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From the Editor



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Middle East Journal of Internal Medicine wishes all her editorial board, readers authors and the production team a good start for the year. The journal has witnessed major improvements and is highly read and recognized in the region and we are looking to continue the path toward better future of medical research with your help. In this issue various topics were discussed.

A prospective, parallel group comparative study was conducted in 100 patients with uncomplicated lower UTI in India. Patients were assessed for clinical and bacteriological success over the study period. 89 patients of the total of 100 patients enrolled in the study completed the study. E.coli was the most common organism isolated in both the groups. Patients in levofloxacin group showed improvement in clinical symptoms by 95.35 percent, as compared to 89.13 percent in cefuroxime group. The authors concluded that the results of our study show that cefuroxime axetil in a dose of 250 mg twice daily and levofloxacin 500 mg once daily for three days, are equally efficacious in treating patients with uncomplicated lower UTI. The comparative clinical and bacteriological successes between the two groups were statistically not significant, and both drugs were well-tolerated by the patients.

A prospective study of 400 women attending antenatal outpatients' clinic was conducted at King Hussein Medical Center, Jordan. The objective was to assess the current frequency of carpal tunnel syndrome during pregnancy in our area and to assess the course of carpal tunnel syndrome during pregnancy in those patients. During the study period, 74 (18.5%) women were found to have carpal tunnel symptoms. Most of them were in third trimester of pregnancy 81.1% (no=60) followed by the second trimester 16.2% (no=12) . The authors conclude that a large number of pregnant women suffer from the frequent occurrence of CTS in pregnancy and are first noted during the third trimester, but only in half of women CTS symptoms disappeared one year after delivery.

A retrospective study was conducted in a pediatric intensive care unit at Queen Rania Al-Abdullah Hospital for children. The chest radiographs of 25 patients who had been mechanically ventilated during the study period were reviewed using the picture archiving and communication system. Of the 25 patients, 13 (52 %) were males and 12 (48 %) were females. the age ranged between 1 day and 14 years of life . The authors concluded that the daily routine chest radiography in mechanically ventilated children had diagnostic and clinical usefulness.

A paper from Iraq looked at the effects of Benfotiamine and Methylcobalamin on Paclitaxel induced Peripheral neuropathy. The authors stressed that reports indicate that paclitaxel causes a dose-limiting distal and symmetrical sensorimotor peripheral neuropathy. This study was designed to evaluate the protective effects of benfotiamine and methylcobalamin on prevention of paclitaxel induced peripheral neuropathy. Twenty four rats and twenty four mice were involved in this study. Each animal group was allocated to two main experimental groups [control group (n=6) and paclitaxel model group (n=18)]. Paclitaxel administration produced significant increase in latency, but decrease in amplitude and conduction velocity in peripheral motor nerves in rats. The authors concluded that Benfotiamine 100mg/kg was very efficient in prevention of sensorimotor neuropathy induced by paclitaxel, whereas the suggested methylcobalamin (500µg/kg) twice weekly did not sufficiently prevent peripheral motor nerve destruction induced by paclitaxel, while the administration of high dose methylcobalamin every day is efficient in removal of thermal nociception induced during paclitaxel treatment.

Key: Benfotiamine; Methylcobalamin; Paclitaxel; peripheral neuropathy

A Case control descriptive study from Iraq attempted to determine the seropositivity of toxoplasmosis in women with bad obstetric history and factors that influence seroprevalence .

The study included 293 women with BOH and 245 women with normal pregnancy outcome. Serological study carried out to determine T.gondii IgG and IgM using ELISA kits.

The overall seroprevalence rate of T. gondii IgG was 29%, with no significant difference between women with BOH (27%) and women with normal pregnancy (31.4%). However, there was significant difference between pregnant (20.3%) and non pregnant (31.4%) women. The current T. gondii infection overall rate was 0.9%, with significantly higher rate in women with BOH (1.7%). Both T. gondii IgG and IgM were significantly varied with women age. Odd ratio confirmed the association of T, gondii IgG and women age, residence , and education.

The authors concluded that the seropositivity of Toxoplasma was significantly influenced by age, residence, and education levels.

Carpal tunnel syndrome during pregnancy

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Introduction

Carpal tunnel syndrome (CTS) is an entrapment median neuropathy, causing paresthesia, pain, numbness, and other symptoms in the distribution of the median nerve due to its compression at the wrist in the carpal tunnel(1). Most cases of CTS are of unknown causes, or idiopathic(2), but CTS may be associated with trauma, and with any condition that causes pressure on the median nerve at the wrist. Some common conditions that can lead to CTS include obesity, oral contraceptives, pregnancy, hypothyroidism, arthritis and diabetes. Up to one third of cases of carpal tunnel syndrome occur in association with such medical conditions (3). So Carpal tunnel syndrome is one of the most common peripheral neuropathies, and is one of the commonest elective clinical conditions presenting to hand surgery departments(4).

Carpal tunnel syndrome is common during pregnancy and is considered to have a short and benign course. It occurs most frequently in the third trimester but can develop at any time. Conservative therapies for the patient with mild symptoms of CTS are appropriate and common initial measures with very few cases require surgery. The symptoms resolve after delivery in most women with pregnancy-related carpal tunnel syndrome(5). However, in moderate to severe cases, surgery is the only treatment that provides cure. The basic principle of surgery is to increase the volume of the carpal tunnel by dividing transverse carpal ligament to release the pressure on the median nerve(6).

In the general population, the prevalence of CTS is approximately 9.6%, approximately 2.3% to 4.6% of patients with CTS are pregnant, and up to 50% of all pregnant women have nocturnal hand symptoms, mostly in the third trimester. Swelling in the hand and wrist caused by fluid retention compresses the median nerve. Also hormonal changes in pregnancy may explain this increase because a similar predisposition has been reported with menopause(7).

In spite of the public health importance of CTS, there are no universally accepted diagnostic clinical and laboratory criteria. However, it is agreed that certain electrophysiological abnormalities support the diagnosis. The most frequently used parameters are distal motor and sensory latencies as well as the sensory conduction velocity across the carpal tunnel(8). The diagnosis of CTS is traditionally based on clinical history, physical examination results, and electrophysiologic study results. More recently, ultrasonography (US) has been shown to be an accurate and useful diagnostic tool in patients with CTS(9).

ABSTRACT

Objectives: To assess the current frequency of carpal tunnel syndrome during pregnancy in our area and to assess the course of carpal tunnel syndrome during pregnancy in those patients.

Material and Methods: This is a prospective study of 400 women attending antenatal outpatients' clinic. This study was conducted between the 1st of July 2009 and the end of August 2010 at King Hussein Medical Center, Jordan. At each demographic details and issues related to their problems were obtained.

Results: During the study period, 400 pregnant women attending antenatal outpatients' clinic in our hospital, 74 (18.5%) women were found to have carpal tunnel symptoms. Most of them were in third trimester of pregnancy 81.1% (no=60) followed by the second trimester 16.2% (no=12) and the least were in the first trimester 2.7% (no=2). The most common complaint was numbness, particularly during the daytime (78.4%), while the least frequent symptom reported was pain. However, about half of women with CTS during pregnancy still complained of CTS symptoms one year after delivery.

Conclusion: A large number of pregnant women suffer from the frequent occurrence of CTS in pregnancy and are first noted during the third trimester, but only in half of women CTS symptoms disappeared one year after delivery.

Key words: Carpal tunnel syndrome, pregnancy, prevalence.

The present study was undertaken with the aim of assessing the current frequency of carpal tunnel syndrome during pregnancy in our area in patients attending this hospital in Jordan and to assess the course of carpal tunnel syndrome during pregnancy.

Methods

This is a prospective study of 400 women attending antenatal outpatients' clinic. This study was conducted between the 1st of July 2009 and the end of August 2010 at King Hussein Medical Center, Jordan. The study was approved by the ethics committee and informed written consent from all participants was obtained.

History and clinical examination of the patients was performed for all women. Maternal demographics, obstetrical events, delivery outcome, previous medical and surgical history were evaluated. All the data were compiled and continuous variables were analyzed using Student t-test. CTS were diagnosed clinically based on patient history, physical examination and electrophysiological findings.

The exclusion criteria include patients with diabetes mellitus, gestational diabetes mellitus, eclampsia, preeclampsia, thyroid disorders, trauma to the hand or wrist, and prior history of CTS.

All the women who were found to have carpal tunnel symptoms with electrophysiological proven CTS were followed in the neurosurgical clinic throughout their pregnancy and one year after delivery. Those patients were treated in different modalities. Symptoms follow up was done.

Results

During the study period (2009-2010), 400 pregnant women attending antenatal outpatients' clinic in our hospital, and 74 (18.5%) women were found to have carpal tunnel symptoms and were sent to the neurosurgical clinic. All of them were subjected to nerve conduction study for objective assessment of CTS, and electrophysiological test proven CTS. So the current incidence of carpal tunnel syndrome amongst women attending our hospital was 18.5%. Most of them were in the third trimester of pregnancy 81.1% (no=60) followed by the second trimester 16.2% (no=12) and the least were in the first trimester 2.7% (no=2).

The most common complaint was numbness, particularly during the daytime (78.4%), while the least frequent symptom reported was pain, especially pain that awakened patients at night (16.2%) as seen in Table 1.

In addition, the study revealed that neurophysiological evaluation provided diagnosis of CTS in around half of women (45% were positive in one hand at least). Comparison of baseline and follow-up data showed a significant spontaneous improvement of patient-oriented and neurophysiologic measurements. However, about half of women with CTS during pregnancy still complained of CTS symptoms one year after delivery, despite symptomatic and electrodiagnostic improvement, 42% of patients still had diminished median distal sensory conduction velocities.

Discussion

Carpal tunnel syndrome is a disorder of the hand caused by pressure on the median nerve as it runs through the wrist. During pregnancy, hormonal fluctuations, fluid shifts, and musculoskeletal changes predispose women to carpal tunnel syndrome. In pregnancy hormonal changes may result in fluid retention, which can compress the median nerve. CTS triggered during pregnancy usually resolves soon after birth. Symptoms may be exacerbated by repetitive hand movements, holding hands in sustained positions or by putting weight through outstretched hands(10).

Existing data reports a prevalence of CTS in pregnancy to be as high as 62%(11) and as low as 0.23%(12). Most of these data are based on clinical symptoms. Our findings were in agreement with those of a study by Bahrami et al that showed that 17% of pregnant women had CTS during pregnancy(13). Also our findings were in agreement with those of a study by Khosrawi et al(14) that showed that 63% had CTS hand symptoms during their third trimester of pregnancy, while in two other studies in the third trimester; the prevalence was 28% and 43%(15,16).

However, unlike many studies, numbness and tingling sensation were prominent symptoms in our study of pregnant women with CTS(78.4%). Pain was reported to be quite common among patients by other authors(17,18). We found that the incidence of numbness/tingling during daytime was slightly higher than at night among the women, which is at odds with the classical description of nocturnal paraesthesia in such patients in many orthopaedic textbooks.

Symptoms	No. (%)
Pain during daytime	16 (21.6%)
Pain during night	15 (20.3%)
Numbness during daytime	58 (78.4%)
Numbness during night	46 (62.2%)
Awakened at night by numbness	25 (33.8%)
Awakened at night by pain	12 (16.2%)
Physical examination	
Muscle atrophy (thenar)	4 (5.4%)

Table 1: Clinical findings among patients with carpal tunnel syndrome (n = 74).

In our study, neurophysiological evaluation provided diagnosis of CTS in around half of women (45% were positive in one hand at least) as seen by Padua et al study(19).

Almost all reported a short follow-up with disappearance of symptoms. Our study confirms that pregnancy-related CTS has a benign course: improvement of symptoms was evident at one year follow-up, but about half the women still complained of symptoms one year after delivery as Mondelli et al(20) reported that at one-year follow-up improved in 40% of women, did not change in 46.7% and 55.6% and worsened in 13.3% and 4.4%, respectively.

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The Importance of Daily Routine Chest Radiography in Mechanically Ventilated Children

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ABSTRACT

Objective: To assess the usefulness of daily routine chest radiography in mechanically ventilated children.

Methods: This retrospective study was conducted in a pediatric intensive care unit at Queen Rania AL-Abdullah Hospital for children during the period between February 1 and April 30, 2010. The chest radiographs of 25 patients who had been mechanically ventilated during the study period were reviewed using the picture archiving and communication system.

Results: Of the 25 patients, 13 (52 %) were males and 12 (48 %) were females. The age ranged between 1 day and 14 years of life. 245 chest radiographs were evaluated by a pediatric intensivist. 23 % of all radiographs showed cardiopulmonary abnormalities, 12 % showed malpositioned endotracheal tubes and 9 % malpositioned central venous catheter. 14% of chest radiographs had findings that altered management. The most frequent management changes done were repositioning of central venous catheters, and changes in drug therapy.

Conclusion: We conclude that the daily routine chest radiography in mechanically ventilated children had diagnostic and clinical usefulness.

Key words: pediatric, Intensive care, chest radiography, Intubation.

Introduction

The portable chest roentgenogram is one of the most frequent and effective diagnostic examinations used in the intensive care unit (1).

Obtaining daily routine chest-X Ray is a labor-intensive strategy, while diagnostic and therapeutic yields of daily routine chest-X Rays are low (2). Chest radiographs are routinely obtained in critically ill patients to monitor both clinical condition and to evaluate placement of invasive instruments such as central venous catheters and endotracheal tubes (3).

The consensus opinion of the American College of Radiology Expert Panel is that daily routine chest radiographs are indicated in patients with acute cardiopulmonary problems and in patients receiving mechanical ventilation (4).

Methods

This retrospective study was conducted in a pediatric intensive care unit at Queen Rania AL-Abdullah Hospital for children during the period between February 1 and April 30, 2010. The Queen Rania AL-Abdullah Hospital for Children is one of the affiliated hospitals of King-Hussein Medical Center in Amman, Jordan. The pediatric intensive care unit is an 18 bed mixed medical-surgical unit admitting children from birth to 14 years of age. Portable chest radiographs are routinely done every morning at 8 AM for mechanically ventilated children. Chest radiographs which are done when clinically indicated are called on demand chest X-Rays. The indication for on demand chest X-Rays includes placement of central venous catheters, endotracheal intubation and chest tube drain insertion. The chest radiographs are reviewed on daily morning rounds by pediatric intensive care consultant and fellows. These chest radiographs are accessible in the picture archiving and communication system (PACS) to the attending physicians.

Results

Of the 25 patients, 13 (52 %) were males and 12 (48 %) were females. Age ranged between 1 day and 14 years of life. Over a three month period 245 chest radiographs were done for 25 mechanically ventilated children. The main causes of admissions are shown in Table 1. 23 % of all radiographs showed cardiopulmonary abnormalities, 12 % showed malpositioned ET tubes and 9 % malpositioned CVC. 14% of chest radiographs had findings that altered management. The most common management changes were repositioning of CVC and changes of drug treatment.

Medical diagnosis (n=16)	Number (n)
Chronic lung disease	1
Pneumonia	1
Acute respiratory distress syndrome	5
Acute bronchiolitis	1
Laryngomalacia	2
Inborn error of metabolism	2
Septic shock	1
Status epilepticus	1
Congenital heart disease	2
Surgical diagnosis (n=9)	
Intestinal obstruction	4
Tracheo-esophageal fistula	3
Trauma	1
Abdominal mass resection	1

Table 1: The Main diagnoses of the study group (n =25)

Discussion

Whether chest radiographs in mechanically ventilated patients should be routinely obtained or only when an abnormality is anticipated remains debated (5).

While most medical studies evaluating daily chest X-Rays in patients in the ICU have been in adult populations, a few on children are available (3).

Our study showed that 14% of chest X-Rays had findings that changed management in the form of antibiotic coverage and repositioning of CVC. These results indicate clinical and diagnostic usefulness of daily routine chest X-Rays in mechanically ventilated pediatric patients.

Previous studies have evaluated the efficacy of daily routine chest X-Rays in mechanically ventilated children.

Sivit CJ et al prospectively evaluated the efficacy and clinical usefulness of bedside chest radiography in a pediatric intensive-care unit, where seven hundred and ninety-five radiographs were evaluated in 126 patients over a 10-week period in Children's Hospital National Medical Center, Washington, D.C and their data indicated that bedside radiography in the pediatric intensive-care setting has a high efficacy and clinical utility (6).

Brainsky et al observed that 20% of routine chest X-Rays performed in a medical ICU had major important findings, and 8% prompted a change in management. The majority of changes related to diuretic use, antibiotic coverage, initiation

of a diagnostic test, or decisions regarding ventilator weaning (7).

In a prospective study, Hall et al compared bedside clinical diagnosis with the diagnosis made from the routine chest X-Ray. A total of 538 chest radiographs were examined; of these, 354 (65.8%) did not disclose either new major or new minor findings but one hundred and sixty-three radiographs disclosed only new minor findings, 40.5% of which were anticipated by bedside assessment (8). However, in 13 (17.6%) of the 74 patients, new major findings were discovered only by chest radiography. These data demonstrate that, while a large percentage of radiographs will not disclose new findings, routine daily studies have a substantial impact on the management of intubated, mechanically ventilated patients in the ICU which support the use of daily chest radiographs in critically ill patients (8).

On the contrary to the findings of our study, many studies have questioned the usefulness of daily routine chest X-Rays on diagnostic and therapeutic level and its association with economic cost.

A study conducted by Karine A et al in Amsterdam-Netherlands on 1780 daily routine chest-X-Rays in 559 hospital admissions, reported low value of daily routine chest-X-Rays (2).

Hejblume G et al compared routine and on-demand chest radiography in 21 intensive care units at 18 hospitals, in France. They strongly support adoption of an on-demand strategy in preference to a routine strategy to decrease use of

chest radiographs in mechanically ventilated patients without a reduction in patients' quality of care or safety(9).

Bekemeyer et al found that 27% of both routine and non-routine chest-X-Rays revealed clinically unsuspected abnormalities, but that non-routine films were more likely to change investigative or therapeutic management (10).

Price et al found that 37% of chest-X-Rays could be avoided by establishing specific indications, thereby resulting in significant cost savings (11).

Chahine-Malus N et al evaluated the diagnostic and therapeutic efficacy of daily routine and clinically indicated chest-X-Rays in a prospective controlled blinded study in a nonacademic, mixed medical-surgical ICU., In addition, the effects of abandoning the daily routine chest X-Rays strategy on chest Ray volume, ICU length of stay, readmission rate, and mortality were evaluated during a 6-month period. The results confirm and corroborate previous data indicating that the diagnostic yield and therapeutic consequences of daily routine chest- X-Rays are very low (12).

In summary we conclude that daily routine chest radiographs in mechanically ventilated children had diagnostic and therapeutic usefulness but we need a study to compare between daily chest X-Rays and on demand chest X-Rays with more patients to be included and figures to be statistically analyzed to support our opinion.

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Toxoplasma gondii seroprevalence in women with bad obstetric history

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ABSTRACT

Background: Toxoplasmosis is a well documented cause of bad obstetric history (BOH).

Objective: To determine the seropositivity of toxoplasmosis in women with bad obstetric history and factors that influence seroprevalence.

Study design: Case control descriptive study.

Patients and Methods: The study included 293 women with BOH and 245 women with normal pregnancy outcome. Serological study carried out to determine T.gondii IgG and IgM using ELISA kits.

Results: The overall seroprevalence rate of T. gondii IgG was 29%, with no significant difference between women with BOH (27%) and women with normal pregnancy (31.4%). However, there was a significant difference between pregnant (20.3%) and non pregnant (31.4%) women. The current T. gondii infection overall rate was 0.9%, with significantly higher rate in women with BOH (1.7%). Both T. gondii IgG and IgM were significantly varied with women's age. Odd ratio confirmed the association of T. gondii IgG and women's age, residence, and education.

Conclusion: The seropositivity of Toxoplasma was significantly influenced by age, residence, and education levels.

Key words: TORCH, BOH, Toxoplasma, Pregnancy, Iraq

Introduction

Primary infection with any of the TORCH agents during pregnancy can lead to adverse outcomes, which are initially inapparent or asymptomatic and thus difficult to diagnose on clinical grounds (1). The ultimate consequences of intrauterine infection can be any one of the following (2): no significant problem, asymptomatic chronic infection, spontaneous abortion, intrauterine fetal death, stillbirth or neonatal death, fetal malformation or neonatal infection.

Spontaneous abortion is a new issue in terms of its social and economic impact. Pregnancy loss has been attributed to several factors involved in human reproduction; genetic and uterine abnormalities, endocrine and immunological dysfunctions, environmental pollutants, psycho-genetic factors and endometriosis, infectious agents, are most important causes of spontaneous abortion (3). The rate of spontaneous abortion from foetal infection by the infectious agents like TORCH is believed to range from 10-15% (4).

Toxoplasma gondii is considered one of the most widespread parasites in the world causing abortion. It is an intracellular protozoan that infects humans and other warm-blooded animals (5). The organism is transmitted to humans by accidental ingestion of water, food, or soil contaminated with *T. gondii* oocysts or consumption of meat containing *T. gondii* cysts that is eaten raw or undercooked (6). This disease is clinically insignificant in immunocompetent adults. The immunologic response to primary infection is followed by encystment of the parasite (latent toxoplasmosis), providing life-long immunity. Possible reactivation of latent infection in an increasingly immunosuppressed population, however, makes toxoplasmosis an important opportunistic infection. In addition, toxoplasmosis has long been known as a major cause of perinatal morbidity. *T. gondii* infection in pregnant women can be transmitted to the fetus and cause mental retardation, blindness, epilepsy and death (7).

In Iraq [Baghdad], Abdulmohymen (8) reported that there was a significant difference ($p < 0.05$), in the serum level of *Toxoplasma gondii* specific IgM among the three investigated patients groups (Recurrent spontaneous abortion, non-recurrent spontaneous abortion, and successful pregnancy). A similar result was obtained by Abbas (9), who showed that 21.5% of women with first abortion have positive only IgM. Al-Fertosi (1-) and Salman (11) showed 19.17% of women with single or repeated abortion. In addition, there is more than one *T. gondii* strain with difference in virulence among isolates in the nature (12). This strains' difference could be a potential explanation regarding the high prevalence of toxoplasmosis.

The relatively high frequency of toxoplasmosis in women with abortion as Abdulmohymen (8) reported could be due to the sample selection. Their samples were collected from Al-Kadhimiya Teaching Hospital which is a reference hospital for the surrounding rural areas where they have habits in favor of acquiring toxoplasmosis by eating unwashed raw vegetables or unpeeled fruits. In addition, in the rural cities there is close contact with cats and consequent exposure to sporulated

oocysts by ingestion of these oocysts that contaminate soil during gardening, or eating undercooked meat contaminated with cysts (8). Moreover, the low level of education in the women about the risk factors for toxoplasmosis may play an important role in the high rate of infection (13).

Furthermore, Abdulmohymen's (8) study showed a highly significant difference between the women group with recurrent spontaneous abortion and the women group with successful pregnancy in acute infection of *T. gondii*, but no significant difference in the mean value between recurrent spontaneous abortion and non recurrent spontaneous abortion (non-RSA) and non-RSA and those with successful pregnancy. It has been proposed that during pregnancy, systemic maternal immune response is biased in favor of Th2 cytokine (14,15). Moreover, Th2 cytokines pattern of pregnancy induces the susceptibility to toxoplasmosis infection, together with risk of placental infection and congenital transmission (16). Evidence from murine and human pregnancy showed that since Th1 type cytokine mediated pregnancy loss, a shift towards Th1-type immunity during *T. gondii* infection may help to explain pregnancy failure (17,18). Thus, a considerable amount of evidence suggests that Th1 cytokine might well be implicated in adversely affecting pregnancy, directly by interfering with trophoblast survival and function, and indirectly by activating cell-mediated immune effectors (19).

The aim of the present study is to provide a picture about frequency, distribution, risk and determinants of the seroprevalence of *T. gondii* infections during pregnancy and their association with high delivery risk factors.

Patients and Methods

Settings:

Kirkuk General Hospital, Primary Health Care Centers in Kirkuk Governorate.

Study Design:

The study design is a Descriptive Case Control Study.

Study area:

This descriptive case-control study was conducted at the antenatal clinic of Kirkuk General Hospital and Primary Health Care Centre in Tessean. Women (pregnant or non pregnant) with bad obstetric history were recruited from those attending outpatient Gynaecology Clinic Kirkuk General Hospital or the outpatient Clinic at Tessean PHC.

Study Population:

The study population is women of childbearing age. Study population was recruited from Primary Health Care Centers located in urban and rural areas in Kirkuk Governorates. In addition, one of the study population group was recruited from pregnant women who were in labor to select the group of pregnant women with risky outcomes.

Group 1: Pregnant women with age range of 17-45 years, and with normal pregnancy.

Group 2: Non pregnant women with age range of 17 - 45 years, and

with normal pregnancy.

Group 3: Pregnant women with Risk factor (BOH) depending on their previous pregnancy and /or delivery outcome which included pregnancy loss, intrauterine deaths, preterm deliveries and intrauterine growth retardation. Their age ranged from 17 to 45 years.

Group 4: Non-pregnant women with Risk factor depending on their previous pregnancy and /or delivery outcome which included pregnancy loss, intrauterine deaths, preterm deliveries and intrauterine growth retardation. Their age ranged from 17 to 45 years.

The demographic information of these groups is shown in Table 1. The target number recruited for each group was 150 women. However, the total number of women included in the study was 538, of these 293 (54.5%) had BOH, and 245 (45.5%) had normal pregnancy history. In the BOH group, 144 (49.1%) women were pregnant, while in the normal pregnancy group, 117 (47.7%) were pregnant.

Collection of data

The designated investigators visited the outpatient department daily, selected the study subjects, and screened them using a predesigned pretested schedule considering the inclusion and exclusion criteria till the study subjects recruitment could be identified. The next available age-matched multiparous antenatal woman without BOH was included in the control group subjects.

Clinical examination and laboratory investigations were carried out for the study subjects to exclude other causes of foetal wastage, such as hypertension, diabetes mellitus, syphilis, Rh (rhesus) incompatibility, physical causes of abortion, and consanguinity. Subjects with known causes of foetal wastage were excluded from the study. All of them were interviewed to ascertain age, medical and obstetric information.

Sample Collection:

For serological analysis, 5-10 mL of venous blood was collected in a sterile container with strict aseptic precautions from each study subject. The serum was separated and stored in

numbered aliquots at -20 °C till assayed. All the serum samples collected from the study and control groups were tested for HSV 2 IgM and IgG antibodies by commercially available (ELISA) kits. The results were read by a Microwell reader and compared in a parallel manner with controls; optical density was read at 450 nm on an ELISA reader.

Ethical approval

The ethical committee of the concerned institute approved the research protocol. The purpose and procedures of the study were explained to all the study subjects, and informed consent was obtained from them. The study design was approved by the ethical committee of TUCOM that is now registered in the USA [U.S. Department of Health and Human Services (HHS)& Registration of an Institutional Review Board (IRB)]. IORG #: IORG0006885. Institution: Tikrit University College of Medicine [TUCOM] OMB No. 0990-0279

Methods:

ELISA was used for determination of IgM and IgG for HSV-2 and the test was performed according to manufacturer instructions. The kit was purchased from BioCheck, Inc, 323 Vintage Park Dr, Foster City, CA 94404.

Analysis of data

Collected data were compiled in Microsoft Excel spreadsheet. The proportion and the mean value were computed in appropriate situations. To find out any association between categorical data, Chi square test was employed using the SPSS (Version 16). If the sample size in BOH group did not reach the targeted number, Power Analysis was performed to determine the accuracy of findings.

The study finding data are presented as frequency \pm SD and 95% Confidence Interval. Bivariate Regression Line Analysis calculated Odd Ratio for determination of association between the two variables. The determinants for *T.gondii* infection was determined by calculation of Odd Ratio using Logistic Regression Line Analysis. Confounding factors such as age, socio-economic status, etc. were standardized when serological determinants were calculated.

Table 1: Study population

Group		Number	Mean age \pm SD in years
Women with bad obstetric history	Pregnant	144	27.38 \pm 7.5
	Non pregnant	149	28.56 \pm 6.7
	Total	293	27.97 \pm 7.1
Women with normal pregnancy	Pregnant	117	26.00 \pm 6.2
	Non pregnant	128	30.16 \pm 10.9
	Total	245	28.16 \pm 9.2
Grand total		538	28.06 \pm 8.1
P value	ANOVA	NS	

Results

The overall seroprevalence rate of *T. gondii* IgG was 29%, with no significant difference ($X^2=1.293$) between women with BOH (27%) and women with normal pregnancy (31.4%) (Table 2). However, there was a significant difference ($X^2=18.59, P=0.000$) between pregnant (20.3%) and non pregnant (31.4%) women (Table 3). The current *T. gondii* infection overall rate was 0.9%, with significantly ($X^2 =4.22, P=0.04$) higher rate in women with BOH (1.7%).

Table 2: Toxoplasma seroprevalence in women with bad obstetric history

Group [Number]		Number positive [Percent]	
		IgM	IgG
Bad obstetric history	Pregnant [144]	4 [2.8]	40 [27.8]
	Non- pregnant [149]	1 [0.7]	39 [26.2]
	X^2	1.937	0.096
	P value	NS	NS
	Total [293]	5 [1.7]	79 [27]
Normal pregnancy	Pregnant [117]	0 [0]	13 [11.1]
	Non- pregnant [128]	0 [0]	64 [50]
	X^2	-	42.89
	P value	-	0.000
	Total [245]	0 [0]	77 [31.4]
Grand total [538]		5 [0.9]	156 [29]
X^2 BOH versus Normal Pregnancy		4.22	1.293
P value BOH versus Normal Pregnancy		0.04	NS

Table 3: Toxoplasma seroprevalence in pregnant compared to non-pregnant women

Group [Number]	Number positive [Percent]	
	IgM	IgG
Pregnant [261]	4 [1.5]	53 [20.3]
Non- pregnant [277]	1 [0.4]	103 [37.2]
X^2	2.003	18.59
P value	NS	0.000

Both *T. gondii* IgG and IgM were significantly varied with women's age (IgG, $X^2 =54.4, P=0.000$; IgM, $X^2=6.36, P=0.01$). Current *T. gondii* infection was detected in the age group of 20 to 29 (2.1%) years only. *T. gondii* IgG seroprevalence was 31.1% in women with age of 15-19 years, then declined to reach 17.2% in women with age of 20-29 years. However, IgG seroprevalence increased in women aged 30 and above to the plateau of 66.7% in age group of 40 - 48 years (Table 4). Odd ratio confirmed the association of *T. gondii* IgG and women age of lower or upper than 30 years ($OR=2.66, P<0.0001$). Although, *T. gondii* IgM demonstrated high OR, it did not give significant confirmation of the association and this was due to the small number included in the analysis (Table 5).

Table 4: Frequency of *T. gondii* in regard to age

Age group in years	Number	T. gondii Number [%]	
		IgM	IgG
15 – 19	74	0 [0]	23 [31.1]
20-29	238	5 [2.1]	41 [17.2]
30-39	172	0 [0]	56 [32.6]
40 -48	54	0 [0]	36 [66.7]
Chi Square		6.36	54.4
P value		0.01	0.000

Table 5: Odd ratio of T. gondii in regards to age of women lower than 30 years

Variable	Odd ratio [95% Confidence interval]	P value
T. gondii IgM	8.1024 [0.4457-147.2835]	NS
T. gondii IgG	2.66 [1.8157 – 3.8982]	<0.0001

T.gondii IgG seroprevalence was significantly higher ($X^2=7.439$, $P=0.006$) in women living in urban areas (32.2%) as compared to women living in rural (20%) areas. However, current infection was significantly ($X^2=7.638$, $P=0.006$) predominant (about 10 times) in rural areas (2.9%) than in urban (0.3%) areas (Table 6). OR confirmed the association between residence and both T.gondii IgM ($OR=11.6765$, $P=0.02$) and IgG ($OR=1.896$, $P=0.006$) (Table 7 - next page).

Table 6: Frequency of HSV 2 IgG and IgM in regard to sociodemographic characteristics

Variable	[Number]	Number positive [Percent]	
		IgM	IgG
Residence	Rural [140]	4 [2.9]	28 [20]
	Urban [398]	1 [0.3]	128 [32.2]
	X^2	7.638	7.439
	P value	0.006	0.006
Occupation	House wife [497]	5 [1]	149 [30]
	Working [41]	0 [0]	7 [17.1]
	X^2	0.416	3.065
	P value	NS	NS
Education	Uneducated [34]	0 [0]	11 [32.4]
	Primary [331]	1 [0.3]	109 [32.9]
	Secondary [105]	4 [3.8]	26 [24.8]
	College & above [68]	0 [0]	10 [14.7]
	X^2	11.83	12.53
	P value	0.019	0.014
Crowding Index	≤ 3 [478]	5 [1.04]	141 [29.5]
	3.1 – 8 [60]	0 [0]	15 [25]
	X^2	0.634	0.524
	P value	NS	NS

T.gondii IgG seroprevalence was higher (about double) in housewives (30%) as compared to working women (17.1%), but the difference did not reach a significant level. In addition, all the current T. gondii infections were in housewives. Furthermore, OR did not confirm the association between occupation and both IgG and IgM seropositivity (Tables 6 & 7).

About 96% of women who participated in this study were educated and only 4.1% were uneducated. Relationship between infection with T.gondii and education was significant ($P=0.014$), also current infection had a significant association with education ($P=0.019$). OR confirmed T.gondii seropositivity and education for remote (IgG), but not current infection (IgM) (Tables 6 & 7).

T.gondii IgG and IgM seroprevalence was higher in small size families (<3 crowding index). However, OR did not confirm an association between T.gondii infection and family size in women included in our study population (Tables 6 and 7).

Table 7: Association of HSV 2 seropositivity with sociodemographic characteristics using Bivariate analysis.

Variable		Odd ratio [95% Confidence interval]	P value	
Occupation [Housewife versus Employed]	IgM	0.9296 [0.0504-17.0558]	NS	
	IgG	2.2020 [0.9582-5.0603]	0.06	
Crowding Index [<3 versus >3]	IgM	1.4055 [0.0768-25.7347]	NS	
	IgG	1.2552 [0.6776-2.3253]	NS	
Education	Uneducated	IgG	2.7740 [1.038-7.415]	0.04
	Primary		2.8477 [1.401-5.787]	0.003
	Secondary		1.9089 [0.8541-4.2662]	NS
	College & above		2.7739 [1.0378-7.4146]	0.04
	Uneducated vs. Educated	IgM	2.9353 [0.3433-26.641]	NS
Residence [Rural versus Urban]	IgM	11.6765 [1.2938 – 105.3785]	0.02	
	IgG	1.896 [1.1818-3.0174]	0.006	

Discussion

The result of TORCH testing suggests that 29% of women of 15-48 years in age in Kirkuk , Iraq were seropositive for T. gondii. Thus 71% of studied population were susceptible to infection with Toxoplasmosis. Pregnant women should take appropriate precautions to protect themselves against infections. Such precautions include cooking meat, handling raw meat or working in soil ; and avoiding contact with cat faeces (20).

The result of this study and that reported by others (21,22), based on serological tests, confirmed expectation that Toxoplasmosis is indeed endemic in Kirkuk and that a substantial proportion of the examined patients' sera showed evidence of earlier infection (IgG), whilst fewer had evidence of current infection (IgM). The prevalence and risk factor for transmission of T. gondii varies substantially between countries and geographical regions (23). In this study Toxoplasma gondii IgG antibodies were found to be 32 times more common than IgM antibodies (29% versus 0.9% in the study group). Clearly the overall prevalence of IgG antibodies, reflecting earlier infection with Toxoplasma gondii among the tested samples from the study population indicated that between 1 in 3 and 1 in 4 had experienced earlier infection and these values are broadening in line with reports from other countries (23,24). However, changes of prevalence of IgG seropositivity across the age groups revealed a more complex story. In 82.8% of woman with age group of 20- 29 years (44.2% of study

population) were negative for Toxoplasma gondii IgG and these 4/5ths were susceptible for Toxoplasma gondii infection during their pregnancy.

However, the Toxoplasma gondii IgG seropositivity was higher in the 15-19 years age group. This could be attributed to less meat consumption and catabolism of passively transferred antibodies; prevalence then increased markedly with each successive age class as reported previously in other studies (25-31), peaking in the older subjects at over 66%. This rising trend with age, reflects the constituting risk of infection throughout adult life and arises from cumulative infection . However studies reported for Iraq indicated that Toxoplasma gondii IgG seroprevalence reduced with age (32-36). Risk of exposure and infection with age in an environment where transmission is encouraged by the high density of feral cats (23).

Interestingly the age related trend in prevalence of IgG antibodies in the combined study group (A=all tested samples), was also seen in each of the groups (BOH pregnant, BOH not pregnant, normal pregnancy and normal non pregnancy) representing their subdivision in regard to bad obstetric history). The overall Toxoplasma gondii IgG seroprevalence (29%) in woman from Kirkuk governorate was similar to reported studies from Egypt (37-42), Morocco (43,44), Saudi Arabia (45,46), Iraq (29,21,22,36,38,47-54), Libya (55,56), Tunisia

(57). Although our finding for IgG seropositivity was higher than that reported for Iraq (8,28,58,59,60), Bahrain (61) and Palestine (62). These studies performed in Arab countries indicated that seroprevalence of *T. gondii* varies substantially between geographical regions, and the variation demonstrated between the studies performed in Iraq.

In Kirkuk, 3 studies were reported. Ali (21) reported seroprevalence of 61 % in 100 pregnant woman where Kader et al (22) reported a seroprevalence of 36.6% in 319 pregnant woman and 52% in 121 aborted woman, giving an overall seroprevalence of 44.3%. In addition, Salman (60) reported a very low (4.84 %) seroprevalence of IgG in 184 woman with bad obstetric history. The present study finding indicated that overall seroprevalence was lower than that reported by Ali (21) and Kadir et al (22), but higher than that reported by Salman (60). Furthermore the global *T. gondii* IgG seroprevalence in pregnant woman was from 0.48 in Brazil (90 %) to (83.5%)

in Madagascar (63), while the range in woman with BOH was from 19.44 % reported by Natu et al (64) to 55.2% in Nepal (65). The above information collected together indicated that there was a worldwide variability in the prevalence rate of *Toxoplasma gondii* seropositivity among pregnant and non pregnant woman. The relationship between education and *Toxoplasma* infection was recorded in this study, thus women who cannot read and write and with primary school level were more infected than educated woman (32.4 % and 32.9 % respectively), with a highly significant difference between the education level groups. In the United States the risk of *Toxoplasmosis* is associated with low level of education (66). The *T. gondii* IgG seroprevalence significantly varies ($P=0.014$) with the education level. In addition, the OR confirm that uneducated women and those with primary education have a chance to be detected three times more than women with secondary education and above.

Although, 94 % of educated but uneducated woman still are more prone to infection by *Toxoplasma gondii*. This might be due to fact that uneducated women were of ideal health condition or may not be caring about that. However, uneducated woman may be less likely to wash boards with soap or bleach after cutting raw meat or using the same knife for salad preparation. The present study finding was in agreement with that reported for Basrah (28), Tikrit (36) and Sudan (67), while none of the 9 studies performed in Iraq reported any information on such variables (26,29,30,32,33,34,35,43,68). From the present study, it was speculated that high education linked with good hygiene sanitary practices reduce the transmission of the parasite. This finding confirmed using both Logistic regression and Bivariate analysis, as it indicated that higher education was protective against infection ($X^2=0.614$, $P=0.000$).

The present study indicated that *T. gondii* infection was more predominant in housewives (30 %) compared to employed (17.1 %). Thus occupation plays a key role in the transmission of the disease when occupation is related to direct contact with meat, soil and animals. The majority of women (92.2%) in this study were housewives and few of them are working

in jobs not related to soil or meat but (?) mostly they are house wives. The predominance of infection in housewives as this study indicated was in agreement to that reported for Kirkuk (22,60), Almothana (69), Al-Najaf (30), and Tikrit (36). However, prevalence rate was much higher than that reported by Salman (3.49 %)(60) for Kirkuk in 2007, while it was about similar to that reported by Kadir (22) for Kirkuk in 2011.

Another two studies performed in Iraq, for Najaf (68) and Basrah (34) reported lower predominance rate of *Toxoplasma gondii* infection. One study reported for Basrah, Iraq (28), did not find a relationship between *Toxoplasma gondii* infection and occupation. Although the prevalence rate for *Toxoplasma gondii* infection was higher in housewives but the OR did not confirm the responsibility of such occupation as bivariate as logistic regression analysis demonstrated.

The present study has revealed that the prevalence rate of *Toxoplasmosis* varies remarkably in relation to residence and it was significantly more predominant in urban areas (32.2 %) than that for rural (20 %) areas. The OR confirmed that women living in urban areas have more of a chance to be infected than those living in rural areas. This finding was in agreement to that reported in Iraq, for Najaf (30), Karbala (33), and Tikrit (36). However, other studies in Iraq reported that prevalence rate was more in rural areas, in AL-Anbar (29), Diyala (32), Tikrit (35) and Kirkuk (22). All the studies reported that high prevalence in rural areas presented their data as frequency and did not perform any statistical test to determine the association. In addition, the study population size of most of the studies (except 22) was smaller than ours, which may influence their findings. Globally, seroprevalence estimates from human population vary greatly among different countries, among different geographical areas within one country, and among different ethnic groups living in the same area (70).

Toxoplasma gondii IgG seroprevalence was higher in families with crowding index of less than 3 (29.5 %). However, OR did not confirm a significant association between family size and *Toxoplasma* IgG seroprevalence. The presence of IgM antibody in 5 women suggests that 0.9% active infection may be present in the studied population. Four of them are pregnant and thus IgG avidity testing is the preferred method to confirm the recent infection (71), because IgM antibodies can persist for months after initial infection in some individuals (72,73). Alternate testing algorithms use higher IgM serologic titers as good indicators of acute infection; economic considerations prompt additional tests (74,75).

T. gondii IgM seroprevalence in high risk women declined from 1.05 % in the previous 3 years (Retrospective study) to 0.9 % in our prospective study (15 % decline), but this was not the case for IgG seroprevalence. The latter is a measure of individuals infected months or years earlier; therefore, it is unlikely we would detect a decline until incidence decreases significantly for 5 to 10 years. Declining of IgM seroprevalence suggests that knowledge about how to prevent *T. gondii* infection may have improved, the prevalence of *T. gondii* cysts in food animals in the region are declining, or the feral cat control is reducing the quality of oocysts entering the environment. The association of *T. gondii* with abortion, does

act as an impact on society to increase the awareness towards prevention of infection. There is one problem that emerged recently which may affect *T. gondii* in Iraq, which is the prevalence of *T. gondii* in meat, most likely sheep and goats, imported into Iraq for human consumption is unknown.

Reports from other countries in the region since 2001 found *T. gondii* prevalence of 23 % to 25 % in sheep (76-82), suggesting that lamb, if it is under cooked, could be a source of *T. gondii* infection. Since there is no well designed feral cat control program, thus infected cats may be responsible for parasite spread. *T. gondii* seroprevalence was significantly higher in non-pregnant (37 %) women as compared to pregnant women (20.3 %). This finding is in agreement with that reported by others (21) for Kirkuk.

In conclusion, the seropositivity of *Toxoplasma* was significantly influenced by age, residence, and education levels.

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Effects of Benfotiamine and Methylcobalamin on Paclitaxel induced Peripheral neuropathy

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ABSTRACT

Background: Reports indicate that paclitaxel causes a dose-limiting distal and symmetrical sensorimotor peripheral neuropathy. This study was designed to evaluate the protective effects of benfotiamine and methylcobalamin on prevention of paclitaxel induced peripheral neuropathy.

Methods: Twenty four rats and twenty four mice were involved in this study. Each animal group was allocated to two main experimental groups [control group (n=6) and paclitaxel model group (n=18)]. The paclitaxel model group in rats was subdivided into 3 subgroups [paclitaxel group (6mg/kg i.p.) for 4 weeks, paclitaxel + benfotiamine (100mg/kg orally, daily for 8 weeks) and paclitaxel + methylcobalamin (500µg/kg i.p., twice weekly for 8 weeks)]. Whereas the paclitaxel model group of mice was subdivided into 3 sub groups [paclitaxel group (6mg/kg i.p. for 4 weeks), paclitaxel + benfotiamine (100mg/kg orally, daily for 6 weeks) and paclitaxel + methylcobalamin (500µg/kg orally, daily for 6 weeks)]. Electrophysiological and histological investigations, as well as a number of classical behavioural tests of nociception were performed.

Results: Paclitaxel administration produced significant increase in latency, but decrease in amplitude and conduction velocity in peripheral motor nerves in rats. Degenerative changes of sciatic nerve were observed in rats. The paw withdrawal latency for heat hyperalgesia and the tail withdrawal latency for cold (allodynia and hyperalgesia) in mice were significantly reduced. Benfotiamine administration significantly ameliorated all electrophysiological changes induced by paclitaxel in peripheral motor

nerves. Moreover benfotiamine decreased histological changes in rat's sciatic nerve. In mice benfotiamine administration significantly ameliorated the reduced withdrawal latencies for cold and hot. Methylcobalamin administration together with paclitaxel attenuates the reduction in conduction velocity in rats but had no effect on the reduced amplitude. Methylcobalamin reduced degenerative changes in Schwann cells but had no effect on reduced myelin thickness. While in mice daily methylcobalamin administration significantly reduced the decreased withdrawal latencies for cold and hot.

Conclusion: Benfotiamine 100mg/kg was very efficient in prevention of sensorimotor neuropathy induced by paclitaxel, whereas the suggested methylcobalamin (500µg/kg) twice weekly did not sufficiently prevent peripheral motor nerve destruction induced by paclitaxel, while the administration of high dose methylcobalamin every day is efficient in removal of thermal nociception induced during paclitaxel treatment.

Key words: Benfotiamine; Methylcobalamin; Paclitaxel; peripheral neuropathy

Introduction

Approximately 1.5 million new diagnoses of cancer were anticipated in 2009 in the United States (1). Improved medical treatments and advances in technology have allowed many people with cancer to increase their lifespan; however, these life-saving interventions come with many potential risks. Chemotherapy induced peripheral neuropathy (CIPN) is a debilitating and disabling condition that affects approximately 3% to 7% of patients who are treated with a single agent, and more than 38% of patients being treated with a combination of drugs(2).

Peripheral neuropathy is a common and potential dose-limiting complication of cancer chemotherapy. Involvement of the peripheral nervous system may be in the form of purely sensory and painful neuropathy, which occurs after therapy with cisplatin, oxaliplatin and carboplatin, or mixed sensory-motor neuropathy which may be accompanied by dysfunction of the autonomic nervous system, that results after therapy with vincristine, taxanes, suramin and other drugs (3, 4).

Paclitaxel is one of the most effective and commonly used anti-neoplastic drugs originally derived from the bark of the western yew tree, *Taxus brevifolia*, with activity against several tumors including ovarian cancer not responsive to primary treatment methods, metastatic breast cancer, Kaposi's sarcoma, bladder, testicular, lung, and head and neck cancers (5,6).

Paclitaxel-induced sensory disturbance is characterized by preferential impairment of myelinated fiber function in cancer patients.

Studies have shown that paclitaxel administration inhibits the usual regenerative response of axons and Schwann cells to nerve crush injuries in rodent models (7).

There have been several in vivo and in vitro experimental studies of taxane neurotoxicity. Cultured sensory neurons show proliferation and aggregation of neurotubules; application of nerve growth factor inhibits this effect (8).

Painful peripheral neuropathy occurs with other agents in the taxane class, as well as with chemotherapeutics in the vinca alkaloid and platinum-complex classes. The cause of the neuropathy and of the pain syndrome is unknown.

This study was designed to evaluate the neuroprotective effects of benfotiamine and methylcobalamin in paclitaxel induced peripheral neuropathy.

Materials and Methods

Animals

The experiments were performed on 24 male albino rats and 24 male albino mice. The rats were used for both nerve conduction studies and nerve biopsy, whereas the mice were

used to detect the effect of each drug on heat nociception stimuli.

Before experiment, the animals were kept in the animal house of the college of Medicine / Hawler Medical University. They were housed in groups of six per cage, on sawdust, maintained on a 12h-12h light-dark cycle. They were given food rich in nutrient and tap water. Room temperature was maintained at 25 C°.

Anaesthesia

The rats were anaesthetized by a combination of Ketamine and xylazine which were injected intra-peritoneally at a dose of 35 mg/kg, and 5mg/kg body weight respectively (9). After six minutes a state of anesthesia was reached. They were placed on a heated table to maintain their body temperature at around 37 °C.

Induction of peripheral neuropathy

Peripheral neuropathy was induced by paclitaxel-induced peripheral neuropathy model. In the paclitaxel-induced peripheral neuropathy model, paclitaxel (6 mg/kg) was injected intraperitoneally once a week for 4 weeks - Days 0, 7, 14, and 21- (10, 11).

All experiments were conducted according to the guidelines of the Hawler Medical University Research Ethics Committee for Research Ethics Committee Approval.

Experimental design

The rats were divided into two groups. The first group consisted of 6 rats and served as a control group (injected with 0.5 ml sterile saline intraperitoneally). The second group consisted of eighteen rats which received paclitaxel (6 mg/kg) injection intraperitoneally (i.p.) once a week for 4 weeks) and served as a Paclitaxel model. The second group was subdivided into three subgroups of six rats each (first subgroup served as a positive control that received paclitaxel (6 mg/kg) injection, second subgroup received benfotiamine 100 mg /kg orally, daily for eight weeks and the third subgroup received methylcobalamin 500 µg /kg, intraperitoneally twice weekly for eight weeks).

The mice were divided into two groups. The first group consisted of 6 mice and served as a control group (injected with 0.5 ml sterile saline intraperitoneally). The second group consisted of eighteen rats that received paclitaxel (6 mg/kg) injection i.p. once a week for 4 weeks) and served as a Paclitaxel model. The second group was subdivided into three subgroups of six mice each (first subgroup served as a positive control received paclitaxel (6 mg/kg) i.p. injection, second subgroup received benfotiamine 100 mg /kg orally, daily for six weeks and the third subgroup received methylcobalamin 500 µg /kg, orally, daily for six weeks).

Motor nerve conduction studies

Electrophysiological measurements were conducted at Hawler Teaching Hospital/Neurophysiology Unit. The data were analyzed using (Nicolet, Madison, WI, USA) software program.

Experimental animal nerve conduction studies were done by using the invasive techniques, with needle electrodes (12, 13).

Latency and Amplitude were measured. Motor Nerve Conduction Velocity (MCV) was calculated by dividing the distance between the stimulation point and recording electrode by the motor latency.

Motor nerve conduction studies (MNCS) were determined 30 to 35 days after last dose paclitaxel. Nerve conduction studies were performed using standard equipment (Nicolet, Madison, WI, USA) on anaesthetized rats.

Tail-immersion test

Antinociception was evaluated by measuring response latencies in cold water tail-immersion (tailflick) assay (14, 15, and 16).

Response latencies were measured as the period of time the animal took to respond to the thermal stimuli. The temperature of cold water ($4\pm 1^\circ\text{C}$) for cold hyperalgesia and ($10\pm 1^\circ\text{C}$) for cold allodynia. Water was maintained at the right temperature by the addition of ice cubes. The duration of tail immersion was manually recorded (1 sec. precision), with a cut-off time of 20 sec.

Tail-flick test was performed by gently holding the mouse in a terry cloth towel and immersing between 2 and 3 cm from the tip of the tail into the water, and the response was defined as the removal of the tail from the cold water (17).

The paw hot plate test for hot hyperalgesia

This test consists of introducing a mouse into an open-ended cylindrical space with a floor consisting of a metallic plate that was heated by the electrical current (18). The plate was heated to a constant temperature ($50\pm 1^\circ\text{C}$) the response produced was in the form of two behavioral components that can be measured in terms of their reaction times, namely paw licking and jumping. To determine latencies, the time was recorded from start of introducing a mouse to the occurrence of the first avoidance response, with a cut-off time of 20 seconds.

Statistical analysis

All data are expressed as means \pm standard error of means ($M \pm SEM$) and Statistical analysis was carried out using statistically available software (SPSS Version 11.5). Data analysis was made using one-way analysis of variables

(ANOVA). Comparisons between groups were done using Duncan test and unpaired student t-test. $P < 0.05$ was considered as statistically significant.

Results

Effects of paclitaxel, methylcobalamin and benfotiamine on the Motor Nerve Conduction Studies (MNCS).

Effects on latency of sciatic nerve in rats

The mean latency of sciatic nerve in the control group was $0.92 \text{ ms} \pm \text{SE } 0.086$ (Table 1); it was increased significantly in paclitaxel receiving group rats to $1.74 \text{ ms} \pm \text{SE } 0.087$ (Table 1 - next page). In Benfotiamine and paclitaxel receiving group the mean latency was $0.94 \text{ ms} \pm \text{SE } 0.074$ (Table 1), While in the methylcobalamin and paclitaxel receiving group the mean latency was $1.2 \text{ ms} \pm \text{SE } 0.094$ (Table 1).

Effects on amplitude of sciatic nerve in rats

The mean amplitude of sciatic nerve in the control group was $27.5 \text{ mv} \pm \text{SE } 2.1$ (Table 1). It was reduced significantly in the paclitaxel receiving group rats to $12.02 \text{ mv} \pm \text{SE } 0.92$ (Table 1). The mean amplitude in the benfotiamine and paclitaxel receiving group was $26.66 \text{ mv} \pm \text{SE } 1.22$ (Table 1). While the mean amplitude in methylcobalamin and paclitaxel receiving group was reduced significantly to $18.4 \text{ mv} \pm \text{SE } 2.5$ (Table 1).

Effects on conduction velocity of sciatic nerve in rats

The mean conduction velocity of sciatic nerve in the control group was $56.24 \text{ m/s} \pm \text{SE } 5.1$ (Table 1); it was reduced significantly in the paclitaxel receiving group rats to $29.04 \text{ m/s} \pm \text{SE } 1.46$ (Table 1). In the benfotiamine and paclitaxel receiving group the conduction velocity was $54.46 \text{ m/s} \pm \text{SE } 3.95$. There wasn't a significant change (Table 1), whereas the conduction velocity in methylcobalamin and paclitaxel receiving group was also reduced to $42.7 \text{ m/s} \pm \text{SE } 3.26$ (Table 1) but better than in the paclitaxel group.

Effects of paclitaxel, methylcobalamin and benfotiamine on Tail thermal threshold in mice

Tail immersion test for cold allodynia ($10\pm 2^\circ\text{C}$) in mice

The mean withdrawal latency of cold allodynia for all groups of mice was measured weekly and is shown in Figure 1.

On day 28 the withdrawal latency of the control group was $17.8 \text{ sec.} \pm \text{SE } 1.7$ and in the paclitaxel group was reduced significantly to $10.3 \text{ seconds.} \pm \text{SE } 2.6$ ($P=0.042$). While compared to the control group the paclitaxel and benfotiamine receiving group was $16.5 \text{ seconds} \pm \text{SE } 1.6$ no significant change was observed. The paclitaxel and methylcobalamin receiving group was $17.7 \text{ seconds.} \pm \text{SE } 1.7$ compared to the control group and no significant differences were seen.

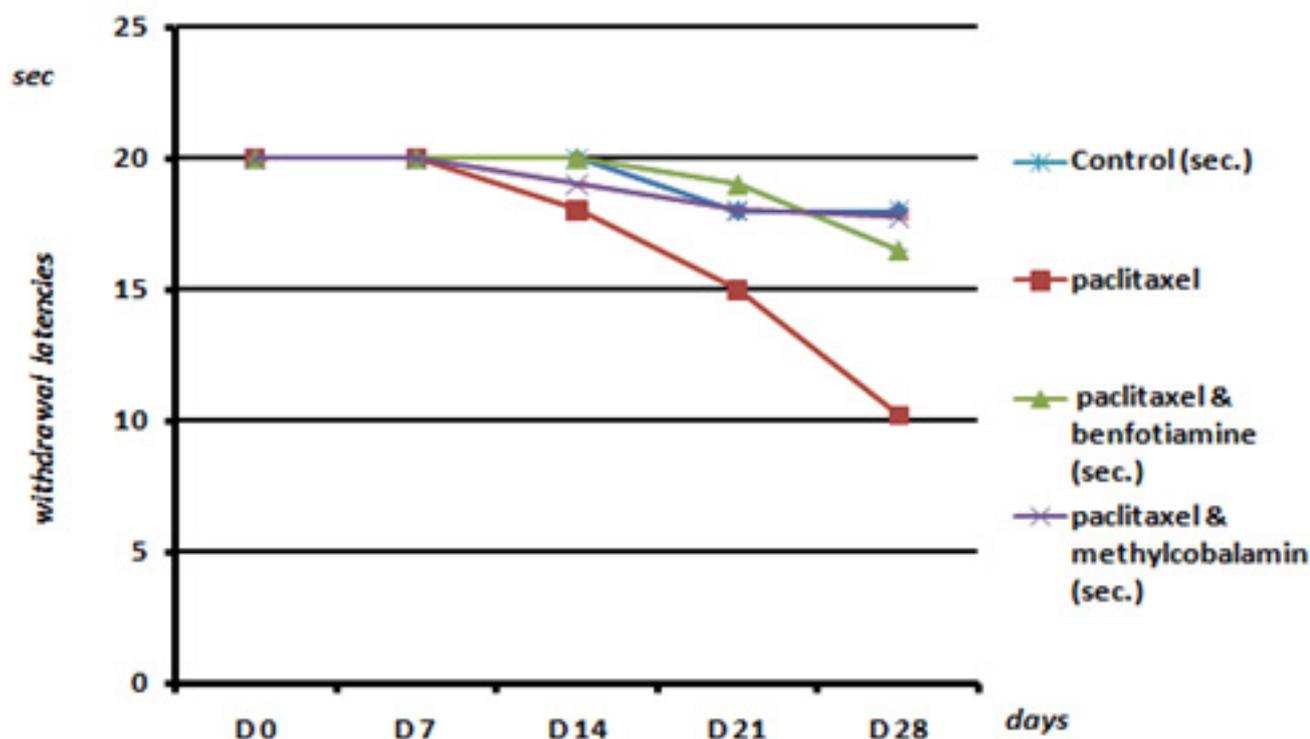
Tail immersion test (cold hyperalgesia $4\pm 1^\circ\text{C}$) in mice.

There was a significant reduction in the mean withdrawal latency for cold hyperalgesia in the paclitaxel receiving group which was $3 \text{ seconds} \pm \text{SE } 1.09$ ($P = 0.0001$) compared to the

Table 1: Effect of paclitaxel, paclitaxel and methylcobalamin and paclitaxel and benfotiamine on motor nerve conduction study (n=24)

MNCS sciatic nerve with recording at gastrocnemius muscle	Control	paclitaxel	paclitaxel & benfotiamine	paclitaxel & methylcobalamin
Latency (millisecond) ms	0.92 ± 0.086 a	1.74 ± 0.087 c	0.94 ± 0.074 a	1.2 ± 0.094 b
Amplitude millivolt (mv)	27.5 ± 2.1 A	12.02 ± 0.92 b	26.66 ± 1.22 a	18.4 ± 2.5 b
Conduction velocity (meter per second) m/s	56.24 ± 5.1 A	29.04 ± 1.46 c	54.46 ± 3.95 a	42.7 ± 3.26 b

- The same letters mean that there is no significant difference
- The different letters mean there is a significant difference at P < 0.05

**Figure 1: Tail immersion tests for cold allodynia (10±2°C), withdrawal latencies (sec.) measured on weekly bases for all the groups each group with six mice**

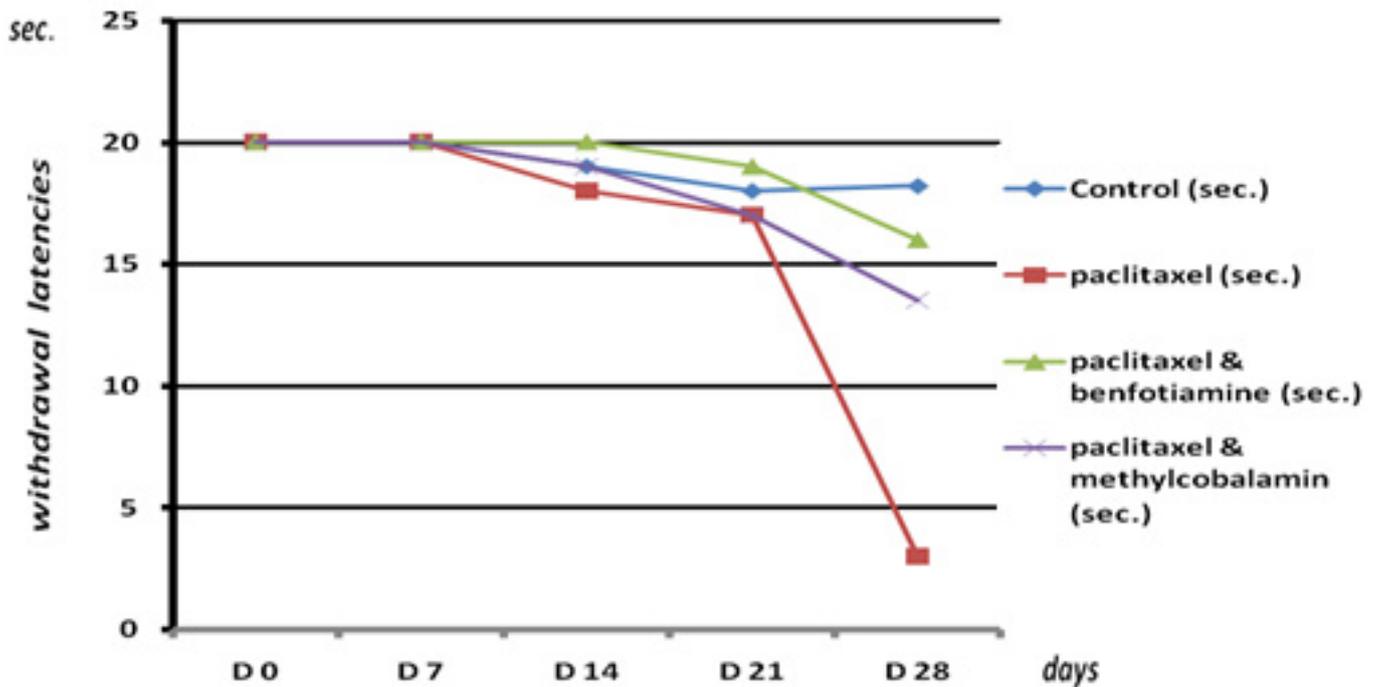


Figure 2: Tail immersion tests for cold hyperalgesia ($4 \pm 1^\circ\text{C}$), withdrawal latencies (sec.) measured on weekly bases for all the groups each group with six mice.

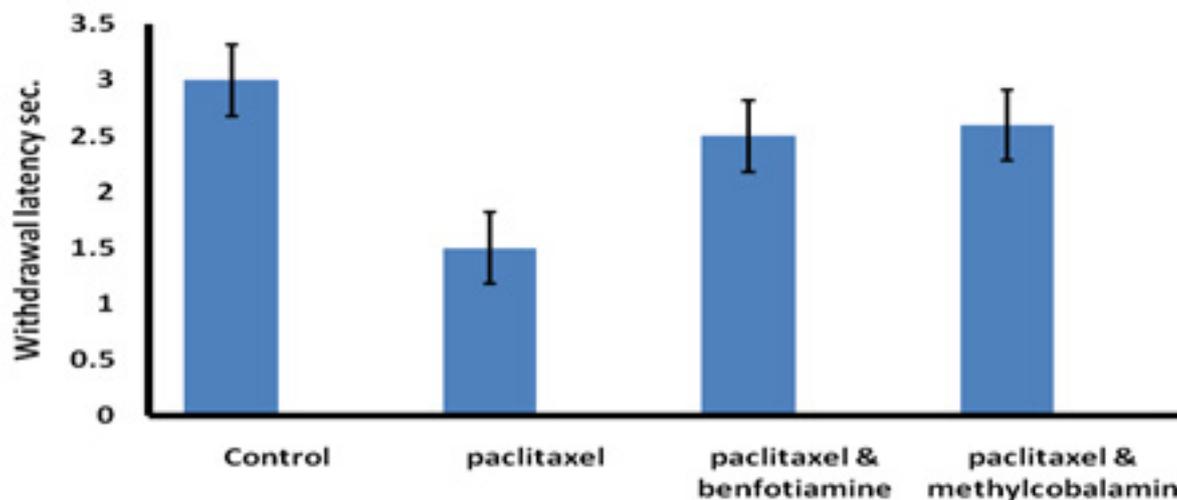


Figure 3: The mean paw withdrawal latencies in four mice groups, each group (n=6) 7 days after last dose of paclitaxel (28th day).

control group. Whereas in the paclitaxel and benfotiamine receiving group it was $16 \pm \text{SE } 2.5$ ($P = 0.46$) which is non significant compared to the control group. The mean tail withdrawal latency in the paclitaxel and methylcobalamin receiving group was $(13.5 \pm \text{SE } 2.9, P = 0.19)$, compared to the control group where no significant change was seen (Figure 2).

Effects of paclitaxel, methylcobalamin and benfotiamine on paw thermal threshold in mice.

The mean paw withdrawal latency in the control group was $3 \text{ sec} \pm \text{SE } 0.44$, (Figure 3). Compared to the control group the mean paw withdrawal latency in the paclitaxel group was reduced significantly to $1.5 \text{ sec} \pm \text{SE } 0.22$ ($P = 0.017$) whereas compared to the control group no significant changes were observed in mean paw withdrawal latency for both paclitaxel

and benfotiamine and paclitaxel and methylcobalamin groups. The mean paw withdrawal latencies were $2.6 \text{ seconds} \pm \text{SE } 0.24$ ($P = 0.45$) and $2.5 \pm \text{SE } 0.22$ ($P = 0.34$) respectively.

In vitro study: Histopathological section of rat's sciatic nerve stained by E &H stain.

Sciatic nerve for control group:

The histopathological results of this study showed normal architecture of rat's sciatic nerve fibers in the control group in which most of the nerve fibers were equal in size, diameter with regular thickness of myelin, continuation of myelin cell basement membrane and normal nucleus of myelin cell (Figure 4 - next page).

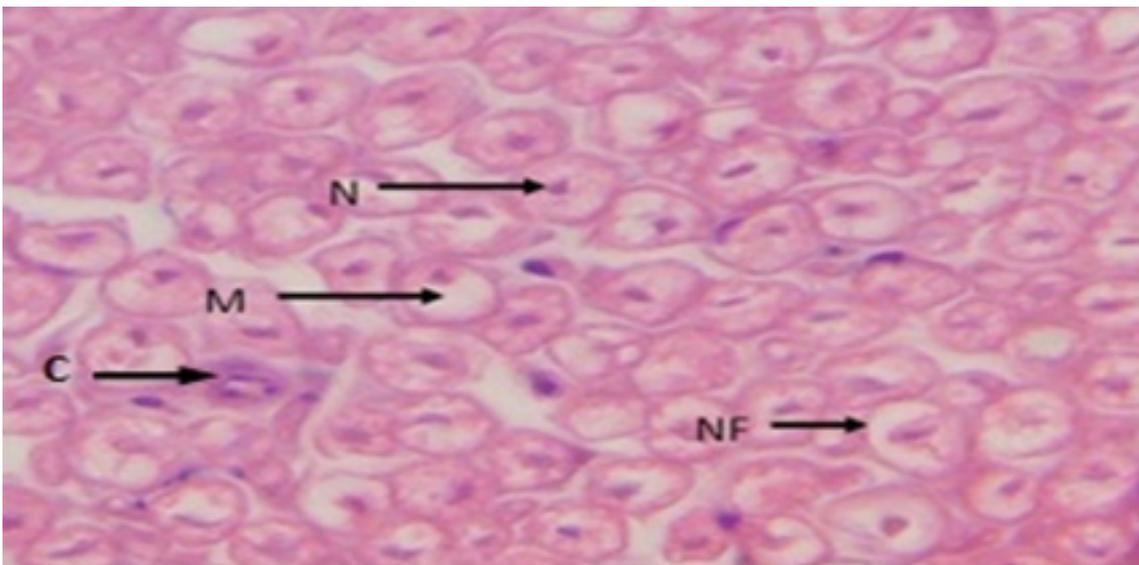


Figure 4: Cross section from the SN of a normal control specimen showing normal appearance of the individual nerve fibers (nucleus and myelin) of Schwann cells (arrows) (N= nucleus , M= myelin, NF= nerve fiber, C=capillary) E & H stain X 400.

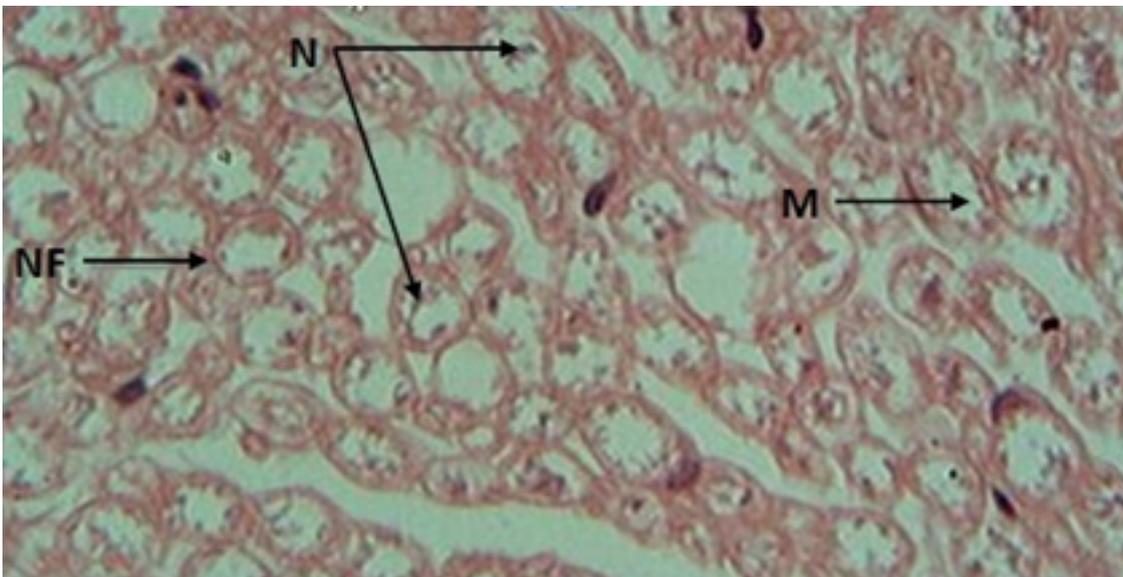


Figure 5: Cross section of SN from the paclitaxel receiving group specimen showing abnormal appearance of the individual nerve fibers (nucleus degeneration and disruption of myelin sheath) of Schwann cells and multiple different size nerve fibers (arrows) (N= nucleus , M= myelin , NF= nerve fiber,) E & H stain X 400.

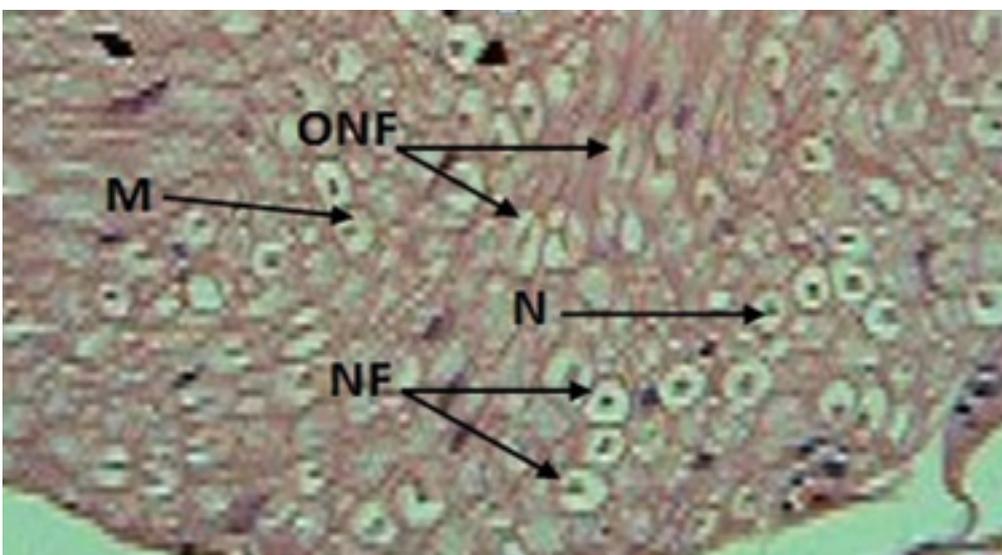


Figure 6: Cross and oblique sections of SN from paclitaxel and benfotiamine receiving group specimen showing most nerve fibers normal, with normal nucleus, normal myelin thickness and maintenance of basement membrane of Schwann cells (arrows) (N= nucleus , M= myelin, NF= nerve fiber, ONF= oblique view nerve fiber) E & H stain X 400.

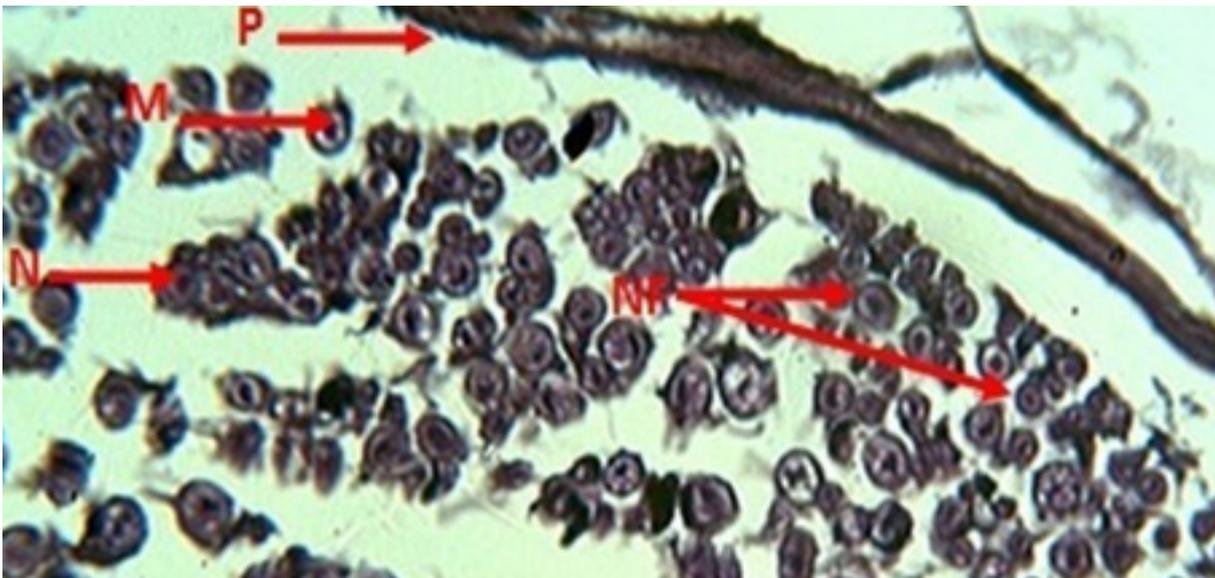


Figure 7: Cross section of SN- B (lower) - Cross and oblique section of SN, from paclitaxel and methylcobalamin receiving group specimen showing marked reduction in myelin thickness and multiple different size nerve fibers but, with maintenance of basement membrane of Schwann cells (arrows) (N= nucleus , M= myelin , NF= nerve fiber, ONF= oblique view nerve fiber, P = perineurium) E & H stain X 400.

Effect of paclitaxel on sciatic nerve

The result of this study showed that 6 mg/kg paclitaxel once a week for four weeks resulted in marked destruction of sciatic nerve fibers in rats, as shown in Figure (5).

Effect of paclitaxel and benfotiamine on sciatic nerve

In this study the results showed that with daily administration of benfotiamine 100mg/kg together with paclitaxel and continued for four weeks after last dose of paclitaxel preserves most nerve fibers from destruction (Figure 6)

Effect of paclitaxel and methylcobalamin on sciatic nerve

The result of this study showed that administration of methylcobalamin 500 µg /kg, intraperitoneally twice weekly together with paclitaxel in rats for eight weeks inhibits destruction of Schwann cells but, resulted in significant reduction of myelin thickness in most of the cells (Figure 7).

Discussion

Neurotoxic effect of paclitaxel on peripheral nerves in rats

Peripheral neuropathy that induced by chemotherapeutic substances such as paclitaxel, thalidomide, and cisplatin represents beside other adverse effects of these drugs, a major clinical problem due to the frequency of this toxic process and the lack of therapeutic measures to treat the resultant disability. Furthermore, this adverse effect often represents the dose-limiting factor in therapeutic oncologic regimen, where higher doses might be otherwise desirable (3,19, 20).

In this study, a motor nerve conduction study (MNCS) of rat's sciatic nerves in the paclitaxel group showed marked prolongation in the mean latency, moreover there was a reduction in conduction velocity and amplitude compared to the control group. This pattern might explain the possibilities of axonal degeneration and demyelination with subsequent neuropathy. Axonal neuropathy is identified by nerve

conduction study (NCS) as a low compound muscle action potential; pure demyelinating neuropathy is identified by NCS as slow conduction velocity and prolonged latency (21).

This result was in agreement with Lipton et al, (1989) and Sahenk et al, (1994) who have concluded that in paclitaxel-induced neuropathy, both axonal degeneration and demyelination patterns were possible on NCS.(22,23)

Authier et al, (2000) reported that exposure to paclitaxel at a single dose of 16 or 32 mg/kg did not change NCV in vitro; they concluded that this might be due to the low sensitivity of electrophysiological methods in early detection of neuropathy. The same researchers reported that NCV decreased following paclitaxel treatment 6mg/kg once a week for 5 weeks (24).

Moreover the model of paclitaxel-induced neuropathy in mature rats, with minimal effects on general health, by using two intravenous injections 12 mg/kg, 3 days apart, showed reduction in amplitudes of sensory compound nerve action potentials in the tail. Motor amplitudes were not affected, but both motor and sensory conduction velocities decreased. These effects persisted for at least 4 months after treatment (25).

This study also showed shortening of the tail withdrawal latencies for cold allodynia and hyperalgesia; there was shortening of the paw withdrawal latency in hot plate test. This is in agreement with several studies performed on laboratory animals in which Paclitaxel 6 mg/kg was given intraperitoneally (i.p.) once a week for 4 weeks which significantly shortened the paw withdrawal latency in acetone test compared with vehicle for cold hyperalgesia and decreased the travelled distance compared with vehicle in the balance beam test (11).

Flatters and Bennett, (2004) concluded that four (i.p.) injections on alternate days of 2 mg/kg paclitaxel induced a pronounced cold allodynia and hyperalgesia (26).

Polomano et al, (2001) in an experimental paclitaxel-induced painful peripheral neuropathy concluded that paclitaxel at low doses 0.5, 1 and 2 mg/kg caused heat-hyperalgesia and cold-allodynia, but had no effect on motor performance (27).

The mechanism of chemotherapy-induced neuropathy is still uncertain. Direct toxic damage to axons and Schwann cells and disturbed cytoplasmic flow are considered to be the main pathogenic factors (3).

Spontaneous improvement of nerve function over time, as observed in some animal models, suggests involvement of components of the nerve which have regenerative capacity, unlike neurons themselves (25). However, involvement of the vasa nervorum is a more attractive hypothesis since the majority of substances causing this type of neuropathy, i.e., paclitaxel, thalidomide, and cisplatin exhibit antiangiogenic properties in addition to their direct effects on tumor cells (28, 29).

Dvorak et al, (1995) and Kirchmair et al, (2005) found that the neuropathy caused by a chemotherapeutic drug was due to destruction of the blood supply of the nerve, i.e., the vasa nervorum.(30,20)

Kirchmair et al. (2005) showed that cisplatin-induced neuropathy is associated with the induction of endothelial cell apoptosis and destruction of the vasa nervorum and is reversed or inhibited by the angiogenic cytokine vascular endothelial growth factor (VEGF) (20).

The mechanism of chemotherapy-induced neuropathy also could be due to chemotherapeutic drugs that cause high levels of oxidative stress and are thought to rely, in part, on using this stress mechanism to kill cancer cells, but Perumal and Shanthi (2005) concluded that oxidative stress might actually reduce the overall effectiveness of chemotherapy because oxidative stress slows the process of cell replication but, during cell replication, chemotherapy actually kills cancer cells, therefore slower cell replication can mean lower effectiveness of chemotherapy. One approach to addressing this problem is the addition of certain antioxidants at specific dosages to lessen oxidative stress, thus making the chemotherapy treatment more effective (31).

Cameron and Cotter (1997) in an experimental study have shown that reactive oxygen species (ROS) also have effects on blood vessel function, which compromise perfusion of several organs including peripheral nerves. That was responsible for the earliest defects in nerve function in experimental models and will exacerbate nerve damage by causing further ROS-dependent ischemia-reperfusion effects (32).

Protective effect benfotiamine on paclitaxel neurotoxicity

The result obtained in this study from daily administration of benfotiamine 100 mg /kg orally for eight weeks together with paclitaxel 6 mg/kg weekly for four weeks, showed significant decrease in latency of sciatic nerve and subsequently an increase in nerve conduction velocities. An increase in amplitude of compound motor action potential reached that of the control group. The protective effect of benfotiamine against paclitaxel induced neuropathy could be explained by radical scavenging property of benfotiamine, because benfotiamine exhibited an antioxidant effect by reducing the oxidative stress and genomic damage caused by mitogenic model compounds; such effect was found to be related to the direct antioxidant effect of benfotiamine (33).

Cameron and Cotter, (1999) in an antioxidant study observed that oxidative stress makes a marked contribution to the etiology of nerve dysfunction in experimental diabetes because reactive oxygen species (ROS) cause vascular endothelium dysfunction which reduces NO mediated vasodilatation and increases local vasoconstrictor production and reactivity. This reduces nerve perfusion, causing endoneurial hypoxia which results in conduction deficits (33).

However nitric oxide (NO) is an important vascular target for ROS. Superoxide neutralizes NO and the peroxynitrite formed is a source of hydroxyl radicals that can cause endothelial damage (34, 35).

Regarding peripheral nerves, Nagamatsu et al, (1995) and Low et al, (1997) suggested that ROS can directly damage neurons and Schwann cells (36,37).

Recently, a new study showed that benfotiamine reduces superoxide and hydroxyl radical levels in the heart of diabetic mice by inducing the activation of pentose phosphate pathway, which regenerates the antioxidant NADPH (38).

Cascinu et al, (2002) suggested that increased levels of the reduced form of glutathione may be one of the possible mechanisms to prevent neurotoxicity because of glutathione's possible mechanism in reducing neurotoxicity of platinum-based drugs. Reactive oxygen species generated by platinum drugs result in neuronal cell death. GSH, as an ROS scavenger, may prevent such damage (39).

This result is supported by an in vitro study in which cisplatin induced apoptosis of mouse neurons, was prevented by pre incubation with N-acetylcysteine, a precursor to GSH (40).

The result of this study is in agreement with the result of a study performed on experimental animals where NCV was normalized by benfotiamine after three months of administration (41, 42).

Moreover in this study, compared to the control group no significant changes were observed in withdrawal latency of tail immersion test for cold (allodynia and hyperalgesia) and paw withdrawal latency in hot plate test in mice treated with oral benfotiamine 100 mg/kg, daily for six weeks and paclitaxel 6 mg/kg, i.p. once a week for four weeks. This result is in agreement with Winkler et al, (1999) who concluded that benfotiamine is effective in large doses and even in smaller daily dosages in treatment of painful diabetic neuropathy(43).

Protective effects of methylcobalamin on paclitaxel neurotoxicity

In this study, the results obtained from administration of methylcobalamin 500 µg /kg, intraperitoneally twice weekly and paclitaxel 6 mg/kg once a week for four weeks, showed decrease in latency of sciatic nerve and subsequently increase in nerve conduction velocity in comparison to the paclitaxel receiving group but did not reach that of the control group.

While the amplitude of compound motor action potential (CMAPs) was very low in sciatic nerve compared to the control group, this may be due to insufficient dose of methylcobalamin in this study as Yamatsu et al, (1976) observed that daily injection of 500 µg /kg of methylcobalamin produced a significant increase in the weight of the soleus muscle which recovered to the extent of being the same weight of the contra lateral 4 weeks after the nerve-crush. These results suggest that methylcobalamin may have an inhibitory effect on Wallerian degeneration and also a facilitatory effect on the neural regeneration of the crushed sciatic nerve of rats (44). Watanabe et al, (1994) examined the effects of ultra-high dose of methylcobalamin on the rate of nerve regeneration in rats with acrylamide neuropathy, using the amplitudes of compound muscle action potentials (CMAPs) after tibial nerve stimulation as an index of the number of regenerating motor fibers. Those treated with ultra-high dose showed significantly faster CMAP recovery than saline-treated control rats, whereas the low-dose group showed no difference from the control (45).

Furthermore the result of this study, did not show significant change in withdrawal latency of tail immersion test for cold allodynia/hyperalgesia and paw withdrawal latency in hot plate test in mice treated with oral methylcobalamin 500 µg /kg, daily for six weeks and paclitaxel 6 mg/kg once a week for four weeks compared to the control (saline treated) group. This is in agreement with Mizukami et al, (2011) who suggested that correction of neural oxidative stress may be attributed to the beneficial effects of methylcobalamin (10 mg /kg every other day, intramuscularly which is a higher dose than the dose used in this study) in normalization of nerve conduction velocity of diabetic nerve (46).

Histopathology

In this study histological examination by light microscope showed features of segmental demyelination, such as a thinning and destruction of myelin sheaths, nucleus degradation of Schwann cells and multiple different size

cells in the paclitaxel receiving group compared to the control group. The result of this study was in agreement with Hashimoto et al. (2004) who concluded that the local paclitaxel injection showed features of segmental demyelination, such as a marked decrease in large-diameter myelinated nerve fibers, thinning and destruction of myelin sheaths, and atrophy of axons (47). Furthermore histological changes in the paclitaxel group agreed with Kawashiri, (2009) who concluded that Paclitaxel (6 mg/kg, i.p.) induced the decrease in the density of myelinated fibers and the degeneration of myelinated fibres in rat sciatic nerve(11).

In this study, light microscope histopathology examination of sciatic nerve in a group that received benfotiamine 100 mg /kg daily and paclitaxel 6 mg/kg weekly for four weeks, showed nerve fiber architecture near to that of the control group, in which most of the cell had normal nucleus, normal myelin thickness and maintenance of basement membrane of Schwann cells. This result might be explained by improvement of a nerve conduction study in this group as Raso et al, (2005) and Mazzer et al, (2008) concluded that maintenance of the basement membrane of Schwann cells surrounding the original nerve fibers were intact despite the disrupted axon enabled Schwann cells to provide pathways to guide the regenerating axons (48,49). After contact with the periphery is established, the regenerating nerve fibers enlarge and myelinate (50).

Light microscope histopathologic examination of sciatic nerve in rats which received methylcobalamin 500 µg /kg, (i.p.) two times weekly and paclitaxel 6 mg/kg once a week for four weeks, showed a marked reduction in myelin thickness and multiple different size nerve fibers but, with maintenance of basement membrane and nucleus of Schwann cells. This result showed that methylcobalamin 500 µg /kg, two times weekly enhanced improvement of nerve but did not reach that of the control group, as Yagihashi et al, (1982) observed that methylcobalamin at high daily dose of 500 µg /kg for 16 weeks resulted in decreased demyelination and protection of nerve fiber density and size in streptozotocin-diabetic rats (51).

Conclusion

Benfotiamine 100mg/kg was very efficient in prevention of sensorimotor neuropathy induced by paclitaxel. Whereas the suggested methylcobalamin (500µg/kg) twice weekly did not sufficiently prevent peripheral motor nerve destruction induced by paclitaxel, while the administration of high dose methylcobalamin every day is efficient in removal of thermal nociception induced during paclitaxel treatment.

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Evaluation of Complications And Anesthesia Practice In Cases With Cesarean Section For Placenta Previa

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ABSTRACT

Background: It is reported that preterm births related to placenta previa increase perinatal mortality.

Material and Method: This retrospective study evaluated operation records for cesarean sections performed at Mustafa Kemal University between January 2009 and December 2012 for which a diagnosis of placenta previa was made.

Results: We evaluated 67 cases (Table 1). Nineteen cases (28.4%) were urgent and 48 cases (71.6%) were elective. Although no differences existed according to mean age of gravida and number of previous cesarean section operations, significant differences were found between the urgent and elective cases with respect to many other characteristics, including preoperative and postoperative hemoglobin values, operation periods, number of cases requiring hysterectomy, hypogastric artery ligation, number of patients requiring blood transfusion, and number of patients requiring postoperative intensive care.

Conclusion: To decrease maternal and fetal morbidity and mortality, performing preoperative preparations carefully, choosing the right anesthesia method, effectively evaluating blood loss, and optimizing communication between anesthesiologist, obstetrician, and blood bank workers are necessary to manage cesarean section in pregnant women with placenta previa. Cesarean sections that are urgent, related to previa, and in cases where parity is equal to or greater than 2 can result in the need for hysterectomy. These conditions increase operation periods, blood transfusion needs, and risk of admission to an intensive care unit. Necessary preparations must be performed preoperatively.

Key words: Cesarean section, placenta previa, anesthesia

Introduction

Placenta previa is defined as the placenta covering the internal cervical opening partially or completely; it is the settlement of placenta within the uterus. When the placenta covers all of the internal part of the uterus, it is called total; partial coverage is called partial placenta previa, and settling closely is termed marginal placenta previa(1). Bleeding caused by obstetric procedures in general is one of the most important causes of maternal mortality and morbidity (2, 3). Insufficient or untimely preoperative preparations can lead to more bleeding and probable and common intravenous coagulation defections.

Placenta previa is associated with an increase in preterm birth and perinatal mortality and morbidity (4). Cases with the anomaly of placental settling have high rates of coagulation, intensive care unit admission, and mortality and morbidity. For these reasons, anesthesiologists and obstetricians should know how to manage peripartum bleeding based on the anomaly of placental settlement. The aim of this study was to retrospectively evaluate results with the use of anesthesia in placenta previa during cesarean section.

Material and Methods

After obtaining the approval from the Local Human Ethics Committee, obstetric and gynecologic operation and anesthesia records in pregnant women who received a diagnosis of placenta previa and underwent cesarean section operation between January 2009-2012 were evaluated retrospectively. Cases in which bleeding and coagulation disorders manifested were excluded from the study. The following information was recorded for every patient: age; whether an urgent or elective operation was performed, anesthesia methods (general or regional), gravida, parity, number of abortions, previous cesarean section numbers, newborn 1-minute and 5-minute Apgar scores, duration of operations; hemoglobin values of preoperative and postoperative and hysterectomy, hypogastric artery ligation, history of bladder repairing, and number of existing to postoperative intensive care and blood transfusion needs were recorded.

Events were classified according to whether an operation was urgent (Group U) or elective (Group E), and also according to whether the woman was going to have 2 or more (parity > 2; Group P > 2) or less than 2 (parity<2; Group P<2) parity numbers. Events in group U and group E were compared with respect to preoperative and postoperative hemoglobin values, operation periods, number of intraoperative complications (hysterectomy, hypogastric artery ligation, bladder reparation) numbers; number of patients taken to postoperative intensive care; and number of patients receiving intraoperative blood transfusions. Some parameters were compared for Group P > 2 and Group P<2. Statistical analysis was performed with the SPSS (SPSS for Windows, release 13.0) statistical package and data are presented as means and standard deviations. Comparison of intraoperative and postoperative complications between groups was made with Chi-square and Fisher's Exact tests; data obtained from measurement was evaluated by Mann-Whitney U tests. Results were evaluated with a reliability interval of 95%, and the significance level is P<0.05.

Results

A total of 67 cases were examined. Average age of subjects at the time of the cesarean sections was 31 (5).

The operations lasted for between 45 minutes and 180 minutes; average period was 89.6 (40.2) minutes.

General anesthesia was used in 60 (89.6%) of cases; in the other 7 cases (10.4%) regional anesthesia was used. Prior cesarean sections ranged from 0-3 and the average was 1.3 (0.8) (Table 1).

Number of patients (n)	67
Age (year)	31 (5)
Gravida (n)	3.3 (1.5)
Parity(n)	1.7 (1.0)
Abortus (n)	0.4 (0.9)
Live (n)	1.7 (0.9)
Operation time (minute)	89.6 (40.2)
Preoperative Hb (g/dl)	10.8 (1.2)
Postoperative Hb (g/dl)	9.7 (1.0)
Cesarean section number	1.3 (0.8)
Apgar I	7.1 (1.8)
Apgar II	8.5 (1.7)
Method of anesthesia	
General (n+%)	60 (89.6%)
Regional (n+%)	7 (10.4%)

Table 1: The demographic data of the patients with anesthetic and operative management

Fifty-eight (86.6%) of the sixty seven cases involved in the study were in women who had at least one previous cesarean section. With respect to hysterectomy, none of the 9 women with no cesarean section had undergone the procedure; 2 (6.9%) of patients with one cesarean underwent hysterectomy; and 4 patients (66.7% of the total) with 3 cesarean sections in their medical history had undergone hysterectomy. When the cases are classified as Group U and Group E, 19 (28.4%) of procedures were urgent, and 48 (71.6%) were elective. No difference existed between these two groups according to age, gravida, and number of previous cesarean sections. Preoperative (10.2 [1.2] and 11.0 [1.1]; P=0.33) and postoperative (9.3 [0.9] and 9.9 [1]; P=0.027) hemoglobin values, duration of operations (107.5 [39.4] and 82.5 [38.7]; P=0.015); number of hysterectomies (8 [42.1%] and 8 [16.7%]; P=0.028) were found to be significantly different between those undergoing elective or urgent surgery. Some other points of comparison between group U and group E, respectively, for which very significant differences were found include hypogastric artery ligation (14 [73.7%] and 16 [33.3%]; P<0.01); number of patients requiring blood product transfusion (15 [78.9%] and 16 [33.3%]; P<0.01); and number of patients exiting to the intensive care unit (5 [26.3%] and 2 [4.2%]; P<0.01) (Table 2) (Graph 2).

State of Operation	Group U (n=19)	Group E (n=48)	p
Age (year)	31 (4)	31 (5)	0.403
Gravida (n)	1.5 (1.3)	3.2 (1.6)	0.130
Parity(n)	1.9 (1.3)	1.6 (0.9)	0.514
Abortus (n)	0.3 (0.4)	0.4 (1.1)	0.525
Ceserean section number	1.6 (0.9)	1.2 (0.7)	0.181
Preoperative Hb (g/dl)	10.2 (1.2)	11.0 (1.1)	0.033*
Postoperative Hb (g/dl)	9.3 (0.9)	9.9 (1)	0.027*
Operation time (minute)	107.5 (39.4)	82.5 (38.7)	0.015*
Hysterectomy (n+%)	8 (42.1%)	8 (16.7%)	0.028*
Hypogastric artery ligation (n+%)	14 (73.7%)	16 (33.3%)	0.003**
Bladder repairing (n+%)	2 (10.5%)	2 (%4.2)	0.326
Intensive care unit exit (n+%)	5 (26.3%)	2 (%4.2)	0.008**
Blood transfusion (n+%)	15 (78.9%)	16 (%33.3)	0.001**

Table 2: Comparison of groups for according to operations. Group U; Urgent, Group E; Elective. *p<0.05,**p<0.01

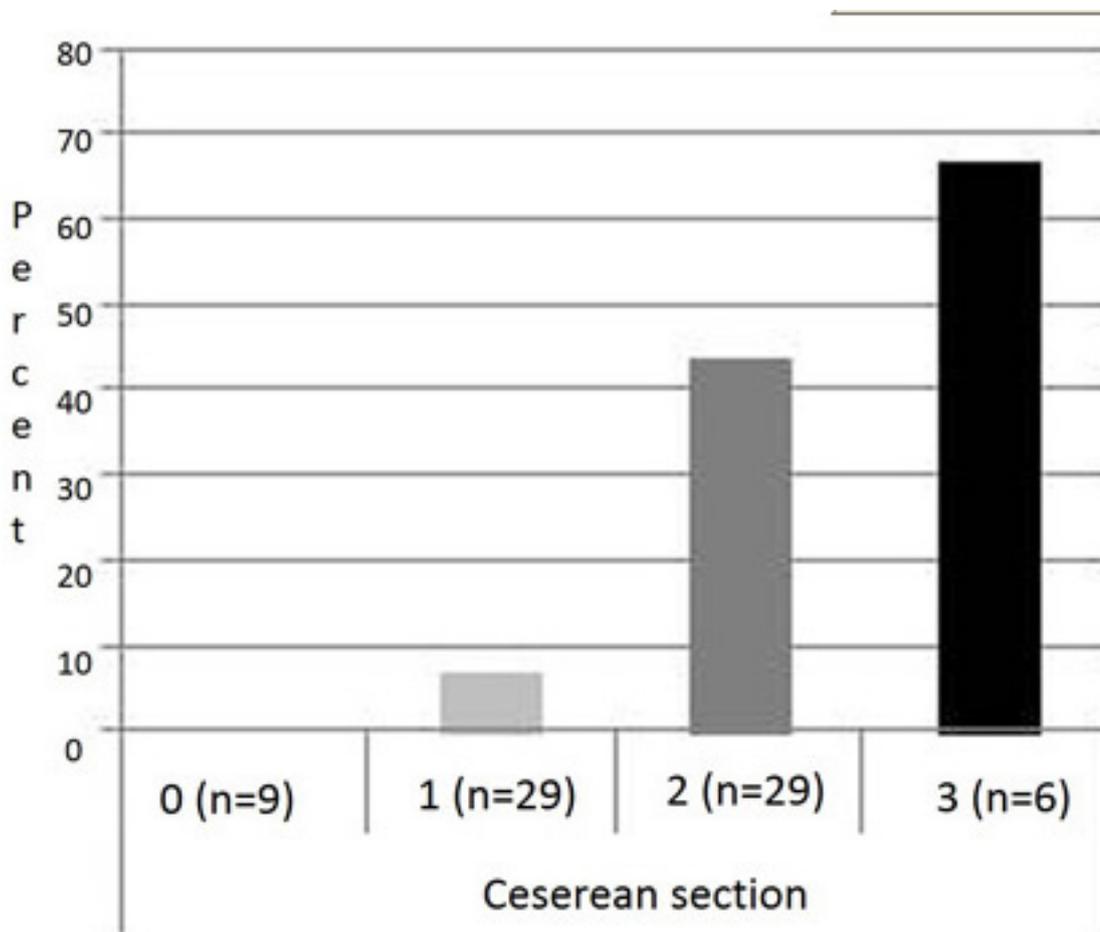


Figure 1: The percentage of blood transfusion according to the state for operations *P?0.01, Group U; Urgent, Group E; Elective

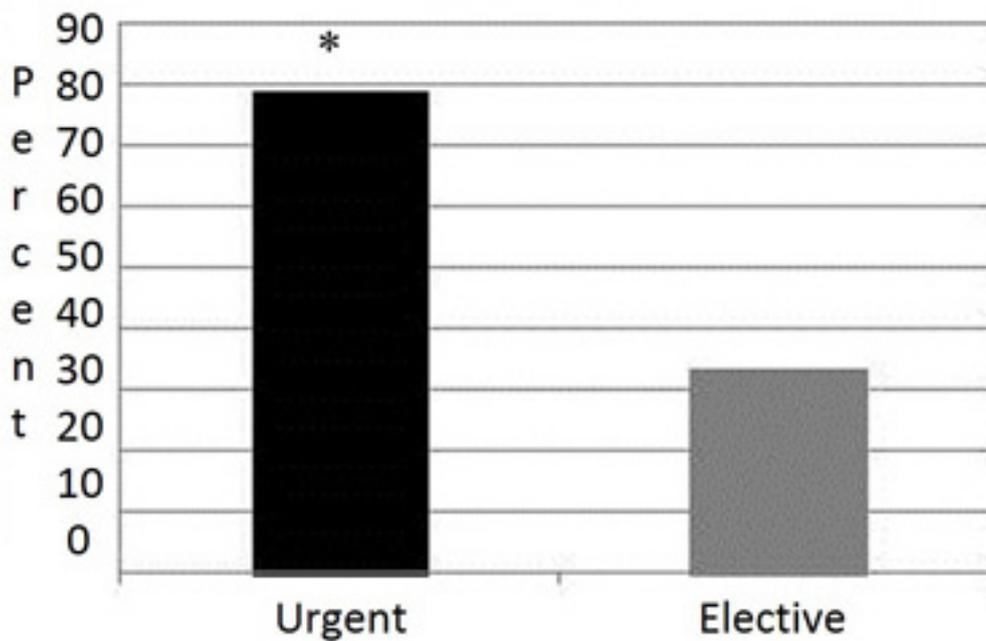


Figure 2: The percentage of hysterectomy with the number of previous cesarean

Parity	Group P≥2 (n=38)	Group P<2 (n= 29)	p
Preoperative Hb (g/dl)	10.5 (1.2)	11.1 (1.1)	0,157
Postoperative Hb (g/dl)	9.5 (1.0)	10.1 (0.9)	0,073
Operation time (minute)	107.3 (41.4)	66.4 (23.8)	0,000**
Histerektomi (n+%)	14 (36.8%)	2 (6.9%)	0,005**
Hypogastric artery ligation (n+%)	23 (60.5%)	7 (24.1%)	0,003**
Bladder repairing (n+%)	4 (10.5%)	0 (0%)	0,075
Intensive care unit exit (n+%)	7 (18.4%)	0 (0%)	0,015*
Blood transfusion (n+%)	25 (65.8%)	6 (20.7%)	0,000**

Table 3: Comparison of groups according to the number of parity .Group P > 2; Parity > 2, Group P<2; Parity <2. *p<0.05,**p<0.01

The cases were grouped according to the number of parity, if parity number was 2 (Group P > 2) case numbers were (43.3%) 29, and if parity number was <2 (Group P<2), that was (56.7%) 38. No differences existed between groups according to age, preoperative and postoperative hemoglobin values, or number of bladder repairs. For the patients who were exited to postoperative intensive care (7 [18.4%] and 0 [0%]; P= 0.015), significantly different operation periods were found (107.3 [41.4%] and 66.4 [23.8%]; P<0.01) incidence of hypogastric artery ligation (23 [60.5%] and 7 [24.1%]; P<0.013) incidence of hysterectomy (14 [36.8%] and 2 [6.9%]; P<0.013) and number of patients needing blood product transfusions (25 [65.8%] and 6 [20.7%]; P<0.01) were also significantly different (Table 3).

Discussion

A diagnosis of abnormal placentation can cause life-threatening consequences and affects obstetric surgery and anesthesia methods (5). In cesarean operations with placenta previa, complications can include more bleeding, disseminated intravascular coagulation, sepsis, reoperation, hysterectomy, bladder and ureter injuries depending on the placental set-

tlement place. Furthermore, placenta previa cases have high rates of admission to intensive care(6). This complication can affect surgical procedures as well, including the time it takes to perform surgery and intraoperative liquid management (blood transfusion is also common). Insufficient preparation can cause an increase in perioperative mortality and morbidity risk.

The evaluation of patients before the operation in terms of clinical and laboratory data has great importance for planning anesthesia methods. Urgency of surgery and patient preference guide choice of anesthesia method(7).

Placenta previa is seen in approximately 0.5% of the general population; its incidence is higher in women who have undergone multiple cesarean sections, who smoke, or who have a uterine scar. Other factors include high maternal age, multiparity, previous abortions, drug utilization, pathologic presentation, uterine anomalies, and preterm activities (8, 9). A study by Milosevic et al reported frequently the recurrent cesarean numbers that caused risk factors for placenta previa. In our study, while there was no cesarean history in 13.4% of

cases, cesareans were done in 86.6% at least (10). In the study by Zaki and colleagues in 23,070 births, it was shown that pregnant women with placenta previa have a higher risk rate for postpartum bleeding and intraoperative blood product use (11). Placental settlement anomalies can be seen with bladder invasion and so cause for a radical operation for the patient. So the operation period can prolong and increase the need for blood products during surgery (12, 13). Although intravenous oxytocin is administered after birth to women with placenta previa, placenta implantation place cannot be contracted adequately and so there is a direct correlation between placenta previa and blood transfusion as a result (14).

In cesarean section operations in patients diagnosed by placenta settlement anomaly, it is important to have an adequate blood supply and cardiovascular support protocols in place, as placenta previa is an important reason for obstetric bleeding (1,6,15). Gaundan A et al have reported that in 13.71% of urgent cesarean sections and 5.06% of elective cases that is included (15). In our study, 46.3% of all study cases needed blood transfusion, and the difference was significantly different between urgent or elective cesarean section cases with placenta previa taken to the operating room. While blood products were needed in 78.9% urgent cesarean section cases, they were given in 33.3% of cases with elective cesarean section operations. The placental settlement anomaly is one of the most common causes for peripartum hysterectomy (16). Complication rates are higher in urgent cesarean sections than in instances where it is an elective surgery (17). In our study, patients undergoing elective cesarean received from previa according to the emergency cesarean hysterectomy, hypogastric artery ligation, bladder repairing, and removal rates of postoperative intensive care unit was different. Having recurring cesarean section operations also contributed to complications because it made placenta previa more likely and also caused uterine scars (18). Patients with complete placenta previa or placenta accreta who have cesarean section operations in their history have a high risk of postpartum bleeding, transfusion, obstetric hysterectomy, and perinatal morbidity (19). In cesarean sections executed because of placenta previa, the risk of hysterectomy is approximately 4 times higher. In one study, it was asserted that for one cesarean section the risk was 0.65%, ascending to 1.5% with 2 cesarean sections, 2.2% with 3, and more than 10% with 4 cesarean sections (20). In this study, while one of the women with placenta previa and no cesarean history had to undergo hysterectomy, 6.9% of cases of placenta previa that had one cesarean section underwent hysterectomy; this percentage increased greatly to 43.5% with two cesarean sections and 66.7% with 3 cesarean sections. Overall, hysterectomy was performed in 27.6% of women who had cesarean section before. On the other hand, hysterectomy was performed in none of the women who had not undergone cesarean section before. Although the difference was insignificant, it is thought to be due to the limited number of our study cases. Furthermore, high parity and existing placenta previa also combine to increase the risk of hysterectomy (21-23).

Of our 67 cases of placenta previa in this study, 38 (56.7%) had parity of 2 or more. A significant difference existed with parity < 2 versus >2 in terms of the incidence of hysterectomy, hypogastric artery ligation, operation period, blood product transfusion, and rate of existing postoperative intensive care.

General and regional anesthesia had no difference in intraoperative effects for these patients (6). We also found no difference between general and regional anesthesia in caesarean sections. Type of anesthesia also had no significant impact in many of the other parameters studies (hysterectomy, blood product transfusion, hypogastric artery ligation, and bladder reparation).

As a conclusion, decreasing maternal and fetal mortality and morbidity with cesarean sections performed due to placenta previa requires careful preoperative preparations, the right anesthesia method, effective evaluation of blood loss, and strong communication between the anesthesiologist, obstetrician, and blood bank workers. Cesarean sections that are related to previa urgent in cases where parity is equal to or greater than two can result in hysterectomy. These conditions increase operation periods, blood transfusion needs, and risk of intensive care admission; necessary preparation should therefore be performed preoperatively.

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A study to compare the safety and efficacy of levofloxacin versus cefuroxime axetil in patients with uncomplicated lower UTI in a North Indian Medical College and Hospital

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ABSTRACT

Background and Objectives: Uncomplicated lower UTI accounts for around 150 million cases worldwide, every year. Antibiotics commonly used for the treatment of uncomplicated lower UTI include fluoroquinolones, trimethoprim-sulphamethoxazole, nitrofurantoin, cephalosporins, and amoxicillin. No comparative study between levofloxacin and cefuroxime axetil in patients with uncomplicated lower UTI could be searched. So, this randomized study was designed to compare the efficacy and tolerability of levofloxacin 500 mg once daily with cefuroxime axetil 250 mg twice daily in the treatment of uncomplicated lower UTI in adult Indian patients.

Methods: This prospective, parallel group comparative study was conducted in 100 patients with uncomplicated lower UTI. Patients were assessed for clinical and bacteriological success over the study period.

Results: 89 patients of the total of 100 patients enrolled in the study completed the study. E.coli was the most common organism isolated in both the groups. Patients in levofloxacin group showed improvement in clinical symptoms by 95.35 percent, as compared to 89.13 percent in the cefuroxime group. However, the intergroup difference was not statistically significant ($p>0.05$). Levofloxacin group showed decrease in bacteriological scoring by 95.35 percent, and cefuroxime group showed decrease by 86.96 percent. The difference in bacteriological scoring between the two treatment groups was not significant ($p>0.05$).

Conclusion: The results of our study show that cefuroxime axetil in a dose of 250 mg twice daily and levofloxacin 500 mg once daily for three days, are equally efficacious in treating patients with uncomplicated lower UTI. The comparative clinical and bacteriological successes between the two groups were statistically not significant, and both drugs were well-tolerated by the patients.

Introduction

Urinary tract infections (UTI) include a heterogeneous group of clinical syndromes and diseases with a worldwide incidence of at least 150 million cases annually. (1) UTI can be broadly divided into lower UTI, which involves urethra, bladder; and upper UTI that involves kidney, ureter, and prostate. Patients with lower UTI present with features of frequency of micturition, dysuria, urgency, suprapubic pain and tenderness, foul smelling urine and hematuria(2), whereas patients of upper UTI present with loin pain and tenderness, fever and systemic upset.(3)

Escherichia coli are the most common organism (71 to 78 percent) causing uncomplicated UTI, followed by *Proteus* (4-12 percent), *Klebsiella*, *Enterococcus faecalis* and occasionally *Pseudomonas* and *Staphylococcus*.(2,4,5) Diagnosis of UTI depends on the symptoms and urine culture. Treatment of acute, uncomplicated lower UTI includes mainly oral or parenteral antibiotics. Antibiotics commonly used for the treatment of uncomplicated lower UTI include fluoroquinolones, trimethoprim-sulphamethoxazole, nitrofurantoin, aminoglycosides, cephalosporins, and amoxicillin.(5,6,7,8)

Levofloxacin, the S-isomer of ofloxacin is active against a wide range of gram negative and gram positive organisms including *Staphylococcus* spp., *Streptococcus*, *H. influenzae*, *Escherichia coli*, *Klebsiella* spp, *Proteus*, *Pseudomonas aeruginosa* and atypical bacteria accountable for causing lower UTI.(9, 10) Comparative studies in lower UTI have demonstrated similar or significantly better results with levofloxacin versus ciprofloxacin, norfloxacin or ofloxacin, and other conventionally used antibiotics e.g. amoxicillin, trimethoprim-sulphamethoxazole (TMP-SMX).(5,11,12,13) The drug levofloxacin is well-absorbed, its bioavailability approaches 100 percent, and it is widely distributed throughout the body.(14) The drug is well-tolerated with a low incidence of resistance.(15,16)

Cefuroxime axetil, an oral second generation broad spectrum cephalosporin is also effective against Gram positive and Gram negative bacteria including *Staphylococcus* spp., *Streptococcus*, *Nisseria*, *E.coli*, *Klebsiella*, *Proteus* responsible for causing lower UTI, but not *Pseudomonas aeruginosa*. Cefuroxime also is well-tolerated, with incidence of resistance similar to levofloxacin and much lower as compared to TMP-SMX and amoxicillin.(15, 17,18) Studies in patients with acute uncomplicated lower UTI treated with cefuroxime axetil, show overall cure rate ranging from 86 percent to 97 percent (19,20) In another study, at one week post therapy, 88 percent of the patients in the cefuroxime axetil group were clinically and bacteriologically cured.(21) Naber and Koch reported a multicentre study done on 163 women with acute uncomplicated lower UTI, with clinical cure and improvement seen in 84.8 percent and 95.2 percent of patients treated with 125 mg cefuroxime axetil twice daily for three days and 100 mg ofloxacin twice daily for three days, respectively.(18) Seven to nine days after therapy, bacteriuria had been eliminated in 80.3 percent and 89.1

percent of the patients receiving cefuroxime axetil and ofloxacin respectively.

No comparative study between levofloxacin and cefuroxime axetil in patients with uncomplicated lower UTI could be searched. So, this randomized study was designed to compare the efficacy and tolerability of levofloxacin with cefuroxime axetil in the treatment of uncomplicated lower UTI in adult Indian patients.

Materials and Methods

Study design and population

This prospective, randomized, comparative, open-label, parallel group study was done in 100 patients suffering with uncomplicated lower UTI visiting the outpatient medicine department of Government Medical College and Hospital, Patiala during the period from 2006 to 2007; conducted in association with department of medicine, microbiology and pharmacology.

Patients of either sex, between 18 to 60 years of age, suspected to have uncomplicated UTI due to typical symptoms of dysuria, frequency, and/or urgency, sensitivity to both levofloxacin and cefuroxime axetil and willing to give written informed consent were included in the study. Patients with signs and symptoms of complicated UTI (fever, flank pain, costovertebral tenderness), pregnancy, diabetes, epilepsy, abnormalities of urinary tract, UTI within the last two weeks, use of antibiotics within the last 3 days, history of hypersensitivity reaction to the test drugs, or unable to give informed consent were excluded from the study. The study was approved by the Institutional Ethics Committee.

Patients visits to the medicine OPD were planned as per the following schedule: During the first baseline visit (Visit 1), detailed history and clinical examination of the patient were performed and urine sample was sent for microscopic examination, culture and sensitivity. The next visit was planned after 2 days (Visit 2), when the urine culture and sensitivity report became available. Based on urine culture and sensitivity report, patients were randomized into group A and group B. Patients in Group A were prescribed tablet levofloxacin 500 mg once daily for 3 days whereas Group B received tablet cefuroxime axetil 250 mg twice daily for 3 days. Patients were then called at the fourth day after starting the treatment (Visit 3), when the symptoms were recorded to assess clinical improvement and urine sample was sent for microscopic examination, culture and sensitivity.

Outcome measurements

The outcome measures used for efficacy variable were clinical success, which comprised of a sum total of clinical cure (improvement in all three symptoms) and clinical improvement (improvement in one or two symptoms); and bacteriological success (complete eradication of infecting organisms on culture).

Statistical analysis

The results were analyzed using Fisher's exact test and unpaired students t test, using Instat Graphpad 3.10 version software. A p-value <0.05 was considered statistically significant.

Results

Of the total of 100 patients (49 on levofloxacin, i.e. Group A and 51 on cefuroxime axetil, i.e. Group B) who were enrolled in the study, 89 patients (43 in Group A and 46 in Group B) completed the study. Eleven patients, six in group A and five in group B did not come for follow-up. The data was calculated for these 89 patients (33 Male, 56 Female) who completed the study.

Demographic and Baseline data

At the baseline visit (Visit 1), there was no significant difference ($p>0.05$) in demographic and clinical characteristics between the two treatment groups (Table 1). 62.92 percent (67.44 percent in group A and 58.70 percent in group B) of the patients were female. Increase in frequency (all patients in both groups A and B) was the most common symptom, whereas dysuria was the least common symptom at baseline visit. *E. Coli* (74.41percent in group A, 82.6 percent in group B) was the most common organism in both the groups, as shown in Table 2.

Clinical success

At visit 3, patients in group A showed mean percentage decrease in symptoms of increased frequency, urgency and dysuria by 72.09 percent, 70 percent and 94.12 percent,

Table 1: Demographic and clinical characteristics of the two treatment groups at baseline visit (Visit 1)

Characteristics	Group A (Levofloxacin 500 mg od)	Group B (Cefuroxime axetil 250 mg bd)	p-value
No. of patients	43	46	
Age in years (Mean ± SD)	35.65 ± 9.56	35.08 ± 9.36	0.78 ^a
Sex (M:F)	14: 29	19:27	0.51 ^b
Symptoms			
- Increased Frequency	43	46	
- Urgency	40	42	
- Dysuria	34	38	

a Value determined using two-tailed unpaired student "t" test.

b Value determined using Fisher's exact test.

Table 2: Distribution of organisms in the two treatment groups seen on bacteriological culture at visit 2

Characteristics	Group A (Levofloxacin 500 mg od) (n=43)	Group B (Cefuroxime axetil 250 mg bd) (n=46)
Culture Organism		
- <i>E. Coli</i>	32	38
- <i>Proteus</i>	8	6
- <i>Klebsiella</i>	2	1
- <i>Staph. aureus</i>	1	1

Figure 1: Changes in clinical symptoms among the treatment groups after 3-days treatment

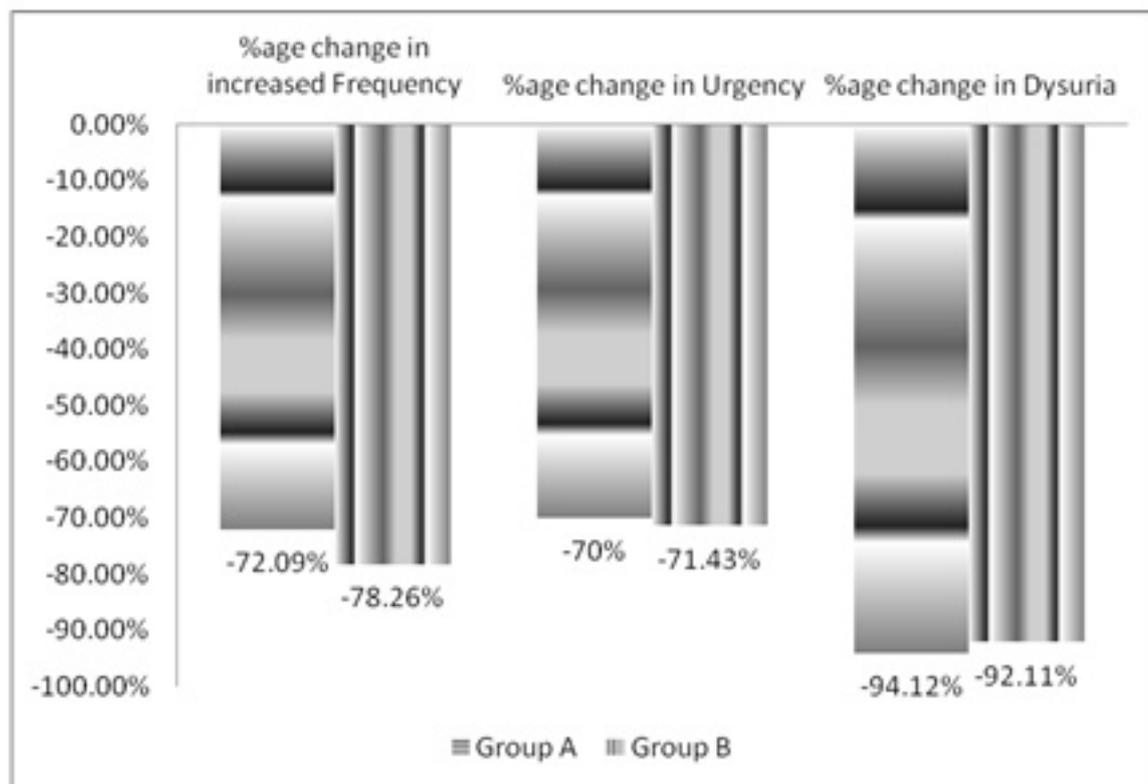
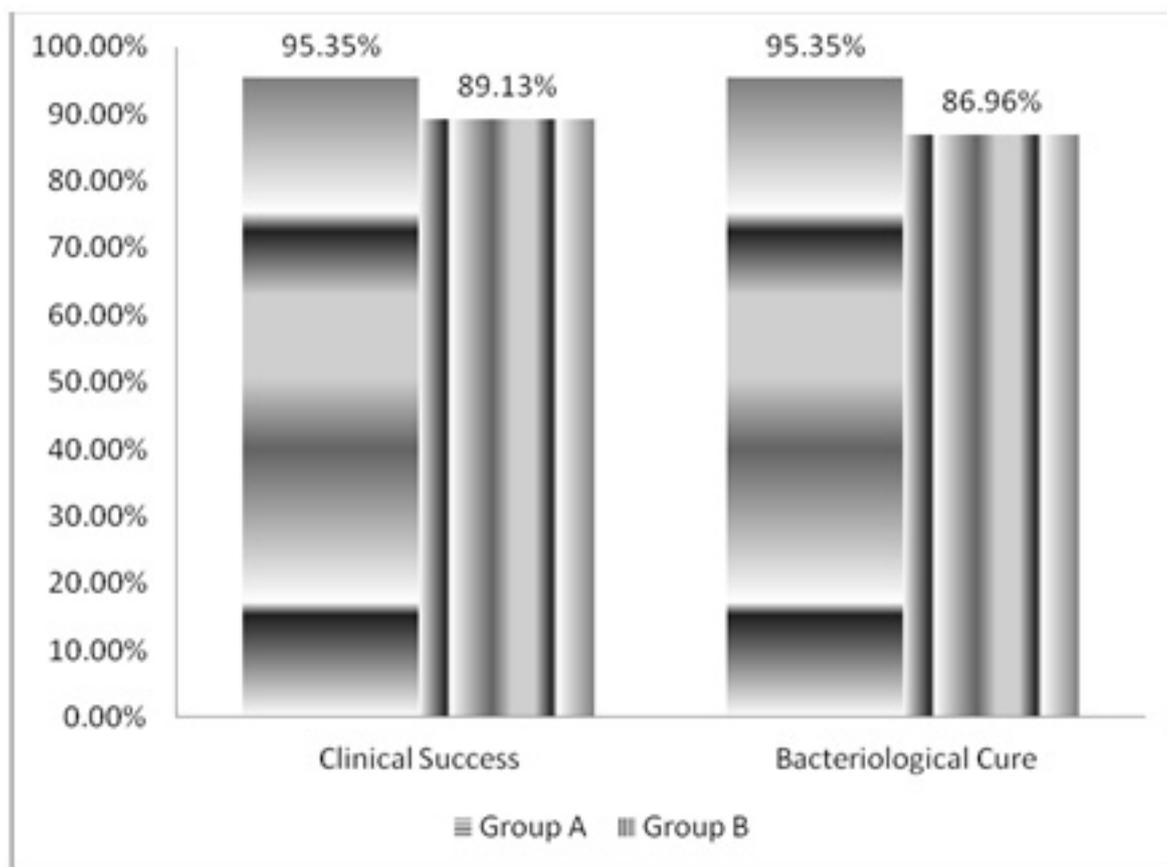


Figure 2: Comparison in clinical success and bacteriological success seen among the treatment groups



respectively. Similarly, patients in group B showed mean percentage decrease in symptoms of increased frequency, urgency and dysuria by 78.26 percent, 71.43 percent and 92.11 percent, respectively (Figure 1). Also, of the total of 43 patients in levofloxacin group A, 23 showed clinical cure, 18 had clinical improvement and 2 patients showed no improvement in any of the symptoms of lower UTI, thus, showing a mean percentage improvement in clinical symptoms by 95.35 percent. In cefuroxime group B, 22 out of the total 46 patients showed clinical cure and 19 showed clinical improvement, however, 5 patients showed no improvement in any of the symptoms. Thus, patients in group B showed a mean percentage improvement in clinical symptoms at visit 3 by 89.13 percent (Figure 2). However, the difference between the two treatment groups was not statistically significant ($p > 0.05$), although levofloxacin (95.35 percent versus 89.13 percent) decreased clinical success scores slightly more than cefuroxime (Figure 2).

Bacteriological Success

Mean percentage improvement in bacteriological success score, from baseline to visit 3 of the study period was 95.35 percent for group A (41 had bacteriological cure, 2 had bacteriological failure), and 86.96 percent for group B (40 had bacteriological cure, 6 had bacteriological failure), as shown in Figure 2. The inter-group difference between the two treatment groups A and B was not-significant ($p > 0.05$), although levofloxacin decreased bacteriological scores slightly more than cefuroxime.

Safety

Of the 89 patients who completed the study, only three patients (6.98 percent) in the levofloxacin group developed adverse effects with the drug. Two patients (4.65 percent) in levofloxacin group reported nausea and one patient (2.33 percent) complained of headache with the drug. Of the patients on cefuroxime, two patients (4.35 percent) complained of nausea with the drug. The comparison in the incidence of adverse effects between the two treatment groups was statistically non-significant ($p = 0.67$), and was done using Fisher's exact test.

Discussion

Urinary tract infections (UTI) are among the most common bacterial infections and the treatment of UTI is aimed at improvement of clinical symptoms and eradication of infection. In uncomplicated acute lower UTI, short-course three-day therapy with cefuroxime axetil or levofloxacin antibiotics is found to be effective, as shown by various studies.(13)

The results of our study show that *E.coli* was the most common pathogen isolated, similar to the findings seen in other studies.(2,4,5) Also, cefuroxime axetil in a dose of 250 mg twice daily and levofloxacin 500 mg once daily were found to be equally efficacious in treating patients with uncomplicated lower UTI. There was no statistically significant difference ($p > 0.05$) between the clinical and bacteriological success rates of the two treatment groups,

and both drugs were well-tolerated by the patients. The levofloxacin group showed slightly better response than cefuroxime axetil, maybe because fluoroquinolones are known to have superior action than cephalosporins against gram negative organisms responsible for causing uncomplicated lower UTI.

In a study by Richard et al, the clinical success rate for levofloxacin vs ofloxacin was 98.1 percent versus 97 percent and bacteriological success rate was 96 percent with levofloxacin and 93 percent for ofloxacin. Our study showed similar response to levofloxacin, although the dose of levofloxacin used in this study was 500 mg od, as compared to 250 mg od in the previous study.(13) In a study by Lee et al in 2011, the susceptibility of *E.coli* to levofloxacin was 77.5 percent.(22)

The current study shows the effect of cefuroxime axetil was also quite similar to that seen in previous studies. In a study by Naber et al, the clinical success rate for cefuroxime axetil vs ofloxacin was 84.8 percent vs 95.2 percent and bacteriological success rate was 80.3 percent with cefuroxime axetil and 89.1 percent for ofloxacin.(18) The dose of cefuroxime axetil used in this study was 125 mg twice daily for 3 days. Our study was quite similar and showed clinical success rate 89.13 percent and bacteriological success rate 86.96 percent to be slightly better, probably as the dose used was 250 mg twice daily. Another study where patients were prescribed cefuroxime axetil 125 mg twice daily for 7 days, showed clinical success and bacteriological success rate to be 97 percent.(23) The study by Lee et al shows 86.1 percent susceptibility of *E. coli* to cefuroxime.(22) In another study the susceptibility of *E. coli* to oral cefuroxime was 68.6 percent versus 97.1 percent to parenteral cefuroxime.(24)

Our study revealed that the two drugs were well tolerated when used for three day therapy. The adverse events of nausea and headache with the test drugs resolved in a few hours in both treatment groups.(12,18) No patient withdrew from the study because of adverse effects, showing good tolerance to study drugs. The adverse effects were lesser in our study in both the groups as compared to earlier studies.

In conclusion, our study shows both drugs cefuroxime axetil 250 mg twice daily and levofloxacin 500 mg once daily to be effective in the three-day treatment of patients with uncomplicated lower UTI, with no statistically significant difference between the efficacy of cefuroxime axetil and levofloxacin, although levofloxacin showed slightly better response than cefuroxime axetil. Both the drugs were well-tolerated.

There are certain limitations in our study: First, more number of patients in each group would make the results more significant. Second, prolonged follow-up visit would have revealed better any cases of relapse or treatment failure.

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