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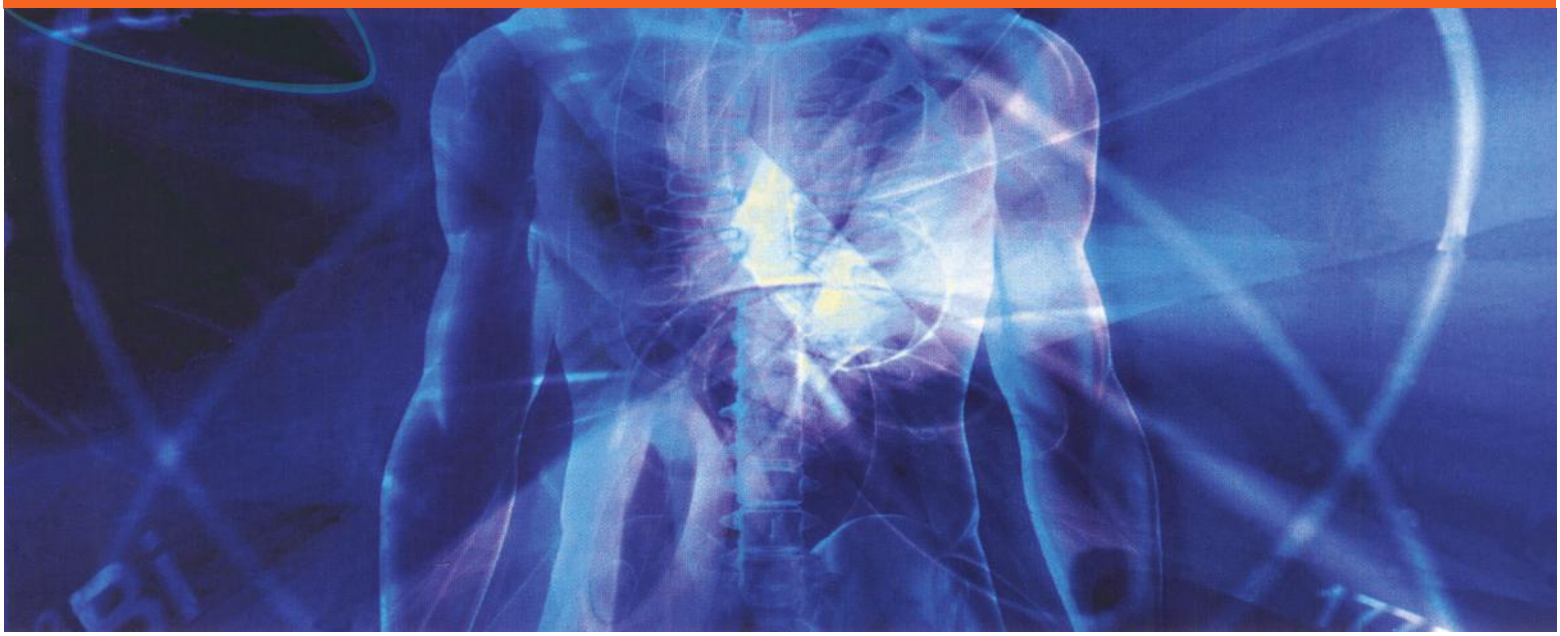

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EDITORIAL

Breast cancer awareness in Pakistan

Rafat Murad

Breast cancer is the malignancy of the breast tissue which is the most frequently diagnosed cancer in women worldwide. Globally it is accounted for 23% of all cancer cases.[1] All women despite of their racial or ethnic origin, or heritage are at risk of breast cancer.[2] According to WHO, more than 1.2 million people are diagnosed with breast cancer worldwide every year.[3]

Among Asian countries, Pakistan has the highest rate of breast cancer. Evidence from Karachi cancer registry indicates that the age standardized annual rate of breast cancer is 69.1 per 100,000. This figure is equivalent to European and North American rates.[4] In Lahore, over a period of 8 years, there were 3,338 cases of breast cancer which presented at Shaukat Khanum hospital. Current figures indicate that in Pakistan, breast cancer affects both young and middle-aged women and can affect women as young as 20 years of age.[5]

Because of other compelling healthcare issues, breast cancer is not regarded as a health care priority and cancer awareness programs are either nonexistent or dysfunctional in the third world. Just to give a quick comparison, 75% of the women conduct Breast Self-Examination (BSE) in the United States,[6] in contrast only 30.3% of the females from Saudi Arabia have even heard of BSE.[6] In Iran 1402 women were interviewed recently and only 61% of the respondents knew about breast cancer.[7] Similarly, awareness about breast cancer screening in Pakistan can be recognized from the fact that only 14% of mammography tests performed at the leading cancer institute were for a screening purpose.[8]

In most of the developing countries, the incidence of breast cancer is currently low, but rapid industrialization, westernization of lifestyle, urban development, an increase in life expectancy, and delayed and reduced fertility are some of the factors responsible for increasing the incidence of breast cancer and it seems that the incidence will continue to grow in the years to come.[9]

Breast cancer awareness is an effort to raise consciousness and reduce the stigma of breast cancer through education on symptoms and treatment. Supporters hope that greater knowledge will lead to earlier detection of breast cancer, which is associated with higher long-term survival rates, and that money raised for breast cancer will produce a reliable and permanent cure. It is the most frequent malignancy of women, and leading cause of female cancer related mortality. Breast cancer rates are increasing in developed as well as developing countries. Prognosis and survival rates of breast cancer are better in developed countries due to early diagnosis and treatment.[10] In countries with limited resources, majority of females present at advanced or metastatic stage, leading to poor outcome.[11]

Breast cancer advocacy and awareness efforts are a type of health support. Breast cancer advocates raise funds and lobby for better care, more knowledge, and more patient empowerment. In our socioeconomic set-up, the only feasible solution to promote early detection of breast cancer is to create 'breast cancer awareness' among female population. This is only possible, if we know the present level of knowledge, attitudes and practices of our female population towards this disease.[12]

(a)Government agencies, non-government organizations and the media can play a major role in increasing awareness about breast cancer among the general public. It should be ensured that awareness campaigns are in regional languages to have a better penetration. Awareness about breast feeding and its protective effects also needs to be imparted to decrease the risk of breast cancer.

(b) If local celebrities can be involved to promote the cause, it will further strengthen awareness activities.

(c) There is also a need to strengthen the cancer-related curriculum in medical schools, focusing on breast cancer awareness and screening methods.

(d) Public health workers can be trained in Clinical Breast Examination to reach out to the length and width of the country.

(e) Programs should be devised for surgeons to train them in the appropriate surgical management and referral. Continued medical education can help in training the general surgeons in basic skills of breast surgery. Guidelines for breast cancer management are feasible and practical.[13]

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REVIEW ARTICLE

Diarrhea Management in children of Developing Countries by Mothers and General Practitioners

Farhan Muhammad Qureshi[1], Anne Krayer[2], Tahira Zamir[3]

ABSTRACT:
Despite continuous improvement and advancement of treatment, diarrhoeal disease is the second leading cause of death in children under the age of five years globally and is a major cause of concern in developing countries. Research suggests that lack of proper and timely management leads to increased mortality and morbidity. The aim of this review is to assess the knowledge, attitude and practices of mothers/caregivers and general practitioners (GPs) toward management of diarrhoea in children under the age of five years in developing countries. A systematic review was performed using observational evidence. A thematic approach was used for the analysis of the data and narrative synthesis methodology to summarise the review findings. Results suggest that oral rehydration salts solution are not considered a sufficient cure for childhood diarrhoea and, are given, mostly with traditional medicines and unnecessary non-prescribed drugs. Health care seeking and feeding practices were also found to be very poor. Prescribing practices among GPs were influenced by professional knowledge as well as a number of factors, such as, fear of losing patients, loss of prestige, family demands, and external pressures like hospital work load and pharmaceutical interests. Barriers of recommended childhood diarrhoea management were linked to lay beliefs, economic constraints, and lack of education.

Keywords: Diarrhea, Children, Mothers/caregivers, General practitioners, Management, Developing countries

INTRODUCTION:

Childhood diarrhea is a major cause of concern in developing countries because of lack of hygiene, unsatisfactory health and nutritional status, and most importantly lack of proper and timely management that leads to increased mortality and morbidity rates. It is responsible for killing 1.5 million children every year that makes diarrhea, a second leading cause of death in children under five years of age. Death due to diarrhea is mainly due to its complication i.e. dehydration (loss of water and salts from body) which can be treated simply and effectively by giving extra fluid by mouth at home, commonly referred to as oral rehydration therapy (ORT).[1]

Recommendations for the treatment of diarrhea have been developed by the WHO and UNICEF more than 20 years ago advising a single formulation of ORS. This was followed by revised recommendations in 2004 by a joint statement which focused on two main elements: the low osmolarity ORS to prevent dehydration and zinc treatment. ORS became well known from the 1990s onwards but unsatisfactory application and unawareness created problems in diarrheal diseases control.[1,2]

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Repeated episodes of childhood diarrhea are also a major contributor to malnourishment. Undernourished children are more susceptible to infections because of their impaired immune system and are more likely to suffer from diarrhea and its consequences, which further impede their development.[3] Satisfactory sanitation and good hygiene are key factors in improving diarrhea, but unfortunately lack of these are common in developing parts of the world.[4]

An estimated 2.5 billion cases of diarrhoea occur in children under 5 years of age every year.[5] Although mortality rate in children in year-2004 decreased from an estimated 5 million deaths to 1.5 million over last two decades, diarrhoea is still the second leading cause of child death worldwide. It was found that 80% of children were under two years of age, among these 1.5 million children died.[6] In developing countries, children under three-year-old experience on average three episodes of diarrhoea every year. More than 80 percent of deaths occurred in Africa and Southern Asia where malnutrition continues to be a major public health problem. A total of 15 countries account for three quarters of all deaths by diarrhea per year, out of which India has a very high rate.[1,7](Table-1)

Knowledge and awareness among mothers towards diarrhea treatment has a great impact on child health. Other factors influencing successful treatment of diarrhea and consequently morbidity and mortality rates include attitude and behavior- collectively or individually. Traditional beliefs and cultural factors are also related to the occurrence of diarrhea.[8]

The proper management of diarrhea depends on skills, and good understanding of appropriate ORS dose with its composition. There are deficits in the knowledge of physicians regarding the correct treatment of childhood diarrhea, and especially its dietary and nutritional management. Importantly, there is also a lack of training to upgrade knowledge of physicians in developing countries and especially in the rural areas. Inadequate

knowledge regarding correct management of diarrhea may contribute to the underutilization of oral rehydration solution.[9] In addition, the practice of prescribing unnecessary antibiotics and a range of ineffective and sometimes harmful drugs for diarrhea treatment is still continuing in developing countries.[10]

This literature survey was conducted to gather information regarding general awareness, attitude, perceptions and practices of mothers/caregivers and general practitioners toward diarrhea treatment in children of developing countries.

METHODOLOGY:

The standard five stages of a systematic review were followed, which includes:

1. Protocol Development
2. Mapping exercise: includes developing Inclusion/Exclusion criteria and identification of studies according to the Inclusion/Exclusion Criteria.
3. Quality appraisal of studies identified
4. Data extraction: study findings and characteristics
5. Analysis and synthesis of findings

For the purposes of this review, a comprehensive online literature search was undertaken using CINAHL, MEDLINE, Pub Med, Cochrane, Research gate, Global Health, Bioline International from the year 1990 onwards using various key words and phrases related to the topic. Grey Literature in the form of topic relevant books on qualitative research, doctoral thesis and dissertation, official policies, health/clinical guidelines and reports of national and international organizations including policies issued by WHO and UNICEF were also located and reports were searched for relevant references. All published observational and qualitative studies after 1990 in English with study sample of mothers/caregivers of children less than 5-year of age and general practitioners/Paediatricians on diarrhoea management practices in the developing part of the world were selected. The short-listed papers were then each critically appraised using Critical Appraisal Skills Programme (CASP) tool developed by the Public Health Resource Unit (PHRU) within the National health services (NHS), United Kingdom.

The data was extracted using forms adapted from the National Institute for Health and Clinical Excellence (NICE) data extraction form templates.[11] The analysis of the extracted data was done by thematic analysis technique and narrative synthesis methodology was used to synthesize overall review findings.

RESULTS:

MOTHERS AND CAREGIVERS:

General awareness and attitude:

The use of ORS depends on the mother's knowledge and her attitude towards ORS use.[12] Mothers showed reasonable knowledge and familiarity with ORS and dehydration but exhibited gaps in their understanding of what ORS actually does and consequently there was a lack of trust that ORS would be enough to treat diarrhea.[13] Parents who knew about ORS also knew that it could replace fluid and prevent dehydration but as with previous study, it was not viewed as sufficient treatment to reduce frequency or stop diarrhea,[5] thus mothers used additional medicines like antibiotics, herbal remedies and traditional medicines.[14,15,16,17] There was a significant relationship between literacy status of mothers and feeding practices and fluid replacement during diarrhea which affected overall health of children.[18]

Uneducated mothers were mainly using traditional herbal and spiritual healing methods. In contrast, a study in Iran found that education had no positive effect on mother's diarrhea management practices because of the continuation of their fallacious beliefs regarding diarrhea management.[19]

Awareness and knowledge of ORS of mothers/caregivers depended on the media exposure and education by practitioners (for example at immunization days, during consultations).[19,21] Mothers exposed to electronic media on a regular basis were more aware of ORS for childhood diarrhea and showed better practice in management. Together, these findings suggest that education through media and medical information raised awareness of ORS. This seemed to be influenced by mother's background. If mothers were unaware or unconvinced of the effectiveness of ORS, they also used other medicines– either Western drugs and/or traditional herbal remedies.[19,20,21]

Perceptions:

Childhood diarrhea was not considered as illness, and consequently treatment was not given in all cases. Parents believed that diarrhea was a normal problem in children under age 5-year and a major milestone in growing up in all developing countries. Teething or just overeating was the cause of diarrhea and so nothing effective could be done to cure diarrhea. In some cases, parents thought that diarrhea could be transmitted from mothers via breast milk, due to contaminated food and unclean water. Mothers also linked diarrhea to malaria when accompanied by fever. Serious or life threatening cases of diarrhea were often associated with external agent such as the evil eye, demons, evil spirits or a jealous person and transgression of sexual taboos by parents, especially mothers. Hence, it was treated with traditional and spiritual therapies. Perceptions of mothers/caregivers regarding the cost, worth and status of different ORS treatment was influenced by the prescribing patterns of medicines. Cheap rates and free of cost availability of WHO-ORS made it undervalued and was considered as an inexpensive and unimportant medicine. Commercially prepared flavored ORS brands made according to consumer expectations have found to be more acceptable to children as well as caregivers. Advertising in the media raised awareness of caregivers and physicians of certain brands and influenced prescribing.[5,14-16,20]

Practices:

Diet and fluid restriction was also very common in

developing countries.[12,16,17,18,19,21] It was a common misconception among mothers that no fluid to be given during diarrhea.[12] There was a belief that excess fluid increased the frequency and quantity of stools and continued feeding worsened diarrhea.[16] These fallacious beliefs were the result of lack of knowledge and awareness in relation to feeding practices during diarrhea.[19] Ogunbiyi & Akinyele, discussed in their study that beliefs regarding food restriction were common among caregivers regardless of their educational level as it passed down through families.[21]

Self-medication and unauthorized usage of medicines were common in developing countries.[22] Treatment practices at home begin in the form of special foods and use of herbs as remedies for diarrhea management.[14] Mothers used a combination of drugs including anti-diarrheal, antibiotic, and herbal medicine within first 24 hours of the illness.[5,16] These drugs were usually prescribed by mothers themselves and in some cases by shop vendors or chemists and contributed to the high use of these drugs over oral ORS.[15]

Seeking healthcare outside the home was influenced by several factors. Within a house-hold, it was not only the decision of mothers but other family members- especially male members and elders of the family, usually mother-in-law, who was the primary decision-maker in child care. She decided on feeding practices and home-based traditional therapies (which had been passed down through generations). Generally, parents waited for some time and treated domestically until condition worsened, then they considered taking the child to see a doctor or go to hospital. The delay in pursuing health care and using it as a last effort increased the risk of mortality and morbidity.[5,14,20,21]

GENERAL PRACTITIONERS

General awareness and attitude:

The medical practitioners who treated childhood diarrhea cases knew the importance of ORS in diarrhea management, but only a limited number of them knew WHO-recommended formula of ORS.[23] Most of them had heard and believed in the efficacy of ORS, - the source of knowledge for the majority was their medical school. Other sources were journals, mass media and other health personal.[7] Physicians accepted efficacy of ORS for dehydration caused by diarrhea but most of them still prescribed commercial formulations guided by pharmaceutical company representatives, which might not had the correct chemical composition of WHO-ORS.[23,24] In addition, GPs had limited access to continuous medical education programs, except those sponsored by pharmaceutical companies. Thus, GPs prescribe anti-diarrheal and other drugs especially locally made commercial brand-ORS due to pressure from these companies. In comparison private GPs did not prescribe ORS at all compared to the pediatricians. The rationale behind this did seemed to be lack of knowledge.[25]

Practices:

Over-prescription in relation to antimicrobials and anti-diarrheal medicines was more common in GPs. Moreover, it was a common practice to use intravenous fluids for mild or moderate dehydration to prevent possible complications and to treat children quickly in order to keep their reputation as a good doctor.

Work-settings had a significant impact on prescription writing habits of doctors. Financial motives influenced prescription, and over-prescription of private practitioners as they could charge extra money if they dispensed medicine to patients. In public sector hospitals, there

Table: 1
Child deaths per year in developing countries[1]

RANK	COUNTRY	TOTAL NO OF ANNUAL CHILD DEATH DUE TO DIARRHOEA
1	INDIA	386,600
2	NIGERIA	151,700
3	DEMOCRATIC REPUBLIC OF CONGO	89,900
4	AFGHANISTAN	82,100
5	ETHOPIA	73,700
6	PAKISTAN	53,300
7	BANGLADESH	50,800
8	CHINA	40,000
9	UGANDA	29,300
10	KENYA	27,400
11	NIGER	26,400
12	BURKINA FASO	24,300
13	UNITED REPUBLIC OF TANZANIA	23,900
14	MALI	20,900
15	ANGOLA	19,700

was great time pressure because of heavy workload of patients and thus very limited time to explain to mothers/caregivers practicalities of disease management and medicine. Physician's reputation for satisfying parents/caregivers did not benefit the public sector hospitals; it assisted in promoting their prestige resulting in an increased patient flow in their private practice. This acted as a financial incentive.[24, 25] Expectations of mothers and caregivers had a strong impact on prescribing practices of physicians. Practitioners working for the public sector were less likely to over-prescribe due to financial incentives but were more likely to have less time for consultations.[24,25,26,27,28] Another strong influence was drug companies pushing certain brands which might not have corresponded to WHO-ORS formula. Practitioners prescribed unnecessary drugs because of pressure from mothers/care givers and a fear to lose patient.[26,29,30,31] Parents preferred home-based traditional medicines because of the cost and unavailability of medical services.[32,33,34,35] Lack of access to health service facilities due to shortage of health staff, medicines and equipment was a major issue.[36,37] It contributed to a large part to diarrhea-related mortality and morbidity especially in developing countries.[22] Monetary consideration also affected continuity of health care or lack thereof.[38] Mass media was especially useful in countries or areas where illiteracy rates were high among mothers.[39] Health promotional activities to promote ORS and zinc use involving families and communities with support from governments and NGOs was very effective to raise awareness of diarrhea.[40]

CONCLUSION:

This review suggested a range of factors that could influence use of ORS recommended by WHO/UNICEF. This included: mothers/caregivers education, family influences and exposure to electronic media. It was found that cultural practices influenced decision-making powers of mothers/caregivers regarding treatment of diarrhea. Lay beliefs and culture were another aspect of improper diarrheal management among mothers. This included, not considering diarrhea as an illness, change in normal feeding practices, use of traditional medicines and self-medication at home. Overall, barriers existed at several levels: this included individuals' behaviors but also wider social, cultural and economic influences.

RECOMMENDATIONS:

Health promotional activities to promote ORS and zinc use involving families and communities with support from governments and NGOs can be very effective to raise awareness of diarrhea.

Strong public health systems are vital to combat high mortality and mortality rates– especially in developing countries. WHO and UNICEF emphasize the need to strengthen health care system through: improvement in training programs for staff, reduction in staff turnover, and the need to motivate health workers at community level by using creative techniques. The co-ordinationdof networks between private and public sector medical practitioners is weak in developing countries. Regulatory frameworks for controlling and updating health products do not exist in most of the developing nations. Drugs like antibiotics are easily available from medical stores, pharmacies or chemists**,** which should be prevented. Although there is progress, but enough is not done to reach the target of MDG 4, which is to reduce the mortality rate of children under-five-year age by two thirds, between 1990 and 2015.

Change can only be achieved through involving communities and providing education and health promotion activities; community-based approaches are most effective. Consumer research is needed to improve marketing and acceptability of WHO-ORS and zinc solutions. Health systems need to be flexible and effective and provide prevention and treatment services at local and national level. Education, awareness raising and training is needed for health practitioners in the private and public sector. The information gained through present review can contribute to developing strategies for the promotion and use of recommended ORS and zinc supplement as a first line therapy for childhood diarrhea at domestic level.

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ORIGINAL ARTICLE

Psychological Impact of Sub Fertility on the Couples

Shabnum Sibtain[1], Aaleen Azeez [2], Ahmad Zunair Wasim[3], Mujtaba Azeez[4]

ABSTRACT:
Objective: To evaluate the psychological aspect of subfertility and treatment on the couples.
Methodology: This Prospective survey study was carried out in the department of Obstetrics and Gynaecology at a private hospital in Lahore, Pakistan. 40 couples undergoing fertility treatment were enrolled. A Self-report questionnaire included age, level of education, social status, duration of marriage , duration of infertility, causes of infertility, duration of treatment, social stress, effect of infertility on marital relationship, expected likelihood of achieving pregnancy, anticipation of stress during treatment, and emotional reactions to infertility was given to all the participants of the study.
Results: The majority (70%) of women undergoing fertility treatment were of ages 25-34 years. 62.5% couples were married for 1 to 5 years. Majority of couples were educated and belonged to the middle-class family. 55% had been undergoing treatment for 3 years and more. In half, the causes of infertility were known. 67.5% had failed treatment and 32.5% became pregnant with treatment. All the couples experienced emotional trauma with treatment and needed psychological help despite the outcome. 62.5% suffered with depression, 30% anxiety and 7.5% had anger. 15% women needed psychiatric medication besides counselling and behavioural therapy. 60% couples had sexual dysfunction leading to marital problems. 80% couples complained of behaviour changes. Specific questionnaires were structured for assessing different psychological aspects on infertile women, men or couples. The hospital Anxiety and Depression Scale and demographic and fertility information questionnaire was given to all infertile couples. The psychological impact was more on females 82.5% compared to males 17.5%. All the couples underwent social pressure.
Conclusions: Psychological factors play an important role in the infertility. It is important to manage this devastating problem, which has cultural and social impact.
Keywords:
Infertility, Mental health, Stress, Counselling, Psychosocial factors, Assisted reproduction

INTRODUCTION:

According to World Health Organization, definition of infertility is unable to get pregnant after 24 months of trying and this definition is used in clinical practice and research.[1] Infertility affects about 10%-15% of couples of reproductive age.[2,3] The infertility rates vary between countries and regions. Infertility is a medical condition but also has social and economic issues. It is a chronic stressor with long-lasting negative social and psychological consequences. In recent years, the number of couples seeking treatment for infertility has increased due to factors such as delaying childbearing in women and development of new successful techniques of fertility treatment.[3,6] The increasing awareness of infertility has given consideration to the association between psychiatric illness and infertility. Some studies in literature have suggested that psychological factors may be a primary cause of infertility, others have suggested that the state of infertility itself can provoke psychological symptoms.[7] Researchers have looked into the psychological impact of infertility and prolonged exposure to infertility treatments on mood and well-being. Infertility has an effect on a couple's mental health. Different psychological factors have been shown to affect the reproductive ability of both partners. The mechanisms by which depression could directly affect infertility involves the physiology of the depressed state such as elevated prolactin levels, disruption of the hypothalamic-pituitary-adrenal axis, and thyroid dysfunction.[4]

The inability to conceive children is a stressful situation for couples. The consequences of infertility are manifold and cause social repercussions and personal suffering. Infertile individuals experience the distressing emotions, which include shock, grief, depression, anger, and frustration, loss of self-esteem, self-confidence, stigma.[5,6,7,8]

The way in which people deal with infertility is partly affected by the values and socio-cultural norms of the community in which they live. In an Asian society, women childbearing is associated with stabilizing their marriage and closer bonds with the spouse family. Thus, childbearing for women is expected to bring happiness

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and family harmony.[9,10] There is a lot of pressure on couples to have a child after the first year of marriage and this pressure increases during third and fourth years.[11] Their relationships may suffer not only with the spouse, but also with friends and family members offering well-meaning but misguided opinions and advice. Couples dealing with infertility may avoid social interaction with pregnant friends and families with children. They may have anxiety-related sexual dysfunction and other marital conflicts.[5, 12, 13]

There is enough evidence that lower stress levels mean better female and male natural fertility, though there is no conclusive experimental evidence that lower stress levels result in better fertility treatment outcome.[14] Psychological interventions, especially those emphasizing stress management and coping-skills training, have been shown to have beneficial effects for infertility patients.[15]

METHODOLOGY:

This prospective study was done in the Mid-City hospital, a multi-disciplinary private hospital in Lahore offering fertility services to infertile couples. All sub fertile couples under 40 years of age were included and the participants with any mental health organic diseases were excluded. Forty couples undergoing fertility treatment were enrolled. Questionnaires were given to all couples undergoing infertility treatment. This questionnaire included age, level of education, social status, duration of marriage, duration of infertility, causes of infertility, duration of treatment, social stress, effect of infertility on marital relationship, expected likelihood of achieving pregnancy, anticipation of stress during treatment, and emotional reactions to infertility.

RESULTS:

The frequency of age, number of years the couples were married, social set up (independent living or extended family system), educational status and job description of male partner has been shown in Figure-1 and 2. The duration of treatment has been given in Figure-3. In half 50% (20), causes of infertility were known and the other 50% (20) had unexplained infertility. All (100%) couples experienced emotional trauma with treatment and needed psychological help despite the outcome. 62.5 %(25) suffered with depression, 30% (12) anxiety and 7.5 % (3) had anger (Figure-3). 62.5% (25) couples had initially approached general practitioner, 22.5% (9) couples used remedies advised by family and 15% (6) took advise from religious leader before seeing the fertility specialist. 67.5% (27) had failed treatment, whereas 32.5% (13) became pregnant with treatment. 15% (6) women needed psychiatric medication besides counselling and behaviour therapy. 60% (24) couples had sexual dysfunction leading to marital problems. 80% (32) couples complained of behaviour changes. The psychological impact was more on females 82.5% (33) compared to males 17.5% (7). All (100%) couples underwent social pressure

Figure-1

Age of the female (Years)	Number of years they were married	Extended vs. Independent family
25-29 (16)	1 to 5 (25)	extended (28)
30-34 (12)	6 to 10 (13)	independent family (12)
35-39 (7)	More than 10 (2)	
20-24 (5)		

Figure-2

Level of education of the female	**Level of education of the male partner**	**Profession of the male partner**
Illiterate (1)	illiterate (1)	business men (11)
Primary (1)	secondary (7)	professionals (7)
Secondary (11)	graduate (8)	bankers (6)
Graduate (16)	Post graduates (11)	lecturers (9)
Post graduates (11)		private company employees (7)

Figure-3

Duration of the treatment (Years)	Cause of infertility	Emotional Trauma in couples
1 to 2 (18)	known (20)	Depression (25)
3 to 4 (17)	unknown (20)	Anxiety (12)
5 to 6 (3)		Anger (3)
Greater than 6 (2)		

Figure-4

Initial treatment	male vs female	psychological impact on females
By general practitioner (25)	male (7)	Psychological medication (6)
Home remedies (9)	female (33)	Counselling and behavioural therapy (34)
Advice by religious leaders (6)		

DISCUSSION:

Mental distress has been suggested to be an etiological factor in infertility,[16] and has been linked to increased risk of diminished ovarian reserve.[17] However, the existing literature supports the hypothesis of infertility causing mental distress than the other way round.[16,18] It has been reported that women who seek medical care for infertility have higher levels of mental distress and symptoms of anxiety and depression and lower quality of life compared with control samples without fertility problems.[16,19-24] One-third of women seeking help for infertility scored above the cut-off values for a mental condition.[20,25,26]

In a study done by Chen et al[27] on 112 participants, 40.2% had a psychiatric disorder. The most common diagnosis was generalized anxiety disorder (23.2%), followed by major depressive disorder (17.0%), and dysthymic disorder (9.8%). Our study showed 15% had psychiatric disorder, 62.5% suffered with depression, 30% anxiety and 7.5% had anger. There was less number of psychiatric disorders in our study, whereas depression and anxiety were higher. There is a possibility we may be missing the number by incorrect diagnosis or the sample size of our study was small. In another study,[28] half of the patients dropped out of fertility treatment as a result of emotional distress. Various other studies showed that major reason for discontinuation of infertility treatment were psychological stresses.[29,30]

In a prospective study done by Dhaliwal et al[31] on one hundred and twenty infertile couples, psychological components were found to play a significant role in infertility of unknown etiology. Similarly in our study, half of the couples had infertility of unknown etiology. It may be worth exploring that infertility might have been due to psychological causes.

The psychological impact was more on females (82.5%) compared to males (17.5%). Most researchers have also concluded that infertility is more stressful for women than it is for men.[16,32,33,34] The woman's age is the most important factor influencing the success of fertility treatment. Over half (53%) of women receiving fertility treatment were aged 20-29 years which was a positive indicator for fertility treatment outcome. Fertility declines at age of 30 and more steeply from age of 35 (Figure-1). 32.5% became pregnant with treatment, which was a pretty respectable outcome. According to Human fertilization and embryology authority in 2010, women having in vitro fertilisation resulting in a live birth (national average) was 32.2% for women aged under 35.[38]

Infertility has a major impact on women's quality of life and emotional well-being. The resulting interpersonal problems extend to women's sexual relationships, with a high proportion of infertile women reporting sexual problems[5,12,35] which were also highlighted by our study (60% sexual dysfunction). Family-influences play an important role in the outcomes of infertility.[9] Family interference is either felt as a negative pressure or as an encouragement. 70% of our couples lived in extended family system. Economic is a specific distressing factor for the infertile couple. The infertility treatment fee globally is quite high in relation to the average income. However, participants in this study were able to afford the cost of treatment. This might be because the couples had to reduce their expenses and save all their money for infertility treatment. There was a possibility that family might have contributed to these expenses. The fact that more than half of the couples recognised their fertility problem within five years of marriage showed the importance for couples for having children at an early age. Majority of the couples had initially approached the general practitioner which indicated the awareness of the problem and took steps in the right direction.

CONCLUSION:

The psychological dimension of infertility affects all aspects of couple's personal lives including social and economic ones. The vulnerability can be tackled by implementation of evidence-based screening for psychological distress and appropriate referral for

support. The training of staff in communication skills, promoting shared decision making and prioritizing psychological interventions can improve the outcome. More large-scale, long-term prospective cohort studies which address the social as well as psychological consequences of infertility are needed. Further research is needed to understand the association between distress and fertility outcome, as well as effective psychosocial interventions.

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ORIGINAL ARTICLE

Association of Obstetrical Variables with Induction to Expulsion Interval in Misoprostol-Induced Mid-Trimester Abortion

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ABSTRACT:

Objective: To investigate significance association of obstetric history (maternal age, gravidity, parity, gestational age & previous LSCS) with induction to expulsion interval (IEI) in Misoprostol-induced- Mid-Trimester (MI-MT) abortion cases.

Methodology: This prospective cohort study was conducted at CMH Nowshera from January 2014- June 2015. One hundred and six candidates were included. Termination of pregnancy was carried out with Misoprostol using two regimens. Regimen A included 400ug Misoprostol given 6 hourly with maximum of 4 doses for 24 hours for gestational age 13-20 weeks. In Regimen B 200ug Misoprostol with the same protocol was given for gestational age 21-26 weeks. Failure of induction was considered after 72 hours. Cohort was stratified according to categorical variables of maternal age, parity, gravidity, gestational age and previous LSCS. Outcome variable was Induction to expulsion interval (IEI).

Results: Null hypothesis (H_0) of no significant association between obstetrical variables (maternal age, parity, gravidity, gestational age, previous LSCS) and outcome variable (IEI) was tested using chi square and Fisher's exact tests with 1000 bootstrapping. Simpson's paradox effect was adjusted using Restriction method.

Significant associations were found between gravidity, gestational age and previous LSCS with IEI (P value <0.05), that is, lower gravidity; higher gestational age and presence of previous LSCS were associated with longer IEI.

Conclusion: This study emphasized the significance of obstetric history in MI-MT abortion cases. It also emphasized important obstetrical parameters to consider hence provide guidance to clinicians and researchers for counseling, antenatal care and treatment in such cases.

Keywords: Misoprostol-induced Mid-trimester (MI-MT) abortion, Obstetric history, Induction to expulsion interval

INTRODUCTION:

There are around 30-35% of 205 million pregnancies worldwide that remain unintended. Out of which 15 to 20% end in induced abortion.[1,2] Indications most commonly described for termination of pregnancy are missed miscarriage, intrauterine fetal demise and fetal anomalies. Less common indications are preterm premature rupture of membrane (PPROM) and severe oligohydramnios.[3] Ultrasound has contributed in early recognition of conditions like fetal anomalies and fetal demise resulting in increased number of patients reporting in second trimester for termination of pregnancy.[3] Second trimester also called mid trimester is taken from 13 to 28 weeks of gestation. Around 10 to 15% of total induced abortions happen in mid trimester. With the increasing incidence of LSCS and associated complications, termination of pregnancy for some valid reasons, such as fetal abnormalities, has also increased.[4] It is a great challenge for obstetricians to deal with such patients. The most appropriate method for induced abortion is still debatable. Both medical and surgical methods have been suggested for induced abortion.[5] Medical method is preferable to surgical technique because of lower maternal morbidity and mortality, cost effectiveness and short hospital stay.[6] During the last two decades, prostaglandins are used for induction of labour, both E1 and E2 analogues.[7] Misoprostol, a synthetic E1 analogue is typically used to prevent and as a cure for peptic ulcer. Guidelines are available regarding use of Misoprostol in obstetrics and gynaecology.[8]

In low resource settings like ours, off label use of Misoprostol has been reported specially for termination of pregnancy at various gestational age, cervical ripening and labour induction in term pregnancy and also for prevention of postpartum haemorrhage.[9,10] Misoprostol can be given orally, sublingually, vaginally or rectally.[11] The routes of administration vary with the patients' compliance and the doctors' experience.[12] Side effects like diarrhea, fever and shivering are not uncommon. Sometimes at term pregnancies, misoprostol may cause uterine hyper-stimulation, CTG changes, foetal bradycardia and foetal demise.[13]

Obstetrical history of the patients plays a vital role in decision making in cases of induced abortions. There are many factors which can influence the outcome of the method used for induced abortion like maternal age, parity, gravidity, gestational age, and history of previous LSCS. Dose regimen also contributes to influence the outcome.[14] Researchers have also focused on outcome in terms of induction to expulsion interval.[15] Knowledge about induction to expulsion interval and factors influencing the time needs to be studied more as enough research has not been done on this issue.[16] This study is focused to explore the relationship between parity, gestational age and induction to expulsion time.

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METHODOLOGY:

This prospective cohort study was conducted after approval from ethical committee of the hospital. Patients with intra uterine death (IUD), foetal anomalies, and missed abortion with unknown causes who were in mid-trimester were included in the study. Abortions earlier than 13 weeks and later than 26 weeks of gestation were excluded.

The cohort was given Misoprostol orally according to gestational age as prescribed in the medical literature. Regimen A included 400ug Misoprostol given 6 hourly with maximum of 4 doses for 24 hours for gestational age 13-20 weeks, in Regimen B 200ug Misoprostol with the same protocol for gestational age 21-26 weeks. Time from induction of abortion to complete expulsion of product of conception was taken as induction to expulsion interval (IEI). Induction was considered failed after 72 hours.The cohort of misoprostol-induced mid-trimester MI-MT abortion cases was investigated for significant association of obstetric history of the patient with IEI. Five variables were taken from patient's obstetric history. These variables were maternal age, gravidity, parity, gestational age and previous LSCS. Each of these variables was taken as categorical variable that means each of them was divided into categories as shown in Figure-1. Each variable was tested against the null hypothesis of no significant association H_0 using non-parametric chi square, likelihood ratio and Fisher exact tests. For all the three tests 1000 boot strappings were performed. Each categorical variable shown in Figure-1 was tested for Simpson paradox effect.

Simpson paradox effect is a phenomenon in which the effect of a variable (association of obstetrical variables) with another variable (IEI) is reversed when a sub-category within a categorical variable (obstetrical variable here) is tested. For this purpose, gravidity was sub categorized into groups G1= Gravidity of 2 and 3, G2= Gravidity of 4 and 5 (Table-1). Other obstetrical variables were also sub categorized but none of them showed Simpson paradox effect.

Table-1
Cross tabulation of sub categories G1 and G2 of Gravidity of patients with Induction expulsion interval IEI showing the number of patients in each sub category

Gravidity of patient * Induction Expulsion Interval (IEI) Cross tabulation						
	Induction Expulsion Interval (IEI)					
Sub categories of Gravidity	< 12 HRS	12-24 HRS	24-48 HRS	48-72 HRS	FAILED INDUCTION	Total
G1	27	33	4	2	3	69
G2	16	14	3	2	2	37
Total	43	47	7	4	5	106

Figure: 1
A total of 106 Misoprostol-induced mid-trimester (MI-MT) abortion cases were taken as cohort (n=106). Number of patients shown for each obstetrical variable

Gestational Age	
13 – 20 weeks	86
21 – 26 weeks	20
Maternal Age (Years)	
15 -20	16
21 -30	80
31 -40	10
Parity	
0	6
1	36
2	44
3	18
4	2
Gravidity	
2	30
3	39
4	24
5	13

RESULTS:

Each of the categorical variables extracted from the patients' obstetric history was cross tabulated with IEI. However, none of the failed induction cases happened in gravida 2. Majority of failed induction happened in gravida 3 cases. Few cases of failed induction were also seen in gravida 4 and 5 (Figure-2).

Cross tabulation of gestational age with IEI showed that more than 80% of IEI of less than 12 hours belonged to early mid-term abortion, that is, 13-20 weeks (Table-1). In contrast, more than 80% of failed abortion cases belonged to late mid-term abortion. Figure-3 showed a very interesting staircase pattern of IEI in opposite directions for the early 13-20 week and late 21-28 week abortions. Figure-4 showed a relatively higher proportion (60%) of total cases of failed abortion occurred in patients with history of previous LSCS.

All the categorical variables were tested for their significant association with IEI using Chi square, Fisher exact and likelihood tests. Three categorical variables were significantly associated with IEI. These included gravidity, gestational age and history of previous LSCS (Table-2 – Table-4). Other categorical variables like maternal age and parity were not significant in determining IEI. Gravidity (number of pregnancies) was found important associating factor compared to parity (number of live births); although the two variables were found significantly correlated (P value <0.05).

Figure: 2

Bar chart showing the number of patients within each subcategory of Gravidity. Colour of bars shows the Induction Expulsion Interval (IEI) for each subcategory Gravida=2-5

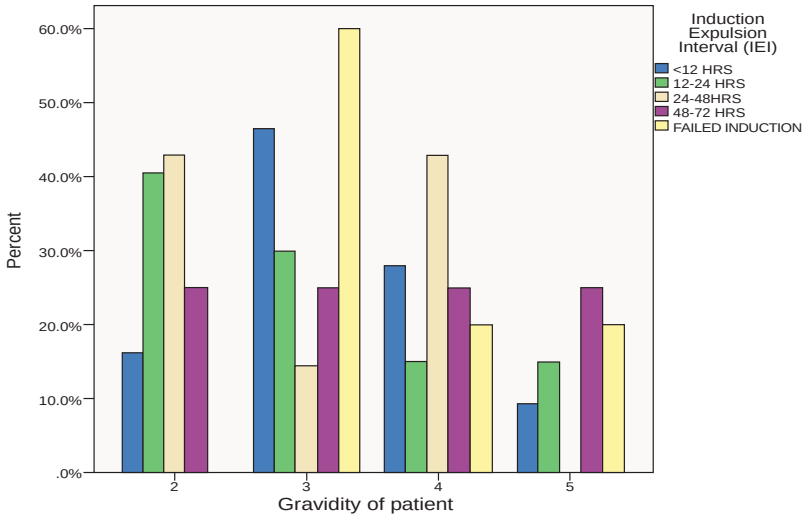

Figure: 3

Bar chart showing percentage of patients in each subcategory of gestational age. Colour of bars shows IEI for each subcategory, Gestational age: 13-20 week and 21-26 week

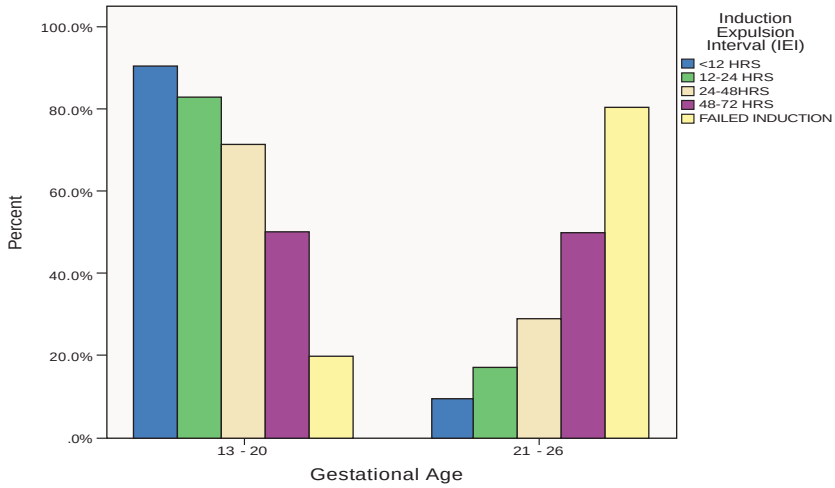

Figure: 4
Bar chart showing percentage of patients with and without history of Previous LSCS. Colour of the bars shows IEI for each subcategory: History of previous LSCS=Yes or No

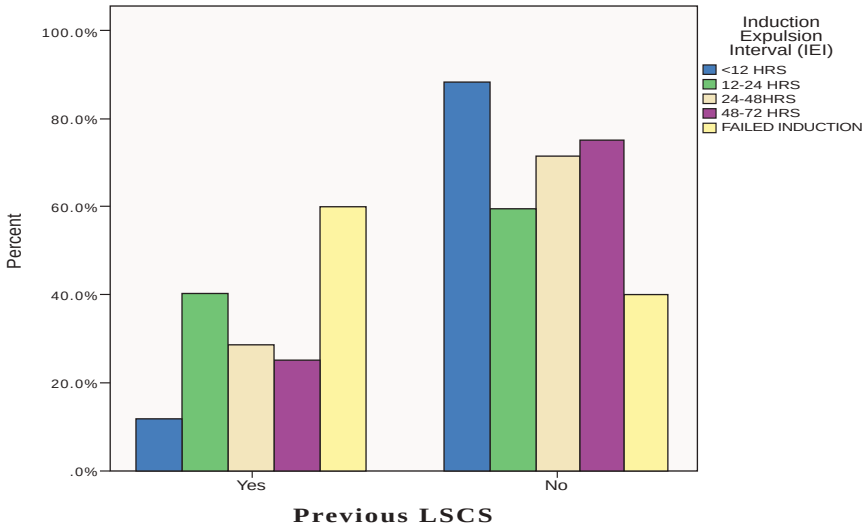

Table-2
Significant relationship of Gravidity of patient (only subcategory with Gravidity <= 3) with Induction to Expulsion Interval (IEI). Other subcategories (described in Methodology) did not show significant relationship with IEI

	Value	Degree of freedom	Asymptotic P value (2-sided)	Exact P value. (2-sided)
Pearson Chi-Square	10.013	4	0.040	0.023
Likelihood Ratio	11.315	4	0.023	0.039
Fisher's Exact Test	9.728			0.018
Linear-by-Linear Association	0.051	1	0.822	0.835
N of Valid Cases	69			

Table-3
Significant relationship of Gestational age with Induction to Expulsion Interval (IEI)

	Value	Degree of freedom	Asymptotic P value (2-sided)	Exact P value. (2-sided)
Pearson Chi-Square	17.845	4	0.001	0.002
Likelihood Ratio	14.247	4	0.007	0.006
Fisher's Exact Test	14.834			0.002
Linear-by-Linear Association	16.940	1	0.000	0.000
N of Valid Cases	106			

Table-4
Significant relationship of History of previous LSCS with IEI

	Value	Degree of freedom	Asymptotic P value (2-sided)	Exact P value. (2-sided)
Pearson Chi-Square	11.793	4	0.019	0.017
Likelihood Ratio	12.367	4	0.015	0.019
Fisher's Exact Test	12.364			0.008
N of Valid Cases	106			

DISCUSSION:

This study was aimed to investigate the significance of patient's obstetric history in estimating the induction to expulsion interval (IEI) in Misoprostol-induced mid-trimester (MI-MT) abortion cases. Results suggest that three of the obstetrical variables namely gravidity, gestational age and previous LSCS showed significant association (P value<0.05) with induction to expulsion interval (IEI). Reliability of the results was enhanced by the use of multiple statistical tests and 1000 boot strappings.

Mid trimester abortions constitute 10-15% of all induced abortions. Decision to perform the induction is made by evaluating factors that are associated with the risks and complications of the procedure. Studies suggest that the procedure of induction is more risky and complicated in cases of late gestational age as well as multiparity.[17, 18] Scioscia et al. 2007[19] reported only parity as a significant associating factor with IEI. His study was based on 423 cases of mid trimester abortion. Results have shown an association of higher parity with longer duration of IEI and early gestational age with shorter IEI.[17] Another study[20] studied 956 cases and found an association of parity and early gestational age with shorter duration of IEI. However, there are some studies that showed no significant association of parity, gravidity or gestational age with outcome of mid-trimester Misoprostol induced abortion.[21]

In the present study, the association of gravidity, gestational age and history of previous LSCS with IEI were found significant. It is worth mentioning that instead of parity which was described in the literature mentioned above as an important factor associated with outcome of Misoprostol mid trimester abortion; gravidity was found significantly associated with IEI. However, these two obstetrical variables: parity and gravidity were found significantly correlated with each other showing P-value <0.05. Although multi-gravidity has been described as a risk factor for abortion, very few studies were found that reported its effect on IEI. In this way, this study reported an interesting finding about the associating factors of IEI.

While performing the statistical analyses for significant associations of categorical variables paradoxical calculations must be kept in mind.[22] In fact, Simpson paradox is a classic example of confounding that may mask the true relationship of the two variables. Studies have suggested randomization and restriction method to overcome this problem.[23] In this study, restriction methods were used to sub categorize each categorical variable except previous LSCS. However, each sub category of three categorical variables namely gestational age, parity, and maternal age did not show paradoxical association. Only gravidity sub categories G1 and G2 showed Simpson paradoxical effect. Therefore, it is recommended that the categorical variables used for association studies in MI-MT abortion cases must be sub categorized to avoid paradoxical conclusions.

Limitations of the Study:

In this study two dose regimens for Misoprostol were used. Cohort was divided into sub-cohorts A and B on the basis of these two regimens. These two regimens were given according to gestational age of the patient. Therefore, the effects of the two regimens were addressed by categorizing gestational age according to the regimens used. However, these two regimens might have confounding effect on other categorical variables. It might be useful to study the effect of confounding variable on each categorical variable of obstetric history. However, a smaller sample size may be a limiting factor for further analyses. A larger sample size would be required to analyze the two sub cohorts separately. Studies have suggested shorter IEI with early gestational age and high parity.[24] However, results may vary due to socio-demographic factors.[25] Therefore, it is mandatory to consider the obstetrical parameters which may differ among the cohorts of different settings. Moreover, Misoprostol must be given with caution in cases of previous LSCS. Uterus rupture and need for surgical evacuation have been reported in different studies.

CONCLUSION:

This study emphasizes the importance of obstetrical history in determining the outcome of the Misoprostol induced mid trimester (MI-MT) abortion. Three of the variables namely gestational age, gravidity and previous LSCS showed significant result. Percentage distribution of number of cases in each of the three variables showed that lower gravidity, higher gestational age and presence of previous LSCS are associated with longer IEI. However, it is not justified to conclude that other variables like maternal age and parity did not influence the outcome of induced abortion. A larger sample size and a more comprehensive study design may reveal other factors associated with outcome of MI-MT abortions.

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ORIGINAL ARTICLE

Frequency Of Bracket Bond Failure In Orthodontic Patients With Normal Over Bite And Deep Bite

Ahmad Hasan

ABSTRACT:

Objective: To find out the frequency of bracket bond failure in patients with normal overbite and deep bite. **Methodology:** Sample consisted of 100 patients undergoing fixed orthodontic treatment at Orthodontic Department of Rawal Institute of Health Sciences, Islamabad between July 2014 and June 2016. Patients were divided into 2 equal groups. 50 patients were with normal overbite (0-2mm) and 50 patients were with deep bite(>2mm). All patients were bonded with metal brackets and were kept under observation for 12 months for bracket bond failure. SPSS 21 was used for statistical analysis.P-value <0.05was considered statistically significant.

Results: 43 patients showed bracket bond failure. 76 % patients with deep bite, while 10 % patients with normal overbite showed bracket bond failure (p-value <0.05). Female patients showed more bracket bond failure (43.9 %) than male subjects (41.2 %). Bracket bond failure in maxillary arch was 69.8 %, whereas it was30.2 % in mandibular arch. Bracket breakage was seen in buccal segment in 53.5 % of cases, while incidence was 46.5%in labial segment.

Conclusion: Bracket bond failure was more common in patients with deep bite. Female patients showed greater incidence and most common location was buccal segment in maxillary arch. Most frequent tooth with bracket bond failure was second premolar.

Keywords: Bracket breakage, Bond failure, Deep bite

INTRODUCTION:

Three-dimensional control of teeth during orthodontic treatment plays an important role in achieving optimum treatment results. This control of tooth movement is possible with the help of fixed appliances which are directly bonded on tooth enamel. For timely finishing of an orthodontic case, it is important that bonded appliance should survive till the end of treatment. However, some bonded brackets show bond failure during different stages of orthodontic treatment.[1] The ideal bond strength should be enough to withstand the masticatory forces, and it has to be away from the given forces throughout the phase of fixed appliance treatment. It should be in the optimum range to facilitate easy removal of bracket at the time of debonding without enamel fracture.[2]

Usually bonding is done with the application of 37% phosphoric acid on tooth enamel for 15 seconds followed by application of unfilled composite resin and placement of bracket on tooth surface having filled composite resin at its base. Composite resin is cured with the help of either light-cure or chemical cure initiation.[2,3]

Success of bonding is dependent on bonding technique used, concentration of etchant gel and application time of etchant, bracket base structure and operator expertise. Patient's factors which also include eating habits play an important role in preventing bracket bond failure.[1,2,3,4]

Investigators have previously studied prevalence of bracket bond failure in relation to gender and site of bond failure.[1,2,3,4,5] Researchers have also studied bond strength of different bonding materials on brackets and type of bonding technique used which may be either direct or indirect.[6,7,8,9,10,11]

However, in our research we investigated the frequency of bracket bond failure in patients with deep bite and normal overbite, so that relationship of bracket debonding in normal overbite and deep bite can be established.

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METHODOLOGY:

This cross-sectional comparative study was conducted at the Orthodontic Department of Rawal Institute of Health Sciences, Islamabad between July 2014 and June 2016. The sample size (n) was calculated by the following formula[12]

$n = Z^2 P(1-P) / d^2$, where n= sample size, Z= Z statistic for a level of confidence (it was set at 95%) P= Prevalence from a previous study, and d= precision (d= 0.05).

In this research 100 patients undergoing fixed orthodontic treatment were included. Patients were divided into 2 groups; 50 patients were with normal overbite (overbite 0-2mm) and 50 patients were having deep bite (overbite > 2 mm).[13]

Patient's incisor relationship was recorded according to British standard classification of incisor relationship.[14] Patient's gender was noted and patients were also divided in teens and adults depending on age.

Patients with enamel defects like fluorosis, amelogenesis imperfecta and with skeletal or dental cross bites were not included in this study. Patients having crowns, bridges and fillings on buccal or labial surface of the teeth were also excluded from the study. It was also ensured that no occlusal interferences were present after

bonding.
Teeth from second premolar to second premolar were bonded in both maxillary and mandibular arches. Teeth to be bonded were etched with 37% phosphoric acid (Swisstec SL Etchant Gel manufactures by Coltene Whaledent) for 15 seconds followed by rinsing of acid with water for 30 seconds. After drying the tooth with air, a thin layer of unfilled composite resin (Bonding agent) was applied on tooth surface and was cured for ten seconds with the help of light emitting diaode (LED). On the mesh surface of metal bracket, bonding agent was applied followed by placement of filled composite resin. Bracket was placed on labial or buccal surface of a tooth and was cured for 20 seconds with the help of LED. Transbond XT light cure adhesive system manufactured by 3M Unitek (USA) was used for bonding all brackets in this study. Metal brackets used in this study were manufactured by Ortho Organizer (USA) with slot size of 0.022 X 0.028" and these were with MBT Bracket Prescription.
All the clinical work was done by a single operator. All the patients included in this study were bonded with similar etchant, light-cure orthodontic adhesive system, light emitting diode lamp and metal brackets from the same manufacturer. It was ensured that during whole clinical procedures recommended clinical guidelines were followed. Good isolation was also ensured during bonding procedure. After bonding initial aligning archwire of 0.012 Niti was ligated in the brackets with the help of elastomeric ligatures.
Bracket bonding date was noted and patients were examined for bracket bond failure at monthly follow-up visits for 12 months from the day of bonding in case of patients with normal overbite and in patients with deep bite, they were observed till correction of deep bite. Bracket debonding was noted during intra-oral examination with naked-eye and was confirmed with the help of dental mirrors and tweezers.
In case of bracket bond failure, site of bracket breakage was noted. A bracket bond failure in a patient was recorded once and subsequent bracket breakages in the same patient were not included in the study. SPSS 21 was used for statistical analysis. Chi-Square test was used to find relationship of bracket debonding in both groups of deep bite and normal overbite.A p value of <0.05 was considered as significant.

RESULTS:
Our sample consisted of 100 patients (50 patients with normal overbite and 50 patients with deep bite). 34 patients were male and 66 patients were female. Table-1 showed the debonding status in patients with normal overbite and deep bite. Out of 100 patients, bracket bond failure was noted in 43 patients. 76 % (38 patients) showed debonding in patients with deep bite, while 10 % (5 patients) showed debonding in patients with normal over bite.There was statistically significant difference between bracket bond failure in the two groups of deep bite and normal overbite as p-value was < 0.05.
Table-2 showed debonding status according to gender. Female patients showed more bracket bond failure (43.9 %) than male subjects (41.2 %). Difference of bracket bond failure between male and female subjects was statistically insignificant as p-value is 0.791. Table-3 showed frequency of debonding noted in the two arches. Maxillary arch showed more bracket bond failure (69.8 %) as compared to mandibular arch (30.2 %).
Table-4 showed frequency of debonding noted according to site. Buccal segment showed more bracket bond failure (53.5%) as compared to labial segment which showed bracket bond failure in 46.5% of the total patients.

Table: 1
Cross Tabulation of Debonding Status in Normal Overbite and Deepbite

			Overbite		Total
			Normal Overbite	Deep Bite	
Debonding Status	No Debonding Noted	Count	45	12	57
		%	90.0%	24.0%	57.0%
	Debonding Noted	Count	5	38	43
		%	10.0%	76.0%	43.0%
Total		Count	50	50	100
		%	100.0%	100.0%	100.0%

Table: 2
Cross Tabulation of Bracket Bond Failure According to Gender

			Debonding Status	
			No Debonding Noted	Debonding Noted
Gender	Male	Count	20	14
		% within Gender	58.8%	41.2%
	Female	Count	37	29
		% within Gender	56.1%	43.9%
Total		Count	57	43
		% within Gender	57.0%	43.0%

Table: 3
Frequency of Bracket Bond Failure Noted in Maxillary and Mandibular Arches

			Debonding Noted
Arch	Maxillary Arch	Count	30
		%	69.8%
	Mandibular Arch	Count	13
		%	30.%
Total		Count	43
		%	100.0%

Table: 4
Frequency of Bracket Bond Failure Noted in Buccal and Labial Segments

			Debonding Noted
Site	Buccal Segment	Count	23
		%	53.5
	Labial Segment	Count	20
		%	46.5%
Total		Count	43
		%	100.0%

DISCUSSION:

In this study only frequency of debonding in patients with normal overbite and deep bite was studied. Patients with deep bite showed more bracket bond failure than patients with normal over bite. This study agreed with the previous study by Atashi[15] which showed more debondings in patients with deep bite. The higher bracket bond failure in patients with deep bite may be due to the stronger masticatory forces in these patients as compared to the patients with normal overbite or open bite.

Bracket bond failure in our patients with normal overbite (10%) was comparable with the results of previous international studies[16] but did not match with the debondings reported in our patients with deep bite (76 %). In a national study by Rasool,[5] bracket bond failure was found 59.3 % and in our study overall bracket debonding found in the whole sample (patients with deep bite as well as with normal overbite) was 43%, which was very high than the bracket debonding reported in international studies. The reasons for this difference may include improper care of brackets and failure to follow proper dietary instructions by our population in addition to other reasons.

In our study dental class II patients showed more debonding as compared to other types of malocclusion. This agreed with a previous study by Bherwani[4]. Atashi[15] on the hand found no difference in frequency of debonding in various types of malocclusions. Our research findings demonstrated that debonding was more common in maxillary arch as compared to mandibular arch. These results agreed with the previous research by Rasool,[5] however, did not agree with the previous studies by Sukhia[1] and Pseiner[17] which concluded more bracket bond failure in mandibular arch as compared to maxillary arch. Marquezan[18] has reported equal bracket breakage in both maxillary and mandibular arches.

There were more debonding in buccal segment than labial segment in the present study. Previous studies by Sukhia[1] and Purmal[19] also showed greater bracket bond failure in buccal segment. This may be due to greater magnitude of masticatory forces in posterior segment as compared to the anterior segment.[20]

Most common tooth for bracket bond failure was second premolar which might be because of difficulty in moisture control, reaching the buccal surface of the tooth and presence of aprismatic enamel.[21]

In our study debonding rate in female patients was more as compared to male patients. This was in agreement with the previous studies by Rasool[5] and Liu.[22]However; studies by Sokucu[23] and Leizer[24] have indicated more bracket breakage in male subjects as compared to the female subjects. Research by Moninuola[25] has shown equal distribution of bracket debonding in both gender subjects.

In the present study, teens showed more bracket debonding than adult patients. Previous studies by Rasool[5], Ammar[26] and Yang [27] have also shown more bracket bond failure in young patients as compared to adult patients. This could be due to increased level of self-awareness and greater motivation for esthetic

improvement in adults as compared to teens. The difference in the results of this study and other studies may be due to the difference in the sample size, material used for bonding and in type of brackets used. Limitation of this study were; not considering the reasons for brackets bond failure which apart from other factors also include magnitude of masticatory forces associated with various facial types, dietary habits, other characteristics of malocclusion and type of mechanics involved during the treatment.

It is clear from this study that while bonding brackets in patients with deep bite strict clinical guidelines must be followed as chances of bracket bond failure is greater in patients with deep bite.

CONCLUSION:

It was concluded that bracket debonding was more common in patients with deep bite and most common site for frequent debonding was maxillary arch and buccal segment. Second premolar was the tooth which showed most frequent bracket bond failure.

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ORIGINAL ARTICLE

Antimicrobial Susceptibility Pattern of Acinetobacter Baumannii and Rate of Carbapenem Resistance at a Tertiary Care Hospital in Karachi

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ABSTRACT:

Objective: To know frequency of carbapenem resistance in Acinetobacter baumannii and its antimicrobial susceptibility pattern at PNS Shifa Hospital Karachi.

Methodology: This study was carried out at PNS Shifa Hospital, Karachi, from 1st January 2015 till 31st October 2016. Samples from patients having different sites of infection were received in the laboratory from different wards of hospital and inoculated on culture plates. After 24 hours incubation, identification of non-lactose fermenter colonies of Acinetobacter baumannii was done by conventional methods. Antimicrobial susceptibility was recorded for ß-lactam group of antimicrobials, ß-lactam/ß-lactamase inhibitor combination group, tetracyclines, fluoroquinolones and aminoglycosides as per CLSI guidelines.

Results: During the study period, a total of 117 Acinetobacter baumannii isolates were identified from culture of different samples representing 5.0% of all bacterial isolates (n=2352) and 7.5% of all Gram-negative bacilli (n=1559) throughout the hospital. Out of one hundred and seventeen isolates, 52.1% (n=62) were found carbapenem resistant. Higher percentages of Acinetobacter baumannii were isolated among samples received from medical wards (26.4%). Percentage of Acinetobacter baumannii isolated was highest from the blood culture specimens (22.2%). Isolates showed higher resistance against ceftriaxone (84.6%) followed by cotrimoxazole (65.8%) and ciprofloxacin (63.2%). Comparatively low resistance against doxycycline and minocycline (23.9%), and tigecycline (38.9%) was observed. Resistance pattern to other antimicrobials was gentamycin (54.7%), amikacin (55.6%), piperacillin-tazobactam (48.7%), cefoperazone-sulbactam (51.35%), meropenem (52.1%) and imipenem (52.1%).

Conclusion: Carbapenem resistance in Acinetobacter baumannii is increasing and therapeutic options left to treat are highly toxic especially for patients with co-morbidities.

Keywords: Acinetobacter baumannii, Carbapenems, Frequency, Antimicrobial susceptibility pattern

INTRODUCTION:

Acinetobacter baumannii (AB) is catalase positive, oxidase negative and non-motile gram negative rod. It survives in aqueous environment, therefore it colonizes irrigating and intravenous solutions in hospital settings.[1,2,3] It has become clinically important due to its ability for outbreaks and resistance to antibiotics including carbapenems.[2,3,4,5] Associated risk factors with multidrug-resistant Acinetobacter baumannii include older age, prolong hospital stay, using drainage catheters for longer duration, prior antimicrobial therapy and intensive care unit (ICU) stay.[5,6,7,8] In the last 10 years, the incidence of Acinetobacter baumannii infections and carbapenem resistance has increased in a number of regions in the world.[8,9]

Carbapenems belong to ß-lactam group of antibiotics. These antimicrobials target cell wall of bacteria. This group includes meropenem, imipenem, doripenem and ertapenem. Carbapenems have been used as most effective and safe antimicrobials against gram negative rods till resistance against these antimicrobials developed.[9,10] Since ten years, resistance have been reported from hospitals of several countries against it. Many clinicians still believe that it is the most effective antimicrobial against gram negative rods. In most of hospitals carbapenems are used as empirical treatment to treat infections until culture reports are being obtained.[10]

It is important to know carbapenem resistance rate and susceptibility to other antimicrobials in hospitals and community of local settings. The purpose of this study was to provide data to clinicians regarding recent susceptibility pattern of carbapenems related to Acinetobacter baumanii infections.

METHODOLOGY:

A descriptive study was conducted at PNS Shifa Hospital Karachi from 1st January 2015 to 31st October 2016.

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Repeat samples from same patients were excluded from the study. Samples of wound/pus swab, naso-bronchial lavage, blood, sputum, urine, pleural fluid, tracheostomy tip, central venous line tip, sinus fluid and endotracheal tube tip were received in the microbiology laboratory from medical and surgical wards, intensive care unit (ICU), neonatal and pediatric wards/ ICU and out patients department (OPD) for culture and sensitivity.

All samples were inoculated on blood agar (oxoid) and MacConkey's agar (oxoid). Culture plates were incubated at 37° C in CO_2 incubator at ambient air for 24 - 48 hours. Techniques used for identification of Acinetobacter baumannii included colony morphology, catalase test, oxidase test, gram staining and species differentiation by biochemical reactions using API 20 NE (bioMerieux) were done.[2] Isolates showing grey, shiny, small colonies on blood agar, and oxidase negative non-lactose fermenting colonies on MacConkey's agar were included in study. All isolates were screened for carbapenem-resistant Acinetobacter baumannii (CRAB) with Imipenem 10µg and meropenem 10µg discs following Kirby-Bauer disc diffusion method according to clinical and laboratory standards institute (CLSI) guidelines.[11] The isolates with zone diameter equal to or less than 22mm against Imipenem disc and equal to or less than 18mm against meropenem disc were considered as CRAB as per CLSI guidelines[11]

Bacterial suspension equal to 0.5 McFarland solution of all isolated CRAB was inoculated on a Mueller-Hinton (oxoid) agar plate. Antimicrobial susceptibility or resistance against minocycline (30µg), tigecycline (15µg), doxycycline (30µg), cotrimoxazole (25µg), ciprofloxacin (5µg), amikacin (30µg), gentamycin (10µg), piperacillin-tazobactam (100/10µg), cefoperazone/sulbactam (75/30 µg) and polymyxin B (MIC) was carried out as per CLSI guidelines.[11] Descriptive statistics were applied and data was analyzed on IBM SPSS 22. The significance threshold was set at $P<0.05$.

RESULTS:

During the study period of two years, a total of 117 Acinetobacter baumannii isolates were identified from culture of different samples representing 5.0% of all bacterial isolates (n=2352) and 7.5% of all Gram-negative bacilli (n=1559) throughout the hospital. All Acinetobacter baumannii isolates were screened for carbapenem resistance. Out of one hundred and seventeen isolates, 62 (52.1%) were found to be carbapenem resistant. Most of the microorganisms were isolated in samples received from medical ward (26.4%) (Table-1).

Percentage of Acinetobacter baumannii isolated from different specimens has been shown in Table-2. It was highest from blood samples (22.2%).

In this study, the isolates showed higher resistance against ceftriaxone (84.6%) followed by other antimicrobials (Figure-1).

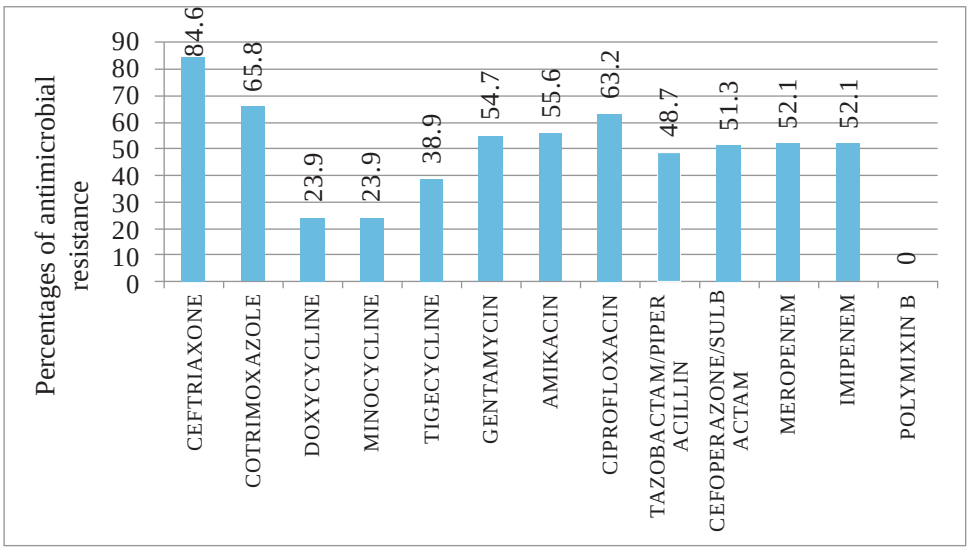
Table: 1
Percentages of Acinetobacter baumannii isolated from different wards of PNS Shifa Hospital from 2015-2016

WARD	n=117	%
Medical ward	31	26.4
Adult intensive care units	26	22.2
Outpatient department	20	17.1
Neonatal intensive care unit	16	13.7
Surgical ward	14	12.0
Pediatric intensive care unit	07	6.0
Pediatric ward	03	2.6

Table: 2
Percentages of Acinetobacter baumannii isolated from different samples at PNS Shifa Hospital Karachi from 2015-2016

SAMPLE	n=117	Acinetobacter baumannii isolated%
Blood	26	22.2
Naso-bronchial lavage	21	17.9
Pus culture	21	17.9
Sputum	15	12.8
Endotracheal tube tip	12	10.3
Wound culture	05	4.3
Pleural fluid	06	5.2
Tracheostomy tube tip	04	3.4
Urine	04	3.4
Central venous catheter tip	03	2.6

Figure: 1
Percentages of Acinetobacter baumannii isolates resistant against different antimicrobials at PNS Shifa Hospital Karachi from 2015-16



DISCUSSION:

Acinetobacter Baumannii is a multidrug resistant, opportunistic microorganism, usually found in Intensive Care settings and recognized as a known nosocomial pathogen leading to different types of infections such as bacteremia, nosocomial or ventilator associated pneumonia, meningitis, and skin and soft tissue infections.[6,7,12]

Acinetobacter baumannii strains are classified as multi-drug resistant (MDR): non-susceptible to ≥1 agent in ≥3 antimicrobial categories, extensive drug resistant (XDR): non-susceptible to ≥1 agent in all but ≤2 antimicrobial categories and, pan-drug resistant (PDR): non-susceptible to all antimicrobial agents available.[13,14] However these definitions will change with developing resistance. Now Carbapenem resistance rates are increasing to such an extent that it is threatening the world and this situation is gradually becoming a routine phenotype for the microorganism.[14,15] Factors responsible for developing resistance include impermeable outer membrane, enzymes responsible for breakdown of antibiotics especially ß-lactamases, class D OXA-type and class B metallo-ß-lactamases allowing the organism to resist carbapenems, porin channel alterations and efflux pumps.[13,14]

In the present study, more than half of Acinetobacter baumannii (52.1%) isolates were resistant to carbapenems (meropenem and imipenem). Higher resistance (90%) to carbapenem was reported in a study conducted at hospital of Turkey in 2010-2012.[16] This shows increasing resistance in Acinetobacter baumannii to carbapenems from other countries as well. In our study 22.2% of total AB isolates were identified among samples received from adult ICU which was high as compared to a study conducted in ICU settings of different hospitals where AB related infection was19.2%, 17.1%, 14.8%, 13.8%, 5.6%, 4.4% and 3.7% in Asia, Eastern Europe, Africa, Central and South America, Western Europe, Oceania and North America respectively.[2] This shows increasing ICU related infections due to AB. In our study ICU related infections were high most likely due to improper use of disinfectants and room irrigation techniques before and after patient's discharge from hospital.

In the present study most of the AB were isolated from the blood culture specimen (22.2%) followed by respiratory tract, pus discharge and pleural fluid samples. According to some studies the mortality rates were high because of bacteremia.[14,15,17] While taking samples special consideration should be given to sampling techniques as in most of the wards proper aseptic techniques were not followed. Hence isolates could be contaminants or might have been introduced in blood during sampling.[6,7,18]

In our study there was higher resistance against ß-lactam antibiotics as compared to other groups of antimicrobials. Polymyxin B with 0%, tigecycline 38.9%, doxycycline 23.9% and minocycline 23.9% were among least resistant antimicrobials. However these antimicrobials have limitations related to their side effects.[19] There was no resistance against polymyxin B in our study. Similar data was found in a study conducted in National Hospital of Tropical Diseases (Hanoi, Vietnam) in 2009 where susceptibility rates against ß-lactam antimicrobials were low as compared to minocycline, tigecycline or doxycycline and all isolates were sensitive to polymyxin B.[20] However, some resistance (3%) was reported against polymyxin B in a study conducted in Songklanagarind Hospital in Songkhla Province, Thailand in 2010.[21] This was frightening as last resorts have been started compromising also. Moreover, problem globally was of less concern for pharmaceutical companies towards development of newer antimicrobials.[19,22] Keeping in view such threats studies have been done to evaluate in

vitro susceptibility of combination therapy like colistin and imipenem, colistin and rifampicin, cefoperazone/sulbactam combined with imipenem and combination of imipenem with rifampicin.[21] One limitation of our study was that Rifampicin was not included in this study. Cefoperazone/sulbactam combined with rifampicin had better response against AB infection.[21] According to different studies, combination therapy was superior to mono-therapy because of toxicity, and hetero-resistance to polymyxin B due to prolonged use.[21,23,24,25]

In our study, better options for treatment in case of carbapenem-resistant strains of AB were minocycline, doxycycline and Polymyxin B. The judicious use of these agents is the need of the day, as these are the last resorts available for treating such resistant pathogens. To overcome this challenge a multidisciplinary approach is needed to prevent infections.

CONCLUSION:

Laboratories play an important role in providing appropriate antibiogram related to pathogens isolated in hospitals. This study has demonstrated that Carbapenem resistance in Acinetobacter baumannii is increasing and therapeutic options left to treat are highly toxic especially for patients with co-morbidities. In this way, empirical treatment is guided following regional or local antimicrobial susceptibility pattern of pathogens.

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ORIGINAL ARTICLE

Frequency And Motive Behind Shisha Smoking Among Students Of Private Universities Of Karachi

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ABSTRACT:

Objective: To determine the frequency and primary motive behind the initiation of smoking Shisha (waterpipe) among the students of private universities of Karachi.

Methodology: It was a Cross sectional study conducted in three private universities of Karachi comprising of 400 students of different disciplines. The study was questionnaire based. Data was entered on SPSS version 23 to derive results.

Results: Our study consisted of 400 subjects, out of which 261 (65.3%) were male and 139(34.8%) were female. The mean age of the students was 21.12 (STD± 3.07). 195(74.7%) male and 87(64%) female students agreed that they had tried Shisha smoking. The students of Engineering (n= 125, 31.33%) were found more into the practice of smoking Shisha. Pleasure was the primary motive for initiation of Shisha smoking (29.75%). Mint flavour was highest in demand recommended by 69% male students (n=199/288). Regarding knowledge related to harms, 212 students out of 363 agreed upon the fact that smoking Shisha is more harmful as compared to cigarettes, whereas 37 students (9. 25%) did not respond to the question. Also 282 (70.5%) agreed to the fact that Shisha is less addictive.

Conclusion: High prevalence of Shisha smoking was observed among engineering students due to pleasure and socialization. Interventions should be implemented in order to promote awareness concerning health hazards and necessary measures ought to be carried out to extricate youth from this trend.

Keywords: Shisha, Waterpipe, Pleasure, Socialization, Health hazards

INTRODUCTION:

Evidence has shown that trend of tobacco smoking is increasing in developing countries leading to tremendously high risk of tobacco related diseases[1]. World Health Organization ascribes 4.9 million deaths per year because of tobacco use, a figure expected to rise to more than 10 million by 2030 if the current trend continues[2]. Various researches focussed on the prevalent trends and patterns of tobacco usage, namely cigarettes and smokeless tobacco, but did not consider those prevalent in developing countries such as waterpipe, namely, Shisha[3].

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Waterpipe smoking commonly known as Shisha, Muassel, Hookah, Nargilha or Hubble bubble, in different countries and cultures, has gained immense popularity in Middle East countries and being practiced in Arabian Peninsula, Turkey, India, Pakistan, Bangladesh and China[4].

It is a form of tobacco intake in which the smoke passes through water before inhalation[5]. This habit of smoking was traditionally confined to older men and women in the Indian subcontinent and Arab countries; however, it is rapidly spreading among youth. Factors which promote its fame may include its social acceptance as a part of cultural heritage, modern trends, easy availability, attractive designs and flavoured aromatic tobacco called "Muassel"[6]. It has now paved its way to commercial cafés, restaurants and even at homes. The most common users are university and college students. Shisha is a smoking device widely used in Arabian Peninsula to smoke Jurak, a mixture of tobacco and fruit cooked to produce a dark coloured paste. It is perceived by youth, the general public and even health professionals as being less harmful than cigarette smoking[6], for instance, nicotine is lower than quantity found in cigarettes, as water used in Shisha filters out all noxious chemicals consisting of carbon monoxide, tar and nicotine, and less harmful and irritating to pharynx and respiratory system; due to Muassel[7].

A detailed study had been conducted on the estimated amounts of carboxyhaemoglobin saturation in Shisha and cigarette smokers relative to the number of Shisha or cigarettes smoked a day[8].The carboxyhaemoglobin concentration in blood has been shown to be a useful marker of absorption of tobacco smoke[8, 9]. As compared to a cigarette, which involves inhalation of approximately 500–600ml of smoke (i.e., 10–13 puffs of about 50 ml, on average)[10,11], a single waterpipe use episode involves inhalation of approximately 90,000ml of smoke[12]. The

use of Shisha may be associated with coronary heart disease[13], pulmonary diseases[14], and even bronchogenic carcinoma[15]. An evidence from a recent study verified that, as compared to non-smokers, both daily waterpipe tobacco smokers and cigarette smokers had higher levels of carcinoembryonic antigen (CEA), a tumour forming protein[16]. Waterpipe smoking also causes deterioration of dental[17] and foetal health[18]. It also involves sharing the same waterpipe, which increases risk of transmitting infectious diseases[19].

Keeping this background in mind, the objective of this study was to find the frequency of students indulged into the habit of shisha smoking belonging to different disciplines, recognition of motive behind initiation of this practice and to assess their awareness regarding its side effects and addiction, and their perception of being less or more lethal as compared to other patterns of smoking

METHODOLOGY:

This cross-sectional study was conducted in selective 3 private universities of Karachi during January and February 2016. A total of 400 students belonging to different disciplines like MBBS, BDS, Engineering, MBA, BBA, Computer studies and Psychology participated in the study. The permission was requested from these private universities through appropriate channel with assurance that names of the institute would be kept confidential. Informed verbal consent was obtained from the participants. The study was based on self-administered questionnaire, comprising of age, gender, discipline, duration, frequency, flavour and place of smoking, knowledge regarding its harms, and primary motive behind adoption of shisha smoking habit. Responses were entered into the system using SPSS version 23.

RESULTS:

Our study comprised of 400 subjects, out of which 261 (65.3%) were male and 139 (34.8%) were female. The age range varied between 15- 40 years, with mean age of 21.12 years (STD± 3.07). These subjects were inquired whether they had ever tried shisha smoking. 195(74.7%) male students, whereas, 87(64%) female students agreed they had. The incidence of smoking shisha was higher in male students. The frequency of consistent Shisha smoking was seen in students of ages 20(19.5%) and 21(19.3%).

The students of Engineering were found more into the practice of smoking Shisha (figure-1) with a frequency of n=125 (31.3%), followed by MBBS (n=105, 26.32%). Regarding primary motive, 119 students out of 363(32.78%, 80 males and 39 females) agreed pleasure to be the main reason (table-1), whereas, 67 students stated eliminating boredom or passing time. Regarding the flavour, Mint was most popular among males (69%, 199/288). Majority of the respondents did not smoke on daily or weekly basis. 39.65% (n=115) students agreed to smoke Shisha once a month (table-2) In our study, 149 students out of 363 believed that smoking Shisha is less harmful as compared to cigarettes, whereas 212 students disagreed to the perception of being less harmful whereas 37 students (9. 25%) did not respond to the question. Also, 282 (70.5%) agreed that Shisha is less addictive and can be quitted easily. 273 subjects (68.25%) agreed that Shisha can be the leading cause of cancer.

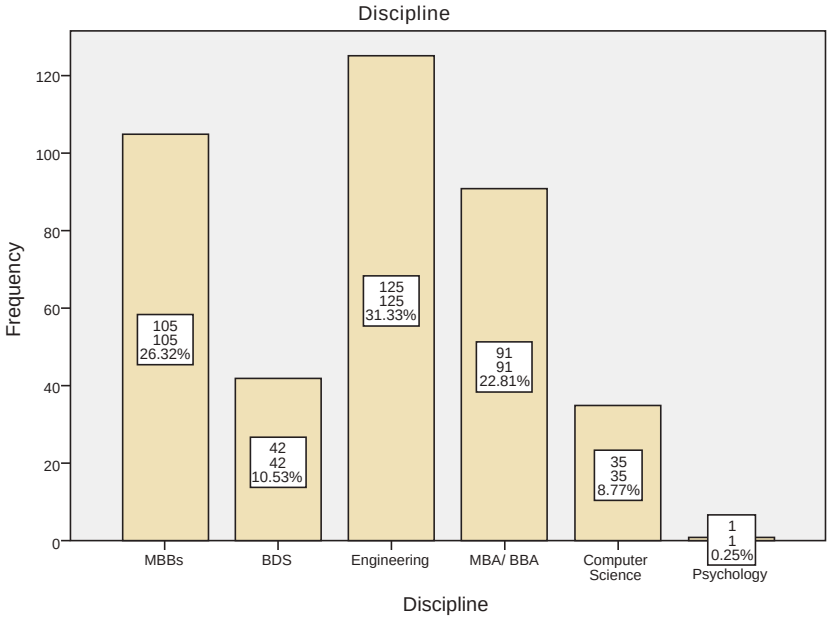
Table: 1
Cross Tabulation of motive with gender for shisha smoking

Motives	Gender		Total
	Male	Female	
Pleasure / fun	80	39	119
Peer pressure	25	27	52
Boredom / passing time	43	24	67
Inspiration by father or brothers	9	7	16
Relieve of tension and stresses	36	15	51
Don't Know	47	11	57
Total	**240**	**123**	**363**

Table: 2
Frequency of Shisha Smoking

Smoking Habits	Responses (n)	Percentage of Respondents %
Once a week	32	11.03
Twice a week	39	13.44
Once a month	115	39.65
Less than a month	104	35.86

Figure-1:
Cross tabulation of Frequency to Discipline of respondents



DISCUSSION:

Several studies regarding Shisha smoking had been conducted locally and internationally, which were population based, at university level, and even among adolescents of secondary schools of Saudi Arabia and Syria depicting the prevalence, attitude, practices and perceptions regarding its harms. In few Arab countries, Shisha smoking had been considered less disgraceful than cigarette smoking, with less gender disparity[20,21]. Respondents believed it to be less harmful than smoking cigarettes [20-22], whereas, our study had come up with better awareness of the respondents who had disagreed that, Shisha smoking is less harmful when compared to cigarette smoking. This fundamental point distinguishes our study from previous researches[20-22]. Secondly, this study also revealed ratio of female smokers to be considerably higher than previous studies conducted in Pakistan[22].

Our study presented information regarding frequency and primary motive behind adoption of Shisha smoking, and also, awareness regarding its harms and addiction. The participants hail from better socio-economic status, probably indulged into this habit since young age; inspired by family members (inspiration), influenced by friends (peer pressure), to get relief from tough study schedule (stress reliever), elimination of free time (boredom) or to just spending leisure time (pleasure). The percentage of waterpipe smokers in our study was 70.5%, considerably higher than a study conducted at Syrian University which showed a prevalence of 45.3% (males and females 62.6% and 29.8% respectively)[22]. Another study from Beirut University showed prevalence of smoking to be 43%[23]. This drastic increase may be due to the fact that the former study[23] was conducted in 2001 and present results showed significant increase among modern well educated youth of Pakistan. Also, a tremendous rise in the proportion of female smokers was noteworthy. It was almost compatible to the females of Pakistan in the National Health Survey[24]. A similar study conducted in Egypt showed prevalence of smokers (81- 92%) who were aware of the hazards of waterpipe use associated with asthma, respiratory diseases, heart diseases and transmission of infection[25].

The current study showed that Shisha smoking was more common among engineering students (31.33%). This was probably due to the fact that these students belonging to sound socio-economic status accepted this trend for seeking pleasure, socializing and status symbol. Probably, they had been into the practice of smoking since long time influenced by their family background and continued as fashion.

In our study, pleasure seeking was the primary motive behind initiation of smoking shisha with 33.3% (n=80) male and 31.7% (n=39) female which was considerably higher than a study conducted by Pakistan Medical and research council (PMRC) in 2012[26].

The mean age in this study for initiation of smoking shisha was 21 years, compared to 17-18 years in PMRC study[26], whereas, a study conducted among secondary school adolescents at Al Hassa, Saudi Arabia[27] showed average age to be 15 years. Surprisingly, there were more than twelve Arab countries where 10% of the girls between 13-15 years of age smoke[28].

The frequency of Shisha smoking in this study (table-2) indicated that it was mostly for socialization and fun, without likelihood of addiction. These respondents fell into the category of occasional smokers. This result was in agreement to the study conducted by Maziak et al, comprising Syrian university students who smoked occasionally[6].

Consistent previous studies depicted that smoking shisha was neither harmful nor addictive as compared to

cigarettes[29-31]. Another study in Israel surveyed 388 high school students on their beliefs and observed that majority of them, as well as parents perceived shisha smoking to be less harmful than smoking cigarettes[32]. Another study described perception of using a waterpipe was likely to be less lethal due to presumed "filtering" effects of water[33]. In our study, 58.4% students disagreed to the belief of shisha being less harmful as compared to cigarettes, which meant they were aware of the hazards and consequences, and smoked occasionally.

CONCLUSION:

Modern social trends have opened new avenues for prevailing Shisha smoking as trend setter in our society. This social influence provokes youth to become a part of modern society. Increasing number of females is indulging into the habit of shisha smoking, mostly for seeking pleasure. Among different disciplines, engineering students were more. Most of the subjects were aware of the health hazards of Shisha smoking, and were occasional smokers.

RECOMMENDATIONS:

Essential measures should be taken by the health care providers in educating adolescents and young adults regarding hazards of Shisha smoking. This could be enforced in the form of precise disclosure of shisha when implementing standardized assessments and clarify that shisha tobacco smoke contains same toxicants as cigarette smoke, even in higher quantities.

LIMITATIONS OF THE STUDY:

This study limits itself for evaluation of frequency and primary motive behind shisha smoking among students of private universities of Karachi for discipline of MBBS, BDS, MBA, BBA, Engineering, Computer Studies and Psychology only. This was due to the fact that only respective universities offered themselves for evaluation and sample size was also limited due to the same reason. The results described in this study may further be improved by encouraging more and more respondents among various other institutes located in Karachi or other urban areas of Pakistan.

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ORIGINAL ARTICLE

In- Vivo Comparison of Anticonvulsant Effects of Gabapentin and Verapamil alone and in Combination with Diazepam on Acute Seizure Model

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ABSTRACT:

Objective: To compare in-vivo anticonvulsant effects of gabapentin and verapamil alone and in combination with diazepam in acute seizure model of mice.

Methodology: This experimental study was conducted in H.E.J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences, Karachi University, from May 2009 to July 2011.

Pentylenetetrazol (PTZ) was used in the dose of 90 mg/kg subcutaneously to induce acute seizures in mice. The test drugs Gabapentin (GBP) and Verapamil (VP) were administered by intraperitoneal route in six doses individually as well as in combination. The reference drug Diazepam (DZ), and test drugs were administered 40 minutes before PTZ intraperitoneally. The acute anticonvulsive activities of test drugs individually and in combinations were evaluated in-vivo by comparing with anti-seizure effects of reference drug DZ. After administration of PTZ, mice were observed for next 40 minutes for latency to onset of threshold seizures and for the presence or absence of seizure behaviors. The duration of seizures was divided into Rearing and falling (R & F) and Hind limbs tonic extensions (HLTE). R & F was the time calculated from beginning of seizure phase to rearing and falling of mice. HLTE was the time recorded from rearing and falling to development of generalized tonic clonic phase of seizure. The cut off time was 40 minutes.

Results: As individual treatment regimens the anti-seizure scores and mortality protection of GB: PTZ as well as VP: PTZ were significantly inferior to DZ in all seizure patterns, however, combination regimen of GBP:VP:PTZ in the last two higher doses exhibited highly significant antiseizure effects with 100% mortality protection which were equivalent to reference drug DZ.

Conclusion: The Combination regimen was novel and at higher doses exhibited potent acute anti-seizure activities equal in efficacy to DZ.

Keywords: Antiepileptic drugs, Gabapentin, Verapamil, Diazepam, Status epilepticus

Introduction:

Status epilepticus is a common neurological and life threatening medical emergency[1]. The patient is labeled as under status epilepticus when the patient has continuous rapidly repeated attacks of seizures without gaining consciousness between them. It must be treated or else it may cause serious damage to the brain and even death in many cases.[2,3] Despite the improvements made in managing status epilepticus patients, mortality is still very high, thus indicating that there is a substantial need to improve measures for both the prevention and effective management of this syndrome. There are various causes of status epilepticus including sudden withdrawal of antiepileptic drugs, central nervous system infections, high grade fever, hypoglycemia, brain tumors, refractory epilepsy, hypocalcemia, vitamin B deficiency and various metabolic abnormalities.

Lorazepam and DZ are the first line drugs, and only benzodiazepines recommended for the acute short term management of status epilepticus.[4,5] If the seizures are uncontrolled then Phenytoin, Phenobarbitone and Valproate are given intravenously for long term control of status epilepticus.[6,7] Many anti-epileptic drugs (AED) share potential drug-drug interactions and various harmful short term and long term side effects.[8,9]

GBP has established antiepileptic effects when used as an adjunct or monotherapy for partial as well as for generalized tonic clonic seizures. High doses of GBP are needed for improvement in seizure control, however, the high doses are mostly tolerable and its safety and tolerability is rated as good to excellent. Its major side effects are tremors, headache, ataxia, dizziness and somnolence.[10,11] Though VP is basically anti-hypertensive and anti-arrhythmia drug but its unique anti-seizure effects have been noted in pharmaco-resistance epilepsy and in patients of refractory epilepsy suffering from severe myoclonic epilepsy of infancy.[12,13] Verapamil when used as adjunctive therapy, controlled seizures including status epilepticus.[14] The present study was aimed to studyin-vivo comparison of anticonvulsant effects of gabapentin and verapamil alone and in combination with diazepam on acute seizure model of mice.

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METHODOLOGY:

This experimental study was carried out in Hussain Ebrahim Jamal (H.E.J.) Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, from May 2009 to July 2011. The use of animals was approved by the Institutional Scientific Advisory Committee. Male NMRI albino mice weighing 20-25 g, in a group of 12 were used,which had 80% power to detect differences in the means.

Experimental animals were divided into three sections, i.e. A, B and C. In each section, animals were divided into ten groups comprising of 12 mice each. In each section, Group I served as control and was given normal saline, group II received only PTZ 90mg/kg subcutaneously; groups III to VIII were treated with six different doses of tested drugs intraperitoneally.[15,16] Group IX, treated with DZ served as standard antiepileptic drug for status epilepticus, a single dose of 7.5mg/kg was given 40 minutes before administration of 90 mg/kg of PTZ.[17,18] Six groups of section-A received GBP in doses of 100, 200, 300, 400, 500 and 600mg/kg intraperitoneally.[19,20] Section B received VP in doses of 5, 10, 15, 20, 25 and 30 mg/kg by intraperitoneal route. Section C received combined GBP: VP in doses of 100:5, 200:10, 300:15, 400:20, 500:25 and 600:30mg/kg respectively, forty minutes before administration of 90 mg/kg of PTZ,as per recommended dose for international animal studies.[21,22] After injecting PTZ, mice were isolated and closely observed for next 40 minutes (2400 seconds) for latency to onset of threshold seizures (LOTS) and for the presence or absence of seizure behaviors. The mortality protection (number of mice survived) was recorded in percentage. This model of epileptic seizure was employed to induce status epilepticus. After administration of PTZ latent time (LOTS) was recorded, i.e., period (time in seconds or minutes) immediately after administration of PTZ or combination of PTZ with test drugs and before the beginning of first sign of seizure phase in mice, in order to determine threshold of seizures affected by PTZ and test drugs.Then, total duration of seizure behavior from the beginning to tonic clonic phase was recorded. We had split the complete duration of seizures into two behaviors; Rearing and falling (R & F) and Hind limbs tonic extensions (HLTE) for complete analysis of our results. R & F(time calculated from beginning of seizure to rearing and falling of mice) and HLTE(time recorded from rearing and falling to development of generalized tonic clonic seizure) were the actual duration of seizures induced by PTZ with or without test drugs. Period of 40 minutes was taken as seizure protection after administration of PTZ with or without tested drugs. The anticonvulsive effects of GBP and VP alone, or in combination regimen was evaluated in-vivo by recording durations of LOTS, R& F, HLTE and seizure protection in percentage, and then comparing with anti-seizure effects of reference drug DZ.

STATISTICAL ANALYSIS:

The statistical analysis was performed using SPSS version 17. Results were reported as mean±SEM.Data of seizure activity was analyzed by nonparametric Student's t-test and ANOVA with post hoc Dunnett's multiple comparison tests. The sequential differences among means were calculated at the level of $p<0.05$.

RESULTS:

Table-1 shows the results of section A experimental animals with the treatment of GBP: PTZ as a monotherapy from 100: 90 to 600: 90 mg/kg six doses. GBP: PTZ exhibited mortality protection from 41.66% in lower doses while the mortality protection increased to 66.66% in higher doses. Anti-seizure effects recorded in LOTS, R&F and HLTE of GBP: PTZ compared to PTZ induced seizures by t test have shown that results were highly significant. The reference drug DZ with PTZ exerted 0.00 anti-seizure score at the cutoff time of 2000 seconds in all three patterns of seizure behaviors

Table: 1
Seizure patterns recorded in the acute model of PTZ-induced seizures in mice following treatment with GB. Each value represents the Mean ± SEM of 12 animals per group

Group	Dose (mg/kg)	LOTS (sec)	R & F (sec)	HLTE (sec)	Mortality (%)	% of Mice Suffering from R & F	Mortality Protection %
Normal Control	0.9 % Saline	0.00	0.00	0.00	0.00	0.00	0.00
PTZ	90	184 ± 46	330 ± 50	686 ± 66	100	100	0.00
GBP : PTZ	100 : 90	230 ± 56 **d**	430 ± 77 **b,d**	0.00 **b,d**	0.00	75.00	100
GBP : PTZ	200 : 90	260 ± 62 **b,d**	480 ± 71 **b,d**	0.00 **b,d**	0.00	75.00	100
GBP : PTZ	300 : 90	330 ± 80 **b,d**	590 ± 125 **b,d**	0.00 **b,d**	0.00	66.66	100
GBP : PTZ	400 : 90	360 ± 73 **b,d**	760 ± 229 **b,d**	0.00 **b,d**	0.00	50	100
GBP : PTZ	500 : 90	590 ±76 **b,d**	930 ± 280 **b,d**	0.00 **b,d**	0.00	50	100
GBP : PTZ	600 : 90	740 ± 74 **b,d**	0.00 **b,d**	0.00 **b,d**	0.00	0.00	100
DZ : PTZ	10 : 90	0.00	0.00	0.00	0.00	0.00	100

n= 12
Values are mean ± S.E.M
LOTS= latency to onset of threshold seizures
R & F = rearing and falling
HLTE=hind-limbs tonic extension
b P ≤ 0.005 highly significant as compared to PTZ
d P ≤ 0.005 highly significant as compared to DZ

(Table-1).
Table-2 shows the results of section B experimental animals treated by VP: PTZ as a single agent therapy at six different doses from 5:90mg/kg to 30:90mg/kg.Values of LOTS, R&F and HLTE are shown. VP: PTZ groups in acute model of epilepsy exhibited 100% mortality in three lower doses however, in higher doses mortality reduced to 66.67%. The maximum mortality protection was 33.33% in higher doses and nil in lower three doses. Anti-seizure mean scores and mortality protection of VP: PTZ as a single agent when compared to reference drug revealed them to be significantly inferior to it in all seizure patterns (Table-2).

Table: 2
Seizure patterns recorded in the acute model of PTZ-induced seizures in mice following the treatment with VP.
Each value represents the Mean ± SEM of 12 animals per group

Group	Dose (mg/kg)	LOTS (sec)	R & F (sec)	HLTE (sec)	Mortality (%)	% of Mice Suffering from R & F	Mortality Protection %
Normal Control	0.9 % Saline	0.00	0.00	0.00	0.00	0.00	0.00
PTZ	90	186 ± 44	340 ± 50	700 ± 57	100	100	0.00
VP : PTZ	5 : 90	200 ± 19 **d**	400 ± 24 **d**	770 ± 45 **d**	100	100	0.00
VP : PTZ	10 : 90	230 ± 23 **b,d**	440 ± 32 **d**	880 ± 34 **d**	100	100	0.00
VP : PTZ	15 : 90	290 ± 19 **d**	500 ± 19 **d**	910 ± 19 **d**	83.33	83.33	16.33
VP : PTZ	20 : 90	320 ± 34 **a,d**	560± 39 **a,d**	940 ± 24 **a,d**	83.33	83.33	16.33
VP : PTZ	25 : 90	400 ± 48 **a,d**	630 ± 109 **a,d**	1010 ± 122 **a,d**	75.00	75.00	25.00
VP : PTZ	30 : 90	480 ± 54 **a,d**	700 ± 122 **a,d**	1100 ± 138 **a,d**	66.66	75.00	33.33
DZ : PTZ	10 : 90	0.00	0.00	0.00	0.00	0.00	100

n= 12
Values are mean ± S.E.M
LOTS= latency to onset of threshold seizures
R & F = rearing and falling
HLTE=hind-limbs tonic extension
a P ≤ 0.05 significant as compared to PTZ
b P ≤ 0.005 highly significant as compared to PTZ
c P ≤ 0.05 significant as compared to DZ
d P ≤ 0.005 highly significant as compared to DZ

Table-3 demonstrates section C experimental animal results. The Combined regimen of GBP: VP: PTZ exhibited mortality protection of 58%- 83.33% in first four doses, whereas, in 5th and 6th doses, the mortality protection was 100% in cut off time of 2400 seconds. The effect of last two doses was equivalent to reference drug DZ (Table-3).

Table: 3
Seizure patterns recorded in the acute model of PTZ-induced seizures in mice following the treatment with GBP: VP

Group	Dose (mg/kg)	LOTS (sec)	R & F (sec)	HLTE (sec)	Mortality (%)	% of Mice Suffering from R & F	Mortality Protection %
Normal Control	0.9 % Saline	0.00	0.00	0.00	0.00	0.00	0.00
PTZ	90	190 ± 49	365 ± 50	700 ± 55	100	100	0.00
GBP : PTZ	100 : 5 : 90	360 ± 30 [a,d]	510 ± 108 [a,d]	0.00 [b]	0.00	66.66	100
GBP : PTZ	200 : 10 : 90	420 ± 45 [b,d]	650 ± 196 [b,d]	0.00 [b]	0.00	50	100
GBP : PTZ	300 : 15 : 90	570 ± 37 [b,d]	980 ± 374 [b,c]	0.00 [b]	0.00	41.66	100
GBP : PTZ	400 : 20 : 90	750 ± 70 [b,d]	1230 ± 524 [b,c]	0.00 [b]	0.00	25	100
GBP : PTZ	500 : 25 : 90	1060 ± 72 [b,d]	0.00 [b]	0.00 [b]	0.00	0.00	100
GBP: PTZ	600 : 30 : 90	0.00 [b]	0.00 [b]	0.00 [b]	0.00	0.00	100
DZ : PTZ	10 : 90	0.00	0.00	0.00	0.00	0.00	100

n= 12
Values are mean ± S.E.M
LOTS= latency to onset of threshold seizures
R & F = rearing and falling
HLTE=hind-limbs tonic extension
a $P \leq 0.05$ significant as compared to PTZ
b $P \leq 0.005$ highly significant as compared to PTZ
c $P \leq 0.05$ significant as compared to DZ
d $P \leq 0.005$ highly significant as compared to DZ

DISCUSSION:

The rationale for selecting GBP and VP combination had many reasons including their reported characteristics of having inhibitory and modulating effects on the voltage-gated calcium channels of CNS.[23,24] GBP has inherent potential of antiepileptic properties which can be augmented if given in combination with other drugs like calcium channel blockers i.e. VP. GBP has been approved by the FDA as monotherapy for partial and complex partial seizures with or without generalized tonic-clonic seizures.[25,27] VP is a typical calcium channel blocker which is not an approved AED for the treatment or add-on therapy for epileptic disorders. However, in various research studies it has proved its blocking and inhibitory effects on voltage-gated calcium channels of CNS.[28,30]

We proposed that anti-seizure actions of GBP can be augmented or modified if given in combination with VP. Our study is supported by various animal and clinical studies. It was revealed that calcium channel antagonists possess anticonvulsant potential in experimental models of epilepsy and potentiate the protective activity of some AEDs.[31,32] Influx of Ca^{2+} into the neuron plays an important role in the genesis of epileptic seizures, and current research suggests that calcium entry blockers such as VP which blocks N- and P/Q-type calcium channels may have anticonvulsant activity by blocking effects on both these channels.[33,34] Amlodipine (at 10 mg/kg) reduced PTZ-induced clonic and tonic convulsions in mice and enhanced the anticonvulsant properties of Valproate and Phenobarbitone.[35] Nimodipine showed a decrease in seizure frequency in patients with intractable epilepsy caused by organic brain lesions when used in combination with other AEDs.[36,37] Modulating effects of Nimodipine and Nifedipine were observed in experimental convulsions in acute model of epilepsy in mice.[38] VP as a calcium channel blocker possessed anticonvulsant activity in acute model of epilepsy in mice.[39] Various studies observed significant enhancing anti-convulsant effects of calcium channel blockers on AEDs.[40] One clinical study showed successful treatment with intravenous calcium channel blockers in patients with continuous focal epileptic seizures intractable to conventional antiepileptic therapy.[41] Hence Ca^{2+} antagonists which penetrate the blood-brain barrier and bind to neuronal tissue may emerge in future as a novel class of anticonvulsants.[42] Hence, there are compelling reasons to state that present study has significant clinical potential. Our proposed objective was to compare the anti-seizure effects of GBP and VP as individual and combination regimens with DZ in acute seizure model in mice. We examined and analyzed the combination therapy from multiple dimensions in acute model of seizures.

In the present study, GBP as monotherapy exhibited mild to moderate anti-epileptic effect. Seizure protection by GBP at the doses of 100–200mg/kg, 300-400mg/kg and 500-600mg/kg was 41.66%, 50%-58.33% and 66.66% respectively. This shows that maximum seizure protection was 33.34% inferior to reference drug DZ.

Thus, GBP as individual drug failed to show significant anticonvulsant effects at all tested doses compared to DZ. VP alone demonstrated poor anti-epileptic effects in lower doses and mortality was 100%, however, in higher doses it exhibited insignificant dose dependent anti-seizure effects, much inferior to DZ. VP-treated group showed 33.33 % maximum seizure protection at the dose of 25-30mg/kg, which was very weak compared to DZ. When anti-seizure effects of combination therapy were compared to reference drug DZ, LOTS demonstrated that seizure inhibition was equal to the effects of DZ. However, in case of R&F, combination therapy of GBP and VP completely inhibited the seizure behavior at the dose of 500-600 mg/kg GBP and 25-30 mg/kg VP thereby, demonstrating that combination therapy in higher two doses was equivalent in efficacy to DZ.

Combination therapy of GBP with VP in six different doses in PTZ-induced acute seizures elicited seizure protection of 58.33%, 66.66%, 83.33%and 100 % respectively. The maximum anticonvulsant effects were seen in the groups receiving 500-600 mg/kg GBP / 25-30 mg/kg VP where in seizure protection of 100% was observed. While reference drug DZ exhibited 100% seizure protection/mortality protection and no seizure scores were observed in all three seizure behavior.DZ completely abolished the effects of PTZ. We compared the combined regimens of GBP/VP groups receiving 500-600 mg/kg GBP / 25-30 mg/kg VP doses with reference drugs D.Z. We observed no difference in seizure/ mortality protection. From the above discussion we are inclined to hold that the combination regimens exhibited zero seizure score and 100 % seizure/mortality protection at the last two higher doses and were equivalent to reference drug diazepam.

CONCLUSION:

In acute Model of epilepsy we observed that GBP as single therapy exhibited mild to moderate anti-epileptic effects. Our data has demonstrated that none of the doses of GBP as individual treatment regimens demonstrated 100 percent seizure protection. VP alone demonstrated poor anti-epileptic effects in lower doses and mortality was 100%, however, in higher doses it exhibited dose dependent anti-seizure effects and those were much far inferior to reference drug DZ and were insignificant. The combined regimen of GBP/VP regimen groups receiving higher doses when compared with reference drugs DZ we observed no difference in seizure protection. The mortality protection was 100 percent as exhibited by DZ, while all three seizure behavior characteristics results were equivalent to DZ. Combined regimens anti-seizure effects at higher doses were equivalent to reference drug DZ. It can reasonably be presumed that the instant regimens of GBP: VP may probably contribute to be the alternative regimens for the management of both status epilepticus and in resistance/refractory cases of status epilepticus. The combination regimens may have significant potential for short term and long term management of status epilepticus. Such query requires elaborate further in vitro animal studies as well as clinical trials.

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ORIGINAL ARTICLE

Comparative Effects of Combination Therapies; Methotrexate with Leflunomide & Sulfasalazine in the Treatment of Rheumatoid Arthritis

Qurrat-ul-Ain Bukhari[1], Moosa Khan[2], Kausar Moin Mirza[3], Muzna Hameed Dar[4]

ABSTRACT:

Objective: To study the role of combination therapies in the treatment of rheumatoid arthritis.

Methodology: This open-label, randomized 180-day clinical trial was conducted in the Department of Pharmacology and Therapeutics, BMSI and Medical unit ward 6, after approval of JPMC ethical committee, in which enrolled patients were 89. Patients were divided into two groups, A and B. 44 patients of group A received methotrexate (MTX) 7.5-20 mg/ week orally and Leflunomide (LEF) 10-20 mg/ day orally as maximally tolerated. 45 patients of group B were given MTX 7.5-20 mg/ week orally and Sulfasalazine (SSZ) 500 mg to 1 gm daily orally as maximally tolerated.

Result: Comparing the combination of group A with group B, group B showed highly significant improvement in mean swollen joint count (1.9±0.9) and morning stiffness (46.0=19.06) as compared to group A (2.9=1.71, 54.4=10.14). The drugs of group A showed significant improvement in mean pain (2.9= 1.71), physician's global assessment (2.80±0.97) and patient's global assessment (1.4=0.66) as compared to group B (1.9= 1.45, 3.8±1.22, 2.0=0.99). Therefore, our study revealed that patients receiving combination of MTX and LEF responded slightly better than MTX and SSZ. Both the combination treatments were well tolerated.

Conclusion: Both combinations of MTX & SSZ and MTX & LEF were well tolerated but the efficacy of MTX and LEF was marginally superior to combination of MTX and SSZ.

Key words: Rheumatoid Arthritis, Methotrexate, Leflunomide, Sulfasalazine, Disease Modifying Anti-rheumatic Drugs.

INTRODUCTION:

Rheumatoid arthritis is a chronic, systemic inflammatory disease that affects many tissues and organs, but mainly attacks synovial joints. The cause of rheumatoid arthritis is unknown; autoimmunity plays an important role in both its chronicity and progression. Rheumatoid arthritis is considered as a systemic autoimmune disease.[1] It affects 0.5-1% of population all over the world[2]. Studies from Nigeria, Indonesia and Africa showed lower prevalence than that reported from the western countries. The prevalence of rheumatoid arthritis in India is 0.75%. In the urban populatio of southern Pakistan, Karachi, its prevalence is 0.14%, whereas in northern Pakistan the estimated prevalence is 0.55%.[3] Women are three times more commonly affected than men. Onset is most frequent between ages of 40- 50 years, but people of any age can be affected.[4] If rheumatoid arthritis remain untreated, patients will become permanently disable.[5] Therefore, various treatments for rheumatoid arthritis are available. Analgesics and anti-inflammatory drugs, including steroids, are used to suppress the symptoms, while disease-modifying antirheumatic drugs (DMARDs) are required to inhibit the underlying immune process and prevent long-term damage.[6]

One of the new approaches has been the combinations of DMARDs. The increase in the use of combination therapies is due to the fact that monotherapy with DMARDs is often ineffective. Although, the use of combination therapies has increased, but it is not known that which combination therapy is most useful.[7] To address this question, we compared two combinations of DMARDS; methotrexate with leflunomide, and methotrexate with sulfasalazine. Methotrexate is on the World Health Organization List of Essential Medicine.[8]

Leflunomide is an immunosuppressive disease-modifying anti-rheumatic drug (DMARD).[9] Its uses include active, moderate to severe rheumatoid arthritis and psoriatic arthritis. Mechanism of action of leflunomide is inhibition of pyrimidine synthesis.[10] Sulfasalazine is a sulfa drug and a derivative of mesalazine, formed by combining sulfapyridine and salicylate with an azo bond. It is used in the treatment of inflammatory bowel disease, including ulcerative colitis and Crohn's disease, rheumatoid arthritis and other types of inflammatory arthritis (e.g. psoriatic arthritis). It is often well tolerated compared to other DMARDs.[11] It has also been used in the treatment of liver cirrhosis in chronic alcoholics, where it reversed scarring of tissue in clinical trials.[12] It is also used in idiopathic urtricaria not responding to antihistamines.[13] With this background, the purpose of this study was to compare the effects of combination therapies, methotrexate with leflunomide and sulfasalazine in patients of rheumatoid arthritis.

METHODOLOGY:

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This randomized, open-label, clinical trial was conducted in the Department of Pharmacology and Therapeutics, BMSI and Medical unit ward 6, with the approval of JPMC ethical committee for six months .

Patients of Rheumatoid arthritis of either sex, 30-60 years old, with 6-month history of active disease, and at least 3 of the following 4 features: erythrocyte sedimentation rate (ESR)>28 mm/hour, duration of morning stiffness ≥ 45 minutes, ≥ 8 tender joints, and ≥ 3 swollen joints, despite monotherapy with methotrexate since 6 months were included in the study. Written informed consent was taken from enrolled patients.

110 patients were enrolled, divided into two groups, A and B, with 55 patients in each group. Randomization was done by allocation ratio 1:1 and it was blocked at every sixth patient i.e. first three patients were given methotrexate and leflunomide; next three patients were given methotrexate and sulfasalazine[14]. Out of these, 89 patients completed the study, 44 patients in group A and 45 patients in group B. Group A (n=44) was treated by methotrexate 7.5-20 mg/ week orally and leflunomide 10-20 mg/ day orally as maximally tolerated. Group B (n=45) were treated by methotrexate 7.5-20 mg/week orally and sulfasalazine 500 mg to 1 gm daily orally as maximally tolerated.

The enrolled patients were evaluated every 7th day until 30th day, then every 30th day. If there was no improvement in symptoms at the 60th day of evaluation, it was considered as an ineffective treatment. If they improved, they were evaluated every 30th day for the duration of next 90 days and then after 90 days. Efficacy was assessed by patient's global assessment, physician's global assessmrnt, erythrocyte sedimentation rate, morning stiffness, Numeric pain scale scoring, number of tender joint count and number of swollen joint count. The pain of the patients was assessed by patient's global assessment. It was measured by visual analogue scale (VAS) from 0cm (no pain) to 10cm (severe pain) which was marked by the patient. VAS was horizontally placed on which patient was asked to mark from 0 cm to 10 cm[15] (Figure-1).

Figure-1: Visual Analogue Scale

0 cm	5 cm	10cm
No Pain		Worst possible pain

Pain assessed by physician's global assessment[16].

Physicians scored pain on a six-point scale of global assessment of arthritis. This scale consists of:

- 0= None- No pain.
- 1= Mild- slight, tolerable pain.
- 2= Moderate- pain causing discomfort.
- 3= Severe- unbearable pain.
- 4= Very severe pain.
- 5= Worst possible pain

ESR determines degree of non-specific inflammation in the body. It is governed by balance between pro-sedimentation factors, mainly , and factors resisting sedimentation, namely negative charge of erythrocytes (zeta potential). When an inflammatory process is present, the high proportion of fibrinogen in the blood causes red blood cells to stick to each other. The red cells form stacks called 'rouleaux,' which settle faster, due to their increased density.

The patients of rheumatoid arthritis who had morning stiffness,[17] of ≥ 45 minutes were included and evaluated. In baseline, most of the patients gave history of morning stiffness which persisted for two hours. Sometimes it lasted throughout the day. It was observed noticeably in the joints of fingers and hand; wrist, elbow, knee, ankles, feet, shoulder, hip, and jaw were also affected in different enrolled patients.

Tenderness and swelling were assessed as present or absent. Shoulder, elbow, wrist, metacarpophalangeal, proximal and distal interphalangeal joints and knee were examined.[18]

Numeric Pain Scale determined pain according to following score: 0-none, 1-3-mild, 4-6-moderate, 7-10-severe.[19]

Monitoring of toxicity: Before enrolment for the study, following investigations were done for all the patients: ECG, X-ray of chest and hands, liver function test, complete blood cell counts, ESR, urine D/R (Detailed Report) and at every follow-up visit. Patients were excluded from the study if their laboratory results were deranged.

Concurrent therapy with systemic corticosteroids was continued if dosage remained stable throughout the study period and patient took no more than 10 mg of prednisone (or its equivalent) per day. We also permitted non-steroidal anti-inflammatory drugs.

The data analysis was done by SPSS version 16.0.The results were given as Mean and Standard deviation (SD) for quantitative variables (age, duration of diseases, pain score, ESR, laboratory investigations etc.) and percentage/proportion for categorical qualitative variables (gender, complaints, ECG and x-ray findings, efficacy and side effects etc.). Efficacy and side effects were compared among treatment groups by Chi- square test. An analysis of variance (ANOVA) was used to compare the average change (mean ± SD) in outcome over treatment period among the two groups.

RESULTS:

Group A was randomly dispensed MTX and LEF, and B was treated by MTX and SSZ for six-month duration. At baseline, the difference in the age of the patients, disease duration, rheumatoid factor positivity, percentage

of females, and percentage of steroid usage in two treated groups were non-significant. The mean MTX dosage ranged from 16.0 to 17.0 mg/week. The mean SSZ dosage ranged from 1.5 to 1.6 gm/day. The mean LEF dosage ranged from 16.0 to 17.0 mg/day.

At the end of study period, that is 6 months, there was insignificant decrease in mean tender joint count in group B as compared to group A. However, there was highly significant decrease in mean swollen joint count in group B, when compared to group A. When mean patient's global assessment scale and mean physician's global assessment scale (for pain and quality of life) in group A were compared with group B, the decrease in both parameters was highly significant in group A. At the same time, there was non-significant decrease in mean erythrocyte sedimentation rate in both groups A

Table: 1
Comparative effects of Group A (MTX & LEF) and Group B (MTX & SSZ) in rheumatoid arthritis

PARAMETERS	MTX & LEF Vs MTX & SSZ	p-value
Tender joint count (maximum 38)		
Baseline (day 0)	14.5±7.22 13.7±7.08	>0.05
6 months	5.8 ± 3.71 4.0 ± 3.63	>0.05
Swollen joint count (maximum 38)		
Baseline (day 0)	11.3±4.59 8.6±4.37	
6 months	2.9± 1.71 ** 1.9 ± 0.9	**<0.01
Global assessment – Patient's (0-10 scale)		
Baseline (day 0)	5.2±0.76 5.6±1.64	>0.05
6 months	** 1.4 ± 0.66 2.0± 0.99	**<0.01
Global assessment – Physician's (0-10 scale)		
Baseline (day 0)	4.6±1.23 5.6±1.46	>0.05
6 months	** 2.8 ± 0.97 3.8 ± 1.22	**<0.01
ESR (mm/ hour)		
Baseline (day 0)	87.2±13.10 86.2±18.87	>0.05
6 months	56.5 ± 8.15 56.1 ± 10.41	>0.05
Morning stiffness (minutes)		
Baseline (day 0)	82.8±15.89 71.6±19.06	>0.05
6 months	54.4 ± 10.14 ** 46.0 ± 19.06	**<0.01
Pain (0-10 scale)		
Baseline (day 0)	5.4±1.26 6.0±1.65	>0.05
6 months	* 1.3±1.11 1.9±1.45	*<0.05

Significant p-value *<0.05, highly significant**<0.01
MTX=methotrexate, LEF=leflunomide, SSZ=sulfasalazine

Figure: 2
Comparison of group A (Methotrexate & Leflunomide) and Group B (Methotrexate & Sulfasalazine) after 6 months

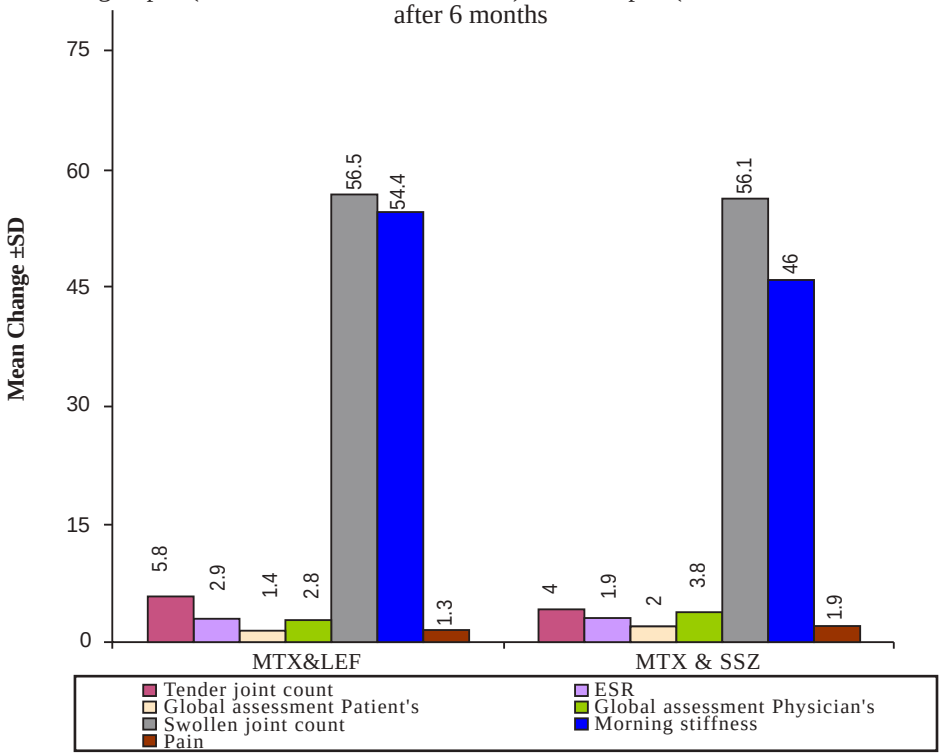

Table: 2
Observed side effects of combination therapies in rheumatoid arthritis patients

	Group A (MTX & LEF)	Group B (MTX & SSZ)
No. of patients	44	45
Headache	2(4.5%)	1 (2.3%)
Rash	1 (2.3%)	2 (4.4%)
Pneumonia	-	-
GIT distress	2 (4.5%)	2 (4.4%)
Weight loss	-	-
Total	5	5
Percentage of side effects	11.4%	11.1%

and B. A highly significant decrease was seen in the mean morning stiffness in group B when compared to group A. A significant decrease in mean joint pain in group A was observed when compared to group B (Table-1, Figure-2).

DISCUSSION:

Due to the advancement in pathophysiology of rheumatoid arthritis, its management is continuously evolving. Traditional DMARDs will undoubtedly remain the chosen initial treatment. Recent guidelines promote early and continued use of DMARDs.[20] Various studies demonstrate the effectiveness of combination therapy over monotherapy in the treatment of rheumatoid arthritis.[14] Most of DMARD therapies have a weakness that their comparison with active therapy have not been done.

The treatment of rheumatoid arthritis with MTX and LEF, and MTX and SSZ had already been established[21]. In the present trial, we compared the efficacies of these combination therapies. The results of the present trial proved the effectiveness, improvement in symptoms and slowing of progression of disease.

The study conducted by Dougados et al.[9] showed that the mean changes in the DAS during one-year-follow up of the study was -1.15, -0.87, -1.26 in the SSZ, MTX, and SSZ + MTX group respectively, in accordance with our study. This study showed the minimum advantage of combination of MTX and SSZ over other therapies, as it was indicated in our study that combination of MTX and LEF showed marginal benefit over combination of MTX and SSZ.

In another study,[22] combination therapy of DMARDs was prescribed. 199 patients with early and active rheumatoid arthritis were enrolled in this cohort study. The patients were initially randomized to receive the treatment with a combination of methotrexate, sulfasalazine and leflunomide with prednisolone or

treatment with single DMARD with or without prednisolone. The results of this study were also in accordance with our study by proving that combination of MTX and LEF was marginally benefited over combination of MTX and SSZ.

In contrast, Haagsma et al.[23] indicated that combination of methotrexate and sulfasalazine had no significant difference in comparison with monotherapy with either of the drug alone.

A randomized, double-blind, placebo-controlled trial[24] was also in accordance with our study, indicating the effectiveness of methotrexate and leflunomide therapy in the patients of rheumatoid arthritis. Adverse effects were mild or moderate similar to our study but the percentage was more i.e. 89.25%. In our study, adverse effects were only 11.4% (Table-2), this means our study showed better result both in terms of adverse effects and response of the patients.

CONCLUSION:

The patients of rheumatoid arthritis responded slightly well to the combination of methotrexate and leflunomide in terms of efficacy and safety.

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ORIGINAL ARTICLE

Comparison of Performance of Risk Assessment Tools for Low BMD and Fracture Risk Identification in Pakistani Women

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ABSTRACT:

Objective: To evaluate the efficacy of four risk assessment tools for identifying low Bone Mineral Density (BMD) in a sample of Pakistani females.

Methodology: It was a cross sectional study including 200 females above 40 years. DXA scans were performed. Subjects were categorized into low risk and high risk categories for low BMD on the basis of T scores. Questionnaires were filled and risk indices were calculated for all subjects. Sensitivity, specificity, positive and negative predictive values were calculated, Receiver Operating characteristic (ROC) curves were plotted and Area Under Curve (AUC) were obtained.

Results: A total of 200 females including 174(87%) postmenopausal, and 26(13%) premenopausal were included. Average age was 60.76±10.52 years with average age of menopause being 47.64±6.63 years. In terms of sensitivity, specificity and AUC, the WHO risk assessment tool FRAX showed the best performance with a sensitivity of 79%, specificity 94% and AUC of 0.869 for detecting low BMD.

Conclusion: It is not cost effective to use DXA for screening purposes. We propose that risk assessment tools such as FRAX may be utilized to identify individuals with low BMD. This may prove beneficial in minimizing the medical and social burden that fragility fractures pose to developing health care systems.

Keywords: Bone Mineral Density, Pakistan, Prediction, Risk Assessment tools, Screening

INTRODUCTION:

Osteoporosis is a silent disease commonly associated with aging. It is characterized by a decrease in bone strength or the bone mineral density.[1,2] A fragility fracture is usually the first sign bringing this condition to clinical attention. Such events may lead to consequent disabilities causing considerable morbidity and mortality.[3,4] Osteoporotic fractures are the cause of immense medical, economic and social burden in most Asian countries.[5] In Pakistan 9.91 million people are affected by osteoporosis, and these numbers are estimated to rise to 11.3 million by 2020.[6] There is no data available for hip fracture incidence in Pakistan. Osteoporosis remains largely underdiagnosed in this part of the world.[7] The International Osteoporosis Foundation has emphasized the need for development of fragility fracture prevention policies in Pakistan.[8]

DXA (Dual Energy X-ray Absorptiometry) is the WHO recommended gold standard technique used for diagnosing osteoporosis. Unfortunately this technique remains expensive and is not readily available in developing countries.[6] Amarnath et al reported overuse of DXA in low risk females and its underutilization among high risk females in a study published in 2015.[9] Furthermore, use of DXA for mass screening is not cost effective without the selection of a high risk population. A number of risk indices have been developed for this purpose.[10-12] These indices are based on the various risk factors that contribute to the development of low BMD and osteoporosis.

Therefore the objective of this study was to assess the utility of four of these risk indices namely OSTA, ORAI, OPERA and FRAX without BMD when applied to a sample of Pakistani women. The Osteoporosis Self-Assessment Tool for Asians (OSTA) was developed by a multicenter large population based study which was carried out in eight Asian countries by Koh et al. In this study risk factors pertinent to osteoporosis in postmenopausal women were assessed. A formula containing only two variables; age and weight was then derived.[10] It is a simple formula based index and has shown good sensitivities in different Asian populations.[13,14]

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Osteoporosis Risk Assessment Index (ORAI) utilizes three variables including age, weight and current estrogen use. The Osteoporosis Prescreening Risk Assessment Tool (OPERA) predicts low BMD on the basis of five variables, including previous fracture history and early menopause in addition to weight, age and steroid use. A person is considered at risk of low BMD if positive for two of these variables (Table-1). This index showed good validity in Italian postmenopausal women.[11] The WHO developed FRAX risk indicator is part of osteoporosis management guidelines in different countries. This is a web based calculator which computes fracture risk probabilities on the basis of a person's history.[15]

METHODOLOGY:

This cross sectional study was conducted from March to August 2016 at the Nuclear Medicine Department, Ziauddin Hospital, Clifton Campus, Karachi, after obtaining approval from the Ethics Review Committee of Ziauddin University. A total of 200 females above forty years of age were recruited by consecutive sampling technique, from the Gynecology OPD of Ziauddin Hospital. We excluded patients with any prior diagnosis or treatment for osteoporosis, malignancies with metastasis to bone or females having history of oophorectomy with or without hysterectomy and pregnant females.

After taking informed consent from all participants, their height, weight and BMI were recorded. Participants were interviewed and a questionnaire including information on demographic profile and risk factors of low BMD was filled for all subjects. DXA scanning was performed and BMD was estimated using Hologic Discovery Wi (S/N 88577) DXA Scanner. BMD was calculated from three sites including hip, spine (L1 to L4) and 33% of distal forearm (one third radius). Diagnosis of low BMD was based on the basis of the lowest T score observed for any of the three measured sites according to WHO recommendations. Participants were classified as either normal, osteopenic or osteoporotic according to the International Society for Clinical Densitometry (ISCD) guidelines. Categorization of postmenopausal women was based on T scores which represent the standard deviations by which the measured BMD differs from the mean BMD of a similar gender young adult. Z scores were used for premenopausal females which is the SD by which the measured BMD differs from the mean BMD of a healthy population of same gender and age. Postmenopausal women were categorized into three categories; normal females having T score $\geq$ -1 SD , osteopenic females having T score between -1 and -2.5 and osteoporotic females having T score $\leq$ 2.5 SD. Premenopausal females were divided into two categories on basis of Z score; normal BMD i.e. Z score upto $\pm$1.9 SD and low BMD i.e. Z score $\leq$ -2 SD. Four risk assessment tools (OSTA, OPERA, ORAI and FRAX without BMD) were calculated for each participant on the basis of information from the anthropometric data and questionnaires. Developer recommended cutoffs were used for each risk index. On the basis of these cutoffs participants were categorized into high and low risk groups for having low BMD. (Table 1)

Data was analyzed using SPSS version 20. Descriptive statistics (means, standard deviations, frequencies and percentages) were used to define the characteristics of sample. Sensitivity, specificity, positive and negative predictive values (PPV and NPV) were calculated on 95% confidence level. Sensitivity refers to the ability of a risk index to correctly classify persons at risk of low BMD (true positive fraction). Specificity was defined as the percentage of persons correctly classified as having normal BMD as low risk (true negative fraction). The PPV and NPV represent the proportion of females who were tested as having high risk or low risk on the basis of risk indices and who actually had low or normal BMD values respectively on DXA results. These values were calculated at T-score thresholds of -1 and -2.5 to determine their performance for predicting low BMD and osteoporosis respectively. The sensitivity, specificity, NPV and PPV were calculated separately for different anatomical sites (hip, spine and forearm). ROC curves were plotted for each index to graphically represent the overall accuracy of a test. Diagnostic accuracy of different tools was measured by the AUC.

RESULTS:

The average age of females in our sample was 60.7$\pm$10.52 years, ranging from 40 to 93 years. The average age at menopause was 47.6 years. 13% of the women were premenopausal and 87% of the sample comprised of postmenopausal women. The prevalence of low BMD was found to be greater among postmenopausal group. According to WHO criteria 55 women (27.5%) had normal BMD (T score>–1 for postmenopausal and Z score upto 1.9 SD for premenopausal women). 74 women (37%) were osteopenic (T score between –1 and –2.5 for postmenopausal and Z score = -2 SD for premenopausal women. 71(35.5%) were classified as osteoporotic (T score<-2.5). Table 2 represents the demographic data.

Table: 1
Risk Indices Description

RISK INDEX	RISK FACTORS	CALCULATION	CUT OFF VALUE
OSTA	Body weight, age	0.2x (body weight in kg – age in years): round off to the closest integer	< 2
ORAI	Weight, age and current estrogen use	Age ≥ 75 +15 Age 65–74 years +9 Age 55–64 years +5 Age 45-54 years 0 Weight <60 +9 Weight 60–69 kg +3 Weight > 70 0 Current estrogen use 0 No current estrogen use 2	Total score≥9
OPERA	Age, weight, low trauma fracture history, early menopause, steroid use	Age ≥ 65 years Weight < 57 kg History of low trauma fracture after age 45 Early menopause before 45yrs Steroid use> 6 months > 5mg/day Each factor carries 1 point	Total score ≥2
FRAX	Age, sex, ethnicity, weight, height, history of prior fractures, parental history of hip fracture, current smoking, glucocorticoid use, rheumatoid arthritis secondary osteoporosis, alcohol use	Computer based Algorithm Major Osteoporotic and Hip fracture risks were computed.	Age-specific fracture intervention thresholds were used.[16]

Table: 2
Study sample characteristics

Variables	Mean ± SD
Age of Patients	60.76±10.52
Age at Menopause	47.64±6.63
Height	155.02±6.33
Weight	69.25±15.32
BMI	28.74±5.79
BMD Hip	0.8194±0.15
BMD Spine	0.924±0.18
BMD Forearm	0.591±0.099
T-score Hip	-1.00±1.26
T-score Spine	-1.08±1.610
T-score Forearm	-1.58±1.616

Sensitivity, specificity, NPV and PPV for all tools was calculated at T scores of < -1 (low BMD) and at T score < -2.5 respectively. FRAX showed best sensitivities 79% and 83% for T score <-1 and <-2.5 at any one of the three measured sites. The sensitivities of the simpler tools; OSTA, ORAI and OPERA were 66%, 77% and 63% respectively for T score<-1. All four risk indices showed better sensitivities in detecting osteoporosis, T score<-2.5, but lower specificities were observed at this T score cutoff. All indices showed good PPVs at T score<-1 ranging from 89% to 97%. (Table 3)

Table: 3
Performance of Risk Indices by T score cut offs for any site

Tools	Any Site <-1				Any Site <-2.5			
	Se	Sp	PPV	NPV	Se	Sp	PPV	NPV
OSTA	66	78	89	47	80	60	49	86
ORAI	77	80	91	56	85	51	46	78
OPERA	63	96	97	50	68	63	48	80
FRAX	79	94	97	63	83	53	47	86

Se: sensitivity, Sp; specificity, PPV: positive predictive value, NPV: negative predictive value

BMD was calculated at three sites including hip, spine and the non-dominant forearm at T score <-1. These are presented in Table 4. All tools showed good sensitivities for detecting low BMD at hip, ranging from 70% for OPERA to 88% for FRAX. Overall, FRAX performed efficiently for low BMD detection at all sites with sensitivity ranging from 80% at the spine to 88% at the hip.

Table: 4
Performance of risk indices by BMD sites for low BMD

Tools	Total Hip				Spine				Forearm			
	Se	Sp	PPV	NPV	Se	Sp	PPV	NPV	Se	Sp	PPV	NPV
OSTA	77	65	65	77	69	62	67	64	69	70	79	58
ORAI	84	58	62	81	75	55	65	67	79	67	80	66
OPERA	70	72	68	75	65	73	72	65	63	79	83	57
FRAX	88	65	68	86	80	64	71	74	80	75	84	70

Se: sensitivity, Sp; specificity, PPV: positive predictive value, NPV: negative predictive value

Table: 5
AUC for the risk indices at T<-1 and T<-2.5 for any site

Tools	Area Under Curve (AUC)	
	Any Site <-1	Any Site<-2.5
OSTA	0.670	0.713
ORAI	0.781	0.676
OPERA	0.799	0.657
FRAX	0.869	0.680

Figure: 1
Receiver Operating Characteristics based on T score<-1 (low BMD)

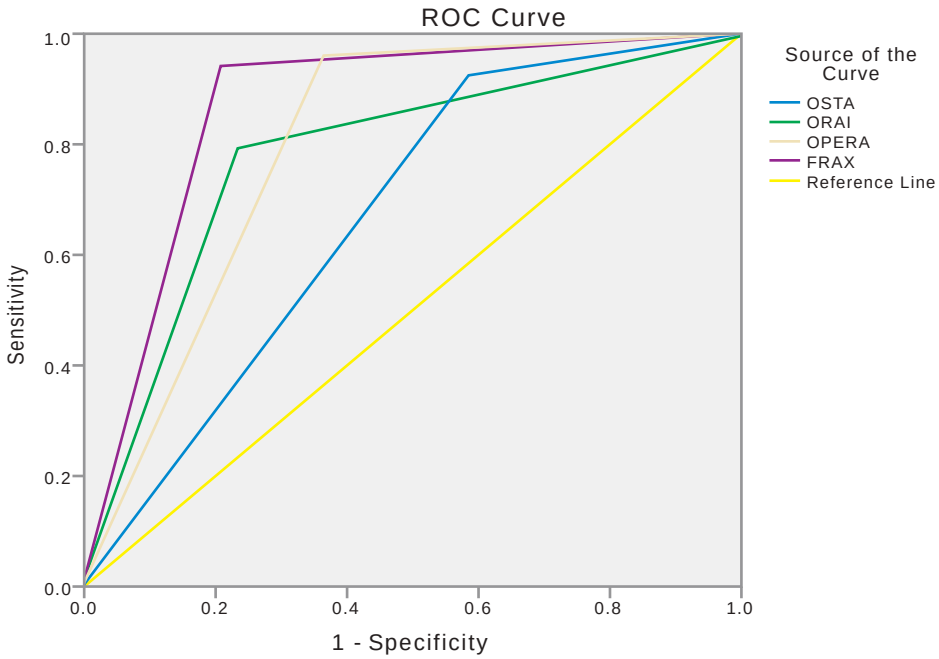

Figure: 2
Receiver Operating Characteristics based on T score<-2.5

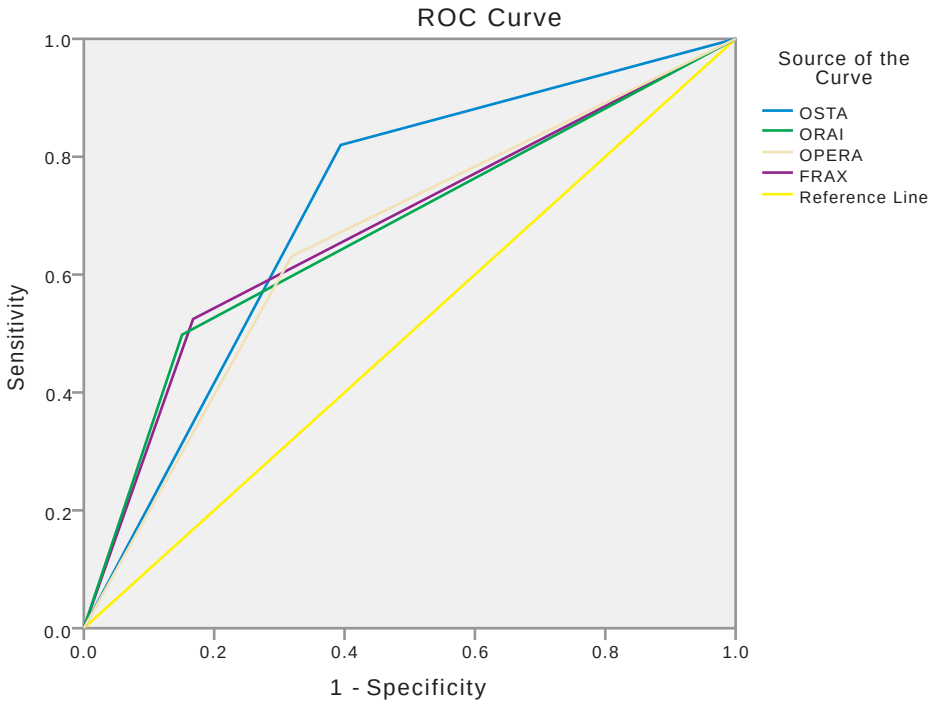

Table-5 represents area under ROC curves (AUC) values for the four risk indices by T score cut-offs. The AUC represents the diagnostic accuracy of a tool. It ranges from 0.5 for a non-informative tool to 1.0 for perfect concurrence. FRAX showed very good accuracy for detecting low BMD with AUC of 0.869. However, OSTA performed better than FRAX at T score<-2.5 (for osteoporosis) and an AUC of 0.713.

DISCUSSION:

Osteoporosis has been defined as a disease with high risk of fragility fractures accompanied by low BMD (T score< -2.5 SD) by the National Institute of Heath Consensus Conference. Low BMD values have been

found to be strongly correlated to hip fractures, the most devastating outcome of this disease.[18] It has long been debated that risk factors be included in osteoporosis diagnosis. This concept has led to the development of risk indices for identifying high risk individuals. WHO developed fracture assessment model FRAX has found its place in many national guidelines.[19]

In our study, FRAX showed high sensitivity for low BMD detection at all measured sites with 80% sensitivity at lumbar spine to 88% for hip. Among the simpler risk indices, ORAI also showed good sensitivities ranging from 75% at lumbar spine to 84% for total hip. The AUC was greatest for FRAX at T<-1, which is an indicator of its efficiency in detecting low BMD. However, for osteoporosis detection (T<-2.5), OSTA performed better than all other tools represented by AUC of 0.713.

These differences in risk indices performance may be explained by the fact that these indices have been developed in different population samples. The OSTA index was derived from a multicenter cohort comprising mainly Chinese population. This tool includes body weight as part of risk calculation.[10] Since weight is an anthropometric measure that differs substantially among populations, this tool might work more efficiently in one ethnic sample than another.[14, 20] Secondly OSTA was developed for identification of low BMD at the T<-2.5 in its development study,[10] this could be a reason for OSTA's relatively better performance at T<-2.5 in our study group. FRAX on the contrary is a country specific model with country specific intervention thresholds. The WHO Collaborating Centre at Sheffield recommends using country specific intervention thresholds which have been developed according to its hip fracture incidence and demographics.[14] Due to these factors and inclusion of multiple risk factors for generation of fracture risks FRAX showed better performance. FRAX had an AUC of 0.869 in our study which is comparable to the AUC of 0.79 for FRAX without BMD in American females[21] and AUC of 0.857 in Thai females.[22]

For a tool to be used for screening purposes, it should have an AUC of 0.7 or greater. The AUC for ORAI and OPERA were 0.781 and 0.799 respectively showing fairly good diagnostic accuracy for low BMD detection. These results are comparable to results from other studies assessing simple tools and comparing simple and complex ones.[13]

Dabbagmanesh et al reported a sensitivity range of 70% at spine to 80% at femoral neck for OSTA and a range of 73% at spine to 84% at femoral neck for ORAI which is comparable to our study.[23] Patel et al conducted a study including seventy two perimenopausal females in 2014. He reported 70% sensitivity and 85% specificity of OSTA for identifying T<-1 which is higher than our values of 66% and 78% respectively.[24] These slightly higher values may be due to the fact that Quantitative Ultrasound(QUS) was employed for BMD measures in his study while we used DXA in our study. Secondly, sensitivity and specificity values were calculated in a subgroup of 50 to 55 years in his study, while we calculated these values for the whole sample. Generalizability and practicability are essential characteristics of a good screening tool.[25] In our study we identified the best tool that may be applied to the whole high risk population which may prove as a more practical approach for screening purposes rather than advising different indices in different age groups.

Many studies have compared the power of complex models to simpler ones. Majority of them have concluded that simpler models like OSTA and ORAI provide similar or in some instances even better performance compared to the more complex ones like FRAX.[12,22,26] Our results reflect a greater AUC for FRAX, value >0.8 in predicting low BMD (T<-1). This value is slightly higher but comparable to that observed for ORAI and OPERA. Both of these models have values above 0.7 for T<-1 which reflects their considerable diagnostic accuracy. The OSTA tool showed not so good performance (AUC= .670) for T<-1. But it was the only tool to have an AUC above 0.7 for detecting osteoporotic females (T<-2.5). This may be explained by the fact that OSTA has been shown to have considerably good performance among older females who are more prone to exhibit osteoporotic T scores. Most of the studies reporting high diagnostic accuracies for OSTA have calculated the predictive power for T<-2.5, [27,28] while we have calculated these values for detecting low BMD i.e. individuals with osteopenia and osteoporosis(T<-1) and for BMD values of osteoporosis alone(T<-2.5). Secondly most of these studies were conducted on cohorts comprising of only postmenopausal older females while we included both pre and post-menopausal females above 40 yrs.[13,28,29] Mean age of Singaporean females in the study conducted by Chan et al was 68.4 ± 5.5years[13] which was considerably higher compared to mean age of our sample which was 60.7 years.

As with most studies, our study also had certain limitations. For instance, our study sample was recruited from females visiting outpatient department of a tertiary care. The subjects may differ from the general population in some ways. Another limitation was the small sample size due to budget constraints.

CONCLUSION:

Measuring BMD is undoubtedly the best method for low BMD detection. However, DXA screening of large population is not cost effective. The FRAX tool may be used for this purpose. The high specificity observed for FRAX and simpler indices may prove beneficial in identifying true negatives and thus lowering the overutilization of DXA by avoiding unnecessary exams.

In a country where the health care system is still developing, diagnostic and therapeutic facilities are not readily accessible to all people, such measures may prove to be advantageous. Further studies on a greater sample size are required for further assessment of the clinical utility of these risk indices

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ORIGINAL ARTICLE

Application of Hematological Indices for the Differential Diagnosis of Beta Thalassemia Trait and Iron Deficiency Anemia

Sajid Abbas[1], Shaista Khurrum[2], Tahira Zamir[3]

ABSTRACT

Objective: To apply various hematological indices for the differential diagnosis of ß-Thalassemia trait (ß-TT) and iron deficiency anemia (IDA).

Methodology: This retrospective descriptive study was conducted at Dar-ul-Sehat Hospital, Gulistan -e- Johar, Karachi. We retrospectively analyzed complete blood count (CBC) of 2480 patients, who came to the OPD for various problems during the year 2014 from January to December so as to identify hypochromic microcytic patients. Mentzer's index (MI), Shine and Lal index (S and L index) and Ehsani's formula were applied on the CBC report of identified microcytic hypochromic patients.

Results: It was found that among a total of 2840 patients, 385 (13.55%) patients were suffering from hypochromic microcytic anemia identified on their CBC report. These included 44 males (6.74%), 300 females (33.33%) and 41 (14.48%) children. Application of Mentzer's index (MI), Shine and Lal index (S and L index) and Ehsani's formula screened the hypochromic microcytic patients into patients suffering from ß-Thalassemia trait and Iron deficiency Anemia.

Conclusion: Application of hematological indices can be taken as the most useful method for differentiating ß-TT from IDA by simply considering CBC report.

Keywords: Hematological Indices, Iron deficiency anemia, ß-thalassemia trait, Mentzer's index, Shine and Lal Index, Ehsani's Formula

INTRODUCTION:

Anemia resulting from lack of sufficient iron to synthesize hemoglobin is the most common hematological disease in Pakistan. The World Health Organization (WHO) estimates that worldwide, 42% of pregnant women, 30% of non-pregnant women (aged 15-50 years), 47% of preschool children (aged 0-5 years) and 12.7% of men older than 15 years are anemic.[1] The most commonly encountered disorders with mild microcytic anemia are iron deficiency anemia (IDA) and ß-thalassemia trait (ßTT).[2] Iron deficiency anemia is most commonly associated with inflammatory bowel diseases, pregnancy, menstruation, lactation, surgery, physical trauma, vegetarians and children who drink more than 16-24 ounces a day of cow milk.[3] Without enough iron, body cannot produce enough hemoglobin in red blood cells that enables them to carry oxygen.[4] On the other hand, ß-thalassemia trait is a hereditary microcytic hypochromic anemia characterized by the production of abnormal hemoglobin. Approximately, 1.5% of the world's population is a carrier for ß-thalassemia trait. It is a carrier state in which only one allele is mutated. Individuals with the ß-thalassemia trait are usually asymptomatic and may be unaware of their carrier state unless diagnosed by investigations.[5] It is the most common type of hemoglobinopathy transmitted genetically. According to one study, 8 million people are carriers of thalassemia in Pakistan.[6]

It has been observed that the CBC (Complete Blood Count) results of both these types of microcytic anemia usually overlap. Traditional approach followed by most general practitioners is a trial of iron treatment which imposes a significant burden on global healthcare.[7] A definitive differential diagnosis between ß-TT and IDA is based on the result of HbA_2 electrophoresis, serum iron levels, and a ferritin calculation.[8] Many formulas have been proposed by researchers having the ability to differentiate iron deficiency anemia from ß-thalassemia trait (Table-1). These formulas include a minimum of two CBC parameters in various combinations. The only purpose of using CBC indices for the discrimination of microcytic hypochromic anemia is to reduce unnecessary investigation cost of iron therapy and problems of iron overload.[9] It is simple and inexpensive tool to give a clue to differentiate both diseases and identify patients who require follow up and counseling.[10] In outpatient department (OPD) of one local hospital especially in Pakistan where resources are limited, the exclusion of thalassemia minor could be achieved mathematically using the CBC indices.[11] In this study, Mentzer's index (MI), Shine and Lal index (S and L index) and Ehsani formula were applied on the CBC report of these identified microcytic hypochromic patients.[12]

METHODOLOGY:

This retrospective descriptive study was conducted at

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Dar-ul-Sehat Hospital, Gulistan-e- Johar, Karachi for a period of 1 year from January 2014-December 2014. We retrospectively analyzed Blood CBC of 2480 patients who came to the OPD for various problems. None of them had received a transfusion or had an acute bleeding episode in the previous month. Patients included were males, females and children (less than 14 years of age). Blood samples were collected in EDTA anticoagulant tubes. Automated cell counter was used for CBC test at Dar-ul-Sehat Laboratory for hematological testing. Patients of Microcytic Hypochromic anemia were identified after analyzing CBC reports using WHO standard cutoff values.[13] Hematological indices were then calculated for each case so as to make differential diagnosis of patients either as iron deficiency anemia or ß-Thalassemia Trait.

RESULTS:

Among 2480 patients who reported to the OPD, 900 patients were males, 1200 females and 380 children. Their CBC report was analyzed retrospectively for identification of anemia. It was found that 385 (13.55%) patients were suffering from hypochromic microcytic anemia. These included 44 males (6.74%), 300 females (33.33%) and 41 (14.48%) children (Table-2). We applied Mentzer's index (MI), Shine and Lal index (S and L index) and Ehsani formula on the CBC report of these identified microcytic hypochromic patients.

Table: 1

Hematological Indices and Mathematical Formula used to differentiate between IDA and ß-TT[14]

Hematological index	**Formula**
Mentzer index (MI)	MCV/RBC
RDWI	MCV × RDW/RBC
Shine and Lal (S and L)	MCV × MCV × MCH/100
Srivastava	MCH/RBC
Green and King (G and K)	MCV × MCV × RDW/Hb × 100
Sirdah	MCV - RBC - (3 × Hb)
Ehsani	MCV - (10 × RBC)
England and Fraser (E and F)	MCV - (5 × Hb) - RBC - 3.4
Ricerca	RDW/RBC
MDHL	(MCH/MCV) × RBC
MCHD	MCH/MCV

MDHL index: Mean Density of Hb/Liter of blood; MCHD index: Mean cell Hb Density

Table: 2

Data of patients included for CBC report

S. No	Number of Patients (N=2840)	Age Range (Years)	Normal	Microcytic Hypochromic Anemia	Percentage (%)
1	Male 900	15-60	652	44	6.74%
2	Female 1200	15-60	900	300	33.33%
3	Children 380	Less than 14	283	41	14.48%

According to Mentzer's index, 41 (93%) men presented with IDA, 3 men (7%) presented with ß-TT (7%), 293 females (97.66%) presented with IDA, 7 (2.33%) females presented with ß - TT, 37 (90.24%) children presented with IDA, 4 children (9.75%) presented with ß- TT

Table: 3
Differential Diagnosis of Patients based on Mentzer's Index (MI)

Gender	IDD	Percentage (%)	ß-TT	Percentage (%)
Male	41	93 %	3	7%
Female	293	97.66%	7	2.33%
Children	37	90.24%	4	9.75%

According to Shine and Lal index (S and L index), 39 (88.63%) men presented with IDA, 5 (11.36 %) men presented with ß -TT, 292 (97.66%) females presented with IDA, 8 (2.66%) females presented with ß-TT. Children who had IDA were 38 (92.68%) and those with possible ß-TT were 3 (7.31%)

Table: 4
Differential Diagnosis of Patients based on Shine and Lal (S and L) index

Gender	IDD	Percentage (%)	ß-TT	Percentage (%)
Male	39	88.63 %	5	11.36%
Female	292	97.33%	8	2.66%
Children	38	92.68%	3	7.31%

According to Ehsani's formula, men presented with IDD were 41(93.1%), presented with ß-TT were 3 (6.8%), women who suffered from IDA were 296 (98.6%), had ß-TT were 4(1.3%), children who were found to have IDA were 39(95.1%) and possibly had ß-TT were 2 (4.8%).

Table: 5
Differential Diagnosis of Patients based on Ehsani's formula

Gender	IDD	Percentage (%)	ß-TT	Percentage (%)
Male	41	93.1 %	3	6.8%
Female	296	98.6%	4	1.3%
Children	39	95.1%	2	4.8%

DISCUSSION:

Differentiation of iron deficiency anemia from thalassemia minor is clinically significant because each disease has entirely different etiological factors, management, genetic counseling and dietary plan. In addition to genetic counseling, in case of thalassemia carriers, iron therapy is warranted because the thalassemia heterozygote should not be given iron to normalize MCV.[15] Health experts claim that approximately 5000 children are diagnosed with Thalassemia major every year in Pakistan. On the other hand iron deficiency anemia is more common in children and adult women especially during reproductive time period. Diagnosis of ß-Thalassemia trait is established by the presence of characteristic RBC microcytosis and elevated levels of serum iron (SI), transferrin saturation (TS) and ferritin with increased levels of HbA2.[16] Decreased levels of SI, TS and ferritin with increased levels of SBC are the main diagnostic criteria for IDA.[17] A variety of formulae and indices have been proposed to facilitate the screening procedure of iron deficiency anemia and ß-thalassemia trait like Mentzer's index, England and Frasen, Shine and Lal, and Ehsan and Shrivastve formulae.[18] These formula can be taken as the most reliable and predictive for differential diagnosis of iron deficiency anemia from ß-Thalassemia trait by simply considering CBC. Moreover, these can be helpful in preventing the fatal disease, ß-Thalassemia major.[19] Different RBC indices can correctly identify 61-91% of patients with microcytic anemia.[20]

In our study, we successfully applied three formulae on large number of patients coming to Dar-ul-Sehat hospital and diagnosed to have microcytic anemia so as to differentiate them into IDA and ß-TT.

Results of our study indicated that 54.55% of the population including male, female and children were suffering from microcytic hypochromic anemia and application of these various formulae on the CBC indices of these patients successfully identified patients of IDA and ß-TT.

In 2009, Ehsani et al showed that the best discrimination index according to Youden's criteria was the Mentzer index (90.1%), followed by Ehsani index (85.5%).[21]

According to our results, percentage of patients diagnosed varied with various formulae. None of the formula was found superior to other in terms of percentage.

In 2007, Saud et al in their research work applied nine formulae of RBC indices on a population of 153 confirmed cases of microcytic anemia and measured validity using Youden's index. They found that the E and F index had the highest Youden's index (98.2%), specificity and sensitivity in correctly differentiating IDA and Thalassemia minor patients.[22] Fakher and Bijan[23] also applied various formulae on 323 confirmed cases of microcytic anemia and showed that the S and L index had the highest Youden's index (89%) in patients younger than 10 years of age while RDW and RBC indices have the highest Youden's index 93% and 90% respectively in patients older than 10 years of age. Nitaios et al used six indices for differentiation between 373 patients of microcytic anemia and found that G and K index had the highest reliability, followed by E and F, RBC Count, MI and RDWI. RDW completely failed to differentiate between IDA and TT.[24]

Beyan et al in 2007 identified 66 cases of ß-TT and 45 cases of IDA. Patients and groups were evaluated according to RBC, MI, S & L, E & F, S I, G & K and Ricevca index. They concluded that none of these formulae is superior in differentiating IDA from ß-TT and total body iron and HB A2 level should be obtained for accurate differential diagnosis.[25] The results of our study were in accordance to the results of Beyan et al.

All formulae used should have a good sensitivity score so as to detect maximum number of patients and these should be able to eliminate as many other patients as possible to avoid false positive results. The formulae we have used have high sensitivity and specificity as confirmed by various researchers.[26]

CONCLUSION:

According to our study, these hematological indices can be useful for differential diagnosis of ß-TT from IDA by simply considering CBC report. This can be helpful in preventing ß-thalassemia major disease and iron overload in future.

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ORIGINAL ARTICLE

Evaluation of the Integrity of Amalgam-Composite Interface with Two Resin Based Intermediate Materials

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ABSTRACT:

Objective: To evaluate the effect of intermediate materials at Amalgam-Composite interface.

Methodology: This *in-vitro* study was conducted at IRCM COMSATS Lahore**.**100 High copper-Spherical amalgam (Aristalloy) specimen were stored in deionized water for two weeks. They were randomly assigned to one of the following groups after being polished. Control Group comprised of fifty bars of Amalgam bonded to Hybrid composite(SolareXGC) with Amalgam bonding agent (Framingdale NY-USA). Experimental group comprised fifty bars of Amalgam bonded to composite with resin modified glass ionomer cement (GC Fuji).The shear bond strengths were tested using the Universal testing machine at acrosshead speed of 0.5mm/min.

All the collected data was entered in SPSS version 19.0. ANOVA was used to determine the mean SBS (Shear Bond strength) values of control and experimental groups**.**

Results: On comparison, there was no significant difference in the bond strength of Amalgam-Composite interface with Amalgam Bonding Agent and Resin Modified glass Ionomer cement.

Conclusion: There is less significant effect of type of the adhesive on interfacial integrity, rather it is based more on the adhesive's thickness, method of application and other manipulative variables.

Keywords: Amalgam, Composite, Interface, Shear Bond strength, Resin Modified Glass ionomer Cement, Amalgam Bonding agent.

INTRODUCTION:

Dental amalgam is known as the reliable and durable restorative material for more than a century.[1]Good mechanical properties, wear resistance, sealing ability, ease of handling and cost effectiveness,[2] make it an important part of dental care plan in the developing nations where there is a lack of funded health policy for dental diseases.[2,3]

The grey or the metallic color of restoration gives unaesthetic look to the tooth. The other reasons behind replacement of Amalgam restorations include; secondary carries, marginal fracture, wear, and loss of anatomic contours.[4,5] These factors may be compounded by the presence of undermined enamel.[6] Therefore total replacement of defective and unaesthetic amalgam restorations represents a major part of restorative treatment. Dentistry's attempts to compensate these issues are the development of composite resins and bonding agents.[7,8]

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Composite resin provides an esthetic alternative to the dental amalgam. Its adhesion to the tooth structure is facilitated by dentine bonding agent which forms an effective bond at the tooth-composite interface and strengthens tooth structure by minimal intervention during placement.[2] With a variety of shades, translucencies, effects, opacities, and innovative placement techniques, today's composites allow simple reproduction of dynamic properties of natural dentition.[9] Concerns of bonding breakdown due to polymerization shrinkage and low strength in large restoration, still favor the placement of dental amalgam.[10] Bonding agents originally developed for composites only, are now being formulated to improve the bond strength at the tooth-amalgam interface. Reduction of microleakage is another benefit. The reason is their adherence with hydrophobic amalgam and the hydrophilic enamel of tooth. Their sealing ability reduces secondary caries, staining and sensitivity.[3,7] Various generations of bonding agents are available.[11] Combined amalgam composite or "Amalcomp" could be a solution to the problems related with both materials. The blend of esthetics of the composite with good mechanical properties of amalgam improves microleakage at the interface. Better marginal adaptation results due to sealing by an intermediate material. Composite reinforcement of the weakened tooth increases fracture resistance due to minimal invasion.[2] This is an alternative option for treatment of defective and old amalgam restorations. Repair involves removal of defective tissue adjacent to the defective area and restoration of the prepared site. This procedure allows preservation of sound tooth structure and allows only minimal intervention. Multiple factors influence Bond strength values such as type and age of tooth, mineralized content of dentin, and type of test and storage media.[5,12] Amalgam bonding systems and resin modified glass ionomer are used to bond amalgam to the composites.

They form a micromechanical bond between amalgam and composite resin. They are composed principally of 4-META (4-Methacryloxytrimellitic Anhydride) like other dental adhesives, but with additional Poly-methyl-methacrylate (PMMA).[2,7]

Resin modified glass ionomer is applied as a thin intermediate layer between the two materials.[7] It serves multipurpose functions; to mask the restoration by opacifying amalgam background,[13] it provides adhesion between amalgam and composite and, also prevents microleakage.[14]

If the existing amalgam is repaired, it will also save time taken otherwise to remove the restoration, and cost of complete resin restoration.[15,16] Bond strength values are determined by tensile analysis and shear analysis. Shear Mode of analysis can detect local bonding conditions and provide accurate results.[17] Less shaping of the specimen reduces risk of early failure and high coefficient of variation.[18] The durability of bond strength between composite resin and amalgam is still controversial and little is known about it.[7] Therefor, there is a need for further studies to be conducted to elaborate this subject.

METHODOLOGY:

This *in-vitro* study was conducted at IRCM COMSATS Lahore. 100 specimens were taken, which were divided into 2 groups. Group A (Control group) Amalgam bonding agent and Group B (Experimental group) Resin modified glass (low).

Preparation of Amalgam-Composite samples:

Specimens consisting of amalgam and resin composite bars with a thin layer of intermediary material between them were fabricated as follows:

100 bar samples of High copper spherical Amalgam Alloy-31% copper (Aristalloy, cookson Birmingham, UK) were prepared using PTFE split (Poly tetra Flouro-ethylene) molds (fig-1.1). Pre-proportioned Amalgam capsules were triturated in an SDS Kerr 4000 amalgamator (Kerr Hawe) according to the manufacturer's instructions and condensed into the mold space (2x4x2) to serve as matrix. In all the samples, amalgam was condensed using a serrated round condenser with a diameter of 1mm by a single operator to ensure standardization. The alloy samples were allowed to set for 30 minutes prior to mold removal.

In control group, surfaces of amalgam samples were treated with amalgam bonding agent (Parkell, Farmingdale, New York). All samples were etched with 37% Phosphoric acid and rinsed with air water syringe and air dried after 15 seconds. Amalgam Bonding agent was then light cured through the mold for 20 seconds with a 500mw/cm.^{2} output hand-held curing light (Belle glass, Orange, CA, USA). Surfaces of the samples in experimental group were treated with Resin modified glass ionomer cement (luting-GC Fuji Corporation.). Manufacturer's instructions were followed accordingly. Finally the samples were Photo activated for 20 seconds with a curing lamp.

The samples (fig-1.2) were allowed to set for 24 hours at room temperature and then subsequently abraded with 400 grit Silicon Carbide burrs to eliminate possible contaminants and cause surface roughness for the retention of the adhesive systems. All specimens were then air dried for 24 hours and subsequently stored in deionized water for 1 week at 37^{o}C in drying oven (WiseVen WOF-15509525003). Fractured, broken or samples with varied dimension were excluded from the study. They were divided randomly into control and experimental groups.

The amalgam-composite slabs were stored in deionized water for one week to simulate aging, prior to their assembling on PMMA Base. PMMA (Poly-methyl-methacrylate) l discs were prepared manually with a recess of 4x4x4 in the center for fixation of amalgam-resin samples. The whole assembly was allowed to polymerize sufficiently at room temperature for 24 hours.

Shear Bond Strength Testing: The samples were examined under digital microscope (Optika-B-600 MET) at 50X magnification with digital camera (Optikam-PRO 5-Model-4083.12 LT) to ensure the inclusion criteria (Fig-2.2). The specimens were checked for the presence of cracks, asperities and interfacial gaps to avoid pre-test failures.

The sample Assembly (fig-2.1) was locked in a fixture attached to the compression load cell of an Instron testing machine (fig-2.3: Instron Corp, Canton MA, USA, Model, 1195) with 1KN load cell moving at a cross head speed of 0.5mm/min until fracture. Magnifying glass was used before the application of load to determine the focus of load cell on the interface. The shear forces were recorded in MPa and were obtained directly from Instron computer software.

RESULTS:

Table-2 shows the descriptive analysis and comparison of control and experimental group. Using ANOVA (table-3), it was also concluded that there was no statistical difference in the mean of all four study groups (p-value = 0.971).

The mean SBS (Shear Bond Strength) value in Amalgam-composite samples with ABA as an intermediate material (Control group) was 3.02 ± 0.84 whereas, in Amalgam-Composite samples with RMGIC as an intermediate material (Experimental group) the mean SBS was 2.93 ± 0.

Table: 1
Intraoral adhesive systems used in the study

Material	Material Description	Composition	Manufacturer
Control group Amalgam bond plus (ABA)	Light cured etch and rinse system	4-META(4-Methacryloxyethyl trimellitic Anhydride), Bisphenoldimethacrylate, HEMA(hydroxyethyl Methacrylate, tri-ethylene glycol methacry late, silver filler	Parkellfarmingdale, NY.USA
Experimental group RMGIC	Light cure	Flouroaluminosilicate glass and poly-acid modified liquid with HEMA and water	Luting-GC Fuji

Table: 2
Descriptive analysis and comparison of SBS in Control (Amalgam bonding agent) and Experimental groups (Resin modified glass)

	Amalgam bonding agent Control group	Resin modified glass ionomer Experimental group
N	25	25
Mean	3.02	2.93
Std. Deviation	0.84	0.65
Std. Error	0.17	0.13
95% C.I for Lower	2.67	2.67
Mean Upper	3.37	3.20
Minimum	1.40	1.60
Maximum	4.40	4.30

Table: 3
ANOVA

	Sum of Squares	Df	Mean Square	F	P-value
Between Groups	0.143	3	0.048	0.079	0.971

Figure: 1.1
PTFE Mold used for specimen preparations

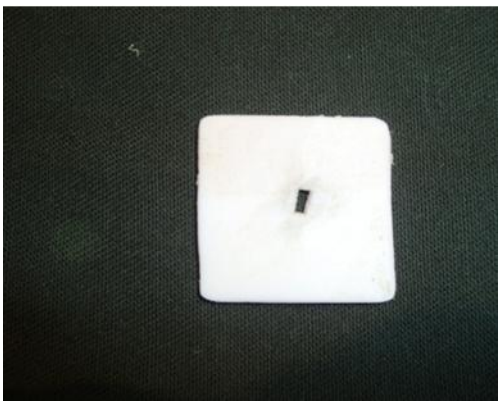

Figure: 1.2
Amalgam composite samples

Figure: 2.1
Amalgam-Composite Specimen

Figure: 2.2
Microscopic image of Amalgam-composite interface
Mounted on the PMMA Base

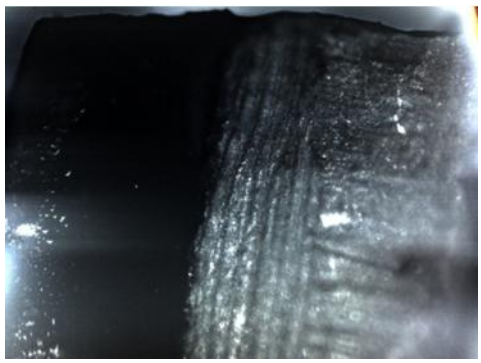

Figure: 2.3
Sample Assembly fixed in Instron
(Universal Testing Machine)

DISCUSSION:

Suggested techniques used for amalgam repair or veneering are based on mechanical or chemical procedures. Mechanical techniques include roughening the amalgam with undercuts and grooves through burrs. Chemical techniques include use of multipurpose adhesives.[14,20,21]

The present study was based on the concept of reinforced Amalcomp restorations by using adhesive/intermediate material. Adhesives are used due to their ability to bond porcelain, resin composite, alloy and amalgam to enamel and dentin. Further, they have been used in the similar studies on amalgam bonding.[19, 20] They seal dentin and reduce microleakage and consequently the pulpal sensitivity. That is why they are known to increase interfacial bond strength in combined amalgam-composite restorations.[22]

Enhanced bond strength values demonstrate good interfacial integrity, along with reduction in marginal leakage and associated issues like sensitivity, pulpal changes and the development of secondary caries , the most common reason for failure of amalgam restorations.[23,24]

The ultimate objective of determination of bonding capacity is the prognosis of deterioration of the interfacial bond with time as function of environmental conditions.[25] Mode of bond strength testing has few limitations as shear stress is not evenly distributed and focused on true interface.[26, 27] But less aggressive specimen preparations reduces the risk of early failure and high coefficient of variation therefore shear analysis is usually preferrred.[18]

Adhesives used in the current study included Amalgam bonding agent and Resin Modified Glass ionomer cement (RMGIC). The choice of these materials was based on the fact that they perform well in terms of interfacial strength. Amalgam bonding agent is recommended by the manufacturer for critical situations, where mechanical retention is deficient and additional bonding is required. The powder consists of Poly-methyl-methacrylate fibers, which improve bond strength through mechanical union between amalgam and the composite.[28, 29]

Evidences have been reported by the studies that adhesives with 4-META and PMMA powder produced significantly higher Shear bond strength.[19,21,30,31] But still the existence of true chemical bond is controversial and bond strength studies have contradictory results.[1,14,32]

The other adhesive used in this study was RMGIC. The

choice of material was based on the demonstrated use of certain glass ionomer formulations as an adhesive with amalgam.[23,33] Available data suggested 4-META/HEMA based bonding agents.[23,33,34] could be beneficial for composite veneering of amalgam, if preceded by intermediates like adhesives or RMGIC.[21] RMGIC as a liner reinforces the interface of amalgam and composite.[35] It has been observed as an effective esthetic material and adhesive than resin bonding systems for combined restorations.[22,36]

It has been suggested that glass ionomer during its initial reaction phase adheres chemically to the base metals, especially silver and tin. This ensures marginal sealing and reduced marginal leakage in the clinical cases.[35] The basis of selection of RMGIC in this study[37] was its association with increase in fracture resistance of teeth with combined restorations.[38,39,40] Mechanically RMGIC showed substantial plastic deformation in compression, due to its polymeric nature overcoming the shortcomings of crazing on dehydration, brittleness and low fracture resistance in conventional GIC.[37]

One limitation of this veneering technique was the production of an additional amalgam-composite interface apart from the tooth amalgam-interface, because there was no chemical interaction between the two. RMGIC filled the interface with a compatible material.[2,13,41] The mean values of Shear Bond Strength in control group (Amalgam bonding agent) and experimental group (RMGIC) showed no statistical difference between the two groups. The reason could be the variation in the mechanical properties of the luting agent (RMGIC) and shorter storage time of samples which resulted in lack of complete curing of the samples and affected mechanical strength.[37]

Additionally, presence of HEMA in RMGIC although improved bonding, but it could cause cross-linking of polyacid chains too far apart, which effected the integrity of material.[37] Therefore manipulative variables have been proved to have more detrimental effect on SBS values than the chemistry only.

CONCLUSION:

Adhesive bonding at Amalgam-composite depended more on manipulative variables. They included factors based on adhesive's manipulation, which encompassed water-powder ratio (RMGIC), thickness of adhesive and mode of curing; and factors based on the bonding substrates, which comprised sample geometry, dimensions, preparation methods, surface abrasion and duration of aging. Storage in water caused hydrophilic degradation of the interface while short term aging just gave the baseline values.

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COMMENTARY

Chikungunya Fever

Hina Wasti[1], Shomaila Farman[2], Uzma Naseeb[3]

ABSTRACT:
Chikungunya fever is caused by the chikungunya virus (CHIKV), a mosquito-borne emerging pathogen, which was first revealed on the borders of Mozambique and Tanzania in 1952. Currently it is stretched over 40 countries globally. It is an arthropod-born virus endemic in Africa, Southeast Asia and India. Aedes aegypti and Aedes albopictus are the mosquito vectors which spread this virus. Blood, saliva and urine are the samples for investigation. Since there is no definite treatment available, identifying ways to abolish mosquito populations is the most useful strategy to control the disease. As the virus has facility for global spread, there is need to take preventive measures as well as rapid diagnostic tests to improve identification of Chikungunya patients.

Keywords: Aedes mosquito, Chikungunya fever, IgM antibody, Severe sepsis, Vector-borne infections.

INTRODUCTION:
Chikungunya fever is caused by the chikungunya virus (CHIKV), a single stranded (+) RNA virus, belonging to the genus Alpha virus of the Togaviridae family. The word Chikungunya, comes from the Bantu language of Makonde people of northern Mozambique and southeast Tanzania, meaning, "That which bends up", ascribing to the stooped posture which develops due to arthritic symptoms.[1] First identified on the borders of Mozambique and Tanzania in 1952, it has now been classified as grade C priority pathogen, because of its spread to over 40 countries worldwide.[2] It is transmitted by mosquitoes, predominantly Aedes aegypti, and Aedes albopictus.[1]
Both CHIKV and Dengue virus are disseminated by same pattern. The infected mosquitoes bite throughout the day, with spikes in early morning and late afternoon. The Aedes albopictus mosquito breeds in a wider range of water-filled breeding sites than aegypti mosquito, which includes coconut husks, cocoa pods, bamboo stumps, tree holes and rock pools. The assorted habitats help to explain the abundance of Aedes Albopictus in rural and periurban areas.[2]

EPIDEMIOLOGY:
Historic accounts indicate the emergence of (CHIKV) as early as 18th century in Indonesia and America, by sailing ships which carried susceptible humans and peri-domestic mosquito vector, Aedes aegypti for on-board circulation. Next to its discovery in 1952, the first documented CHIKV emergence provoked urban outbreaks in India and Southeast Asia, the second one was found in coastal Kenya in 2004[3] which dispersed independently into islands in the Indian Ocean and to India, via infected air travelers. Subsequently, autochthonous transmission occurred in Italy and France, drafted by infected travelers from India.
Twelve cases of travel-associated CHIKV have been reported in USA, while France and UK have reported 850 and 93 cases respectively. More CHIKV-infected travelers have also been identified in Australia, Belgium, Canada, Czech Republic, French Guiana, Germany, Hong Kong, Italy, Japan, Kenya, Malaysia, Martinique, Norway, Switzerland, and Sri Lanka.[4]
The latest outbreaks were documented in Reunion, the Seychelles and India. The virus emerged in Africa, Mauritius, India and coastal Italy as well in October 2013. It has scoped to at least 45 countries and territories.[5]
CHIKV has come a long way, with several mutations assimilated. In India, approximated 1.3 million people across 13 states were reported to be infected. The increased spread is put down to an increase in global travel. Recently, risk of CHIKV to non-endemic regions has been highlighted. These cases have been archived in European countries, Australia, Asia, and United States.[6]

INCUBATION PERIOD:
The incubation period of can range from 2-12 days, most commonly between 3-7 days.

CLINICAL PRESENTATION:
Clinical course is divided into two phases: an acute phase and a chronic phase. Acute infection presents with polyarthralgia, high fever, asthenia, headache, nausea, vomiting, rash, insomnia and myalgia with joint swelling.[7] These symptoms usually persist for weeks (Table 1). Iridocyclitis, uveitis, and retinal lesions may also occur. On skin involvement, 50% of patients may exhibit maculopapular rash. Facial edema, bullous eruptions with sloughing; localized petechiae and bleeding gums are less common skin manifestations.
Newborns and older adults (≥65 years) have risk of

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more severe disease. Presence of hypertension, diabetes and heart disease also relate with severity of infection. In chronic stage of infection, poly-arthralgia lasts for weeks to years longer than the acute stage.[2]

COMPLICATIONS:

Even though chikungunya usually has a mild course, severe life-threatening complications can develop. It can be complicated by multiple organ failure which leads to death. Very recently, the first cases of severe sepsis and septic shock that could be attributed to CHIKV infection were reported.[8] Further potential long-term or severe complications include prolonged myalgia and fatigue, gastrointestinal upset, encephalitis, depression, lung, kidney and heart dysfunction.[9]

LAB INVESTIGATIONS:

The useful test within first 7 days is RT-PCR, which is very specific and sensitive, as it detects viral RNA when patient is in the acute phase of infection. Unfortunately its cost contributes to a decrease in extensive use. The second diagnostic tool is serologic assay like ELISA immunofluorescence, complement binding, and haemagglutination inhibition. Enzyme-Linked Immunosorbent Assays (ELISA) may test both anti-Chikungunya virus Immunoglobulin, IgM and IgG. They are the most economical and easy to perform, which makes them useful diagnostic tests.[2]

Within first week after the symptoms appear, saliva can be used for the molecular detection of CHIKV, but it has a lower sensitivity compared to blood. So blood remains the sample of choice.[10] A positive serum sample along with presence of clinical signs and symptoms of infection makes a conclusive diagnosis.

PREVENTION:

Chikungunya fever is confirmed by: isolation of the virus, molecular methods, detection of IgM antibody, and demonstration of a rising titer of IgG antibody.[11] Till now, no specific antiviral agent or vaccine is available against the infection, however, most would agree that the best weapon against CHIKV is prevention. The live recombinant measles-virus-based chikungunya vaccine is safe and has good immunogenicity.[12]

Although live CHIKV vaccines are still under trial, one way to achieve the target is to construct a consensus-based DNA vaccine, as it can have a greater safety profile as compared to live or attenuated vaccine, and produced more rapidly than protein-based vaccines. The most effective is one which has an ability to induce both humoral and cellular immune responses.[13]

TREATMENT:

Treatment is supportive, involving rest, proper diet, movement and mild exercise.[6] In order to minimize the spread of virus, preventative measures should be taken like, vector-control, sleeping with long-sleeved shirts and long pants and sleeping with mosquito nets covering the bed. Sleeping with air conditioning cooling system can also help to reduce transmission. These measures are prescribed as they are effective and easy to execute.[2] Pain relief medication, such as naproxen, ibuprofen or paracetamol may also alleviate fever and aches.[6] Adaptive immunity has a decisive role in controlling and beating CHIKV after initial IFN-a/b and other innate immune responses have been abated. In this respect Abs could have the prime impact in anti-CHIKV immunity.[14,15]

Table: 1
Clinical presentation of patients with Chikungunya Virus & Dengue Virus

Clinical Features	Chikungunya Virus (CHIKV)	Dengue Virus (DENV)	Reference
1) Fever, asthenia	Common	Common	[6,8]
2) Myalgia	Possible	Very common	[6]
3) Polyarthtitis	Very Common, edematous	None	[56]
4) Tenosynovitis	Yes	None	[57]
5) Leukopania	None	Yes	[58]
6) Thrombocytopaenia	None	Yes	[59]
7) Rash	Days 1-4, important skin edema	Days 3-7	[6,35,58]
8) Retro-orbital pain	Rare	Common	[60]
9) Hypotension	Possible	Common, Days 5-7	[60,61]
10) Minor bleeding	Chronic polyarthritis up to 1 year	Common	[17,56]
11) Second stage	Possible; Tenosynovitis at M2-M3 Raynaud's syndrome at M2 -M3	Fatigue up to 3 mo	[6,56,57,58,62,63]

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CONCLUSION:

Chikungunya has spread to over 40 countries worldwide since its emergence and globally there have been severe outbreaks which remain predominantly limited to Southeast Asia and Central Africa. Chikungunya fever must be considered in travelers who develop fever and arthritis after traveling to areas affected by an ongoing epidemic; in this regard Public health global initiatives should be alerted on these areas in an attempt to reduce the spread of the virus to neighboring continents. Travelers to areas of epidemicity should be informed of the risk of infection and of adequate preventive

measures, such as protection against mosquitoes. To reduce contact with vectors, it is essential to develop outbreak control plans, including educational efforts for the public.

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STUDENTS CORNER

BLOOD DONATION DRIVE 2017

Aqsa Mehfooz[1]

A student run welfare organization of the Bahria University Medical and Dental College, organizes a blood donation camp in the university premises twice every year. The purpose of this initiative is to collect blood for patients suffering from Thalassemia and other diseases that require a continuous supply of blood from the donors.

This time, the Blood Drive was held on 17th of January, 2017, in collaboration with the **Indus Hospital Blood Bank**, in the Skills Lab of BUM&DC.

The event started with a ribbon cutting ceremony by the presidents of Bahria Medics, **Osama Waheed** and **Aqsa Mahfooz**, at 10:30 hours. Director General BUMDC, Vice Admiral Tehseen Ullah Khan HI(M) (R), Dean, Professor Dr. Asad Ullah Khan, Professor Dr. Hassan Ali (HOD Biochemistry) and all the faculty members graced the ceremony with their presence. After the ceremony, both the presidents gave briefing to the Director General and the faculty members about whole procedure, from donating the blood till it reaches the patient. This included the safety procedures before drawing blood of the donor, transport, screening, storage and the procedure of how someone in need can avail it. In order to spread awareness and motivate the students to play their vital role in this noble act of humanity, short lectures were organized for every class on the day. Miss. Syeda Sara Zafar (Marketing Executive, Indus Hospital) delivered the lectures. Class Representatives from each class were already chosen and were assigned the task of motivating their class fellows for donation. The procedure of donating blood started by measuring body weight of the donor, and then demographic data was recorded. This was followed by brief history taking and recording of vitals (pulse, blood pressure, body temperature) and then Hemoglobin level was checked. If the standard criterion was met, the donor was then ready to donate blood. Intense care was taken before drawing out blood of the donor. When blood withdrawal was complete, the donor was given a pack of biscuits and juice to revive blood sugar levels. In case of any complications, Dr. Dawood (of Indus Hospital) was also present at the blood camp. Each donor would get a certificate of acknowledgement and screening reports from blood bank.

All the students and faculty members displayed great enthusiasm towards the noble cause. The tireless efforts of the team of Bahria Medics and Professor Dr. Hassan Ali (HOD Biochemistry) made this blood drive a huge success with collection of 89 pints of blood. Such activities play a pivotal role in inculcating a sense of responsibility towards humanity in the future doctors of the country.

Director General ensure the safety of blood donation

Blood prick for blood grouping and matching

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Checking vitals and hemoglobin level present in a sample of blood

The blood drive team with the Director General and faculty members.

CASE REPORT

Ruptured Second Trimester Ectopic Tubal Pregnancy: Case Report

Insia Ashfaq[1], Junaid Iqbal[2], Sara Zafar[3], Ambreen Ibrahim[4], M. Kashif Shazlee[5], Irfan Lutfi[6].

ABSTRACT:

Ectopic pregnancy (EP) is one of the leading causes of maternal mortality. Its frequency in Pakistan is 1:13 pregnancy.[1] Tubal ectopic often becomes symptomatic in first trimester by eroding the tubal wall and causing hemorrhage and shock. It is very rare for an ectopic to progress into second trimester and remain asymptomatic[2]. We are reporting a rare case of tubal ectopic pregnancy which ruptured at 16 weeks of gestation with non-viable fetus.

We report a case of 27-year-old female who presented to the emergency of Dr. Zia Uddin Hospital, North Nazimabad, Karachi, with bleeding per vagina and abdominal pain with history of 4 months of amenorrhea. Ultrasound showed 16 weeks fetus in abdomen without cardiac activity and severe hemoperitoneum. She was diagnosed as a case of non-viable, ruptured, tubal ectopic pregnancy of 16-week gestational age.

Diagnosis of ectopic pregnancy in first trimester can avert rupture and potential mortality and morbidity. Very few cases of second trimester ectopic pregnancy are reported. The purpose of this case report is to draw the attention for the potential of such incidence in this region and prompt management of such situation.

Keywords: Ectopic pregnancy, Rupture, Ultrasound

INTRODUCTION:

Incidence of EP ranges between 0.25% to 2% of all pregnancies and 15% of all maternal deaths[3]. The ampullary portion of the fallopian tube is the most common location[4]. The diagnosis of ectopic pregnancy is typically based on a combination of quantitative assay for ß-HCG and findings on pelvic sonography[5]. Tubal pregnancies generally rupture between 5 and 11 weeks of gestation[6].

However, some cases of advanced tubal pregnancies have been reported with a different presentation. This event is rare because it is unusual for the fallopian tube to dilate to the point of containing a second or third trimester fetus[7]. We report an unusual case of ruptured advanced tubal pregnancy, which we have observed for the first time in our unit.

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CASE REPORT:

A 27-year-old patient, primigravida, unbooked case presented with 16 weeks of gestation and was admitted with bleeding per vagina and abdominal pain. Her general medical history revealed no other problems. Her current obstetric care had included one clinic visit without any sonographic examination.

The patient was hemodynamically unstable with abdominal tenderness. A mass, around 15 cm in diameter with regular contour, was palpable between the umbilicus and the pubic bone on the right side of the abdomen. Mobilization was limited and painful.

An emergency transabdominal ultrasound was performed which revealed an empty, ante-verted bulky uterus with a fetus in the abdominal cavity. The endometrial thickness was 1.8cm. Both ovaries visualized in cul-de-sac appeared unremarkable. An intra-abdominal fetus corresponding to gestational age of 16-week was identified with surrounding amniotic sac at the level of umbilicus with posterior placental attachment. No cardiac activity was appreciated. Massive fluid with echoes was seen in pelvis and at hepatorenal angle which on ultrasound guided aspiration revealed hemorrhagic fluid.

An emergency laparotomy was carried out. A large vascular mass, 15 cm x 15 cm was found which proved to be the right fallopian tube, ruptured at isthmus and containing a fetus weighing 190gm. The uterus was small with a normal left tube and both ovaries. Massive hemorrhagic fluid was also drained from peritoneal cavity. Gross morphological examination showed a placenta invading the external surface of the fallopian tube. Histopathology revealed second trimester villi with areas of inter villous fibrin deposit and hemorrhage. The patient had an uneventful postoperative recovery.

DISCUSSION:

Incidence of Ectopic pregnancies ranges from 0.25% to 2% of all pregnancies[3]. Ninety-five percent of ectopic

pregnancies occur in the fallopian tube. Diagnosis and exact location of ectopic pregnancy is usually easy during the 1st trimester of pregnancy by ultrasonography. Ampulla is the most common site for ectopic tubal pregnancies[8]. They generally rupture between 5 and 11 weeks of gestation[6]. The diagnosis of ectopic pregnancy is typically based on a combination of quantitative assay for ß-HCG and findings on pelvic ultrasound.

Hemorrhage from ectopic pregnancy is the leading cause of pregnancy-related maternal death in the first trimester. Thus, prompt and accurate diagnosis is critical[5]. However, in extremely rare conditions they may be carried up to an advanced gestational age and may be associated with diagnostic difficulty[8].

In developing countries ectopic pregnancies are most often discovered when ruptured. Cissé et al[9], in a study in Senegal, reported 242 out of 255 (94.9%) cases being detected at the time of rupture. The incidence of late diagnosis is the consequence of late antenatal care and absence of ultrasound facilities and is responsible for significant mortality: 1.2% in the study of Cissé et al.

Risk factors for ectopic pregnancy include a previous ectopic pregnancy, the presence of tubal damage from an infection or prior abdominal/pelvic surgery, a history of infertility, treatment for in vitro fertilization, increased maternal age and smoking[10].

The treatment of advanced tubal pregnancy is always a total salpingectomy. Even if the patient has the desire for future child-bearing, it would be difficult to perform conservative tubal surgery due to excessive deformation of the fallopian tube[6]. In our case, laparotomy was performed due to the site of the ectopic pregnancy being near the interstitial portion of the tube.

CONCLUSION:

Second trimester un-ruptured tubal pregnancy is rare among ectopic pregnancies. Ultrasonography is still the diagnostic modality of choice. Diagnosis of ectopic pregnancy in first trimester can avert rupture and potential mortality and morbidity. There is need for health education to encourage women to attend clinic early in pregnancy, especially when experiencing unusual symptoms of lower abdominal pain and irregular vaginal bleeding. That could help in the diagnosis of un-ruptured ectopic pregnancy.

Figure: 1

Ultrasound scan uterus shows dilated endometrial canal without intrauterine pregnancy

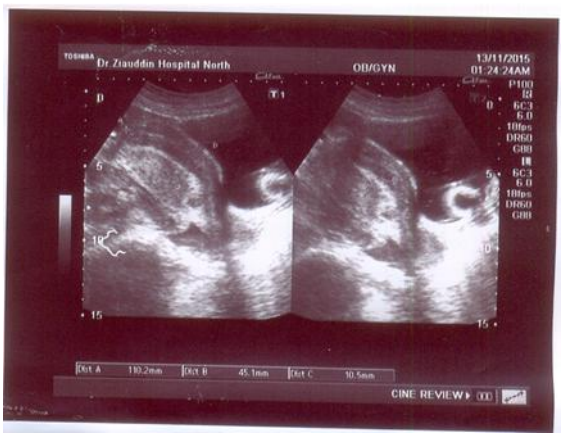
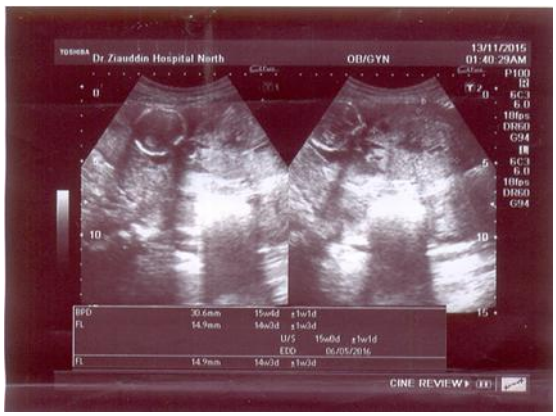


Figure: 2

Ultrasound scan abdomen shows extra uterine (ectopic pregnancy). BPD & FL equivalent to 15-week fetus



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LETTER TO EDITOR

Self-Medication: Pros and Cons

Syeda Hira Abid

To,
The editor,

Modern healthcare systems are progressing with every passing day. Self-medication, which has been there for a long time, has been successfully integrated in many of those systems and now remains as an important part of the healthcare in this era. The products associated with self-medication are those which can be easily acquired. They do not require a medical prescription and can be used by the patient to treat, and prevent ailments and symptoms. A patient can easily manage those products. But, if the issue persists, and there's no change, then the patient could consult a doctor. Over the years, it is the increase in the competition, as in, the promotion of self-medication products which has assisted greatly in the self-medication and patient awareness of the availability of self-medication products. Self-medication, however, is not without its pros and cons. One of the major self-medication issues is its usage. People tend to self-diagnose and treat themselves, but it can go the other way too. Lack of information related to ailments and symptoms can lead to further issues. The availability of the drugs is also too much, and there tends to be less control. The perception regarding certain drugs is built through marketing by pharmaceutical companies. An example would be the painkillers. Prolonged use of painkillers can lead to various problems. For example, Paracetamol is an antipyretic and analgesic, and its usage in large dosage can cause liver problems. The other example of this is the potential growth of resistance against antibiotics, which can prove dangerous to a person.[1] It can be said that the use of over-the-counter (OTC) self-medication drugs such as analgesics is widespread and the potential impact from the use of these drugs on the development of chronic renal failure may be significant.[2.] Moreover, there have been reports received of OTC medicines being misused by people addicted to drugs.[3,4] Self-medication, however, has its good aspects too. It can help a person get rid of an ailment without consulting a doctor. The immediate relief is one of the most important aspects of it. Self-medication can be made available to remote places where immediate availability of doctor is an issue. A person, through self-medication, gets chance to understand their body better. Cost saving, as well as time saving is also there. In many cases, self-medication products are also understood to mean alternative medicines, food supplements, vitamins, herbs or other substances contained in commercially available products.[5]

In conclusion, it can be said that self-medication remains an essential part of modern-day healthcare system, but there needs further study, along with informing the masses about its pros and cons. The data available is still insufficient, and that needs to be taken care of. Self-medication, undeniably, is something that should not be stopped; rather the people should be encouraged to be more informed about it. Advice to the consumer/patient should include a detailed description, on the usage of the product without medical supervision and the circumstances in which referral for medical advice is required. Having said that, self-medication should still be considered something secondary to proper consultation with a doctor.

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List all contributors who do not meet the criteria for authorship, such as a person who provided purely technical help, writing assistance, or a department chair who provided only general support. Financial and material support should also be acknowledged.

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The Cardiac Society of Australia and New Zealand. Clinical exercise stress testing. Safety and performance guidelines. Med J Aust 1996; 164: 282-4

c) No author given

Cancer in South Africa [editorial]. S Afr Med J 1994;84:15

d) Chapter in a book

Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78

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