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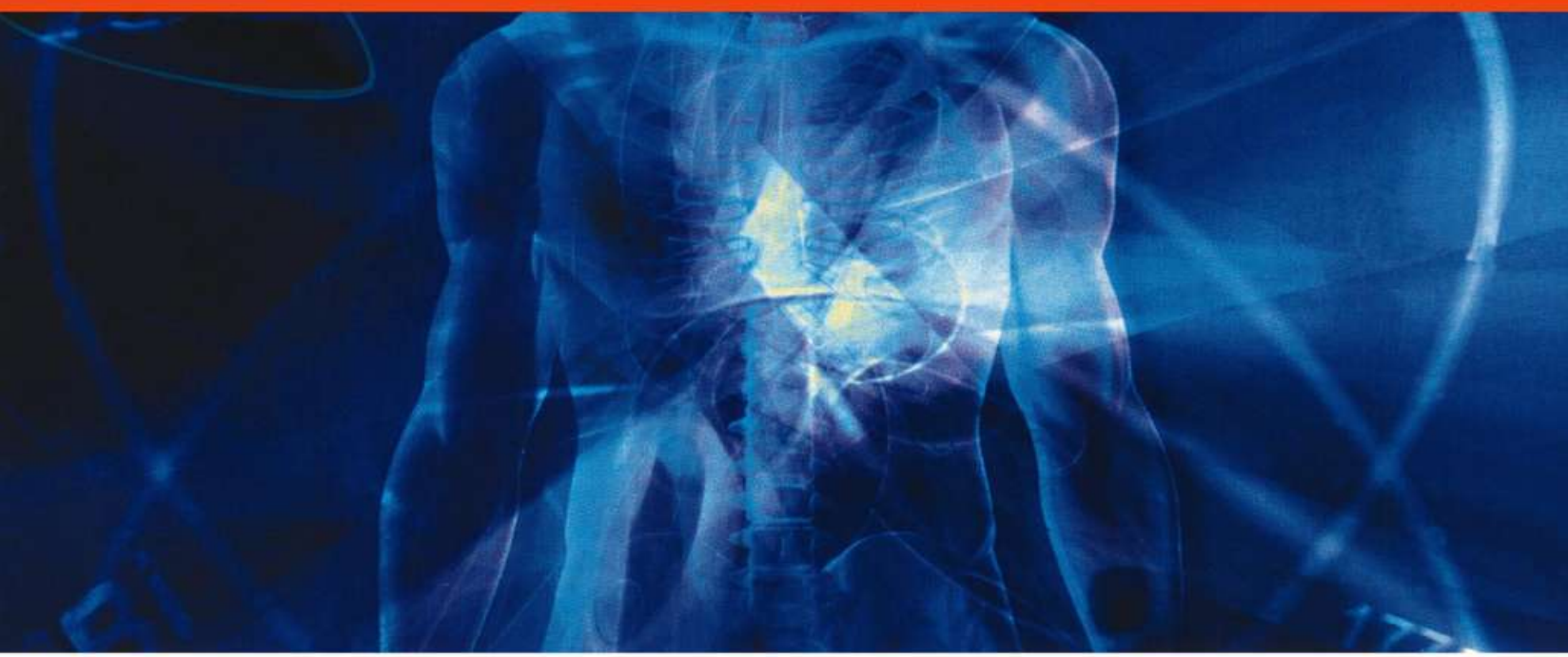

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# CONTENTS

# Naegleria Fowleri – Simple Facts About Brain Eating Amoeba

Irfan Ali Mirza

Year after year, the inhabitants of Karachi have to face the fear and panic of Naegleria fowleri which can cause deadly disease called meningoencephalitis. A common citizen remains extremely wary of what to do and what not to do. The health authorities do come up with awareness campaigns mounted on large sized billboards, yet the simple facts remains eluded to even majority of health care personne[1].

It was in 1958 that Culbertson and his colleagues first described the concept that free living soil and water amoebae can cause disease in humans. Since then number of fatal cases of acute meningoencephalitis have been reported.[1] Naegleria is a free living amoeba, commonly found in warm freshwater for example, lakes, rivers, hot springs and soil. Only one of the specie of Naegleria known as Naegleria fowleri is pathogenic and infects humans. This parasite infects people when water containing the amoeba enters the body through the nose. This normally occurs when people swim or dive in warm freshwater places, like lakes and rivers. The amoeba then travels up the nose to the brain via olfactory nerve where it destroys the brain tissue.[2] As this amoeba can be found in warm freshwater, such as lakes and rivers, swimming pools that are poorly maintained, minimally chlorinated, and/or un-chlorinated, so the recreational water users should be aware that there will always be a low level risk of infection when entering these waters. Different behaviors associated with the infection include diving or jumping into the water, submerging the head under water or engaging in other water-related activities that cause water to go up the nose.[3]

Naegleria fowleri grows best at higher temperatures of up to 115°F (46°C). It occurs in three forms, a cyst, a trophozoite (amoeboid) and a flagellate. It is to be remembered that it does not form a cyst in human tissue. Only the amoeboid trophozoite stage exists in human tissue and actually is the pathogenic form. Trophozoites encyst due to unfavorable conditions. Factors that induce cyst formation include overcrowding, desiccation, accumulation of waste products, and cold temperatures. Naegleria fowleri has been found to encyst at temperatures below 10 °C/50°F. Trophozoite stage is reproductive stage of the protozoan organism, which transforms near 25 °C/77°F and grows fastest at around 42 °C/106.7°F proliferating by binary fission. The trophozoites are characterized by a nucleus and a surrounding halo. They travel by pseudopodia, temporary round processes which fill with granular cytoplasm. The pseudopodia form at different points along the cell, thus allowing the trophozoite to change directions. In their free-living state, trophozoites feed on bacteria. In tissues, they phagocytize red and white blood cells and destroy tissue.[2] Pathogenic form (trophozoite) is less likely to be found in the water as temperatures decline. While infections with Naegleria fowleri are rare, they occur mainly during the summer months of July, August, and September. Infections usually occur when it is hot for prolonged periods of time, which results in higher watertemperatures and lower water levels.[4,5]

Naegleria fowleri causes the disease Primary Amoebic Meningoencephalitis (PAM), a brain infection that leads to the destruction of brain tissue. In its early stages, symptoms of PAM may be similar to symptoms of bacterial meningitis. Initial symptoms of PAM start about 5 days (range 1 to 7 days) after infection. The initial symptoms may include headache, fever, nausea, or vomiting. Later symptoms can include stiff neck, confusion, lack of attention to people and surroundings, loss of balance, seizures, and hallucinations. After the start of symptoms, the disease progresses rapidly and usually causes death within about 5 days (range 1 to 12 days). The infection destroys brain tissue causing brain swelling and death.[2,6]

Currently, a great deal of work is being done to determine what factors specific to Naegleria fowleri makes it pathogenic and if these virulence factors could be targeted by drugs. One potential factor in motility of the "amoeba" is the protein coded by Nfa[1] gene. When the Nfa1 gene is expressed in non-pathogenic Naegleria gruberi and the amoebae are co-cultivated with target tissue cells, the protein is found to be located on the food cup which is responsible for ingestion of cells during feeding. Subsequen to those researches, Nfa1 gene expression knockdown experiments have been performed using RNA interference. In these experiments, double stranded RNA targeting the Nfa1 sequence was introduced and subsequently expression levels of the gene product dramatically decreased. This method could potentially be a technique applicable for knockdown of expression of pathogenicity factors in Naegleria fowleri trophozoites.[7]

The analysis of CSF of affected persons reveals decreased glucose, and increased protein concentrations. Leukocytes may range from several hundred to > 20,000 cells/mm$^2$.Gram stain and cultures of CSF are negative. The wet mount of CSF placed on a slide and covered with cover slip examined as soon as possible is observed for characteristic motile trophozoites. The amoeba can be grown in several kinds of liquid axenic media or on non-nutrient agar plates coated with bacteria. Escherichia coli can be used to overlay the non-nutrient agar plate and a drop of cerebrospinal fluid sediment is added to it. Plates are then incubated at 37 °C and checked daily for clearing of the agar in thin tracks, which indicate the trophozoites have fed on the bacteria. Detection in water is performed by centrifuging a water sample with E. coli added, then applying the pellet to a non-nutrient agar plate. After several days, the plate is microscopically inspected and

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Naegleria cysts are identified by their morphology. Final confirmation as regards the specie can be performed by various molecular or biochemical methods. Confirmation of Naegleria presence can be done by a so-called flagellation test, where the organism is exposed to a hypotonic environment (distilled water). Naegleria, in contrast to other amoebae, differentiates within two hours into the flagellate state. Pathogenicity can be further confirmed by exposure to high temperature (42 °C): Naegleria fowleri is able to grow at this temperature, but the nonpathogenic Naegleria gruberi is not.[2, 8]

As regards the treatment Amphotericin B is effective against Naegleria fowleri in vitro, but the prognosis remains poor for those who contract PAM, and survival remains less than 1%. On the basis of the in vitro evidence alone, the Center for Disease Control and Prevention (CDC) currently recommends treatment with Amphotericin B for primary amoebic meningoencephalitis, but unfortunately no evidence supports this treatment affecting outcome. Treatment combining miconazole, sulfadiazine, and tetracycline has shown limited success only when administered early in the course of an infection.[8, 9]

Prevention remains the only plausible solution to minimize the risk of acquisition of this parasite. Public awareness campaigns combined with adequate chlorination of water systems and swimming pools are recommended to prevent this infection. The swimmers are also advised to be careful not to allow water get up their nose. It is also advisable to be careful while cleansing the nose during religious practices when contaminated tap or faucet water is imminent. Naegleria fowleri can grow in pipes, hot water heaters, and water systems, including treated public drinking water systems. Hence public health authorities have to ensure the adequate chlorination of water at all times. Personal actions to reduce the risk of Naegleria fowleri infection should focus on limiting the amount of water going up the nose in all activities which involve contact with water.[2,10]

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**REVIEW ARTICLE**

# Family Medicine: Necessity But Still A Neglected Medical Specialty In Pakistan

Farheen Navaid[1], Tahira Zamir[2]

**ABSTRACT:**
Family Medicine is the primary care medical specialty concerned with provision of widespread health care to the person and the family irrespective of sex, age or kind of problem. It is the specialty of extensiveness that integrates the natural, medical and behavioral sciences. It is emerging as a frame of knowledge that is being constantly developed , explored and qualified as an integrative entity. In our country, this specialty was announced in late eighties. The number of qualified family medicine specialists is still alarmingly low in our society. There is also a lack of understanding in majority of our population regarding the existence as well as importance of Family Medicine. Rotation of students in family medicine facility as part of undergraduate medical curriculum may help in fostering an interest among medical students in this newly emerging subspecialty which could have profound effect on delivery of quality health care in Pakistan.
**Key words:** Primary care, Family medicine, Importance, Quality health care, Pakistan.

## INTRODUCTION:

Before the arrival of various medical specialized fields, a single doctor was accustomed to take care of all the different sorts of diseases. At the start of the 20th century, nearly all physicians in the domain were general practitioners, and there is no evidence for the significant growth of specialism in the United States before 1851.As the health awareness gradually increased, it became difficult for a single doctor to be proficient in all the fields of medicine. In 1880s, specialization was perceived as a necessity of medical science[2] and thus numerous specialties were derived. There were definite benefits of this trend as a specialist who deals with a single domain has to refine his skills in a particular field instead of trying to be master of all the fields. Patients encouraged this situation as they found competent doctors dealing with their illnesses and doctors became happy as they had to focus on their own specific fields. With this inclination, the specialists and specializations received popularity and became a source of provision of more economic benefits. The trend of specialization discouraged doctors to serve as a general physician and majority of the doctors entered into a struggle to become specialist. In several disciplines the deficiency of doctors is increasingly visible, and at this instant general practice faces a deficit[3].The increasing shortage of doctors in the profession of general practice is also being observed in other countries such as Great Britain, Israel and Canada.[4,5,6] In view of this change patients found that their family physicians gradually started disappearing from the scene. More than 2 decades ago, the Graduate Medical Education Advisory Committee issued a report predicting an excess of specialists and a need to produce more generalist physicians.[7] More over no single doctor was capable enough to look after the different common ailments of all the members of a family by remaining available to them all the time. These circumstances led to the renewal of noble Family Doctor.

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## METHODOLOGY:

A literature search was conducted from the period of 1995-2015 .The search engines used were Pubmed, Google Scholar, Medscape. Keywords and phrases used were primary care, role of general practitioner, history of family medicine, specialty choice and perception of medical student about family medicine. In addition, the references from the articles obtained were searched to find additional articles. In this review, the content of the articles has been arranged in a roughly chronological fashion as: history of family medicine, importance of family medicine and its benefits to the community, choice of family medicine as a specialty and future of family medicine in Pakistan.

### Emergence of Field of Family Medicine:

In continuation to the background mentioned above, it was decided to introduce the field of family medicine. It represents the common trunk from which the several twigs of medicine emerged and later developed as separate specialties and sub-specialities[8].It is now accepted as a discrete medical entity, with a demarcated core of abilities, a distinct group of information and a set of arrogances and assurance.[9] The first academic college of family physicians/general practitioners was established in USA in 1947.Followed by Britain in 1952, Canada 1954, Australia 1958, Philippines 1961, Singapore 1971, Malaysia 1973, New Zealand 1974, and Sri Lanka 1974.10 By 1984 about 85% of American medical schools had established family practice training programs or had become affiliated with them. Now nearly a quarter of all young doctors enter the family practice residency each year.

### Family Medicine in Pakistan:

In 1986, The Aga Khan University Medical College was the first to incorporate the family medicine program for undergraduate within its curriculum. In 1990, the College of Physicians and Surgeons of Pakistan held the first diploma in family medicine examination. This was the start of the recognition of family medicine in Pakistan as a separate discipline. In 1990, the Department of Community Health Sciences at Aga Khan University took on its first batch of family medicine residents. In1994, the College of Physicians and Surgeons of Pakistan (CPSP) approved a fellowship in family medicine by accepting it as a specialty in its own

right[11]. It is obvious that family medicine is a new but steadily growing field.

**Family Medicine Integrates Primary Health Care System:**

It is a definite fact that quality health care system of a country depends upon the effectiveness of its primary health care system which is defined as essential health care made universally available to individuals and families in the community and acceptable to them through their full contribution and at a reasonable cost[12].People and countries with adequate access to primary care facilities, utilize a number of health care and monetary benefits, including the following:

- Better preventive care for the community[13,14]
- Less use of emergency departments and hospitals [15,16]
- Reduced all-causes of mortality caused by cardiovascular and respiratory diseases [17]
- Better recognition of breast cancer, reduced frequency and mortality caused by colon and cervical cancer[18,19,20]
- Fewer tests, higher patient satisfaction, less medication use, and lower care-related costs [21,]
- Reduced health discriminations, particularly for areas with the highest income inequality, including improved vision, more complete immunization, better blood pressure control, and better oral health [22, 23, 24]

Thus family medicine is one of the primary medical care disciplines. Like internal medicine and pediatrics, it is a speciality of first contact with patients and works as an entry point for patients, into the health care system. Different studies have showed that in countries where family physicians rather than specialists provide first access to the health care system, health care costs are lower. In 1996, Forrest and Starfield suggested that ambulatory expenditures can be reduced up to 50% by this system of care25.Greater patients satisfaction has also been found in systems where family physicians are first-contact providers.[26]

**Family Medicine Integrates Emergency Medicine:**

Family Medicine and Emergency Medicine are the first contact services where 90% of population healthcare needs are provided[27].Common illnesses like infections, cerebro-vascular accidents, myocardial infarctions and road traffic injuries present in the acute form to the Emergency Departments (EDs).[28] However, these patients may also present to the family medicine clinics initially and are subsequently referred to Eds. During this process of shuttling between ED and family medicine clinic, patient care is compromised due to lack of coordination and integration of the services at most places. This results in duplication of investigations, treatment, and over and under diagnosis, with huge resource consumptions without fruitful outcomes. It seems very logical that with such terrible healthcare services and manpower crisis in Pakistan, we should aim for organized and systematic ways of movement of patient from ED to Family Medicine and vice versa.[29] In this way patients will more likely receive resource efficient (time, cost and manpower) care for all their health problems.

**Family Medicine Committed to "Health for All":**

Family medicine, however, is not restricted by age or sex and is devoted to providing comprehensive preventive, supportive and curative care with emphasis on the family unit including the community and social environment. It is a discipline characterized by its breath, which squeezes knowledge content from all medical disciplines at a certain level and grasps it all together with the distinctive skills and attitudes required for providing person focused, extensive, primary health care for people in their own atmosphere, on a continuing care basis[30].

The family physician frequently interacts with people affected by chronic diseases[31,32] Pakistan is facing quadruple burden of problems like communicable diseases, non-communicable diseases, mental health problems and accidents / injuries.[33] This is an absolute fact that with growing chronic disease burden, the workload of all doctors is increasing. This combined with huge lack of resources in our country is resulting in major work related stress. This specialty was meant to properly tackle common problems of all the members of a family. These problems usually constitute about 80% of the health problems faced by people. The training of family medicine specialists was planned in a way to make them competent to independently tackle most of these common health issues and for the remainder uncommon issues they could arrange referrals to the concerned specialists.

**Perception of Medical Student as a Career in Family Medicine:**

Although family medicine is recognized as a specialty by the College of Physicians and Surgeons, Pakistan, up till now it is explained as a core subject in the undergraduate medical school curriculum, certified by the Pakistan Medical and Dental Council. Family medicine as a career choice is not on the priority list of many medical undergraduate students around the world.[34,35] The reasons mentioned in different studies have been student's lack of awareness and interest in the subject and student's perceptions that it is a specialty with low prestige, money and personal growth.[36] The status of undergraduate training in family medicine seems to be an important factor that may influence student career choices in this primary care specialty. Very few Pakistani medical students select family medicine or general practice as their career of first choice. A study was conducted in Ziauddin Medical University Karachi has suggested that in career choice, clinical specialties were highly rated as compared to family medicine.[37]

**Factors Affecting the Choice of Family Medicine:**

A number of studies conducted internationally have pointed the factors affecting the specialty preferences,[38] however, there is limited data available for Pakistani medical students.[39] As students learn new skills, acquire clinical exposure, gather knowledge and interact with consultants, residents, patients and fellow medical students, their ambition to progress forward in their profession brightens.[40] *Some important factors identified* while choosing a career were: life-style of clinical practice, salary, gender of the student, social issues they face and prestige related to certain specialties.

(1)-Gender: Various studies have found higher proportions of women than men choosing family medicine but none of the differences were statistically significant.[41]

(2)-Age: Two studies looking at age had contradictory results;

one study suggested that older age was associated with an interest in family medicine[42] and the other suggested that there was no association of age with career choice in family medicine.[43]

(3)-Socioeconomic background: Kassebaum in 1996 reported that parents' income over $100,000 decreased the likelihood of plans for a family practice specialty[44] but there relation was observed among parent' education and career choice in family medicine.

(4)-Geographic Background: Since 1993, three studies have been conducted and all have found that rural background is more related to choose family medicine as a speciality[45]

(5)-Morals and Awareness to family medicine on Entry to Medical College: Studies have provided some evidence that values on entry to medical school that are corresponding with a choice of family medicine are related to an ultimate choice of the specialty. Beliefs of high income in a medical career were negatively related to plans for family practice. Medical Students from those schools which produce low rate of primary care graduates were significantly less likely to found family medicine as a specialty than were students at a school with high rates of primary care graduates. [46]

(6)-Career Aims on Entrance in Medical College: Preference for family medicine as a choice at the time of entry to medical college increased the chance of subsequent plans for family practice.[47]A decline in initial interest in family medicine was observed and documented by various studies[48] It is documented that interest of students at high school level is positively related to an eventual choice of family medicine. However preferences for a particular specialty develop considerably during the years of medical school. An important addition to the data available in 1995 is that there may not be any relationship between stated career intentions before admission to medical school and those indicated after admission[49]

(7)-Type of practice: One study suggested that at matriculation level plans to practice in a rural setting or plans to practice in a socioeconomically deprived area were related to interest in family medicine.[50]

(8)-Departmental Structure: Several studies found that existence of a department of family medicine increased the possibility of students planning a career in family medicine. However others did not find a relationship between departmental status and production of family medicine graduates[51]

(9)-Third- and Fourth-Year MBBS Curricula: There have been a number of studies examining third year MBBS students that supported the positive relationship between required time in family medicine and selection of family medicine as a specialty. One study have found lowered rates of students selecting family medicine if their internal medicine clerkship was ambulatory[52]

(10)-Faculty Composition: The increasing proportion of clinical faculty who are family physicians is associated more with specialty choice of family medicine.

(11)-Faculty Role Models: A research conducted in 1999 suggested that having role models is related to specialty choice; positive role models should be important in specialty selection, negative role models were mentioned as a reason for moving away from family medicine[53]

**Family Medicine Rotation as Part of Undergraduate Curriculum:**

In 2008, SHIFA College of Medicine introduced a two-week rotation in family medicine for their third-year medical students and a study was conducted over 46 students rotated in family medicine. Before starting their rotation only fifteen students were aware of family medicine as a specialty and only 3 showed an interest to pursue family medicine as a future career. At the start only 15 students were able to give correct definition of family medicine. On completion of rotation, a significant number of students that is 37% considered having a career in family practice and 80% were able to give correct definition of family medicine.[54] The results of this study are quite hopeful. The fact that students considered a career in family practice upon a short exposure to the subject reinforces the perception that family medicine needs to be consolidated as a permanent feature in Pakistani medical undergraduate curricula. In Pakistan some institutions like the Aga Khan University and Ziauddin Medical University have integrated family medicine into their curricula but this trend needs to establish in other medical colleges as well. The national need for Pakistan is for our graduates to practice as trained family physicians.[55] *For this family physicians are required as mentors* and leaders in medical colleges, but this will be a challenge as there are very few institutions in our country which are recognized for providing an organized training program or a continuous professional development program for family physicians. The only examples are the Aga Khan University in Karachi and Fatima Memorial College in Lahore.[56]

**Career Options for Family Physicians in Pakistan:**

A lot of opportunities are available for future career options in the field of family medicine. These include clinical, academic, administrative and research fields. Clinical opportunities include private or group practice in ambulatory or hospital settings to provide primary health care delivery to patients of all ages. This could be at the primary or district level where properly trained physician are strongly needed. Academic opportunities include the teaching and expansion of family medicine. Pakistan Medical and Dental Council promotes training in family medicine at undergraduate level but lacks qualified teachers at present. With current needs, it is hoped that programs in family medicine will be established at medical schools throughout Pakistan. Mentors will be required for these programs and graduates would meet these needs. With the start of numerous medical and dental colleges in Pakistan, we have produced a total of 111,193 registered MBBS doctors till August, 2008, but only 21,048 doctors have registered in different specialities.[57] Almost three quarters

of the graduates entered into general practice armed solely with their undergraduate degree. Most of these graduates do not have a general approach in managing patients. They focus on symptomatic treatment of diseases, and although they may be filling a gap in our poor quality health care infrastructure but they create hazards in terms of polypharmacy and faults in judgment due to inadequate training[58,59] Hence for enhancement of health care services in Pakistan, adequate primary services need to be established by trained family physicians with a proper referral system. Health care authorities should help and encourage advancement of family medicine as a specialty, and medical educators should construct a curriculum of family medicine and implement it in their respective institutions. At present with a shortage of trained family physicians in the country, very few could act as role models for their students and educate them about this field of medicine. At this time, all medical colleges need to introduce this subject in their undergraduate curriculum so that more students could gain an interest and would consider pursuing it as a future career. This could have a very positive influence on cost-effective delivery of health care in Pakistan.

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ORIGINAL ARTICLE

# Surgical Treatment Of Chronic Subdural Hematoma- Single Burr Hole: Clinical Characteristics And Outcome

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**ABSTRACT:**

**Objective:** To evaluate the clinical characteristics and outcome of single burr-hole evacuation in chronic subdural hematoma(CDHs).

**Materials and Methods:** A total of 67consecutive cases who underwent single-burr hole drainage for CSDH were included in this study. We analyzed patients with CSDH admitted at PNS SHIFA Hospital from 31st Dec 2013 to 1st Nov 2014. Single burr-hole evacuation was done in all cases. Age, sex, clinical feature, etiology, clinical outcome, and recurrence were reviewed.

**Results:** There were 45 (67.16%) male patients, 22(32.83%) female patients. The age range was 30-82 years. The principal presentation was with headache (60%) followed by hemi-paresis (35.8%) and cognitive disturbances (19.4%). Most patients were admitted with history of trauma (60 cases, 89.55%). Recurrence was observed in only 4 cases.

**Conclusion:** Chronic subdural hematoma is a common neurosurgical problem. Most of the patient presented with headache and hemi-paresis. Single burr-hole evacuation has excellent outcome with minimal complications.

**Keywords:** Chronic subdural hematoma, surgical treatment, Single -Burr hole, Complications, outcome.

## INTRODUCTION:

A chronic subdural hematoma (CSDH) is a gradually evolving collection of blood and its products sited in between the subdural cavity. A CSDH is the product of injuring of the bridging veins of cerebral convexity, generally created by trauma, and other causes include brain atrophy or concomitant use of anticoagulant drugs. Moreover, according to the CT scan brain findings and on the basis of the density of hematoma, chronic subdural hematoma can also be defined as a hypo dense subdural hematoma when compared with brain parenchyma, which usually presents after 21 days.[1,2] It is also known as one of the common type of traumatic intracranial hemorrhage. [3,4]

Surgical management has been recognized as one of the most efficient way to treat CSDH. There is overall consonance that indications for surgical management exists, however the optimal technique has not been agreed upon as yet[5,6,7]. The three main surgical methods used for treatment of CSDH includes burr hole with or without irrigation which may or may not be with drainage system, twist drill trephination and craniotomy[8]. Burr hole is the most commonly used technique for management of CSDH. The burr hole method is comparatively less invasive with better cure percentage, even for elderly or high-risk patients. Nevertheless, some patients had been reported as cases of recurrence after surgical management, with an incidence varying from 3.7 to 30%[8,9]. At PNS -SHIFA, single burr hole with irrigation is the surgical treatment of choice in such cases. Present study was designed to evaluate clinical characteristics and outcome of single burr-hole evacuation in patients having chronic subdural hematoma.

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## MATERIALS AND METHODS:

This prospective study was conducted at PNS-SHIFA hospital from 31st December 2013 to 1st November 2014. 67 patients with CSD were analyzed. On admission, neurologic examination was performed using the Glasgow Coma Scale score. History was collected from patient or their family members, of trauma, symptoms or use of anticoagulant drugs. Coagulation profile, Liver function tests, blood biochemistry was undertaken in all patients.

CT scan brain was performed in all patients to diagnose CSDH before the surgical procedure (Single burr hole) that showed hypo-dense or iso-denseor mix dense hemispheric collection of blood layered over the cerebral convexity. In some selected patients MRI was also done. Decision of surgery was made based on clinical findings of CT scan and coagulation profile.

A single burr hole was made at the site of its maximal hematoma thickness under local anesthesia. Local anesthesia was used because it has fewer complications and is safe especially in elderly patients with comorbid. Perioperative antibiotic cover was also given with 2nd generation cephalosporin Inj. Cefuroxime 1.5gm IV. Once dura mater was exposed and the outer membrane of the hematoma, the collection of blood was evacuated under its own tension and by suction, and irrigation was performed using saline solution until clear fluid came out. Dura and burr hole was left open to allow any residue leftover to seep into subcutaneous tissue. Wound was closed in layers without inserting any drain in the hematoma cavity.

Patients were discharged as soon as symptoms related to the CSDH had disappeared and a follow-up CT scan (within 48hrs) had shown a total or significant reduction in the thickness of the CSDH.

Age, sex, the presenting signs and symptoms, causes, site

of hematoma (unilateral or bilateral), density of hematoma, post-operative complications and the recurrence of CSDH for each patient were recorded. When the neurological status did not improve after the surgery or new neurological symptoms developed CSDH recurrence was confirmed with the help of CT scan/MRI brain showing re-accumulation of a subdural hematoma.

**RESULTS:**

There were a total of 67 patients included in the study out of which, 45 were men (67.16%) and 22were women (32.83%). Age of patients varied from 30 to 82 years. The characteristics and clinical findings of 67 patients are shown below. The causes of CSDH in these 67 cases were, 60 cases(89.55%) had history of head trauma, 2 cases(2.89%) had coagulopathy and 5 cases (7.4%) used an anticoagulant therapy( Table 1a).

Table: 1a
Clinical Findings of Patients
N=67

| | |
|---|---|
| Sex | |
| Male (%) | 45(67.16%) |
| Female (%) | 22(32.83%) |
| Range of age | 30-82 years |
| Causes | |
| Head Trauma | 60(89.55%) |
| Anticoagulant Therapy | 5 (7.4%) |
| Coagulopathy | 2(2.89%) |

The most common presentation was with headache 40 cases (60 %), which was followed by altered behavior in 4cases (5.9%) and hemiparesis in 24 cases (35.85 %).The frequency of the presenting symptoms is shown in Table 1b.

Table: 1b
Presentation of Patients with CSDH
N=67

| | |
|---|---|
| Headache | 40(60.0%) |
| Hemiparesis | 24(35.85) |
| Cognitive disturbances | 14(19.4%) |
| Altered behavior | 4(5.9%) |
| Seizures | 2(2.9%) |

Upon preoperative CT unilateral chronic subdural hematoma were reported in 53 cases (79.10%), while 14cases (20.89%) were reported to have bilateral chronic subdural hematoma (CSDH).Hematoma classified according to size , there were 19 cases(28.36%) of hematoma with size of 1-1.5 cm, while rest 48 cases(71.64%) had hematoma of more than 1.5 cm. According to CT scan preoperatively, CSDH was classified into three groups according to density of hematoma , Iso-dense hematoma were found in 38 cases (56.72%), in 22 cases (32.83%) it was mix density hematoma, while only in 7 cases(10.45%)high density hematoma was found (Table 2).

Results of post-operative CT scan brain done after 48 hours of burr hole, showed residual hematoma in total 4 cases: 2 cases (3.77%) were reported in patients which had preoperatively unilateral hematoma and 2 cases (14.29%) were also reported in patients who had preoperatively bilateral hematoma, while in other patients hematoma resolved completely irrespective from the fact whether they had unilateral or bilateral hematoma preoperatively. (Table 3)

Table: 2
Preoperative CT Scan Findings

| | |
|---|---|
| Hematoma location | |
| Unilateral | 53(79.10%) |
| Bilateral | 14(20.89%) |
| Size of hematoma | |
| 1-1.5cm | 19(28.36%) |
| >1.5cm | 48(71.64%) |
| Hematoma Density | |
| Iso | 38(56.72%) |
| High | 7(10.45%) |
| Mix | 22(32.83%) |

Table: 3
Post-operative CT Scan after 48 hours

| Hematoma location | Residual hematoma | Complete resolution |
|---|---|---|
| Unilateral | 2(3.77%) | 51(96.23%) |
| Bilateral | 2(14.29%) | 12(85.71%) |

Post-operative complications: reoccurrence occurred only in 4 cases (5.97%), neurological deficit in 2 cases (1.49%), pneumonia4 cases (5.97%), UTI 7cases (10.45%), seizures 5cases (7.46%) (Table 4)

Table: 4
Post-operative Complications

| | |
|---|---|
| Reoccurrence | 4(5.97%) |
| Neurological deficit (Fresh) | 2(1.49%) |
| Pneumonia | 4(5.97%) |
| UTI | 7(10.45%) |
| Seizures | 5(7.46%) |

**DISCUSSION:**

CSDH arises in between subdural cavity which is sited between the layers dura mater and the arachnoid [10].Formation of CSDH mainly includes membrane formation around the hematoma and further enlargement of the hematoma, which occurs due to recurrent micro hemorrhages taking place in hematoma or due to abnormal increase in permeability of vessels, which are said to be part of neo- capillary system of outer layer[11]. This study showed male dominance (67.16%), one explanation for male dominance could be that men generally have a more exposure to injuries as compared to female population[12].Meanwhile trauma was found to be one of the leading cause of CSDH. The history of trauma was attained

in 89.55% of patients. This is similar to many studies that demonstrate an average of 60.4-71% of CSDH patients had history of trauma[13].

Patients on anticoagulants are also at increased risk for developing CSDH. It has been anticipated that use of anticoagulant drugs causes a process of producing asymptomatic microbleeds which leads to the evolution of symptomatic hematoma[14]. Generally ageing population is the one who is on anticoagulant therapy, which multiplies the risk of development of CSDH by as far as 42.5 times. Our results showed only 7.4 % of CSDH patients were on anticoagulant drugs and only 2.89% had coagulopathy history. This is in contrast to a study done in Switzerland that showed41% of CSDH patients admitted in a local neurosurgical center were on anticoagulant therapy [15].

In our study common symptoms with which patients presented were headache and hemiparesis and these same were also common in related studies.[16,17]

Computed tomography is the most valuable diagnostic tool of CSDH. It helps in revealing the site, size, midline shift and the density of hematoma. .The density of CSDH in CT scan brain reveals the extent of fresh blood clots in a hematoma cavity. High density indicates that there is fresh bleeding going on in CSDH. This means blood vessels are dynamically nurturing into the membrane of CSDH leading to raise number of fresh blood clots in hematoma[18].As CT scan brain was done in all the patients included in the study; in 79.10 % unilateral hematoma was found while rest 20.89 % had bilateral CSDH. Meanwhile majority of hematomas were Iso-dense 56.72%, rest were mix-density 32.83% and high density 10.45%.

The treatment of chronic subdural hematomas has significantly progressed over time [19,20]. There are several types of management for CSDH which includes both conservative and surgical treatment. At present, conservative management is used for asymptomatic patients with a small hematoma. Generally studies have supported surgical treatment for CSDH[21].Burr-hole is the most common procedure out of all procedures which are being used for treatment of CSDH[22, 23]. It is a commonly known procedure because it is simple with morbidity of 0 to 9%[24, 25] Single- burr hole is usually drilled and hematoma is spontaneously evacuated. The hematoma is repeatedly irrigated with saline until the irrigation returns become clear.

In our study urinary tract infections, seizures followed by reoccurrence of hematoma or pneumonia were common post-operative complications. The overall recurrence rate in our present series was 5.97%.

Craniotomy, as compared to burr hole is more invasive procedure with greater morbidity, however there is no significant difference in postoperative recurrence incidence[26].Nonetheless, craniotomy as a management in CSDH is indicated in a large solid hematoma or multiple recurrences[26] Twist drill craniostomy is also an option for treatment of CSDH. It is a bed side procedure that can be performed on patients with multiple co-morbid, but however there are chances of contamination[27]. In comparison to these two procedures overall, Burr-hole evacuation is a safe and effective method of treatment for chronic subdural hematoma and the recovery is complete in majority of patients.

**CONCLUSION:**

Chronic subdural hematomas are quite common in neurosurgical practice, associated with significant morbidity and mortality. In our study, headache and hemiparesis were the most frequent signs and symptoms of CSDHs. A single-burr hole evacuation is a simple, effective and safe way of treating CSDH, and it has a low incidence of complications.

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# Clinical Profile Of Acute Myocardial Infarction Patients At PNS -SHIFA Hospital Karachi

Madiha Mohyuddin[1], Imtiaz Ahmed Khan[2], Wajahat Lodhi[3]

**ABSTRACT:**

**Objective:** To study the risk factors, complications and use of streptokinase in patients of acute myocardial infarction (MI) presenting at Coronary Care Unit (CCU) of PNS SHIFA Hospital Karachi.

**Materials and Methods:** This study was conducted at CCU, PNS SHIFA Hospital Karachi, from January 2008 to December 2012. It is a retrospective cohort study with non-probability convenient sampling. Diagnosed MI cases were included in the study from all age groups, gender and backgrounds. Patients with other cardiac/non-cardiac diseases presenting with symptoms similar to MI were excluded.

**Results:** Acute myocardial infarction patients were 418, out of the total 2250 admissions in CCU, 71.29% were males. 67.7% were smokers, 60.2% had sedentary life style, 56.2% patients were known hypertensive and 42.1% were known diabetics. 63.63% were eligible for streptokinase administration at the time of admission. Left ventricular failure developed in 13% patients and 6.6% went into cardiogenic shock.

**Conclusion:** Acute myocardial infarction was found to be fairly common cardiac emergency among all cases admitted in the CCU. It has strong association with male gender, smoking, sedentary life style, hypertension, diabetes mellitus and hyperlipidemia. Left Ventricular failure was the leading complication. 63.63% were eligible for streptokinase administration and mortality rate was 5%.

**Keywords:** Acute myocardial infarction, Streptokinase, Clinical profile, Risk factors, Complications.

## INTRODUCTION:

Acute Myocardial Infarction (AMI) is a clinical syndrome resulting from a coronary artery occlusion with cardiac myocyte death in the region supplied by the culprit artery[1]. WHO has estimated in 2004 that 12.2% (7.2 million) of worldwide deaths were from ischemic heart disease with it being the leading cause of death in high or middle income countries and second only to lower respiratory infections in lower income countries.[2] Cardio-vascular diseases are a significant health burden on a country or as general on the health system. In the year 2005, 58 million people died of cardiovascular diseases (CVD) accounting for 30% of all deaths worldwide; more than half of these deaths were in the developing countries[3]. Characteristic presentation of acute myocardial infarction (AMI) is with central chest pain radiating to neck, jaw and upper or even lower arm. The pain is typically dull constricting, choking or heavy and may also be associated with breathlessness, sweating and nausea[4]. The WHO criteria were refined in 2000 to give more prominence to cardiac biomarkers. According to new guidelines cardiac troponin rise accompanied by either typical symptoms, pathological Q waves, ST elevation or depression, or coronary intervention is diagnostic of MI[5]. Over the years, careful monitoring of the Framingham Study population has led to the identification of major CVD risk factors, as well as valuable information on the effects of these factors such as hypertension, [6] obesity, smoking[7] age, gender, and psychosocial issues. Diabetes[8] and lack of physical activity [9] are also important risk factors. Coronary artery occlusion is considered the basis for and consequence of myocardial ischemia. In most cases of acute MI, permanent damage to the heart occurs when the perfusion of the myocardium is severely reduced for an extended interval of (usually lasting 2 to 4 hours). This delay in the onset of permanent myocardial injury provides the rationale for rapid diagnosis in acute MI to permit early coronary reperfusion, the purpose of which is to establish reperfusion and salvage as much at risk myocardium as possible.[10]

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## MATERIALS & METHODS:

The study was conducted at PNS-SHIFA hospital Karachi, a tertiary care hospital from January 2008 to December 2012. It is a retrospective cohort study in which 418 patients were included presenting at the coronary care unit of PNS SHIFA with acute myocardial infarction. The sampling technique was non-probability convenient sampling. All the cases in which diagnosis of MI was confirmed by clinical evaluation and laboratory studies were included in the study. Patients having other cardiac or non-cardiac diseases presenting with symptoms similar to MI were not included.

The patients were managed according to Standard PNS-SHIFA protocols (AHA/ACCA guidelines) for emergency management of AMI. The diagnosis was made on the basis of targeted history, examination, ECG changes and elevated cardiac enzymes/markers (CK-MB, Troponin). The ECG changes included ST segment elevation over the area of damage, ST segment depression in leads opposite to infarct, pathological Q waves, reduced R waves and inverted T waves. Cardiac enzyme CK MB was found out in Units per Liter by using International Federation of Clinical Chemistry (IFCC) method using P 800 (cobas) by company Roche, Trop I was done using Electro Chemiluminescence immunoassay (Eclia) using Cobas E411 by Roche. Treatment was started without any delay after establishing the diagnosis. Anti-platelet agents Aspirin 160-325 mg orally and Clopidogrel 600 mg orally were given.[10] In hypoxemic patients oxygen 2-4 liters per minute was given by nasal prongs or face mask and the need for oxygen administration was reassessed after 6-8 hours. Sublingual Nitroglycerine

was given in a dose of 0.4 mg up to three doses 5 minutes apart. Oral Beta Blocker Metoprolol 25-50 mg 6 hourly was given. Streptokinase was administered 1.5 million units per 1 hour infusion to patients presenting within first 10-12 hours of AMI and met the streptokinase eligibility criteria.[11] Angiotensin converting Enzyme Inhibitors Captopril was also given.[12] After stabilizing the patients, a detailed history was obtained regarding predisposing risk factors. The anatomical location of infarct was determined on the basis of 12 lead ECG findings. The patients were observed for development of any complications and managed accordingly.[13] The data was collected on a predesigned proforma after obtaining an oral consent from the patients. Data was analyzed using SPSS 15 software and results are expressed as percentages, frequencies.

**RESULTS:**

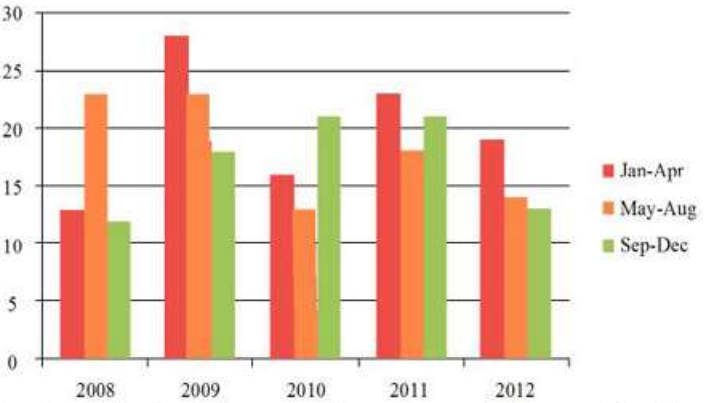
A total of 2250 patients were admitted at CCU of PNS SHIFA, out of which 1076 (47.8%) had Acute Coronary Syndrome and 418 suffered from Acute Myocardial Infarction which makes 18.5% of total patients and 38.8% of ACS patients. As shown in table 1, out of 418 AMI patients 298 were males and 120 were females. 157 out of 418 were between the ages of 46 to 60 years (Table 1)

Table: 1
Non-Variable and Variable Risk Factors
N=418

| | | | | |
|---|---|---|---|---|
| Non-Variable: | | | | |
| Gender | Males | Females | | |
| | 71.29% | 28.70% | | |
| Age(years) | 30-45 | 46-60 | 61-75 | 76-90 |
| | 16.2% | 37.5% | 33.2% | 13.1% |
| Genetic predisposition (family history) | 31.8% | | | |
| Variable: | | | | |
| Smokers | 67.7% | | | |
| Sedentary life style | 60.2% | | | |
| Hypertension | 56.2% | | | |
| Diabetes | 42.1% | | | |
| Hyperlipidemia | 37.8% | | | |
| Psychosocial Factors | 20.3% | | | |

Out of 418 AMI patients 266(63.63%) met the eligibility criteria for streptokinase administration while 152(36.36%) patients were not given streptokinase as they did not meet the criteria or presented late at the CCU. 276(66%) patients suffered from Anterior Wall MI, 121 (28.9%) had Inferior Wall MI and only 21 (5%) suffered from lateral wall MI. (Figure 1)

Figure: 1
Quarterly Strength of Streptokinase Eligible AMI patients




Left ventricular failure was the most common complication which was seen in 56 out of 418 (13%) followed by complete heart block, 38 patients out of 418 (9%), cardiogenic shock occurred in 28 patients (6.6%) and death occurred in 21 patients (5%). 275 out of 418 had an uneventful recovery to be discharged from CCU with follow up visits at OPD for long term management or referral to Armed Forces Institute of Cardiology(AFIC) Rawalpindi or National institute of cardiovascular diseases (NICVD) Karachi for further evaluation and coronary interventions (Table 2)

Table: 2
Complications of Acute Myocardial Infarction

| Complications | Percentage (%) |
|---|---|
| Left Ventricular Failure | 13 |
| Complete Heart Block | 9 |
| Cardiogenic Shock | 6.6 |
| Death | 5 |

**DISCUSSION:**

An Acute Myocardial Infarction (AMI) requires immediate medical attention. Treatment attempts to salvage as much myocardium as possible and to prevent further complications, hence the phrase "time is muscle".[12] Antiplatelet regimen is started as soon as diagnosis of AMI is established. It includes Aspirin 160-325 mg loading dose in acute setting followed by 75 mg daily, continued indefinitely have proven to be beneficial in decreasing mortality. It acts by irreversible acetylation of cyclooxygenase which inhibits synthesis of thromboxane $A^2$ leading to rapid decrease in its plasma levels thus interfering with platelet aggregation.[14,15] Clopidogrel 600mg has been associated with reduction in infarction size compared with lower dose of 300 mg and it should be continued for up to 1 year after infarction at dose of 75mg per day. It acts by irreversibly blocking ADP receptor(P2Y12) on platelet.[15,16] There is less data to support or refute use of oxygen therapy in the care of AMI patients, its use is particularly restricted to hypoxemic patients (oxygen saturation less than 90%), according to a pooled Cochrane analysis of 3 trials there is 3 fold higher risk of death of patients with AMI treated with oxygen than patients treated at room

temperature.[11,12] Nitroglycerine causes smooth muscle relaxation, thus decreasing myocardial oxygen demand by reducing pre-load and increasing myocardial oxygen supply by dilatation of infarcted and collateral coronary vessels. It also relieves or diminishes chest discomfort.[17] Fibrinolysis is the most effective pharmacological means to achieve artery patency leading to coronary reperfusion limiting infarct size, decreasing left ventricular dysfunction and improving survival.[20,21] Fibrinolytic therapy ideally should me administrated within first 30 minutes (door to needle time is 30 minutes) or up to 12 hours of myocardial infarction to patients who meet the eligibility criteria. Fibrinolytic agents work by promoting conversion of plasminogen to active plasmin form which lysis the fibrin clot. Absolute contraindications to fibrinolytic therapy include known structural cerebral vascular lesion, malignant intracranial neoplasm, ischemic stroke within 3 months except acute ischemic stroke within 4.5 hours, significant closed-head or facial trauma within 3 months, suspected aortic dissection. Active bleeding or bleeding diathesis, intracranial or spinal surgery within 2 months, severe uncontrolled hypertension, prior streptokinase treatment in last 6 months. In our study 63.63% met the eligibility criteria and were timely administered streptokinase, while 36.36% patients did not meet the criteria or presented late at CCU. Late presentation was the main reason for ineligibility for streptokinase, because of lack of awareness and education and people presenting from rural areas where these facilities are not available.[22] Aspirin and Clopidogrel should be administered to patients with AMI who receive fibrinolytic therapy for better outcome level of evidence is according to American Heart Association guidelines for treatment of ST Elevation Myocardial Infarction.[12] Intravenous Beta Blockers should be started in first 24 hours of AMI who are not at risk of cardiogenic shock, have signs of heart failure or evidence of low output state, they help reduce pain and reduce risk of re-infarction or ventricular fibrillation.[12,18] Angiotensin Converting Enzyme (ACE) Inhibitors leads to reduction in ventricular remodeling and dilatation with subsequent decrease in congestive heart failure. Angiotensin converting enzyme inhibitors in the convalescent phase more than three days after the onset of symptoms) has also been well documented in clinical trials. [19,20,21,22] The administration of these drugs during the healing phase of infarction and thereafter in patients with left ventricular ejection < 40% whether symptomatic or not reduces morbidity and mortality.[23] ACE inhibitors are now recommended in every patient with acute MI, to be started within first 24 hours and continued up to six weeks, unless there are contraindications[24]

Our most common complication was Ventricular failure that developed in 13% of patients soon after presentation that emphasizes on the role of ACE inhibitors in the emergency management, followed by complete heart block in 9% of patients, cardiogenic shock went on developing in 6.6% of the patients. Despite all our efforts and treatment, 5% of patients did not survive because of extensive damage to the myocardium, late presentation or development of complications. One of the studies has documented a mortality rate of 10.5% [20]

Our study showed that males are at more risk than women and the highest incidence of AMI presentation was between ages of 46 to 60. Yusuf et al has concluded median age of AMI in South Asia to be 53 (46-61) which is close to our findings. [25] Among the variable risk factors in our study, smoking has the highest association 67.7% followed by sedentary life style 60.2% then was hypertension 56.2%, diabetes 42.1% and 37.8% hyperlipidemia. Pais et al has also related smoking as the strongest variable risk factor followed by diabetes and hypertension which is similar to our findings.[26] Rosengren et al in their study has associated psychosocial stressors with AMI and our study showed 20.3% patients had psychosocial factors affecting their lives highlighting the importance of addressing these stressors in the preventive strategies. [27,28]

## CONCLUSION:

Myocardial infarction (MI) is a fairly common cardiac emergency of all cases admitted in PNS SHIFA CCU. It has strong association with male gender, smoking sedentary life style, hypertension, diabetes mellitus and hyperlipidemia. Left Ventricular failure was the leading complication. 63.63% were found to be eligible for streptokinase administration and mortality rate was 5%.It is important to identify high risk groups, keep them under medical surveillance and if presentation is with AMI the variable risk factors should tried to be modified.

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# Frequency Of Dental Caries On Individual Tooth Surfaces Of First Permanent Molars Between 6-13 Years Old Children

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**ABSTRACT**

**Objective:** To determine the frequency of dental caries of first permanent molars and compare its distribution by age, arch and involved surface of the tooth.

**Materials and Methods:** This observational study was carried out in the Operative Department of Bahria Dental College, Karachi during the period of January2014 -December 2014.Total of two hundred and twenty one first permanent molars were examined for caries on different tooth surfaces. (Occlusal, Mesial, Distal, MOD).Children were divided into three groups on the basis of their ages .Data was entered in SPSS version 17 for descriptive analysis and to check statistically significant relationship between different age groups and involved surfaces of the tooth.

**Results:** There were 134 males and 87 females. Frequency of caries in left mandibular first molars was 33.50%, highest among all molars. In 6-8 years old children, frequency of caries was 14%, this percentage increased to 41.63% in 9 to 11 years old, and further increased to 44.34% in 12-13 year old children. Highest occurrence of caries was observed on the occlusal surface 50% in all age groups, followed by MOD surface 21.74%.%. Significant relationship was found between ages and involved surface of teeth with p-value 0.000.

**Conclusion:** Based on this study's results, it can be concluded that the risk of developing caries on the permanent first molars' occlusal surfaces was high around the age of 12 year.

**Keywords:** Caries, First permanent molars, Occlusal caries, Mesial surface, Distal surface.

## INTRODUCATION:

Dental caries is a transmissible infection of the teeth and is one of the most prevalent chronic diseases of childhood.[1] The first permanent molars are very vulnerable to caries attack because of their early eruption in the mouth, their anatomical structure and their positioning in the mouth which makes it difficult for a young child to keep it plaque free.[2] If left untreated, dental caries can lead to pain, infection, loss of function, and eventually loss of the tooth.[1,3] These molars are acknowledged by many authors as a mirror of the entire oral health status, predicting the condition of other teeth and if one of the first permanent molars gets decayed in the first year after its eruption, it will predict with high probability caries extension to the other first permanent molars.[4] Many studies show high prevalence of caries in the first permanent molars, even shortly after their eruption.[5,6]

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Even in countries where local and general caries preventive measures are routinely applied, occlusal surface of the first permanent molar remains the place of choice for the carious process.[7]

The prevalence of caries amongst young children has been reported in many publications. A study done in China concluded that the prevalence of dental caries in the deciduous and permanent dentitions of 7- to 8-year-old children was high.[8] Various studies explained that susceptibly of the first permanent molar is related to factors such as tooth eruption time and type, special anatomy and incomplete enamel calcification.[2,9] Seyedein in a study involving 43772 students of fifth grade from all provinces and districts of Iran, classified by gender and place of residence, found that the DMFT index in 12-year-old students was 1.67 in 1994 and the highest prevalence of caries was seen in the first permanent molars.10The prevalence of early childhood caries in Clifton cantonment area of Karachi, Pakistan was known to be 29.1% with the mean DMFT of 1.14 ± 2.223.11A study done in Iran reported 21.8% occlusal surface of the samples was decayed and there was a significant correlation between the amount of plaque on the occlusal surface and also DMFT with occlusal carries (p=0.03).[12] Knowledge of disease epidemiology and pattern of caries in population aids in disease diagnosis and prevention. It is essential to obtain base line data regarding the condition of the first permanent molars in young adolescents so that appropriate prevention and treatment options can be planned.[13]

The aim of this study was to determine the frequency of dental caries developed on the first permanent molars of 6- to 13-year-old children and compare their age groups with the arch and individually involved surfaces of the tooth.

## MATERIALS AND METHODS:

It was a descriptive study carried out from Jan 2014-to December 2014 in children attending the outpatient department of operative dentistry of Bahria Dental College. The study group included two hundred and twenty one children (aged 06 to 13 years) with carious lesion in first permanent molars. Convenience sampling technique was used. Informed consent

of all subjects was obtained after explaining the nature of the study. Inclusion criteria include children with age range of 6-13 years old, co-operative children with carious lesion only on one first permanent molar. Children with pain and infection in their first permanent molars, children who had systemic diseases as confirmed by their medical records and those with visible calcification disturbances of the dentition were excluded from the study.

The first permanent molars were examined in standard lighting conditions provided by the dental unit. Visual examination was performed on clean and air-dried teeth. Proforma designed to record the information regarding age, gender, arch, tooth numbers and surface involved was used. The data was collected and analyzed with SPSS software version [17]. Mean and standard deviation for age was determined. Chi-square test was used to assess significant relationship between age and involved tooth surface.

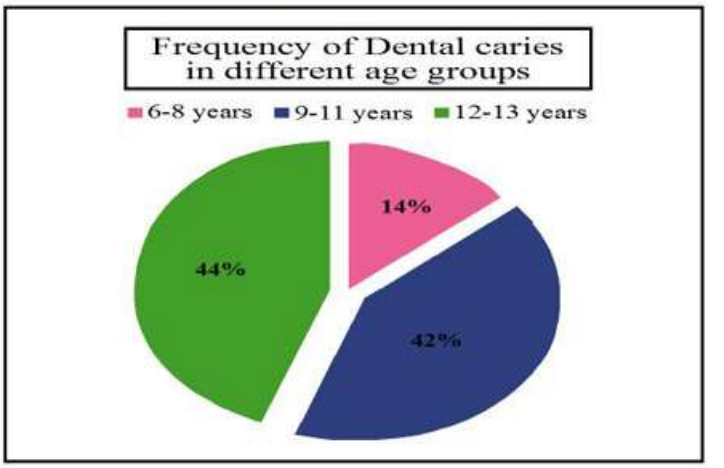
**RESULTS:**

The total numbers of subjects were 221 (Table. 1), out of which 134 (60.6 %) were males and 87 (39.4 %) were females with age ranged from 06 to 13 year old. Children were divided into three age groups, 31 out of 221 children belonged to age group 6-8 years, 92 to age group 9-11 years and rests of 98 were 12-13 years old. As one may notice, 14% of the 6-8 years old children had caries in their first molar, this percentage increased to 41.63% in 9 to 11 years old, and further increased to 44.34% in 12-13 year old children. (Fig 1)

Table: 1
Frequencies and Percentages of Different Variables

| | Variables | Frequency | Percent |
|---|---|---|---|
| Gender N=221 | Male | 134 | 60.6 |
| | Female | 87 | 39.4 |
| Age N=221 | 6-8 Years | 31 | 14.0 |
| | 9-11 Years | 92 | 41.6 |
| | 12-13 Years | 98 | 44.3 |
| Arch N=221 | Maxillary | 84 | 38.0 |
| | Mandibular | 137 | 62.0 |
| Teeth No. N=221 | Upper right first molars | 48 | 21.7 |
| | Upper left first molars | 36 | 16.3 |
| | Lower left first molars | 74 | 33.5 |
| | Lower right first molars | 63 | 28.5 |
| Surface Involved N=221 | Occlusal | 125 | 56.6 |
| | Mesial | 45 | 20.4 |
| | Distal | 13 | 5.9 |
| | MOD | 38 | 17.2 |

Figure: 1
Percentages of Dental Caries in 6- 13 Year Old Children in their First Permanent Molars




In the 6-8 years age group: Out of 31 children, 74.19% were males and 25.81% were females. The anatomic distribution of the involved teeth; frequency of right mandibular first molars (n=14) were highest in all teeth followed by left mandibular first molars (n=9). (Table 2) Highest prevalence of caries was noticed on the occlusal surface 38.71%, followed by MOD surface 22.58%.

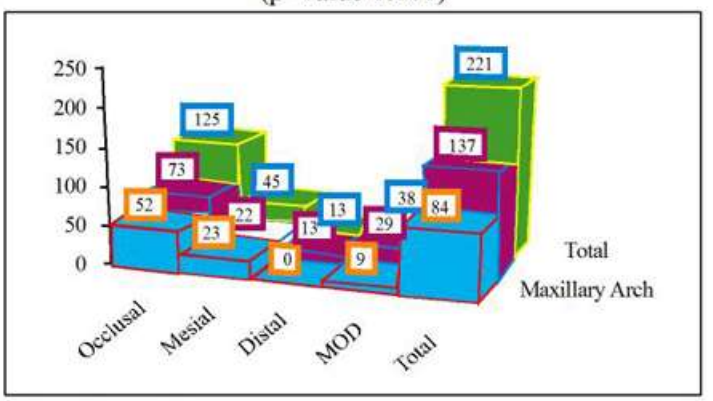
In the age group of 9-11 years: 92 children were examined in this group, 44 were males and 48 were female. 38 maxillary molars and 54 mandibular molars had caries. The anatomic distribution of the involved teeth; frequency of left mandibular first molars (n=46) were highest in all teeth followed by right mandibular first molars (n=36). Highest frequency of caries was observed on the occlusal surface 50%, followed by MOD surface 21.74%.
(Table 2)

In the age group of 12-13 years: Out of 98 children, 67 were males and 31 were females. Frequency of caries in maxillary and mandibular molars was 39 and 59 respectively. Frequency of left mandibular first molars (n=32) were highest in all teeth followed by right mandibular first molars (n=27). Highest frequency of caries was found on the occlusal surface 68.37%, followed by mesial surface 20.41%. Significant relationship was present between different age groups and involved surface of teeth with p-value 0.000 (Table 2). Out of 221 examined molars, 61.99% mandibular molars had carious lesion (53.29% on occlusal surface, 16.06% on mesial surface, 9.49% on distal surface, 20.17% on MOD surface). 38.01% Maxillary molars were affected by carious lesion, (61.91% located on occlusal surface, 23.81% on mesial surface, no caries on distal surface, and 10.72% on MOD surface). Chi-square test showed a significant relationship (Fig 2) between tooth numbers and involved surfaces with p- value 0.004.

Table: 2
Frequencies & Cross Tabulation Between Different Age Groups and Variables
(Gender, Arch, Tooth Numbers, Tooth Surfaces)

| Variables | | 6-8 Years | 9-11 Years | 12-13 Years | Chi-Square test P-Value |
|---|---|---|---|---|---|
| Gender | Male | 23 | 44 | 67 | 0.004 |
| | Female | 8 | 48 | 31 | |
| | Total N=221 | 31 | 92 | 98 | |
| Arch | Maxillary | 7 | 38 | 39 | 0.158 |
| | Mandibular | 24 | 54 | 59 | |
| | Total N=221 | 31 | 92 | 98 | |
| Tooth number | Upper right first molars | 7 | 19 | 22 | 0.259 |
| | Upper left first molars | 1 | 18 | 17 | |
| | Lower left first molars | 14 | 33 | 27 | |
| | Lower right first molars | 9 | 22 | 32 | |
| | Total N=221 | 31 | 92 | 98 | |
| Surface Involved N=221 | Occlusal | 12 | 46 | 67 | 0.000 |
| | Mesial | 6 | 19 | 20 | |
| | Distal | 6 | 7 | 0 | |
| | MOD | 7 | 20 | 11 | |
| | Total N=221 | 31 | 92 | 98 | |

Figure: 2
Cross tabulation between Arches and involved surfaces in first permanent molars in 6- 13 years old children
(p- value 0.000)




## DISCUSSION:

Dental caries is a multi-factorial disease influenced by many factors including age, sex, diet, microorganisms, trace elements, saliva, genetic predisposition and tooth morphology.[14] In this study, only the first permanent molars were evaluated since they are a key to the permanent dentition and have almost erupted for about 6 years in the mouth. In addition, the first permanent molars are at greater risk of damage and loss, because of their special morphology. This study showed that majority of the patients reporting to operative department had carious lesion in mandibular first molars. This might be due to improper oral hygiene measures or mandibular first molar erupting earlier than maxillary first molar.

Dental caries is a disease that shows a strong relationship with age as stated by Simon Hilson's study.[15] Similar result was observed in our study, dental caries occurrence has been increasing in children with age. The present study also shows a higher percentage of caries in males compared to females. The number of males attending the hospital was higher compared to females. Lukacs and Largaespada in their study showed that when dental caries rates are reported by sex, females are typically found to exhibit higher prevalence rates than males.[16]

This study demonstrated that caries was predominantly located on the occlusal surfaces in maxillary and mandibular first molars. An explanation for this finding is that dental caries is an infectious disease, and it is likely that the permanent first molars' occlusal surfaces are easily colonized by bacteria due to their special morphology and functional characteristics, as well as to the surrounding conditions the newly erupted permanent molars have to face (e.g. immediate proximity of carious primary molars). Also, the significant positive relationship between the child's age and permanent first molars' occlusal surface caries implied that as age increases, the probability of developing caries is greater[17]. Even in countries that traditionally apply general and local caries prevention programs, the occlusal surface of the first permanent molar remains the choice location for caries shortly after its emergence.[18] Thus, McDonald pointed out the high frequency of occlusal caries on the first permanent molar for all age groups.[19] Anne Norblad stated that the "high risk" dental surfaces in children under 10 years of age are the occlusal surfaces of the first molars20 while another study reported that by the age of six 4.9% of the children already have caries on the first permanent molar[21]. Epidemiological studies conducted in Romania show similar results.[22] Grivu reported for Timisoara high caries prevalence in first permanent molars – 33.33% at the age of 7, 72.52% at the age of 8 and 91.66% at the age of 9.23 Luca et al. reported a 77.67% frequency of occlusal caries on the first permanent molar in children aged 6 to 9 years old living in a rural area and a similar figure, of about 70%, for groups of children aged 6 to 12 years old examined and treated in the Clinic of Pedodontics in Bucharest.[24] In terms of caries topography on the first permanent molar, this study is consistent with many existing studies in the literature[25,26,27,28] indicating caries development in the occlusal pits and fissures and also with those that note caries occurrence shortly after the eruption of the teeth.[29]

## CONCLUSION:

Caries of the first permanent molar grafted mostly on the pits and fissures at shortly after their eruption arcade. Dental health status of children from our study draw attention to the need of establishing certain national and community caries preventive programs for children starting at kindergarten-age in order to decrease the prevalence and severity of tooth decay in permanent dentition.

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ORIGINAL ARTICLE

# Safety Profile Of Methotrexate And Leflunomide In Rheumatoid Arthritis

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**ABSTRACT**

**Objective:** To compare the safety profile of Methotrexate and Leflunomide in patients of rheumatoid arthritis.

**Material and Methods:** A 24-week, single-blind, interventional, study was carried out on 274 patients of either sex, aged 29-69 years, diagnosed to have rheumatoid arthritis. One group was given tablet Methotrexate, 10 mg (four 2.5 mg tablets), once weekly and the other was put on tablet Leflunomide, 20 mg, once daily, orally. At each follow up laboratory parameters (Hb%, TLC, ESR, PC, SGPT,S Creatinine) and adverse effects were evaluated.

**Results:** Of the 274 patients, 126 were on Methotrexate (70.63 % females, 61.11% RF positive, mean age 45.57 + 10.32 years) and 148 on Leflunomide (79.72 % females, 73.64 % RF positive, mean age 46.35 + 9.68 years). Laboratory parameters (TLC, SGPT, creatinine) between the two groups showed statistically significant results at the end of the study. Nausea was seen in 30.2% & 10.8% patients at 6 weeks and 5.6% and 0% at 24 weeks in the Methotrexate and Leflunomide groups respectively while alopecia was seen in 0% & 19.6% patients at 6 weeks and 1.6% & 24.3% at 24 weeks in the Methotrexate and Leflunomide groups respectively. All values were significant statistically.

**Conclusion:** Leflunomide was found to have a better safety profile than Methotrexate as it produced greater improvement in laboratory parameters with lesser adverse effects in comparison to the traditionally used, first-choice, drug Methotrexate.

**Keywords:** Rheumatoid arthritis, Methotrexate, Leflunomide, Laboratory parameters, Adverse effects.

## INTRODUCTION:

Rheumatoid arthritis (RA) is a chronic, progressive, systemic, autoimmune disease in which joint destruction and loss of function is followed by deterioration in life quality [1]. It has a worldwide prevalence of 1%, the highest incidence being in the fifth decade, and a female preponderance, affecting women three to five times as often as men[2]. India and Pakistan have prevalence rates of 0.5% and 0.2-1% respectively [3]. Genetic association with (HLA-DR4), cigarette smoking, use of decaffeinated coffee, presence of Herpes virus, Epstein-Barr virus and Human Herpes Virus- 6 infections are all risk factors that make a person susceptible to RA [4,5]. Patients present with joint inflammation and constitutional symptoms like fever, malaise, anorexia, weight loss, pain, local edema, synovial thickening and joint erosion. They have painful, mostly symmetrical small joint involvement, initially of the hands, feet and cervical spine with subsequent involvement of the large joints. Morning stiffness is present whereas, the presence of rheumatoid nodules, usually seen in 20-30% of patients, is indicative of a poor prognosis. Extra-articular manifestations are seen in about 15% of individuals 6. Eventually, synovitis and resultant joint erosion leads to deformity and loss of function.

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Diagnosis is based upon a combination of physical examination, laboratory tests, x-rays and the American College of Rheumatology (ACR) criteria (1987) [7]. The latter are:

- Stiffness of joints lasting for more than 1 hour in the morning Inflammation and swelling of more than 3 of 14 joints or groups of joints
- Inflammation of joints of the hands
- Arthritis of the same joints on both sides of the body.

The above given points must be present for a minimum of six weeks ,while other features are the presence of subcutaneous nodules, rheumatoid factor and changes involving erosion of joints seen on radiography. A person fulfilling four of seven given criteria can be said to be suffering from RA.

Disease-modifying anti-rheumatic drugs (DMARDs) are the mainstay in the current treatment of RA. Of these Methotrexate, Leflunomide, Penicillamine, Cyclosporine, the newer biologics along with NSAIDs and Corticosteroids (where and when needed) are the common choices. However, the traditionally used first- choice drug is Methotrexate. Present study was designed to evaluate the safety profile of the first-choice drug, Methotrexate, and Leflunomide; two commonly prescribed drugs in our population.

## MATERIALS AND METHODS:

This twenty-four week, interventional, prospective, single-blind study was conducted from October, 2009 to March, 2011 after being approved by the Institutional Review Board (IRB) and Board of Advanced Studies and Research (BASR), Dow University of Health Sciences (DUHS). It was carried out on patients visiting the out-patients department of a private teaching hospital and a private consultant's clinic in Karachi. 317 patients, fulfilling the ACR criteria, were included after an informed, written consent. Each patient was asked to pick a chit from a box which had previously been filled with chits labeled with alphabets 'A' and 'B'. The Principal Investigator was the only one aware that 'A' stood for Methotrexate and ''B' for Leflunomide. In this way two groups of patients were obtained, one taking tablet Methotrexate (159) and the other taking tablet Leflunomide.

(158). 33 patients in group A and 10 patients in group B were lost to follow-up. Remaining 274 patients who completed the study consisted of 126 patients on tablet Methotrexate, 10 mg weekly (4 tablets of 2.5 mg, orally) and 148 patients on tablet Leflunomide, 20 mg, orally daily. They were advised to continue with (or were prescribed) NSAIDs or corticosteroids which they had been taking when included into the study and were told to return for follow up at 6, 14 and 24 weeks. Laboratory parameters as hemoglobin (Hb), total leucocyte count (TLC), erythrocyte sedimentation rate (ESR), platelet count (PC), C-reactive protein (CRP), serum creatinine and serum glutamic pyruvic transaminase (SGPT) were evaluated at baseline and at each follow up till 24 weeks. Statistical analysis was done on SPSS version 18.0. Independent t-test was used for continuous variables. Chi-square test was used for categorical variables. P value of < 0.05 was taken as significant.

**RESULTS:**

The Methotrexate group (126) consisted of 89 (70.63 %) females with 77 (61.11%) patients positive for Rheumatoid factor while Leflunomide (148) group consisted of 118 (79.72 %) females with 109 (73.64 %) patients positive for Rheumatoid factor.(Table 1)

In methotrexate group mean age was 45.57 + 10.32 years whereas in leflunomide group mean age was 46.35 + 9.68 years. Baseline laboratory parameters did not show statistical difference between the groups.(Table 2). Comparison of laboratory parameters of total leucocyte count, SGPT and serum creatinine showed statistically significant results at 24 weeks between the two drugs with more decrease being produced numerically by leflunomide.(Table 3) Comparing the adverse effects in the two groups nausea was seen in 38 (30.2%) patients using Methotrexate and 16 (10.8%) patients using Leflunomide at 6 weeks which fell to only 7 (5.6%) patients in the Methotrexate group at 24 weeks; all being very highly significant (p = 0.004). Mouth ulcers were seen in 14 (11.1%) patients taking Methotrexate and 10 (6.8%) patients taking Leflunomide at 6 weeks (p = 0.204) but were absent at 24 weeks. Diarrhea was seen in 10 (7.9%) patients taking Methotrexate and 14 (9.5%) patients taking Leflunomide at 6 weeks only and had subsided by the next follow-ups, being statistically insignificant (p= 0.657). Rash was similarly seen only at 6 weeks in 3 (2.4%) patients taking Methotrexate and 4 (2.7%) patients taking Leflunomide, both values being statistically insignificant (0.866). Alopecia was seen in 29 (19.6%) patients using Leflunomide at 6 weeks which increased to 36 (24.3%) patients at 24 weeks whereas it was seen in only 2 (1.6%) patients at 24 weeks who were on Methotrexate; all values being very highly significant (p< 0.001) (Table 4).

Table: 1
Gender and Rheumatoid factor

| | METHOTREXATE N=126 | LEFLUNOMIDFE N=148 |
|---|---|---|
| | No of paticnts (%) | No of paticnts (%) |
| Sex: | | |
| Females | 89 (70.63) | 118 (79.72) |
| Males | 37 (29.36) | 30 (20.27) |
| Rheumatoid factor: | | |
| Present | 77 (61.11) | 109 (73.64) |
| Absent | 49 (38.88) | 39 (26.35) |

Table: 2
Age and Baseline laboratory parameter

| PARAMETERS | METHOTREXATE N = 126 Mean ± S.D. | LEFLUNOMIDFE N = 148 Mean ± S.D. | P Value |
|---|---|---|---|
| Age | 45.57±10.32 | 46.35±9.68 | 0.520$^{NS}$ |
| Hemoglobin (g/dl) | 10.76±1.12 | 10.81±1.07 | 0.651$^{NS}$ |
| Total leucocyte count (per cubic mm) | 8572.1±1445.1 | 8318.1±1,716.8 | 0.185$^{NS}$ |
| Erythrocyte Sedimentation Rate (per cubic mm) | 81.03±17.98 | 82.10±14.36 | 0.591$^{NS}$ |
| Platelet count (per cubic mm) | 2,90,277.8± 688,813.7 | 2,96,165.5± 63,475.8 | 0.462$^{NS}$ |
| C-Reactive Protein (microgram/dl) | 2.33±0.69 | 2.39±0.75 | 0.540$^{NS}$ |
| Serum glutamic pyruvic transaminase (SGPT, IU/l) | 31.67±7.37 | 31.84±6.38 | 0.711$^{NS}$ |
| Serum creatinine (mg/dl) | 0.95±0.16 | 0.94 0.18 | 0.838$^{NS}$ |

S.D = Standard deviation, NS= non-significant statistically, Independent T-test utilized

Table : 3
Methotrexate v/s leflunomide laboratory parameters at 24 weeks
N=274

| | METHOTREXATE Mean ± S.D N=126 | LEFLUNOMIDE Mean ± S.D. N= 148 | P Value |
|---|---|---|---|
| Hemoglobin (g/dl) | 12.43±0.92 | 12.63±0.89 | 0.078$^{NS}$ |
| Total leucocyte count (per cubic mm) | 7,142.46± 1,332.23 | 6,727.70± 1,171.65 | 0.007$^{**}$ |
| Erythrocyte Sedimentation Rate (per cubic mm) | 40.14±15.79 | 39.01±12.88 | 0.522$^{NS}$ |
| Platelet count (per cubic mm) | 2,33,738.10± 59,769.58 | 2,37,418.92± 60,968.27 | 0.616$^{NS}$ |
| Liver enzyme (SGPT, IU/l) | 55.29 ± 21.97 | 38.01±17.32 | <0.001$^{***}$ |
| Serum creatinine (mg/dl) | 1.106 ± 0.14 | 0.936±0.13 | <0.001$^{***}$ |

** = highly significant statistically *** = very highly significant statistically, NS= non-significant
Statistically, S.D. = standard deviation, Independent T-test utilized

**DISCUSSION:**

DMARDs have been the drugs of choice as, besides relieving the symptoms, they have demonstrated the potential to retard joint destruction; a hallmark of disease progression. Permanent joint damage begins relatively early in subjects having active, polyarticular RA; initiating early therapy with an effective DMARD improves prognosis whereas delaying therapy, for as little as a few months after the onset of symptoms, worsens it. Though drugs resulting in a cure or leading to permanent remission would be the ideal solution the ground reality is that treatment options currently available, though aiming for remission, should adequately control the acute symptoms with a minimum of adverse effects and lead towards a good prognosis in the long run [8].

Methotrexate acts by inhibiting amino-imidazole- carboxamide ribonucleotide (AICAR) transformylase and thymidylate synthetase. AICAR produces accumulation of adenosine monophosphate (AMP) which in turn is converted to adenosine and inhibits inflammation. Whereas Leflunomide inhibits dihydroorotate dehydrogenase leading to arrest of stimulated cells in the G1 phase of the cell growth. Comparing the effect of Methotrexate and Leflunomide on laboratory parameters at baseline was non-significant indicating equally matched patients in both groups whereas at 24 weeks both drugs revealed suppressant effects on the bone marrow; more so

Table: 4
Adverse effects
Methotrexate / Leflunomide
N=126/148

| At 6 weeks Drug | Nausea Present | Absent | P-value |
|---|---|---|---|
| Methotrexate | 38 | 88 | 0.001$^{***}$ |
| Leflunomide | 16 | 132 | |
| | Mouth Ulcer | | |
| | Present | Absent | |
| Methotrexate | 14 | 112 | 0.204$^{NS}$ |
| Leflunomide | 10 | 138 | |
| | Diarrhoea | | |
| | Present | Absent | |
| Methotrexate | 14 | 116 | 0.657$^{NS}$ |
| Leflunomide | 10 | 134 | |
| | Rash | | |
| | Present | Absent | |
| Methotrexate | 3 | 123 | 0.866$^{NS}$ |
| Leflunomide | 4 | 144 | |
| | Alopecia | | |
| | Present | Absent | |
| Methotrexate | 0 | 126 | 0.001$^{***}$ |
| Leflunomide | 29 | 119 | |
| At 24 Weeks Drug | Nausea | | P-value |
| | Present | Absent | |
| Methotrexate | 7 | 119 | 0.004$^{**}$ |
| Leflunomide | 0 | 148 | |
| | Mouth Ulcer | | |
| | Present | Absent | |
| Methotrexate | 0 | 126 | N/A |
| Leflunomide | 0 | 148 | |
| | Diarrhoea | | |
| | Present | Absent | |
| Methotrexate | 0 | 126 | N/A |
| Leflunomide | 0 | 148 | |
| | Rash | | |
| | Present | Absent | |
| Methotrexate | 0 | 126 | N/A |
| Leflunomide | 0 | 148 | |
| | Alopecia | | |
| | Present | Absent | |
| Methotrexate | 2 | 124 | 0.001$^{***}$ |
| Leflunomide | 36 | 112 | |

*** = very highly significant statistically, NS = non-significant statistically, NA= not applicable Chi square test utilized by leflunomide.

An increase in, hemoglobin level was seen with both drugs. In a comparative study carried out by Emery et al it was seen that treatment with these drugs showed an improvement in the hemoglobin level accompanied with a fall in the leucocyte and platelet counts[9]. Smolen et al found a significant increase (p= 0.01) in hemoglobin levels with Leflunomide i.e from a baseline of 12•15 g/dL to 12•55 g/dL along with a significant reduction in the leucocyte count (p< 0.0001) [10].

Upon comparing the levels seen between the drugs at 24 weeks the decline was numerically greater in the Leflunomide group indicating a more potent control of the disease process than Methotrexate. Changes in the platelet count were not significant when comparing the 24-week values for the two drugs in our study. These features indicate that our patients had tolerated the drugs well and the blood indices had not deteriorated to the extent that any dose alteration was needed. This may have been due to the fact that they belonged to a younger age group (mean ~ 46 years) in comparison to the studies mentioned above.

Researchers, using Methotrexate and Leflunomide have found a significant reduction (p=0.001) in the ESR values viz. 52.5 to 34.3 mm of Hg in patients using Methotrexate and 51.2 to 36.8 mm of Hg in patients using Leflunomide 11. Hansen et al, using Leflunomide, showed a fall of ESR values from 52 mm of Hg to 32 mm of Hg [12]. Our study also showed similar results with ESR values falling from 81.03 to 40.14 mm of Hg in patients put on Methotrexate and from 82.10 to 39.01 mm of Hg in patients using Leflunomide. Rau and Herborn studying the benefits and risks of Methotrexate in RA found elevated serum creatinine levels in their patients which subsided on stopping therapy. Serum creatinine in our patients too rose from a baseline level of 0.95 mg/dl to 1.11 mg/dl[13].

Several studies have shown that both Methotrexate and Leflunomide are hepatotoxic (with the former causing fibrosis), the degree of damage being judged by an increase in the SGPT levels, the cut-off point being a greater than two-fold increase. These changes are reversible if the dose of the drugs is reduced or they are stopped where severe damage has resulted. An Indian study, in which Leflunomide was used as monotherapy, reported a figure of just 3% patients who had raised transaminase levels [14]. Attar studying the adverse effects of Methotrexate in RA demonstrated elevated SGPT levels in 14.1% of her patients [15]. Curtis et al using Leflunomide and Methotrexate in RA patients found 14-22% incidence of SGPT elevation[16]. Similarly, elevations in liver enzymes were also seen in several Western studies [17,18,19].

Changes in the SGPT levels in our study were statistically very highly significant (p<0.001) regarding comparison of drugs at 24-week.. In our study a total of 27 (9.9%) patients showed alteration in SGPT levels with 19 (15.1%) patients on Methotrexate and 8 (5.4%) patients on Leflunomide, the ratio between the two being 2.7 in favor of Methotrexate. The difference seen in the number of patients affected is most probably due to the fact that our patients were younger and our values were obtained at the end of 24 weeks as opposed to the other studies which were of a longer duration (52 weeks). Furthermore, the incidence of liver toxicity seen in our patients with Methotrexate treatment may have been due to the lack of folate supplementation which is known to ameliorate this effect of Methotrexate [20, 21].

An incidence rate of 34% mild to moderate adverse effects was seen in a trial conducted by Hoekstra et al who studied the efficacy and safety of Methotrexate in patients with RA[22]. Ahmed et al in a study carried out in Lahore, Pakistan, obtained an overall figure of 20% in their patients given Leflunomide [23]. In our study 119 (43.43%) patients complained of adverse effects with 89 (32.5%) patients suffering from at least one adverse effect, a figure which is in accordance with that obtained by Hoekstra et al.

Gastrointestinal adverse events (nausea, diarrhea, mouth ulcers) and rash were reported at a rate of 14.5% and 12% respectively in a study by Kalden et al where they compared different treatment strategies in early RA [24]. Silverman et al in their patients on Leflunomide found nausea in 28% with diarrhea and alopecia each in 15% of patients as compared to nausea (34%), diarrhea (17%) and alopecia (6%) in patients given Methotrexate [25]. Similarly Buhroo and Baba studying the effects of low dose Methotrexate demonstrated 21% GIT side effects [26].

In our study gastrointestinal adverse events (nausea, diarrhea, mouth ulcers) and rash were found at an average of 32.1% and 2.6 % respectively. The difference in values in our patients may be due to different demographics between the two patient groups as well as the fact that we did not use folic acid which was used in the above studies. It can be seen that Methotrexate showed a lesser number of patients complaining of diarrhea, rash and alopecia while Leflunomide showed better numerical improvement in blood parameters like hemoglobin, leucocyte count, ESR, platelet count and a lesser increase in the SGPT levels. It also had fewer numbers of patients complaining of nausea and mouth ulcers. It is thus evident that Leflunomide, although not a drug of first choice in RA, is superior to Methotrexate, the traditionally considered drug of first choice in context of effects and safety profile in patients having rheumatoid arthritis in our local setting.

## CONCLUSION:

Leflunomide has a better safety profile than Methotrexate. It produced greater improvement in laboratory parameters with less adverse effects and better control of the disease in comparison to the traditionally used, first-choice, drug Methotrexate. Large, multi-centric studies are needed to further ascertain the effects and safety profile of Methotrexate and Leflunomide in our population.

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# Toxic Effects Of Corn Oil On Liver Histology In Albino Rats

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**ABSTRACT:**
**Objective:** To evaluate whether high quantities of unsaturated fats such as corn oil can produce fatty liver in albino rats.
**Materials and Methods:** This experimental study was carried out at BMSI, JPMC after obtaining ethical approval, from October to November 2008. Forty adult albino rats, weighing 200 to 240 grams were divided into 2 groups according to dietary regimen. Group A received control diet and Group B received high-corn oil diet (20 ml corn oil in 100 gm of diet).The groups were further divided into A1, A2 and B1, B2 on the basis of duration of treatment, that is 4 weeks and 8 weeks respectively. The rats were sacrificed, liver removed and processed for haematoxylin and eosin staining.
**Results:** Haematoxylin and eosin stained sections revealed swollen hepatocytes having vesicular appearance with absent or pyknotic nuclei in high-corn oil group as compared to control animals.
**Conclusion:** This study has proved that use of high quantities of unsaturated fats, such as corn oil can lead to fatty liver.
**Key words:** High-corn oil diet, Fatty liver, Steatohepatitis, Metabolic Syndrome

## INTRODUCTION:

The prevalence of obesity due to excessive consumption of carbohydrate and fat, and inadequate energy expenditure has increased dramatically over the past decade. It is recognized as a low grade and chronic inflammatory state, which leads to the metabolic syndrome, including insulin resistance, type II diabetes, atherosclerosis, hypertension, and fatty liver disease[1-3].

There has been a drastic change in the human diet over the past half century or so, especially in the types of fats and fatty acids consumed. Use of vegetable oil in cooking food is a common practice all around the globe. Of them, the good oil must have a hypolipidemic action. However, this action of cooking oils has led to their excessive use, leading to chronic diseases such as cardiovascular diseases, obesity, cancer, immune-related diseases as well as fatty liver[4,5]. In industrialized nations, on average, over 40% or more of daily energy intake is supplied by dietary fats, although most nutritional guidelines recommend that caloric intake from fats should not be more than 30% of daily caloric intake. 1gram of fat provides 9 Kcal or 38 KJ/gram after complete oxidation, about more than twice that for the same weight of carbohydrates or proteins[6,7].Although polyunsaturated fatty acids inhibit synthesis of triglycerides in the body, they are considered as risk factor for free radical formation. It is a known fact that polyunsaturated fatty acids(PUFA) are more susceptible to lipid peroxidation than saturated fatty acid.[8,9,10,11,12] Corn oil has been shown to enhance liver injury and steatosis in rats after chronic alcohol intake[13].Corn oil is a good source of polyunsaturated fatty acid and its nutritional properties are excellent as it is cholesterol free. The fatty acids found in corn oil are Linoleic acid, Oleic acid, Palmitic acid, Stearic acid and Myristic acid[14].

The westernization of diet has led to chronic liver pathologies not only in western world, but their incidence is increasing at an alarming rate in developing nations as well. The prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing in proportion with the prevalence of obesity[15]. NAFLD has been estimated to occur in 35% of lean and up to 70% of obese patients[16].It ranges from simple fatty liver (steatosis) to nonalcoholic steatohepatitis (NASH) and even cirrhosis, leading to hepatocellular carcinoma. Key events that contribute to the initiation and progression of NAFLD are described as a multi-hit model. In this model, dysregulated metabolism of free fatty acids (FFAs) is considered as the first-hit of pathogenesis, which leads to insulin resistance and fat accumulation in the liver Inflammatory response, oxidative stress, apoptosis, and even autophagy serve as "following-hits" that contribute to the ongoing inflammation[17,18].With this back ground, since only a few studies are available that evaluated the role of corn oil on the liver if used under a high-fat diet regimen, this study was undertaken to assess the effects of high-corn oil diet on the histology of liver.

## MATERIALS AND METHODS:

This study was conducted in the department of Anatomy, Basic Medical Sciences Institute (BMSI), Jinnah Postgraduate Medical Center, Karachi after obtaining ethical approval for 8 weeks from October to November 2008.Forty adult, healthy albino rats, 90-120 old, weighing 200 to 240 gram were taken for this prospective experimental study. The susceptibility of rats to develop fatty liver in response to a high-fat (HF)

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diet is same as in humans[19]. The animals were observed for one week prior to the commencement of the study for the assessment of their health status and amount of food intake. The animals were divided into two groups according to type of diet (Table-1).

Table: 1
Calories of Diet/day for Experimental Albino rats

| | | Normal Diet | | | | High-Corn Oil Diet | | | |
|---|---|---|---|---|---|---|---|---|---|
| Items of Diet | Quantity | Energy | Fat (G) | Protein (G) | Carb (G) | Energy | Fat (G) | Protein (G) | Carb (G) |
| Wheat flour (G) | 11.2 | 38.08 | 0.22 | 1.34 | 7.84 | 38.08 | 0.22 | 1.34 | 7.84 |
| Chick peas (G) | 2 | 4.93 | 0.07 | 0.26 | 0.82 | 4.93 | 0.07 | 0.26 | 0.82 |
| Milk powder (G) | 2.8 | 14.05 | 0.72 | 0.7 | 1.62 | 14.05 | 0.72 | 0.7 | 1.62 |
| Corn oil(ml) | 3.2 | - | - | - | - | 26.56 | 2.94 | - | - |
| Drinking water | Ad Libitum | - | - | - | - | - | - | - | - |
| Final Energy | - | 57.06*, 3.56** | 1.01 | 2.3 | 10.28 | 83.62*, 4.35** | 3.95 | 2.3 | 10.28 |

Key:*Kcal, **Kcal/G of diet, Carb = Carbohydrate

Each group was further divided into two subgroups A1, A2 and B1, B2 based on the duration of treatment i.e. 4 and 8 weeks respectively. Each subgroup had 10 animals. In this study, unsaturated fat was used in the form of corn oil Coroli, made by Cebag ME, Abu Dhabi in the dose of 20 ml/100 gm (20%) of diet20. It contained 830 Kcal, 92 gm fats/100ml, out of which 54 gm were polyunsaturated, 26 gm monounsaturated and 12 gm were saturated, and free of cholesterol. Group A: comprising of 20 animals served as control. They received normal diet[21].

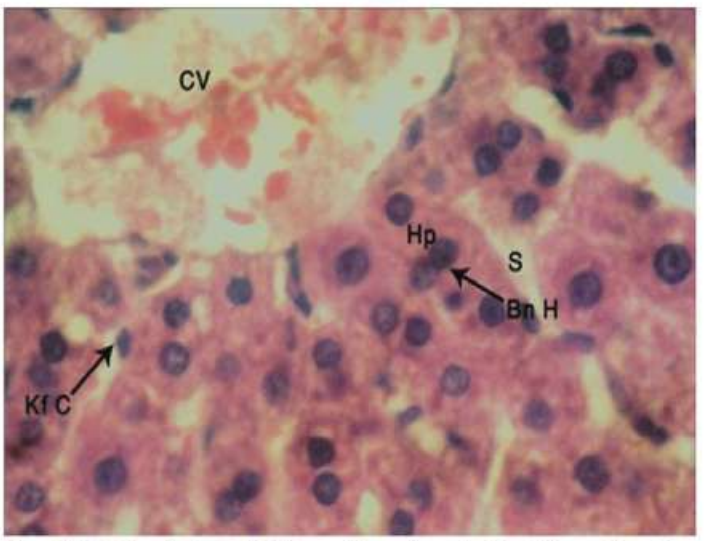
Group B: comprising of 20 animals received high-corn oil diet (20 ml corn oil in 100 gm of diet).

The animals were weighed and kept in cages, with twelve hour light and dark cycle, under laboratory environment. Calculated amount of food with respective constituents and water ad libitum was provided to them (Table-1). The animals were sacrificed at the end of the study period.A midline, longitudinal incision was given in the abdomen. Liver was exposed by incising the diaphragm and was removed and washed with normal saline. A block of tissue comprising of 2mm was taken from the right lobe and fixed in buffered neutral formalin for 24 hours. Then it was processed in ascending grades of alcohol and embedded in paraffin. Four micron (4μm) thick tissue sections were cut on rotatory microtome and taken on albumenized glass slides. Paraffin embedded tissue was stained with Haematoxylin and Eosin[22] to study the general architecture of liver tissue under oil immersion lens.

**RESULTS:**

The haematoxylin and eosin stained sections in control group A showed polygonal hepatocytes arranged in the form of anastomosing plates, one cell thick, separated by the anastomosing sinusoids draining into the central vein. The plates of cells as well as sinusoids radiated from the central vein to the periphery of the lobule. Central vein had normal caliber, with distinct endothelial lining. Hepatocytes showed distinct boundaries with uniformly distributed, granular, acidophilic cytoplasm. Nuclei were large and spherical and occupied the center of the cell, showing even distribution of chromatin. Binucleate cells were also seen. Hepatic sinusoids showed variation in caliber, but lining was smooth and endothelial cells were visible. Fixed monocytes (Kupffer cells) were present in the lining of sinusoids (Figure-1).

Figure: 1

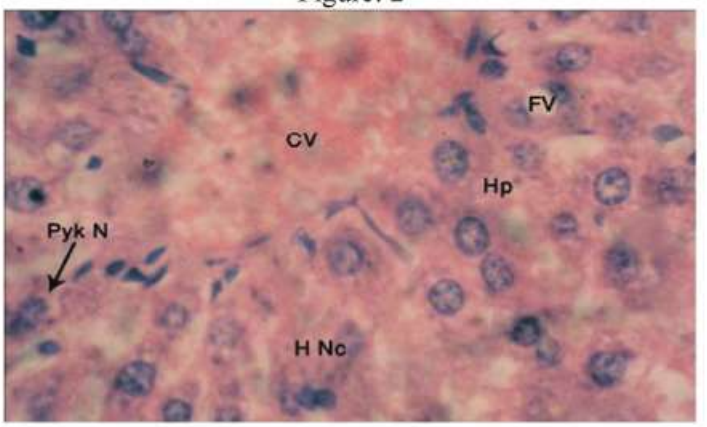



H and E stained, 4μm thick section of control rat liver showing hepatocytes (Hp), central vein (CV), binucleate hepatocytes (Bn H),regular sinusoids (S) and Kupffer cells (Kf C) (Photomicrograph x1000).

The haematoxylin and eosin stained sections in subgroup B-1 showed that normal anastomosing pattern of hepatocytes was retained. Central vein was congested. Sinusoids had varying calibers, at some places they were narrow, whereas at other places they were dilated. Hepatocytes showed vesicular appearance due to the presence of fat granules which were washed out during tissue processing. Nuclei of many hepatocytes were pyknotic. Many hepatocytes showed nuclei with clumped chromatin and disrupted nucleoli. Vacuolated hepatocytes were seen depicting presence of coalesced lipid granules. Necrosed hepatocytes were also seen. Kupffer cells were prominent (Figure-2).

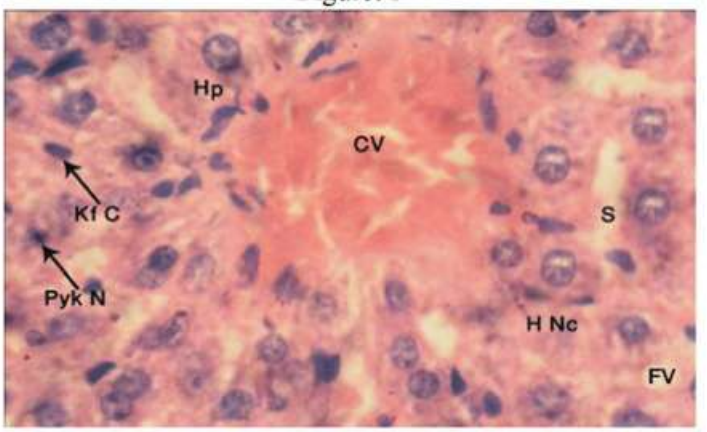
In subgroup B-2, hepatic lobular architecture was highly disorganized. Central vein was dilated and congested. Sinusoids were also slightly dilated. Hepatocytes were ballooned up with indistinct cell membranes and large empty spaces due to presence of fat vacuoles. Hepatocyte nuclei had all stages of disintegration. Many cells showed pyknotic nuclei, nuclei with clumped chromatin and absent nucleoli. Necrosed hepatocytes were also visible. Kupffer cells were prominent (Fig-3).

Figure: 2




H and E stained, 4µm thick section of rat liver showing central vein (CV), hepatocytes (Hp), with pyknotic nuclei (Pyk N), fat vacuoles (FV) and necrosed hepatocytes (H Nc) after 4 weeks treatment with corn oil (Photomicrograph x1000).

Figure: 3




H and E stained, 4µm thick section of rat liver showing central vein (CV)hepatocyte (Hp) with pyknotic nuclei (Pyk N), fat vacuole (FV), necrosed hepatocytes (H Nc) and prominent Kupffer cells (Kf C) in the lining of sinusoids (S) after 8 weeks treatment with corn oil (Photomicrograph x1000).

**DISCUSSION:**

Corn oil is a commonly used food item. Dietary fat composition is believed to affect body weight regulation independent of the quantity of fat consumed[23]. Accumulation of fat results from an imbalance between input/output/oxidation of fatty acids leading to altered impaired lipid metabolism[24].

The present study was designed to observe if high quantity of unsaturated fat, with zero cholesterol can lead hepatic damage in albino rats, because it is a general belief that unsaturated fats are harmless. High unsaturated fat diet was used in the form of corn oil in the dose of 3.2 ml along with normal diet, which makes 20% (20 ml in 100 gm of diet), same as used by Tannenbaum[20] to observe the effect of high-fat diet on basal and stress-induced hypothalamic-pituitary-adrenal activity in adult male rats. In this study, there was preservation of hepatic lobular architecture in 4-week high-corn oil treated animals, although they had developed marked fatty infiltration in hepatocytes. This fat accumulation resulted from the imbalance between the energy intake and energy output as the rats were confined to their cages in addition to receiving high-corn oil diet. Similar changes were observed by Polavarapu11 who demonstrated fatty infiltration in hepatocytes along with necrosis when corn oil was given in addition to ethanol in diet having 35% calories from fat. These findings were also similar to Alarifi[25], who also observed vacuolar degeneration in the cytoplasm of hepatocytes with necrotic foci in lead acetate induced hepatic damage in albino mice. Furthermore, these animals did not show any improvement in liver histology after giving corn oil. The tissue sections from 8 week, high-corn oil treated animal`s revealed disorganization of hepatic lobular architecture, with dilated and congested central vein and sinusoids. Hepatocytes were ballooned with damaged cell membranes and large empty spaces due to the presence of fat vacuoles. Hepatocyte nuclei were pyknotic, with disintegrated chromatin and disrupted nucleoli. Necrosed hepatocytes were also visible. The hepatic damage seen in these animals was a time related process. The accumulation of fat in hepatocytes was due to increased influx of fats because of increased amount of corn oil in the diet (3.95 gm of fat as compared to 1.01gm in control animals). This resulted in accumulation of fat within the hepatocytes in the form of vacuoles as excess fat could not be removed from the liver because enough apo-proteins were not available to transport excess fat from the liver. These findings were in accordance to Tinikios[15] who observed hepatocellular ballooning, that is enlarged hepatocytes, with rarefied cytoplasm, having a reticulated appearance predominantly located in acinar zone 3, around central vein, in liver biopsy from high fat diet using individuals. They have demonstrated that in NAFLD, the processes of lipid transport from liver to the peripheral adipose tissues for storage are dysregulated with resultant increased intra hepatocellular lipids. Excessive lipid storage in hepatocytes contributes to organelle failure, including mitochondrial dysfunction and endoplasmic reticulum(ER) and other organelle stress, and may play a role in hepatic insulin resistance.

**CONCLUSION:**

Polyunsaturated fats, such as corn oil, if used in excess amount produce hepatocellular damage. In this study, high amount of corn oil in diet (3.2 ml per hundred gram of diet) resulted in more than 40% calories from fat, as compared to recommended nutritional guide lines, in which calories from fat should be less than 30% of the diet. Thus vegetable oil, without cholesterol can produce fatty liver. This study can form a base line for the extension of its results to human subjects.

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**ORIGINAL ARTICLE**

# Impact Of Maternal Education On Children's Health In Slum Area Of Karachi

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**ABSTRACT:**

**Objective:** To determine the impact of maternal education on children's health in a slum area of Karachi.

**Materials and Methods:** A population survey (cross-sectional study) was conducted on 390 children under 5years of age residing in Sharifabad, a slum area of Karachi. Systemic random sampling procedure was adopted to select 390 children. The selection of children was irrespective of gender, ethnicity and religion.

**Results:** Out of total 390 mothers, 273 (70%) mothers were illiterate and 117 (30%) were literate. In the literate group 21 mothers could read only, 42 had primary, 23 middle, 24 matric, 5 intermediate and 2 mothers had education up to graduate level. Overall a total 162 (41.54%) children were underweight, 205 (52.56%) were stunted and 89 (22.82%) had wasting. Maximum malnutrition regarding underweight and stunting was seen in children whose mothers had no education (illiterate). Maximum wasting was seen in children whose mothers could read only. There was a significant difference regarding underweight and stunting between the children whose mothers were illiterate in comparison to the children whose mothers had some education ($P<0.05$), but non-significant difference regarding wasting was found.

**Conclusion:** Mother's literacy status has a definite association with malnutrition of the children < 5 years of age which is one of the important risk factors.

**Key words:** Mother's literacy, Malnutrition, Children < 5 years, Slum area, Karachi.

## INTRODUCTION:

Malnutrition may be defined as pathological state resulting from inadequate nutrition, including under-nutrition (protein-energy malnutrition) due to insufficient intake of energy and other nutrients; over-nutrition (overweight and obesity) due to excessive consumption of energy and other nutrients; deficiency diseases due to insufficient intake of one or more specific nutrients such as vitamins or minerals.[1] Under-nutrition is a global public health problem considered to be a principal cause of ill-health and premature morbidities. A total of 162 million and 99 million children aged <5 years were estimated to be stunted and underweight in 2012, respectively.[2] Under-nutrition is also a cause of high child mortality and has long-lasting physiological effects on children.[3] It is also considered to have critical adverse health effects among those children who survive to adulthood.[4,5] Despite economic developments, child under-nutrition still remains a major public health issue in third world countries as India, Pakistan, Bangladesh, Nepal, Sri Lanka etc. whose underlying cause is considered to be poverty .[4,6,7]

Adult literacy is defined as population aged 15 years and over who can both read and write with understanding a short, simple statement on his/her everyday life. Maternal literacy is said to be directly related to child`s nutritional status. A literate mother has increased awareness and importance of breast feeding, dietary components of her child and improved feeding practices, personal hygiene of herself and her child, importance of family planning, importance of vaccination of her child, and last but not the least a literate mother has a higher social network. Therefore an urban mother who has a higher educational status is expected to have children healthier than that of a rural mother. This awareness as a result of improved maternal literacy can prevent a child from severe and recurrent infections which definitely could have an impact on child's health. Therefore we can reach our goal with " TEACH THE MOTHER AND REACH THE CHILD".[8,9,10]

Children whose weight-for-age (W/A), children whose height-for-age (H/A) and children whose weight-for-height (W/H) is below minus two standard deviation (-2SD) from the median of the reference population (National Centre for Health Statistics) are considered to be under-weight, stunted and wasted respectively. According to the national figures of Pakistan given by the State of world's children UNICEF 2015, total adult literacy rate is 55% and in females it is 63% as a male adult literacy rate i.e. only 63 females are literate if there are 100 literate males that is mother's literacy status is more decreased. Among children under five years, prevalence of underweight, stunting and wasting are 32%, 45%and11% respectively in Pakistan.[11]

There is no scientific data available on prevalence of malnutrition among children under five years of age in slum area of Sharifabad, Karachi. The present study was designed to assess the prevalence of malnutrition and to identify the impact of maternal education on child's health.

## MATERIAL AND METHODS:

A community based cross-sectional survey was conducted in Sharifabad, It is located in the industrial area of the Korangi town, Karachi. This area was established in 1983-84. It has a population of about 10,000 to 12,000 people and comprises of different ethnic groups. Study area consisted of different blocks spread over whole area of Sharifabad. Sample was taken from the area comprised of nearly 1000 households. Through statistical formula sample size was derived as

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$$n = \frac{Z^2 \alpha/_2 \; P\,(1 - p)}{B^2}$$

Z = Confidence interval = 95% i.e. 1.96

P = Prevalence= 50% i.e. 0.5

B = Bound of error=5% i.e. .05

$n = (1.96)^2 0.5\,(1 - 0.5) / (0.05)^2$

$n = 384.5 = 385$

At 95% confidence interval, we used the prevalence of 50% (underweight / stunting) and bound on error of 5%. We needed at least 385 children for the study. In this study 390 children were included. Systemic random sampling procedure was adopted to select 390 children. All the data was collected on a pre-defined questionnaire. This data was fed and analyzed on SPSS version 20.00.

The tools for data collection included:

1. Questionnaire for household information and child's information
2. Anthropometric measurements as weight and length (height) were taken to assess the nutritional status of the children.[12, 13]

The age of the child was determined by co-relating the date of birth with Islamic date or events as Ramadan or Eid, local and political events.

An infant weighing scale having a maximum weight capacity of 20 kg was used. Children were weighed with minimal clothing, and the weight was recorded to the nearest of 0.1 kg.

Recumbent length of the children was noted. Each child was made to lie on an adjustable wooden measuring board and length measurements were recorded to the nearest of 0.1 cm.

**RESULTS:**

The total children included in this study were 390, 174(44.62%) males and 216 (55.38%) females. Frequency distribution of age variables in these children was 90 (23.10%) up to one year, 93 (23.85%) between > 1 year and up to 2 years, 82 (21.00%) > 2 years and up to 3 years, 70 (17.95%) > 3 years and up to 4 years and 55 (14.10%) children were more than 4 years. (Table 1).

Table 1

Frequency Distribution of Age groups of Children

N=390

| Age groups | Number | Percentage |
|---|---|---|
| Up to 1 year | 90 | 23.10 |
| > 1 year to 2 years | 93 | 23.85 |
| > 2 years to 3years | 82 | 21.00 |
| > 3 years to 4 years | 70 | 17.95 |
| > 4 years to 5 years | 55 | 14.10 |
| Total | 390 | 100 |

Considering the educational status of the mothers, majority of them, 273 (70%) were illiterate and 117(30%) were literate. Among literate group 21 could read only, 42 had primary, 23 middle, 24matric, 5 intermediate and 2 received education up to graduate level (Table 2).

Association of 390 mother's education with the nutritional status in the children was analyzed. Among 390 children, 162(41.54%) children were underweight, 205(52.56%) stunted, and 89(22.82%) had wasting (Table 2).The mother's educational status was cross-tabbed with the type of malnutrition. We divided mothers of 390 children into two groups. Mothers of 273(70%) children were included in group one that is they were illiterate and second group comprised of 117 (30%) mothers, who had received some education that is mostly primary to matric. In group one (Illiterate Mothers), there were 129 (47.25%) children who were under-weight, 156 (57.14%) stunted and 64 (23.44%) wasted. In second group (Mothers with some education), 33 (28.21%)

Table 2

Frequency Distribution of Mother's Education by Type of Malnutrition

| S.No. | Education | Total | Weight for Age | | Height for Age | | Weight for Height | |
|---|---|---|---|---|---|---|---|---|
| | | | Normal | Under Weight | Normal | Stunting | Normal | Wasting |
| 1. | Illiterate | 273 | 144 | 129 | 117 | 156 | 209 | 64 |
| | | (70.00%) | (52.75%) | (47.25%) | (42.86%) | (57.14%) | (76.56%) | (23.44%) |
| 2. | Can read only | 21 | 12 | 9 | 9 | 12 | 11 | 10 |
| | | (05.38%) | (57.14%) | (42.86%) | (42.86%) | (57.14%) | (52.38%) | (47.62%) |
| 3. | Primary | 42 | 27 | 15 | 21 | 21 | 34 | 8 |
| | | (10.77%) | (64.29%) | ((35.71%) | (50.00%) | (50.00%) | (80.95%) | (19.05%) |
| 4. | Middle | 23 | 18 | 5 | 14 | 9 | 18 | 5 |
| | | (05.90%) | (78.26%) | (21.74%) | (60.87%) | (39.13%) | (78.26%) | (21.74%) |
| 5. | Matric | 24 | 21 | 3 | 18 | 6 | 22 | 2 |
| | | (06.15%) | (87.50%) | (12.5%) | (75.00%) | (25.00%) | (91.67%) | (08.33%) |
| 6. | Inter | 5 | 4 | 1 | 4 | 1 | 5 | 0 |
| | | (01.28%) | (80.00%) | (20.00%) | (80.00%) | (20.00%) | (100%) | (0%) |
| 7. | Graduate | 2 | 2 | 0 | 2 | 0 | 2 | 0 |
| | | (00.51%) | (100%) | (0%) | (100%) | (0%) | (100%) | (0%) |
| | Overall | 390 | 228 | 162 | 185 | 205 | 301 | 89 |
| | | | (58.46%) | (41.54%) | (47.44%) | (52.56%) | (77.18%) | (22.82%) |

were under-weight, 49 (41.88%) stunted and 25 (21.37%) had wasting .There was a significant difference regarding underweight and stunting between the children whose mothers were illiterate in comparison to the children whose mothers had some education($P<0.05$), but non-significant difference regarding wasting was found ($P > 0.05$). (Table 3)

Table3

Frequency Distribution of Type of Malnutrition by Mother's Educational Status

| | Normal | Underweight | P-Value |
|---|---|---|---|
| No Maternal Education | 144 | 129 | 0.000 |
| Some maternal Education | 84 | 33 | |
| | Normal | Stunting | |
| No Maternal Education | 117 | 156 | 0.005 |
| Some maternal Education | 68 | 49 | |
| | Normal | Wasting | |
| No Maternal Education | 209 | 64 | 0.662 |
| Some maternal Education | 92 | 25 | |

**DISCUSSION:**

Our study's results showed that literacy status of mothers strongly affects the nutritional state of the children where illiterate mothers are a risk for the development of malnutrition in children <5 years of age especially underweight and stunting. This coincides with the studies of Sanghvi[14], Correia[15], Deshmukh[16], Ferdous[17], Islam[18] and Chen.[19] All of them have identified illiteracy of mothers as a strong risk factor for malnutrition in children < 5 years of age.

In our study, 205 (52.56%) children were found to be stunted. Majority of these children i.e. 156 (76.10%) belonged to illiterate mothers. Maximum underweight and wasting were found in 129(79.63%) and 64 (71.91%) children respectively and their mothers had no education. This coincides with the studies of Abuya[20], Ojofeitimi[21] and Ahmed.[22] In our study population , 273 (70 %) mothers of the 390 children were illiterate. Of these 273 mothers, 129 children were underweight and 156 children were stunted which on statistical evaluation was found to be significant $P<0.05$. This coincides with the studies of Rikimaru[23] and Lu[24], while wasting was found in 64 children which were found to have non-significant association with mother's education on statistical evaluation. . This coincides with one of our previous studies conducted in rural area of Malir Karachi[25] In our study, 47.25% children were underweight, 57.14% stunted and 23.45% were wasted. This does not coincides with the national figures of Pakistan i.e. 32% underweight, 45% stunting and 11% wasting which has been stated in "State of World's Children - 2015 by UNICEF".[11] This is probably due to the location of the study. Our sample was from a slum area with poor basic health facilities whereas the national survey included children from the entire country population.

**CONCLUSION:**

Mother's education has significant impact on the state of nutrition of children. It is therefore recommended that education of females especially in the slum areas should be promoted and given due importance.

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ORIGINAL ARTICLE

# Comparative Study Of Verapamil And Amytriptyline In Acute Opioid Abstinence Syndrome

Muhammad Yousuf Salat[1], Naseer Baloch[2], Musarrat Sultana[3], Syed Saud Hasan[4], Sheikh Nadeem Ahmed[5]

**ABSTRACT:**

**Objective:** To evaluate the effectiveness of verapamil and amitriptyline in the treatment of acute opioid withdrawal syndrome in patients with chronic dependence on opioids.

**Materials and Methods:** The study was conducted at Psychological Medicine Ward, Civil Hospital Karachi and Arshi Hospital, Naseerabad, F.B.area, Karachi. A total of forty (40) patients were admitted for ten (10) days in hospital. No treatment was given during the first two days of admission after abrupt termination of opioid to observe the acute opioid withdrawal signs and symptoms. Patients were divided into 2 groups. Each group had 20 opiate addicts. One group was given verapamil orally in a 40mg dose thrice daily and the other group was given amitriptyline orally in a 10mg dose thrice daily from day 3 to day 9 of admission. The intensity of signs and symptoms were recorded by using subjective and objective opiate withdrawal questionnaire. Urine analysis for opioids was done on day 1, 5 and 10 of admission.

**Results:** Verapamil in comparison to amitriptyline significantly decreased the intensity of signs and symptoms of acute opioid withdrawal from day 4 to day 10 of admission. Urine analyses for opioids were positive on day 01 while zero on day 10.

**Conclusion:** Verapamil in comparison to amitriptyline was found to be safe and effective for the treatment of signs and symptoms of acute opioid withdrawal in in-door patients without any significant side effects.

**Keywords:** Opioids, In-patients Verapamil, Amitriptyline, Acute abstinence syndrome.

## INTRODUCTION:

The term opioid is used to designate a group of drugs that are, to varying degrees, opium or morphine like in their properties.[1] The word opium is derived from OPOS, the Greek word for juice, the drug being derived from the juice of the opium poppy, Papaver somniferum.[2] Opioid drugs are used primarily for the treatment of pain. Some of the CNS mechanisms that reduce the perception also produce a state of well-being or euphoria. Thus, opioid drugs also are taken outside of medical channels for the purpose of obtaining the effects on mood. One of the hazards in the use of opioids to alter mood and feeling is that some individuals eventually develop drug abuse and drug addiction.[3] The most commonly abused drugs in this group are heroin, morphine, oxycodone and meperidine.[4]

Opioid abstinence syndrome has been a medical problem ever since the availability of opioid drugs. In addition with powerful withdrawal symptoms during abstinence, opioid relapses were difficult to prevent without an adequate treatment program. Successful approaches to pharmacotherapy in opioid addiction continue to rely largely on substitution of short-acting agonists such as heroin and oral administration of long acting high-efficacy agonists (methadone) or partial agonists (buprenorphine).[5,6] Notably, all opioids that produce analgesia also can cause tolerance, addiction and withdrawal and all of the available opioids are misused.[7] Hence it necessitates the search for a non-opioid treatment for opioid detoxification and dependence.[8,9,10]

Amitriptyline, an antidepressant drug is now- a- days widely used for controlling opioid abstinence. However evidence of its efficiency in the management of withdrawal from opioids is scanty.[11] On the other hand Calcium ($Ca^{++}$) channel blocking drugs are reported to decrease the severity of opioid withdrawal in rats.[11,12] Calcium channel blockers also reduced the body weight loss and diarrhea of abstinence as produced by naloxone in morphine dependent animals.[13,14] With this background present study was designed to evaluate the effectiveness of a calcium ($Ca^{++}$) channel blocking drug, verapamil and an antidepressant drug amitriptyline in the treatment of acute opioid withdrawal syndrome in patients with chronic dependence on opioids.

## MATERIALS AND METHODS:

This study was carried out in the department of Pharmacology and Therapeutics Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre (JPMC), Karachi. The forty selected opioid addicts between 21 and 45 years of age seeking treatment for opioid dependence of at least 4 months of duration were enrolled and admitted to the inpatient Psychological Medicine ward, Civil Hospital Karachi and Arshi Hospital Naseerabad F.B area Karachi for ten days. Patients having any psychiatric illness, systemic or debilitating disease or dependence on other drug in addition to opioids were excluded.[15,16] The materials used were tablet verapamil (calan, calcium channel blocker orally in a dose of 40mg thrice daily), tablet amitriptyline (tryptanol, an antidepressant orally in a dose of 10mg thrice daily) and the Front line

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Opiates Test Strips.

Parameters: The patients were assessed on the basis of following parameters:

(1) Subject – Reported Measures: They were in the form of subjective opiate withdrawal scale (SOWS) which contained twenty one typical opiate withdrawal symptoms (muscle cramps, flushing, painful joints, yawning, restlessness, watery eyes, runny nose, chill or gooseflesh, sick to stomach, sneezing, abdominal cramps, irritability, backache, tense and jittery, sweating, depressed, trouble getting to sleep, shaky or tremulous, hot or cold flashes, bothered with noise, and skin clammy and damp).[15]

(2) Observer – Rated Measures: They were in the form of objective opiate withdrawal scale (OOWS) containing six observable physical signs (lacrimation, rhinorrhea, yawning, perspiration, piloerection or gooseflesh and restlessness). The intensity of signs and symptoms were rated on a five point graded scale in which 0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, and 4 = extremely.[15]

(3) Urinalysis Measures: Urine samples were collected on day 1, 5 and 10 of admission. All samples were collected under staff observation to deter bogus urine samples and tested immediately for opioids by using one-step dip and-read chromatographic test strips (Frontline Opiate test strips).[17]

Permission was obtained from the Head of the Department of Psychological Medicine unit of Civil Hospital Karachi and Arshi Hospital Karachi for the clinical trial. Written consents were obtained from all patients for this study that required an abrupt withdrawal from opioids after admission to the hospital. The patients were divided into 2 groups. Each group comprised of 20 opiate addicts. One group was treated with verapamil and the other group was treated with amitriptyline. The patients received single blind placebo capsule orally during day 1 and day 2 of admission. Single blind treatment with verapamil (40mg TDS) and amitriptyline (10mg TDS) was given from day 3 to day 9 of admission. From day 2 to day 10 of admission, the patients were observed and rated for the presence or absence of opioid withdrawal signs and symptoms experienced during the previous 24 hours. Urine samples were collected on day 1, 5 and 10 of admission and tested immediately for opioids by test strips. Patients were discharged when they were experiencing minimal or no withdrawal symptoms. Total period of study was six months. Data was statistically evaluated by using SPSS version [16].

**RESULTS:**

All patients had subjective symptoms and objective signs of opiate withdrawal and urine specimens showing positive results when tested with frontline opiates dipsticks. During the study it was observed that subjects on verapamil treatment, showed no adverse effects that were not attributable to mild opioid withdrawal; on the other hand the adverse drug effects observed with amitriptyline group were dry mouth (15%), blurring of vision (5%), orthostatic hypotension (5%) and headache (10%). The results in figures show the cumulative scores of opiate withdrawal signs and symptoms on day 2 to day 10 of admission. The degree of withdrawal signs and symptoms was assessed according to the scoring system described in materials and methods.

Group I: Twenty patients were given a placebo treatment on day 1 and day 2 of admission. Thereafter from day 3 to day 9 of admission the patients received 40 mg of verapamil orally three times daily. Diazepam 5 mg for night time sedation and aspirin 300 mg three times a day for muscle pain were used by seven patients on treatment days 1 and 2 of therapy that is days 3 and 4 of hospitalization. Placebo had no significant effects on the cumulative scores of symptoms of acute withdrawal from opioids. A mean score of 17.25±0.781 was obtained on day 2 of admission, which increased to a peak of 31.1±0.777 on day 3 of admission (Figure 1a). Similarly placebo had no significant effects on the cumulative scores of signs of acute withdrawal from opioids. A mean score of 5.4±0.319 was obtained on day 2 of admission, which increased to a peak of 10.20±0.236 on day 3 of admission (Figure 1b).

Group II: Twenty patients were given a placebo treatment on day 1 and day 2 of admission. Thereafter from day 3 to day 9 of admission the patients received 10mg of amitriptyline orally three times daily. Diazepam 5mg for night time sedation, aspirin 300 mg three times a day for muscle pain, intravenous dextrose 5%1000cc/day for anorexia, promethazine (phenergan) 5 mg three times a day for vomiting and hyoscine (buscopan) 10 mg three times a day for abdominal cramps were given to thirteen of the patients on treatment days 1, 2 and 3 of therapy that is days 3, 4 and 5 of hospitalization. A mean score of 14.65±0.658 was obtained on day 2 of admission, which increased to a peak of 31.25±0.627 on day 3 of admission (Figure- 2a). A mean score of 5.55±0.303 was obtained on day 2 of admission, which increased to a peak of 10.95±0.343 on day 3 of admission (Figure 2b).Placebo had no significant effects on the cumulative scores of signs of acute withdrawal from opioids. The amitriptyline group in comparison to verapamil group showed more severe withdrawal symptoms during the entire regimen (Figures 1a, 2a, 3a). On day 4 to 10 of admission the mean score of opiate withdrawal symptoms in verapamil treatment group were 16.7±0.567,13.1±0.510, 7.65 ± 0.326, 3.5 ± 0.320, 1.25 ± 0.099 , 0.85 ± 0.131 , 0.1 ± 0.1 whereas in amitriptyline group the mean score of opiate withdrawal symptoms were 30.85±0.616,28.65 ± 0.519,25.95 ± 0.336,15.0 ±0.205,12.05 ± 0.419,7.35 ± 0.254,6.95 ±0.234.From day 4-day 10 statistical evaluation showed highly significant results ($P<0.001$). Similarly the amitriptyline group in comparison to verapamil group showed more severe withdrawal signs during the entire regimen (Figures 1b, 2b, 3b). On day 4 of admission the mean score of opiate withdrawal signs in verapamil treatment group was 4.6 ± 0.265 whereas in amitriptyline group the mean score of opiate withdrawal signs was 10.20 ± 0.286. On day 5 of admission the mean score of opiate withdrawal signs in verapamil treatment group was 2.9 ± 0.289 where as in amitriptyline group the mean score of opiate withdrawal signs was 8.95±0.825. On day 6 of admission the mean score of opiate withdrawal signs in verapamil treatment group was 1.5±0.223 whereas in

amitriptyline group the mean score of opiate withdrawal signs was 6.15±0.587. On day 7 of admission the mean score of opiate withdrawal signs in verapamil treatment group was zero (0) where as in amitriptyline group the mean score of opiate withdrawal signs was 4.85±0.149. On day 8 of admission the mean score of opiate withdrawal signs in verapamil treatment group was zero (0) where as in amitriptyline group the mean score of opiate withdrawal signs was 2.7±0.206. On day 9 of admission the mean score of opiate withdrawal signs in verapamil treatment group was zero (0) where as in amitriptyline group the mean score of opiate withdrawal signs was 1.1 ± 0.216. On day 10 of admission the mean score of opioid withdrawal signs in verapamil treatment group was zero (0) whereas in amitriptyline group the mean score of opiate withdrawal signs was 1.05±0.223. The effects of verapamil to decrease the signs of acute withdrawal from opiates when compared with amitriptyline from day 4 to day 10 of the admission were highly significant (P<0.001)

Figure: 1a
Effects of Verapamil treatment on subjective symptoms of acute withdrawal from opioids

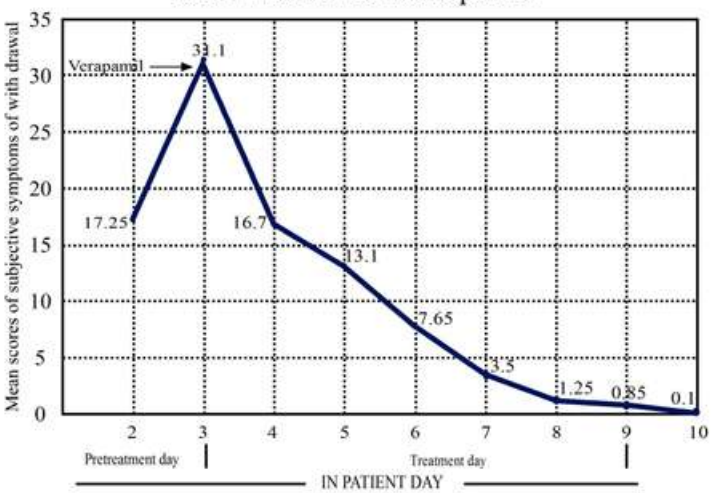



Figure: 1b
Effects of Verapamil treatment on objective signs of acute withdrawal from opioids

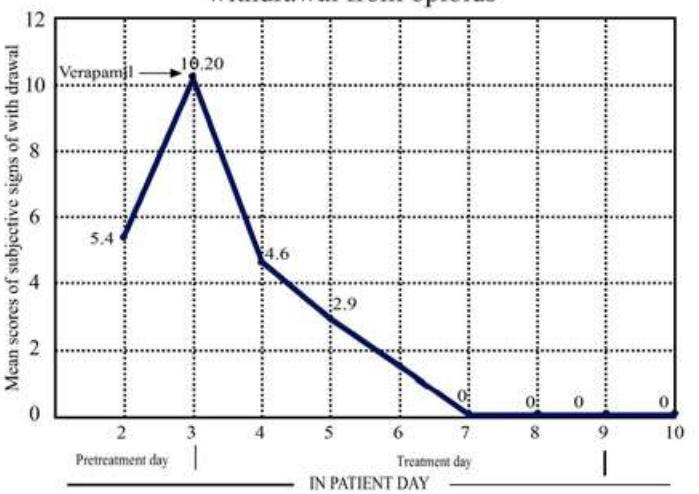



Figure: 2a
Effects of Amitriptyline treatment on subjective symptoms of acute withdrawal from opioids

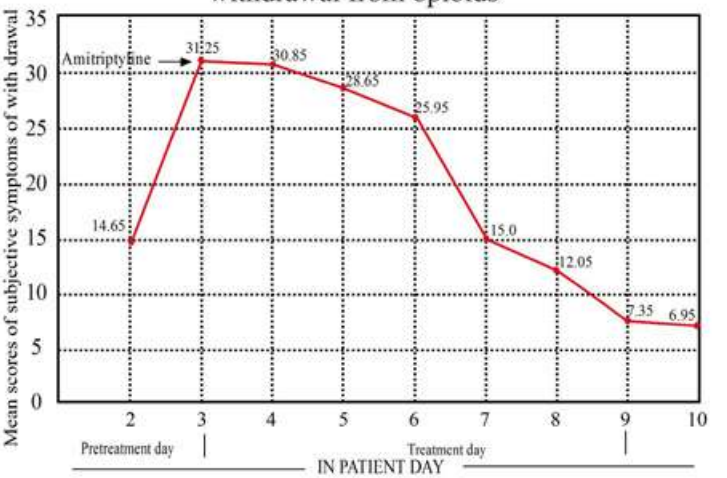



Figure: 2b
Effects of Amitriptyline treatment on objective signs of acute withdrawal from opioids

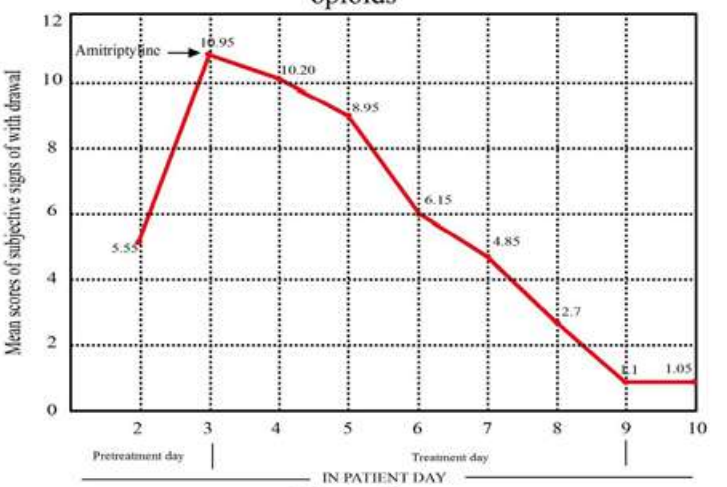



Figure: 3a
Comparison of effects of treatment with Verapamil and Amitriptyline on subjective symptoms of acute withdrawal from opioids

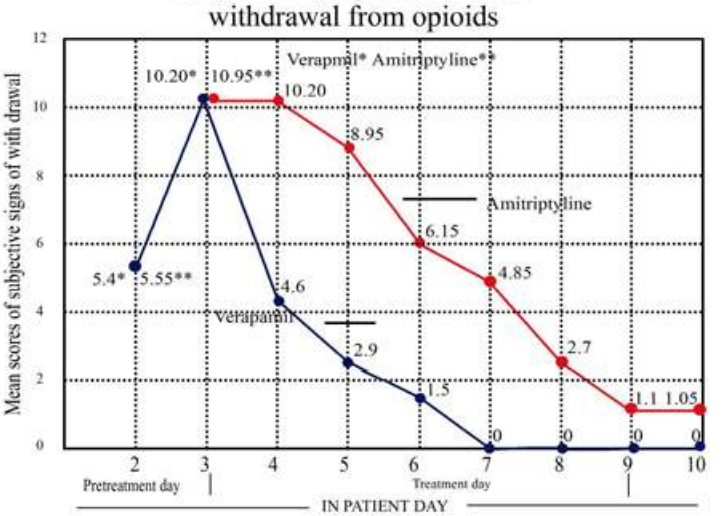
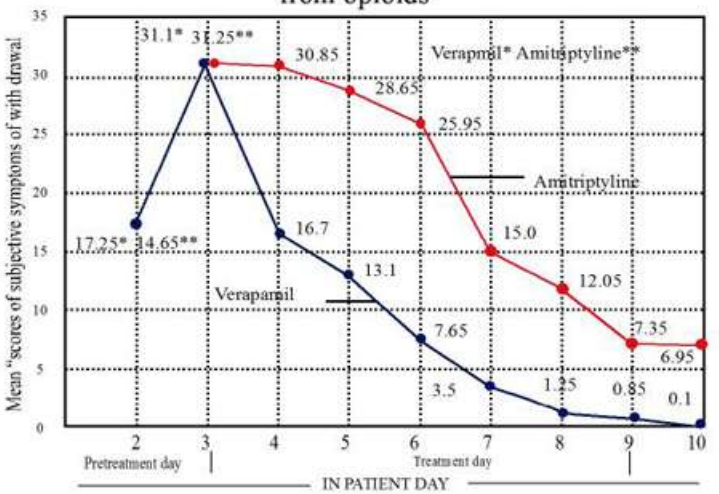


Figure: 3b
Comparison of Effects of Treatment with Verapamil and Amytriptyline on objective signs of acute withdrawal from opioids




## DISCUSSION:

A study was conducted by Baloch[18] and Mahesar[19] on role of verapamil in opioid dependence in guinea-pigs in vivo and in vitro in the department of Pharmacology and Therapeutics BMSI, JPMC, Karachi. Their observations showed a highly significant effect of verapamil in vivo and vitro, which initiated a proposal of conducting a pilot study in opioid addict's hospitalized patients. The purpose of this single blind pilot study was to conduct a clinical trial and to investigate the efficacy of verapamil in acute opioid abstinence syndrome in hospitalized patients. Amitriptyline is in vogue at present in the treatment of opioid abstinence in various hospitals of Karachi. We have compared the therapeutic effect of verapamil with amitriptyline. Verapamil being a safe drug with fewer side effects was used in minimal dose of 40 mg TDS and for short duration. When the data for withdrawal scores for verapamil treatment were statistically evaluated it showed that subjective symptoms and objective signs were significantly reduced from day 3 to day 10 of admission. Our results are compatible with the work of Baloch[18]and Mahesar[19] who observed the effect of verapamil in morphinc dcpcndent animals subjected to naloxonc in vitro and vivo. They observed that calcium channel blocker was effective in reducing the abstinence in vivo and in vitro effects. Our results are also compatible with the study done by Baeyense[13] in which verapamil was given to morphine dependent rats intraperitoneally (i.p.) (10, 20 and 40 mg/Kg) and intra- cerebro- ventricularly (i.c.v.) (160µg) 30 minutes and 10 minutes respectively before naloxone challenge. This study showed that verapamil prevented diarrhoea after its i.p. but not after its i.c.v. injection due to its peripheral action and also that verapamil reduced body weight loss and jumping only after its i.c.v. administration due its central action. This study reported that verapamil caused no overt behavioural effects which could have interfered with the expression of the abstinence syndrome. Our results are also consistent with the work of Bongianni[14] who observed withdrawal signs in two different groups of morphine dependent rats injected with naloxone intraperitoneally. The animals constantly lost approximately 8% of their body weight in 1 hour. Furthermore they displayed diarrhoea, wet dogshakes, agitation, grooming, teeth chattering and lacrimation. The administration of verapamil subcutaneously to morphine dependent rats 20 minutes before naloxone challenge reduced the appearance of most of the behavioral signs of abstinence syndrome. Our results are highly in accordance with the work of Seth et al20 who observed a significant dose-dependent attenuation of naloxone-induced morphine withdrawal syndrome in mice with calcium channel blockers verapamil 20 mg/kg ($P < 0.05$) and diltiazem 30 mg/kg ($P< 0.01$).

Chronic dependence on opioids demonstrated an adaptive increase in number of calcium channels. This increased calcium channels, precipitate in opioid abstinence syndrome. Thus, the signs and symptoms of opioid abstinence syndrome can be attenuated or prevented by administration of calcium channel blockers following opioid withdrawal.[21] Thus calcium channel blockers may be rational and useful therapeutic agents in clinical management of drug dependence and withdrawal[22,23,24] especially as they appear to have no significant addicting properties themselves and show anticonvulsant action in condition of central nervous system hyper-excitability, which is a general feature of drug withdrawal[25] The other objective of this study was to investigate the efficacy of amitriptyline compared with verapamil. It is obvious from observations that the amitriptyline was not significantly effective in suppressing withdrawal signs and symptoms from day 3 to day 10 of admission. The pattern of withdrawal symptoms and signs in amitriptyline group is not incompatible with a rather ineffective treatment or even simply a placebo effect. When unmodified by treatment the withdrawal syndrome for opiates reached its peak intensity between the 3rd and the 6th day and thereafter, the severity decreased gradually and most of the grossly observable symptoms disappeared in 7 to 10 days.[11] This pattern is broadly the same as that shown by amitriptyline group.

## CONCLUSION:

Verapamil therapy is safe, effective and more pronounced in treating the acute opioid withdrawal syndrome than amitriptyline in patients with chronic dependence on opioids. This treatment will facilitate opioid addicted patients to directly enter in a maintenance program for detoxification. It may also be of use in preventing the occurrence of the protracted or secondary abstinence syndrome because of possible rapid normalization of opiate system. Comparative studies examining a number of factors, such as patient's compliance, its efficacy in larger groups and its role in detoxification utilizing verapamil and amitriptyline are open venues for future research.

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# Knowledge, Attitude and Practice Regarding Pulmonary Tuberculosis Awareness Among Non-Medical Students of Karachi

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**ABSTRACT:**
**Objective:** To evaluate the level of awareness among non -medical students about Tuberculosis.
**Materials and Methods:** A questionnaire-based, knowledge, attitude, practice (KAP) survey was conducted among non- medical students of two universities of Karachi from 6th April-30th May 2013. A pre-validated questionnaire, consisting of 10 questions, was distributed to students. Simple random sampling technique was used for selecting the participants. After verbal consent, 110 students participated in the study. Ten questionnaire forms were rejected due to incomplete filling.
**Results:** Out of 100 students, 85% responded "yes" that they had heard about TB, 24% identified cough as a main symptom of TB, 36% responded "yes" that disease is contagious. Asking about mode of transmission, 40% responded "they don't know" and 36% stated sexual contact is the reason.90% agreed that patients hide their disease because people will avoid them.39% said that they will not visit there houses.47% said that patients should go to chest specialist for treatment. 42% said vaccination is the better way of preventing the disease. Only14% knew that 9 months is the duration of treatment.
**Conclusion:** Assessment of awareness regarding knowledge, attitude and practice of TB among non- medical students was found to be deficient.
**Keywords:** Awareness, Tuberculosis, Non- medical, Students, Universities

## INTRODUCTION:

Tuberculosis (TB) is an infectious bacterial disease caused by various species of mycobacterium, usually Mycobacterium Tuberculosis in humans[1]. The disease is transmitted through air droplets and causes damage to the lungs and other organs in the human body as kidneys, spine, brain etc. It is highly contagious and spreads when tuberculosis patients cough, sneeze, spit and talk. However it does not spreads by shaking hands, sharing food and drinks, touching beds and linen. When mycobacterium tuberculosis become active and immune system cannot stop them from growing, this is called as tuberculosis disease. In this phase, people are sick and are capable of spreading bacteria to other people with whom they spend time every day.

Tuberculosis remained a major health problem worldwide, most noted in developing countries[2] Despitethe availability of effective drugs and the widespread use of the Bacille Calmette-Guerin (BCG) vaccine in 1993, the World Health Organization (WHO) declared TB as a global emergency. In terms of the number of cases, Southeast Asia carries the biggest burden of disease.[2] World Health Organization (WHO) which indicates that, in the year 2010 alone, an estimated number of 8.8 million people worldwide were infected with tuberculosis while an estimated 1.4 million of the infected patients died from it.[3] Although vaccines, antibiotics and scientific research have been made available around the world to help reduce the spread of tuberculosis, the efforts and measures has thus far been less effective than anticipated.[4] Despite various scientific studies carried out, there is still lack of research on the social science perspective especially on the spread of the disease[5].It is an important public health problem that is preventable and curable. If left untreated, each active tuberculosis (sputum positive) case can infects 10 to15 people in one year.1In 2009, 9.4 million new cases of tuberculosis were reported. The prevalence of tuberculosis was estimated as 137cases per 100 000 population globally. Highest number of cases occurred in Asia (55%) followed by Africa (30%), Eastern Mediterranean region (7%), European region (4%) and the region of Americas (3%).6 The five countries with largest number of cases were India, China, Afghanistan, Indonesia and Pakistan. Pakistan stands 5th among 22 countries with high burden of tuberculosis. Estimated prevalence of tuberculosis in Pakistan is 350cases per 100 000 population.[7] Tuberculosis has been identified to be second to HIV/AIDS in causing mortality around the world8. Social factors play an important role in managing tuberculosis disease[9]. One of the most important social factors is the stigma within the society towards tuberculosis patients10. Tuberculosis is highly contagious and due to the ease of infection, anyone can contract the disease. Unfortunately not many people are aware about the disease. This lack of knowledge and awareness is a problem all around the globe. Therefore this study was conducted to evaluate the level of awareness regarding TB in the non- medical students of two universities of Karachi.

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## SUBJECTS AND METHODS:

This cross sectional study was conducted among the non-medical students of two universities in Karachi namely NUST and Bahria University from6th April to 30th May 2013.Sample size was 100 while simple random method of sampling was adopted. After taking verbal consent, a pre-validated questionnaire adopted from studies conducted previously was filled by students. Data was analyzed using SPSS [15].

**Questionnaire:**

Regarding knowledge:

- Have you heard about tuberculosis (TB)?
- Which Gender is more involved in tuberculosis?
- What are the symptoms of tuberculosis?
- Is tuberculosis contagious?
- How does tuberculosis spread?

Regarding attitude:

- Why do tuberculosis patients hide their disease?
- Have you ever visited the houses of TB patients?

Regarding practice:

- Where tuberculosis patients can get medical care?
- How can we prevent T.B?
- What is the duration of treatment for TB?

## RESULTS:

A sample of 100 students was taken from two universities out of which 67% were males and 33% were females (Table-1). 85% responded "yes" that they have heard about TB (Table-2a). 50% of students responded that male and female both are affected by tuberculosis equally (Table-2b).Regarding knowledge about symptoms 24% identified cough ,17% cough with sputum, 10% increase in temperature, 14% loss of appetite and weight loss and 30% identified other symptoms, 11% responded that they don't know about tuberculosis (Table-2c). 36% responded "yes" that TB is contagious, 40% responded don't know and 24% responded TB is not contagious (Table-2d). Asking about mode of transmission 40% responded they don't know about it, 35% thought sexual contact is the mode of transmission, 11% through needle prick, and3% by sharing food and articles (Table-2e).

When they were asked about the reason why patients want to hide the disease? 90% of students agreed that people will avoid them.38 % students said they will not visit them at homes, 33% responded yes and 29% responded don't know (Table-3a). When asked have you ever visited the house of a tuberculosis patient? Only 33% responded "yes" (Table-3b)

59% agreed that TB is a serious disease. When they were asked about consultation of doctor 38% said they should go to family doctor 47% responded that they should go to chest specialist (Table-4a). Regarding prevention of disease 42% responded vaccination is a better way to prevent the disease 37% avoid close contact with patients and 10% wearing mask (Table-4b).when students were asked about duration of treatment 19% said 6 months ,14% 9 months , 26% didn't know 14% said 3months (Table-4c).

Table: 1
Gender distribution of students

| GENDER | FREQUENCY | PERCENTAGE |
|---|---|---|
| Male | 67 | 67 |
| Female | 33 | 33 |
| Total | 100 | 100 |

Table: 2a
Have you heard about tuberculosis?

| RESPONSE | FREQUENCY | PERCENTAGE |
|---|---|---|
| Yes | 85 | 85 |
| No | 9 | 9 |
| Don't know | 6 | 6 |
| Total | 100 | 100 |

Table: 2b
Which gender is more involved in tuberculosis?

| | |
|---|---|
| Male | 18% |
| Female | 4% |
| Both | 50% |
| Don't know | 28% |

Table: 2c
What are the symptoms of tuberculosis?

| | |
|---|---|
| Cough for 3 weeks | 24% |
| Increase in temp | 10% |
| Cough with sputum | 17% |
| Increase in evening temp | 3% |
| Loss of appetite, weight loss | 14% |
| Don't know | 11% |
| Others….constipation, night sweats, blurring of vision, skin rash | 30% |

Table: 2d
Is tuberculosis a contagious disease?

| | |
|---|---|
| Yes | 36% |
| No | 24% |
| Don't Know | 40% |

Table: 2e
How does tuberculosis spread?

| | |
|---|---|
| Cough | 10% |
| Needle prick | 11% |
| Sharing food | 3% |
| Sexual contact | 35% |
| Transmit from mother | 1% |
| Don't know | 40% |

Table: 3a
Why do tuberculosis patients hide their disease?

| | |
|---|---|
| People will avoid them | 90% |
| Will lose job | 1% |
| Will lose friends | 4% |
| No one will marry | 2% |
| others | 3% |

Table: 3b
Have you ever visited the house of a tuberculosis patient?

| | |
|---|---|
| Yes | 33% |
| No | 38% |
| Don't know | 29% |

Table: 4a
Where tuberculosis patient can get medical care?

| | |
|---|---|
| Family doctor | 38% |
| Hakeem | 4% |
| Chest specialist | 47% |
| Don't know | 20% |

Table: 4b
How can we prevent tuberculosis?

| | |
|---|---|
| Vaccination | 42% |
| Wearing masks | 10% |
| Avoid close contact with patients having tuberculosis | 37% |

Table: 4c
What is the duration of treatment for tuberculosis?

| | |
|---|---|
| 3 months | 16% |
| 4 months | 5% |
| 6 months | 19% |
| 8 months | 7% |
| 9 months | 14% |
| 1 year | 4% |
| More than 1 year | 12% |
| Don't know | 26% |

**DISCUSSION:**

Tuberculosis (TB) is a chronic infectious disease caused by Mycobacterium tuberculosis. Almost one-third of the world population (about 2 billion people) is infected with this disease and during the past decade there has been a resurgence of tuberculosis. Currently, TB is the leading cause of mortality among infectious diseases worldwide but 95 percent of TB cases and 98 percent of deaths due to TB occur in developing countries[11]. Our study revealed that out of 100 students 85 % have heard about disease. TB spreads through droplet nuclei that become aerosolized when an infected person coughs, speaks, sneezed or talks[12].It was reported that persistence cough for 2 or more weeks, coughing up sputum with blood, chest pain and weight loss were the common sign and symptom of TB. Through the air when a person with TB sneezes or coughs, and sharing cups with the patient were the common perceived modes of transmission in different studies[13]. Our results revealed that most of the respondents were not sure and have in-accurate understanding about the spreading mechanism of disease. Regarding knowledge of symptoms mostly knew that cough is the main symptoms and few said evening fever is the associated symptom however almost half of the respondent told irrelevant symptoms associated with TB. Students most likely gave wrong answers to TB knowledge questions. Study participants were of the opinion that TB can be transmitted by sexual relations. Other studies from Zambia, Pakistan and Malaysia also reported poor knowledge about transmission of disease. [14, 15,16] This could be another important target group for educational interventions with different methods including peer education being strengthened as an effective educational activity for youth.

A significant number of university students in Georgia reported that they would try to hide having TB from others. Almost one-third of prior TB patients who did not hide their diagnosis experienced a negative change in relationships after disclosing their illness.[17] Our study revealed the view of students that most of the patients try to hide their disease because of negative attitude of society and people will avoid them. Majority of the respondents indicated that patients would feel fear or scare and sadness or hopelessness if they found they have TB. Similar feelings have been associated with TB in Pakistan [18]. One of the most important social factors is the stigma within the society towards TB patients.[19,20] In our survey half of the participants thought that T.B can affect ones later life in terms of education, marriages, family and social relations. Association of these stigmas with such a curable disease is quiet unfortunate. Comparable Studies also revealed that TB carries strong stigma in many countries.[21] Most of the respondents agreed that patient should consult a doctor or hakeem for the treatment however respondents' knowledge regarding the duration of treatment was found to be deficient. Comparable findings have been reported from other studies of same nature. [14,15] Accordingly, covering mouth and nose when a person with TB coughs or sneezes, using a separate room for the patient, avoid sharing cups with the patient, early treatment and good nutrition as a prevention

methods were similarly documented by an earlier study from Ethiopia[22]. However, home based and community treatment of patients should be promoted.[23]

Prevention is considered as one of the main factor that leads to limit TB. In current study most of the respondents were in favor of vaccination and believed that it can prevent the disease. This finding is in line with those reported in an earlier study.[24] However only 10% of respondents were aware of the fact that wearing mask is the important mean to limit TB. Current findings revealed poor knowledge of study respondents. Initiatives for raising awareness, though active information and education strategies would be quite helpful.[25] Therefore, health care managers must devise health promotion strategies to improve knowledge about the cure and preventive measures of tuberculosis.

**Conclusion:**

Results of the study exposed limited knowledge and misconceptions about TB among non- medical students The National TB Program should use various information channels including TV, newspapers, community and faith based organizations to stimulate a positive attitude towards TB. Every action should be taken to increase TB related knowledge emphasizing that TB is curable and improving information regarding where and how to access services, as well as to create greater demand for TB prevention and treatment services.

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COMMENTARY

# Misconceptions: How To Diagnose And Clarify Them In Undergraduate Medical Students

Sara Shakil

**ABSTRACT:**
A big challenge for medical educationists is to search for learning strategies that promote meaningful learning and discourage rote learning. Clinical expertise is achieved by acquiring large amounts of biomedical knowledge structured as concepts linked together in a loosely connected semantic network. Medical students using concepts maps can successfully retrieve information in the short term. Concept maps allow students to recognize the relationship between concepts, which reflects the kind of real-world thinking predominant in the clinical setting. Conceptual thinking occurs when a student goes beyond the surface structure of a problem and recognizes how the problem can be solved, and in addition, possesses the content knowledge integral to solve the problem. Without both components a student may not just be able to critically analyze one problem, but will also fail when given a similar problem in a different context. Hence, there is great need for identification of these learning difficulties mainly in the form of confusions, ambiguities and misconceptions in the learner's mind.

**Keywords:** Misconceptions, Meaningful learning, Concept map, Conceptual thinking, Undergraduate medical students

## INTRODUCTION:

### What are misconceptions?

These are deep rooted ideas that are not in harmony with the scientific truth and are very resistant to change. They arise due to lack of peer interaction, least participation in small group discussions and inadequate exchange of ideas in undergraduate medical students. This makes it difficult for the individual to register information in memory structures resulting in poor retrieval in real-settings[1, 2]. Conceptual learning is grounded on constructivist approach for teaching and learning. It greatly emphasizes that learners synthesize new knowledge, based on prior learning experiences and make judgments by modifying their existing knowledge[3]. There are great chances of false registration of knowledge creating confusion and perplexity in the learner`s mind[4].

### Strategies to identify misconceptions:

Unveiling preconceptions is done by taking a detailed interview regarding any topic in which thought-provoking questions are asked. Subsequent questions are raised from the previous answer which would enable the student to think and express his views more efficiently[1,2]. If the learner is unable to answer a successive set of questions and realizes that he is unable to justify whatever he is saying, he surely bears a strong misconception somewhere in his mind[5]. Learners may also be told to construct a concept map as they reflect the organization of the pre-concept and reveals areas of weakness[6]. They also help in elaboration of their knowledge and use of meaningful patterns in relevant context. This technique would help in the identification of difficulties in reasoning. Defective concepts can also be determined by assigning tasks where the learners would surely not understand the challenge and end up writing a wrong answer due to lack of meaningful integration of knowledge. The inability to understand and attempt such exercises would clearly show that his personal models of reality are actually scientifically incorrect[7].

Besides the above mentioned techniques to reveal misconceptions, learners may be instructed to take word association tests. Such tests would allow students to write as many related words on a given topic in a specific time period. Use of structured communication grids would give teachers the opportunity to observe logical sequencing of the answers next to their respective question.

### Creating a conceptual conflict: [1, 8]

Tutorial session and allowing students to defend their stance is an excellent approach to identify erroneous concepts. This is done through small group discussions[1] and carefully listening to the entire conversation during the class. Failure in providing scientific support to his statements and inability to justify himself in front of his peer group would reveal his misconceptions. Hesitation in performing a hands-on demonstration on a relevant topic may be an evidence for the learner's inability to provide scientific reasoning1.

### Use of hypothetico-deductive reasoning models:

Indulging students in situations where they would carry out tasks and compare their work with peers is also one of the most astonishing strategies to reveal misconceptions[9]. Inability of students to relate meaningful information in relevant clinical contexts points towards the need of enabling students to actively engage in the problem solving process.

### Clarification of misconceptions:

Once success has been achieved in determining the underlying reasons for such false concepts, it is the prime responsibility of teachers to help the students go through a complete restructuring of their knowledge[10].In order to reform their concepts, "Conceptual Change Strategies" should be applied[11].Students realize that their existing knowledge is not helping them solve any task, nor answer questions correctly and would end up in great dissatisfaction. They would also feel that the new knowledge is far more applicable in solving daily life problems and would be confident in explaining this new concept to his colleagues. They would better be able to use this new knowledge to fit in their mental models with a feeling of acceptability[12].Active engagement in cooperative learning would broaden their perspectives and

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clarify any misconception at hand by listening to their peers and generating discussions. There would be exchange of ideas which would probably enable students to rectify their misconceptions and improve their communication skills as well[13].Students must also be trained to be strategic and develop keen interest in the subject. This would happen if they adopt a step-by-step approach towards accepting information that is based on scientific evidence. For meaningful learning to occur, they would need to grasp scientific knowledge and understand theories based on evidence.

Since medical students are exposed to loads of new experiences in daily life which they use to construct new ideas, they need meta cognitive self- questioning from time to time. This is because once students develop a habit of being aware of their strengths and weaknesses in the journey of struggling for the correct concept; they would surely excel in attaining plausible and believable ideas[7,14]. Increase elaboration and evaluation of ideas greatly benefits learners. Concept maps not only reveal misconceptions but play a major role in correcting them. By advising students to construct concept maps, teachers enable them to build connections of prior knowledge and the new content resulting in better retrieval[4]. Moreover if students want to develop a clear concept, they must also get actively engaged in discussions with incorporation of concept maps.[6,7] This surely would be the best strategy to remove any misconception in mind[8].

Students need to understand the essential characteristics of scientific theories. Since students are heading towards becoming an expert, firstly they need to understand each and every detail of the subject[9]. They must spend a lot of quality time paying attention, to read text and learn to analyze evidences that support or negate a hypothesis. They must learn to fill the gap between theory and evidence by comparing and contrasting various propositions in a scientific text[15]. Reflective thinking may enable novices to look into themselves and identify their weaknesses. To become an adept professional the undergraduate medical students must have clear concepts in mind. This would be achievable once they develop a habit of pondering over their performance and judge their competencies by themselves[16]. Once they are able to critically analyze their poor performance, they would clearly see faulty knowledge structures in their mind and realize the need for concept maps, conceptual change and critical thinking.

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CASE REPORT

# Heterotopic Pregnancy Following Ovulation Induction By Clomiphene Citrate And A Normally Growing Intrauterine Pregnancy: A Case Report

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**ABSTRACT:**

A heterotopic pregnancy is defined as the presence of a combined intrauterine and ectopic pregnancy. Heterotopic pregnancy is rare, estimated to occur in 1/30,000 pregnancies. It is also reported to be as high as 1% after the use of assisted reproductive technology. Simultaneous extra and intrauterine pregnancy after the induction of ovulation with clomiphene citrate has been reported. Clomiphene citrate which increases the rate of twining could be associated with a heterotopic pregnancy rate of 1/900, which is much less than using assisted reproductive technology. Heterotopic pregnancies are diagnostic and therapeutic challenges for obstetricians. If they continue without diagnosis, a life- threatening situation may occur even when surgical intervention with laparotomy is performed.

**Key words:** Heterotopic pregnancy, Ovulation induction, Clomiphene citrate, Laparotomy

## INTRODUCTION:

A heterotopic pregnancy is defined as the presence of a combined intrauterine and ectopic pregnancy.[1,2] Heterotopic pregnancy is rare, estimated to occur in 1/30,000 pregnancies.[3,4] It is also reported to be as high as 1% after the use of assisted reproductive technology, but clomiphene citrate which increases the rate of twining, could be associated with a heterotopic pregnancy rate of 1/900, which is much less than using assisted reproductive technology.[5,6] A corneal ectopic pregnancy is one of the most life threatening types of ectopic gestations, which accounts for 2-4% of all the ectopic pregnancies and it has a mortality rate which is 6-7 times higher than that of the ectopic pregnancies in general. Heterotopic pregnancies are diagnostic and therapeutic challenges for obstetricians because findings in patients with heterotopic pregnancy include abdominal pain, adnexal masses, peritoneal irritation etc. which are usually non specific. Moreover the features of an ectopic gestation are often masked by the co-existing intrauterine gestation, If heterotopic pregnancy continues without diagnosis, a life- threatening situation may occur even when surgical intervention such as laparotomy is performed.[7]

## CASE REPORT:

A 30-year-old, primigravida presented to gynaecology emergency with history of 9 weeks gestation and severe lower abdominal pain for 1 hour duration along with brief episode of dizziness and palpitation. She had undergone laparotomy due to left ovarian endometrioma 3 months back followed by ovulation induction. She was prescribed clomiphene citrate 50mg from day 2-6 of the cycle and Injection IVF-M 5000 IU on day 9th of cycle. Fertile period was explained to her. With this treatment she conceived in the 3rd cycle. During pregnancy her first obstetric ultrasound was done in 6th week of pregnancy that showed single intrauterine pregnancy. She visited outpatient department of the gynaecology OPD with lower abdominal pain at 8 weeks of gestation. She was hospitalized and kept under observation and conservative treatment was given. Her 2nd ultrasound was done that showed single intrauterine pregnancy of 9 weeks and corpus luteal cyst in left ovary. Rest of the scan was normal. She became stable and was then discharged from the hospital.

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Figure: 1a
Intrauterine pregnancy with left tubal ectopic At 10 weeks gestation

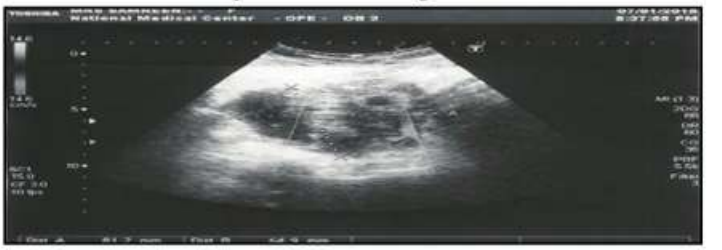


Figure : 1b
Operative findings in emergency laparotomy showing ruptured left tubal pregnancy and an increased globular uterus

Figure: 2a
Viable intrauterine pregnancy on 2nd day of laparotomy at 11 weeks gestation

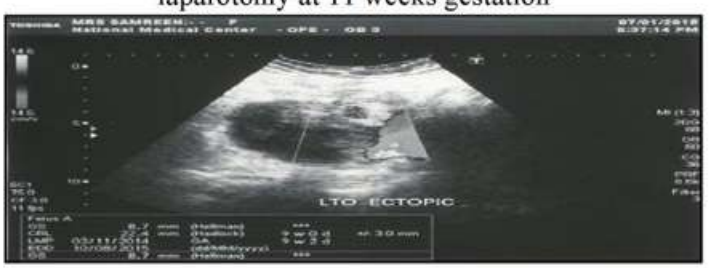
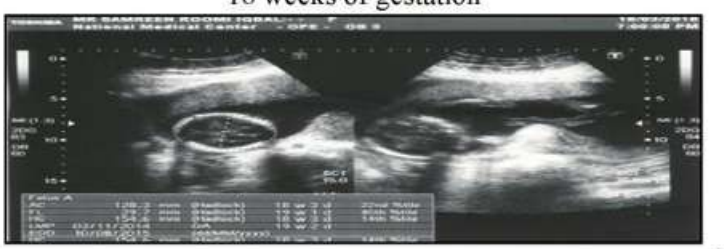



Figure: 2b
Viable intrauterine pregnancy at 18 weeks of gestation



After one week she presented in gynaecology emergency with severe lower abdominal pain and dizziness. On examination she was pale, pulse 102/min, BP 90/60 mm Hg, temp 97F, R/R 18/m, lower abdominal tenderness was positive. Pelvic ultrasound was done for the sake of cause that showed heterotopic pregnancy with small amount of blood in peritoneal cavity (Figure 1). Written informed consent was taken and emergency laparotomy was done. On opening she had right tubal ruptured ectopic pregnancy with about 100ml of blood in peritoneal cavity. (Figure 2) Left tube and ovary was normal. Right sided salpingectomy was then done. After operation she recovered well. On 2nd post-operative day ultrasound was repeated and intrauterine pregnancy was found to be viable. (Figure 3) The diagnosis was confirmed on histology report of salpingectomy specimen. After operation, she had routine antenatal visits and at 18 weeks repeat ultrasound showed a viable intrauterine pregnancy (Figure 4). At the time of case submission the patient is 30 weeks of gestation and her intrauterine pregnancy is growing very well.

**DISCUSSION:**

Heterotopic pregnancy was first described by Duverney in 1708 at autopsy. However diagnoses in life, is still rare.[8] Now-a- days, the use of assisted reproductive technology and fertility agents such as clomiphene citrate can increase a patient's risk of a heterotopic pregnancy. Indeed, any factor predisposing a patient to an increased risk of ectopic pregnancy could contribute to heterotopic pregnancy. In our patient, pregnancy also occurred in association with ovulation induction by clomiphene citrate.

The majority of heterotopic pregnancy cases are diagnosed late. Even though it is reported that 20-50% of ectopic pregnancies cannot be confirmed by ultrasonography.[3] Significant morbidity and occasional mortality have been reported as a result of a delay in diagnosis. As no single investigation can predict the presence of a heterotopic pregnancy, it should be suspected in any patient who presents with lower abdominal pain in the early phase of an obvious intrauterine pregnancy following fertility treatment[7].Often, abdominal and pelvic ultrasonogram fails to show the ectopic pregnancy or is misinterpreted because of the awareness of an existing intrauterine pregnancy, Moreover, if an adnexal mass is seen, it may be interpreted incorrectly as a corpus luteum cyst but demonstration of an intrauterine pregnancy is no longer a reliable indicator for excluding an ectopic pregnancy.[1,2] In our case, persistent lower abdominal pain at 9 weeks of gestation drew attention to the heterotopic pregnancy. It was later on confirmed on trans-abdominal ultrasound when it got ruptured.

The standard treatment for ectopic pregnancy is surgery by laproscopy or laparotomy depending on condition of the patient.[5,9] The use of medical treatment such as intramuscular administration of methotrexate is limited to cases where the intrauterine pregnancy is not viable.[10,11] Fertility results are found to be same after laproscopy or laparotomy. However, some authors have reported a 40% loss of intrauterine pregnancy following surgical treatment of heterotopic pregnancy.[10] The good outcome as in our case is not always the rule. Timely diagnosis of the ectopic pregnancy component and an emergency laparotomy could be very helpful. As in our case, timely intervention by laparotomy did not affected the intrauterine pregnancy.

**CONCLUSION:**

This case report suggests that a heterotopic pregnancy must always be considered in patients presenting with pelvic pain even in a confirmed intrauterine pregnancy, particularly after the induction of ovulation by clomiphene citrate or assisted reproductive technology. Every clinician treating women of reproductive age should keep this diagnosis in mind. It also demonstrates that early diagnosis is essential in order to salvage the intrauterine pregnancy and avoid maternal morbidity and mortality.

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## LETTER TO EDITOR

# Walking: Step Towards Healthy Life

Sajid Abbas

To,
Editor,

Health benefits of regular physical activity are noticeably increased in recent years and considered as a critical step towards a healthier population. Walking is one of the most accessible forms of physical activity which is appropriate for all age groups and costs nothing.[1] Several studies have shown that walking has higher levels of adherence than other forms of physical activity, possibly because it is convenient and overcomes many of the commonly perceived barriers to physical activity such as lack of time, lack of fitness or lack of skill. It is now becoming obvious that walking may provide some of the same health benefits as do more vigorous types of physical activities along with a lower risk of injury and sudden death.[2] Walking has been shown to have a definite role in prevention of major non communicable diseases, including type-2 diabetes, cardiovascular diseases, musculoskeletal conditions, osteoporosis and cancer. Association between walking and reduction in deaths from all causes, ranging from 19–30 per cent depending on the frequency and length of walking is well documented. As regards to type 1 and 2 diabetes one death per year could be prevented for every 61 people who pursue walk at least two hours per week.[3] Regular walking has also been shown to increase maximum aerobic capacity and decrease blood pressure, cholesterol and other cardiovascular risk factors with as little as one hour of walking per week. Walking also has impact on mental health and can relieve symptoms of depression, anxiety, stress and improve cognitive performance. The usual recommendation for adults is 30 minutes daily walk for at least five times a week. A recent study of 400, 000 people have found that just 15 minutes a day of brisk walking can add up to 3 years of life expectancy. Every additional 15 minutes of daily exercise reduced all-cause death rates by a further 4 per cent. Though walking has health benefits at any pace, brisk walking (at least 3 miles per hour) is particularly said to be beneficial than slow walking4.Center for Disease Control (CDC) has recommended an easy rule of thumb for gauging levels of physical activity, the talk test" If we are doing moderate intensity activity we can talk but upon vigorous activity, one will not be able to say more than a few words, without pausing for a breath.[5] This simple test can help us guard our pacing while walking. As doctors there is a dire need that we should stick to walking and be a role model for the community and our patients. The message may clearly be conveyed as "Let`s start walking from today as prevention is always better than cure" and " Improvement in quality of life is the promise made by brisk walking" .

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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.

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

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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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