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# From the Editor

Ahmad Husari *(Chief Editor)*
Email: editor@me-jim.com

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 carpel 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, the 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

**Kholoud Abdelnabi**

**Correspondence:**
Dr. Kholoud Abdelnabi
Specialist, Department of Obstetrics and Gynecology.
Royal Medical Services
Jordan
Mobile: 00962776134468
**Email: mkateeb@lycos.com**

## 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 carpel 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.**

## 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).

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 carpel 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 carpel 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 carpel 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

**Ahmed Alissa**

**Correspondence:**
Ahmed Alissa, MD
Department of pediatrics
Queen Rania AL-Abdullah Hospital for Children
Royal Medical Services
P O BOX 855100
Postal code 11855
Amman, Jordan
**Email:** aalissa68@yahoo.com

## ABSTRACT

**Objective: To asses 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-esophagial 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-Netherland 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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# Effects of Benfotiamine and Methylcobalamin on Paclitaxel induced Peripheral neuropathy

**Kawa F. Dizaye**
**Chro Y. Qadir**

**Hawler Medical University, Iraq**

**Correspondence:**
Dr. Kawa Dizaye. Professor of Pharmacology,
Head of Dept of Pharmacology.
Hawler Medical University, Iraq
**Email:** dr_kawadizaye@yahoo.com

## 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 35days 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±1°C) for cold hyperalgesia and (10±1°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±1°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 ± standard error of means (M ± 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 ms ± SE 0.086 (Table 1); it was increased significantly in paclitaxel receiving group rats to 1.74 ms ± SE 0.087 (Table 1 - next page). In Benfotiamine and paclitaxel receiving group the mean latency was 0.94 ms ± SE 0.074 (Table 1), While in the methylcobalamin and paclitaxel receiving group the mean latency was 1.2 ms ± 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 mv ± SE 2.1 (Table 1). It was reduced significantly in the paclitaxel receiving group rats to 12.02 mv ± SE 0.92 (Table 1). The mean amplitude in the benfotiamine and paclitaxel receiving group was 26.66 mv ± SE 1.22 (Table 1). While the mean amplitude in methylcobalamin and paclitaxel receiving group was reduced significantly to 18.4 mv ± 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 m/s ± SE 5.1 (Table 1); it was reduced significantly in the paclitaxel receiving group rats to 29.04m/s ± SE 1.46 (Table 1). In the benfotiamine and paclitaxel receiving group the conduction velocity was 54.46 m/s ± 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 m/s ± 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±2°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 sec. ± SE 1.7 and in the paclitaxel group was reduced significantly to 10.3 seconds. ± SE 2.6 ($P=0.042$). While compared to the control group the paclitaxel and benfotiamine receiving group was 16.5 seconds ± SE 1.6 no significant change was observed. The paclitaxel and methylcobalamin receiving group was 17.7 seconds. ± SE 1.7 compared to the control group and no significant differences were seen.

**Tail immersion test (cold hyperalgesia 4±1°c) in mice.**

There was a significant reduction in the mean withdrawal latency for cold hyperalgesia in the paclitaxel receiving group which was 3 seconds ± 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 gastrocnimeus 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 $P < 0.05$

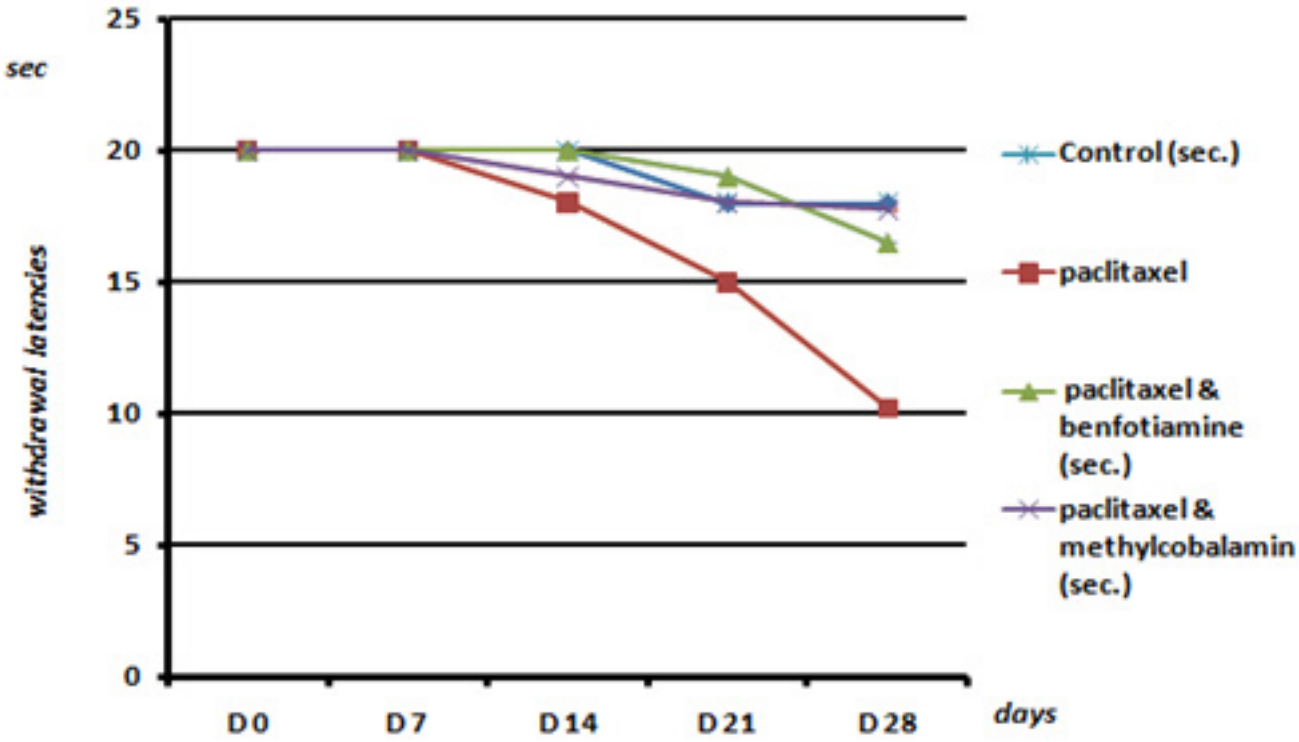


**Figure 1: Tail immersion tests for cold allodynia (10±2°c), withdrawal latencies (sec.) measured on weekly bases for all the groups each group with six mice**

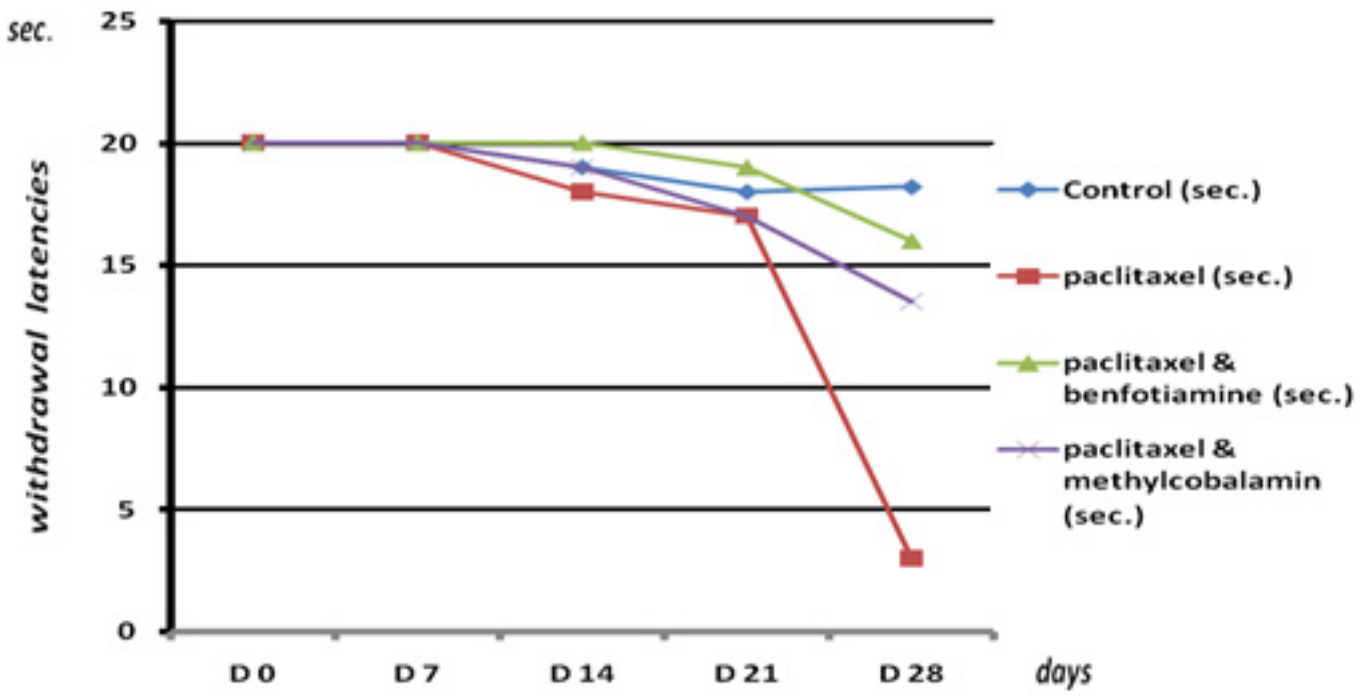


**Figure 2: Tail immersion tests for cold hyperalgesia (4 ± 1°c), withdrawal latencies (sec.) measured on weekly bases for all the groups each group with six mice.**

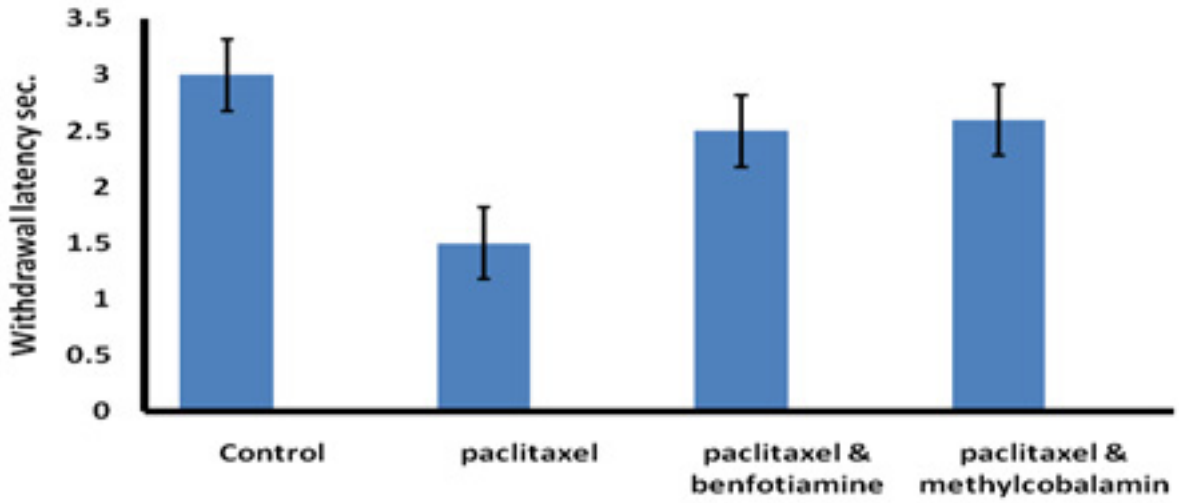


**Figure 3: The mean paw withdrawal latencies in four mice groups, each group (n=6) 7 days after last dose of paclitaxel (28th day).**

control group. Whereas in the paclitaxel and benfotiamine receiving group it was 16 ± 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± 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 sec± 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 sec ± 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 2.6seconds ± SE 0.24 (P= 0.45) and 2.5 ± 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).

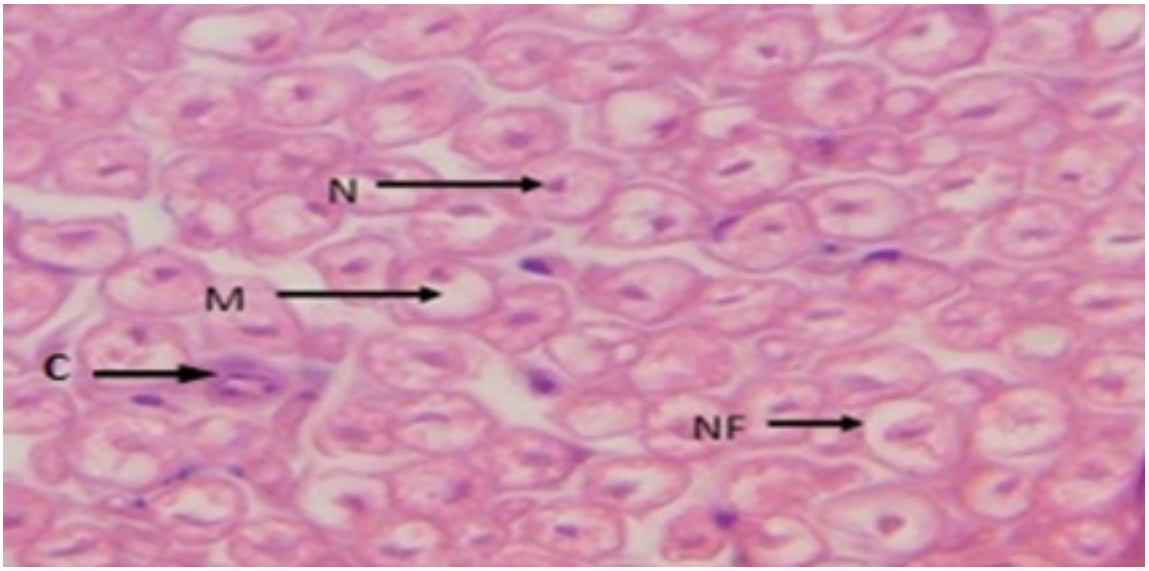


**Figure 4: Cross section from the SN of a normal control specimen showing normal appearance of the individual nerve fibers (nucleus and myelin) of Schwann cells (arrows) (N= nucleus , M= myelin, NF= nerve fiber, C=capillary) E & H stain X 400.**

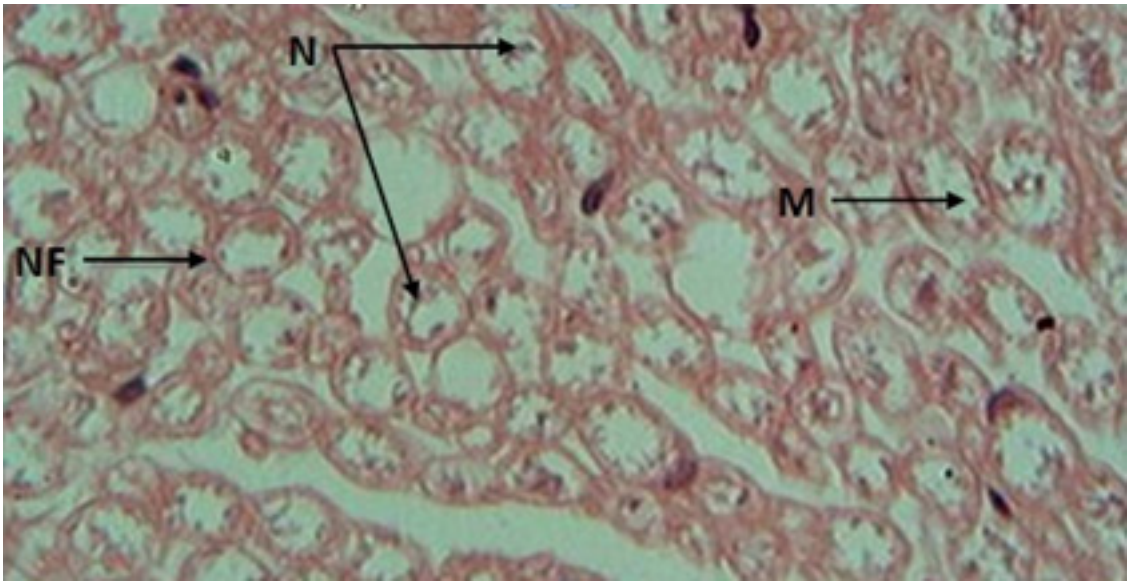


**Figure 5: Cross section of SN from the paclitaxel receiving group specimen showing abnormal appearance of the individual nerve fibers (nucleus degeneration and disruption of myelin sheath) of Schwann cells and multiple different size nerve fibers (arrows) (N= nucleus , M= myelin , NF= nerve fiber,)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

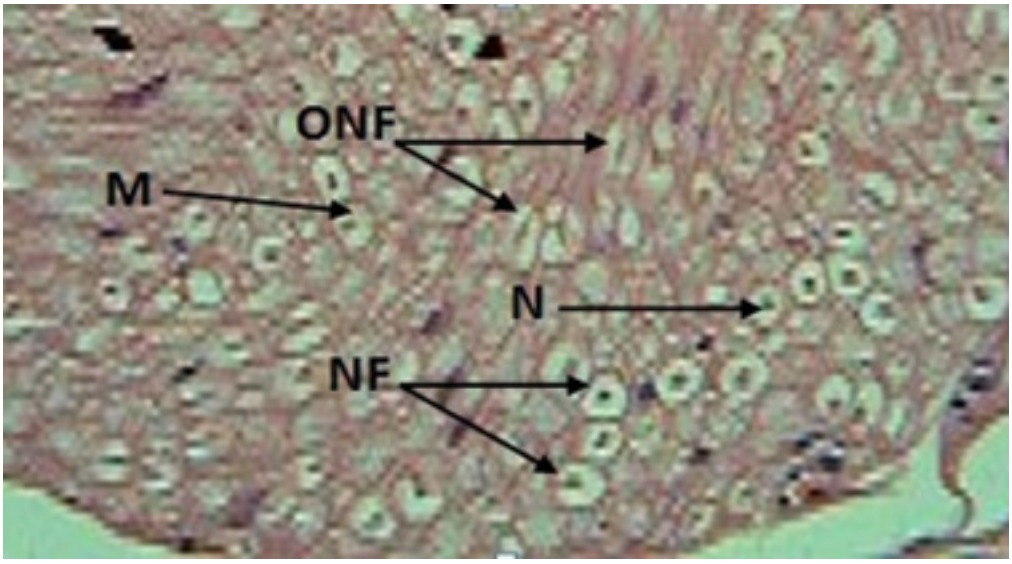


**Figure 6: Cross and oblique sections of SN from paclitaxel and benfotiamine receiving group specimen showing most nerve fibers normal, with normal nucleus, normal myelin thickness and maintenance of basement membrane of Schwann cells (arrows) (N= nucleus , M= myelin, NF= nerve fiber, ONF= oblique view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

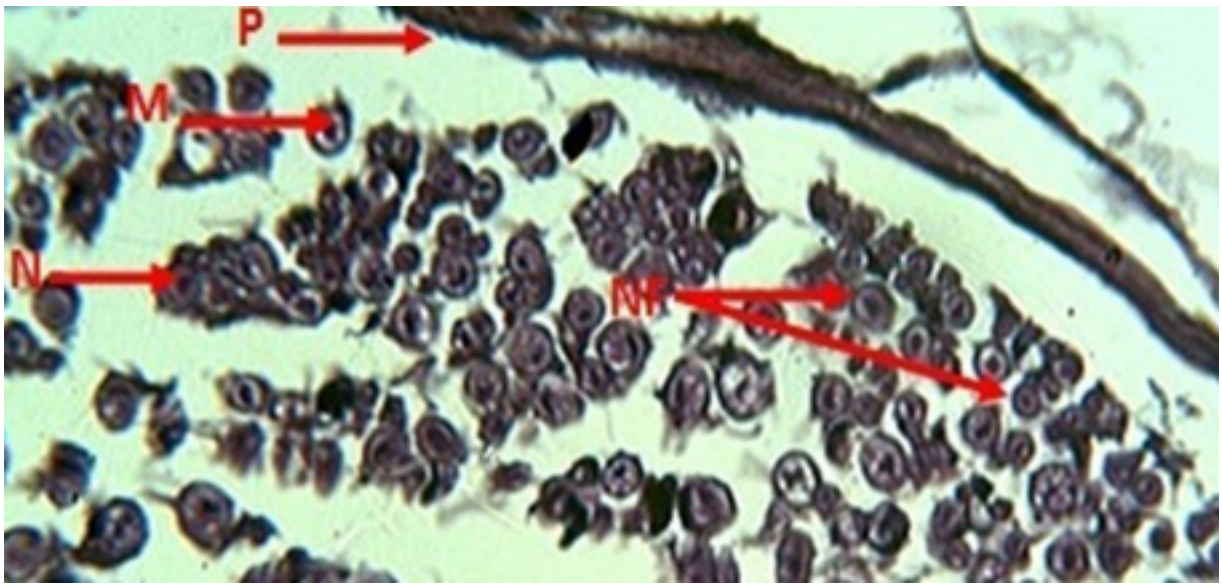


**Figure 7: Cross section of SN- B (lower) - Cross and oblique section of SN, from paclitaxel and methylcobalamin receiving group specimen showing marked reduction in myelin thickness and multiple different size nerve fibers but, with maintenance of basement membrane of Schwann cells (arrows) (N= nucleus , 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 replicationbut, 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

**Sedat Hakimoglu** (1)
**Murat Karcioglu** (2)
**Kasim Tuzcu** (3)
**Isil Davarci** (4)
**Ayse Guler** (5)
**Atilla Karateke** (6)
**Ali Sari** (7)
**Selim Turhanoglu** (8)

(1) M.D; Assistant Professor, Department of Anesthesiology and Reanimation, Mustafa Kemal University Faculty of Medicine (MKUFM), Hatay, Turkey
(2) M.D; Assistant Professor, Department of Anesthesiology and Reanimation, MKUFM, Hatay, Turkey
(3) M.D; Assistant Professor, Department of Anesthesiology and Reanimation, MKUFM, Hatay, Turkey
(4) M.D; Assistant Professor, Department of Anesthesiology and Reanimation, MKUFM, Hatay, Turkey
(5) M.D; Assistant Professor, Department of Obstetrics and Gynecology, MKUFM, Hatay, Turkey
(6) M.D; Resident Doctor, Department of Obstetrics and Gynecology, MKUFM, Hatay, Turkey
(7) M.D; Resident Doctor, Department of Anesthesiology and Reanimation, MKUFM, Hatay, Turkey
(8) M.D; Professor, Department of Anesthesiology and Reanimation, MKUFM, Hatay, Turkey

**Correspondence:**
Sedat Hakimoglu M.D.
Department of Anesthesiology and Reanimation
Mustafa Kemal University Faculty of Medicine, Antakya, Hatay, Turkey
GSM: +90 505 8610750
Phone: +90 326 2291000
Fax: +90 0 326 24556544
**Email:** sedathakimoglu@hotmail.com

## 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) |
| Ceserean 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 |
| İntensive 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**

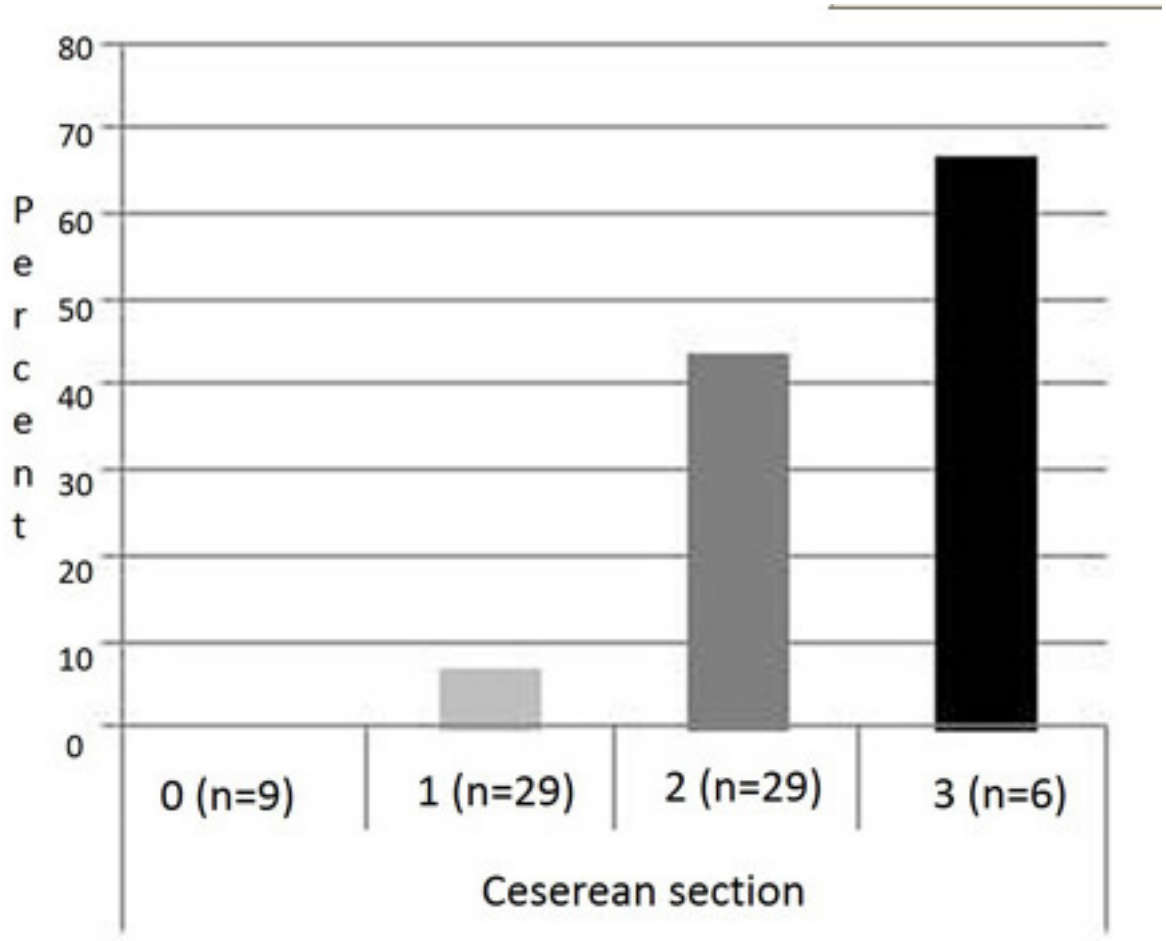


**Figure 1: The percentage of blood transfusion according to the state for operations *P?0.01, Group U; Urgent, Group E; Elective**

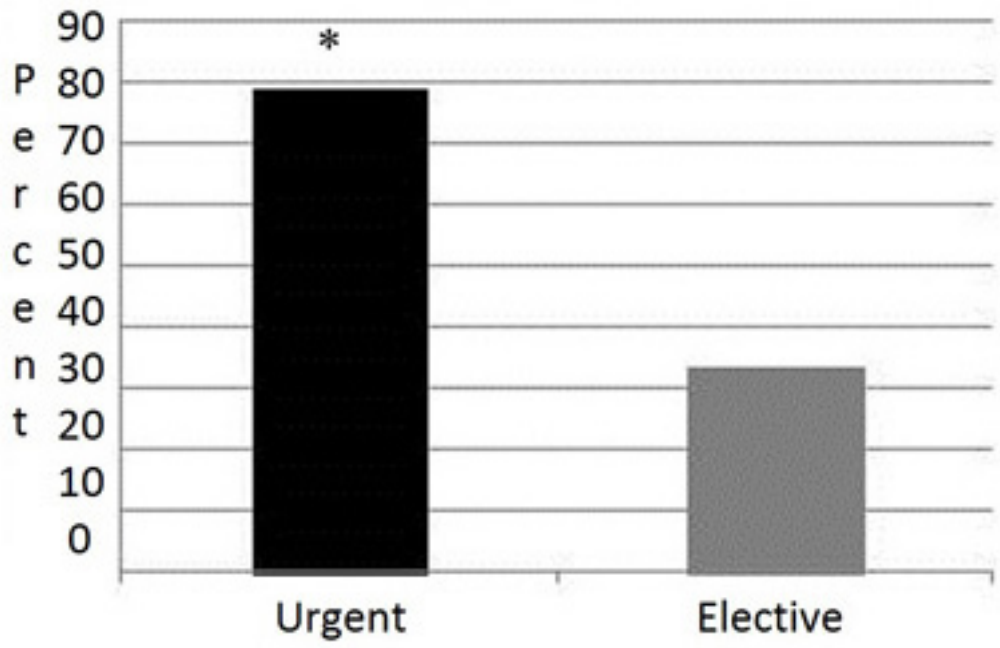


**Figure 2: The percentage of hysterectomy with the number of previous cesarean**

| *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 |
| İntensive 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 (GroupP > 2) case numbers were (43.3%) 29, and if parity number was <2 (GroupP<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 settlement 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 tranfusion, 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 caesarean section cases, they were given in 33.3% of cases with elective caesarean 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 caesarean 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 caesarean 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

**Preeti Garg** (1)
**Amandeep Singh** (2)
**Rani Walia** (3)
**Harbir Kaur Rao** (4)
**Prithpal Singh Matreja** (2)
**Amarjit Kaur Gill** (5)
**PML Khanna** (6)

(1) Assistant Professor, MBBS, MD, Department of Pharmacology, Gian Sagar Medical College and Hospital, Village Ram Nagar, District Patiala, Punjab, India-140601
(2) Associate Professor, MBBS, MD, Department of Pharmacology, Gian Sagar Medical College and Hospital, Village Ram Nagar, District Patiala, Punjab, India-140601
(3) Professor and Head, MBBS, MD, Department of Pharmacology, Maharishi Markendeshwar Institute of Medical Sciences and Research, Mullana, Ambala, India-133207
(4) Professor, MBBS, MD, Department of Medicine, Gian Sagar Medical College and Hospital, Village Ram Nagar, District Patiala, Punjab, India-140601
(5) Professor and Head, MBBS, MD, Department of Microbiology, Adesh institute of Medical Sciences and Research, Bathinda, Punjab, India-151109
(6) Professor & Head, MBBS, DA, MD, Department of Pharmacology, Gian Sagar Medical College and Hospital, Village Ram Nagar, District Patiala, Punjab, India-140601

**Correspondence:**
Dr. Preeti Garg, Assistant Professor, Department of Pharmacology, Gian Sagar Medical College and Hospital, Village Ram Nagar, District Patiala, Punjab, India-140601
Mobile: +91-8146265728
**Email:** preetigarg@gmail.com

## 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, Niesseria, 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 | | |
| - *E. Coli* | 32 | 38 |
| - *Proteus* | 8 | 6 |
| - *Klebsiella* | 2 | 1 |
| - *Staph. aureus* | 1 | 1 |

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

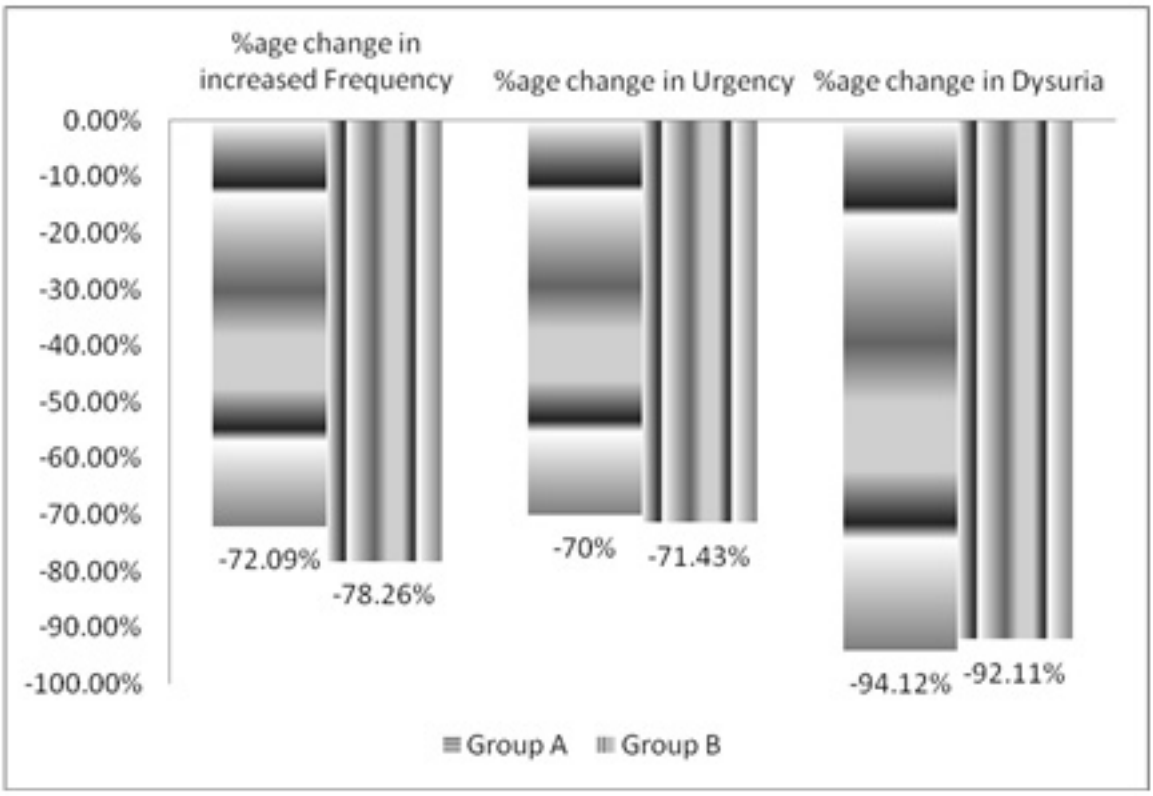
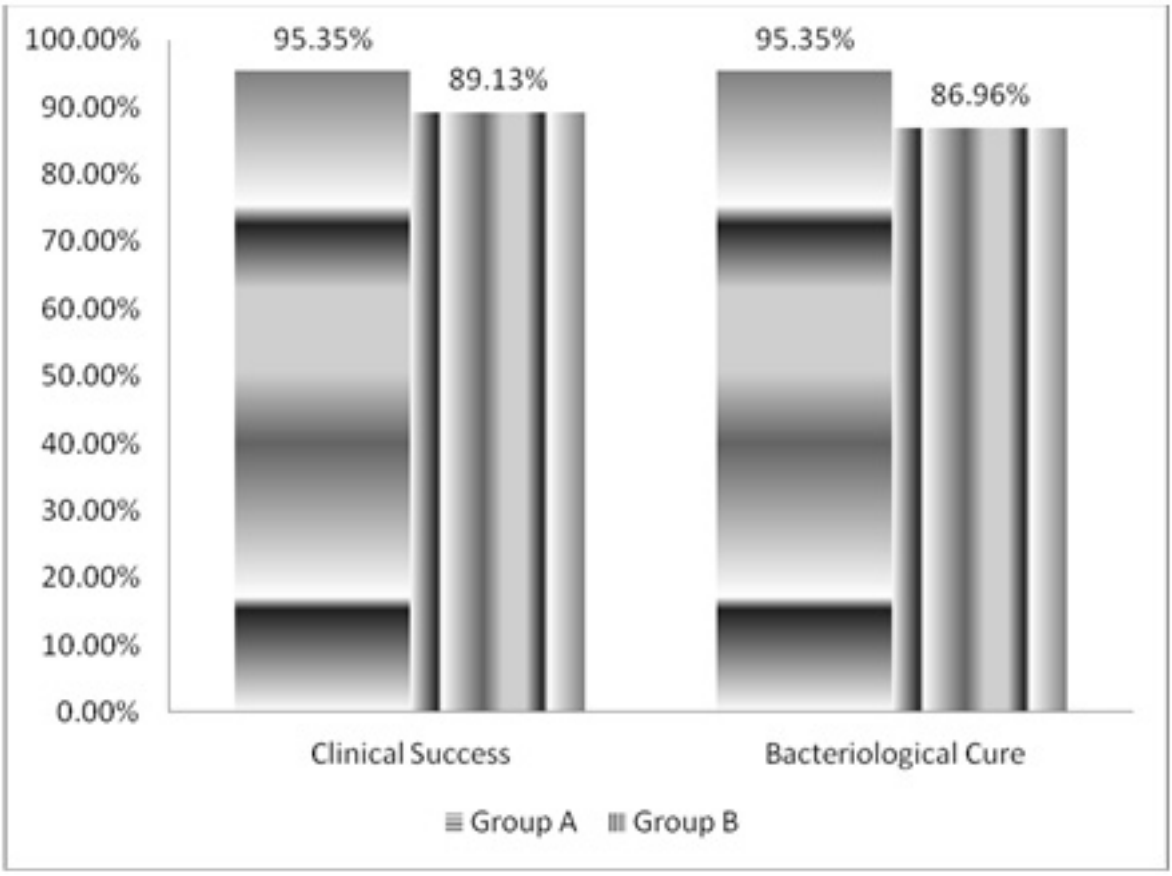



**Figure 2: Comparison in clinical success and bacteriological success seen among the treatment groups**



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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