A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF PIROXICAM AND NAPROXEN IN THE MANAGEMENT OF PAIN IN OSTEOARTHRITIS OF KNEE

By

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In partial fulfilment of the requirements for the degree of

DOCTOR OF MEDICINE
IN
PHARMACOLOGY

Under the guidance of

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DEPARTMENT OF PHARMACOLOGY
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April 2017

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I hereby declare that this dissertation entitled "**A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF PIROXICAM AND NAPROXEN IN THE MANAGEMENT OF PAIN IN OSTEOARTHRITIS OF KNEE**" is a bonafide and genuine research work carried out by me under the direct guidance of **Dr. SARALA N,** $_{MD}$ Professor and Head, Department of Pharmacology, Sri Devaraj Urs Medical College, Tamaka, Kolar.

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Date: Signature of the Candidate

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Dedicated with reverence to Parents & Teachers

LIST OF ABBREVIAIONS

OA	Osteoarthritis
NSAID	Non Steroidal Anti-Inflammatory Drug
COX	Cyclooxygenase
PG	Prostaglandin
VAS	Visual Analog Scale
WOMAC	Western Ontario and McMaster Universities Arthritis Index
PSS	Patient Satisfaction Score
QOL	Quality of Life
ANOVA	Analysis of Variance
iNOS	inducible Nitric Oxide Synthase
IL	Interleukin
TNF	Tumor Necrosis Factor
MMP	Matrix Metalloproteinase
ACR	American College of Rheumatology
ADAMTS	A Disintegrin and Metalloproteinase with Thrombospondin Motifs
TGF	Transforming Growth Factor

ABSTRACT

BACKGROUND

Osteoarthritis (OA) is a degenerative joint disease and a major cause for functional disability. OA of knee is characterished by the insidious onset of pain and limited range of movements. Piroxicam and Naproxen are non-steroidal anti-inflammatory drugs (NSAIDs) used as analgesics in OA, rheumatoid arthritis, acute gouty arthritis, migraine, dysmenorrhoea and postoperative pain. The aim was to compare the efficacy and safety of these drugs in patients with OA of knee.

OBJECTIVES

1. To compare the efficacy of Piroxicam and Naproxen in patiens with OA of knee by using Visual Analogue Scale (VAS) and Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores
2. To assess the safety of the above drugs using WHO causality scale
3. To assess the patient's degree of satisfaction with regard to pain relief using Patient's Satisfaction Score (PSS)
4. To assess the Quality of Life (QOL) using WOMAC score

MATERIAL AND METHODS

This was a randomized, open label, comparative, parallel group, prospective study conducted in patients diagnosed with OA of knee joints. They received either oral Piroxicam 20 mg in group P or Naproxen 500 mg in group N twice daily for six weeks. Intensity of the pain was assessed by using VAS and WOMAC scores at baseline, 2^{nd}, 4^{th} and 6^{th} week. PSS and QOL were also assessed at each follow up. Adverse effects were assessed using WHO causality scale. Descriptive and inferential statistics were used.

RESULTS

Total of 110 patients were recruited, 47 males and 63 females, 100 completed the study (51 in P and 49 in N). Both Piroxicam and Naproxen significantly reduced VAS and WOMAC scores at 2^{nd}, 4^{th} and 6^{th} week (p=0.001) compared to baseline, but this was not significant between the groups. The reduction in WOMAC score implies improvement in quality of life of the patient. There was also an improvement in PSS in both the groups at 4^{th} and 6^{th} week when compared to week 2 and more number of patients expressed satisfaction as 'Good' with the study medications. The adverse effects like epigastric discomfort, nausea, vomiting, dizziness and pruritis were observed with both the drugs but the number was more with Naproxen than Piroxicam.

CONCLUSION

Piroxicam was as effective as Naproxen in relieving pain and improving range of movements in patients suffering from OA of knee with less adverse effects, suggesting it to be a better alternative to Naproxen in patients with osteoarthritis of knee joints.

Key words: Osteoarthritis, knee joint, non-steroidal anti-inflammatory drug, Piroxicam, Naproxen

CONTENTS

LIST OF TABLES

LIST OF FIGURES

Introduction

INTRODUCTION

Pain is the most common complaint in osteoarthritis (OA), which restricts the physical activity of the patients as well as decreases work performance.[1] In OA of knee, pain may arise from periosteal elevation, trabecular microfractures, capsular distension and/or synovial inflammation. Factors complicating determination of source of pain may include varus or vagus deformity, weight issues and the emotional impact of chronic pain. Once the cause of pain is identified, treatment plan can be formulated.[2]

Pain during the night is the most common reason in patients with OA to seek medical help.[3] The current treatment strategies for OA aim to educate the patient about OA, alleviate pain, optimize and maintain joint function and prevent or suppress progression of adverse structural change affecting the joint tissues. Encouraging weight loss in patients to reduce the stress on weight bearing joints will benefit the patient by reducing pain and increasing the mobility in joints.[4]

Commonly used pharmacological agents for pain management are non-steroidal anti-inflammatory drugs (NSAIDs).[5] Most of the patients with OA take medication for a long period and have a number of co-morbidities, which requires concomitant medication, increasing the likelihood of adverse events including gastrointestinal (GI) injury. There is an increasing demand for more effective and safer treatment for osteoarthritis.[6]

Piroxicam is a NSAID, an oxicam derivative, which are enolic acids that inhibit cyclooxygenase (COX) enzyme non selectively. It results in inhibition of prostaglandin production, which is the main mediator of pain. It has a long half-life ($t_{1/2}$) of approximately 50 hours and available as oral formulations, so it is suitable for use in OA.[5] It is also used in the management of postoperative pain, musculoskeletal

disorders and dysmenorrhoea.[7] It has shown clinical efficacy in relieving pain associated with OA and rheumatoid arthritis, especially where there is an associated inflammatory component.[8] It also suppresses primary and secondary lesions of adjuvant arthritis.[9] Naproxen is a NSAID, a propionic acid derivative and is a non-selective COX enzyme inhibitor. It is well absorbed orally and has a $t_{1/2}$ of 14hours.[5] It has clinically proven efficacy with regard to analgesia and relief of morning stiffness.[10] It has side effects like abdominal pain, gastritis, drowsiness, nausea, vomiting, dizziness and pruritis. Both the drugs are non-selective COX enzyme inhibitors, results in inhibition of prostaglandin production, which is the main mediator of pain and inhibits leukocyte migration, decreases oxygen radical production, inhibits lymphocyte function.

Aims & Objectives

AIMS & OBJECTIVES

1. To study the efficacy of Piroxicam and Naproxen in management of pain using Visual Analogue Scale (VAS) and Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores
2. To assess the safety of the above drugs using WHO causality scale
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Review of Literature

REVIEW OF LITERATURE

Historical Aspects

The earliest description of osteoarthritis (OA) was provided by Heberden[11] (Figure 1)[12] and Haygarth[13] (Figure 2)[14] in the 19th century. The term 'arthritis' was coined by Charcot and Virchow, fathers of cellular pathology, in 1869. In 1890 A E Garrod named the disease as 'osteoarthritis'. In the 1930s and 1940s, Stecher showed that idiopathic and post traumatic were the two forms of this disease.[15] Kellegren and Moore in 1950s established the link between Heberden's nodes and large joint OA.[16]

In the 1950s, Jonas Kellgren and John Lawrence developed the first x-ray grading system.[17] Application of this to epidemiology by Lawrence led to the observation of discordance between symptomatic and radiographic OA.[18] As early as the 1950s and 1960s, surgical options were pioneered. The surgical management of these patients was transformed by John Charnley and George Mckee when their landmark papers published during the 1960s.[19,20]

Figure 1.William Heberden

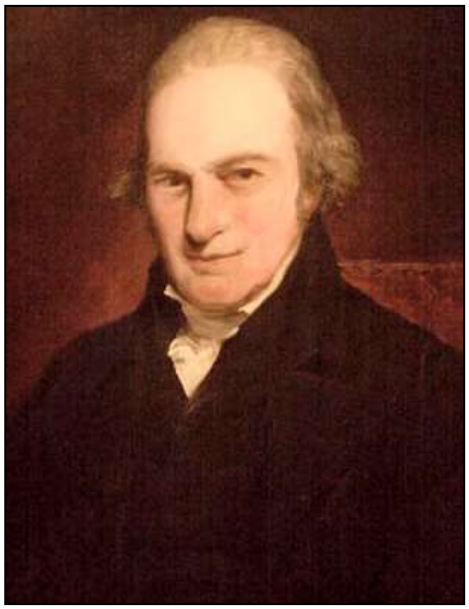


Figure 2. John Haygarth

Anatomy of knee joint[3]

It is the largest synovial joint in the body, which consists of the articulation between the tibia and femur (Figure 3),[21] which is weight bearing and the articulation between the femur and patella, which allows the pull of the quadriceps femoris muscle anteriorly over the knee to the tibia without the tear of tendon. It is a hinge joint that allows mainly flexion and extension. It is strenghtened one on each side by the collateral ligaments. The cruciate ligaments interconnect the adjacent ends of the tibia and femur. It also maintain their opposed positions during movement.

Articular surfaces

The articular surfaces of the bones contributing to the knee joint are covered by hyaline cartilage. The main surfaces involved include the two femoral and tibial condyles. The surfaces of the femoryl condyles that articulate with the tibia in flexion of the knees are curved or round whereas the surfaces that articulate in full extension are flat.

Menisci

There are two menisci in the knee joint. They are fibrocartilaginous C-shaped cartilages. They are medial meniscus and the lateral meniscus, which are attached to facets in the intercondylar region of the tibial plateau.

Synovial membrane

It attaches to the margins of the articular surfaces. It also attaches to the superior and inferior outer margins of the menisci. Anteriorly, an infrapatellar fat pad separates it from the patellar ligament and posteriorly, on either side of the posterior cruciate ligament, it reflects the fibrous membrane of the joint capsule. The synovial

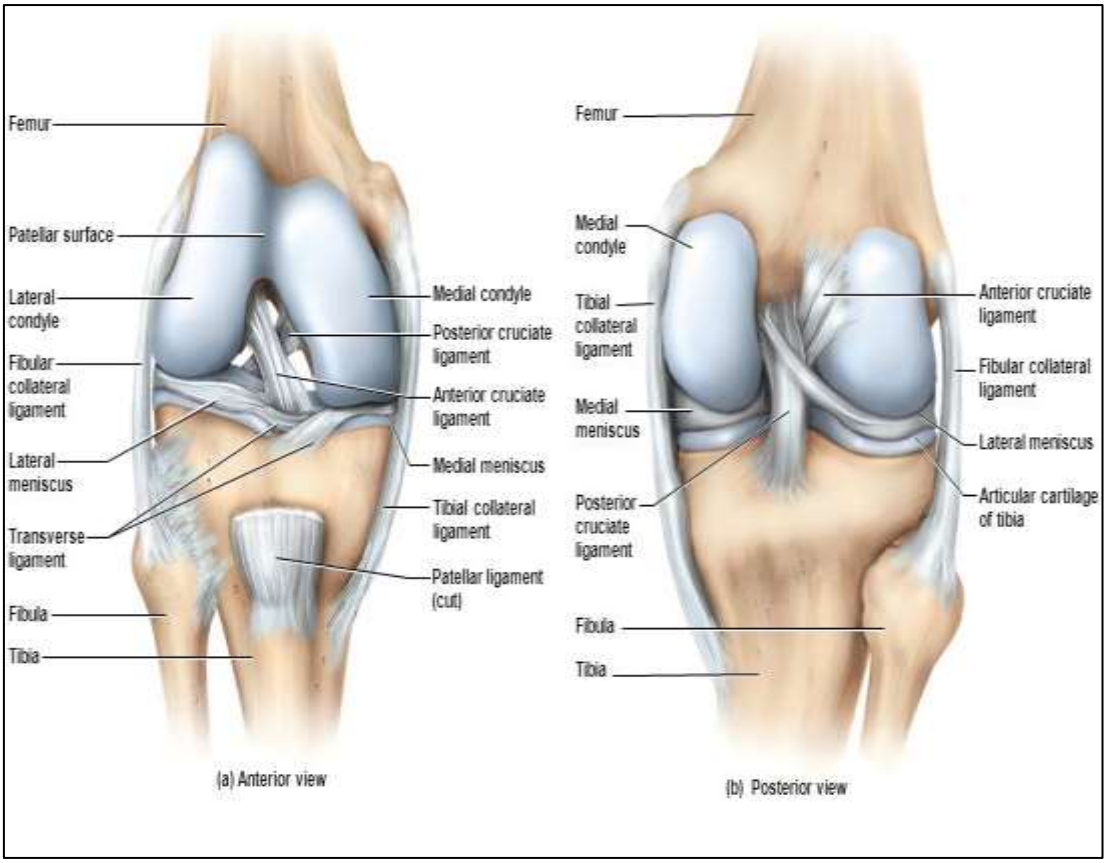


Figure 3. Anterior and posterior view of knee joint

membrane forms a fringed margin on each side of the pad, which projects into the articular cavity.

Biomechanics[3]

The primary plane of knee motion are flexion and extension, but small degrees of rotation, adduction/abduction, and anterior/posterior translation occur as well. Maximum stability is needed when the limb is in the midstance phase of walking or running. The knee is in almost full extension during midstance. In extension, medial rotation of the femur achieves the close-packed, stable position. The femoral condyles have larger articular surfaces than the tibial condyles. Therefore, knee movement has a component of rolling and gliding of the femoral condyles.

The lateral miniscus is displaced forward on the tibia and prevents further motion of the lateral meniscus femoral condyle. As the knee is extended, more highly

curved lateral condyles. The medial femoral condyle continues to glide backward, thus bringing its flatter, anterior surface into full contact with the tibia. Medial roation of the femur also brings the cruciate and collateral ligaments into maximum tension. The tension of the ligaments and the close approximation of the flatter parts of the condyles also make standing in the erect position relatively easy to maintain. An important function of the atella is to reduce the force requirements of the quadriceps muscle by use of a variable-lever arm. As the knee goes into extension, the patella rides up in the femoral notch, thereby increasing the moment arm and extension torque.

Normal articular cartilage

It forms the smooth, gliding surface of the diarthrodial joints. It is largely an avascular, anural and a lymphatic matrix, which is synthesized by the chondrocytes. The cartilage matrix (Figure 4)[22] depending on its relationship to the cells can be further divided into different compartments.

i) **Superficial**: Flattened chondrocytes has high collagen-to-proteoglycan ratio with high water content. Collagen fibrills form thin sheet parallel to articular surface giving the superficial zone an extremely high tensile stiffness.

ii) **Transitional zone**: Small spherical chondrocytes with higher proteoglycan and lower water content compared to superficial zone. Collagen fibrils form arcades by bending.

iii) **Radial Zone**: Occupies 90% of the column of articular cartilage. Upper radial zone has highest proteoglycan content. Collagen directed perpendicular to subchondral bone providing anchorage to underlying calcified matrix. In this zone, chondrocytes are largest and most synthetically active.

iv) Calcified zone: Articular cartilage via a thin layer of calcified cartilage, attached to the subchondral bone. The mineralization front advances during injury and OA, causing cartilage to thin.

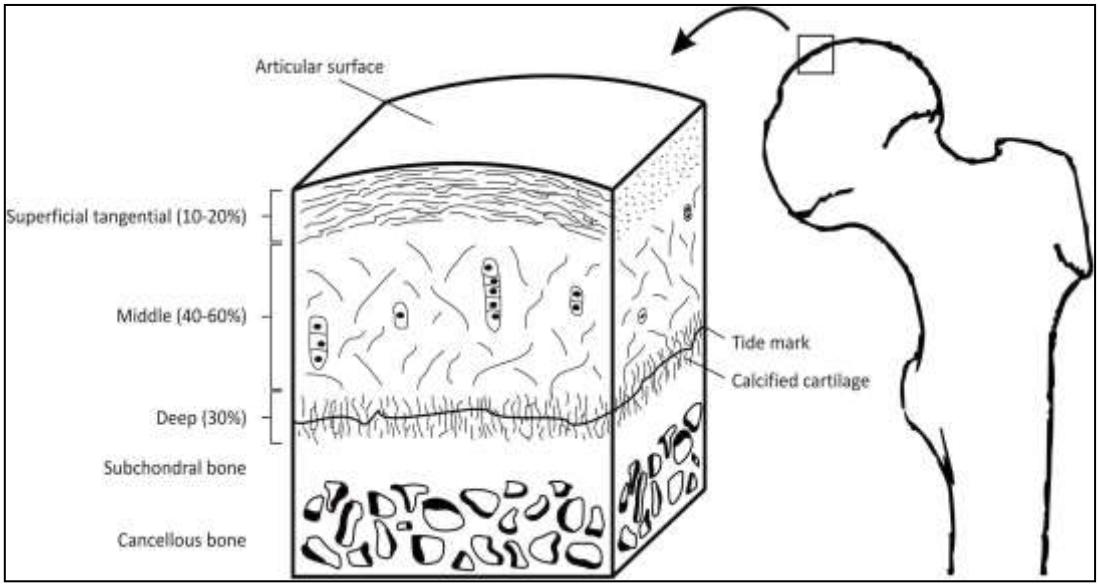


Figure 4. Structure of normal cartilage

The inter territorial cartilage matrix at the supramolecular level, consists of two basic components: a fibrillar and an extrafibrillar matrix. The fibrillar matrix is a network consisting mainly of collagen type II together with other collagens, predominantly types IX, XI and XVI.[23] The core of the collagen type II fibrils is collagen type XI and involved in fibril initiation and limiting fibril diameter.[24] The non-fibrillar component of hyaline articular cartilage predominantly consists of highly sulfated aggrecan monomers.[25]

The chondrocytes - The cells of articular cartilage[3]

Although articular cartilage functions via its extracellular matrix, the cells are not "functionless", as they are the only viable players within the tissue. Thus, the chondrocytes are centrally responsible for the maintenance of the extracellular matrix. In the adult, articular chondrocytes maintain the cartilage matrix by slow renewal of its constituents.

Physiology of joint functioning - Matrix turnover

Aggrecan core and link protein exist as a heterogeneous due to differential post-translational glycosylation and proteolysis in normal human articular cartilage. Normal proteolytic aggrecan turnover is regulated and implemented by the action of matrix metalloproteinases (MMPs) particularly MMP-3.[26] The second cleavage site, the 'aggrecanase' contributes to the proteolytic cleavage of aggrecan in particular in pathologic cartilage degradation. Thus, A Disintegrin and Metalloproteinase with Thrombospondin Motifs 4 (ADAMTS-4) and even more importantly ADAMTS-5 appears to be involved in generating respective aggrecan degradation products.[27] Fiber destabilization can only be brought about by cleavage of the triple helix due to the action of collagenases, for type II collagen being MMP-1 and MMP-13.

Osteoarthritis[3]

Osteoarthritis is defined by the American College of Rheumatology as a "heterogeneous 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 the joint margins."

Cartilage is the part of the joint that cushions the ends of the bones and allows easy movement of joints. The breakdown of cartilage causes the bones to rub against each other, causing stiffness, pain and loss of movement in the joint. OA typically affects only certain joints, such as the hips, hands, knees, low back and neck. Symptoms of OA typically first begin after 40 years and progress slowly. Women are more often affected by OA than men after 50 years.[28]

Etiology

Exact etiology is unknown and multiple factors are known to cause this disorder.

Systemic risk factors for osteoarthritis

Age: The frequency of OA condition escalates markedly in advancing years but OA may also occur in many young people in early twenties. The rapid radiological progression of OA was found in older people.[29]

Gender: Females are found to be more prone severe OA, have more symptoms and often manifest with hand and knee OA.[30]

Genetic: Nodal generalized OA is a polyarticular form characterized by Heberden's nodes occurring mainly in women of perimenopausal age. Thy appear to be inherited independently as an autosomal dominant trait with greater penetrance in women.[31]

Nutritional: Decreased levels of Vitamin C and D are associated with increased risk of OA.

Local risk factors

Injury/surgery: Any direct injury resulting in a fracture of articular surface is a most common cause for OA. Trauma during younger age increases subsequent occurrence of OA in subjects in their sixties.[32]

Obesity: Obesity has been recognized as potent risk factors for OA, especially the knee.[33]

Occupation: An increased risk of OA is seen in patients with repetitive use of joints at work. The risk of developing knee OA was more than two times greater for men whose jobs required both carrying and kneeling or squatting in mid-life than for those whose jobs did not require these physical activities.[34]

Physical activity/sports: There is some evidence that long distance runners are at high risk for the development of knee and hip OA.[35]

Mechanical factors: The relationship between muscle strength and OA is complex, may vary by joint site. Muscle weakness and atrophy commonly associated with knee OAs is due to disuse resulting from pain avoidance.

Laxity: Knee laxity is another potential risk factor for knee OA.

Alignment: Knee alignment (i.e. the hip-knee-ankle angle) is a key determinant of load distribution and any shift from a neutral or collinear alignment of the hip, knee and ankle affects load distribution at the knee.[36]

Other: The other important risk factors for the causation of OA are chondrocalcinosis, crystals in joint fluid / cartilage, prolonged immobilization, joint hyper mobility or instability, peripheral neuropathy, prolonged occupational or sps stress.[37]

Classification of Osteoarthritis[38]

1) Primary osteoarthritis (idiopathic)

A. **Localized:**

1. Hands – nodal osteoarthritis more than three joints involved

2. Hip – eccentric, concentric, diffuse

3. Knee – medial tibiofemoral, lateral tibiofemoral, patellofemoral

4. Spine – apophyseal, intervertebral, spondylosis

B. **Generalized:**

1. Small (peripheral) joints

2. Large (central) joints

3. Mixed and spine

C. **Erosive osteoarthritis**

2) Secondary osteoarthritis

i) Congenital and developmental disorders, bone dysplasia's

ii) Post-surgery / injury – Meniscectomy

iii) Endocrine – Diabetes Mellitus, acromegaly, hypothyroidism, hyperthyroidism, hyperparathyroidism, cushing's syndrome

iv) Metabolic – Hemochromatosis, ochronosis, marfan's syndrome, ehler-danlos syndrome, paget disease, gout, pseudogout, wilson's disease, hurler disease, gaucher's disease

v) Rheumatologic – Rheumatoid arthritis

vi) Neurological – Charcot joints

vii) Hematological – Hemoglobinopathies

viii) Iatrogenic – Intra-articular steroids

Pathology[38]

The joint as an organ

Joints are highly specialized organs that allow repetitive pain free and largely frictionless movements. These properties are provided by the articular cartilage and its extracellular matrix, which under physiological conditions is capable of sustaining high cyclic loading. Articular cartilage covers the joint surfaces and is mainly responsible for the unique biomechanical properties of the joints. They are complex composites of different types of connective tissue. These include subchondral bone, ligaments and the joint capsule, which together provide their own functional capacities thus allowing the functioning of the joint.

The capsule together with the ligaments provides the mechanical stability to the joint, without which the cartilage becomes abnormally loaded and degenerates dramatically, as seen in mal-alignment syndromes of the joints. The synovial membrane with its metabolically highly active surface cells (synocytes) help in nourishing the chondrocytes as well as removing metabolites and degradation

products: this is partly due to their own synthetic activity, partly to diffusion of serum components into the joint space. It is these cells which provide the basic metabolic homeostasis of the joints.

Osteoarthritic joints

Osteoarthritic joints have abnormal cartilage and bone, with synovial and capsular lesions (Figure 5).[39] Macroscopically, the characteristic features are reduced joint space, formation of osteophytes (protrusions of bone and cartilage) mostly at the margins of joints, and sclerosis of the subchondral bone (Figure 6).[40] These changes are the result of several histologic phases.

Phase 1: Edema and micro cracks

The first recognizable change in OA is edema of the extracellular matrix, principally in the intermediate layer. The cartilage loses its smooth aspect, and micro cracks appear. There is a focal loss of chondrocytes, alternating with areas of chondrocyte proliferation.

Phase 2: Fissuring and pitting

The micro cracks deepen perpendicularly in the direction of the forces of tangential cutting and along fibrils of collagen. Vertical clefts form in the subchondral bone cartilage, vertical clefts are formed and clusters of chondrocytes appear around these clefts and at the surface.

Phase 3: Erosion

Fragments of cartilage caused by fissures, detach and “fall” into the articular cavity, creating osteocartilaginous loose bodies and uncovering the subchondral bone, where microcysts develop. These loose bodies result in the mild synovial inflammation of OA.

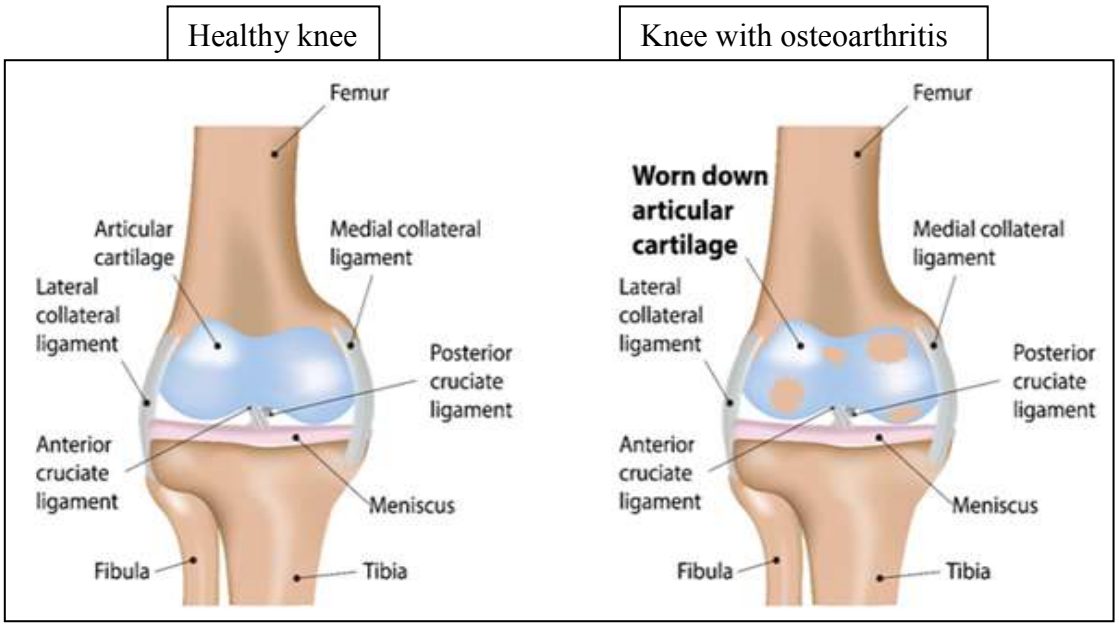


Figure 5. Structure of healthy knee and knee with osteoarthritis

Changes in osteoarthritis[38]

Morphologic changes

The articular cartilage surface becomes irregular and superficial clefts within the tissue become apparent in early OA. On histochemical staining, the proteoglycan distribution is changed. The clefts deepen, increase surface irregularities and the ulceration of articular cartilage, exposing the underlying bone as the disease progress.

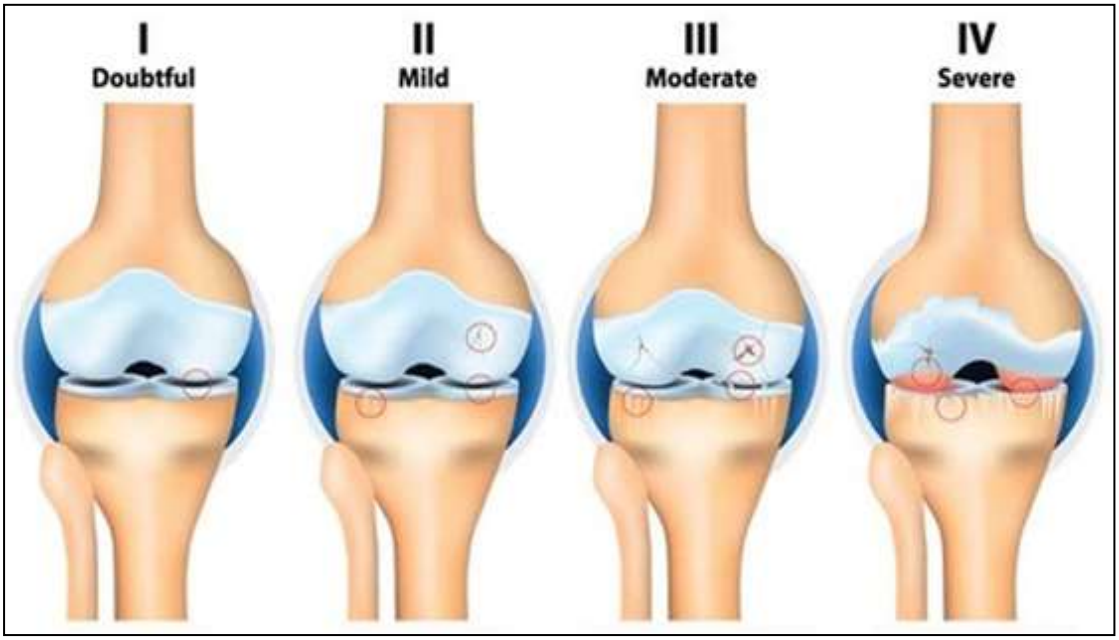


Figure 6. Stages of knee osteoarthritis

Biochemical changes

Two long-standing biomechanical theories of the pathogenesis of OA hold that mechanical stresses injure chondrocytes, causing them to release degradative enzymes, and that mechanical stresses initially damage the collagen network, leading to a breakdown of the matrix. Extracellular matrix breakdown in osteoarthritic cartilage leads to loss of compressive stiffness and elasticity, resulting in greater mechanical stress on chondrocytes, and an increase in hydraulic permeability, resulting in loss of interstitial fluid during compression and increased diffusion of solutes through the matrix.

The biochemical changes that occur in the articular cartilage vary as the disease progress. In early OA, the water content of the articular cartilage significantly increases, causing the tissue to swell and altering its biomechanical properties, in later stages, type I collagen concentration within the extracellular matrix increases and the proteoglycan concentration decreases to 50% or less than normal, with less aggregation and shorter glycosaminoglycan side chains.

Metabolic changes

As the severity of OA progresses, the synthesis and secretion of matrix-degrading enzymes by chondrocytes markedly increase. Early cartilage degeneration is most likely the result of the action of enzymes from the matrix metalloproteinase family of proteinases that degrade proteoglycans (aggrecanases) and collagen (collagenases). Collagenases typically make the first cleavage in triple-helical collagen, allowing its further degradation by other proteases. Aggrecanases in conjunction with other MMPs degrade aggrecan. Serine-dependent and cysteine-dependent proteases and membrane-type MMPs act primarily as MMP activators.

In OA, the expression and production of proteinases is increased. Native collagen has been shown to be cleaved by MMP-1, MMP-8, and MMP-13; the resultant fragments may be susceptible to cleavage by other enzymes such as MMP-2 (gelatinase A), MMP-9 (gelatinase B), MMP-3 (stromelysin 1) and cathepsin B. Of the three major MMPs that degrade native collagen, MMP-13 may be the most important in OA because it preferentially degrades type II collagen.

Matrix changes

In early-stage OA, proteoglycan concentration may increase, and the cartilage consequently may become thicker than normal and exhibit increased staining for proteoglycans. As disease progresses, focal cartilage ulcerations develop. Proteoglycan loss is accompanied by a decrease in its ability to aggregate, with abnormal glycosaminoglycan composition, and a decrease in chondroitin sulfate chain length. When proteoglycan loss reaches a critical threshold, the water content, which was initially increased, decreases.

Osteophyte formation

Osteophytes which are bony proliferations at the joint margins and in the floor of cartilage lesions are partly responsible for the pain and restriction of joint movement in OA. Human osteoarthritic joint osteophytes synthesize cartilage with significant amounts of type I collagen and non-aggregating proteoglycans. Osteophytes occur as a result of penetration of blood vessels into the basal layers of degenerating cartilage or as a result of abnormal healing of stress fractures in the subchondral trabeculae near the joint margins. TGF-β is a known anabolic growth factor that increases the expression of several types of collagen and proteoglycans.

Response of cartilage to mechanical injury

The normal articular cartilage response to injury typically results in suboptimal repair; these injuries often can result in secondary OA. In contrast to tissues that have the ability to regenerate injured regions with new cells and extracellular matrices that closely resemble the original tissue, articular cartilage produces a repair tissue with neither the original structure nor properties of normal cartilage. Chondrocytes in areas surrounding an injured zone are unable to migrate, proliferate, repopulate, regenerate or repair tissue with similar structure, function, and biomechanical properties of normal hyaline cartilage.

The reparative process of cartilage significantly differs from the reparative processes of other tissues because it is avascular. There are three categories of articular cartilage injury namely micro damage or repetitive trauma to the matrix and cells, partial-thickness or superficial injuries or chondral fractures, articular surface injuries that do not penetrate the subchondral plate and osteochondral injuries which extend into the underlying subchondral bone. The host response to each type of injury differs in timing and quality of repair.

Inflammatory molecules produced by articular cartilage[3]

Cytokines and chemokines

In an established OA, the characteristic feature is the increased production of proinflammatory cytokines, such as IL-1β and TNF-α by articular chondrocytes. They exert comparable catabolic effects on chondrocyte metabolism, decreasing proteoglycan collagen synthesis and increasing aggrecan release via the induction of degradative proteases. They also induce chondrocytes and synovial cells to produce other inflammatory mediators, such as IL-8, IL-6, nitric oxide and PG_{E2}. The actions of both are mediated partly by the activation of the transcription nuclear factor κB,

which increases further their own expression and that of other catabolic proteins, such as inducible nitric oxide synthase (iNOS) and COX-2, creating an autocatalytic cascade that promotes self-destruction of articular cartilage.

Proteinases

The main action of cytokines and chemokines produced in OA is to promote cartilage proteolysis by induction of a wide array of proteases, in particular MMPs. The two main families of MMPs are the collagenases that break down type II collagen (especially MMP-1, 8, 13, and 28), proteoglycans (MMP-3, which also cleaves pro-MMPs into their active forms) and the aggrecanases, also known as ADAMTS family.

Nitric oxide

Nitric oxide, produced by iNOS, is a major catabolic factor produced by chondrocytes in response to proinflammatory cytokines such as IL-1β and TNF-α. It exerts multiple effects on chondrocytes that promote articular cartilage degradation, including inhibition of collagen and proteoglycan synthesis, activation of metalloproteinases, increased susceptibility to injury by other oxidants and apoptosis.

Transforming growth factor-1

TGF-α acts as a counter regulatory molecule that opposes the effects of inflammatory mediators in cartilage. TGF-$1\beta_1$ down regulate proteolytic MMP-1, MMP-13, IL-1, and TNF receptors on osteoarthritis chondrocytes. TGF-β_2 selectively suppresses the cleavage of type II collagen by collagenases in osteoarthritis cartilage and decreases MMP and proinflammatory cytokine expression.

Hyaluronic acid

Hyaluronic acid is a marker of cartilage degradation that can be detected in synovial fluid and serum, but it also plays a role in limiting the progression of arthritis.

Prostaglandins

The expression of inducible COX-2 is increased in osteoarthritis chondrocytes. The effects of prostaglandins on chondrocyte metabolism include enhanced type II collagen synthesis, activation of metalloproteinases and promotion of apoptosis. COX-2 inhibition prevents IL-1β induced proteoglycan degradation.

Alterations in synovial tissue

OA is classify as a non-inflammatory arthritis, the synovial fluid leukocyte count is typically less than 2000 cells/mm. The clinical symptoms and signs seen in OA joints are due to synovial inflammation. In OA, synovial inflammation is confined to areas adjacent to pathologically damaged cartilage and bone in contrast to rheumatoid arthritis. The metalloproteinases are produced not only by the cartilage itself, but also by the synovium. Even in patients with mild OA, some degree of synovitis exists. A consequence of these low-grade inflammatory processes is the induction of synovial IL-1β and TNF-α which are likely contributors to the degradative cascade.

The role of mechanics in knee osteoarthritis

OA is a multifactorial condition, in which mechanical factors play an important role. Local mechanical factors such as the adduction moment, malalignment, quadriceps strength potentially make the knee joint vulnerable to the development and progression of OA.[41] The knee has three joint compartments; the patellofemoral, medial and lateral tibiofemoral joints. The medial compartment is subjected to more stress than the lateral, so OA affects the medial tibiofemoral compartment (75%) much more often than the lateral (26%) in men and women.[42]

The load distribution at the knee is affected by any shift from a neutral or collinear alignment of the hip, knee, and ankle joints.[43] The load-bearing axis is

represented by a line drawn from the center of the femoral head to center of the ankle. In a varus deformed knee, this line passes medial to the knee center, an abduction moment arm is created, which increases force across the medial compartment. Varus and valgus malalignment has been shown to increase the risk of subsequent medial and lateral knee OA progression on plain radiographs respectively.[44]

Symptoms of osteoarthritis[3]

Symptoms are often initially insidious and can be highly variable, depending the severity of joint involvement and the number of joints affected.

Pain

The first and predominant symptom of OA is pain that sends a patient to the doctor. It typically is worsened by activities such as long distance walking for weight-bearing joints and is alleviated by rest. It begins within a few minutes of starting an activity and may persist for hours even after ceasing the activity. Pain is unusual at rest or during the night, except in patients with mild OA using joints for several hours especially during sport, in advanced OA with destructive arthropathy and in an acute inflammatory flare of OA mimicking inflammatory arthropathy. Associated bursitis also can be a source of pain.

Stiffness and loss of movement and function

Stiffness may occur in the morning, after a period of inactivity or particularly in the evening. Morning stiffness generally resolves less than ten minutes. Loss of movement and function reflected in limited range of motion observed at physical examination is the main reason for a visit to the doctor. Patients complain limitations in their ability to perform day-to-day activities, such as kneeling. OA also can hamper stair climbing, walking and performing household chores. Limited joint function is

caused by several mechanisms including pain, decreased motion related to reduced joint space, diminished muscle strength and instability.

Physical examination

A physical examination should be done to confirm and characterize joint involvement and to exclude pain and functional syndromes arising from other causes, especially periarticular structures and inflammatory arthritis. Joint enlargement is result from joint effusion or bony swelling or both. Bony swelling is easily recognized in superficial joints, such as the finger joints or knees. A synovial effusion may be seen during OA flares, but also can occur during chronic phase. Joints are usually tender during active motion testing and under pressure. Limited passive movement is the first and only physical sign of symptomatic OA. Crepitus, an audible or palpable sensation of crunching or crackling, is commonly felt on passive or active mobilization of OA of the joint.

The physical examination should include examination of the legs with the patient standing. The knees are farther apart than the feet in the frontal plane in cases of varus (Figure 7)[45] alignment, whereas the knees are closer together than the feet in cases of valgus alignment. Varus and valgus alignments are responsible for medial and lateral tibiofemoral OA. Both can affect the range of motion and accelerate joint space narrowing; they may enhance the development of OA. A weak quadriceps femoris is a known disability factor in knee OA. This weakness can more convincingly explain the knee “giving way” than the often suggested ligament instability.

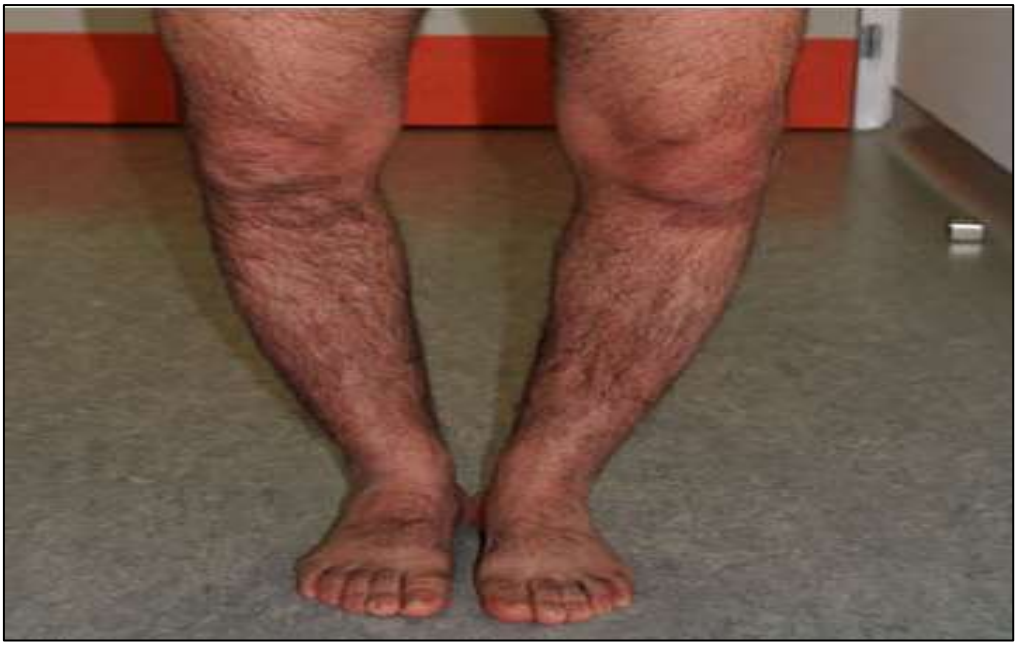


Figure 7. Osteoarthritis of knee with varus deformity

A lax joint is defined by the excess displacement or rotation of the tibia with respect to the femur in the varus-valgus direction. Joint laxity increases functional disability owing to weak muscles. Gait also must be assessed because knee OA results in a characteristic gait. It also is useful for examining the consequence of the pain.

Diagnosis

It is necessary to confirm that joint pain is due to OA in a patient with radiographic evidence to rule out some other cause, like radiculopathy, soft tissue rheumatism, referral of pain from other joint, entrapment neuropathy or some other type of arthritis (eg. septic arthritis). Even though the diagnosis of OA is often straightforward, high prevalence of radiographic OA in asymptomatic individuals is also seen.

Imaging

Radiologic investigation often is unnecessary to confirm the diagnosis of OA. Some regions and clinical scenarios require a radiologic examination such as avascular osteonecrosis. It also useful to establish the severity of joint damage, to

monitor disease activity, progression and response to therapy; and to look for complications of the disorder or the treatment. A standard radiograph cannot diagnose early OA, however osteophytes at the joint margin, indicating new bone formation, are the most characteristic feature of OA and usually precede joint space narrowing (Figure 8)[46].

The main radiographic features include progressive joint space narrowing, subchondral sclerosis and joint line osteophytosis. All the tissues involved in OA can be seen by magnetic resonance imaging including cartilage lesions, fluid effusion, subchondral bone marrow edema, low-grade synovitis and meniscus or ligament lesions. Ultrasound is currently useful only for detecting joint effusions, including a minimal effusion that is below the limit of detection on clinical examination and changes in cartilage, such as fibrillation of cartilage or cleft formation and the proliferation of synovium and osteophytes. Ultrasonography can be used to perform aspirations and injections within the joint and periarticular tissue. It is limited by its inability to visualize the whole cartilage surface. Arthroscopy visualizes cartilage, synovial membranes, osteophytes and meniscal lesions.

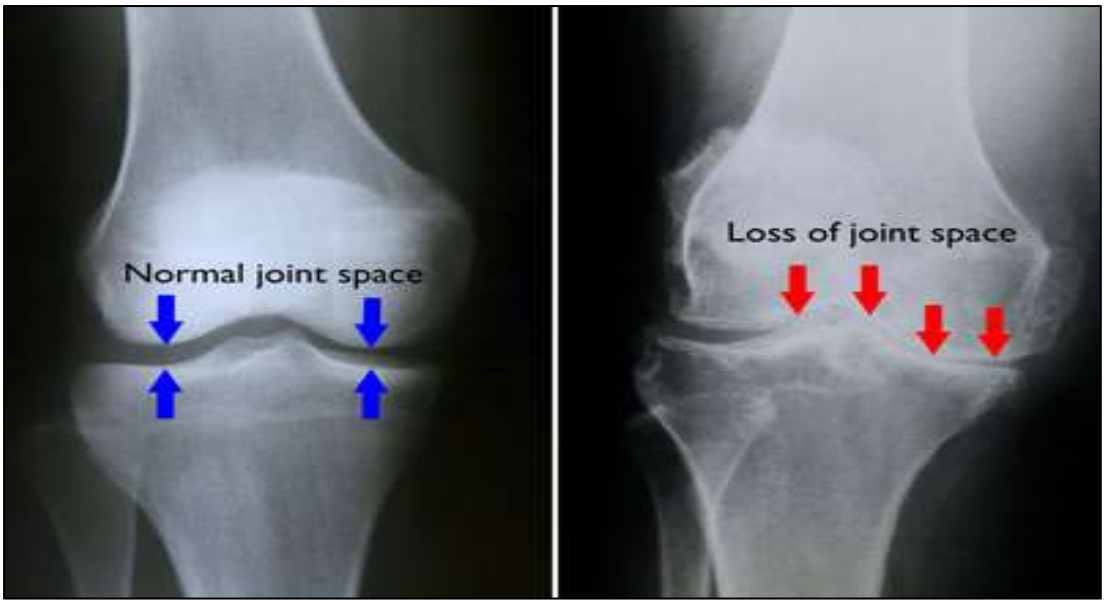


Figure 8. X-ray of normal and osteoarthritis knee

Criteria for defining osteoarthritis

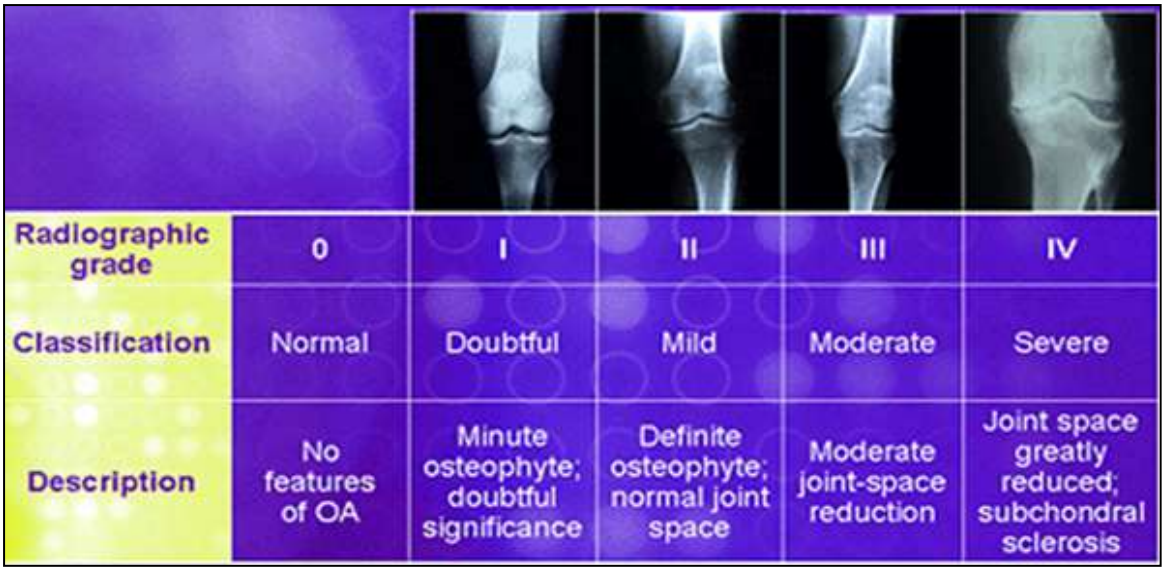
OA patients need to fulfill a set of criteria that includes the clinical and radiologic items proposed by the American College of Rheumatology (ACR). The sensitivity and specificity of the ACR knee criteria are estimated to be 91% and 86% respectively (Table 1).[47]

Table 1. American College of Rheumatology criteria for knee osteoarthritis

Clinical and laboratory	Clinical and radiographic	Clinical
Knee pain plus at least 5 of the following: age >50 years, stiffness < 30 minutes, crepitus, bony tenderness, bony enlargement, no palpable warmth, ESR < 40 mm/h, RF< 1:40, synovial fluid consistent with OA	knee pain plus at least 1 of the following: age >50years, stiffness < 30 minutes, crepitus-plus osteophytes	Knee pain plus at least 3 of the following: age >50 years, stiffness < 30 minutes, crepitus, bony tenderness, bony enlargement, no palpable warmth

The Kellgren and Lawrence (Table 2)[48] based on the presence of osteophytes, joint space narrowing, subchondral sclerosis and bony cysts. A score of 2 or more considered to be diagnosis of OA.

Table 2. Kellgren and Lawrence radiographic criteria



Osteoarthritis clinical assessment[3]

The assessment of a patient with OA should include discrete evaluations of pain and function. A patient's overall, global pain or disability assessment can be evaluated using a Visual Analog Scale and Western Ontario and McMaster Universities Composite Index. It is used mainly for the knee. Pain also can be assessed indirectly by estimating the symptomatic treatment required such as the number of days per week that drugs are required or their consistent dose usage.

Complications:

Capsular herniation: OA of the knee is sometimes associated with a marked effusion and herniation of the posterior capsule (Baker's cyst).

Loose bodies: cartilage and bone fragments may give rise to loose bodies, resulting in episodes of locking.

Spondylolisthesis: in patients over 60 years of age, destructive OA of the apophyseal joints may result in severe segmental instability and Spondylolisthesis

Treatment of osteoarthritis

Treatment aims are to educate the patient, control pain, minimize disability and handicap, and reduce further structural progression. Management (Figure 9)[49] should include:

- **Full explanation of the nature of OA**: This should include risk factors relevant to that individual (e.g., obesity, heredity, trauma) the fact that established changes are permanent but that pain and function can improve.
- **Advice and instruction on appropriate exercise**: This should cover both strengthening and aerobic, preferably with reinforcement by a physiotherapist.

- **Reduction of any adverse mechanical factors**: These include weight loss if obese, shock absorbing footwear, pacing of activities like use of walking stick for painful hip or knee OA.
- **Medications**: Consider the addition of a topical NSAID and then capsaicin for knee OA. The oral NSAIDs and opioid analgesics can be use, bearing in mind the side effects of such agents, especially in the elderly and those with co-morbidity.

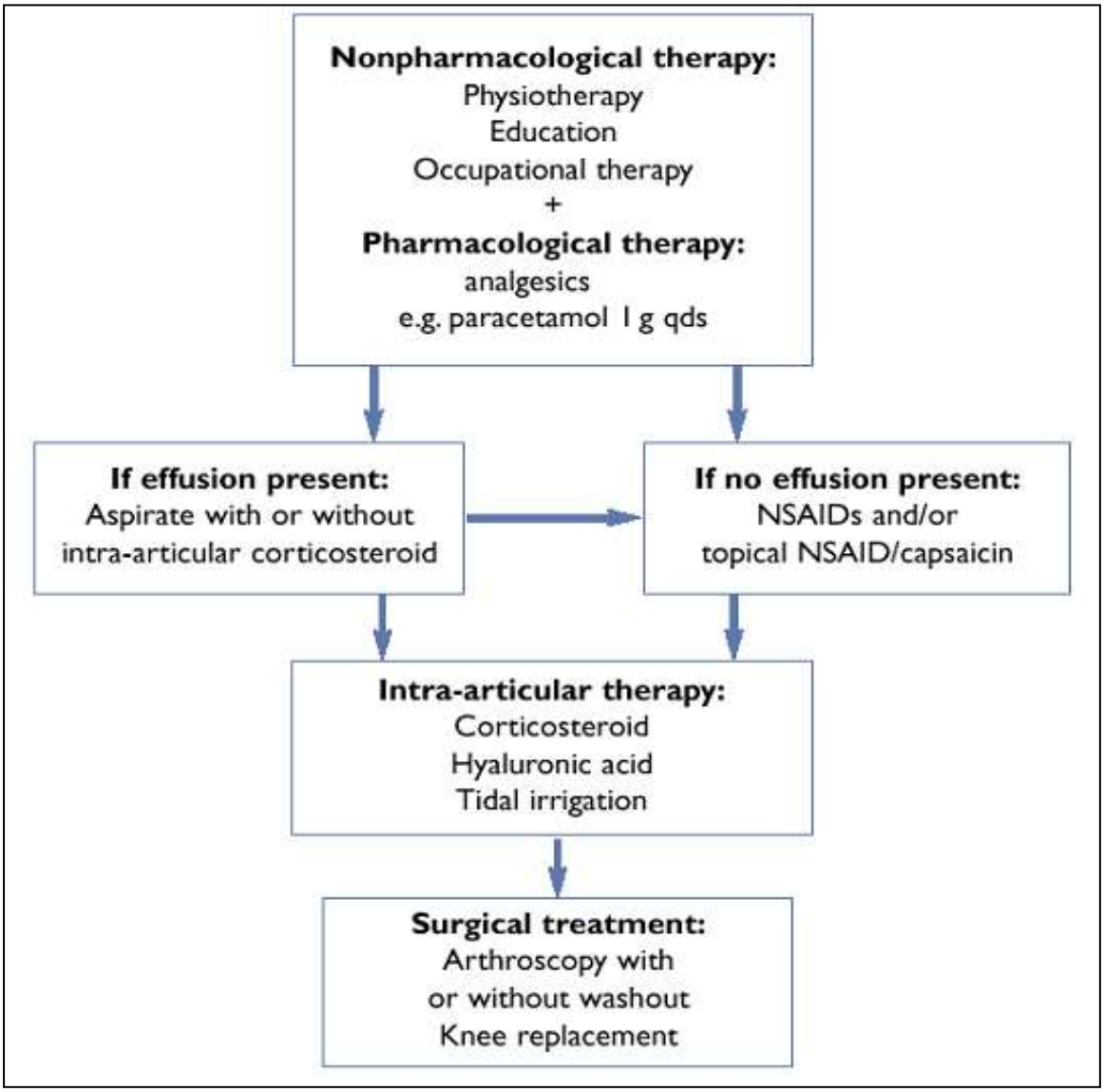


Figure 9. Algorithm for the management of osteoarthritis

Management[3]

The management of OA can be divided into non-pharmacologic interventions, pharmacologic interventions and surgery. Pharmacologic interventions can be further subdivided into symptomatic therapy and potential structure or disease modifying therapy.

Non-pharmacological interventions

Psychosocial interventions

Patient education is an important first step in OA therapy. The patient should be an integral part of the decision-making team. The patient should understand the nature of OA, including its natural history and treatment options. It is often reassuring for the patient to realize that OA is a very common, slowly progressive ailment and is not typically as disabling or deforming as the inflammatory arthritis. Some patients may develop significant emotional disturbances related to the pain and changes in normal daily activities,which may include mood disorders such as depression or sleep disturbances.

Weight loss

Obesity is an important risk factor in the development of knee OA. The higher body mass index has been associated with an increased risk of progression of knee OA. This can be compounded by malalignment like varus and valgus deformities that modulate the effect of weight on knee OA. Regimens of weight loss and exercise have been associated with improvement in pain and disability in OA of the knee.[50] The symptom relieving effects of weight loss have been shown to last as long as one year. The combination of weight loss and exercise can be superior to either intervention alone.[51]

Temperature modalities

Topical applications of heat or cold can be a helpful adjunct to the therapeutic plan. Warm applications can be in the form of warm soaks or heating pads, which should not exceed a temperature of 45°C or last more than approximately 30 minutes.[52] Benefits of warm applications include decreased pain and stiffness, along with relief of muscle spasm and prevention of contractures.

Exercise

Periarticular structures particularly muscles, influence the expression of OA, which is due to their role in providing stability to the joints and in dampening some of the forces acting across joints. Quadriceps muscle weakness has been postulated as a risk factor for OA of the knee. Walking can be beneficial and supervised fitness-walking regimens can improve function in those with knee OA. Home-based exercise interventions also significantly improve symptoms in knee OA. Community-based aquatic exercise programs, such as aquatic aerobics, have merit.[53]

Orthotics and bracing

Orthotics, ranging from insoles to braces can be effective in providing symptomatic relief and are probably underused by most physicians. Valgus bracing of patients with medial compartment OA can reduce pain and increase levels of activity.

Accupuncture

Acupuncture improved pain in knee OA. There was inconclusive evidence when compared with physical therapy for pain or function.

Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) use for three weeks was compared with thrice weekly hyaluronic acid injections in 60 patients with OA of the knee. Pain relief was observed in both groups through the six months of follow-up.

There was superior improvement in the WOMAC physical function subscale score for the hyaluronic acid group.[54]

Pharmacologic Interventions

Non-pharmacological treatment is not adequate to control pain or improve functional status in many patients with OA. Therefore, numerous pharmacological therapies have been advocated for the use in management of OA.

Topical capsaicin

Capsaicin is a pungent ingredient found in red peppers. The mechanism of action is thought to be through selective stimulation of unmyelinated type C afferent neurons, causing the release of substance P.

Topical NSAIDs

Topical NSAID preparations are popular worldwide for the treatment of OA. Safety concerns about traditional oral NSAIDs were the driving force in the use of topical agents.

Acetaminophen

Acetaminophen (Paracetamol) has often been touted as the initial systemic intervention for the management of OA. This is mainly due to its favorable side effect profile but also to a perception of its equivalent efficacy to NSAIDs.

Oral NSAIDs

They reduce pain in OA but the efficacy between among them is similar. The COX-2 inhibitors seem to have similar efficacy as nonselectives. Hence, the choice of NSAID apart from dose should be based on other factors, such as safety and cost. Nonselective drugs have shown the potential for serious gastro intestinal (GI), renal and cardiovascular toxicity.

Risk factors for NSAID-induced GI toxicity include age more than 65 years, history of peptic ulcer disease or upper GI bleeding, use of glucocorticoids or anticoagulants and presence of co-morbid conditions. Although selective COX-2 inhibitors seem to have lower risk of GI toxicity, rofecoxib has been found to be associated with an increased risk of cardiovascular event.

Opioids

A narcotic analgesic should be considered if a patient has failed to respond to other nonpharmacological and pharmacologic modalities and has no additional identifiable causes of pain. The pain of OA is generally responsive to narcotic analgesics. Because of concerns about potential addiction, appropriate patient selection is important. Narcotic analgesics such as Codeine and Propoxyphene have been used effectively in patients with OA, especially in combination with non-narcotic analgesics. Potential side effects include nausea, constipation, and somnolence. Oxycodone has demonstrated efficacy for OA pain. Tramadol is an oral medication with mild suppressive effects on the opioid receptor. It also inhibits the uptake of norepinephrine and serotonin. It is does not have significant addictive tendencies. It has been used for the symptomatic relief of OA.

Intra-articular corticosteroids

Local intra-articular corticoid preparations have a long history in the management of OA but not systemic corticosteroids. Corticosteroids have been shown to down regulate the expression of adhesion molecules. This can reduce cellular infiltration into the joint and subsequent inflammation.

Intra-articular hyaluronic acid

Hyaluronic acid is a component of human synovial fluid that increases its viscosity. In OA, there is decreased of hyaluronic acid in the synovial fluid.

Nutraceuticals for Osteoarthritis

Glucosamine

Glucosamine is natural substance derived from animal products, which stimulats proteoglycan synthesis in articular cartilage and rebuild the damaged cartilage. It takes several weeks to demonstrate the therapeutic effect.

Chondroitin Sulfate

Chondroitin sulfate is a natural substance derived from animal products. It also stimulates proteoglycan synthesis in articular cartilage as seen in glucosamine. There was no evidence from human studies to support this theoretical role in cartilage repair.

Avocado and soya unsaponifiables

Oral preparations of avocado and soya unsaponifiables (ASUs) are proposed as structure or disease modifiers in OA. These are derived from unsaponifiables residue of avocado and soya oil mixed in a 1:2 ratios. ASUs increases the IL-1β levels in OA, which inhibit prostaglandin synthesis by chondrocytes and stimulation of matrix metalloproteinases (MMPs) and nitric oxide (NO) production. It also inhibit the production of IL-6, IL-8, MMPs and stimulates collagen and aggrecan synthesis.

S-adenosylmethionine

S-adenosylmethionine is a naturally occurring compound found throughout the body. It increase proteoglycan synthesis in articular cartilage, indicating an ability to repair damaged cartilage. Other mechanisms of action like decreasing inflammation and providing analgesia have shown to decrease depression.

Other potential structure or disease-modifying therapies

The term chondroprotective has been used to describe structure or disease modifying agents. This is a misnomer, because the goal is to protect the entire joint from the arthritic process. These drugs are intended to prevent, retard, stabilize, or

even reverse the development of OA. They are Tetracycline, metalloproteinase or collagenase inhibitors, chondrocyte and stem cell transplantation, diacerein, growth factor and cytokine manipulation and gene therapy. Unfortunately, to date, no drug has been conclusively proved.

Surgical Intervention

There is lack of evidence based criteria regarding indications for the referral of a patient with OA for surgical treatment. Most consensus recommend that patients who continue to have severe pain with functional limitation of the knee, despite maximal conservative therapy, should be referred for consideration for surgical treatment.

Arthroscopic debridement

In patients with knee OA, there was no benefit from arthroscopic debridement. It is unclear whether arthroscopic debridement would be more efficacious if performed in select patients, such as younger patients with chondral or meniscal lesions amenable to debridement.

Osteotomy

High tibial osteotomy is performed, when knee OA is limited to the medial compartment. The rationale of this procedure is to correct the varus deformity and redistribute the weight-bearing stress of the joint. It can be performed for lateral unicompartmental knee OA.

Total knee replacement/Arthroplasty

The knee replacement improves pain and function in patients with knee OA. Total knee replacement is generally recommended, if it involved more than one compartment. The total knee replacement resulted in significant improvement in health related quality of life.

Pharmacology of Piroxicam[5]

Introduction

Piroxicam is a non-steroidal anti-inflammatory agent of oxicam class. It is highly bound to plasma proteins and has a plasma half-life of nearly 50 hours. Hence once daily administration improved compliance due to long plasma half-life.[55] It is well established for the treatment of osteoarthritis and rheumatoid arthritis. It is also used in the management of dysmenorrhea, musculoskeletal disorders and post-operative pain.[56] In April 6, 1982 the FDA approved Piroxicam for rheumatoid arthritis and osteoarthritis. Unlabelled use for ankylosing spondylitis, menstrual cramps, juvenile rheumatoid arthritis.[57]

Structure and chemistry

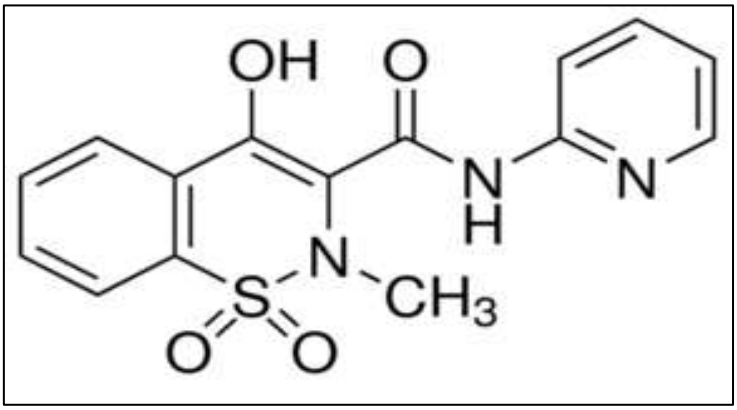


Figure 10. Structure of Piroxicam

Piroxicam chemical name is 4-hydroxyl-2-methyl-N-2-pyridinyl-2H-1,2 benzohiazine-3-carboxamide 1,1-dioxide (Figure 10).[58] It is a white crystalline, sparingly soluble in water, dilute acid and most organic solvents. It is slightly soluble in aqueous solutions and in alcohol. It has a weakly basic pyridyl nitrogen (pKa 1.8) and a weakly acidic 4-hydroxy proton (pKa 5.1).

Pharmacokinetics

Absorption

Piroxicam is well absorbed orally and attained peak concentration 2 hours after administration. The next peak is found between 6 and10 hours which is seen due to enterohepatic recirculation. An almost similar plasma concentration-time curve after oral, rectal, intramuscular and intravenous administration, signify nearly complete oral absorption. The plasma concentration of Piroxicam vary less between consecutive doses than those of other non-steroidal anti-inflammatory drugs due to its long elimination half-life. Food may delay the absorption.

Distribution

An apparent volume of distribution is 0.14L/kg body weight, which is about 10L for a 70kg man. It is extensively (99%) bound to plasma proteins. In patients with rheumatoid arthritis and osteoarthritis, it penetrates into the synovial fluid where mean concentration is 40% of that in plasma. The concentration of Piroxicam in breast milk is 1% of maternal plasma.[58]

Metabolism

Piroxicam is metabolized in the liver by hydroxylation and conjugation with glucuronic acid. Its metabolites have no anti-inflammatory activity and are inactive.[59]

Elimination

The elimination half-life of Piroxicam is 30-60 hours. Only 2-5% of it is excreted unchanged in the urine.

Mechanism of action

Piroxicam hinders the formation of prostaglandins, which are important mediators of pain, by non-selectively inhibiting the cyclooxygenase enzymes. Hence the nociceptive transmission of pain stimulus to the brain decreases, resulting in

analgesia. It may also inhibit the activation of neutrophils, proteoglycanase and collagenase in the cartilage.

Pharmacodynamics

Analgesic effect

The analgesic effect of Piroxicam lasted for 12 hours. It is more active than Aspirin, Ibuprofen, Naproxen, Phenylbutazone but less effective than Indomethacin in decreasing writhing frequency by 50%.

Anti-inflammatory effect

NSAIDs block the release of lysosomal enzymes and superoxide anions which are responsible for the degradation of cartilage by inhibiting the polymorphonuclear aggregation. It is twice as potent as Indomethacin, seven times more potent than Naproxen and forteen times than Phenylbutazone. Orally administered Piroxicam is equipotent with the topical and rectally administered drug.

In rheumatoid arthritis patients, Piroxicam reduces plasma concentration of PG_{E1} and $PG_{E2\alpha}$. It also decreases the synthesis of metabolic regulatory factors in conditioned medium derived from synovial culture containing significant cartilage cell catabolic – inducing activity.

Uses[60, 61]

- Rheumatoid arthritis
- Osteoarthritis
- Ankylosing spondylitis
- Acute gout
- Post-operative pain
- Mesothelioma
- Complex regional pain syndrome

Adverse effects

Dyspepsia, abdominal pain, gastritis, nausea, vomiting, and dizziness

Drug interactions

- Aspirin reduces the plasma concentrations of Piroxicam by about 80% of normal.
- Ritonavir raises its plasma concentrations resulting in increased risk of toxicity.
- Anti-coagulant effect of Acenocoumarin increases by Piroxicam.

Drug dosage and route of administration

- Oral 20 mg as a once or twice daily is the initial adult dosage in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The daily maintenance dose 10-30 mg.
- In acute gout 40 mg daily for five to seven days.
- In post-operative pain 20 mg daily intramuscularly and 40 mg recommended for prolonged operations as in orthopedic surgeries.
- In acute musculoskeletal conditions, an initial dose of 40 mg daily for first two days followed by 20 mg daily for two weeks.
- In children above six years Piroxicam dispersible tablets used.
- Local painful inflammatory conditions topical gel in a concentration of 0.5% is applied three or four times daily.[62]

Pharmacology of Naproxen[5]

Introduction

Naproxen is a non-steroidal agent of propionic acid derivative. Its plasma half-life is 14 hours and is highly plasma protein bound. Hence it is administered twice daily. It is indicated for juvenile and rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, primary dysmenorrhea, tendinitis, bursitis, migraine and acute gout.

Structure and chemistry

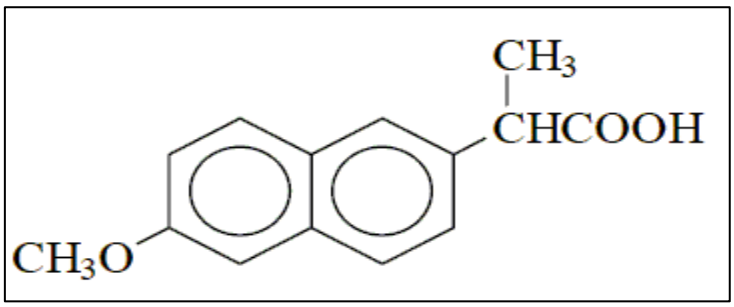


Figure 11. Structure of Naproxen

Naproxen chemical name is 2-naphthaleneacetic acid, 6-methoxy-methyl (Figure 11).[63] It is an odorless, white to creamy crystalline, lipid soluble and a free acid. It is soluble in methanol.

Pharmacokinetics

Absorption

Naproxen is well absorbed orally and attained peak concentration two to four hours after administration and more rapid absorption after the administration of Naproxen sodium. Naproxen is also absorbed rectally but more slowly than oral administration. Food delay the rate but not the extent of absorption.

Distribution

An apparent volume of distribution is 0.16L/kg body weight. It is extensively (99%) bound to plasma proteins. Naproxen crosses the placenta and appears in breast milk at 1% of maternal plasma concentration.

Metabolism

Naproxen is extensively metabolized in the liver by 6-demethylation. Both Naproxen and its metabolite are excreted after conjugation with glucuronic acid.

Elimination

The elimination half-life of Piroxicam is 15 hours. Metabolites of Naproxen are excreted almost entirely in the urine. A small of amount of the drug is excreted in the feces (less than 5%).

Mechanism of action

Naproxen is a non-selective inhibitor of cyclooxygenase enzymes and reduces the production of prostaglandins, which are important mediators of pain. It has prominent inhibitory effects on the leucocyte function.

Pharmacodynamics[5]

Analgesic effect

The analgesic effect of Naproxen lasted for 12 hours. It has slightly better efficacy with regard to analgesia and relief of morning stiffness.

Anti-inflammatory effect

Naproxen block the release of lysosomal enzymes which are responsible for the degradation of cartilage by inhibiting the leucocytes.

Uses

- Juvenile arthritis
- Rheumatoid arthritis
- Osteoarthritis
- Ankylosing spondylitis
- Acute gout
- Migraine
- Tendinitis
- Bursitis

Adverse effects

Abdominal pain, gastritis, drowsiness, nausea, vomiting, dizziness and pruritis

Drug interactions

- Magnesium oxide and Aluminum hydroxide reduces the plasma concentrations of Naproxen
- Sodium bicarbonate raises the plasma concentrations of Naproxen

Drug dosage and route of administration

- Oral 250 mg four times or 500 mg twice daily is the adult dosage in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis
- In children 5mg/kg twice daily

Materials & Methods

MATERIALS AND METHODS

A randomized, open label, comparative, parallel group, prospective study was conducted in patients diagnosed with osteoarthritis (OA) of knee joints. This study was carried out by departments of Pharmacology and Orthopaedics in R.L Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar from January 2015 to June 2016.

Inclusion criteria

1. Patients of either gender, aged between 40 - 70 years
2. Patients with symptomatic idiopathic OA for a minimum period of six months
3. Patients with OA of bilateral knee joint involvement
4. Radiological evidence of OA of knee joints
5. Morning stiffness of less than 30 minutes duration with crepitus on motion

Exclusion criteria

1. Patients with history of surgery or acute trauma to the knee joint within six months
2. Patients with history of peptic ulcer, gastrointestinal bleeding, psychiatric illness and bronchial asthma
3. Patients with history of acute inflammatory arthritis, pseudogout or severe osteoporosis
4. Patients who are hypersensitivity to Piroxicam or Naproxen
5. Patients with deranged hepatic and renal parameters

Method of collection of data

Patients with pain due to OA of knee joints were recruited in the study. They were randomized by simple randomization in a 1:1 ratio into two groups of 55 each,

with group P receiving Piroxicam 20 mg and the group N receiving Naproxen 500 mg orally twice daily for six weeks. Patients were followed up at 2nd, 4th and 6th week. The patients recruited in both groups were matched in terms of age, gender, weight and body mass index (BMI). They were instructed to do mild exercise, apply hot fomentation and use Indian style toilet.

Demographic details and relevant history were collected from the patient at the time of recruitment. Clinical examination including general physical examination and knee joints examination (inspection, palpation, range of movements and measurements) was done. Routine laboratory investigations such as complete haemogram, random blood sugar, blood urea, serum creatinine, liver function test and urine routine were done at baseline. X-rays of knee joints were taken at baseline for diagnosis. Rheumatoid factor was done when required.

The Visual Anologue Scale (VAS)[6] (Figure 10 and Table 3) and Western Ontario and McMaster Universities Arthritis Index (WOMAC)[1] scores were assessed at baseline and at each follow up. The VAS score was graded from 0 to 10 according to patient's response. WOMAC is a subjective score consisting of subscales in terms of pain (Table 4a), stiffness (Table 4b) and physical function (Table 4c). All the parameters were graded on a scale of 0 to 4 depending on the severity, from none to severe. The WOMAC total domain score (range 0-96) is the sum of the pain, stiffness and physical function. The reduction in WOMAC score indirectly indicates improvement in quality of life (QOL). If the VAS score was more than three after initiating the treatment with study drugs, oral tramadol 50 mg was used as rescue analgesic. Patients' satisfaction with respect to pain relief was assessed using Patient's Satisfaction Score (PSS) at each follow up. PSS was graded as 1 = poor, 2 = fair,

3 = good and 4 = excellent. During the follow up, safety of the drugs was monitored using WHO causality scale. The events were classified as:

- **Certain**: if it has a plausible time relationship to drug intake, if the adverse effect subsides on stopping the drug and if on rechallenge the adverse effect occurred
- **Probable**: if it has a reasonable time relationship to drug intake and if the adverse effect subsides on withdrawing the drug
- **Possible**: if it has a reasonable time relationship to drug intake, if the adverse effect can be explained by disease or other drugs
- **Unlikely**: if it has an improbable time relationship to drug intake, if the adverse effect can be explained by disease or other drugs
- **Conditional**: if more data for assessment is required
- **Unassessable**: if data cannot be supplemented or verified

Visual Analog Scale

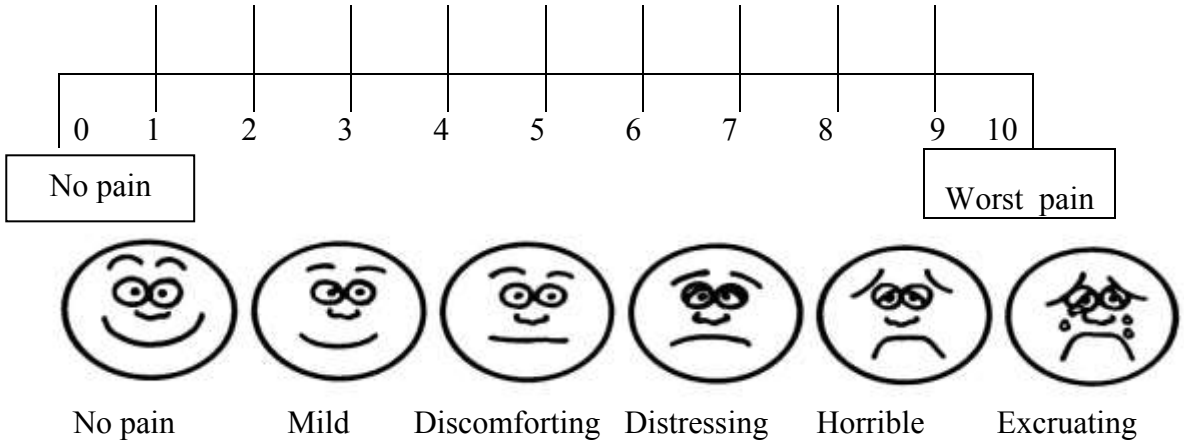


Figure 12. Visual Analogue Scale

Directions – How severe is your pain today? Place a vertical mark on the line above to indicate how bad your pain

Table 3. Graded Visual Analogue Scale (VAS) score

VAS score	Severity of pain
0	No pain
1-3	Mild
4-7	Moderate
8-10	Severe

Western Ontario and McMaster Universities Arthritis Index (WOMAC)

Table 4a. Pain subscale

Sl. No	Situation	None	Mild	Moderate	Severe	Extreme
1.	Walking on flat surface	0	1	2	3	4
2.	Going up/downstairs	0	1	2	3	4
3.	At night	0	1	2	3	4
4.	Sitting/lying	0	1	2	3	4
5.	Standing upright	0	1	2	3	4
					Score =	

Table 4b. Stiffness subscale

Sl. No	Situation	None	Mild	Moderate	Severe	Extreme
1.	How severe is the stiffness after first walk in morning	0	1	2	3	4
2.	How severe is the stiffness after sitting, lying or resting later in the day	0	1	2	3	4
Score =						

Table 4c. Physical function subscale

Sl. No	Situation	None	Mild	Moderate	Severe	Extreme
1.	Descending stairs	0	1	2	3	4
2.	Ascending stairs	0	1	2	3	4
3.	Getting out of chair	0	1	2	3	4
4.	Remaining in standing position	0	1	2	3	4
5.	Bending	0	1	2	3	4
6.	Walking on flat surface	0	1	2	3	4
7.	In/out of car	0	1	2	3	4
8.	Shopping	0	1	2	3	4
9.	Socks/stockings on	0	1	2	3	4
10.	Getting out of bed	0	1	2	3	4
11.	Socks/stockings off	0	1	2	3	4
12.	Lying in bed	0	1	2	3	4
13.	In/out bath	0	1	2	3	4
14.	Sitting	0	1	2	3	4
15.	Toileting	0	1	2	3	4
16.	Heavy domestic duties	0	1	2	3	4
17.	Light domestic duties	0	1	2	3	4
Score =						

Statistical methods

To detect a mean difference of VAS score of 0.98 at the end of one month with effect size of 0.564, power of 80%, alpha error of 5% and dropout rate of 10%, the required sample size was 55 patients per group. The demographic data was analyzed using descriptive statistics. The VAS and WOMAC scores were assessed by Repeated measure ANOVA followed by Bonferroni post hoc test within the group and unpaired 't' test between the groups. Adverse events were analyzed by chi-square test. Patient's Satisfaction Score was analyzed by using Wilcoxon and Mann-Whitney U test. Quality of Life was analyzed by descriptive statistics. p value less than 0.05 was considered statistically significant.

Results

RESULTS

Patients with osteoarthritis of both the knee joints recruited were 110 but 100 patients completed the six weeks study period (Figure 13). Analysis was done for patients who have completed the study.

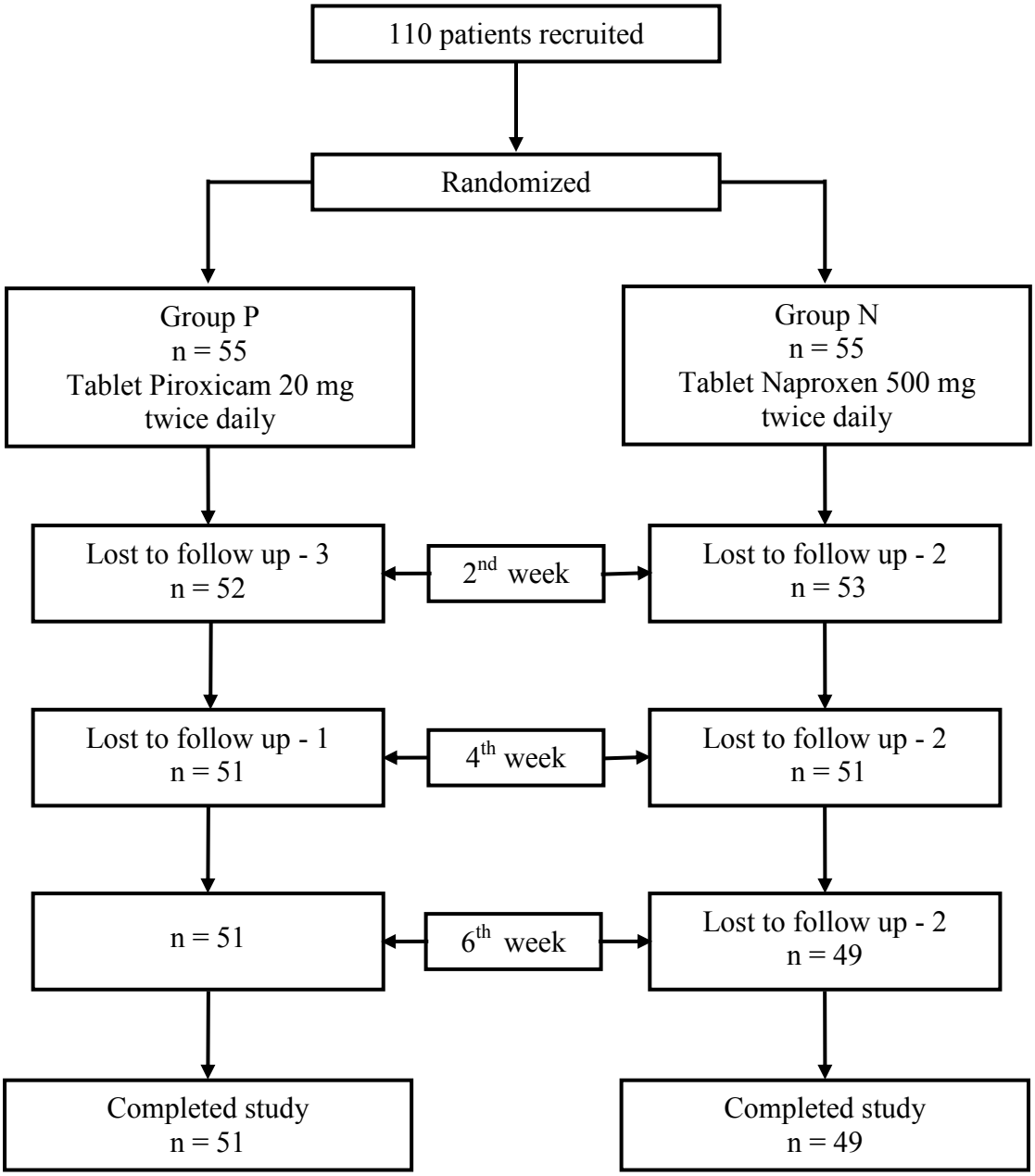


Figure 13. Flow chart representing recruitment, randomization and follow up

Table 5. Demographic parameters

Variables	Group P (n=55)	Group N (n=55)
Age (years) Mean±SD	55.24±9.80	52.03±9.00
Male/female	23/32	24/31
BMI (kg/m^2) Mean±SD	25.80±4.32	26.00±4.57

The demographic parameters were comparable in both the groups. Among 110 patients, majority of patients in both groups were females (57.3%).

Table 6. Occupation of patients in both groups

Occupation	Group P (n=55)		Group N (n=55)	
	Number	Percentage	Number	Percentage
House wife	24	43.6	22	41.0
Farmer	16	29.1	18	32.7
Teacher	8	14.6	9	16.3
Tailor	7	12.7	6	10.0
Total	55	100	55	100

Housewives constituted for more than 40% in both the groups.

Table 7. Comparison of mean VAS scores within the groups

	Group P		Group N	
	Mean±SD	p value	Mean±SD	p value
Baseline	8.00±1.51	-	7.78±1.45	-
2^{nd} week	5.52±1.35*	0.001	5.45±1.32*	0.001
4^{th} week	3.53±1.10*	0.001	3.55±1.12*	0.001
6^{th} week	1.80±0.70*	0.001	1.90±0.60*	0.001

*p value compared with baseline

The reduction in VAS score was statistically significant at each follow up compared to baseline in both groups. By week 6 there was significant decrease in VAS score with both the medications.

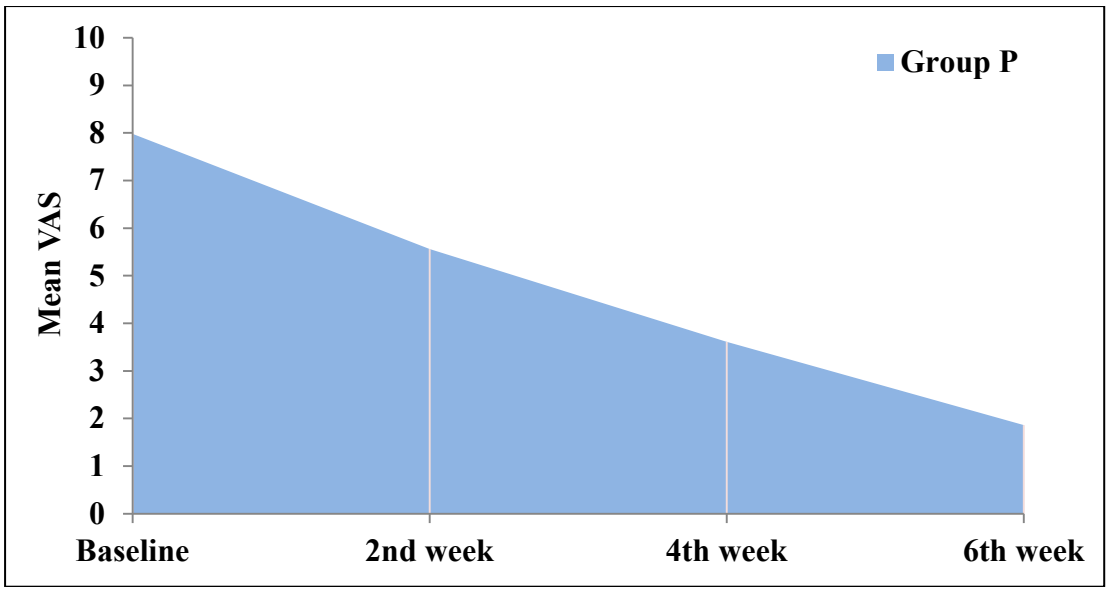


Figure 14. Area under curve – Piroxicam

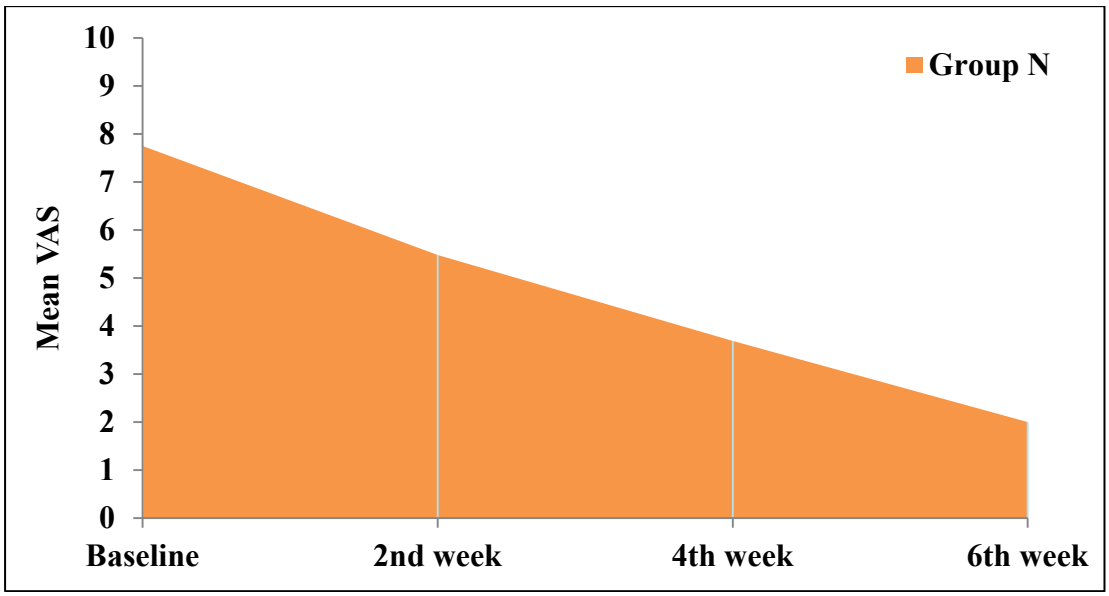


Figure 15. Area under curve – Naproxen

The area under the curve for reduction in pain in patients receiving medications in both the groups (Figure 14 and 15) was calculated by trapezoid method. The decrease in area of trapezoid over a period of time indicates reduced intensity of pain with both medications. When this area was compared between medications it was less with Piroxicam (5.33) compared to Naproxen (5.45) at week 6.

Table 8. Comparison of mean VAS scores between the groups

	Baseline	2nd week	4th week	6th week
Group P	8.00±1.51	5.52±1.35	3.53±1.10	1.80±0.70
Group N	7.78±1.45	5.45±1.32	3.55±1.12	1.90±0.60
p value	0.40	0.20	0.81	0.38

The reduction in mean VAS score was not significant between the treatments at any point of time as shown in the above table.

Table 9. Comparison of subscales of WOMAC

	Group P	Group N	p value
	Mean±SD	Mean±SD	
PAIN SUBSCALE			
Baseline	13.25±2.25	13.27±1.95	0.42
2nd week	09.92±1.74*	09.81±1.62*	0.36
4th week	07.03±1.34*	07.00±1.41*	0.28
6th week	04.35±0.82*	04.41±0.86*	0.17
STIFFNESS SUBSCALE			
Baseline	04.73±0.50	04.58±0.53	0.26
2nd week	03.51±0.50*	03.55±0.54*	0.41
4th week	02.51±0.50*	02.55±0.54*	0.74
6th week	02.00±0.00*	02.02±0.14*	0.32
PHYSICAL FUNCTION SUBSCALE			
Baseline	39.63±3.34	39.56±2.92	0.54
2nd week	29.66±3.57*	30.40±2.85*	0.40
4th week	19.47±3.08*	20.07±3.25*	0.12
6th week	09.52±2.28*	09.89±1.99*	0.20

* p = 0.001, values compared with baseline

The reduction in pain, stiffness and physical function scores were statistically significant at weeks 2, 4 and 6 compared to baseline with both the medications. Based on the physical function subscale of WOMAC, reduction in score indicates gradual improvement in quality of life (QOL) at 2nd, 4th and 6th week. When the scores of

subcales were compared between groups the reduction was insignificant at each follow up.

Table 10. Comparison of mean WOMAC scores within and between the groups

	Group P	Group N	
	Mean±SD	Mean±SD	p value
Baseline	57.60±5.81	57.22±4.92	0.10
2nd week	43.00±5.19*	43.35±4.37*	0.27
4th week	29.12±4.04*	29.60±3.81*	0.94
6th week	15.76±2.54*	16.18±2.39*	0.42

*p = 0.001, values compared with baseline

The reduction in WOMAC score was statistically significant at weeks 2, 4 and 6 compared to baseline with both the medications. More than 75% decrease in the score was observed at week 6. The reduction in mean WOMAC score was insignificant between Piroxicam and Naproxen at all the follow up visits.

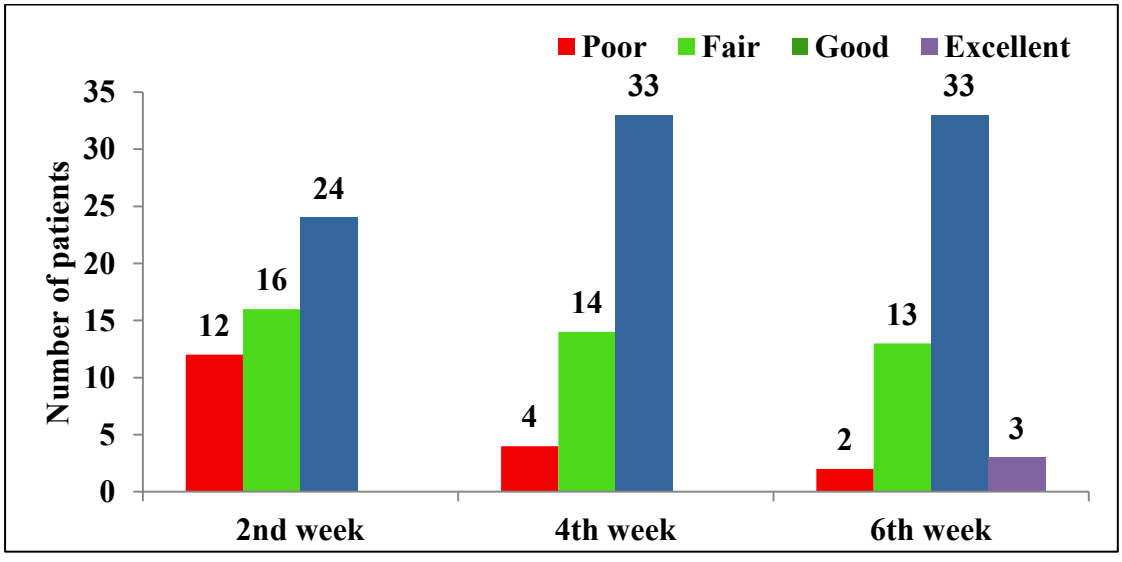


Figure 16. Patient's Satisfaction Score with Piroxicam

In Piroxicam group, 64.7% of patients graded their satisfaction as good at both 4th and 6th week. 5.9% of patients expressed their satisfaction as excellent at week 6. This increase in PSS at both weeks was statistically significant as compared to week 2 (p=0.03).

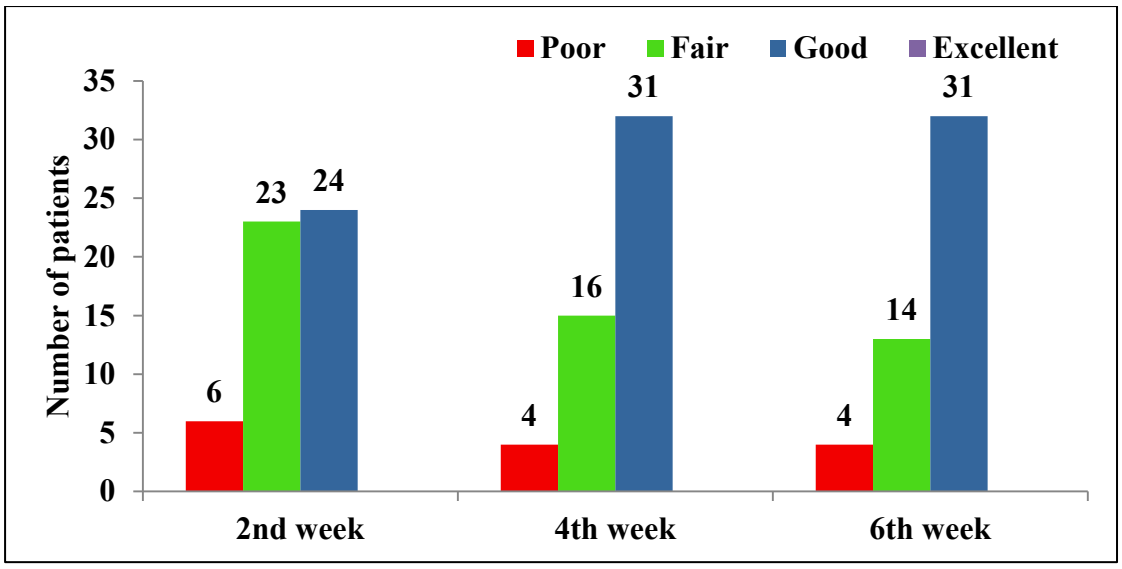


Figure 17. Patient's Satisfaction Score with Naproxen

At 4th week, 60.7% of patients graded their satisfaction as good whereas 63.2% at 6th week in group N. PSS was significantly improved at 4th and 6th weeks compared to 2nd week with Naproxen (p=0.03). PSS was insignificant between the medications (p=0.10).

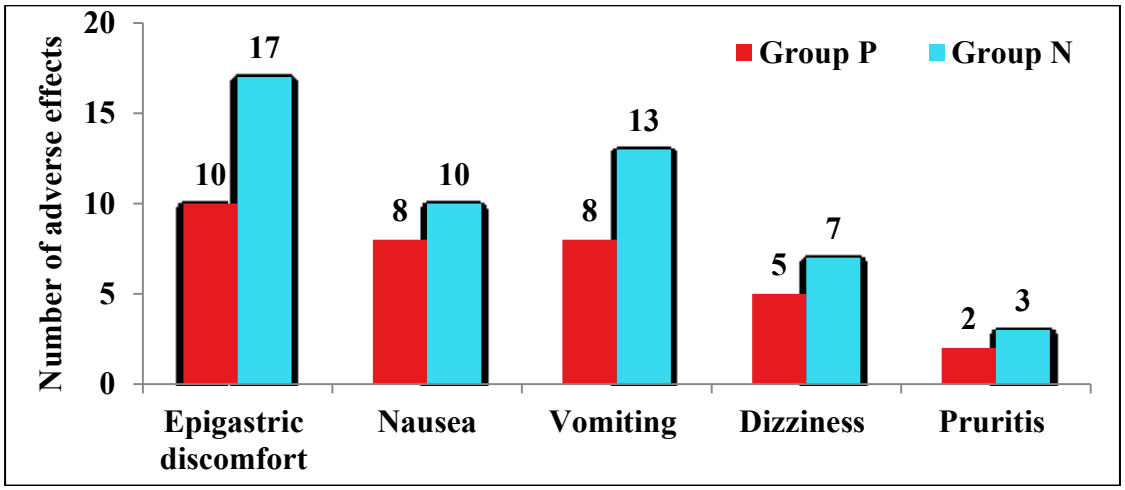


Figure 18. Adverse effects in both the groups

Total number of adverse effects were 33 in group P and 50 in group N as shown in figure 16. The most common adverse effect was epigastric discomfort, which was more with Naproxen.

Discussion

DISCUSSION

Osteoarthritis (OA) is one of the most common degenerative disease particularly affecting the knee joints and it is the major cause of disability in elderly. OA is a disease of synovial joints characterized by cartilage loss along with peri-articular bone response. It is associated with pain and inflammation of the joint capsule, impaired muscular stability, reduced range of movement and functional disability. It rarely occurs before the age of 40 years but by 75 years at least 85% of the population have either clinical or radiographic evidence of the disease. OA is an appropriate model to assess the efficacy of new analgesics at repeated doses.[5] Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of pain in patients with OA. However, they are associated with adverse effects mainly gastrointestinal, such as epigastric discomfort, dyspepsia, abdominal pain, nausea and vomiting. Thus the decision to prescribe NSAIDs is based on their effectiveness to reduce pain with less adverse effects.

In our study, 110 patients diagnosed with moderate to severe OA of both the knee joints were recruited and randomized as shown in figure 13. They received Piroxicam 20 mg in group P or Naproxen 500 mg in group N twice daily for six weeks. One hundred patients completed the study period. Most of the patients (70%) were in fifth decade of life which substantiates that OA occurrence increases as age advances. Some of the factors contributing to OA in elderly could be degenerative changes in the menisci, joint ligaments, increased bone turnover as well as calcification of joint tissues.[64]

The number of female patients were more in both the groups. A study by Rugstad HE et al, comparing Piroxicam 20 mg with Naproxen 750 mg once daily in OA of knee, also had more female patients. [65] This could be because in women,

tendons are more elastic and knee joints are not aligned straight as in men which leads to injuries and may manifest as OA in later part of their life. In addition, female patients whose mothers had OA, might develop this disease in the same joint and at the same age. Estrogen protects cartilage from inflammation but during and after menopause, the estrogen level decreases leading to high risk of OA.[66] Obesity contributes to extra stress on knees, which leads to cartilage breakdown and in this study most patients were overweight.

We observed that both Piroxicam and Naproxen significantly reduced the VAS scores at 2nd, 4th and 6th week compared to baseline (Table 7). The reduction in pain was significant in patients receiving either medication. Between the groups, reduction in VAS score was not statistically significant at follow up (Table 8). In a study by Richy F et al, Piroxicam was similar in efficacy compared to other NSAIDs in reducing pain in patients with OA of knee.[67] Allegrini A et al has reported that Piroxicam patch was effective compared to placebo in reducing pain due to osteoarthritis of lumbar vertebra.[68] Alho A et al study showed that Piroxicam and Naproxen were similar in efficacy when used for OA of hip joint.[69] In our study the intensity of pain experienced by the patients is represented by area under curve and those receiving Piroxicam (5.33) had marginally better pain relief compared to Naproxen (5.45) at week 6 as shown in figures 14 and 15.

The parameters of WOMAC depicting pain, stiffness and physical function were significantly reduced in both groups at each follow up compared to baseline (Table 9). In this study, both the drugs significantly reduced WOMAC score at 2nd, 4th and 6th week compared to baseline (Table 10). Reduction in WOMAC score implies reduction in pain, improvement in flexibility of joints and range of movements. This helps the patient in carrying out day to day activities independently which indicates

improvement in QOL of the patient. There was no significant reduction in WOMAC scores between the groups during the follow up (Table 10). In a study by Smith SR et al, it was observed that NSAIDs like Piroxicam and Naproxen reduced pain similar to opioids in patients with OA of knee.[70] Reduction in VAS and WOMAC scores to same extent by both the drugs in our study implies that they are equally efficacious in reducing the symptoms and signs of OA.

We also assessed the Patient's Satisfaction Score (PSS) at 2nd, 4th and 6th week. In both the groups, more number of patients expressed satisfaction as 'Good' with the study medications. There was an improvement in PSS in both the groups from 2nd week to 4th and 6th week (Figure 16 and 17). There was no significant difference in the satisfaction score between Piroxicam and Naproxen ($p = 0.10$). This shows that patients in both the groups had pain relief and were able to carry out regular activities with less dependence.

In this study, Piroxicam and Naproxen were well tolerated and adverse effects were mild in nature. The adverse effects like epigastric discomfort, nausea, vomiting, dizziness and pruritis were observed with both the drugs but the number was more with Naproxen than Piroxicam (Figure 18). In the study by Richy F et al, patients with OA of knee observed that Piroxicam caused lesser adverse effects compared to other NSAIDs except Meloxicam. The adverse effects were less even with twice daily administration of Piroxicam compared to once daily intake of other NSAIDs.[67] The results of our study indicated that pain relief and patient satisfaction were similar with both the drugs but number of adverse effects were less with Piroxicam, suggesting it to be a better alternative to Naproxen.

Conclusion

CONCLUSION

- Osteoarthritis (OA) of knee is a degenerative joint disease and the most common form of arthritis associated with aging
- This condition impairs patient's day to day activities due to pain, decreased range of movement and functional disability
- Patients received either Piroxicam 20 mg or Naproxen 500 mg twice daily for six weeks
- Patients with OA of both the knee joints were in their fifth decade of life and majority were female
- Mean VAS and WOMAC scores were significantly reduced in both the groups at each follow up compared to baseline but it was insignificant between the groups
- The satisfaction score was graded as 'Good' by 60% of patients
- The above parameters suggests that quality of life had improved in patients with OA
- The most common adverse effect experienced by patients in both the groups was epigastric discomfort and it was more with Naproxen
- Piroxicam was as effective as Naproxen in relieving pain in patients with OA of knee joints

Summary

SUMMARY

Osteoarthritis (OA) is a condition that affects cartilage, the rubbery cushion covering bones in the joints and keep them flexible. Gradually cartilage begins to stiffen, gets damaged more easily and loses its "shock absorber" quality. The bones start rubbing against each other and that causes pain. The most common complaint in OA is pain, which restricts the physical activity of the patients as well as decreases work performance. Most commonly used analgesics are non-steroidal anti-inflammatory drugs (NSAIDs). Patients with OA take medication for a long period and have a number of co-morbidities, which requires concomitant medication, increasing the likelihood of adverse events including gastrointestinal (GI) damage. Piroxicam and Naproxen are NSAIDs which inhibits prostaglandin synthesis and leads to decreased pain and inflammation.

A total of 110 patients with OA of both the knee joints were recruited and one hundred completed the study. They were randomized to receive either Piroxicam 20 mg or Naproxen 500 mg twice daily for six weeks. Intensity of the pain was assessed using VAS and WOMAC scores at baseline, 2^{nd} week, 4^{th} week and 6^{th} week. WOMAC is a subjective score consisting of subscales in terms of pain, stiffness and physical function. The reduction in WOMAC score indirectly improves quality of life. If the VAS score was more than three after initiating the treatment with study drugs, oral tramadol 50 mg was used as rescue analgesic. Patient's Satisfaction Score (PSS) was also assessed at follow up. Adverse effects for both the drugs were monitored and causality assessed.

Most of them were in their fifth decade of life and majority were female patients. The VAS scores were significantly reduced in patients of both the groups at follow up compared to baseline. The intensity of the pain experienced by the patients

represented by the area under the curve was marginally better with Piroxicam at week 6. Between the groups, there was no significant reduction in VAS score at any point of time. The parameters of WOMAC depicting pain, stiffness and physical function were significantly reduced in patients receiving either drug at each follow up compared to baseline. The reduction in WOMAC scores reflects improvement in QOL of the patient in both the groups. The reduction in mean WOMAC scores were not significant between the groups.

PSS was 'Good' in 64.7% of patients in group P and 63.2% of patients in group N at 6^{th} week. There were 5.9% of patients who expressed that satisfaction as excellent at week 6 in Piroxicam group. The most common adverse effect was epigastric discomfort with both the drugs but it was more with Naproxen. The results of our study indicated that pain relief and patient satisfaction were similar with both the drugs but number of adverse effects were less with Piroxicam, suggesting it to be a better alternative to Naproxen in patients with osteoarthritis of knee joints.

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Annexures

PROFORMA

Serial No: Date:

OP No:

1. Name:

2. Age/Gender:

3. Educational status:

4. Occupation:

5. Address with phone no.:

6. Presenting complaints:

7. History of Presenting Complaints:

8.Pain: Mild\ Moderate\ Severe

9.Activity of Daily Living (ADL): Affected / Not Affected

10.Loss of Income:

11.Past history:

12.Drug history:

13. Clinical examination:

a) General Physical Examination:

b) Systemic examination:

- Per abdomen-
- Cardiovascular-
- Respiratory-
- Central nervous system -

c)Local Examination:

Examination of knee joint

- Inspection

- Palpation

- Movements

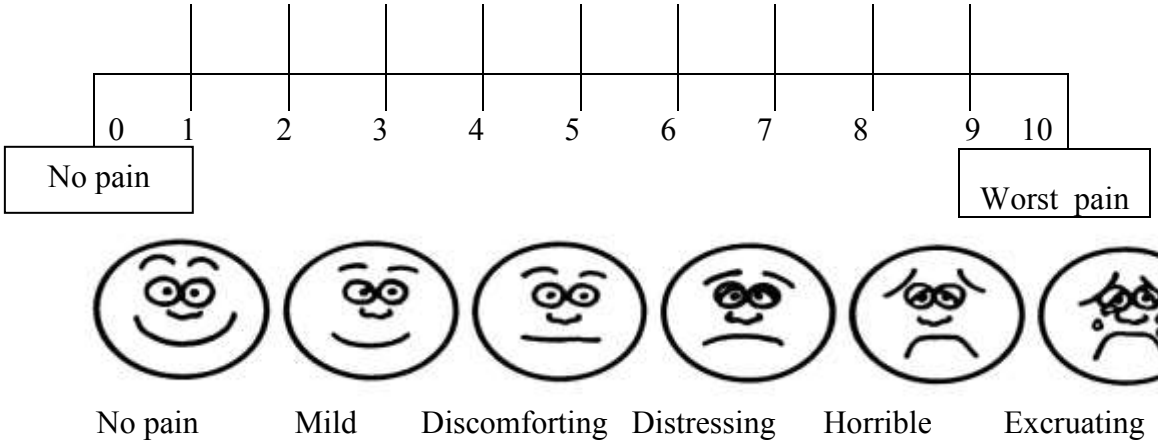
- Measurements

14. X-ray of Knee joint:

15. Diagnosis:

16.Treatment:

Visual Analog Scale



Directions – How severe is your pain today? Place a vertical mark on the line above to indicate how bad your pain

Graded Visual Analogue Scale score

VAS score	Severity of pain
0	No pain
1-3	Mild
4-7	Moderate
8-10	Severe

Western Ontario and McMaster Universities Arthritis Index (WOMAC) scale

Pain subscale

Sl. No	Situation	None	Mild	Moderate	Severe	Extreme
1.	Walking on flat surface	0	1	2	3	4
2.	Going up/downstairs	0	1	2	3	4
3.	At night	0	1	2	3	4
4.	Sitting/lying	0	1	2	3	4
5.	Standing upright	0	1	2	3	4
					Score =	

Stiffness subscale

Sl. No	Situation	None	Mild	Moderate	Severe	Extreme
1.	How severe is the stiffness after first walk in morning	0	1	2	3	4
2.	How severe is the stiffness after sitting, lying or resting later in the day	0	1	2	3	4
Score =						

Physical function subscale

Sl. No	Situation	None	Mild	Moderate	Severe	Extreme
1.	Descending stairs	0	1	2	3	4
2.	Ascending stairs	0	1	2	3	4
3.	Getting out of chair	0	1	2	3	4
4.	Remaining in standing position	0	1	2	3	4
5.	Bending	0	1	2	3	4
6.	Walking on flat surface	0	1	2	3	4
7.	In/out of car	0	1	2	3	4
8.	Shopping	0	1	2	3	4
9.	Socks/stockings on	0	1	2	3	4
10.	Getting out of bed	0	1	2	3	4
11.	Socks/stockings off	0	1	2	3	4
12.	Lying in bed	0	1	2	3	4
13.	In/out bath	0	1	2	3	4
14.	Sitting	0	1	2	3	4
15.	Toileting	0	1	2	3	4
16.	Heavy domestic duties	0	1	2	3	4
17.	Light domestic duties	0	1	2	3	4
Score =						

Master Chart

A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF PIROXICAM AND NAPROXEN IN THE MANAGEMENT OF PAIN IN OSTEOARTHRITIS OF KNEE - Piroxicam group

Sl.No	Age	Gender	Occupation	Pain	Duration	VAS score				PAIN SUBSCALE				STIFFNESS				PHYSICAL FUNCTION				Total WOMAC				PSS			AE
						BL	2nd WK	4th WK	6th WK	BL	2nd WK	4th WK	6th WK	BL	2nd WK	4th WK	6th WK	BL	2nd WK	4th WK	6th WK	BL	2nd WK	4th WK	6th WK	2nd WK	4th WK	6th WK	
1	60	Fe	House wife	S	2	9	7	4	2	14	10	7	4	5	4	3	2	48	34	20	7	67	48	30	13	P	G	G	E
2	70	Fe	House wife	S	10	8				12				5				39				56							
3	6O	M	Farmer	Mo	36	6	4	2	1	10	8	6	4	4	3	2	2	36	30	20	5	50	41	28	11	G	G	E	N
4	58	Fe	House wife	S	20	10	7	5	2	12	9	6	4	4	3	2	2	39	32	15	6	55	44	23	12	F	G	F	E
5	68	M	Tailor	S	24	9	6	4	2	15	11	8	5	5	4	3	2	44	31	20	7	64	46	31	14	G	G	F	E
6	75	M	Teacher	S	12	10	7	4	3	15	11	8	5	5	4	3	2	43	31	19	12	63	45	30	19	P	F	F	V
7	51	M	Teacher	Mo	84	6	4	3	2	10	8	6	4	4	3	2	2	37	27	16	8	51	38	24	14	G	G	G	E
8	65	Fe	House wife	S	60	9	7	4	2	16	11	7	5	5	4	3	2	44	33	22	13	65	48	32	20	G	G	G	E
9	65	Fe	House wife	S	24	10	8	5	3	13	10	7	4	4	3	2	2	40	29	22	9	57	42	31	15	G	F	F	E
10	75	Fe	House wife	S	12	9	6	4	2	16	12	8	4	5	4	3	2	40	31	18	10	61	47	29	16	F	G	G	N
11	60	Fe	House wife	S	12	8	6	4	3	12	8	6	4	4	3	2	2	39	32	23	8	55	43	31	14	G	G	F	V
12	62	M	Farmer	S	9	9	7	5	3	16	12	8	4	5	4	3	2	43	32	21	13	64	46	32	20	F	G	F	E
13	48	Fe	House wife	Mo	10	6	4	3	2	11	8	6	4	4	3	2	2	39	32	23	13	54	43	31	19	G	G	G	N
14	73	M	Farmer	S	22	9	7	5	2	16	13	9	5	5	4	3	2	45	31	21	13	66	48	33	20	F	F	G	N
15	67	Fe	House wife	S	18	10	7			13	10			4	3			40	31			57	44			F			P
16	56	Fe	Teacher	S	20	9	7	5	2	12	9	6	4	4	3	2	2	38	29	18	8	54	40	26	14	F	F	G	D
17	63	M	Farmer	S	24	9	6	4	2	16	12	8	4	5	4	3	2	41	32	23	12	62	47	34	19	G	F	G	N
18	49	Fe	Farmer	S	12	9	7	5	3	12	9	6	4	4	3	2	2	42	33	24	10	58	45	32	16	G	F	F	V
19	52	M	Farmer	S	10	8	6	4	2	12	8	6	4	4	3	2	2	39	31	25	13	55	42	33	19	G	G	G	
20	45	M	Tailor	Mo	7	6	4	3	2	10	8	6	4	4	3	2	2	36	27	17	8	50	38	25	14	F	G	G	
21	67	M	Farmer	S	20	10	7	4	2	15	11	8	5	5	4	3	2	40	32	17	12	60	47	28	19	P	G	G	
22	63	M	Farmer	Mo	16	6	4	3	2	11	8	6	4	4	3	2	2	37	28	19	9	52	39	27	15	G	F	G	V
23	40	Fe	House wife	S	22	9	7	4	2	13	10	7	4	5	4	3	2	40	28	18	10	58	42	28	16	F	G	G	
24	57	M	Farmer	S	10	9	7	5	3	14	10	7	5	5	4	3	2	41	30	20	9	60	44	30	16	F	F	P	V
25	65	M	Farmer	S	22	8	6	4	2	16	12	9	5	5	4	3	2	47	36	26	13	68	52	38	20	F	F	G	
26	72	Fe	House wife	Mo	11	6	4	3	2	10	8	5	3	4	3	2	2	34	20	17	9	48	31	24	14	P	G	G	
27	48	M	Farmer	Mo	7	6	5	3	1	11	8	5	3	4	3	2	2	35	24	16	10	50	35	23	15	G	F	G	E
28	52	M	Farmer	Mo	14	6	4	2	1	10	8	6	3	4	3	2	2	34	25	18	10	48	36	26	16	G	G	E	
29	56	Fe	House wife	Mo	10	6	4	3	2	12	9	6	4	4	3	2	2	38	30	22	12	54	42	30	18	F	G	G	V
30	48	Fe	Teacher	S	14	9	5	3	2	15	11	8	5	5	4	3	2	40	33	23	13	60	48	34	20	F	G	F	N
31	40	Fe	House wife	Mo	6	6	4	2	1	10	7	5	3	4	3	2	2	34	24	19	7	48	34	26	12	G	G	G	
32	44	Fe	House wife	S	8	10	7	4	2	16	12	9	5	5	4	3	2	43	34	26	13	64	50	38	20	P	F	G	
33	48	Fe	Farmer	S	12	9	7	5	3	16	13	10	6	5	4	3	2	43	35	17	8	64	52	30	16	F	G	P	E
34	47	M	Tailor	S	12	9	6	4	1	15	11	8	5	5	4	3	2	40	32	19	11	60	46	30	18	P	P	G	V
35	48	Fe	House wife	S	16	9				16	12			5	4			41	32			62							
36	38	Fe	Teacher	Mo	6	6	3	2	1	14	10	7	4	4	3	2	2	36	27	19	6	54	40	28	12	G	G	G	
37	40	Fe	Farmer	Mo	10	6	4	3	2	14	10	7	4	4	3	2	2	38	25	17	12	56	38	26	18	F	G	G	
38	42	Fe	Teacher	Mo	14	6	4	2	1	11	8	6	4	4	3	2	2	37	27	16	8	52	38	24	14	G	G	G	
39	56	M	Farmer	S	10	10	7	4	2	16	12	9	6	5	4	3	2	43	33	23	8	64	48	34	16	P	P	G	N
40	50	Fe	House wife	S	14	8	5	3	1	16	12	9	6	5	4	3	2	45	34	22	10	66	50	34	18	F	G	E	
41	56	Fe	House wife	Mo	20	7	5	6	1	11	9	6	4	4	3	2	2	39	26	18	8	54	38	26	14	F	F	G	
42	48	Fe	House wife	S	6	9	6	4	1	16	12	8	5	5	4	3	2	41	32	21	9	62	48	32	16	P	G	G	
43	40	Fe	House wife	Mo	8	7	4	2	1	14	10	7	4	4	3	2	2	38	27	17	8	56	40	26	14	G	F	G	
44	47	M	Tailor	Mo	6	6	4	2	1	10	8	6	4	4	3	2	2	34	21	12	6	48	32	20	12	G	G	G	
45	60	M	Farmer	S	8	9	6	3	2	16	12	9	6	5	4	3	2	41	32	18	9	62	48	30	16	P	G	F	P
46	46	Fe	House wife	Mo	12	6	4	2	1	10	8	6	4	4	3	2	2	36	25	14	8	50	36	22	14	G	G	G	D
47	62	M	Tailor	S	22	9	6	3	2	16	12	9	6	5	4	3	2	45	32	20	8	66	48	32	16	G	G	F	D
48	48	M	Tailor	S	8	7	4	2	1	11	8	6	4	5	4	3	2	38	26	15	6	54	38	24	12	G	G	G	D
49	60	Fe	House wife	S	18	8	6	4	2	15	11	8	5	5	4	3	2	40	33	19	11	60	48	30	16	G	G	F	D
50	58	Fe	House wife	S	9	9	6	4	2	14	11	8	5	5	4	3	2	39	27	19	11	58	42	30	18	G	G	F	N
51	42	Fe	Tailor	Mo	6	6	3	2	1	12	9	6	4	5	4	3	2	39	29	21	10	56	42	30	16	P	P	G	
52	43	M	Teacher	Mo	8	6	4	2	1	11	8	5	3	4	3	2	2	39	29	21	9	54	40	28	14	G	G	G	
53	45	Fe	House wife	S	12	10	7	4	2	15	12	9	5	5	4	3	2	42	32	22	11	62	48	34	18	P	P	F	E
54	60	Fe	House wife	Mo	14	6	4	2	1	10	7	5	3	4	3	2	2	34	24	15	7	48	34	22	12	P	F	G	V
55	58	M	Tailor	S	2	9				14				5				37				56							

M-Male, Fe-Female, Mo-Moderate, S-Severe, P-Poor, F-Fair, G-Good, E-Excellent, AE-Adverse effects, ED-Epigastric distress, V-Vomiting, N-Nausea, Pr-Pruritis, D-Dizziness