymphoproliferative disorders and according to HLH 2004 criteria for MAS and treated with pulse of high dose i/v corticosteroid followed by oral prednisolone and cyclosporine A.^{5,6}

In few publications there have been incidences of MAS with pancytopenia and life threatening complications such as myocarditis, respiratory problems. Index of suspicion should remain high for MAS when infections are ruled out, or if there is persistent inflammation even after treatment of underlying infection.¹

Hyperferritinemia is considered to be the best parameter to discriminate between active SLE and MAS with SLE with a specificity and sensitivity of 100%. Glycosylated ferritin levels if greater than 20% indicate MAS related and not inflammatory related activity.¹

The management of SLE with mild to moderate disease activity includes low dose corticosteroids and hydroxychloroquine (up to 6.5mg/kg daily).

For more aggressive disease which causes organ damage treatment includes high dose corticosteroids and immunosuppressive agents such as Azathioprine, Cyclophosphamide, Mycophenolate mofetil and Rituximab.⁷

Several therapeutic regimens are available for MAS, the most commonest being the intravenous methylprednisolone pulse therapy for 3 days followed by oral prednisolone (2-3mg/kg), if there is no improvement then usual add on drug is cyclosporine A (2-7mg/kg).⁸

Cyclosporine A should be given on discharge until 8 weeks as it helps sustaining MAS under control.¹

The HLH 2004 treatment protocol can also be used in patients who are unresponsive to high dose

steroids and Cyclosporine A; it includes dexamethasone, Cyclosporine A and etoposide. Conversely, etoposide causes liver toxicity therefore its use is limited. There have been publications regarding the use of antithymocyte globulin (ATG) as a substitute to Etoposide.⁹

Successful trials have been reported with infliximab¹⁰, alemtuzumab^{11,12} in cases with refractory HLH with SLE.

CONFLICT OF INTEREST: None

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OBITUARY

Professor
Khalida Adeeb Khanum Akhtar
FRCS, FRCOG
(1935-2015)



Professor Khalida Adeeb Khanum Akhtar a leading Gynaecologist and Obstetrician, an outstanding teacher, a prolific writer, mentor, artist and above all an exceptional human being breathed her last on October 16, 2015 due to pneumonia leading to multi organ failure.

Prof. Khalida was born on February 28, 1935 at Rawalpindi. She got her primary education at the Presentation Convent Rawalpindi and Sacred Heart Convent Lahore. In her formative years she developed keen interest in sketching, drawing, painting, embroidery, designing, sewing and décor, which continued throughout her life.

She had her medical education from Fatima Jinnah Medical College, Lahore. She topped the final year MBBS examination of the Punjab University in 1957 breaking all previous records, winning a tally of medals. She earned FRCS (Edin) and MRCOG London in 1969. She was appointed as Head of department of Obstetrics and Gynaecology at Holy Family Hospital in 1970. Later she was awarded fellowship of the Royal College of Obstetricians & Gynaecologists London in 1984. She was also an elected fellow of the CPSP.

She trained many postgraduates for the MCPS, FCPS and MRCOG. I had the privilege of being her student and later a colleague. It has been a matter of great honour to work with this legend.

She authored over hundred papers published and presented at various conferences. She had a keen interest in medical editing and was the chief editor of the Rawalpindi Medical College Journal, editor-in-chief of Shifa, RMC student's magazine and the journal of Pak Society of Obstetricians & Gynaecologists. In 2008 she received "Life Achievement Award" from Airways Media for her contribution to the society as an exemplary doctor, teacher and a mentor.

Professor Khalida always exuded positive energy no matter what the circumstances were. She was a role model, a legend and will continue to enlighten lives of people even after leaving us. She was a gifted speaker and utilized this skill in her lectures and bedside teaching.

She was very kind and caring for her patients and always emphasized her students and colleagues regarding the importance of patient care.

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