"EVALUATION OF EFFICACY AND SAFETY OF LORNOXICAM COMPARED TO ACETAMINOPHEN IN MANAGEMENT OF OSTEOARTHRITIS OF KNEE- A RANDOMISED PROSPECTIVE STUDY"

BY

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This is to certify that, the ethical committee of Sri Devaraj Urs Medical College, Tamaka, Kolar has unanimously approved, *Dr. Soumya Mohandas,* **PG student in the subject of Pharmacology at Sri Devaraj Urs Medical College, Kolar to take up the dissertation work titled** *"Evaluation of efficacy and safety of lornoxicam compared to acetaminophen in management of osteoarthritis of knee- A randomised prospective study"* **to be submitted to Sri Devaraj Urs Academy of Higher Education and Research, Karnataka.**

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Date: *Signature of the Candidate*

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DEDICATED WITH REVERENCE
TO

MY

Parents

WHOSE SELFLESSNESS AND INSPIRATION

MOTIVATES ME IN ALL MY ENDEAVOURS

LIST OF ABBREVIATIONS USED

OA- OSTEOARTHRITIS

NSAIDs-NON STEROIDAL ANTI INFLAMMATORY DRUGS

COX- CYCLO-OXYGENASE

PGs- PROSTAGLANDINS

WOMAC-WESTERN ONTARIO MAC MASTERS OSTEOARTHRITIS INDEX

VAS-VISUAL ANALOGUE SCALE

ACR- AMERICAN COLLEGE OF RHEUMATOLOGY

EULAR- EUROPEAN LEAGUE AGAINST RHEUMATISM

ABSTRACT

Objective

To evaluate the efficacy and safety of Lornoxicam 8mg BD in comparison with Acetaminophen (ER) 650mg BD in osteoarthritis knee.

Materials and methods

A study was conducted in which 120 cases of mild to moderate osteoarthritis of knee were enrolled. Relevant information on each patient was collected according to the proforma designed for the study. These patients were given either Lornoxicam 8mg BD or Acetaminophen ER 650mg BD for 4 weeks. They were followed up at 1, 2, 4 weeks and at the end of 3 months. At each follow up, pain, stiffness, disability, WOMAC and VAS scores were assessed. Safety was assessed by monitoring adverse effects.

Results

In our study, most of the patients were above 45 years and were equal in gender distribution. Patients receiving Lornoxicam 8mg BD and Acetaminophen ER 650mg BD had significantly reduced pain, stiffness, disability, WOMAC and VAS scores at follow up 1^{st}, 2^{nd} and 4^{th} week. Between the groups, lornoxicam significantly reduced all parameters at follow up visits at 1, 2 and 4 weeks. Both groups were equally safe with nausea and dyspepsia being more common with lornoxicam and flatulence common with acetaminophen.

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INTRODUCTION

Osteoarthritis (OA) is a rheumatic disease characterized by articular cartilage degeneration, bone hypertrophy, crepitus and radiographic changes. Knee joint is more commonly affected by degenerative arthritis than any other joint in the body. The joint pain and stiffness associated with OA can lead to significant disability and functional impairment. Among the elderly, OA of the knee is the leading cause of chronic disability; an estimated 100,000 people are unable to walk independently because of knee or hip OA. Therefore, controlling the symptoms is critically important to treatment.[1]

The management of OA remains challenging, despite greater awareness among primary providers and rheumatologists of the importance of lifestyle modifications and availability of new therapies. Non pharmacologic interventions including exercise and bracing are commonly recommended but often not sufficient to adequately manage pain.

Thus, analgesic therapy is frequently required. Since OA is more prevalent in the elderly, many of whom have co-morbidities, selection of an analgesic is often complicated. Additionally, elderly patients are at a greater risk for gastrointestinal (GI) bleeding secondary to the use of NSAIDs.[2]

Analgesics are an important component of treatment during the symptomatic periods of the disease. In this respect, current practice guidelines advocate the use of an analgesic like acetaminophen or an NSAID administered as first- or second-line drug therapy respectively. However, in view of the cardiovascular adverse events

(AEs) associated with the use of cyclooxygenase (COX)-2 inhibitors, a well-tolerated NSAID is needed.

Acetaminophen extended-release (ER) is a long-acting analgesic and antipyretic medication indicated for the temporary relief of minor aches and pains caused by arthritis, headache, toothache and muscular aches. In various studies acetaminophen has been shown to be comparable to NSAIDs for the relief of mild to moderate joint pain associated with OA.[1]

Lornoxicam is an NSAID of the oxicam class with a similar mechanism of action as other oxicams. In vitro studies have demonstrated that lornoxicam is 100 times more potent than tenoxicam as a cyclooxygenase (COX) inhibitor. Its analgesic potency is 12 and 10 times greater than that of piroxicam and tenoxicam, respectively. Lornoxicam has been marketed recently in India. Even though some clinical trials have documented the effectiveness of lornoxicam as a potent analgesic with good anti-inflammatory properties in a range of painful and/or inflammatory conditions, there are no comparative studies with acetaminophen in Indian patients with osteoarthritis.[3]

AIMS AND OBJECTIVES

1. To evaluate the efficacy of lornoxicam compared to acetaminophen in OA of knee

2. To evaluate the safety of lornoxicam compared to acetaminophen

REVIEW OF LITERATURE

Osteoarthritis (OA) has been defined by American College of Rheumatology (ACR) as "A heterogenous group of conditions that lead to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone at joint margins".[4] OA of the knee is no longer considered a disease process with which the patient must learn to live. No drug treatment however restores an osteoarthritic knee to its normal status. The treatment aims for symptomatic relief of pain, maximizing joint function and preventing further joint damage. Analgesics are an important component of treatment during symptomatic periods of the disease. In this respect, current practice guidelines advocate the use of an analgesic like acetaminophen or an NSAID administered either systemically or topically as first or second line therapy respectively.[5]

EPIDEMIOLOGY

Osteoarthritis is more common in women than men but the prevalence increases dramatically with age. 45% of women over the age of 65 have symptoms of OA while radiological evidence is found in 75% of those over 65 years.[6] OA of the knee is one of the major cause of mobility impairment, particularly in females. In the Global Burden of Disease 2000 study, published in World Health Report 2002, OA is the 4th leading cause of Years Lived with Disability (YLD) at global level.[7] In a recent WHO-ILAR COPCORD study done in India the prevalence of OA was 3.9% in rural population.[8]

HISTORY

Numerous historical accounts have pointed out that all forms of chronic arthritis were regarded as gout. It was William Heberden in 1802 who gave a clear description of the disease in Commentaries on history and cure of diseases calling particular attention that it has no connection with gout. In 1793 Sandifort of Leiden described osteoarthrosis of hip and Bell described it again in 1824. John Haygarth in 1805 made a description of polyarticular disease affecting distal interphalangeal and other joints resembling osteoarthritis.

Benjamin Brodie in 1829 was one of the earliest to appreciate a non inflammatory erosion of articular cartilage in the elderly. In 1869, Charcot and Virchow, fathers of cellular pathology used the term ‘arthritis’ for both rheumatoid and osteoarthritis. The disease was given its current title ‘osteoarthritis’ by A E Garrod in 1890. In 1952 Kellegran and Moore linked Heberdens nodules to osteoarthritis naming it primary generalized osteoarthritis.[9]

ANATOMY OF KNEE JOINT

Knee joint is the largest and most complicated articulation in the human body. This is a modified hinge joint. The articulating surfaces are femur, tibia and patella forming femorotibial and patellofemoral joints respectively. In this joint three functional spaces exist; the medial femorotibial space, lateral femorotibial space and patellofemoral space. [10, 11]

The lower end of femur contains a medial and lateral condyle, separated posteriorly by an intercondylar notch or fossa. Medial condyle is larger than lateral condyle and possesses the adductor tubercle. Intercondylar fossa runs between the medial and lateral condyles. The articular surface of femur consists of the condylar areas (femorotibial spaces and the patellar surface (patellofemoral space).

The patella is the largest sesamoid bone in the body. Articular surface of the patella is attached to the femur, which extends onto the anterior surfaces of both condyles like an inverted U. The 'odd' facet contacts the lateral anterior end of the medial femoral condyle in full flexion, when the highest lateral patellar facet contacts the anterior part of the lateral condyle. As the knee extends, the middle patellar facets contact the lower half of the femoral surface; in full extension only the lowest patellar facets are in contact with the femur. Therefore, on flexion the patellofemoral attachment moves proximally.

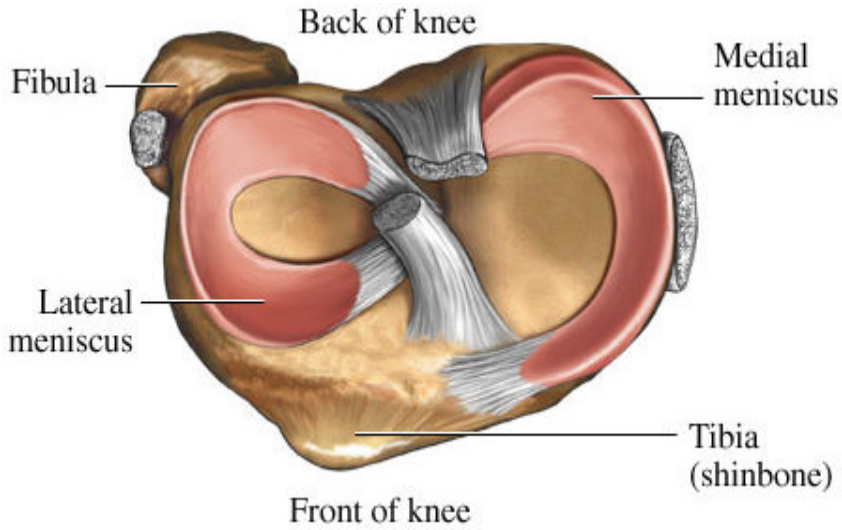
Tibiofemoral joint is a complex synovial joint. The posterior surface, distal to the articular margin, has a rough groove to which the capsular and posterior parts of the medial collateral ligaments are attached. The anteromedial surface of the tibia is separated from the medial surface of the shaft by an inconspicuous ridge. The medial patellar retinaculum is attached to the medial and anterior condylar surfaces, which are marked by vascular foramina. Tibiofemoral congruence is improved by the

menisci, which are shaped to produce concavity of the surfaces on the femur. The lateral femoral condyle has a groove anteriorly which rests on the peripheral edge of the lateral meniscus in full extension. A similar groove is present on the medial condyle, but does not reach its lateral border, where a narrow strip contacts the medial patellar articular surface in full flexion. These grooves demarcate the femoral patellar and condylar surfaces. The differences between the shapes of the articulating surfaces correlate with the movements of the joint.

MENISCI

The menisci (semilunar cartilages) are crescentic laminae deepening the articulation of the tibial surfaces that receive the femur. Their peripheral attached borders are thick and convex, their free borders thin and concave. Their peripheral zone is vascularized by capillary loops from the fibrous capsule and synovial membrane, while their inner regions are avascular.

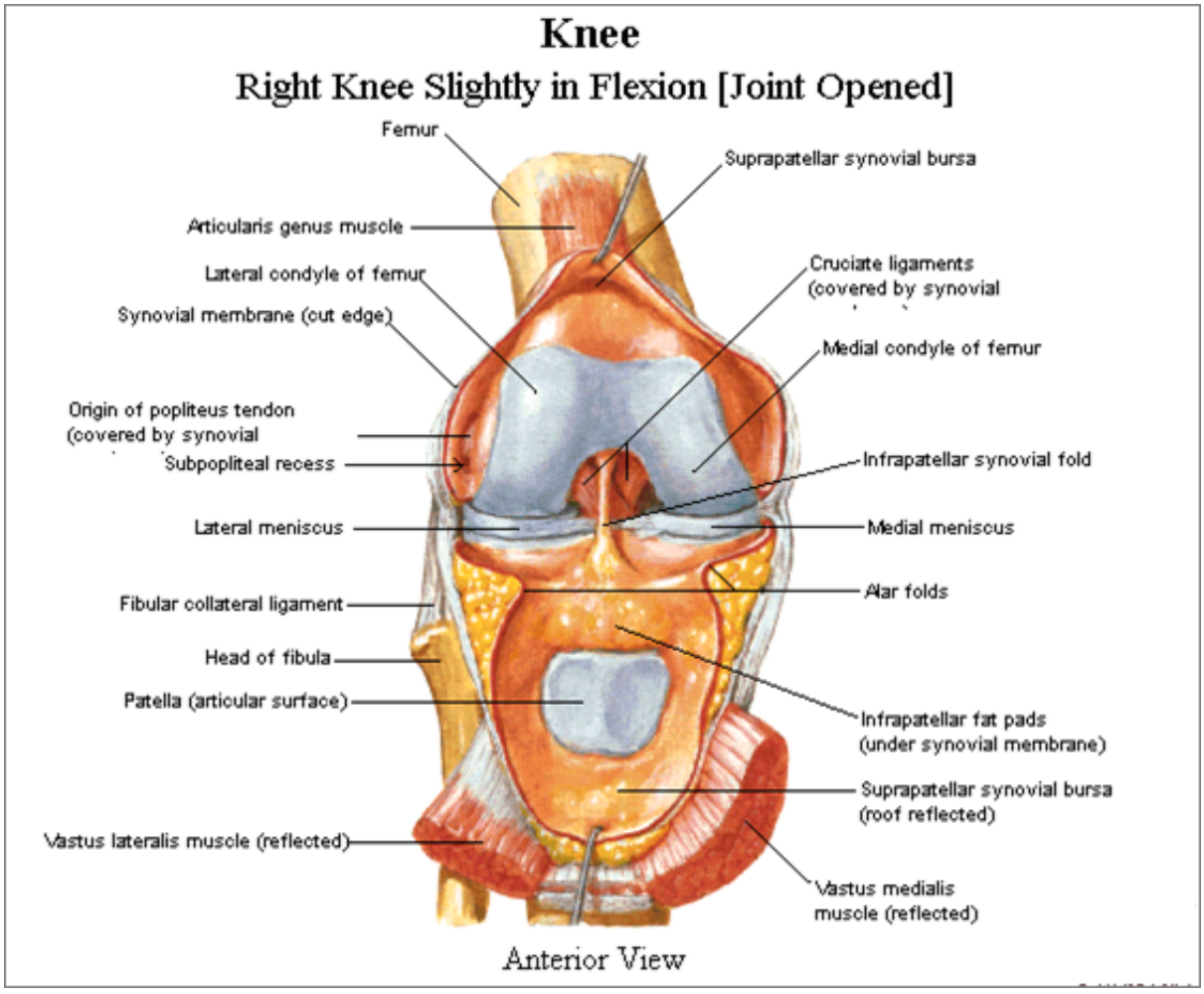
FIGURE-1: KNEE JOINT VIEWED FROM ABOVE



Medial meniscus

The medial meniscus, broader posteriorly, is almost a semicircle in shape. It is attached by its anterior horn to the anterior tibial intercondylar area in front of the anterior cruciate ligament; the posterior fibres of the anterior horn are continuous with the transverse ligament. The posterior horn is fixed to the posterior tibial intercondylar area, between the attachments of the lateral meniscus and posterior cruciate ligament. The tibial attachment is known as the 'coronary ligament'. Collectively these attachments make the medial meniscus relatively fixed and it moves much less than the lateral meniscus.

FIGURE – 2:



Lateral meniscus

The lateral meniscus forms approximately four-fifths of a circle, and covers a larger area than the medial meniscus. Its anterior horn is attached in front of the intercondylar eminence, posterolateral to the anterior cruciate ligament, with. Its posterior horn is attached behind this eminence, in front of the posterior horn of the medial meniscus.

Meniscofemoral ligaments

The two meniscofemoral ligaments (MFLs) connect the posterior horn of the lateral meniscus to the inner (lateral) aspect of the medial femoral condyle. The anterior MFL (aMFL; ligament of Humphry) passes anterior to the posterior cruciate ligament. The posterior MFL (pMFL; ligament of Wrisberg) passes behind the posterior cruciate and attaches proximal to the margin of attachment of the posterior cruciate.

LIGAMENTS

Cruciate ligaments

The cruciate ligaments are very strong and are located a little posterior to the articular centre. They are termed cruciate because they cross: anterior and posterior refer to their tibial attachments. Synovial membrane almost surrounds the ligaments but is reflected posteriorly from the posterior cruciate to adjoining parts of the capsule. The intercondylar part of the posterior region of the fibrous capsule therefore has no synovial covering.

Anterior cruciate ligament

The anterior cruciate ligament is attached to the anterior intercondylar area of the tibia, just anterior and slightly lateral to the medial tibial eminence, partly blending with the anterior horn of the lateral meniscus. It ascends posterolaterally,

twisting on itself and gets attached on the posteromedial aspect of the lateral femoral condyle.

Posterior cruciate ligament

The posterior cruciate ligament is thicker and stronger than the anterior cruciate ligament. The posterior cruciate ligament is attached to the lateral surface of the medial femoral condyle and extends up onto the anterior part of the roof of the intercondylar notch, where its attachment is extensive in the anteroposterior direction. Its fibres are adjacent to the articular surface. The synovial membrane of the knee is the most extensive and complex in the body. It forms a large suprapatellar bursa between quadriceps femoris and the lower femoral shaft at the proximal patellar border.

Bursae

There are numerous bursae associated with the knee. Anterior to the knee there is a large subcutaneous prepatellar bursa between the lower patella and skin; a small deep infrapatellar bursa between the tibia and patellar tendon; a subcutaneous infrapatellar bursa between the distal part of the tibial tuberosity and skin; and a large suprapatellar bursa which is the superior extension of the knee joint cavity.

Vascular supply and lymphatic drainage of knee joint

The vessels involved are the superior, middle and inferior genicular branches of the popliteal artery, descending genicular branches of the femoral artery, the descending branch of the lateral circumflex femoral artery, the circumflex fibular artery and the anterior and posterior tibial recurrent arteries. The venous drainage corresponds in name to the arterial supply and runs with it; the smaller veins drain into the popliteal and femoral veins. Lymphatic drainage is to the popliteal nodes.

Most of the lymph vessels accompany the genicular arteries; some vessels from the joint drain directly into a node between the popliteal artery and the posterior capsule. The popliteal nodes drain mainly into the deep inguinal group.

Innervation of knee joint

The knee joint is innervated by branches from the obturator, femoral, tibial and common peroneal nerves. The genicular branch of the obturator nerve is the terminal branch of its posterior division. Muscular branches of the femoral nerve, especially to vastus medialis, supply terminal branches to the joint. Genicular branches from the tibial and common peroneal nerves accompany the genicular arteries: those from the tibial nerve run with the medial and middle genicular arteries, while those from the common peroneal nerve run with the lateral genicular and anterior tibial recurrent arteries.

Movements

Movements at the knee are customarily described as flexion, extension, internal (medial) and external (lateral) rotation. Flexion and extension differ from true hingeing in that (a) the articular surfaces of the femor and tibia produce a variably placed axis of rotation during the flexion arc, and (b) when the foot is fixed, flexion includes corresponding coupled external (lateral) rotation. These conjunct rotations are due to the geometry of the articular surfaces and also due to the disposition of the associated ligaments. There is differential motion in the medial and lateral tibiofemoral compartments. Laterally there is considerable displacement of the femur on the tibia, with rolling as well as sliding at the joint surface, whereas medially for most of the flexion arc there is minimal relative motion of the femur and tibia, with the motion being almost exclusively one joint surface sliding on the other. In full flexion the lateral femoral condyle is close to subluxation off the posterior lateral

tibia. Medially there is only significant posterior femoral displacement beyond 120° by passive means. The menisci move with the femoral condyles, the anterior horns more than the posterior, and the lateral far more than the medial. The axial rotations have a smaller range than the arc of flexion and extension. These rotations are conjunct, and integral with flexion and extension.

Articular cartilage

Structure

Articular cartilage is a specialized avascular and neural connective tissue that provides covering for the osseous components of diarthrodial joints. It serves as a load bearing material, also absorbs impact and is capable of sustaining shearing forces. Cartilage is composed mainly of a high concentration of proteoglycans (aggrecans) entangled in a dense network of collagen fibres and a large amount of water. This tissue allows frictionless motion of the joint in which it absorbs and dissipates load. Articular cartilage is composed of a group of cells called chondrocytes which are responsible for the synthesis and maintenance of extracellular matrix. The chondrocytes are embedded within the negatively charged extracellular matrix and are subjected to mechanical and osmotic stresses. They act as sensors to these stimuli that alter their metabolism by responding to local physicochemical changes in microenvironment. [12,13]

Cartilage is divided into four zones with different functions:

Zone 1: the superficial zone

Zone 2: middle or transitional

Zone 3: deep or radial and

Zone 4: calcified cartilage zone without a sharp boundary between first three zones.

Superficial zone

The surface of the articular cartilage is covered with an adsorbed layer of hyaluronic acid which is essential for joint function. Beneath this superficial zone lie the elongated chondrocytes and abundant proteoglycans and collagen fibrils and poorly developed endoplasmic reticulum and golgi apparatus.

Transitional zone

This zone is thicker than the superficial zone and has well developed cellular apparatus and more amount of collagen.

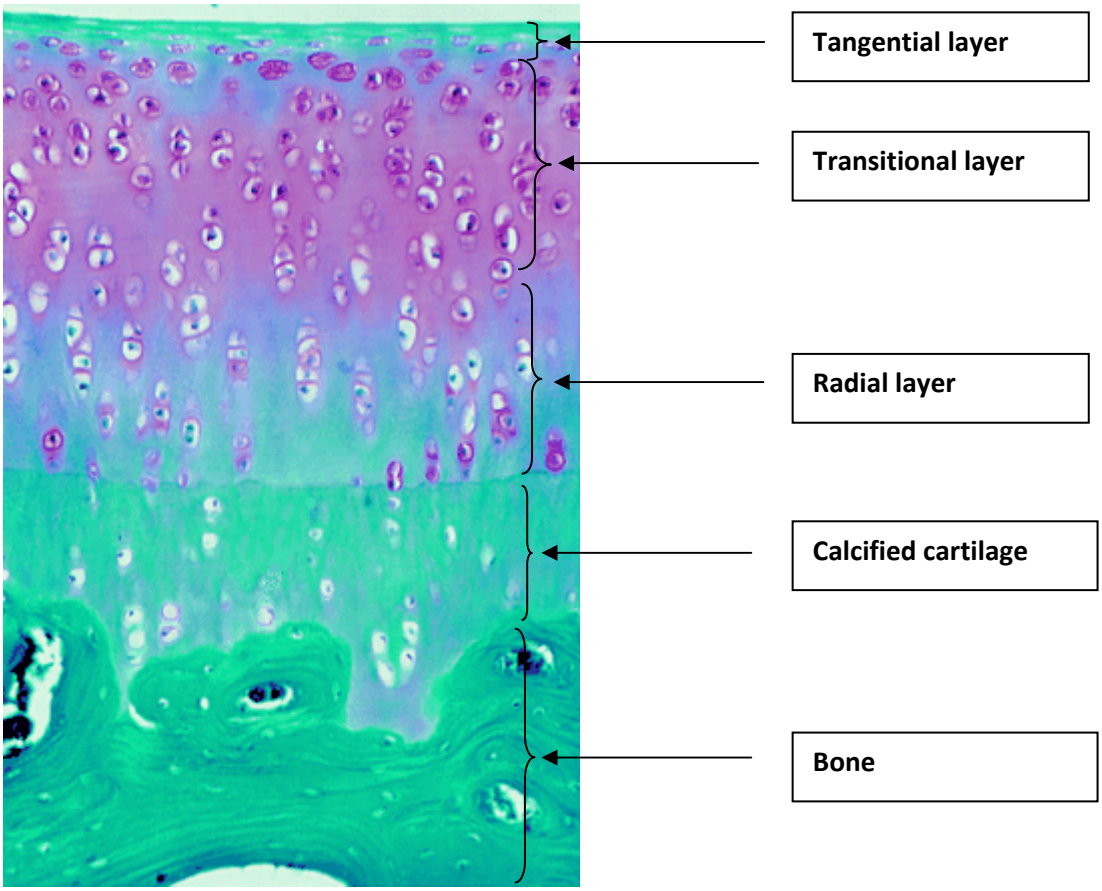
Radial zone

This is the largest zone in the cartilage and cells are similar to transitional zone. The matrix in this zone contains the highest amount of proteoglycan, largest collagen fibrils and lowest water content.

Zone of calcified cartilage

This zone contains irregular cells with calcium hydroxyapatite crystals. Calcified zone is continous with subchondral bone plate and together maintain the stability of the cartilage.

FIGURE – 3: ARTICULAR CARTILAGE H&E



PATHOPHYSIOLOGY OF OA

Arthritis and musculoskeletal diseases are the most common chronic diseases and cause physical disability worldwide. Osteoarthritis is a condition strongly associated with ageing and more prevalent in women. Osteoarthritis is defined as diseases that are as a result of both mechanical and biological events that destabilize normal coupling of degradation and synthesis of articular cartilage chondrocytes and extracellular matrix and subchondral bone. Although they may be initiated by multiple factors including genetic, developmental, metabolic and traumatic, it involves all tissues of diarthrodial joint. Ultimately osteoarthritic diseases are

manifested by morphologic, biochemical, molecular and biomechanical changes of both cells and matrix which lead to softening, fibrillation, ulceration, loss of articular cartilage, sclerosis and eburnation of subchondral cysts.[14]

CLASSIFICATION OF OSTEOARTHRITIS (OA)

Osteoarthritis has been classified by American College of Rheumatology into primary and secondary osteoarthritis based on the pathology.[4] Kellgran and Lawrence in 1957 also graded OA on the basis of radiographic findings.[15] This classification is useful in the management of OA where mild to moderate OA are treated symptomatically with analgesics and anti inflammatory drugs whereas severe OA require joint replacement.

A. Idiopathic- localized and generalized

B. Secondary

Post traumatic

Congenital or developmental diseases

Localized (hip dysplasia)

Generalized (chondroplasias)

Other bone and joint disorders (avascular necrosis)

C. Other diseases

Endocrine diseases (acromegaly, hyperparathyroidism)

TABLE – 1: KELLGRAN AND LAWRENCE RADIOGRAPHIC GRADING SYSTEM FOR OSTEOARTHRITIS

GRADE	CLASSIFICATION	DESCRIPTION
0	Normal	No features of OA
1	Doubtful	Minute osteophyte, doubtful Significance
2	Minimal	Definite osteophyte, unimpaired joint space
3	Moderate	Moderate dimunition of joint Space
4	Severe	Joint space greatly impaired with sclerosis of subchondral bone

TABLE – 2: CROFTS MODIFICATION OF KELLGRAN AND LAWRENCE GRADING SYSTEM (CROFT GRADE)

GRADE	DESCRIPTION
0	No change
1	Definite osteophytes only
2	Joint space narrowing (JSN) only
3	Presence of two of the following: JSN, osteophytosis, subchondral sclerosis (of >5mm), cyst formation
4	Presence of three of the following: JSN, osteophytosis, subchondral sclerosis of >5mm, cyst formation
5	Same as grade 4, but with deformity of femoral head

ETIOPATHOGENESIS OF OSTEOARTHRITIS

Osteoarthritis is a complex of interactive degradative and repair process in cartilage, bone and synovium with secondary components of inflammation. Currently two concepts of osteoarthritis pathways are present. First involves fundamentally defective cartilage with properties directly or indirectly leading to osteoarthritis. Thereby a matrix of cartilage fails under normal loading of the joint. The second cause of osteoarthritis is based on the concept of major physical forces causing damage to normal articular cartilage matrix. Two subpathways are involved in this. Initially there is direct injury to the matrix. Secondly chondrocytes embedded in the matrix are injured by the same forces. Recent research implicates enzymatic breakdown of the cartilage as a cause for disease progression.[16]

RISK FACTORS:

A. Genetic factors

Sex, inherited disorders of type II collagen mutations.

B. Non genetic host factors

Increasing age, overweight, diet, depletion of female sex hormones, developmental and acquired bone and joint diseases, previous joint surgery.

C. Environmental factors

Occupational and physical demands of work.

A. Genetic Factors

i. Gender

Under the age of 50, men have a higher prevalence and incidence than women. However once over 50, women have a higher overall prevalence and incidence than men. This difference tends to become less marked after age of 80. [18]

ii. Chromosomal mutations

Many genes have been linked to osteoarthritis. There is most concordance with chromosome 2q, 4 and 16. The defective genes are often coding for structural proteins of extracellular matrix of joint and collagen proteins. [19]

B. Non genetic factors

i. Age

The normal ageing process is thought to cause increased laxity around joints, reduced joint proprioception, cartilage calcification and reduced chondrocyte function all leading to a propensity for osteoarthritis. The Framingham study found that 27% of those aged 63 to 70 had radiographic evidence of knee osteoarthritis increasing to 44% in over 80 age group. [20]

ii. Obesity

This is the strongest modifiable risk factor. 3-6 times the body weight is transferred across the knee joint during walking. Being overweight at an average age of 36-37 is a risk factor for developing knee osteoarthritis in later life. Losing 5kg of weight reduced the risk of symptomatic knee osteoarthritis in women by 50%.[21]

iii. Diet

People having lower Vitamin C and Vitamin D blood levels have a threefold risk of progression of knee osteoarthritis. [22]

iv. Trauma or surgery of the knee joint

Any injury or operative procedure on the knee joint can weaken ligaments leading to decreased stability of joint. [23]

C. Environmental factors

i. Occupation

Mechanical stress related to occupation is implicated in induction of osteoarthritis in various studies. Occupational knee bending appears to play a significant role in the development of osteoarthritis in various occupations like manual labourers when they continue to use joints even after muscular exhaustion. [24]

ROLE OF BIOMECHANICAL FACTORS

Degeneration of articular cartilage, subchondral bone sclerosis and remodelling are established hallmarks of osteoarthritis. Since knee joint meniscus is a weightbearing tissue which has important mechanical role in normal joint function its mechanical failure results in imposition of abnormally high contact stress on articular cartilage leading to degeneration of cartilage. The exact mechanism of this remains unknown. Chondrocytes are capable of sensing changes in the mechanical environment and normally secrete an extracellular matrix to protect it from injury. Under the influence of mediators like prostanoids, cytokines such as interlukin 1b or TNF alpha, resorption of this extracellular matrix takes place.

ROLE OF BIOCHEMICAL FACTORS

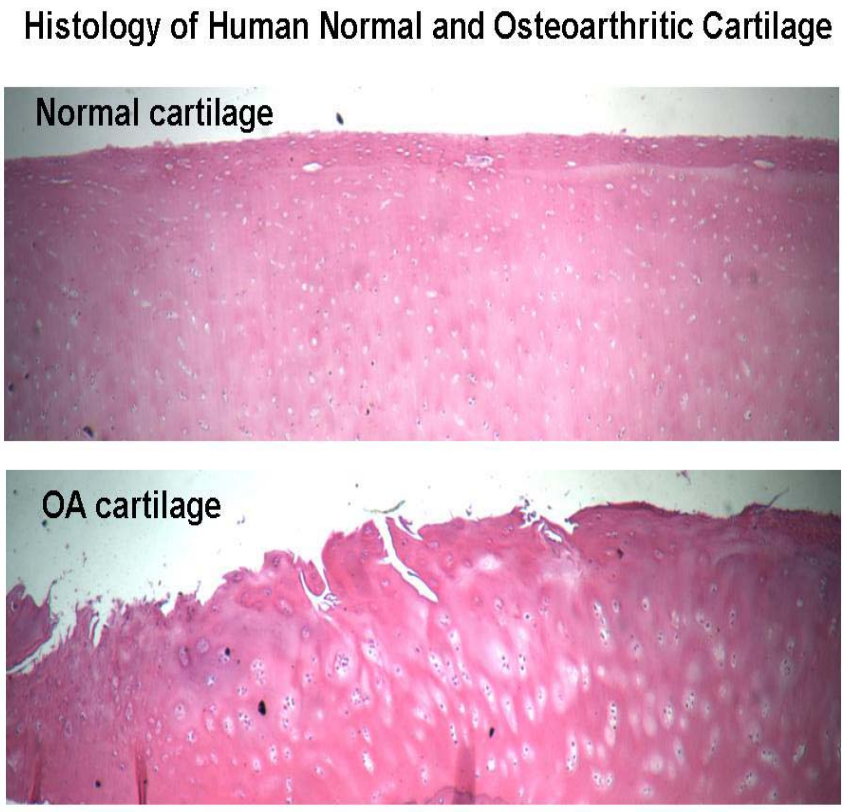
Osteoarthritis is a disease characterized by degeneration of articular cartilage. Biochemical changes in osteoarthritis affect several cartilage components including its major matrix constituents proteoglycan aggregates (aggrecan) and collagens which bring about breakdown of the cartilage matrix, leading to development of fibrillation, fissures, appearance of gross ulcerations and disappearance of full thickness surface

of joint. This is accompanied by hypertrophic bone changes with osteophyte formation and subchondral plate thickening.[25]

CHANGES IN ARTICULAR CARTILAGE

The aggrecans in the matrix are the first to be affected and they are progressively depleted with the severity of disease. In OA cartilage, chondrocytes synthesize proteases that cleave proteoglycan monomer releasing fragments which rapidly diffuse from cartilage into synovial fluid. The newly synthesized aggrecan has a composition similar to juvenile cartilage. In OA as the disease progresses the chondrocytes are unable to compensate for proteoglycan loss even in the presence of increased synthesis.[12,26]

FIGURE – 4:



Evolution of osteoarthritis disease

A. Stage 1- Proteolytic breakdown of cartilage matrix

B. Stage 2- Fibrillation and erosion of cartilage surface with release of matrix molecule breakdown products into synovial fluid

C. Stage 3- Phagocytosis of cartilage matrix breakdown products and other materials by synovial macrophages induces a chronic inflammatory reaction of synovium thereby producing local synthesis of proteases and proinflammatory cytokines such as IL-1, IL-6 and TNF-α. Proteases and cytokines released by synovium diffuse through synovial fluid and into cartilage induce additional cartilage breakdown by direct macromolecule proteolysis and by stimulation of cytokine secretion by chondrocytes to increase synthesis of proteases. In addition to degeneration of articular cartilage OA involves changes in surrounding bone.[16]

CLINICAL FEATURES

SYMPTOMS[16]

1. **Pain**: It is the earliest symptom in osteoarthritis. It occurs intermittently in the beginning but becomes constant over months or years. Initially it is a dull type of pain and starts on activity after a period of rest but later becomes cramp like and comes after activity.

2. **Stiffness**: This is the second most common symptom after pain. Initially it is due to pain and muscle spasm but later capsular contracture and incongruity of the joint surface contribute to it. Stiffness is experienced after sitting or squatting for sometime resulting in difficulty in straightening the involved knee called as ‘gelling’.

3. **Other symptoms** include feeling of instability of the joint or ‘giving away’ and ‘locking’ resulting from loose bodies and frayed menisci.

SIGNS

1. **Deformity** - Varus is the most common deformity associated with degenerative osteoarthritis of knee.

2. **Swelling** - Bony swelling may occur at joint margins due to osteophyte formation. Effusion due to synovitis may also manifest as swelling. This may be associated with local warmth.

3. **Crepitus**- On moving the patella over the underlying femoral condyles crepitus is felt and is described as patellofemoral grating.

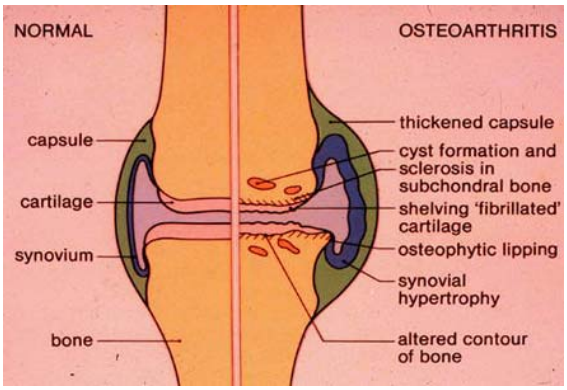
4. **Tenderness** in the retropatellar area and medial and lateral joint line is commonly elicited.

5. **Terminal limitation of joint movement** occurs due to pain on movement.

6. Quadriceps muscle weakness may be present.

7. Subluxation detected on ligament testing.

FIGURE – 5: DIAGRAM SHOWING NORMAL AND OSTEOARTHRITIC CHANGES IN KNEE JOINT



DIAGNOSIS AND MANAGEMENT

The knee joint is frequently affected by primary osteoarthritis and the commonest investigation done for diagnosis is x ray of knee joint.[15,27]

FIGURE – 6: LATERAL AND AP VIEWS OF MILD OA

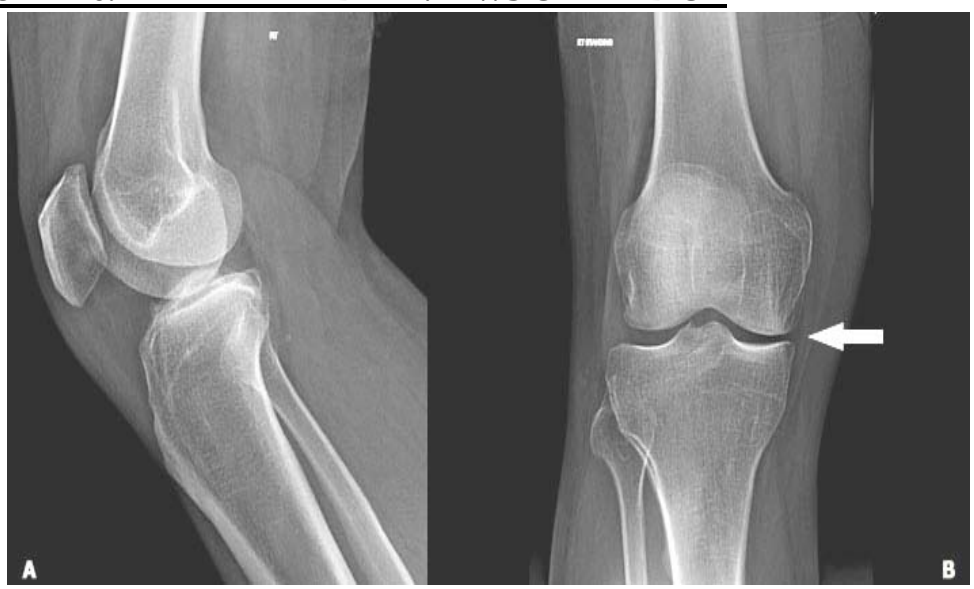


FIGURE – 7: SEVERE OA- AP AND LATERAL VIEW

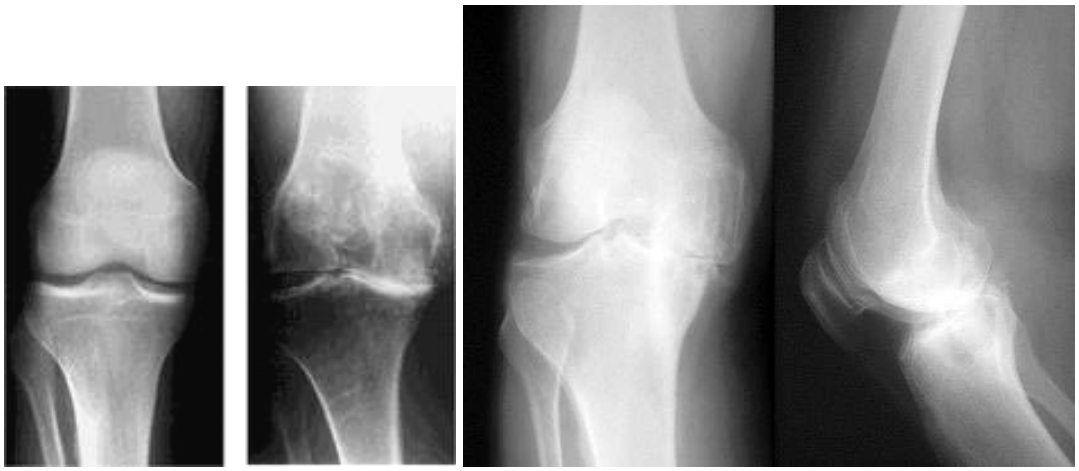


TABLE – 3: RADIOLOGICAL FINDINGS IN OA AND THEIR CAUSES

Radiologic findings	Causes
Narrowing of joint space	Articular cartilage formation
Subchondral bony sclerosis	New bone formation
Marginal osteophyte formation	Proliferation of cartilage and bone
Bone cysts and bony formation	Subchondral microfractures

MANAGEMENT OF OSTEOARTHRITIS

The main objectives in the management of OA are to reduce symptoms, minimize functional disability and limit progression. These goals can be reached through a pyramidal treatment approach. There are three basic modalities of treatment which includes non -pharmacological, pharmacological and surgical treatment.[28]

NON PHARMACOLOGICAL TREATMENT

A. Patient education and support

This treatment modality is well recognized and included in both American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) recommendations. The content of the education program should include information concerning pathophysiology, clinical presentation, and natural course of the disease and also the expected results from the different treatment modalities. Patients should be made aware of exercises which will help to reduce the development of osteoarthritis.[29]

B. Physical measures

There are a variety of physical modalities that can be used to relieve pain, reduce stiffness and limit muscle spasm while strengthening the para articular structures to provide improved joint support. Physical measures may be subdivided into exercise including range of motion and strengthening exercises of concerned muscle groups, thermal modalities, transcutaneous electrical nerve stimulation (TENS), ultrasound, diathermy and other analgesic modalities like acupuncture. Quadriceps strengthening exercises are highly beneficial in knee osteoarthritis and this effect is likely the result of an increase in joint stabilizing and shock absorbing properties of periarticular muscles.

Medial taping of the patella has been advocated for patients with osteoarthritis of patellofemoral component of knee. Knee braces will be useful in patients with tibiofemoral disease. Walking ability and pain in early medial compartment osteoarthritis of knee can be improved by use of a lateral heel wedged insole. All these supports and devices will allow the patient more activities, improve compliance and functional independence.[25]

PHARMACOLOGICAL TREATMENT

A. SYMPTOMATIC THERAPY

1. SHORT ACTING

Topical agents

Non- steroidal anti inflammatory drugs

Acetaminophen

Narcotic analgesics

2. LONG ACTING

Intraarticular depot corticosteroids

Intraarticular hyaluronic acid

Oral chondroitin sulfate

Glucosamine sulfate

Intra articular orgotein

Diacerin

Avocado /soy non- saponifiables

B. DISEASE MODIFYING AGENTS

Tetracyclines

Pentosan polysulfate and glycosaminoglycan furic polysulfuric acid (GAGPS)

Growth factors and cytokines inhibitors

SURGICAL TREATMENT

Osteochondral grafts and stem cell transplantation

Lavage and joint debridement

Osteotomy

Joint replacement

Topical agents

The two most widely used topical agents are preparations containing capsaicin, methyl salicylate and those containing NSAIDs like diclofenac and ibuprofen. Capsaicin is an alkaloid derived from seeds of night shade family of plants. They act by a counter irritant mechanism. On topical application, capsaicin provokes the release of substance P by peripheral nerves which is responsible for transmission of nociceptive stimuli from periphery to CNS and also prevent its reaccumulation.[30] Diclofenac has an analgesic and anti inflammatory property and achieves high concentrations in synovial fluid even after topical application .[31]

Non-steroidal anti-inflammatory drugs

Oral NSAIDs like ibuprofen which are COX inhibitors are widely used for the treatment of OA. There is invitro and invivo evidence pointing to a possible beneficial structural effect to the use of NSAIDs in OA. Due to the potential side effects of

NSAIDs, gastrointestinal (with conventional NSAIDs) and cardiovascular (with coxibs) the current recommendation is to take these drugs for the shortest period of time in the lowest dose.[32]

Narcotic analgesics

Codeine and propoxyphene have been used effectively in patients with OA, especially in combination with acetaminophen. Tramadol is also used either alone or with acetaminophen. All these agents have potential side effects including nausea, dizziness, somnolence and constipation which might be of clinical relevance, particularly in elderly patients.[33]

Intra-articular corticosteroids

Single or repetitive injections of corticosteroids can be used to reduce the inflammation and subsequent pain in OA. Drugs used for intraarticular injections are commonly prednisolone acetate and methyl prednisolone. Side effects include skin atrophy and dermal depigmentation especially with long acting preparations and if injected into the soft tissues. Infection is a rare complication. Repeated injections can also accelerate degradation of the joint .[14]

Hyaluronic acid

Viscosupplementation refers to intra articular injection of hyaluronic acid a high molecular weight polysaccharide which is a major component of synovial fluid and cartilage in order to relieve pain and improve function. The molecular weight and amount of hyaluronic acid decrease in OA. A course of 3-5 injections at monthly intervals provides some relief.[34]

Chondroitin sulfate

Chondroitin sulfate is a macromolecule that provides the framework for collagen formation. Various studies have demonstrated that chondroitin sulfate decreases the progression of joint destruction and improves function.[16]

Glucosamine sulfate

Glucosamine sulfate is commercially derived from chitin from exoskeleton of shrimps and crabs. It has been proved to stop the progression of cartilage degradation and possibly stimulate production of new cartilage but the exact mechanism is not known.[35]

Intraarticular orgotein

Orgotein is the pharmaceutical form of bovine enzyme Cu-Zn superoxide dismutase. Intra articular injection of orgotein has been found to reduce the symptoms in OA due to its anti inflammatory properties.[25]

Diacerein

Diacerein is a rhein derivative used for the treatment of OA. In vitro studies have demonstrated that diacerein can inhibit interleukin -1 and reduce cartilage breakdown and development of cartilage lesions. Diacerein has been implicated in the regulation of transforming growth factor (TGF) β1 and β2 in articular chondrocytes.[36]

Avocado/ Soybean nonsaponifiables (ASU)

ASU is an unsaponifiable extract of avocado and soybean considered more as a dietary supplement. Studies in vitro have suggested that it has inhibitory properties against IL-1 and can stimulate collagen synthesis in chondrocytes.[25]

Tetracyclines

Doxycycline can be used as a potential disease modifying agent based on the fact that this drug inhibited degradation of type IV collagen in invitro studies. It also inhibited mRNA for inducible nitric oxide synthase, an enzyme present in large quantities in OA cartilage, the activity of which results in secretion of matrix metalloproteases by chondrocytes .[16, 37]

GAGPS, an extract of bovine tracheal and bronchial cartilages contains synthetically oversulfated chondroitin 6 sulfate and stimulates cartilage synthesis. **Pentosan polysulfate**, a derivative of beech-wood hemicelluloses, is a heparinoid similar to GAGPS, is also being tried as potential disease modifying agent for OA.[25,38]

Growth factors and cytokines

Polypeptide growth factors are areas of potential intervention. They play a major role in the regulation of articular cartilage, the important ones being insulin like growth factor (IGF-1) and transforming growth factor (TGF-β). Use of cytokine inhibitors like intraarticular injection of IL-1 receptor antagonist anakinra, has been found to be effective.[16]

Osteochondral grafts where the cartilage defect area and the underlying bone is replaced with a matching graft and stem cell transplantation have also been tried in OA.[25]

Lavage of the joint and joint debridement

Tidal irrigation or lavage of the joint removes the debris of cartilage and calcium phosphate crystals that may induce synovitis causing pain in OA. Arthroscopic debridement consists of smoothing rough, fibrillated articular and

meniscal surfaces, removing tibial spine osteophytes that interfere with the movements of the joint.[16, 28]

Osteotomy

Malalignment is an important structural factor for progression of disease. A specific indication for osteotomy is genu valgum in patients with mild to moderate tibiofemoral OA.

Joint replacement

Articular replacement or total knee arthroplasty (TKR) is the gold standard for providing pain relief and restoring function in OA. Total joint replacement is reserved for the most severe and recalcitrant forms of osteoarthritis. When other forms of treatment fail or when patients are unlikely to succeed with lesser therapies, the last option to treat defective cartilage is to replace all or part of the joint. In knee joint replacement, the worn out surfaces of the knee are resurfaced with metal and plastic, replacing the poorly functioning natural joint with new surfaces that slide together smoothly. The dysfunctional joint surface is removed and pain is relieved. Total knee replacement is considered a relatively routine surgery with a 95% success rate at 20 years.[27]

FIGURE – 8: RADIOGRAPHS SHOWING KNEE JOINT BEFORE (A) AND AFTER (B) JOINT REPLACEMENT

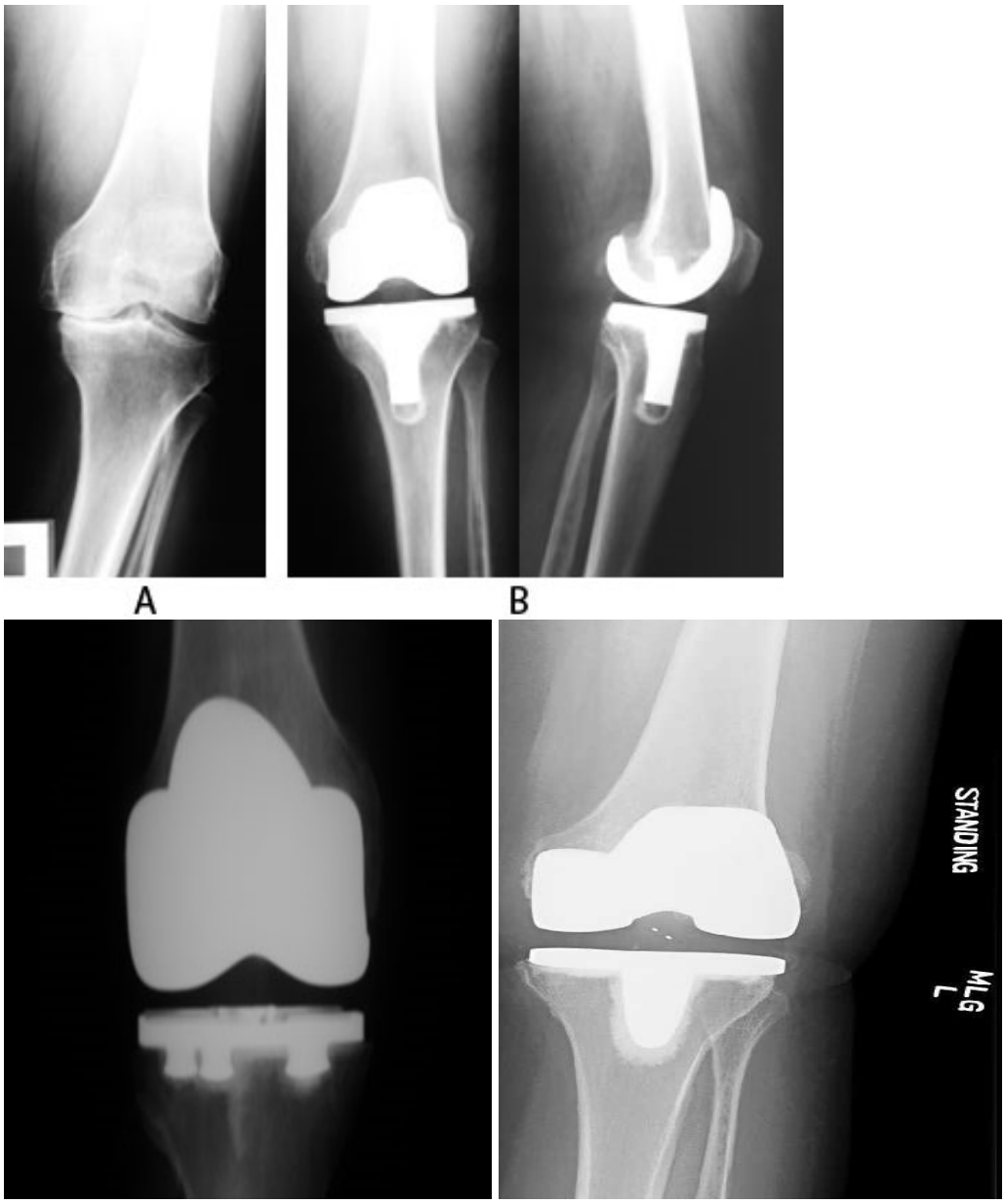
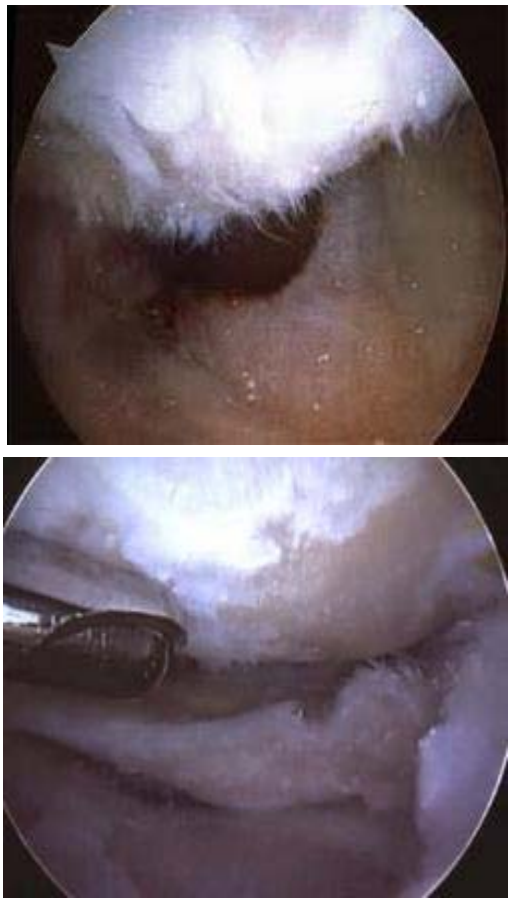


FIGURE – 9: ARTHROSCOPIC PICTURE OF NORMAL KNEE JOINT

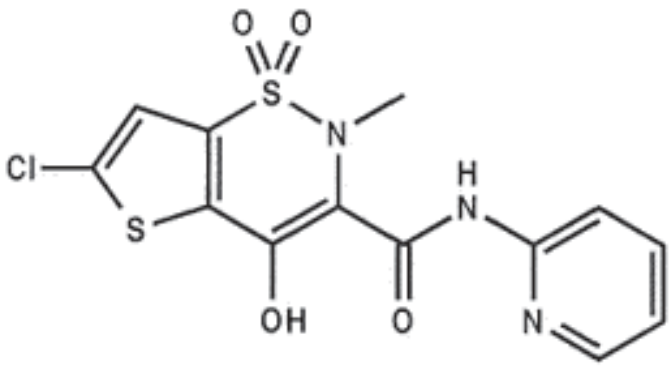
FIGURE – 10: ARTHROSCOPY PICTURE OF OSTEOARTHRITIC KNEE JOINT SHOWING DEGENERATIVE CHANGES



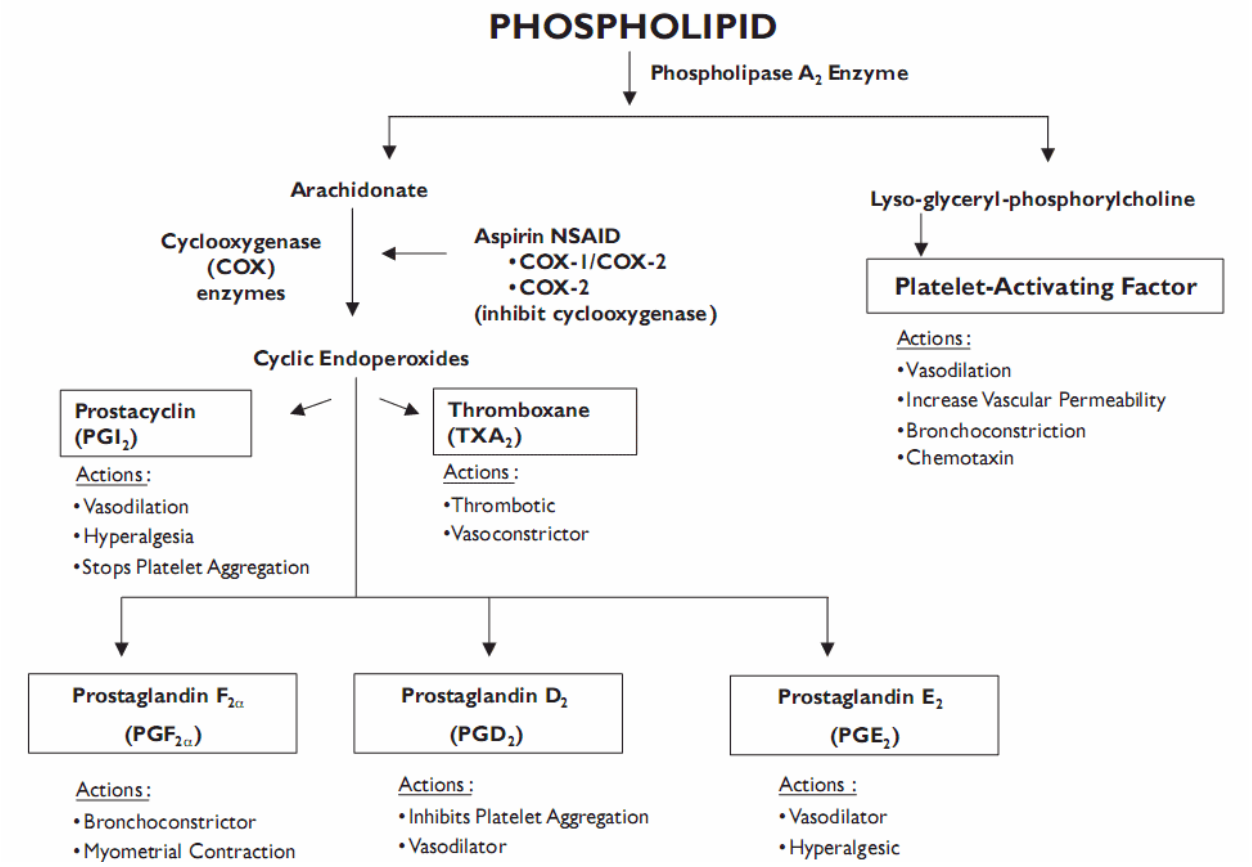
LORNOXICAM

Lornoxicam, a congener of tenoxicam, is a new NSAID belonging to the oxicam class. It is a strong analgesic and anti-inflammatory drug as compared to other NSAIDs. Its analgesic activity is comparable to that of opioids. Lornoxicam combines the high therapeutic potency of oxicams with an improved gastrointestinal toxicity profile as compared to naproxen probably due to the short half-life of lornoxicam as compared to other oxicams. It has good antiinflammatory properties in a range of painful and/or inflammatory conditions, including postoperative pain and RA.[39,40] Lornoxicam has shown protective effects on the development of myocardial infarction in rats under conditions of ischemia and ischemia-reperfusion.[41] Recently, an experimental study in mice has demonstrated its protective effects against herpetic stromal keratitis (HSK), presumably through the down-regulation of nuclear factor kappa B (NF-kappa B) activation. Lornoxicam treatment significantly decreased the incidence of recurrent HSK, attenuated the corneal opacity scores, and also effectively suppressed both NF kappa B activation and TNF-alpha expression.[42]

Structure of Lornoxicam



Mechanism of action[43]



PGI_2 and PGE_2 are important mediators of inflammation causing effects like hyperalgesia, increase in migration of leucocytes, increased capillary permeability and release of cytokines.

Like all NSAIDs, lornoxicam acts by inhibiting the metabolites of COX branch of arachidonic acid pathway. It inhibits both isoforms (COX-1 and COX-2) in the same concentration range.

COX-1 is a constitutive enzyme expressed in many cells as a 'house keeping enzyme' and provides homeostatic prostaglandins. COX-2 is an inducible enzyme, which is expressed at the onset of inflammation in many cell types involved in inflammatory responses. Lornoxicam differs from other oxicam compounds in its potent inhibition of prostaglandin biosynthesis, a property that explains the particularly pronounced efficacy of the drug. Prostaglandins are involved in all phases of inflammatory events

including fever, pain, increased capillary permeability and cytokine release. Physiological functions like intestinal motility, vascular tone, renal function, gastric mucous secretion are also interfered with .[44] It also acts by inhibition of spinal nociceptive processings, elevation of plasma levels of dynorphin and ß endorphin. In vitro tests have shown that lornoxicam also inhibited the formation of nitric oxide.[45,46] Nitric oxide is involved in the promotion of cartilage catabolism in OA through various mechanisms including induction of synovial inflammation and inhibition of synthesis of cartilage macromolecules such as aggrecans. Lornoxicam has also shown marked inhibitory activity on endotoxin induced IL-6 formation in monocytes, with less activity on TNF alpha and IL-1a.[47]

Pharmacokinetics

Absorption

Lornoxicam is absorbed rapidly and almost completely after oral administration. Peak plasma concentration is attained in 2.5 hrs when given orally and almost 20-25 minutes in case of intramuscular administration. Food reduces the absorption of the drug. The absolute bioavailability of lornoxicam is 90-100%.[48]

Distribution

Almost 99% is protein bound exclusively to albumin. And has a low volume of distribution (0.2L/kg). It readily penetrates perivascular interstitial spaces including synovial fluid the proposed site of action in chronic inflammatory arthropathies. Lornoxicam synovial fluid: plasma area under curve (AUC) ratio is 0.5, after administration of 4 mg twice daily.[49] The safety of lornoxicam in pregnancy and lactation has not been established.

Elimination

Lornoxicam is found in the plasma in unchanged form and as its hydroxylated metabolite, 5'hydroxy lornoxicam which does not have any pharmacological activity.[48,50] Cytochromal enzyme CYP2C9 has been shown to be the primary enzyme responsible for the biotransformation of the lornoxicam to its major metabolite, 5'-hydroxylornoxicam which does not undergo enterohepatic circulation. [51] Approximately 2/3 is eliminated via the liver and 1/3 via the kidneys as inactive substance. Unlike other oxicams, it has a relatively short plasma half-life (3 to 5 hours). Glucuroconjugated metabolites are excreted in urine and faeces with a half-life of about 11 hours.

Dosage and Route

It is available in oral and intramuscular and intravenous formulations. Its oral dose is 4mg thrice daily or 8mg twice daily and intramuscular and intravenous dose is 8mg.[52]

Therapeutic uses

Analgesia: Acute and Chronic Pain

Lornoxicam has been shown to produce dose related analgesia. 16 mg and 32 mg were significantly superior to 4 mg with respect to pain relief. Hence it is a useful agent in the treatment of postoperative pain and other acute traumatic painful conditions such as fractures.[53] The duration of analgesic effect of lornoxicam is approximately 4.5 hrs with maximum pain relief occurring at approximately 2 hrs. In osteoarthritis lornoxicam in the dose of 8mg BD significantly reduced pain and improved physical functions.[3] The analgesic effects of intramuscular lornoxicam is not immediate as some time is required to inhibit the arachidonic acid pathway, thus pre operative administration may be more appropriate for those requiring procedures

under 2 hrs. Lornoxicam is found effective in acute sciatica[54] , lumbosciatica and chronic low back pain.[39] Lornoxicam can decrease the opioid requirement when used as an adjunctive analgesic in patients with cancer pain because of its ability to cause endogenous release of dynorphin and beta endorphins.[53,55,56] Lornoxicam also is an alternative to morphine when administered by patient controlled analgesia for treatment of moderate to severe pain after lumbar discectomy.[39] Lornoxicam decreases the number of headache episodes and also reduces the analgesic intake in migraine attacks.[55]

Anti Inflammation

In osteoarthritis, 8mg twice daily improves pain and functional disability. Lornoxicam belongs to a group of acidic antipyretic analgesics. Accumulation of these substances in the synovial fluid contributes to their anti inflammatory effect. In painful inflammatory conditions like OA, the capillaries in the inflamed tissue are damaged and plasma proteins along with the drug are discharged into the extravascular space. The reduced pH in inflamed tissues also contributes to increased entry of drug into extravascular space. In a study by Peter et al lornoxicam was compared with rofecoxib(selective COX- 2 inhibitor) .It was found that the analgesic and anti inflammatory effects of lornoxicam was superior to those of rofecoxib in patients with osteoarthritis.[57] Another study by Kidd et al showed that lornoxicam 4mg TDS or 8mg BD was as effective as diclofenac 50mg TDS in patients with OA.[58]

Other conditions where lornoxicam has been found to be useful are ankylosing spondylitis and Rheumatoid arthritis.[59] Anti inflammatory effects of lornoxicam include prevention of the degenerative bone loss seen in chronic inflammation, by inhibiting polymorphonuclear leucocyte migration effect.[60]

Other effects of lornoxicam include inhibition of release of superoxide from polymorphs and inhibition of the release of platelet derived growth factor (PDGF) from the platelets, both of which are involved in the pathogenesis of RA. Thus lornoxicam can have protective effects in the management of RA. Lornoxicam also stimulates proteoglycan synthesis suggesting possible reparative effects in RA. [61]

TABLE – 4: ADVERSE EFFECTS [39]

General	Headache, dizziness, somnolence, changes in appetite, increased sweating, oedema, allergic reactions (pruritus, flushing, etc.), debility.
Gastrointestinal	Abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, flatulence, dysphagia, constipation, gastritis, dry mouth, stomatitis, gastroesophageal reflux, peptic ulceration with or without bleeding, oesophagitis, haemorrhoidal or rectal bleeding.
Haematological	Anaemia, ecchymosis, prolonged bleeding time, thrombocytopenia.
Eyes	Conjunctivitis, vision disorders.
Hepatic	Increased transaminases.
Musculoskeletal	Cramps in leg, myalgia.
Respiratory	Dyspnoea, symptoms of irritation in upper respiratory tract.
Vascular	Palpitations, tachycardia, changes in blood pressure.

Prostaglandins play an important role in gastrointestinal mucosal protection by strengthening the mucosal barrier for acid and inhibiting gastric acid secretion. Thus the adverse effects of the acidic NSAIDs are mainly because of inhibition of prostaglandin production and thereby interrupting the normal protection and also due to increased gastric acid secretion. The gastric side effects range from mild dyspepsia and heartburn to ulceration and hemorrhage. Risk factors for NSAIDs induced gastropathy include smokers, old age, history of peptic ulcer and those receiving oral corticosteroids and oral anticoagulants.[62,63]

TABLE – 5: DRUG INTERACTIONS [64-66]

Warfarin and anticoagulants	Prolong the bleeding time
Cimetidine	Higher plasma concentration of lornoxicam
Lithium	Increase in the lithium peak concentration and thus a possible increase in adverse events
Digoxin	Decreased renal clearance of digoxin
Loop diuretics	Decreased efficacy of loop diuretics
Methotrexate	Increased serum concentration of high dose methotrexate
Sulphonylureas	May increase the hypoglycaemic effect
Cyclosporine	Increased renal toxicity
ACE inhibitors (ACEI)	Effect of ACEI may decrease → risk of acute renal insufficiency

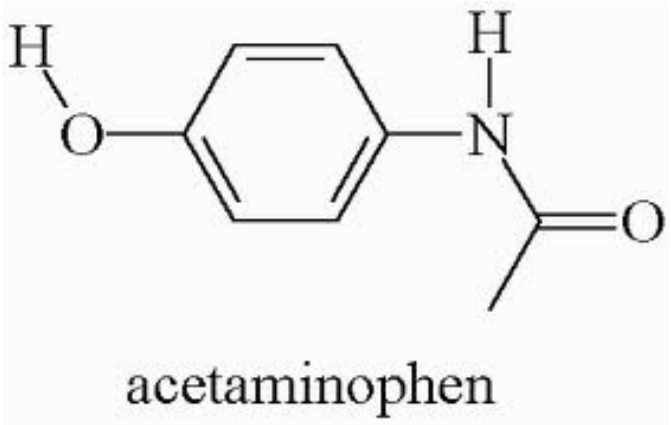
Table – 6: CONTRAINDICATIONS [39,40]

Allergic to lornoxicam or any of its excipients
H/o hypersensitivity reactions (urticaria or angioedema) to other NSAIDs
H/o GI bleeding, cerebrovascular bleeding
Bleeding and coagulation disorders
Active peptic ulceration or h/o recurrent peptic ulceration
Severe liver or renal impairment
Thrombocytopenia
Severe or uncontrolled cardiac failure
Pregnancy and lactation

ACETAMINOPHEN

Acetaminophen or paracetamol is a para-amino phenol derivative, widely used as an analgesic and antipyretic for relief of headaches and minor aches and fever.

STRUCTURE OF ACETAMINOPHEN



Mechanism of action

The main mechanism of action of acetaminophen is by inhibition of cyclooxygenase (COX). While it has analgesic and antipyretic properties comparable to that of aspirin and other NSAIDs, its peripheral anti inflammatory activity is usually limited by several factors one of which is high level of peroxides present in inflammatory lesions.

Antipyretic effects

Endogenous pyrogens produced by leukocytes cause an elevation of prostaglandin E in the cerebrospinal fluid.[67] Acetaminophen reduces fever by blocking the formation and release of prostaglandins in the central nervous system and inhibiting the action of endogenous pyrogens at the hypothalamic thermoregulatory centers.[68-71]

Analgesic action

Acetaminophen is believed to act primarily in the central nervous system, although there are many proposed theories as to the precise mechanism of action. Acetaminophen is thought to produce analgesia by inhibiting prostaglandin synthesis centrally and elevating the pain threshold.[72-74] Recent research suggests that the clinical pharmacologic characteristics of acetaminophen may be the result of its ability to inhibit a specific site on the prostaglandin H2 synthase (PGHS) molecule, the 2 isoforms of which, PGHS1 and PGHS2, are also referred to as COX-1 and COX-2.[72] In vitro assays and studies in human volunteers have demonstrated that acetaminophen inhibits COX-2 activity.[75,76] PGHS has 2 active sites: the COX site and the peroxidase (POX) site.[72] Acetaminophen acts as a reducing cosubstrate at the POX site, while NSAIDs noncovalently bind at the COX site, obstructing the entry of arachidonic acid. Acetaminophen has a highly variable capacity to inhibit prostaglandin synthesis by different cell and tissue types.[72,75,76] The cellular selectivity of acetaminophen is thought to derive from sensitivity to the ambient peroxide levels of various cell types. The central analgesic and antipyretic effects of acetaminophen may be exerted through PGHS inhibition within vascular endothelial cells and neurons, where peroxide concentrations are low. In activated leukocytes and platelets, however, where peroxide concentrations are high, acetaminophen is prevented from affecting inflammation and platelet thrombosis.[72]

Another recently proposed hypothesis suggests that actions of acetaminophen is mediated by indirect activation of cannabinoid CB1 receptors,[77-79] as evidenced by complete inhibition of the analgesic effects of acetaminophen in the presence of CB1-receptor antagonists. Other suggested mechanisms of action include

modulation of the serotoninergic and opioid systems,[80] inhibition of nitric oxide generation,[81] and hyperalgesia induced by substance P.[82]

Pharmacokinetics

Absorption

Food Effects: Although maximum concentrations of acetaminophen are delayed when administered with food, the extent of absorption is not affected. Acetaminophen can be taken independently of meal times.

Immediate Release: Oral acetaminophen is rapidly and almost completely absorbed from the gastrointestinal tract primarily in the small intestine, with negligible absorption occurring in the stomach.[83] This absorption process occurs by passive nonionic diffusion. The relative bioavailability ranges from 85% to 98%.[84]

Extended Release: Each bilayered acetaminophen extended release 650 mg caplet or gelcap contains 325 mg of immediate-release acetaminophen in one layer and 325 mg of acetaminophen in a matrix formulation designed to release slowly in the other layer. The average maximum plasma concentrations occur within 0.5 to 3 hours following ingestion and range from 6.9 to 14.1 mg/mL among individuals.[85]

Distribution

Acetaminophen is widely distributed throughout most body fluids except fat. The apparent volume of distribution of acetaminophen is approximately 0.7 to 1.0 L/kg in children and adults.[86,87] A relatively small proportion (10% to 25%) of acetaminophen is bound to plasma proteins.[88,89] The sulfate and glucuronide metabolites do not bind to plasma proteins even at relatively high concentrations.[90]

Placental Barrier: When given to the mother in therapeutic doses, acetaminophen crosses the placenta into fetal circulation as early as 30 minutes after ingestion, with similar serum concentrations in the mother (5.9 μg/mL) and fetus (7.9 μg/mL).[91]

Breast Milk: Maternal ingestion of acetaminophen in recommended analgesic doses does not present a risk to the nursing infant. Amounts in milk range from 0.1% to 1.85% of the ingested maternal dose.[92-94]

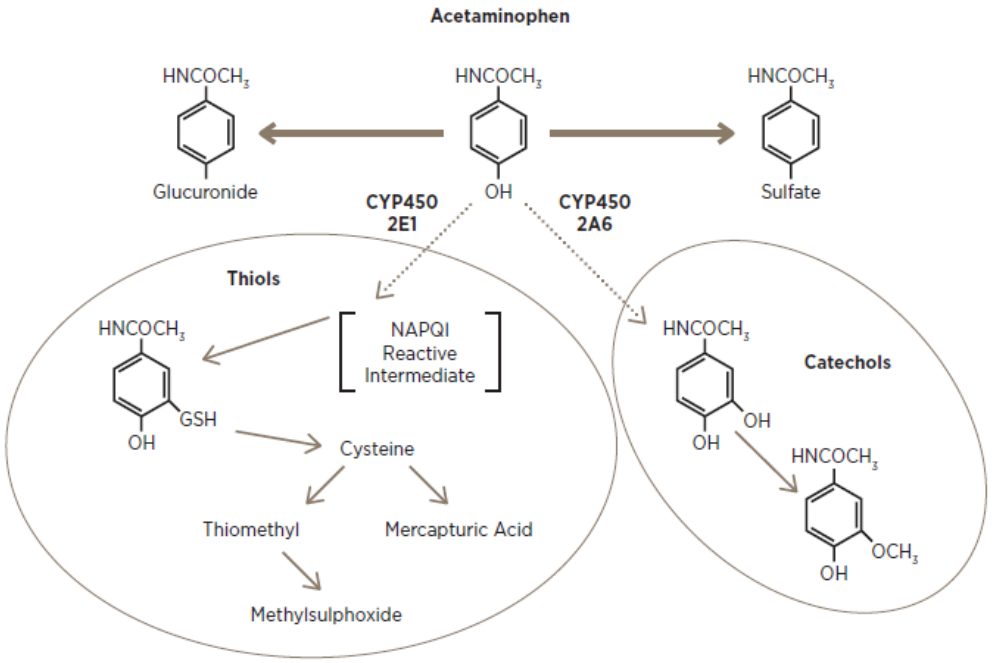
Elimination

Acetaminophen is primarily metabolized in the liver and involves 3 main pathways: conjugation with glucuronide; conjugation with sulfate; and oxidation via the cytochrome P450 (CYP450) enzyme pathway. The oxidative pathway forms a reactive intermediate, *N*-acetyl-*p*-benzoquinone imine (NAPQI), which is detoxified by conjugation with glutathione to form inert cysteine and mercapturic acid metabolites.[95] The principal CYP450 isoenzyme involved in vivo appears to be CYP2E1. Two additional minor pathways are involved in acetaminophen metabolism: hydroxylation to form 3-hydroxy-acetaminophen and methoxylation to form 3-methoxy-acetaminophen. These catechol metabolites are further conjugated with glucuronide or sulfate.[96,97] The metabolism of acetaminophen changes with age.[86] In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulfate. These glucuronide, sulfate, and glutathione derived metabolites lack biologic activity. Hepatic glucuronidation is relatively immature at birth. The sulfate conjugate predominates in premature infants, newborns, and young infants.[98-100]

Acetaminophen has a short t1/2 such that steady state is reached within 8 to 24 hours for almost all population groups, and accumulation is relatively low. The elimination t1/2 of acetaminophen in healthy adults is approximately 2 to 3 hours in

the usual dosage range.[101,102] It is about 1.5 to 3 hours in children, and about 1 hour longer in neonates, in cirrhotic patients,[103,104] and in some ethnic groups like Nigerians and Chinese.[89]

FIGURE – 11: METABOLISM OF ACETAMINOPHEN



Uses and Administration

Acetaminophen is given orally or as a rectal suppository for mild to moderate pain and for fever. It may also be given by intravenous infusion for the short-term treatment of moderate pain, particularly after surgery and of fever. It is often the analgesic or antipyretic of choice, especially in the elderly and in patients in whom salicylates or other NSAIDs are contra-indicated. Such patients include asthmatics, those with a history of peptic ulcer and children. Acetaminophen can be used in pregnancy.

The usual oral dose is 0.5 to 1 g every 4 to 6 hours up to a maximum of 4 g daily. It may also be given as suppositories in a rectal dose of 0.5 to 1 g every 4 to 6 hours, up to 4 times daily.

Acetaminophen is also given by intravenous infusion over 15 minutes; dosage may be calculated by weight - patients weighing over 50 kg, given single doses of 1 g every 4 or more hours, to a maximum of 4 g daily.[105]

Administration in children.

- 3 months to 1 year: 60 to 120 mg
- 1 to 5 years: 120 to 250 mg
- 6 to 12 years: 250 to 500 mg

These doses may be given every 4 to 6 hours when necessary up to a maximum of 4 doses in 24 hours.

Administration in renal impairment**:** In patients with a creatinine clearance of 30 mL/minute or less it is recommended that the interval between each intravenous paracetamol dose is increased to 6 hours.

Headache: Non-opioid analgesics such as acetaminophen, aspirin, and other NSAIDs are often tried first for the symptomatic treatment of various types of headache including migraine. These drugs given at the onset of symptoms can successfully treat an acute attack of migraine. However, absorption may be poor due to gastric stasis which is commonly present in migraine and so it is generally combined with a prokinetic agent like metoclopramide.[105]

Pain: Acetaminophen is used in the management of mild to moderate pain. It is of similar potency to aspirin, but with weak anti-inflammatory activity. Acetaminophen may also be used as an adjunct to opioids in the management of severe pain such as cancer pain. It is also the preferred choice for pain in children because of the association of aspirin with Reye's syndrome in this age group. In the treatment of rheumatic disorders, a weak anti-inflammatory effect limits the role of acetaminophen. However, it may be of benefit for simple pain control in rheumatoid

arthritis and ankylosing spondylitis, although these patients usually require the additional anti-inflammatory effects provided by NSAIDs.

Synovial inflammation is usually only a minor component of osteoarthritis, and paracetamol is generally recommended as first choice of treatment before NSAIDs are tried. ACR Guidelines for the Medical Management of Osteoarthritis, published in 1995 and updated in 2000, recommend acetaminophen in doses up to 4000 mg/day as a preferred firstline therapy in patients with osteoarthritis of the knee or hip. Based on the overall cost, efficacy, and toxicity profile of acetaminophen, the ACR Guidelines state that acetaminophen merits a trial as initial therapy .[4]

Guidelines published by EULAR recommend acetaminophen as the oral analgesic to try first for knee, hip, and hand osteoarthritis and if successful, acetaminophen maybe used as the preferred long-term oral analgesic because of its safety and efficacy profile.[106]

Acetaminophen has been shown in clinical trials to be superior to placebo in relieving the pain of osteoarthritis. Two studies conducted by Pincus and colleagues found acetaminophen 4000mg/day to provide superior pain relief when compared with placebo.[107]

In a 3-month, randomized, double-blind study comparing acetaminophen extended-release 3900 mg/ day and 1950 mg/day with placebo, the higher-dose regimen was found to be superior to placebo on measures of pain, physical function, and patient global assessment.[1] It is useful for the relief of acute low back pain.

ADVERSE EFFECTS

Adverse effects of paracetamol are rare and usually mild, although haematological reactions including thrombocytopenia, leucopenia, pancytopenia, neutropenia, and agranulocytosis have been reported. Skin rashes and other

hypersensitivity reactions occur occasionally. Hypotension has been reported rarely with parenteral use. Overdosage with paracetamol can result in severe liver damage and sometimes acute renal tubular necrosis.[105]

Prompt treatment with acetylcysteine or methionine is essential. Angioedema has also been reported. Fixed drug eruptions and toxic epidermal necrolysis have also occurred.[105]

Table – 7: DRUG INTERACTIONS

Metoclopramide	Accelerates gastric emptying and decreases peak concentration of acetaminophen
Anticholinergics(Propantheline,glycopyrolate)	Decrease gastric emptying and decrease rate of absorption
Alcohol	Increased hepatotoxicity
Ascorbic acid	Inhibits sulfate conjugation of acetaminophen
Isoniazid	Decreases the formation of toxic metabolite NAPQI
Oral contraceptives	Increase the clearance of acetaminophen
Anticonvulsants (Phenytoin, carbamazepine)	Chronic use increases risk of hepatotoxicity
Probenecid	Decreased clearance of acetaminophen

MATERIALS AND METHODS

A study of 120 cases of osteoarthritis of knee was done at R.L. Jalappa Hospital and Research Center, Kolar from Dec 2009 –May 2011.

Source of data

A total number of 120 patients were recruited for the study from the outpatient department of orthopedics, R L Jalappa Hospital, Tamaka, Kolar with clinical diagnosis of osteoarthritis of knee.

Data collection:

A proforma containing detailed information on each patient was prepared according to the protocol designed for the study. Informed consent was taken from all the patients included in the study. Ethical clearance was obtained from the institutional ethics committee.

Inclusion Criteria:

1. Age more than 40 years
2. Symptomatic Idiopathic OA having lasted for atleast 6 months
3. Associated with moderate knee pain requiring analgesics
4. Radiological evidence of OA
5. Morning stiffness of less than 30 minutes duration with crepitus on motion
6. Normal laboratory values like blood urea, serum creatinine

Exclusion Criteria:

1. History of surgery or trauma to the study joint
2. Active gastrointestinal diseases like peptic ulcer or hepatic disease
3. History of psychiatric illness
4. Secondary OA
5. History of acute inflammatory arthritis or pseudogout
6. Allergy to lornoxicam or acetaminophen

Eligible patients with mild to moderate knee pain secondary to osteoarthritis of knee were selected for treatment. Patients were randomized alternatively into two groups of sixty each with one group receiving Lornoxicam 8mg BD and the other group receiving Acetaminophen(ER) 650mg BD for 4 weeks.

At baseline, relevant data like clinical history were collected from patients and detailed examination of the patients was done including general physical examination, knee joint examination including inspection, palpation, range of movements and measurements. WOMAC osteoarthritis index was assessed at baseline. It is a subjective score consisting of pain, disability and loss of physical function scores. All the parameters including pain, stiffness and disability scores were graded on a scale of 0 to 4 depending on the severity as none to severe.

TABLE – 8: WOMAC SCORE

0	1	2	3	4
None	Mild	Moderate	Severe	Extreme

VAS scores of pain were also measured at the baseline. VAS scores were graded on a scale from 0 to 10 where 0 = no pain and 10 = worst possible pain According to the patients representations, pain was graded and compared at baseline and at each follow up visit. The severity was reported as follows: 0=no pain, 1 to 3 = mild pain, 4 to 6 = moderate pain and 7 to 10 = severe pain. Routine lab investigations like RBS, blood urea, serum creatinine, liver function tests and investigations like x- ray were done as and when required.

TABLE – 9: MAXIMUM SCORES OF ALL PARAMETERS

PARAMETER	MAXIMUM SCORES
Pain	20
Stiffness	8
Physical function	68
WOMAC	96
VAS	10

The patients were followed up at weeks 1, 2, 4 and then at the end of 3 months. During each follow-up, physical examination of study joint, WOMAC index including pain, stiffness and physical function and VAS scores were noted. Any adverse drug event during the course of the study will be recorded.

Data were analysed descriptively. Repeated measures ANOVA (post hoc Bonferroni) was used to compare pain, stiffness, physical function, WOMAC and VAS scores within groups and Unpaired ‘t ‘test was used to compare the scores between the groups. A ‘p ‘value of <0.05 was considered significant. SPSS 12.0 was used to analyse data.

RESULTS

TABLE - 10: AGE DISTRIBUTION OF PATIENTS

Age in years	Group L		Group A	
	No	%	No	%
40-50	35	58.3	38	63.3
51-60	20	33.3	15	25.0
61-70	5	8.3	7	11.7
Total	60	100.0	60	100.0
Mean ± SD	49.72 ±6.70		49.25 ±7.23	

L- Lornoxicam A- acetaminophen

Table 10 shows the age distribution of patients in lornoxicam and acetaminophen group. There were 60 patients each in the lornoxicam group and acetaminophen group. The mean age of patients in the lornoxicam group was 49.72±6.70 and that of acetaminophen group was 49.25±7.23 and there was no significant difference between groups.

FIGURE – 12: AGE DISTRIBUTION OF PATIENTS

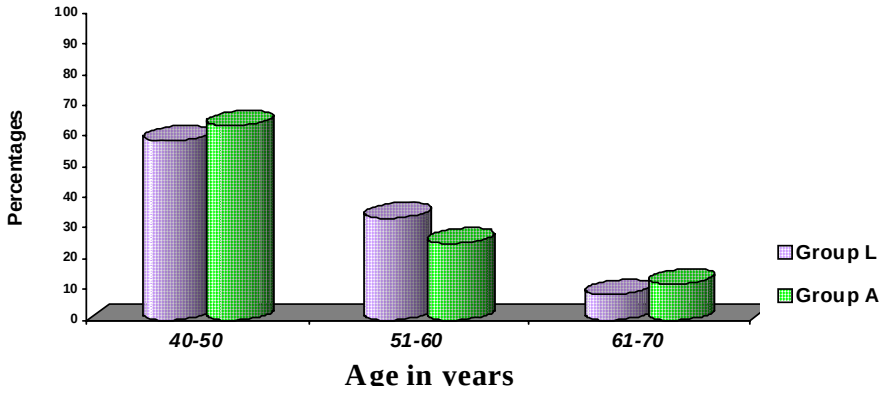


TABLE - 11: GENDER DISTRIBUTION OF PATIENTS

Gender	Group L		Group A	
	No	%	No	%
Male	29	48.3	28	46.7
Female	31	51.7	32	53.3
Total	60	100.0	60	100.0

Table 11 shows the gender distribution in both the groups. Of the 60 patients in the lornoxicam group 48.3% were males and 51.7% were females. In the acetaminophen group among the 60 patients 46.7% were males and 53.3 % were females and there was no significant difference between groups in gender distribution.

FIGURE – 13: GENDER DISTRIBUTION OF PATIENTS

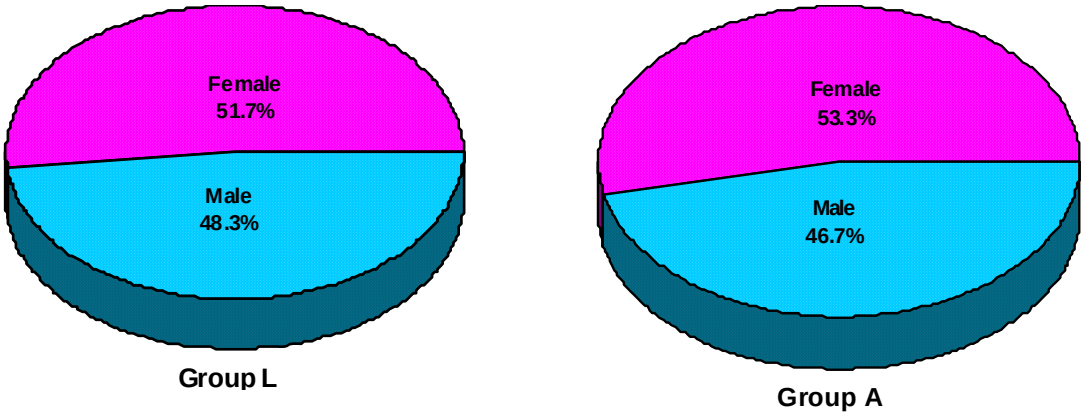
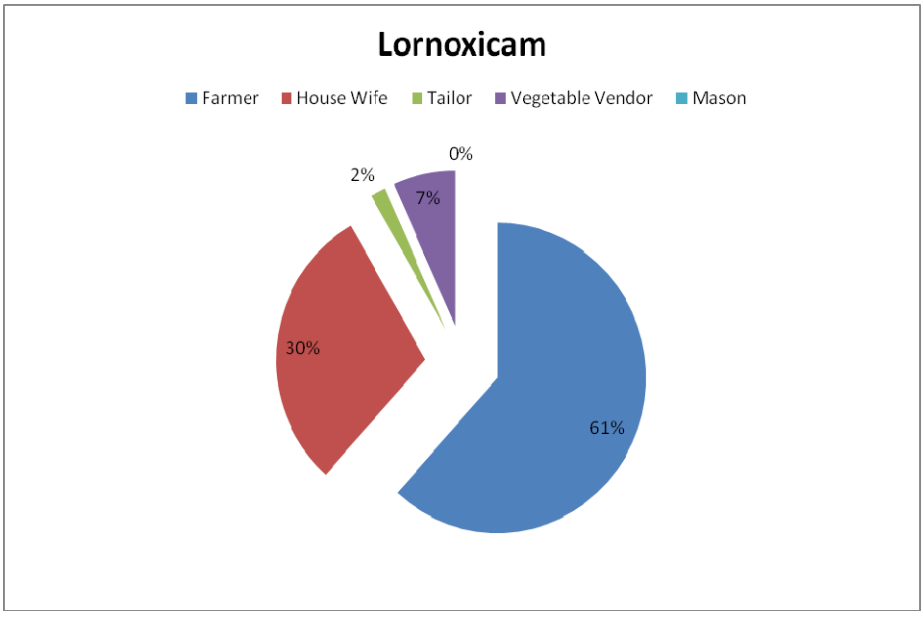


TABLE - 12: OCCUPATION IN BOTH GROUPS OF PATIENTS

Occupation	Lornoxicam	Lornoxicam (%)	Acetaminophen	Acetaminophen (%)
Farmer	37	61.66	29	48.33
House wife	18	30	16	26.66
Tailor	1	1.66	4	6.66
Vegetable vendor	4	6.66	8	13.33
Mason	0		3	5
Total	60	100%	60	100%

Table 12 shows distribution of occupation in different groups of patients. In both lornoxicam (61.6%) and acetaminophen(48.33%) group, majority of the patients were farmers . 30% in the lornoxicam group and 26.6% in the acetaminophen group were housewives.

FIGURE - 14: OCCUPATION IN BOTH GROUPS



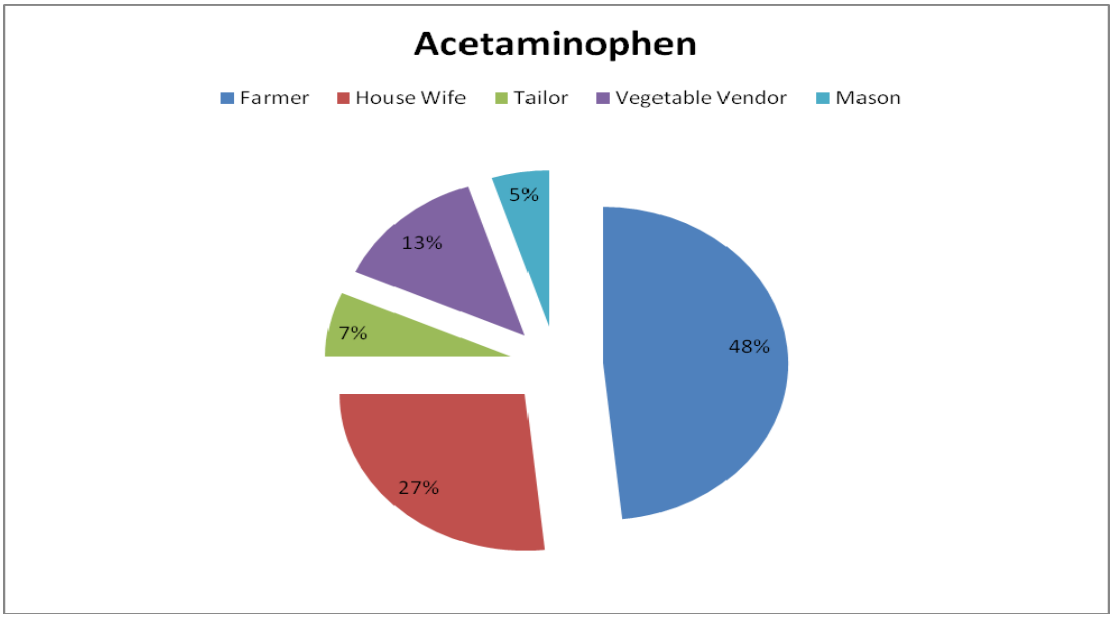


TABLE - 13: COMPARATIVE EVALUATION OF PAIN SCORES IN TWO GROUPS OF PATIENTS

Pain	Group L	Group A	p value
Mean ±SD			
• Baseline	12.42±1.84	12.32±1.78	0.784
• 1st week	9.77±1.69	10.37±1.54	0.035*
• 2nd week	7.61±0.89	8.16±0.86	0.002**
• 4th week	4.17±0.80	4.61±0.70	0.002**
• End of 3rd month	11.82±1.84	12.54±1.52	0.066+
p value from baseline			
• 1st week	<0.001**	<0.001**	-
• 2nd week	<0.001**	<0.001**	-
• 4th week	<0.001**	<0.001**	-
• End of 3rd month	0.0016**	0.713	-

*p value<0.05 **p value<0.01 +p value>0.05

Table 13 shows comparison of pain scores at each follow up in lornoxicam and acetaminophen groups. In the lornoxicam group there was significant reduction in pain scores compared to baseline at follow up visits 1st, 2nd and 4th week and 3rd month. In the acetaminophen group also there was reduction in pain scores significantly at 1st, 2nd and 4th week. Between the groups, lornoxicam significantly reduced pain compared to acetaminophen at follow up visits at 1st, 2nd and 4th week.

FIGURE - 15: PAIN SCORES IN TWO GROUPS OF PATIENTS

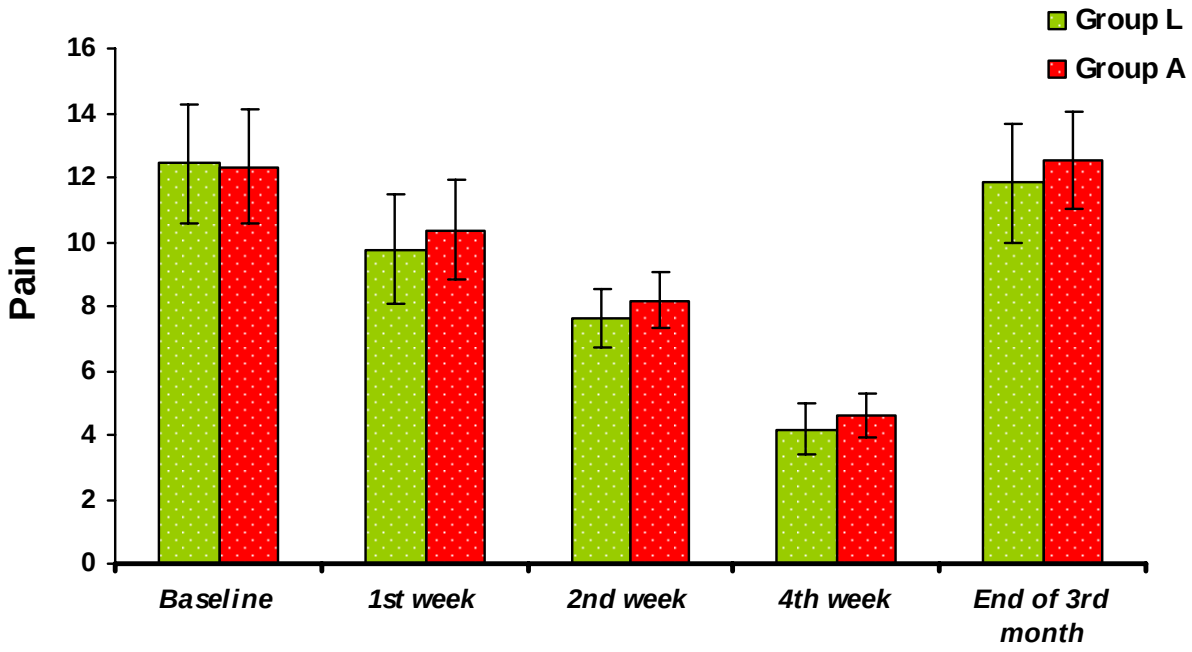


TABLE - 14: COMPARATIVE EVALUATION OF STIFFNESS SCORE IN TWO GROUPS OF PATIENTS

Stiffness	Group L	Group A	p value
Mean ±SD			
• Baseline	4.10±0.44	4.13±0.60	0.646
• 1st week	3.22±0.42	3.40±0.56	0.029*
• 2nd week	2.31±0.46	2.51±0.57	0.050*
• 4th week	2.04±0.27	2.20±0.45	0.008**
• End of 3rd month	3.90±0.41	4.10±0.55	0.050*
p value from baseline			
• 1st week	<0.001**	<0.001**	-
• 2nd week	<0.001**	<0.001**	-
• 4th week	<0.001**	<0.001**	-
• End of 3rd month	0.892	1.000	-

*p value <0.05 **p value<0.01

Table 14 shows comparison of stiffness scores in lornoxicam and acetaminophen groups. In both the groups there was significant reduction in the stiffness scores at 1st, 2nd and 4th week. Between the groups lornoxicam produced a greater reduction in stiffness scores compared to acetaminophen at all follow up visits and this was statistically significant.

FIGURE – 16: STIFFNESS SCORE IN TWO GROUPS OF PATIENTS

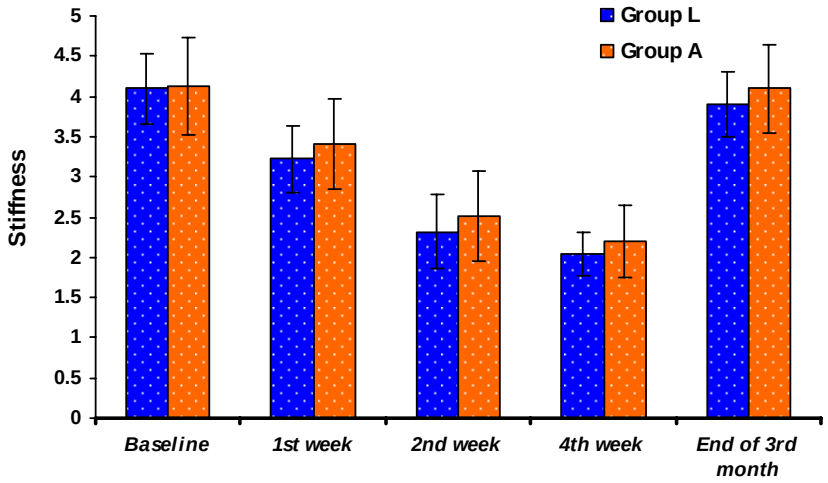


TABLE - 15: COMPARATIVE EVALUATION OF DISABILITY SCORES IN TWO GROUPS OF PATIENTS

Loss of physical function	Group L	Group A	p value
Mean ±SD			
• Baseline	38.93±4.07	39.73±2.67	0.021*
• 1st week	27.95±4.84	30.30±2.16	0.030*
• 2nd week	16.56±3.82	20.49±2.23	<0.001**
• 4th week	5.57±1.79	10.27±1.83	<0.001**
• End of 3rd month	37.71±3.65	39.67±2.52	0.001**
p value from baseline			
• 1st week	<0.001**	<0.001**	-
• 2nd week	<0.001**	<0.001**	-
• 4th week	<0.001**	<0.001**	-
• End of 3rd month	0.004**	1.000	-

*p value<0.05 **p value <0.01

Table 15 shows comparison of disability scores in lornoxicam and acetaminophen groups. In the lornoxicam group there was significant reduction in the disability scores compared to baseline at all follow ups. In the acetaminophen group there was significant reduction in disability scores at 1st, 2nd and 4th week. Between the two groups lornoxicam had greater reduction in the scores compared to acetaminophen at all follow up visits.

FIGURE - 17: DISABILITY SCORES IN TWO GROUPS OF PATIENTS

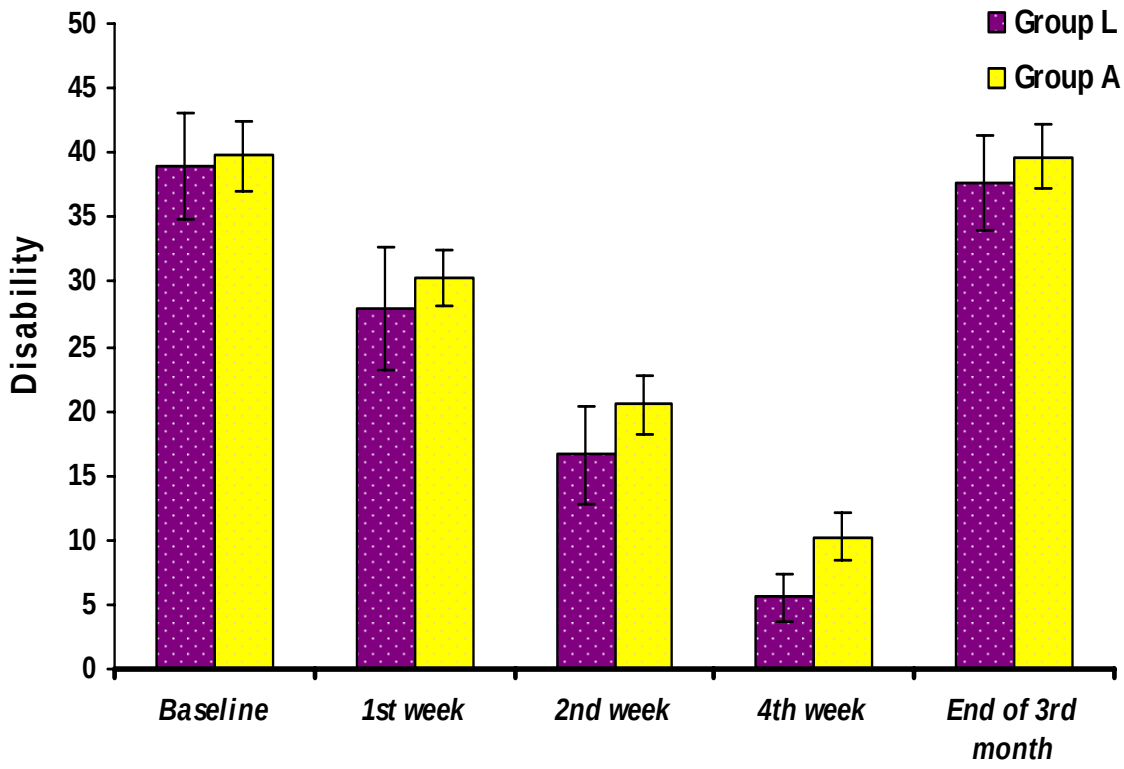


TABLE - 16: COMPARATIVE EVALUATION OF WOMAC INDEX IN TWO GROUPS OF PATIENTS

WOMAC score	Group L	Group A	p value
Mean ±SD			
• Baseline	55.45±5.42	56.18±4.49	0.246
• 1st week	40.93±5.67	44.07±2.91	0.002**
• 2nd week	26.47±4.12	31.16±2.49	<0.001**
• 4th week	11.77±2.48	17.08±2.13	<0.001**
• End of 3rd month	53.43±5.05	56.06±4.23	0.001**
p value from baseline			
• 1st week	<0.001**	<0.001**	-
• 2nd week	<0.001**	<0.001**	-
• 4th week	<0.001**	<0.001**	-
• End of 3rd month	0.002**	1.000	-

*p value<0.05 **p value <0.01

Table 16 shows the WOMAC index scores at each follow up in both lornoxicam and acetaminophen groups. Lornoxicam significantly reduced WOMAC scores at all follow up visits. Acetaminophen group had significant reduction in WOMAC scores only at 1st,2nd and 4th week. Between the groups lornoxicam had significantly higher reduction in WOMAC scores compared to acetaminophen at all follow up visits.

FIGURE – 18: WOMAC INDEX IN TWO GROUPS OF PATIENTS

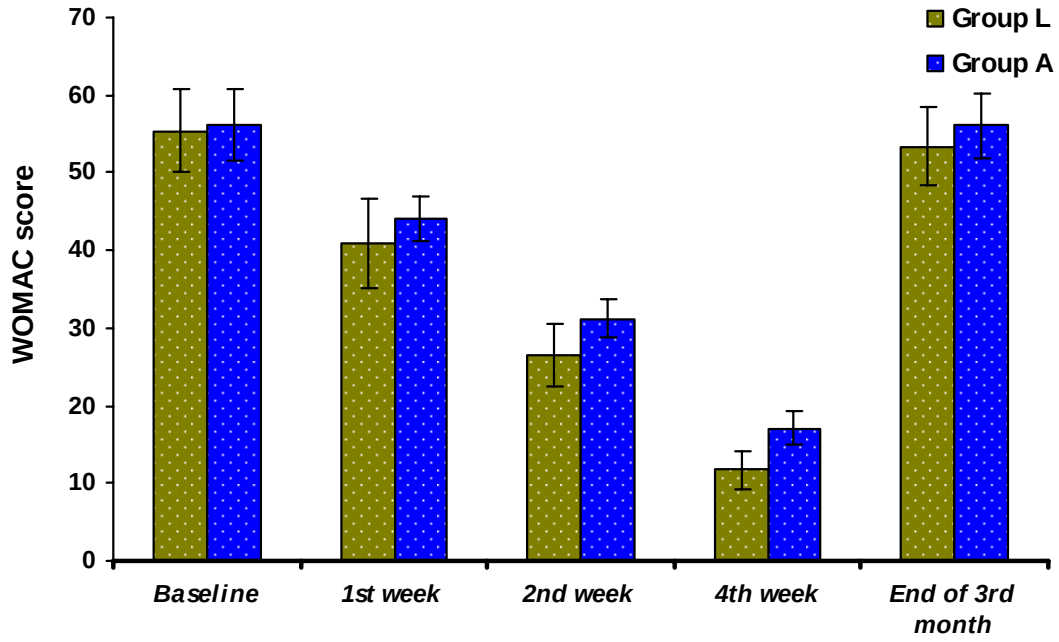


TABLE - 17: COMPARATIVE EVALUATION OF VAS SCORES IN TWO GROUPS OF PATIENTS

VAS score	Group L	Group A	P value
Mean ±SD			
• Baseline	8.07±0.69	8.02±0.85	0.762
• 1st week	5.65±0.78	6.82±0.83	<0.001**
• 2nd week	4.31±0.68	4.91±0.97	<0.001**
• 4th week	2.55±0.75	3.45±0.76	<0.001**
• End of 3rd month	7.25±1.18	7.88±0.88	<0.001**
p value from baseline			
• 1st week	<0.001**	<0.001**	-
• 2nd week	<0.001**	<0.001**	-
• 4th week	<0.001**	<0.001**	-
• End of 3rd month	<0.001**	1.000	-

**p<0.05

Table 17 shows the reduction in VAS scores in both the groups. Lornoxicam significantly reduced VAS scores at all follow up visits. Acetaminophen group had significant reduction in VAS scores at 1st,2nd and 4th week. Between the two groups lornoxicam had significantly higher reduction in VAS scores compared to acetaminophen at all follow ups.

FIGURE - 19: VAS SCORES IN TWO GROUPS OF PATIENTS

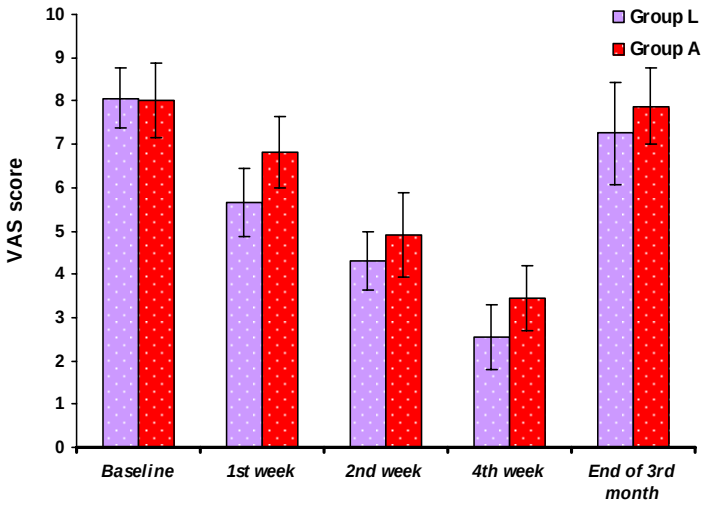
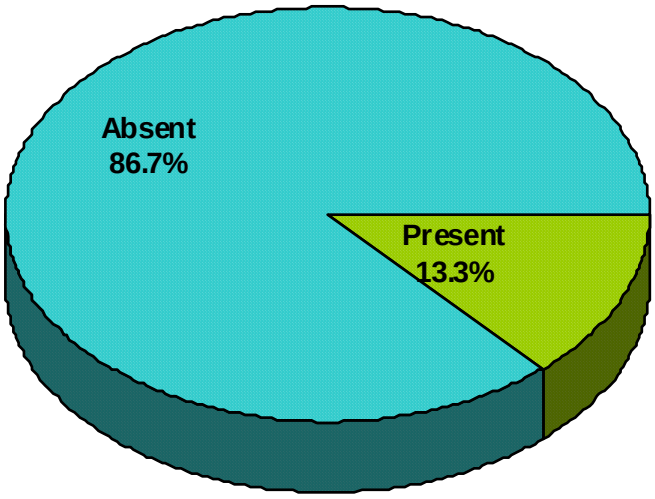


Table - 18: COMPARISON OF ADVERSE EFFECTS IN TWO GROUPS OF PATIENTS

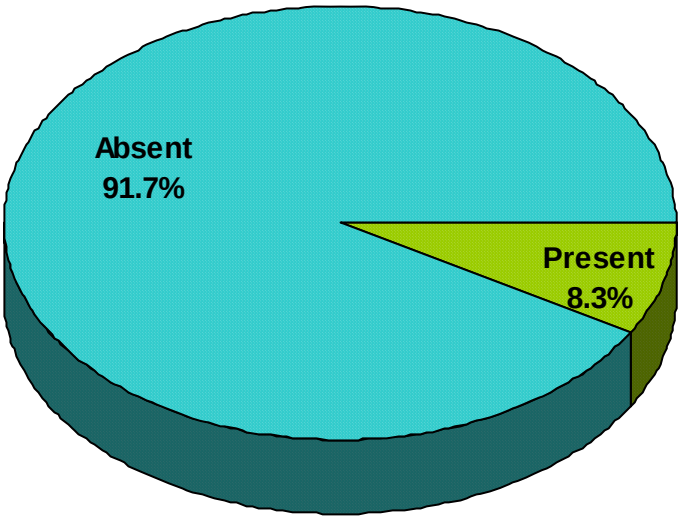
Adverse effects	Group L (n=60)	Group A (n=60)
Absent	52(86.7%)	55(91.7%)
Present	8(13.3%)	5(8.3%)
• Dyspepsia	2(3.3%)	1(1.7%)
• Nausea	2(3.3%)	1(1.7%)
• Flatulence	1(1.7%)	2(3.3%)
• Diarrhea	1(1.7%)	0
• Abdominal pain	1(1.7%)	0
• Rashes	0	1(1.7%)
• Head ache	1(1.7%)	0

13.3% of patients in the lornoxicam group had adverse effects compared to 8.3% in the acetaminophen group. Commonest side effect in the lornoxicam group was nausea and dyspepsia and in the acetaminophen group was flatulence. There were no serious side effects in either group. There was one case each of flatulence, diaarhoea, abdominal pain and headache in lornoxicam group and one case each of nausea, dyspepsia and rashes in acetaminophen group.

FIGURE - 20: COMPARISON OF ADVERSE EFFECTS IN TWO GROUPS OF PATIENTS



Group L



Group A

DISCUSSION

Osteoarthritis (OA) is a rheumatic disease characterized by articular cartilage degeneration, bone hypertrophy, crepitus and radiographic change. The joint pain and stiffness associated with OA can lead to significant disability and functional impairment. In majority, large joints are affected more than smaller joints. Among these large joints, knee joint is the most commonly affected. OA of knee is one of the five leading causes of disability among elderly population. Apart from the permanent cure in the form of costly joint replacement surgery, management of OA of knee generally involves a combination of exercise, lifestyle modification and analgesics.[1]

Lornoxicam is an NSAID of oxicam class recently introduced in the Indian market. It is found to be a better alternative for management of a number of conditions like post operative pain after lumbar discectomy and molar surgery, but less information is available regarding its safety and efficacy in osteoarthritis of knee. Acetaminophen is recommended as the first line therapy for mild to moderate osteoarthritis of knee by American College of Rheumatology because of its long term safety compared to NSAIDS**.** Due to lack of studies between the above drugs, the present study has been undertaken.

In our present study we compared the efficacy and safety of Lornoxicam 8mg BD and Acetaminophen(ER) 650mg BD in symptomatic osteoarthritis knee. The parameters assessed were pain, stiffness, disability, WOMAC and VAS scores.

The incidence of osteoarthritis increases with age. Normal ageing process causes increased laxity around joints, reduced joint proprioception, cartilage degeneration and reduced chondrocyte function, all leading to a propensity for osteoarthritis. Osteoarthritis generally occurs after 50 years. In our study the mean age of patients in

lornoxicam group was 49.72±6.70 and in the acetaminophen group were 49.25±7.23. Majority of patients in both the groups were more than 45 years. This can be explained by the fact that most of the patients in our study were manual labourers and occupation is one of the major risk factors for the early onset of osteoarthritis.[14]

Under the age of 50, men have a higher prevalence and incidence than women for OA. .However above the age of 50 or after menopause women has a higher overall prevalence and incidence for OA. In our study there were 48.3% males and 51.7% females in the lornoxicam group and 46.7% males and 53.3% females in the acetaminophen group. Even though the number of females were more in both the groups, this was not statistically significant. In a study by Goregaonkar et al comparing lornoxicam 8mg BD with diclofenac 50mg TID in OA, there were 58.2% males and 61.1% females and there was no significant difference between the groups.[3]

In our study, both lornoxicam and acetaminophen significantly reduced pain scores at 1^{st}, 2^{nd} and 4^{th} week.($p<0.001$). Compared to acetaminophen, lornoxicam had greater reduction of pain scores at week 1,2 and 4^{th} week ($p<0.05$) and the reduction of pain with lornoxicam increased throughout the medication period. In a study by Yakhno et al, it was found that lornoxicam administered as a quick release formulation was non inferior to diclofenac in terms of pain relief in patients with low back pain ($p<0.05$).[54]

Both lornoxicam and acetaminophen significantly reduced stiffness scores in our study at weeks 1^{st}, 2^{nd} and 4^{th} ($p<0.001$) compared to baseline. But lornoxicam showed greater reduction in stiffness scores compared to acetaminophen at follow up visits at 1^{st}, 2^{nd} and 4^{th} week ($p\leq 0.05$). In a study by Rose et al comparing lornoxicam with rofecoxib in patients with activated osteoarthritis (COLOR study) it was found

that compared to rofecoxib, lornoxicam significantly reduced duration of morning stiffness throughout the study ($p<0.001$).[57]

In the present study lornoxicam group had significant reduction in disability scores at follow up visits 1st , 2nd and 4th week and at the end of 3 month ($p<0.01$). Acetaminophen also significantly reduced disability scores at 1st, 2nd and at 4th week. Altman et al in a double blind randomized study found that acetaminophen ER in the dose of 3900 mg/day was significantly superior to placebo in reducing symptoms of osteoarthritis hip and knee ($p<0.05$).[1] In our study compared to acetaminophen, lornoxicam significantly reduced disability scores at all follow up visits ($p<0.01$).These results are in accordance with the previous studies where lornoxicam has been found to produce significant reduction in all symptoms of osteoarthritis without inferiority in tolerability.[57-59]

In this study both groups had significant reduction in WOMAC scores compared to baseline at weeks 1, 2 and 4. Lornoxicam also significantly reduced WOMAC scores at the end of 3 months. Bradley et al compared an anti inflammatory dose of ibuprofen, analgesic dose of ibuprofen and acetaminophen in a randomized clinical trial of 184 patients with chronic knee pain caused by osteoarthritis and acetaminophen was found to be non inferior compared to ibuprofen in reduction of WOMAC scores ($p<0.05$).[108] In the present study between the two groups lornoxicam significantly reduced WOMAC scores compared to acetaminophen at all follow ups at 1st, 2nd and 4th week.($p<0.01$). Goregaonkar et al , in a 4 week randomized double blind study comparing lornoxicam with diclofenac in patients with osteoarthritis knee found that lornoxicam significantly reduced WOMAC scores(82.9%) compared to baseline at the end of the study ($p<0.05$).[3]

In the current study lornoxicam and acetaminophen reduced VAS scores significantly at weeks 1, 2 and 4 ($p<0.001$). At the end of 3 months the reduction in VAS scores was significant only in the lornoxicam group ($p<0.001$). Compared to acetaminophen, lornoxicam group had significant reduction in VAS scores at all follow up visits ($p<0.001$). Effect of lornoxicam increased over duration of therapy. Sacerdote and Bianchi in their study found that this incremental effect is because lornoxicam inhibits human polymorphonuclear cell migration induced by f-myeloperoxidase, IL-8 and substance P which are important chemotactic mediators of inflammation.[109]

In this study both the drugs were well tolerated and side effects were mild in nature. The incidence was 13.3% in lornoxicam group and 8.3% in the acetaminophen group. Commonest side effect in the lornoxicam group was nausea and dyspepsia (3.3%). In one of the studies comparing lornoxicam with diclofenac, 14.6% patients had adverse events. Dyspepsia was observed more compared to nausea (5.1%). [3] In a study by Vadgama et al similar findings were observed.[110] In the acetaminophen group flatulence was the commonest side effect observed. In previous studies comparing acetaminophen in osteoarthritis, GI upset including diarrhea was the commonest observed side effect.[1,2]

ACR Guidelines for the Medical Management of Osteoarthritis, published in 1995 and updated in 2000, recommend acetaminophen in doses up to 4000 mg/day as a preferred firstline therapy in patients with osteoarthritis of the knee or hip. Based on the overall cost, efficacy, and toxicity profile of acetaminophen, the ACR Guidelines state that acetaminophen merits a trial as initial therapy .[4] Guidelines published by EULAR recommend acetaminophen as the oral analgesic to try first for knee, hip, and hand osteoarthritis and if successful, acetaminophen maybe used as the preferred

long-term oral analgesic because of its safety and efficacy profile.[106] The present findings are also in concurrence with ACR and EULAR guidelines.

In a few studies that were done comparing NSAIDS with acetaminophen, it was found that acetaminophen was equally effective as NSAIDS in reducing symptoms of OA. In our study, lornoxicam had better reduction of scores in relation to pain, stiffness, disability, WOMAC and VAS parameters. These data suggest that acetaminophen may be suited for mild OA and may require further assessment particularly in a wider dose range. Acetaminophen is currently recommended as the first line therapy for treatment of mild OA knee due to its low cost, good efficacy as analgesic and low incidence of side effects. But it has a poor anti inflammatory action due to the presence of peroxides in the synovial fluid in a chronic inflammatory condition like OA. Those patients with mild osteoarthritis or those having any contraindications to the use of NSAIDs such as any history of GI bleeding, peptic ulcer or hypersensitivity to NSAIDS may be advised acetaminophen for symptomatic relief. Whereas lornoxicam in view of its good efficacy as an analgesic as well as an anti inflammatory agent and because of its milder GI side effects , can be recommended in patients not responding to acetaminophen or in cases of moderate OA for the relief of symptoms.

CONCLUSION

The result of the present study shows that lornoxicam in the dose of 8mg BD is an effective and well tolerated therapy for management of patients with mild and moderate osteoarthritis knee. It has effectively reduced pain, stiffness, disability, WOMAC and VAS scores in symptomatic osteoarthritis .The improvement in symptoms were as early as the first week of initiating treatment and progressively increased throughout the course of therapy. Furthermore the patients treated with lornoxicam showed a lower incidence of side effects particularly gastrointestinal intolerance which is common with other NSAIDs. This ensures better patient compliance and makes lornoxicam a good alternative to acetaminophen for management of symptomatic osteoarthritis knee. Acetaminophen can be used for initial stages of OA in patients with contraindications to the use of NSAIDs. Effective pain relief early in the course of OA helps the patient to combine his occupation and activities of daily living and lornoxicam may help in the process.

SUMMARY

A prospective study was conducted on 120 patients with mild to moderate osteoarthritis of knee. 60 patients received Lornoxicam 8mg BD and another 60 were given Acetaminophen (ER) 650mg BD for 4 weeks. The aim of the study was to evaluate the efficacy and safety of the two drugs. Efficacy was assessed by pain, stiffness, disability, WOMAC and VAS scores. Safety was analysed by monitoring adverse effects. Patients were followed up at 1, 2, 4 weeks and at the end of 3 months.

Majority of the patients were in the study were above 45 years with mean age being 49.72 in the lornoxicam group and 49.25 in the acetaminophen group. There was no significant difference in gender distribution between the groups.

Lornoxicam and Acetaminophen significantly reduced pain, stiffness, disability, WOMAC and VAS scores at follow up visits at 1, 2 and 4^{th} week. The reduction in all these parameters was also significant between the groups, where lornoxicam produced better reduction of scores compared to acetaminophen.

The incidence of adverse effects was similar in both the groups. Commonest side effect in lornoxicam group was nausea and dyspepsia and in the acetaminophen group was flatulence.

Lornoxicam is a good alternative to acetaminophen for management of symptomatic osteoarthritis of knee. Acetaminophen can be used for initial stages of OA and in patients with contraindications to the use of other NSAIDs.

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KEY TO MASTER CHART

S. NO- SERIAL NUMBER

M- MALE

F- FEMALE

HOSP NO- HOSPITAL NUMBER

A-ACETAMINOPHEN

L-LORNOXICAM

GRP-GROUP

BL-BILATERAL

WK-WEEK

WOI-WOMAC OSTEOARTHRITIS INDEX

VAS-VISUAL ANALOGUE SCALE

ADVERSE EFF-ADVERSE EFFECTS

PROFORMA

NAME: **AGE:** **OP NO:** **DATE :**

OCCUPATION: **ADDRESS:**

SOCIO ECONOMIC STATUS :

PRESENTING COMPLAINTS:

HISTORY OF PRESENTING COMPLAINTS:

PAIN: MILD\ MODERATE|SEVERE

ACTIVITY OF DAILY LIVING (ADL): AFFECTED\NOT AFFECTED

LOSS OF INCOME:

PAST HISTORY:

DRUG HISTORY:

FAMILY HISTORY:

PERSONAL HISTORY:

GENERAL PHYSICAL EXAMINATION:

BUILT: GENERAL CONDITION:

PULSE: BLOOD PRESSURE:

SYSTEMIC EXAMINATION:

RESPIRATORY SYSTEM:

CARDIOVASCULAR SYSTEM:

PER ABDOMINAL EXAMINATION:

CENTRAL NERVOUS SYSTEM :

LOCAL EXAMINATION:

KNEE EXAMINATION PROFORMA

Inspection

- Alignment
- Attitude
- Swelling/contours / abnormal shifts / prominence
- Wasting
- Scars/ sinuses
- Patellar shape/size/position

Palpation

- Local temperature
- Local tenderness
- Synovium thickening
- Bony palpation-Femur, Tibia & fibula
- Effusion-patellar tap/cross fluctuation
- Popliteal fossa examination-

swelling:

pulsatile +

changes with flexion/extension +

Movements

- Flexion
- Extension
- Active/passive
- lag/deformity/arc
- compare with opposite side

Measurements

- Length of femur & tibiae
- High & calf girth
- Q angle
- Intercondylar distance/ intermalleolar distance
- Lateral thigh-leg angle
- Tibial torsion

WOMAC OSTEOARTHRITIS INDEX

A.PAIN:

The following questions concern the amount of pain you are currently experiencing in your knees. For each situation, please enter the amount of pain you have experienced in the past 48 hours.

	None	Mild	Moderate	Severe	Extreme
1. Walking on a flat surface	( )	( )	( )	( )	( )
2. Going up or down stairs	( )	( )	( )	( )	( )
3. At night while in bed	( )	( )	( )	( )	( )
4. Sitting or lying	( )	( )	( )	( )	( )
5. Standing upright	( )	( )	( )	( )	( )

B.STIFFNESS:

6. How severe is your stiffness after first awakening in the morning?

None	Mild	Moderate	Severe	Extreme
( )	( )	( )	( )	( )

7. How severe is your stiffness after sitting, lying, or resting later in the day?

None	Mild	Moderate	Severe	Extreme
( )	( )	( )	( )	( )

C.DIFFICULTY PERFORMING DAILY ACTIVITIES/DISABILITY:

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities, please indicate the degree of difficulty you have experienced in the last 48 hours, in your knees.

What degree of difficulty do you have with?

	None	mild	moderate	severe	extreme
8. Descending (going down) stairs.	( )	( )	( )	( )	( )
9. Ascending (going up) stairs.	( )	( )	( )	( )	( )
10. Rising from sitting.	( )	( )	( )	( )	( )
11. Standing.	( )	( )	( )	( )	( )
12. Bending to floor.	( )	( )	( )	( )	( )
13. Walking on a flat surface.	( )	( )	( )	( )	( )
14. Getting in/out of car.	( )	( )	( )	( )	( )
15. Going shopping.	( )	( )	( )	( )	( )
16. Putting on socks/stockings	( )	( )	( )	( )	( )
17. Rising from bed.	( )	( )	( )	( )	( )
18. Taking off socks/stockings.	( )	( )	( )	( )	( )
19. Lying in bed	( )	( )	( )	( )	( )
20. Getting in/out of bath	( )	( )	( )	( )	( )
21. Sitting.	( )	( )	( )	( )	( )
22. Getting on/off toilet	( )	( )	( )	( )	( )
23. Heavy domestic duties (Such as lifting heavy grocery bags)	( )	( )	( )	( )	( )
24. Light domestic duties. (such tidying a room, dusting, cooking)	( )	( )	( )	( )	( )

SCORING AND INTERPRETATION:

RESPONSE	NONE	MILD	MODERATE	SEVERE	EXTREME
POINTS	0	1	2	3	4

VISUAL ANALOGUE SCALE

0	1	2	3	4	5	6	7	8	9	10
NONE	MILD			MODERATE			EXTREME			

Interpretation:

- Minimum total score : 0
- Maximum total score : 96
- Minimum pain subscore : 0
- Maximum pain subscore : 20
- Minimum stiffness subscore : 0
- Maximum stiffness subscore : 8
- Minimum physical function subscore : 0
- Maximum physical function subscore : 68

OVERALL ASSESSMENT

	WEEKS			3rd MONTH
	1	2	4	
SYMPTOMS:				
WOMAC-OA index:				
VAS:				
IMPROVEMENT OF ACTIVITY OF DAILY LIVING:				
RESTRICTION OF MOVEMENT:				
ADVERSE DRUG REACTIONS				
Headache				
Giddiness				
Nausea				
Vomiting				
Diarrhoea				
Dyspepsia				
Others				

S. No	NAME	AGE	SEX	OCCUPATION	HOSP NO.	Drug Grp	BL Pain	1 Wk Pain	2 Wk Pain	4 Wk Pain	3 M Pain	BL Stiffness	1 Wk Stiffness	2 Wk Stiffness	4 Wk Stiffness	3 M Stiffness	BL Disability	1 Wk Disability	2 Wk Disability	4 Wk Disability	3 M Disability	Initial WOI	1W WOI	2W WOI	4 W WOI	3M WOI	Initial VAS	1W VAS	2W VAS	4W VAS	3M VAS	Adverse Eff
1	NAGARAJ	63	M	Farmer	593894	L	13	8	6	4	11	4	4	3	2	4	33	30	21	7	33	50	42	30	13	48	7	6	4	1	7	
2	PADMA	43	F	Veg vendor	512675	L	14	10	8	4	12	4	3	2	2	4	36	21	14	5	34	54	34	24	11	50	8	6	5	3	7	
3	KRISHNAMMA	45	F	House wife	603654	L	15	13				5	4				42	31				62	48				9	7				Dyspepsia
4	CHANDRAMMA	48	F	House wife	603713	L	10	8	7	4	9	4	3	2	2	4	37	19	11	4	36	51	30	20	10	49	8	5	4	3	6	
5	PARTASARATHI	53	M	Farmer	561086	L	11	10	8	4	12	4	3	2	2	4	36	21	14	5	35	51	34	24	11	51	8	6	5	3	7	
6	APPANNA	52	M	Farmer	474999	L	15	12	9	5	15	5	4	3	2	4	44	35	18	6	43	64	51	30	13	62	9	6	4	3	9	
7	MADANKUMAR	40	M	Farmer	552595	L	14	10	8	4	13	4	3	2	2	3	36	29	14	5	35	54	42	24	11	51	8	5	4	2	6	
8	KUSUMA	52	F	House wife	541816	L	14	11	8	5	13	4	3	2	2	4	37	28	14	6	38	55	42	24	13	55	8	5	4	3	9	
9	BHAGGAMMA	57	F	Farmer	593729	L	15	13	9			5	4	3			45	27	15			65	44	27			9	7	5			Abdominal pain
10	BALARAJU	42	M	Farmer	518266	L	11	9	7	4	11	3	3	2	2	3	37	30	20	6	38	51	42	29	12	52	7	5	4	2	6	
11	FAISAL AHMED	44	M	Farmer	502325	L	14	12	9	5	14	4	3	3	2	4	48	34	18	7	47	66	49	30	14	65	9	5	3	2	9	
12	NAZEER AHMED	42	M	Tailor	529285	L	12	8	7	3	12	4	3	2	2	4	38	30	20	4	39	54	41	29	9	55	8	5	3	1	8	
13	THIMAKKA	44	F	Veg vendor	529347	L	10	8	7	4	9	4	3	2	2	4	37	31	11	4	37	51	42	20	10	50	8	5	4	3	6	
14	RAMAPPA	59	M	Farmer	636483	L	10	8	7	5		4	3	3	2		38	30	20	12		52	41	30	19		7	5	5	4		
15	SHAHERABANU	56	F	House wife	530761	L	11	10	8	4	12	4	3	2	2	4	36	30	14	5	35	51	43	24	11	51	8	6	5	3	7	
16	MARKANDAPPA	45	M	Farmer	573664	L	12	8	7	3	12	4	3	2	2	4	38	30	20	4	38	54	41	29	9	54	7	5	4	2	7	
17	CHINNAMMA	42	F	Farmer	513542	L	10	8	7	4	9	4	3	2	2	4	37	19	11	4	35	51	30	20	10	48	8	5	4	3	6	
18	LAKSHMI	59	F	House wife	523812	L	11	10	8	4	12	4	3	2	2	4	36	21	14	5	35	51	34	24	11	51	8	6	5	3	7	Nausea
19	REDDARAYAPPA	55	M	Farmer	517680	L	10	8	7	4	9	4	3	2	2	4	36	19	11	4	36	50	30	20	10	49	8	5	4	3	6	
20	NAGAMANI	44	F	Farmer	500877	L	15	12	9	5	12	5	4	3	2	4	44	33	20	6	45	64	49	32	13	61	9	6	4	3	7	
21	BHAGGAMMA	57	F	House wife	593729	L	15	13	9			5	4	3			45	27	15			65	44	27			9	7	5			
22	KRISHNAKKA	40	F	Farmer	530562	L	14	10	8	4	12	4	3	2	2	3	36	23	14	5	35	54	36	24	11	50	8	5	5	3	6	
23	SRINIVAS	43	M	Farmer	601289	L	11	9	7	3	11	4	3	2	2	4	40	33	15	5	42	55	45	24	10	57	8	6	5	2	8	
24	MAGIMAI DASS	62	M	Farmer	589037	L	13	8	6			4	4	3			33	30	21			50	42	30			7	6	5			Headache
25	BHAGYAMMA	48	F	House wife	632827	L	10	8	7	4	9	4	3	2	2	4	37	27	18	4	33	51	38	27	10	46	8	5	4	3	6	
26	VISHALAKSHI	58	F	Farmer	486790	L	13	8	6	5	11	4	4	3	2	4	33	30	21	9	33	50	42	30	16	48	7	6	4	1	7	
27	VENKATAREDDY	55	M	Farmer	431903	L	14	10	8	4	12	4	3	2	2	4	36	21	14	5	34	54	34	24	11	50	8	6	5	3	7	
28	BYRAMMA	48	F	House wife	655891	L	15	13	8	4	15	5	4	3	2	5	42	30	19	8	43	62	47	30	14	63	9	7	5	3	9	
29	SHANKARAPPA	42	M	Farmer	598003	L	10	8	7	4	9	4	3	2	2	4	37	19	11	4	35	51	30	20	10	48	8	5	4	3	6	
30	MALLAMA	44	F	House wife	595374	L	11	10	8	4	12	4	3	2	2	4	36	21	14	5	35	51	34	24	11	51	8	6	5	3	7	

S. No	NAME	AGE	SEX	OCCUPATION	HOSP NO.	Drug Grp	BL Pain	1 Wk Pain	2 Wk Pain	4 Wk Pain	3 M Pain	BL Stiffness	1 Wk Stiffness	2 Wk Stiffness	4 Wk Stiffness	3 M Stiffness	BL Disability	1 Wk Disability	2 Wk Disability	4 Wk Disability	3 M Disability	Initial WOI	1W WOI	2W WOI	4 W WOI	3M WOI	Initial VAS	1W VAS	2W VAS	4W VAS	3M VAS	Adverse Eff
31	MOHISENA	53	F	Farmer	590371	L	14	10	8			4	3	2			36	21	14			54	34	24			8	6	5			
32	SHASHIKALA	45	F	Farmer	561379	L	15	12	9	6	15	5	4	3	2	4	44	31	22	4	42	64	47	34	12	61	9	6	4	3	9	
33	KAMALAMMA	45	F	House wife	568467	L	14	10	8	4	13	4	3	2	2	3	36	29	14	5	35	54	42	24	11	51	8	5	4	2	6	
34	NAGAPPA	42	M	Farmer	491620	L	14	11	8	5	13	4	3	2	2	4	37	28	14	7	38	55	42	24	14	55	8	5	4	3	9	
35	AYASHA BEGAM	45	F	Farmer	552525	L	11	9	7	4	11	3	3	2	2	3	37	30	20	6	38	51	42	29	12	52	7	5	4	2	6	
36	KEMPAMMA	46	F	House wife	565810	L	14	12	9	6	14	4	3	3	2	4	47	33	18	8	40	65	48	30	16	58	9	5	3	2	9	
37	GOPALREDDY	43	M	Farmer	531137	L	10	8	7	3	11	4	3	2	2	4	38	30	20	4	37	52	41	29	9	52	8	5	3	1	8	Vomiting
38	JAMUNA	58	F	House wife	569821	L	10	8	7	4	9	4	3	2	2	4	37	31	11	4	37	51	42	20	10	50	8	5	4	3	6	
39	NARAYANASWAM	43	M	Farmer	532117	L	11	10	8	4	12	4	3	2	2	4	36	30	14	5	35	51	43	24	11	51	8	6	5	3	7	
40	SHANTHAMMA	44	F	House wife	486754	L	10	8	7	3	11	4	3	2	2	4	38	30	20	4	37	52	41	29	9	52	7	5	4	2	7	
41	MANJULA DEVI	48	F	Farmer	610294	L	13	10	7			4	3	2			45	37	20			62	50	29			9	7	5			
42	NARAYANA SWAN	42	M	Farmer	572145	L	13	10	6	3	14	4	3	2	2	4	45	28	22	6	46	62	41	30	11	64	9	7	6	3	9	
43	VENKATAMANACI	50	M	Farmer	590728	L	12	8	7	3	12	4	3	2	2	4	38	30	20	4	38	54	41	29	9	54	7	5	4	2	7	
44	NARAYANA SWAN	62	M	Farmer	580218	L	10	8	7	4	9	4	3	2	2	4	40	19	11	4	39	54	30	20	10	52	8	5	4	3	6	
45	AMARNATH	62	M	Farmer	601625	L	10	8	7	3	11	4	3	2	2	4	38	30	20	4	37	52	41	29	9	52	7	5	4	2	7	
46	SHANTHAMMA	49	F	House wife	627356	L	13	10	7	4	14	4	3	2	2	4	45	36	19	6	46	62	49	28	12	64	9	7	5	3	9	
47	MUBEEN TAJ	46	F	House wife	625390	L	12	10	8	6		4	3	3	4		43	31	19	10		59	44	30	20		8	6	5	4		Dyspepsia
48	ANJANI RAMA SIN	53	M	Farmer	614279	L	13	8	6	5	11	4	4	3	2	4	33	30	21	9	33	50	42	30	16	48	7	6	4	1	7	
49	BYRE GOWDA	50	M	Farmer	603725	L	14	10	8	4	12	4	3	2	2	4	36	21	14	5	34	54	34	24	11	50	8	6	5	3	7	
50	KOKILA	52	F	House wife	626371	L	15	13	9	4	15	5	4	3	2	5	45	32	16	8	43	65	49	28	14	63	9	7	5	3	9	
51	RAMAJULU	56	F	House wife	572843	L	10	8	7	4	9	4	3	2	2	4	37	19	11	4	35	51	30	20	10	48	8	5	4	3	6	
52	KHAMRUNNISA	54	F	Veg Vendor	583759	L	11	10	8	4	12	4	3	2	2	4	36	21	14	5	35	51	34	24	11	51	8	6	5	3	7	
53	AMEER JAN	47	M	Farmer	590386	L	15	12	9	5	15	5	4	3	2	4	44	30	17	5	42	64	46	29	12	61	9	6	4	3	9	
54	NARAYANAPPA	65	M	Farmer	632094	L	13	10	9			4	3	3			45	32	28			62	45	40			9	8	5			Vomiting
55	MSNJULAMMA	53	F	House wife	610892	L	14	12	8	4	13	4	3	2	2	3	36	29	14	5	35	54	44	24	11	51	8	5	4	2	6	
56	VENKATESAN	45	M	Farmer	609182	L	14	11	8	5	13	4	3	2	2	4	37	28	14	7	38	55	42	24	14	55	8	5	4	3	9	diarrhoea
57	NINGAPPA	48	M	Farmer	509271	L	11	9	7	4	11	3	3	2	2	3	37	30	20	6	38	51	42	29	12	52	7	5	4	2	6	
58	LAKSHMAMMA	51	F	Farmer	520198	L	14	12	9	6	14	4	3	3	2	4	49	31	17	8	40	67	46	29	16	58	9	5	3	2	9	
59	BASHEER AHMED	58	M	Veg vendor	492709	L	12	8	7	3	12	4	3	2	2	4	38	30	20	4	39	54	41	29	9	55	8	5	3	1	8	
60	NAGAPPA	46	M	Farmer	510927	L	10	8	7	4	9	4	3	2	2	4	37	31	11	4	37	51	42	20	10	50	8	5	4	3	6	

MASTER CHART

S. No	NAME	AGE	SEX	OCCUPATION	HOSP NO.	Drug Grp	BL Pain	1 Wk Pain	2 Wk Pain	4 Wk Pain	3 M Pain	BL Stiffness	1 Wk Stiffness	2 Wk Stiffness	4 Wk Stiffness	3 M Stiffness	BL Disability	1 Wk Disability	2 Wk Disability	4 Wk Disability	3 M Disability	Initial WOI	1W WOI	2W WOI	4 W WOI	3M WOI	Initial VAS	1W VAS	2W VAS	4W VAS	3M VAS	Adverse Eff
1	VIDYA	53	F	Housewife	329896	A	15	12	9	5	15	3	3	4	3	5	43	31	21	10	42	61	46	34	18	62	9	8	6	4	9	
2	JAGANATH	43	M	Mason	543683	A	15	13	9	5	15	4	3	4	4	5	44	30	18	9	43	63	46	31	18	63	9	7	6	5	8	Vomiting
3	PRAMILAVANI	51	F	Housewife	618349	A	15	13	9			4	3	2			44	30	18			63	46	29			9	7	6			
4	CHIKKANARAYANAPPA	65	M	Farmer	603809	A	11	10	7	4	12	3	3	3	3	6	38	29	18	8	37	52	42	28	15	55	7	6	5	3	7	
5	NARAYANAPPA	40	M	Tailor	553996	A	14	12	9	5	14	4	3	2	3	5	39	27	19	11	40	57	42	30	19	59	8	6	4	3	7	
6	RADHAKRISHNA	53	M	Farmer	563880	A	14	12	10	6	14	4	2	2	3	5	41	31	20	9	41	59	45	32	18	60	9	8	6	3	9	
7	YASHODAMMA	62	F	Housewife	524231	A	12	9	8	5	11	3	3	3	2	5	38	30	23	8	37	53	42	34	15	53	7	6	4	3	7	
8	NASREEN TAJ	45	F	Farmer	541775	A	14	13	9	5	14	3	2	3	2	4	38	28	25	12	36	55	43	37	19	54	8	7	5	3	8	
9	KAMALA	40	F	Housewife	563555	A	15	13	9	6		4	3	3	3	4	41	33	22	11	40	60	49	34	20	44	9	8	7	5	9	
10	SATHISH KUMAR GOWDA	59	M	Farmer	628472	A	11	10				4	4				38	29				53	43				7	6				Dyspepsia
11	MALLAMMA	45	F	Housewife	523086	A	11	9	8	5	12	3	3	2	2	3	36	29	20	11	37	50	41	30	18	52	7	6	4	3	7	
12	BASAMMA	42	F	Veg vendor	507771	A	10	9	8	4	12	4	3	3	2	4	37	29	18	10	38	51	41	29	16	54	7	6	4	3	8	
13	PADHMAVATHAMMA	62	F	Housewife	604823	A	12	10	9			4	3	2			39	32	21			55	45	32			8	6	5			
14	BEERAPPA	43	M	Farmer	530194	A	14	10	8	4	15	4	3	2	2	4	42	33	23	13	43	60	46	33	19	62	9	8	6	5	9	
15	FAKRUDDIN	43	M	Mason	510384	A	12	10	8	5	12	4	3	2	2	4	41	33	24	12	40	57	46	34	19	56	8	7	4	3	9	
16	GULMAZ BEGUM	45	F	Farmer	575697	A	13	10	9	5	13	4	3	2	2	4	43	34	21	13	43	60	47	32	20	60	8	6	5	3	8	
17	MURALIDHAR	43	M	Tailor	559626	A	11	9	8	4	11	4	4	3	2	4	37	30	20	9	37	52	43	31	15	52	7	7	4	3	7	
18	NAGAPPA	44	M	Farmer	534216	A	10	8	8	5	12	4	3	2	2	4	38	30	19	8	39	52	41	29	15	55	7	7	4	3	8	
19	ALIYA MUMTAZ	44	F	Housewife	477961	A	12	10	9	5	12	4	3	2	2	4	39	32	21	12	41	55	45	32	19	57	8	6	5	4	7	
20	ANTHONY RAJ	48	M	Farmer	533769	A	11	8	8	4	11	4	4	2	2	4	35	28	19	9	35	50	40	29	15	50	7	7	4	3	7	
21	NARESH BABU	43	M	Farmer	594362	A	11	8	8			4	3	2			35	26	19			50	37	29			7	7	4			
22	BASAVRAJ	40	M	Tailor	592949	A	14	12	10	6	15	4	4	3	2	4	43	35	20	13	44	61	51	33	21	63	9	8	4	4	7	
23	VIRUPAKSHA	45	M	Farmer	530843	A	15	12	9	5	15	5	4	3	3	5	44	33	24	14	43	64	49	36	22	63	9	8	5	3	9	
24	VENKATAMMA	55	F	Housewife	601284	A	13	10	9	5	12	4	3	2	2	4	43	34	21	13	43	60	47	32	20	59	8	6	5	3	8	
25	SAMPOORNAMMA	40	F	Farmer	516075	A	11	9	8	4	10	4	4	3	2	4	37	30	20	9	37	52	43	31	15	51	7	7	4	3	7	
26	NENKATARAMANAPPA	62	M	Farmer	522328	A	10	8	8	5	11	4	3	2	2	4	38	30	19	8	39	52	41	29	15	54	7	7	4	3	8	
27	THIRUMALAPPA	44	M	Farmer	512675	A	14	12	9	5	13	4	3	2	2	3	38	28	25	12	36	56	43	36	19	52	8	7	5	3	8	
28	GANGAMMA	48	F	Housewife	580213	A	14	12	10			4	4	3			43	35	20			61	51	33			9	8	4			
29	KALAPPA	42	M	Tailor	506926	A	15	12	8	6	14	5	4	3	2	4	41	33	22	11	40	61	49	33	19	58	9	8	7	5	9	
30	SHARADAMMA	43	F	Farmer	593674	A	11	9	7	5	11	3	3	2	2	3	36	29	20	11	37	50	41	29	18	51	7	6	4	3	7	

S. No	NAME	AGE	SEX	OCCUPATION	HOSP NO.	Drug Grp	BL Pain	1 Wk Pain	2 Wk Pain	4 Wk Pain	3 M Pain	BL Stiffness	1 Wk Stiffness	2 Wk Stiffness	4 Wk Stiffness	3 M Stiffness	BL Disability	1 Wk Disability	2 Wk Disability	4 Wk Disability	3 M Disability	Initial WOI	1W WOI	2W WOI	4 W WOI	3M WOI	Initial VAS	1W VAS	2W VAS	4W VAS	3M VAS	Adverse Eff
31	KENCHAPPA	45	M	Mason	554609	A	11	8	7	5	10	4	4	3	2	4	38	30	23	8	37	53	42	33	15	51	7	6	4	3	7	Nausea
32	GANGAMMA	44	F	Farmer	549643	A	15	12				5	4				44	30				64	46				9	7				
33	NASREEN JAN	44	F	Veg vendor	532546	A	10	9	7	4	11	4	3	3	2	4	37	29	18	10	38	51	41	28	16	53	7	6	4	3	8	
34	JAYARAMAPPA	48	M	Farmer	659245	A	14	10	7	4	14	4	3	2	2	4	42	33	23	13	43	60	46	32	19	61	9	8	6	5	9	
35	MUNIYAMMA	42	F	Veg vendor	512937	A	12	10	7	5	11	4	3	2	2	4	41	33	24	12	40	57	46	33	19	55	8	7	4	3	9	
36	NARAYANAMMA	40	F	Farmer	531034	A	13	11	8	5	13	5	4	2	2	4	39	27	19	11	40	57	42	29	18	57	8	6	4	3	7	
37	SHANTABAI	55	F	Housewife	567525	A	14	11	9	6	13	5	3	2	2	4	41	31	20	9	41	60	45	31	17	58	9	8	6	3	9	
38	RESHMA BEGAM	46	F	Farmer	519273	A	10	8	7	4	10	4	4	3	2	4	38	30	23	8	37	52	42	33	14	51	7	6	4	3	7	
39	GEETHAVATHI	51	F	Farmer	559328	A	12	11	8	4	13	5	4	2	2	4	39	27	19	11	40	56	42	29	17	57	8	6	4	3	7	
40	ESHWARAMMA	62	F	Housewife	582372	A	14	12	8	4	14	5	4	2	2	4	44	30	18	9	43	63	46	28	15	61	9	7	6	5	8	
41	SRINIVAS REDDY	63	M	Farmer	538109	A	9	9	7			4	3	3			37	29	18			50	41	28			7	6	4			Rashes
42	LAKSHMI	46	F	Farmer	572538	A	13	11	8	4	14	4	4	3	2	4	43	31	21	10	42	60	46	32	16	60	9	8	6	4	9	
43	MOHAMMED IQBAL	49	M	Veg vendor	501284	A	14	12	8	4	14	5	4	2	2	4	44	30	18	9	43	63	46	28	15	61	9	7	6	5	8	
44	DHALE GOWDA	53	M	Farmer	502471	A	9	9	6	3	11	4	4	3	2	5	38	29	18	10	37	51	42	27	15	53	7	6	5	3	7	
45	GOWTHAMI	48	F	Housewife	592308	A	13	11	9	5	13	5	3	2	2	4	41	31	20	9	41	59	45	31	16	58	9	8	6	3	9	
46	NAVADHARANI	50	F	Housewife	582953	A	10	8	7	4	10	4	4	3	2	4	38	30	23	8	37	52	42	33	14	51	7	6	4	3	7	
47	ANANDHA	54	M	Farmer	601382	A	11	10	8	4	11	4	3	2	2	4	39	32	21	12	41	54	45	31	18	56	8	6	5	4	7	
48	MALLIKARJUNA	60	M	Farmer	579023	A	12	11	8	4	13	5	4	2	2	4	39	27	19	11	40	56	42	29	17	57	8	6	4	3	7	
49	VEENA	43	F	Farmer	610923	A	13	12	8	4		4	3	2	2		38	28	25	12		55	43	35	18		8	7	5	3		
50	LEELAVATHI	47	F	Veg vendor	603281	A	14	12	8	5	14	5	4	3	2	4	41	33	22	11	40	60	49	33	18	58	9	8	7	5	9	
51	SUSHEELAMMA	60	F	Housewife	619274	A	10	9	7	4	11	3	3	2	2	3	36	29	20	11	37	49	41	29	17	51	7	6	4	3	7	
52	MURALI	59	M	Farmer	629033	A	13	11	9	5	13	5	4	3	3	4	41	31	20	9	41	59	46	32	17	58	9	8	6	3	9	
53	JAYANTHI	58	F	Housewife	610928	A	11	10	8	4	11	4	3	2	2	4	39	32	21	12	41	54	45	31	18	56	8	6	5	4	7	
54	SAVITHRI	46	F	Farmer	590372	A	10	8				4	4				38	30				52	42				7	6				Nausea
55	LAKSHMAMMA	45	F	Veg vendor	598794	A	14	12	8			5	4	3			44	30	18			63	46	29			9	7	6			
56	BHAGAVATHI	48	F	Housewife	600281	A	12	11	8	4	13	5	4	3	3	4	39	27	19	11	40	56	42	30	18	57	8	6	4	3	7	
57	NARASHMMA REDDY	54	M	Veg vendor	590102	A	13	11	9	5	13	5	3	3	2	4	41	31	20	9	41	59	45	32	16	58	9	8	6	3	9	
58	LAKSHMAN REDDY	62	M	Farmer	6009127	A	10	8	7	4		4	4	3	2		38	30	23	8		52	42	33	14		7	6	4	3		
59	SHIVAPPA	54	M	Farmer	610945	A	13	11	8	4	14	4	4	3	2	4	43	31	21	10	42	60	46	32	16	60	9	8	6	4	9	
60	NARAYANA REDDY	47	M	Veg vendor	617320	L	10	10	8	4	12	4	3	2	2	4	35	26	14	5	34	49	39	24	11	50	8	6	5	3	7	