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EVALUATED THE SIDE EFFECT OF LEVOFLOXACIN ON KNEE JOINTS IN JUVENILE RATS

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ABSTRACT

Levofloxacin 500 mg/kg/day was given to ten lactating female rats. The results showed an increase in serum levels of transferases [ALT and AST] but a decrease in juvenile total protein and albumin. The histopathological analysis also revealed a decreased thickness with chondrocyte loss and shrunken chondrocytes with pyknotic nuclei.

***Keywords*: levofloxacin, knee joint, rats, Karbala**

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INTRODUCTION

Since these antibiotics have the benefit of an oral treatment regimen that can be administered outside of a hospital setting, there has been growing impetus to utilize fluoroquinolones in pediatric patients in recent years. However, despite the fact that this class of antibiotics is typically still tolerated well, the use of fluoroquinolones in children is restricted out of compassion because of their tendency to cause cartilage toxicity. [1]

According to a different study, levofloxacin decreased glycosaminoglycan production first and DNA synthesis and mitochondrial activity secondarily in cultured rabbit chondrocytes at arthropathic concentrations. However, these changes were reversible and not enough to cause the cells to die.[2,3]

Levofloxacin is an antibiotic with a broad spectrum of activity that belongs to the fluoroquinolone medication class. It can combat the majority of bacterial strains that cause infections of the respiratory, urinary, gastrointestinal, and abdominal tracts, including Gram-[-] [Klebsiella pneumoniae, Escherichia coli, Legionella pneumophila, Haemophilus influenzae, Proteus mirabilis, Moraxella catarrhalis and Pseudomonas aeruginosa], Gram-[+] [, Streptococcus pneumoniae, Staphylococcus aureus Staphylococcus epidermidis, and Enterococcus faecalis], and other microorganisms [Mycoplasma pneumoniae and Chlamydophila pneumoniae]. [4,5] Fluoroquinolone antibiotics are more popular than ever due to their wide antibacterial range, several recognized applications, and excellent pharmacokinetics.[6]

In the United States, levofloxacin was given medical approval in 1996 after being patented in 1985. It is listed as one of the Essential Medicines by the World Health Organization. It is accessible as a generic drug. With more than 3 million prescriptions written, it was the 182nd most popular drug in the US in 2019.[7,8]

Comparing levofloxacin to ciprofloxacin, the fluoroquinolone class shows that levofloxacin has a more improved effect against gram-positive penicillin-sensitive and resistant organisms, such as Streptococcus pneumoniae and less action against gram-negative bacilli, such as Pseudomonas aeruginosa. Legionella spp., Mycoplasma spp.,

and Chlamydia pneumoniae are just a few of the prevalent respiratory pathogens that levofloxacin is effective against. Additionally, compared to other fluoroquinolones, levofloxacin has a better in-vitro action against Mycobacterium tuberculosis, making it the drug of choice for second-line antitubercular treatment.[2]

Fluoroquinolone antibiotics have been linked to a variety of musculoskeletal side effects that affect tendon as well as cartilage, bone, and muscle. Over the past few years, new information has become available regarding the pathoetiology of fluoroquinolone toxicity in musculoskeletal tissues. Although the pathoetiology is undoubtedly complicated, direct toxic effects on the musculoskeletal tissues and changes in cell signalling proteins have both been clearly linked.[9]

Specific medications have been shown to be able to cross the placental barrier and enter the fetal circulation, leading to structural defects in the newborn that can last for an arbitrary amount of time. It has become increasingly clear over the past few decades that many medications, particularly antibacterial compounds used to treat major infections that develop during pregnancy, especially fluoroquinolones, have harmful effects on human and animal embryos. [10,11]

This study aimed to evaluate the effect of levofloxacin on the knee joints of the second generation of rats.

MATERIAL AND METHODS

Animal handling

From the Laboratory Animal Center of the pharmacy college/Karbala university, ten healthy pregnant female rats were recruited. The laboratory animal center of the veterinary college served as the site of the study's animal experiment. For at least a week, all animals were adjusted to the lab environment. The animals were kept separately in air-conditioned rooms with metal cages and were fed unsupplemented pellet meal and tap water.

Experimental design:

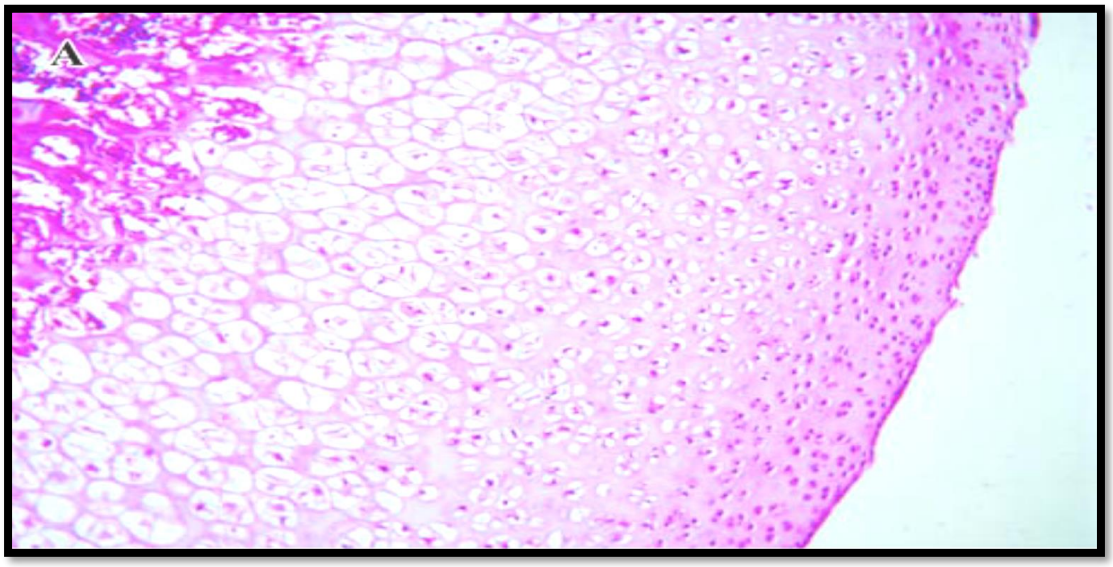
1. Used ten pregnant rats separated into five groups
2. After parturated the four groups of lactating female rats were administrated orally with levofloxacin [500mg/kg] once daily for ten days, and the fifth groups considered control
3. After the final dosing, the juvenile rats randomly taken blood sample and acted biochemical analysis to measure ALT, AST, Albumin and total protein
4. the juvenile rats were sacrificed under isoflurane anesthesia; and surgery was performed to remove the knee joints, and these joints undergo neutral formalin 10% fixation, paraffin embedding, and manual microtome sectioning to produce 4-5 μm thick paraffin pieces. After being dewaxed, the sections are stained with hematoxylin and eosin [H&E], and their histological analysis is then finished by light microscopes. [12,13]

RESULTS

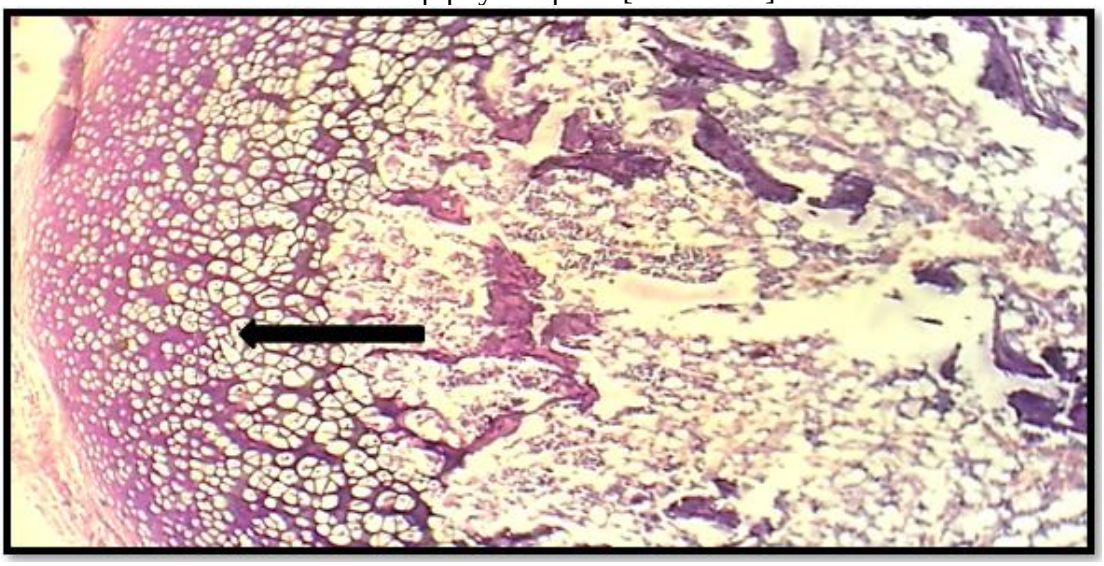
The juvenile rats showed changes in their behaviour after the oral administration of levofloxacin to lactating females, including depression, loss of appetite, weakness, and swelling of knee joint of treated groups, and death of three juvenile rats from two groups that were treated with levofloxacin, and after final dosing administration, the juvenile rats scarified and collected blood sample randomly, When measured biochemically, the serum levels of transferases [ALT and AST] increased while total protein and albumin decreased**.[14]**

Following that, histopathological examination of juvenile rats from treated groups revealed that the knee epiphyseal growth plate cartilage revealed a decrease in thickness with chondrocyte loss when compared to the control [figure1&2].

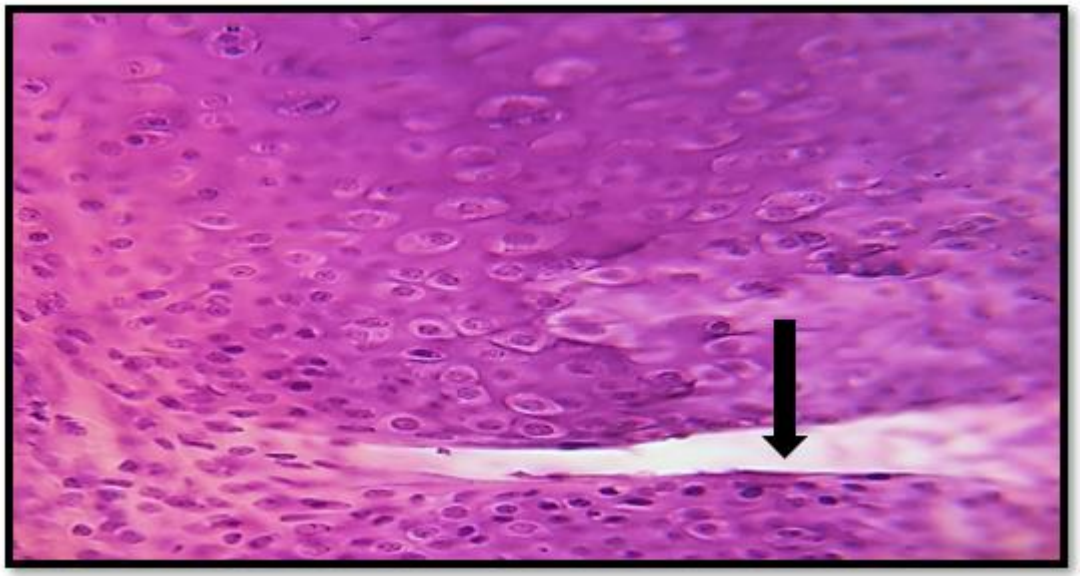
Figure [3]also showed some collagen fibers running into clefts between chondrocyte columns in the articular cartilage. It also revealed irregularities in the articular surface, as well as cavity formation surrounded by shrunken chondrocytes with pyknotic nuclei [figure 4].



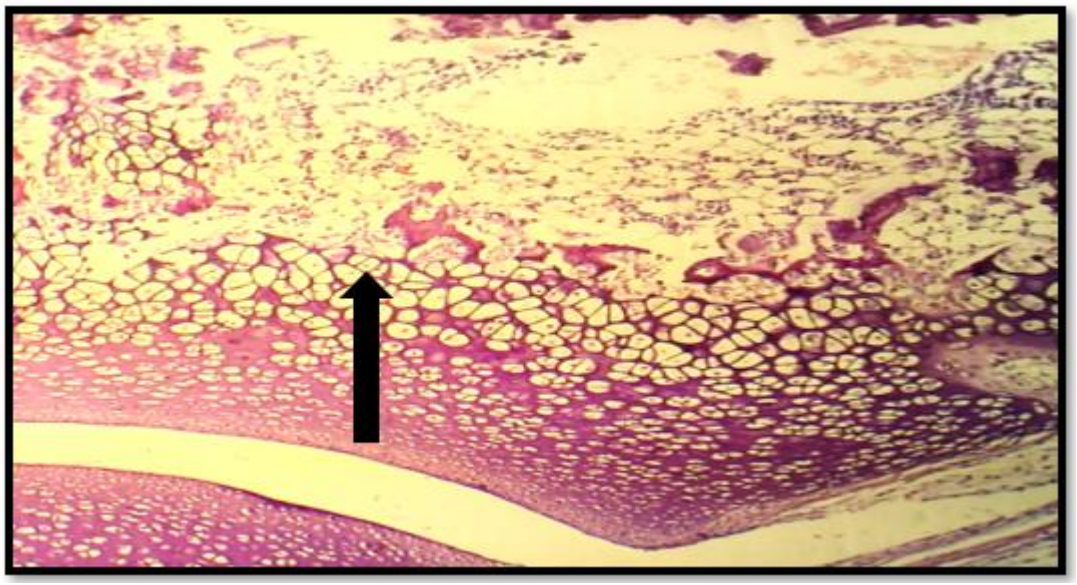
Fig[1] normal histological section of articular cartilage of knee joint of control rat showed the normal thickness of epiphyseal plate [H&E 40x] .



Fig[2] histological section of articular cartilage of knee joint showed the decrease of thickness of articular surface of juvenile rat from levofloxacin treated group [H&E 40 x] [←] .



Fig[3]histological section of articular cartilage of knee joint showed appearance of some collagen fibers covering surface of articular cartilage and running into clefts between chondrocytes [juvenile rat from levofloxacin treated group] [H&E 40x] [↓]



Fig[4] histological section of articular cartilage of knee joint showed cavities between shrunken chondrocytes [juvenile rat from levofloxacin treated group] [H&E 40x][↑].

DISCUSSION

Levofloxacin is a common antibiotic used to treat a variety of infections. However, it is not recommended during pregnancy or in children due to the risk of hepatotoxicity, nephrotoxicity, and damage to growing cartilage in young animals. [15,16]

Depending on the developmental stage, juveniles are especially sensitive to quinolones, with affection of the articular cartilage and/or epiphyseal growth plate.[17]

reported that chondrocytes in the middle zone have the greatest capacity for synthesizing, where mitosis can be seen in growing cartilage. They discovered that these cells were susceptible to the quinolones' DNA gyrase inhibitory effect, resulting in chondrocyte degeneration and cavity formation. [18]

Other authors[19] discovered that a single high oral dose and multiple low doses of ciprofloxacin were chondrotoxic in juvenile rats, causing scarring and erosions of the joint surface.

They linked ciprofloxacin-induced articular damage to the formation of ciprofloxacin-chelate complexes, which have the potential to cause a magnesium deficiency, resulting in cytoskeletal changes. As a result, the fluoroquinolone with the lowest affinity for magnesium may be the least chondrotoxic. [20]

In a similar manner, other authors [21] claimed that magnesium deficiency could cause arthro-pathogenic effects in juvenile rats, including cartilage lesions similar to those caused by quinolones. In this study, it was discovered that the levofloxacin-treated group had some collagen fibers covering the surface of the articular cartilage or surrounding the cavities, as well as running into the clefts between the chondrocyte columns of the epiphyseal plate cartilage.

Similar findings were previously reported by other researchers[22,23] who observed some collagen fibers oriented parallel to the joint surface, adjacent to the cavities, or running perpendicularly into them, as well as collagen fiber aggregation in some of the severely affected joints.

Another study [24] discovered an increased number of fibroblasts with collagen deposition in the matrix of synovial membranes and tendon sheaths, implying that levofloxacin has toxic potentials in muscle, tendon, and synovial membranes rather than articular cartilage.

The articular and epiphyseal growth plate cartilage lesions did not clear, but shrunken chondrocytes were observed with a significant decrease in articular cartilage thickness, indicating the irreversibility of the lesion under these experimental conditions. These findings were consistent with previous research that discovered ofloxacin-induced dose-dependent arthropathy in juveniles that was irreversible. [25]

Also, this study [26] noted the same results about the effect of levofloxacin on tendon, ligament cells and can induce tendonitis and tendon rupture

They conclusion from this study the administration of levorfloxacin during lactation could induce fetal defects and abnormalities, so it is advisable to avoid using this drug during lactation and use the other alterations to avoid these defects also we need more studies and more developed techniques to further information about these important topics .

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