THE EVALUATION OF SAFETY AND EFFICACY OF COLLAGEN PEPTIDE AS AN ADD ON THERAPY TO STANDARD TREATMENT IN COMPARISON WITH THE STANDARD TREATMENT ALONE IN THE MANAGEMENT OF PATIENTS WITH KNEE JOINT OSTEOARTHRITIS

Dissertation submitted to

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IN

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CHENNAI - 600 003

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<u>CERTIFICATE</u>

This is to certify that the dissertation entitled, **"THE EVALUATION OF SAFETY AND EFFICACY OF COLLAGEN PEPTIDE AS AN ADD ON THERAPY TO STANDARD TREATMENT IN COMPARISON WITH THE STANDARD TREATMENT ALONE IN THE MANAGEMENT OF PATIENTS WITH KNEE JOINT OSTEOARTHRITIS"** submitted by DR.G.RAJESH KUMAR, in partial fulfillment for the award of the degree of Doctor of Medicine in Pharmacology by The Tamilnadu Dr.M.G.R.Medical University, Chennai is a Bonafide record of the work done by him in the Institute of Pharmacology, Madras Medical College during the academic year 2012-15.

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CERTIFICATE OF THE GUIDE

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TURNITIN ANTI-PLAGIARISM SOFTWARE – CERTIFICATE

CONTENTS

THE EVALUATION OF SAFETY AND EFFICACY OF COLLAGEN PEPTIDE AS AN ADD ON THERAPY TO STANDARD TREATMENT IN COMPARISON WITH THE STANDARD TREATMENT ALONE IN THE MANAGEMENT OF PATIENTS WITH KNEE JOINT OSTEOARTHRITIS

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ABSTRACT

AIM:

To compare the efficacy and tolerability of collagen peptide as an Add on therapy to standardtreatment compared to standard treatment alonein the management of patients with knee joint osteoarthritis.

METHODOLOGY

This was an open label, comparative, randomized, prospective study. This study included 60 patients with osteoarthritis, who wererandomized into two groups of 30 each. Control group received standard therapy (T.Diclofenac 100mg/day,T.Ranitidine 150mg twice daily and physiotherapy) and Study group received collagen peptide (10g/day) in addition to standard therapy for a period of 12 weeks. They were followed-up once in 2weeks for 12weeks.Pain, stiffness and functional disability were assessed using visual analogue pain scale(VAS) and WOMAC index at baseline and at the end of the study.

RESULTS

126 patients were screened out of which 60 patients were included in the study and all patients completed the study and were included in Analysis.On comparing the groups at the end of 12 weeks there was a statistically significant reduction in VAS and WOMAC INDEX score in Study group. No significant difference in the incidence of adverse events noted between the two groups.

CONCLUSION

Collagen peptide along with standard therapy is highly effective in reducing Pain, Stiffness and Functional disability in patients with Knee joint Osteoarthritis.

KEY WORDS

Collagen peptide,osteoarthritis,diclofenac,VAS,WOMAC index.

INTRODUCTION

Osteoarthritis is the most common form of arthritis affecting millions of people around the world. It is characterized by progressive softening and disintegration of articular cartilage which leads to functional disability. The loss of articular cartilage is accompanied by new growth of bone and cartilage at the joint margins, cyst formation and sclerosis in subchondral bone, mild synovitis and capsular fibrosis.[1]

Osteoarthritis is a dynamic phenomenon. It shows features of both destruction and repair. Cartilage softening and disintegration are accompanied by hyperactive new bone formation, osteophytosis and remodelling. The final outcome is determined by the relative vigour of these opposing processes.[2]

Osteoarthritis can be classified into primary osteoarthritis when there is no identifiable cause and secondary osteoarthritis when there is known cause due to trauma, metabolic and endocrine disturbances, infection etc.

The etiology of Osteoarthritis is multifactorial.[3] The most common risk factor for the development of osteoarthritis include obesity, occupation, participation in certain sports, history of joint trauma, and a genetic predisposition to osteoarthritis. In most cases the precipitating cause of Osteoarthritis is increased mechanical stress in some part of the articular surface.[4] This may be due to increased load or to a reduction of the articular contact area.

The prevalence of Osteoarthritis is higher in older age groups than in younger age groups. Women are more often affected by Osteoarthritis. Worldwide estimates show about 18% of women and 9% of men over 60 years of age have symptomatic osteoarthritis. In India, prevalence of clinically diagnosed Knee Osteoarthritis ranges from 22-39%.[5] Severity of Osteoarthritis also increases with age. Its high prevalence, especially in the elderly, and the high rate of disability related to the disease makes it a leading cause of disability in the elderly.

The most common joints affected in Osteoarthritis are hip, knee, spine and hands. The main symptom in Osteoarthritis is joint pain, which become worse with weight bearing and activity. Other symptoms include stiffness of the joint, crepitus, joint swelling, limitation of movement and deformity.[6]

The symptoms of Osteoarthritis gradually worsens with time. But osteoarthritis treatments can slow the progression of the disease, relieve pain and improve joint function.

Management of osteoarthritis includes muscle strenghthening exercises and weight reduction. Paracetamol is the analgesic of choice for early cases with mild pain. Patients with severe pain require other Non steroidal anti inflammatory drugs (NSAIDs).[7] Intra articular injection of steroids and hyaluronic acid is useful in very severe cases. Other drugs used in management of osteoarthritis include glucosamine sulphate, chondroitin sulphate, collagen peptide, antioxidants etc.

Collagen peptides have gained huge public attention as nutriceuticals used for prophylaxis and management of osteoarthritis.[8] Collagen peptide is produced by enzymatic hydrolysis of collagenous tissue obtained from animals. Collagen peptide contains different aminoacids, predominantly glycine, proline and hydroxyproline, which together represent 50% of the total aminoacid content. Beneficial action is likely due to collagen peptide accumulation in the cartilage and stimulated production of collagen and proteoglycans by the chondrocytes, the cells of cartilage.[9] With this novel mechanism of action, collagen peptide can slow the disease progression and can improve the symptoms in patients with Osteoarthritis.

Collagen peptide has been formally investigated in some clinical trials for the treatment of osteoarthritis but the present data available to support its use is scanty. Hence this study has been undertaken to evaluate the efficacy and safety of collagen peptide in the reduction of symptoms in patients with knee joint osteoarthritis in our population.

REVIEW OF LITERATURE

OSTEOARTHRITIS

Osteoarthritis is the most common form of joint disease affecting elderly people. Osteoarthritis (OA) is commonly known as degenerative joint disease or degenerative arthritis. It is characterized by progressive softening and disintegration of articular cartilage of synovial joints which results in functional disability.

The term 'Osteoarthritis' is derived from the Greek word. The word 'osteo' means "bone", 'ortho' means "joint", and 'itis' means "inflammation". Though the name osteoarthritis implies inflammatory disorder, the inflammation in osteoarthritis is usually restricted locally to the joint area and without any systemic symptoms.[2]

Osteoarthritis is defined by the American College of Rheumatology as "heterogenous group of conditions that lead to joint symptoms and signs which are associated with defective articular cartilage integrity, in addition to related changes in the underlying bone at the joint margin."[10]

CLASSIFICATION:[1]

1) Primary osteoarthritis (idiopathic).

> Localised

> Generalised

> Erosive osteoarthritis.

2) Secondary osteoarthritis.

> Congenital and developmental disorders, bony dysplasias.

> Post surgery, trauma

> Endocrine cause - diabetes mellitus, acromegaly, Cushing syndrome, hypothyroidism, hyperthyroidism, hyperparathyroidism,

> Metabolic - hemachromatosis, ochronosis, Paget disease, Wilson's disease, gout, pseudo gout, Hurler disease, Gaucher disease, Marfans syndrome, Ehler-Danlos syndrome.

> Hematological - hemoglobinopathies.

> Neurological - Charcot joints.

> Iatrogenic – intra-articular steroids

EPIDEMIOLOGY:

Osteoarthritis is estimated to be one of the leading causes of morbidity and disability worldwide. The incidence and prevalence of osteoarthritis increases with increase in age. The prevalence of osteoarthritis is 1% in people below the age of 30 years. It increases to about 50% in those above 60 years of age. In autopsy studies, there is osteoarthritic change in everyone above 65 years of age. The severity of symptoms also increases with age.[2]

Osteoarthritis affects both men and women, but more joints are affected in women. Osteoarthritis is more common in hip, knee, fingers, spine joints and less common in

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elbow, ankle and wrists. Worldwide estimate shows that osteoarthritis is present in 15 to 18% of females and 8 to 10% of males. Females are also found to have more severe form of osteoarthritis.

The involvement of specific joints in osteoarthritis varies in different parts of world. Knee joint involvement is more common in south Asians, but hip and hand joints are affected more in Europeans.[2, 3] The prevalence of knee osteoarthritis in India ranges from 22% to 39%. In people aged above 55 years, about 10% have knee osteoarthritis and one fourth of them are severely disabled.[5]

ETIOLOGY:

Exact etiology of osteoarthritis is unknown and various risk factors are involved to cause this disorder.

SYSTEMIC FACTORS[1, 2]

- **Age**: Although osteoarthritis may occur in young people, the condition is more common with older people. Furthermore, older people are found to have rapid progression of the disease.[11]

- **Sex**: Osteoarthritis is found to be more common in females. They are found to have more severe disease and more number of joints are involved in them.[12]

- **Genetic**: Hip involvement has a significant genetic component. Heberden's nodes in hand osteoarthritis appear to be inherited independently as an autosomal dominant trait with greater penetrance in women.[13]

- **Obesity**: Obesity and overweight are recognized as major risk factors for osteoarthritis of knee and hip. The Framingham Study found that in women who had lost about 5 kg had a 50% reduction in the risk of knee osteoarthritis.[14]

- **Joint location**: Osteoarthritis is more common in hip and knee joint but occurs rarely in ankle.

- **Bone density**: There is a negative association between osteoarthritis and osteoporosis at certain sites particularly the hip.[15]

- **Nutritional:** Low Vitamin C and Vitamin D levels are associated with increased risk of osteoarthritis

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LOCAL FACTORS:

- **Occupation**: Repetitive use of joints at work is associated with an increased risk of osteoarthritis.[16]

- **Physical activity/sports**: Athletes and sportspersons are at high risk for the development of knee and hip osteoarthritis.[17]

- **Injury/surgery**: Major trauma/surgery involving articular surface is considered a cause of osteoarthritis[18]

- **Laxity/Alignment:** Knee laxity and abnormal alignment results in greater compressive stress and is another potential risk.[19, 20]

- **Mechanical factors**: Muscle weakness and atrophy are commonly associated with knee osteoarthritis.

- **Others**: Prolonged immobilization, peripheral neuropathy, chondrocalcinosis are the other risk factors for osteoarthritis.[21]

THE JOINT AND ITS STRUCTURES: [22]

Joints are highly specialized organs and they allow frictionless and pain free movements. The articular cartilage and its extracellular matrix are responsible for these properties. The joint surfaces are covered by the articular cartilage. Other structures involved in joint activity include joint Capsule, ligaments and subchondral bone.
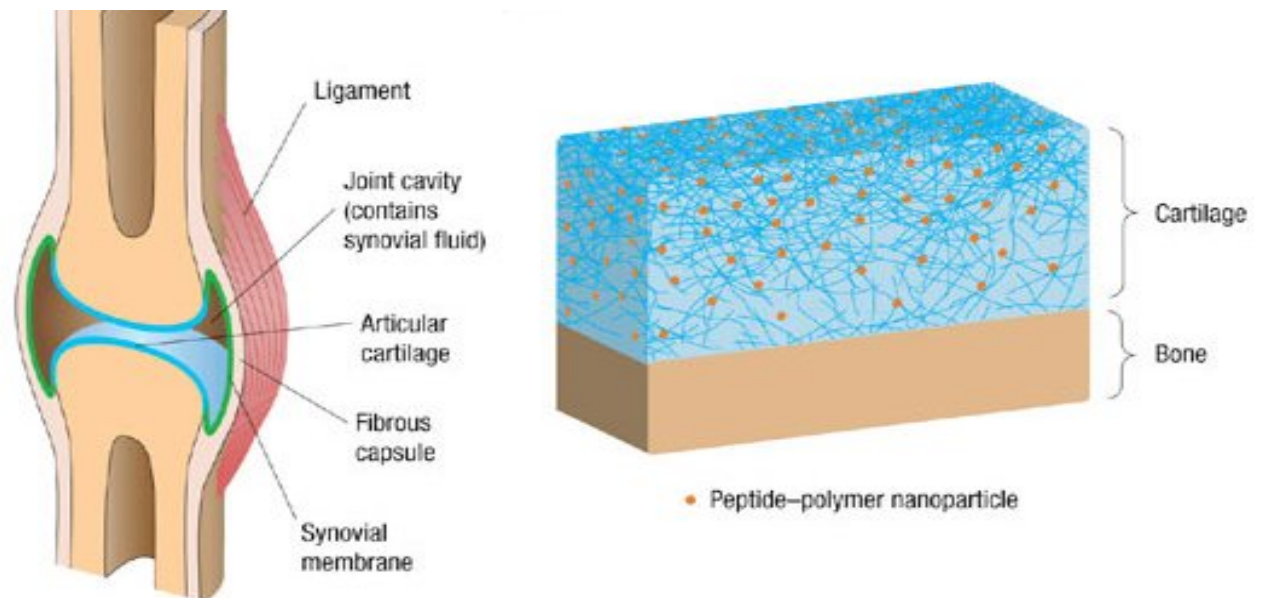
This figure shows the different anatomical structures of the joint

Normal functioning and mechanical stability of the joint is due to the presence of these different structures. The synovial membrane is responsible for providing nourishment to the cartilage cells and maintaining the basic metabolic homeostasis of the joints.

KNEE JOINT FEATURES

The knee joint is the largest synovial joint in the body. Hyaline cartilage covers the articular surface of the knee joint.

It consists of:

- medial and lateral tibiofemoral compartment.

- patellofemoral compartment.

It is a hinge joint which allows mainly flexion and extension and is supported by

- ➢ Two collateral ligaments

- ➢ Two cruciate ligaments

- ➢ Two menisci

Apart from Flexion and extension, small degrees of adduction/abduction and rotation also occur at knee joint.

NORMAL ARTICULAR CARTILAGE:[23, 24]

Articular cartilage is a highly specialized tissue and it forms the smooth, gliding surface of the joints. It is avascular, aneural and alymphatic matrix. It is synthesized by the chondrocytes which are sparsely distributed.[1, 22]

The cartilage matrix substance can be subdivided into different compartments

➢ **Superficial zone:** Collagen fibrils are arranged parallel to the articular surface. Have high collagen to proteoglycan ratio and high water content. This provides high tensile stiffness to the superficial zone.

➢ **Transitional (middle) zone:** Higher proteoglycan and lower water content than superficial zone. Collagen fibrils are arranged in arcade form.

➢ **Radial (deep) Zone:** Proteoglycan content is highest and more chondrocytes are present in this zone. Collagen fibrils are oriented perpendicular to subchondral bone.

➢ **Calcified zone:** A thin layer of this calcified zone attaches the articular cartilage to the subchondral bone.
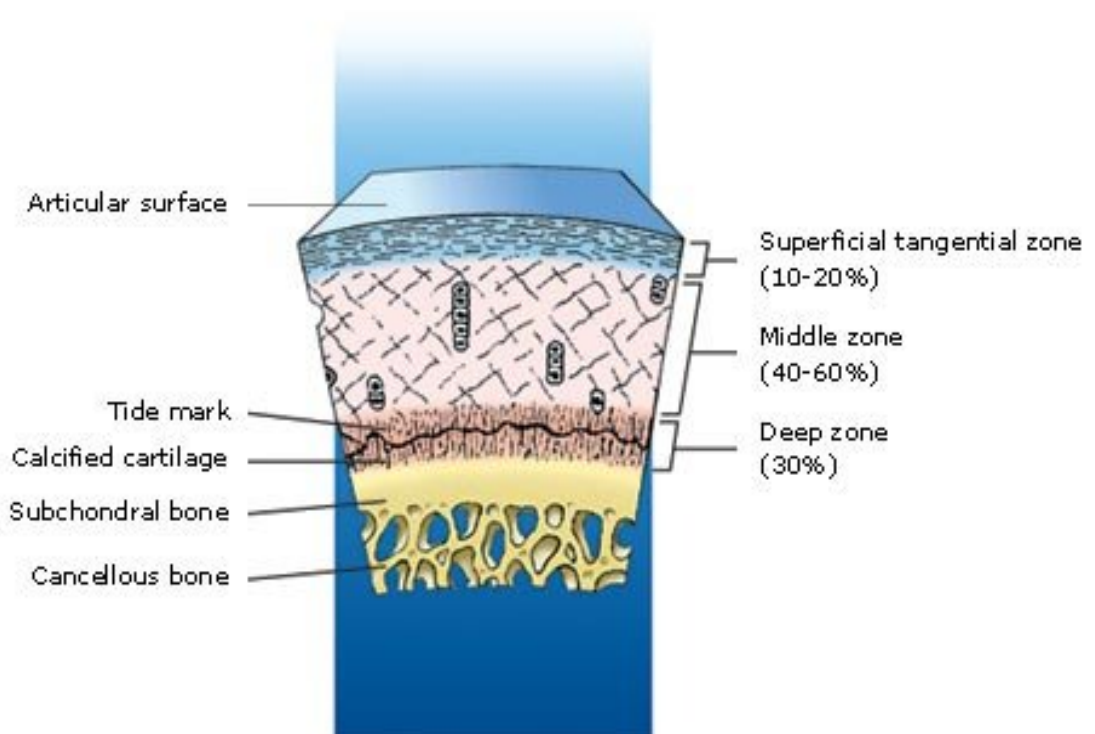
This figure shows the Structure of normal cartilage

At the molecular level, the cartilage matrix consists of two basic components: a fibrillar and an extrafibrillar matrix.

> ➤ The **fibrillar matrix** of articular cartilage consists mainly of collagen type II. Other collagen types IX, XI, and XVI are located within the core of the collagen type II fibrils.

> ➤ The **extrafibrillar component** of articular cartilage consists predominantly of highly sulfated aggrecan monomers (proteoglycan macromolecule) and link protein.

MATRIX TURNOVER:

The type II collagen and aggrecans are the two important molecules present in the cartilage. The proteolysis of aggrecan and its turnover is highly regulated by the action of matrix metalloproteinases (MMPs) and A Disintegrin and Metalloproteinase with Thrombospondin Motifs (ADAMTS-4and ADAMTS-5). The turnover of aggrecan is slow in normal cartilage.

The collagen type II network is extremely stable. The tightly wound collagen fibres are further stabilized by a high-degree of cross linking. Destabilization of fibres is done by cleavage of the triple helix due to the action of collagenases MMP-1 and MMP-13.

OSTEOARTHRITIC JOINTS:[1, 2, 25, 26]

The most characteristic feature of osteoarthritis is narrowing of joint space due to loss of cartilage, accompanied by formation of osteophytes at the joint margins and subchondral bone sclerosis.

The **histologic changes** seen in osteoarthritis are:

Phase 1: Edema and Microcracks of the extracellular matrix.

Phase 2: Fissuring and Pitting of subchondral bone cartilage.

Phase 3: Erosion and Subchondral sclerosis.

Though the cardinal feature of osteoarthritis is progressive loss of cartilage, it is not a disease only of cartilage but also involves synovium, ligaments, meniscus, subchondral bone and other supporting structures.

Biochemical Changes:

The early biochemical changes seen in osteoarthritis is the increase in the water content of the articular cartilage,

In the late stages, the proteoglycan concentration is decreased to less than 50% of normal.

Metabolic Changes:

With the progression of osteoarthritis, the levels of matrix metalloproteinase (MMP) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) increases and are upregulated by IL-1 and TNF.

Biomechanical Changes:

In osteoarthritis, the mechanical stresses produce chondrocyte damage and releases degradative enzymes. This leads to

➢ Loss of compressive stiffness and elasticity.

➢ Bony proliferations (osteophytes) at the joint margins - responsible for the pain and restriction of joint movements

Inflammatory mediators:

Various inflammatory mediators involved in the pathogenesis of osteoarthritis include

➢ IL-1 and TNF - These cytokines induce the chondrocytes to produce proteases, nitric oxide, chemokines, prostaglandins and leukotrienes.

➢ Proteases - MMPs and ADAMTs.

➢ TGF – downregulates proteases and cytokine expression

CLINICAL FEATURES:[1, 6, 12, , 27]

SYMPTOMS:

Symptoms are insidious in onset and varies with the joint affected, the severity of joint involvement, and the number of joints affected.

Pain:

- ➢ First and predominant symptom.
- ➢ Aggravated by activities.
- ➢ Waxing and waning in intensity
- ➢ Relieved by rest.

This is due to stimulation of capsular pain fibers, periosteal nerve fibers, mechanoreceptors (increased intra-articular pressure due to synovial hypertrophy), and by perception of subchondral microfractures or painful entheses and bursae.

Stiffness:

Described as gelling of joint after inactivity with difference in initiating movement.

- ➢ Occur after a period of inactivity.
- ➢ Generally resolves within 10 minutes.

Loss of movement and function:

- ➢ Range of motion involving the affected joint is limited.

- ➢ Difficulty in performing day-to-day activities like walking, kneeling, bending, stair climbing etc.

- ➢ Due to pain, diminished muscle strength, reduced joint space and instability.

Depression and disturbed sleep - leads to a significant deterioration in the quality of life.

SIGNS:

- ➢ Joint swelling**:** due to effusion.

- ➢ Local tenderness: due to effusion, synovial thickening, osteophytes.

- ➢ Joint Deformity: indicates advanced disease of cartilage destruction.

- ➢ Crepitus during passive movements.

- ➢ Bony enlargement around joint margins due to remodeling and osteophytes.

- ➢ Muscle weekness and wasting.

Clinical examination of knee joint disease should also include examination of the hip, ankle and foot joint examination. Assessment of muscle strength, palpation of distal pulses and neurological examination should also be done.

NATURAL HISTORY OF DISEASE AND COMPLICATIONS:[1, 2]

Osteoarthritis usually evolves as a slowly progressive disorder. But the symptoms characteristically wax and wane in intensity. No such fluctuation is seen in x-rays. However, considerable variation is seen between patients in the degrees of destruction and repair. Most of the men and half of the women have a ***hypertrophic*** reaction, with marked sclerosis and large osteophytes. In about 20 per cent of cases, mostly in women reactive changes are more subdued, described as ***atrophic*** or osteopenic osteoarthritis. Occasionally osteoarthritis takes the form of a rapidly progressive disorder resulting in various complications.

Complications of osteoarthritis knee include

- Capsular herniation – Posterior capsule herniation associated with a marked effusion (Baker's cyst).
- Loose bodies - Cartilage and bone fragments may give rise to loose bodies, resulting in episodes of locking.
- Deformity - Advanced destruction of cartilage results in varus deformity.

DIAGNOSIS:[1, 2, 27, 28]

The diagnosis of osteoarthritis is essentially made by history, clinical features and radiological finding. A normal clinical examination does not rule out the diagnosis of osteoarthritis, particularly if the disease is of early nature and of modest severity.

Imaging:[1, 29]

Radiographic assessment not only is very helpful to diagnose osteoarthritis, but also is useful to establish the severity of joint damage; to monitor disease activity, progression, and response to therapy. Standard radiographs are the most common investigations, depending on the region involved. For knee and hip osteoarthritis, Weight-bearing radiographs are advised.

The cardinal radiological features of osteoarthritis includes

- ➢ Narrowing of the 'joint space'
- ➢ Marginal osteophytes
- ➢ Subchondral cysts
- ➢ Subchondral sclerosis
- ➢ Bone remodeling

Kellgren and Lawrence graded the radiological changes seen in osteoarthritis into 4 grades.

Kellgren and Lawrence grading system for osteoarthritis[30]

GRADE	CLASSIFICATION	DESCRIPTION
0	**Normal**	No features of osteoarthritis
1	**Doubtful**	Doubtful joint space narrowing, possible osteophyte nipping.
2	**Minimal**	Definite osteophytes with possible joint space narrowing.
3	**Moderate**	Multiple osteophytes, definite joint space narrowing, sclerosis, possible bone contour deformity
4	**Severe**	Large osteophytes, definite joint space narrowing, severe sclerosis, definite bone contour deformity

Narrowing of joint space is the diagnostic feature of osteoarthritis. However osteophytes (new bone) at the joint margin, usually precedes joint space narrowing and is a more characteristic feature. Subchondral bone sclerosis and joint space narrowing are classically seen in more advanced disease. Joint space narrowing not only is related to a decreased volume of articular cartilage, but also due to meniscal cartilage lesions.

RADIOLOLOGICAL IMAGING OF NORMAL KNEE JOINT AND OSTEOARTHRITIS KNEE JOINT

NORMAL KNEE JOINT

OSTEOARTHRITIS KNEE JOINT

GRADING OF OSTEOARTHRITIS BY KELLGREN AND LAWRENCE GRADING SYSTEM

GRADE-1

GRADE-2

GRADE-3

GRADE-4

Though radiological imaging is useful in grading the severity of osteoarthritis, sometimes the clinical symptoms and radiographic findings are poorly correlated. A standard radiograph cannot diagnose early disease. Many patients with severe symptoms can have only marginally affected x-ray findings and many patients with radiographic evidence of osteoarthritis remain asymptomatic.

Hence the diagnosis of osteoarthritis in patients presenting with knee, hip, or hand pain is based on a comprehensive clinical assessment of the joint, including evaluation of symptoms and signs that favor this diagnosis and exclude other diagnosis. In straightforward presentations, radiologic investigation often is unnecessary to confirm the diagnosis of knee osteoarthritis.

Due to high prevalence of radiographic findings of osteoarthritis in asymptomatic individuals, it is important to ensure that the joint pain in a patient with radiographic evidence is not due to some other cause like other type of arthritis, entrapment neuropathy, radiculopathy, referred pain from other joint etc.

Ultrasonography examination of the joint is useful only for detecting joint effusions and cartilage changes such as fibrillation 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. Ultrasound imaging is limited that it cannot visualize the whole cartilage surface.

Magnetic resonance imaging (MRI)[31] is not indicated as a diagnostic tool in all cases. But it is very useful in assessing the severity of osteoarthritis as it can visualize all the tissues involved in osteoarthritis, including cartilage lesions, fluid effusion, subchondral bone marrow edema, low grade synovitis, and meniscus or ligament lesions.

Arthroscopy visualizes cartilage, osteophytes, synovial membranes and meniscal lesions. Cartilage damage even before the appearance of x ray changes can be seen in arthroscopy.

Radionucleide scanning with Tc 99 shows increased activity in the subchondral regions of osteoarthritis affected joint. This is due to increased vascularity and new bone formation.

Laboratory tests:[28]

Blood tests are not routinely indicated in clearly defined osteoarthritic patients. They may be needed to rule out other differential diagnosis in some patients with atypical presentation. Analysis of synovial fluid in osteoarthritis reveals a WBC count of less than 2000/mm, sterile and without any crystals.

Osteoarthritis assessment of outcomes in clinical trials:

The groups of patients with osteoarthritis who participate in clinical trials for evaluating the efficacy of new drugs should be as homogeneous as possible, and need to fulfill a set of clinical and radiological criteria proposed by the American College of Rheumatology (ACR).

American college of rheumatology (ACR) criteria for knee and hip osteoarthritis

Knee Osteoarthritis:[32]

Knee pain

AND

One of the following features

- Age >50 years

- Morning stiffness <30 minutes

- Crepitus

AND

Radiologic osteophytes

The sensitivity and specificity of ACR knee criteria are estimated to be 91% and 86%.

Hip Osteoarthritis:[33]

Hip pain

AND

At least two of the following features

- ESR <20 mm in 1st hour

- Radiologic osteophytes

- Radiologic joint-space narrowing

The sensitivity and specificity of the ACR hip criteria are estimated to be 91% and 89%.

Assessment of outcomes in clinical trials must be separated from assessment in routine practice. There are different scoring systems available for monitoring the outcome according to the target joint involved.

➢ The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

➢ Knee injury and Osteoarthritis Outcome Score (KOOS)

➢ Arthritis Impact Measurement Scale (AIMS)

➢ Oxford Knee Score

➢ Lequesne index of severity for osteoarthritis

➢ Knee pain scale

➢ International Knee Documentation Committee subjective knee form

are some of the knee specific scoring systems available.

Among the various scales available, The Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index is the one which is widely used to assess pain and disability in knee joint osteoarthritis.[34] It consists of

➢ 5 questions to assess pain

➢ 2 questions to assess stiffness and

➢ 17 questions to assess functional disability

in patients with knee joint osteoarthritis.

The responses to these 24 questions are interpreted in a 5 point Likert scale as

None	- 0
Mild	- 1
Moderate	- 2
Severe	- 3
Extreme	- 4.

The construct validity of this test, when tested against other scales ranges from 0.68 to 0.75. The Reliability estimates for pain, stiffness and functional disability with this test ranges from 0.73 to 0.96.[35, 36]

In addition to the WOMAC questionnaire pain subscale, a 0-to-100 mm visual analogue scale (VAS) is also used to assess the severity of pain in osteoarthritis. It is another tool in measuring the response of patient to the drug in clinical trial.

MANAGEMENT OF OSTEOARTHRITIS:

The goals in treating the patient with osteoarthritis are [1, 7]

- ➢ to relieve pain and stiffness

- ➢ to maintain or improve joint mobility

- ➢ to limit functional impairment

- ➢ to maintain or improve quality of life

- ➢ to reduce further structural progression.

The management of osteoarthritis consists of multimodality approach including
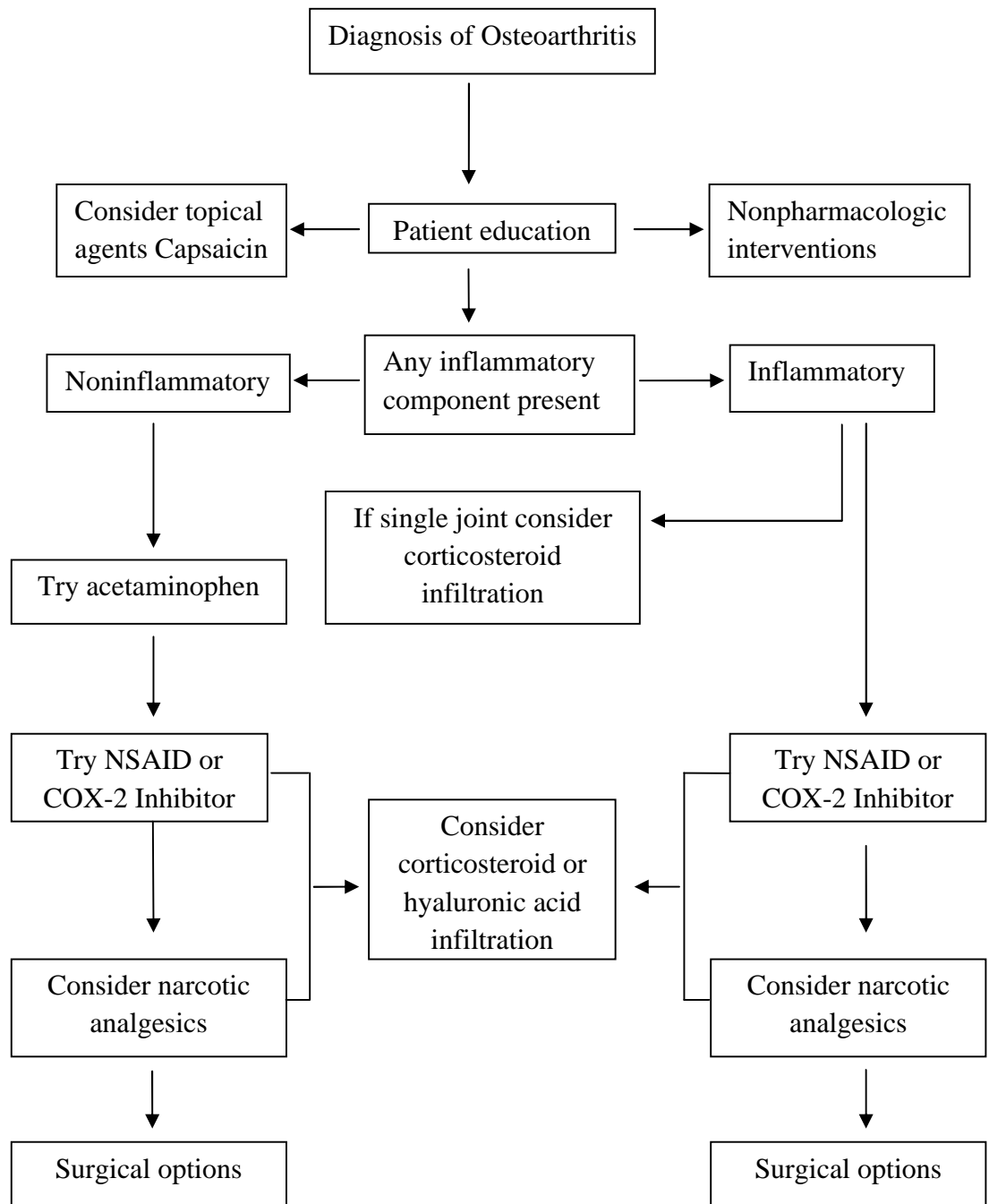
- nonpharmacological interventions

- pharmacological interventions and

- surgical options

Nonpharmacological Interventions: [1, 2, 10]

Patients with mild and intermittent symptoms need only reassurance with non pharmacological interventions like

- ➢ Psychosocial Interventions

- ➢ Weight loss

- ➢ Exercise

- ➢ Temperature modalities

- ➢ Supporting devices

Algorithm for the Management of Osteoarthritis

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                          ┌─────────────────────────┐
                          │ Diagnosis of Osteoarthritis │
                          └─────────────────────────┘
                                      │
                                      ▼
┌──────────────────┐      ┌─────────────────────┐      ┌──────────────────────┐
│ Consider topical │◄─────│  Patient education  │─────►│  Nonpharmacologic    │
│ agents Capsaicin │      └─────────────────────┘      │  interventions       │
└──────────────────┘                 │                 └──────────────────────┘
                                      ▼
┌──────────────────┐      ┌─────────────────────┐      ┌──────────────────────┐
│ Noninflammatory  │◄─────│  Any inflammatory   │─────►│     Inflammatory     │
└──────────────────┘      │  component present  │      └──────────────────────┘
          │               └─────────────────────┘                 │
          ▼                                                        │
┌──────────────────┐      ┌─────────────────────┐◄────────────────┘
│ Try acetaminophen│      │ If single joint consider │
└──────────────────┘      │ corticosteroid          │
          │               │ infiltration            │
          ▼               └─────────────────────┘
┌──────────────────┐      ┌─────────────────────┐      ┌──────────────────────┐
│ Try NSAID or     │      │     Consider        │      │  Try NSAID or        │
│ COX-2 Inhibitor  │─────►│ corticosteroid or   │◄─────│  COX-2 Inhibitor     │
└──────────────────┘      │ hyaluronic acid     │      └──────────────────────┘
          │               │ infiltration        │                 │
          ▼               └─────────────────────┘                 ▼
┌──────────────────┐                                   ┌──────────────────────┐
│ Consider narcotic│                                   │  Consider narcotic   │
│ analgesics       │                                   │  analgesics          │
└──────────────────┘                                   └──────────────────────┘
          │                                                        │
          ▼                                                        ▼
┌──────────────────┐                                   ┌──────────────────────┐
│ Surgical options │                                   │  Surgical options    │
└──────────────────┘                                   └──────────────────────┘
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Psychosocial Interventions:[28]

As in any other chronic disorder, patient education is an important first step in the management of osteoarthritis. The patient should understand the nature of disease and should be an integral part of the decision-making team. The patient should be explained about the relevant risk factors like heredity, obesity, trauma etc.

Explaining that the disease is a very common, slowly progressive ailment and it is not typically as disabling or deforming as the inflammatory arthritis is very reassuring to the patient. The patient should be explained that the changes are permanent but the symptoms of pain and functional ability can improve with proper management.

The simplest effective treatment for many patients is to avoid activities that precipitate pain. Some patients may develop significant emotional disturbances, depression or sleep disorders and changes in normal daily activities related to the pain and should be managed accordingly.

Weight Loss:[37, 38, 39]

Obesity is an important risk factor in the development of osteoarthritis of the knee. This can be worsened by malalignment—namely, varus and valgus deformities that modulate the effect of weight on the knee joint. Each pound of weight increases three to six fold loading across the knee. Hence regular exercises with proper dietary management, resulting in weight loss have been associated with improvement in pain and disability in osteoarthritis of the knee joint.

Exercise:[40, 41]

Periarticular structures, particularly muscles provide stability to the joints and hence weakness of the muscles, influence the symptoms in osteoarthritis. Quadriceps muscle weakness is a risk factor for osteoarthritis of the knee joint.

Quadriceps strengthening exercises – both isometric and dynamic exercises significantly improve symptoms and functional ability in patients with osteoarthritis knee joint. Home-based exercise interventions, supervised fitness walking regimens and aquatic aerobics also significantly improve the symptoms.

Temperature Modalities:[42, 43]

Topical applications of cold or heat are more effective when they are used in superficial joints, such as the knees or hands than in deep ones such as the hip. Warm applications can be in the form of warm soaks or heating pads. Each session should not exceed a temperature of 45°C and not more than 30 minutes. Pain and stiffness are decreased, muscle spasms are relieved and contractures may be prevented by using heat therapy.

Supporting devices:[44, 45, 46]

Supporting devices like braces, orthotic foot wears, crutches, walkers, canes can be used to decrease the load and redistribute the stress across the joint in patients with malalignment like varus or valgus deformity. This results in reduction of pain in the patients with knee and hip osteoarthritis.

Pharmacologic Interventions:[1, 47]

In many patients with osteoarthritis, pain and functional ability is not improved with non-pharmacological treatment. Hence numerous pharmacological therapies have been used in the management of osteoarthritis.

Topical agents:[48, 49]

Topical capsaicin is an alkaloid which is used as irritant to relieve pain in joints. It acts by depleting the release of substance P from peripheral nerves. Adverse effects include erythema, stinging and burning sensation.

Topical NSAID preparations like diclofenac are used for the treatment of osteoarthritis and are effective in controlling mild pain. Though they are not effective in relieving pain like that of oral NSAIDs, they are used mainly because of the various safety concerns about oral NSAIDs.

Topical methylsalicylate can also be used as a rubefacient and provides pain relief for short period. They act by providing counterirritation to the affected joint area.

Acetaminophen:[50, 51]

Acetaminophen (Paracetamol) is the drug of choice for the patients with mild pain. This is mainly due to its favorable side effect profile. However the improvement in overall WOMAC score was small with acetaminophen. This suggests that acetaminophen may be effective for the relief of pain and should not be expected to have a strong effect on stiffness or functional ability. Dose upto 1g four times daily can be used.

Oral NSAIDs: [52, 53]

NSAIDs like diclofenac, ibuprofen and naproxen are the drug of choice for patients not responded to paracetamol. There was no significant difference in efficacy between different NSAIDs. Therefore the choice of NSAID should be based on other factors, such as safety and cost. But patient not responding to one NSAID may respond to another NSAID.

They act by inhibiting the cycloxygenase enzyme resulting in decreased prostaglandin production which is responsible for pain and inflammation. Nonselective NSAIDs are associated with serious gastro intestinal (GI), cardiovascular and renal toxicity. Initially NSAIDs are advised on an "as needed" basis because side effects are less with intermittent doses.

Risk factors for NSAID-induced GI toxicity include age >65yrs, history of peptic ulcer disease or upper GI bleeding, use of glucocorticoids or anticoagulants and presence of co-morbid conditions. Patients should be advised to take NSAIDs after food to minimize the NSAID related GI side effects.

Risk factors for NSAID-induced renal failure in patients include age >65yrs, hypertension, congestive cardiac failure and use of diuretics or ACE inhibitors.

COX-2 inhibitors: [54, 55]

COX-2 inhibitors like rofecoxib, celecoxib are found to have similar efficacy as nonselective NSAIDs in reducing the symptoms in osteoarthritis. Although 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, resulting in its withdrawal from the market.

It is not clear whether this is a class effect for all COX-2 inhibitors. Hence its long term safety is to be followed up.

Opioids:[56, 57]

Some patients obtain only suboptimal pain relief even after treated with this various options. In patients not responding to other nonpharmacologic and pharmacologic modalities, a narcotic analgesic should be considered. The pain is generally responsive to narcotic analgesics. Tramadol is an oral medication with mild suppressive effects on the opioid receptor. It also inhibits the uptake of norepinephrine (NE) and serotonin (5HT) and is not thought to have significant addictive tendencies. Tramadol has been used for the symptomatic relief of osteoarthritis.

Intra-articular Corticosteroids:[58]

Although there is no role for systemic corticosteroids in osteoarthritis, local intra-articular corticosteroid preparations are effective in providing short term relief from symptoms. Corticosteroids down regulate the expression of adhesion molecules. This reduces the cellular infiltration into the joint and subsequent inflammation. But it will not provide any long-term benefits.

Intra-articular Hyaluronic Acid:[59]

Hyaluronic acid is a linear polysaccharide composed of repeating disaccharide units of N-acetyl glucosamine and D-Glucuronic acid. It is a component of synovial fluid in the

joint that increases its viscosity. Osteoarthritis is associated with decreased Hyaluronic acid in the synovial fluid.

Intra-articular multiple injections of Hyaluronic acid spaced 1 week apart has shown greater improvement on pain and function than as compared to intra-articular corticosteroids. Injections are usually well tolerated. Rare adverse effects include local skin reaction, joint swelling, rash, ecchymoses.

Diacerin:[60]

Diacerin is an atypical NSAID which inhibits IL-1, an important cytokine implicated in osteoarthritis. It does not inhibit prostaglandin synthesis. It is used in a dose of 50 mg daily. Adverse effects include diarrhea and discoloration of urine.

Other chondroprotective agents:[61, 62]

Doxycycline and minocycline inhibits articular collagenase activity by inhibiting tissue metalloproteinases. They also prevent proteoglycan cell loss and cell death. Glycosaminoglycan polysulfuric acid (GAGPS) and Glycosaminoglycan peptide complex (GC-P) increase the levels of tissue inhibitors of metalloproteinases. Pentosan polysulfate inhibits granulocyte elastase. These drugs are being evaluated as disease modifying agents in the treatment of osteoarthritis.

Nutraceuticals for Osteoarthritis:

The term 'nutraceutical' was coined from 'nutrition' and 'pharmaceutical' It is defined as "a food (or part of the food) that provides medical or health benefits, including the prevention and/or treatment of a disease."

Glucosamine and Chondroitin Sulfate:[63, 64, 65]

Glucosamine and chondroitin sulphate are natural substances derived from animal products. The exact mechanism and role of glucosamine, chondroitin, or a combination of the two products is still unclear. They may act by stimulating proteoglycan synthesis in articular cartilage and thus rebuilding the damaged cartilage. This is why glucosamine seems to take several weeks to demonstrate its therapeutic effect.

Dosage of glucosamine should be at least 1,500 mg/day and 1,200 mg/day of chondroitin. Adverse events are generally mild and include gastrointestinal symptoms like nausea, bloating. The excellent safety profile makes them especially appealing for use in those at high risk for adverse events, such as elderly patients and in those with multiple morbidities.

Recent reports of various studies demonstrated no significant clinical response to glucosamine therapy or chondroitin therapy alone, or glucosamine–chondroitin combination therapy when compared to placebo across all patients.

Collagen hydrolysate:[8, 9]

Collagen peptides have gained huge public attention as nutriceuticals used for prophylaxis and management of osteoarthritis. Collagen hydrolysate is produced by enzymatic digestion and hydrolysis of collagen extracted from animal bones and skin.

The mechanism of action is likely due to collagen peptide accumulation in the cartilage and results in stimulated production of collagen and proteoglycans by the chondrocytes. With this mechanism of action, collagen peptide can slow the progression of disease and can improve the symptoms in patients with Osteoarthritis.

Other drugs that are investigated in the management of osteoarthritis include[66, 67]

- vitamins C and E
- flavanoids
- Avacoda/ Soyabean Unsaponifiables (ASUs)
- omega 3 PUFAs
- methylsulfonylmethane
- S-adenosyl methionine (SAM)
- ginger and turmeric extract etc.

Newer therapies like gene therapy,[68] growth factors and cytokine manipulation,[69] chondrocyte and stem cell transplantation[70] are still in the early stage and need further evaluation.

Surgical Interventions:[71, 72]

There is lack of evidence based criteria regarding indications for the referral of a patient with osteoarthritis for surgical treatment. Most consensus recommend that patients who continue to have severe pain and functional limitation of the knee or hip, in spite of maximal conservative therapy, should be referred for consideration for surgical treatment. The various surgical options for osteoarthritis treatment are discussed below.

➢ Arthroscopic debridement

➢ Realignment Osteotomies

➢ Arthrodesis

➢ Knee replacement/Arthroplasty

Arthroscopic debridement:

Joint debridement and lavage for removal of loose bodies, interfering osteophytes and cartilage tags are done arthroscopically. But this does not found to improve the symptoms in osteoarthritis.

Realignment Osteotomies:

High tibial Osteotomies can be performed for to realign the knee to lessen the load at medial compartment. This provides pain relief to the patient for years before they require total knee replacement.

Arthrodesis:

Arthrodesis is a reasonable procedure only in osteoarthritis of small joints like hand if stiffness is accepable

Knee replacement/Arthroplasty:[73]

In patients with failed medical treatment modalities and remains in pain with severe limitations of daily physical activities that compromise the quality of life, Knee joint replacement is the surgical procedure of choice. These procedures relieve pain and improve function in majority of patients.

Failure rates are 1% per year and higher in obese patients. The timing of this surgical procedure is important. The success achieved in patients who underwent operation earlier in the disease course will not be achieved in patients who suffer for many years with considerable muscle weakness and substantially declined functional status.
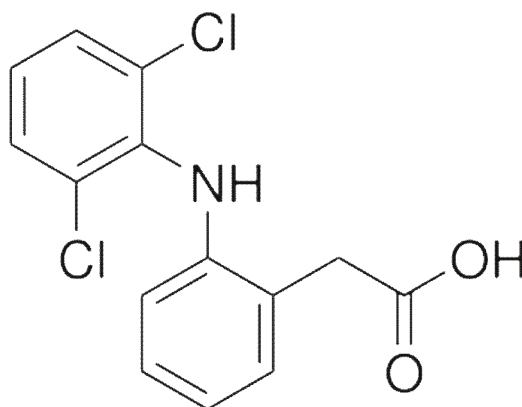
STUDY DRUGS

DICLOFENAC[47]

Diclofenac is a non-steroidal anti-inflammatory drug belonging to the group of aryl-acetic acid derivative.

Chemical name is 2-[(2, 6-dichlorophenyl) amino] benzeneacetic acid.

The molecular weight is 318.14.

Its molecular formula is $C_{14}H_{11}Cl_2NO_2$ and it has the following structural formula.

DICLOFENAC

Pharmacological Properties:

- ➤ Diclofenac inhibits prostaglandin synthesis by inhibiting cyclooxygenase (COX) enzyme activity.

- ➤ Has analgesic, antipyretic, and anti-inflammatory activity.

- ➤ Decreases neutrophil chemotaxis and superoxide production at the inflammatory site

Pharmacokinetics:

Absorption:

- ➤ Complete absorption after oral administration.

- ➤ Peak plasma concentration reached within 2-3 hours.

- ➤ Administration with the food slows the rate but not alter the extent of absorption.

- ➤ Significant first pass effect with only 50% is available systemically.

Distribution:

- ➤ Apparent Volume of Distribution is 1.4 L/kg.

- ➤ The drug is extensively bound to plasma proteins (99%)

- ➤ Half-life is 1-2 hrs.

Metabolism and Excretion:

- ➤ Diclofenac is metabolized in the liver by cytochrome CYP2C subfamily to 4-hydroxydiclofenac, the principal metabolite, and other hydroxylated forms.

- ➤ The metabolites undergo further glucuronidation and sulfation and then excreted in bile and urine.

Dosage forms:

- ➤ Different preparations are available for oral, intramuscular, topical and ophthalmic administration.

- ➤ The oral dose range is 100 to 200 mg daily in two divided doses with meals.

- ➤ The dose for intramuscular injection is 75mg once or twice daily.

Common indications:

- ➤ Musculoskeletal disorders like osteoarthritis, rheumatoid arthritis, spondylarthritis, ankylosing spondylitis,polymyositis, dermatomyositis, gout attacks etc.

> Mild to moderate post-operative or post-traumatic pain.

> Menstrual pain and endometriosis.

Adverse effects:

> Gastrointestinal side effects - abdomen pain, nausea, vomiting, dyspepsia in about 20% of patients and rarely ulcer and bleeding.

> Central nervous system- Headache, tinnitus, and dizziness.

> Cardiovascular - Fluid retention, edema, hypertension, and rarely congestive heart failure.

> Hematologic –rarely causes thrombocytopenia, neutropenia, or even aplastic anemia.

> Hepatic - Modest elevation of plasma hepatic transaminases.

> Renal -Renal insufficiency, renal failure, hyperkalemia, and proteinuria.

> Rashes, pruritus.

> Others adverse events include irritability, depression, disorientation, nightmares, tremors

Contraindications:

> History of allergic reactions to NSAIDs.

> Active gastric / duodenal ulceration or gastrointestinal bleeding.

> Inflammatory intestinal disorders such as Crohn's disease or ulcerative colitis.

> Severe congestive cardiac failure.

> Severe liver and renal insufficiency.

Drug Interactions:

- ➤ With corticosteroids, increases the frequency and severity of gastrointestinal ulceration.

- ➤ With warfarin, the risk of bleeding is increased.

- ➤ Decreases the antihypertensive action of thiazides, frusemide and beta blockers.

- ➤ Displace other drugs like warfarin, methotrexate, lithium, sulfonylureas,from the plasma protein binding sites resulting in toxicity.
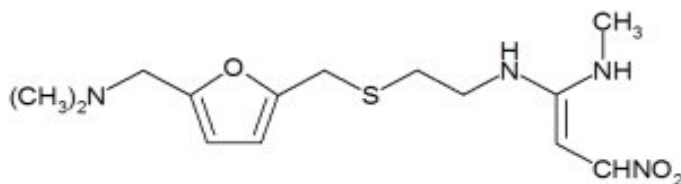
RANITIDINE[74]

Ranitidine is a histamine H_2-receptor antagonist that inhibits production of acid in stomach

Its chemical name is N-(2-[(5-[(dimethylamino) methyl] furan-2-yl) methylthio]ethyl)-N'-methyl-2-nitroethene-1,1-diamine

Molecular weight is 314.4 g

Its molecular formula is $C_{13}H_{22}N_4O_3S$ and has the structural formula

RANITIDINE

Pharmacological properties:

Ranitidine is a competitive, reversible inhibitor of histamine at the histamine H2-receptors found in gastric cells. This results in decreased secretion of acid in stomach.

Pharmacokinetic parameters:

➢ Bioavailability – 50 to70%

➢ Low plasma protein binding – 15%

➢ Metabolism – hepatic

➢ Half life – 2 to 3 hours

➢ Excretion – renal route

Dosage forms:

- Available as tablet, syrup and injection forms.

- Oral dose is 150 mg twice daily.

- Injection dose is 50 mg twice daily.

Common indications:

- Treatment of gastric and duodenal ulcers

- Coadministered with NSAIDs to reduce the risk of ulceration.

- Gastroesophageal reflux disorder (GERD)

- Erosive oesophagitis

- Upper GI bleeding

- Prevention of stress induced ulcer

- Zollinger-Ellison syndrome

- Used along with H1 antihistamines in skin allergic conditions.

Adverse effects:

- Very rarely headache, dizziness, diarrhoea, constipation can occur.

- No significant drug interactions reported.

COLLAGEN PEPTIDE

Collagen peptide is also called as hydrolysed collagen, collagen hydrolysate, gelatin hydrolysate etc. It is obtained from animal sources like fish, horses, cattle, pigs, rabbits etc. It is produced by degradation and enzymatic hydrolysis of collagenous tissues like bone, skin and connective tissues of these animals.

The process of hydrolysis involves combinations of treatment with acid, alkali, heat or enzymes to break down the molecular bonds between individual collagen strands.
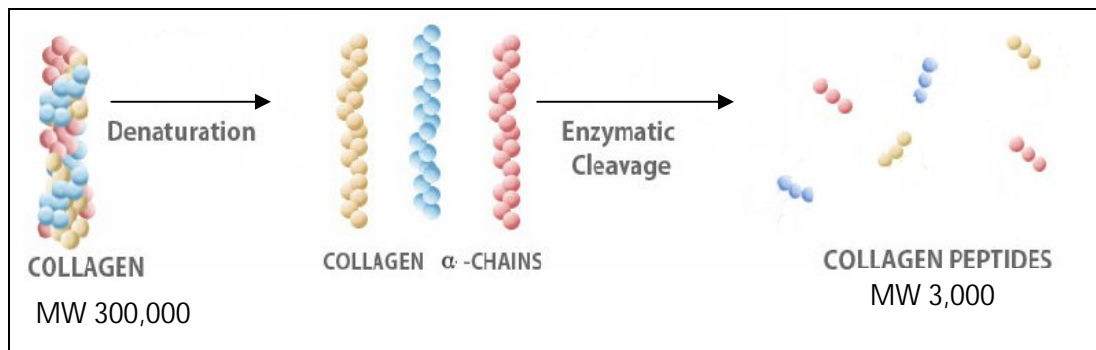
This hydrolysis process results in reducing the collagen proteins with molecular weight of about 300,000 Dalton units into small peptides of molecular weight between 2000 and 5000 Daltons. The reduction in molecular weight helps in greater absorption of the collagen peptide and good bioavailability.[75]

The amino acid content of collagen peptide is same as that of collagen in body. Hence it is a "customised" collagen building substance. It contains about 20 amino acids,

predominantly proline, hydroxyproline and glycine which together represent around 50% of the total amino acid content.

The concentration of proline and glycine is as much as 20 times higher than other food sources of protein. These amino acids play an important role in building fibrous tissues. It contains about 8 out of 9 essential aminoacids.

Pharmacokinetic parameters:

Collagen peptide, a form of collagen is hydrolysed to improve absorption into the bloodstream. Collagen peptides are highly digestible with good oral bioavailability. Studies have demonstrated that over 90% of orally administered hydrolysates are absorbed by the intestines and appeared in blood plasma. Then they are found with measurable accumulation in connective tissues within a few hours of ingestion. This rapid availability ensures the effective delivery of essential peptides and amino acids to the body.[76]

Pharmacological properties:

Collagen Peptide stimulates the anabolic phase of cartilage matrix turnover. This brings about a phase of regeneration and stability in joint cartilage. Collagen peptide stimulates the production of cells responsible for maintaining the joint-cushioning effect by articular cartilage.[77]

They produce dose dependent stimulatory effect on both collagen and proteoglycan synthesis. This indicates that the chondrocytes were stimulated to synthesize increased amounts of the components of extracellular matrix. Collagen peptide causes significant increase of aggrecan RNA expression and increased accumulation of aggrecan in the extracellular matrix. This slows or even halts the progression of articular cartilage tissue degradation in osteoarthritis.[78]

Dosage:

It is recommended that a daily dosage of 10 g for three months can be effective and this can be followed by a daily maintenance dose of 5 to 10 g. It is available as powder form. It can be mixed with water, milk and juices and taken orally.

Clinically Proven Health Benefits:

Collagen peptide is being used as a nutrition supplement for the treatment of degenerative joint diseases and for the management of skin care.

Skin:[79, 80]

Collagen peptide, when orally ingested increases the hydroxyproline content of skin. This improves the viscoelastic properties, smoothness and moisture content of skin. The mechanism of action is due to the accumulation of collagen in skin resulting in increased density of collagen fibrils and the fibroblasts. This improves the water binding capacity of epidermis. Collagen peptide is also available as cream for topical skin application.

Joint & Bone:[81, 82]

Oral ingestion of collagen hydrolysate decreases joint pain and improves the symptoms of osteoarthritis. Patients with severe symptoms show the most benefit. Beneficial action is likely due to the collagen accumulation in the cartilage and the stimulated production of collagen by the chondrocytes. Collagen peptides stimulated differentiation results in more osteoblasts than that of osteoclasts.

Other effects of collagen peptide which are under investigation are weight loss, improved muscle tone and strength, healthy hair and nails, arterial strengthening, organ rebuilding, improvement in chronic fatigue etc.

Adverse effects:[83]

Adverse effects include nausea, fullness of abdomen, flatulence. Collagen peptide is found to be safe for oral consumption in people with other coexisting problems like diabetes and hypertension. No interaction is seen with other drugs.

OBJECTIVES

OBJECTIVE

OBJECTIVE

To evaluate the efficacy and safety of collagen peptide as add on therapy to standard treatment in the management of patients with knee joint osteoarthritis compared to standard treatment alone.

PRIMARY END POINT:

- ➢ Reduction in pain assessment score using visual analogue scale.

- ➢ Improvement in joint mobility using WOMAC osteoarthritis index.

SECONDARY END POINT:

- ➢ Reduction in the requirement of NSAIDs.

METHODOLOGY

METHODOLOGY

The study was conducted in patients with knee joint Osteoarthritis, diagnosed within 1 year and now attending outpatient department of Orthopaedics, Rajiv Gandhi Government General Hospital, Chennai.

Study design:

A randomized, open label, prospective, interventional, comparative, parallel group study.

Study population:

Adult patients with knee joint osteoarthritis attending outpatient department, Institute of Orthopaedics.

Study center:

Institute of Pharmacology, Madras Medical College & Institute of Orthopaedics, Rajiv Gandhi Government General Hospital, Chennai.

Study period:

August 2013 to April 2014.

Study duration:

Treatment period of 12 weeks and

Post treatment follow up period of 4 weeks per patient.

Sample size:

60 patients (Control group - 30, study group - 30).

Inclusion criteria:

- ❖ Age - 40 years to 70 years

- ❖ Sex - both genders

- ❖ Patients with primary osteoarthritis of knee joint diagnosed less than 1 year

- ❖ Patients willing to give written informed consent.

- ❖ Subjects capable and willing to comply with all study procedures.

Exclusion criteria:

- ❖ Patients with secondary osteoarthritis.

- ❖ Patients with genu varum, genu valgum, gouty arthritis, rheumatoid arthritis.

- ❖ Patients with known hypersensitivity to NSAIDs, collagen peptide.

- ❖ Patients on oral or parenteral corticosteroid therapy

- ❖ Patients with chronic systemic illness of liver, heart, kidney, gastrointestinal tract etc.

- ❖ Patients who had taken other osteoarthritis treatment (glucosamine sulphate, chondroitin sulphate, diacerin, hyaluronic acid) within past 1 month.

- ❖ Pregnant and lactating women

Study procedure:

The study was conducted after obtaining the approval from Institutional Ethics Committee, Madras Medical College and it was done in accordance with declaration of Helsinki and Good Clinical practice (GCP) guidelines.

Patients diagnosed with knee joint osteoarthritis attending the Outpatient department, Institute of Orthopaedics, Madras Medical College and Rajiv Gandhi Government General Hospital, were explained about the study purpose, procedure and benefits of the study.

Written informed consent was obtained from those subjects who are willing to participate in the study in the prescribed format in regional language prior to performance of any study related procedures. If the patients were illiterate, left thumb impression was obtained. This was done in the presence of an impartial witness. The demographic details of the patients were obtained and recorded.

The subjects were screened by complete medical history, clinical examination and laboratory investigations. Those who fulfilled all the inclusion and exclusion criteria were enrolled in the study and randomized to receive the standard therapy alone or study drug along with standard therapy.

Randomization:

The enrolled patients were randomized by simple randomization into either control group or study group and received the respective therapy.

- ❖ Control group (n=30) –Standard therapy

- ❖ Study group (n=30) – Standard therapy + collagen peptide 10g per day

TREATMENT PLAN:

Control group

 Standard treatment:

- Tab.Diclofenac 50mg orally twice daily.

- Tab.Ranitidine 150mg orally twice daily.

- Physiotherapy – Muscle strengthening exercises.

Tab.Diclofenac and Tab.Ranitidine were given initially for a period of 2 weeks. Then depending on the pain assessment every 2 weeks, these drugs were continued during the study period

Study group

Standard treatment plus **Collagen peptide 10g sachet orally per day.**

Collagen peptide powder was dissolved in 100 ml water and advised to take before breakfast.

ASSESSMENT PARAMETERS:

- Joint tenderness and pain during Range of movement assessed by VISUAL ANALOGUE SCALE.

- Pain, stiffness and functional disability assessed by WOMAC Osteoarthritis index.

- X-ray Knee joint – Anteroposterior & Lateral view

VISUAL ANALOGUE SCALE (VAS):
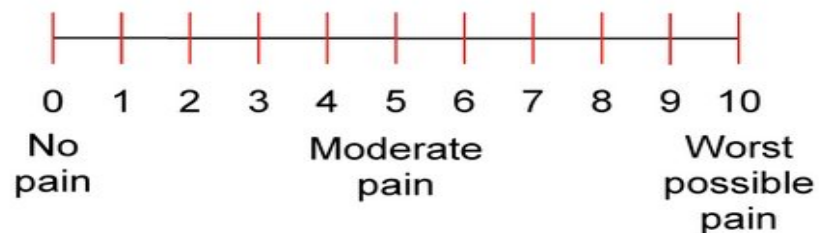
The Visual Analogue Scale consists of a 10 cm line with 0 at one end representing no pain, and 10 at the other end representing the worst pain ever experienced.

WOMAC OSTEOARTHRITIS INDEX:

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is an index which assesses pain (5 activities), stiffness (2 activities) and functional disability (17 activities) in patients with knee joint Osteoarthritis

Pain subscale - Assess pain during

- ➢ Walking on flat surface

- ➢ Going up or down stairs

- ➢ At night while in bed

- ➢ Sitting or lying

- ➢ Standing upright

Maximum score of 4 for each parameter and a total score of 20

Stiffness subscale - Assess stiffness

- ➢ In the morning

- ➢ Later in the day

Maximum score of 4 for each parameter and a total score of 8

Disability subscale - Assess difficulty in

- ➢ descending stairs

- ➢ Ascending stairs

- Sitting on chair

- Standing up from chair

- While standing

- Bending to floor

- Walking

- Getting in and out of bus/auto

- Going shopping

- Rising from bed

- Lying on bed

- Going on/off toilet

- Doing light domestic duties

- Doing heavy domestic duties

- Sitting cross legged on floor

- Rising from cross legged position

- Squatting on floor

Maximum score of 4 for each parameter and a total score of 68

SCREENING:

➢ Written informed consent obtained.

➢ Demographic details obtained.

➢ Medical history taken and recorded.

➢ Vital signs recorded.

➢ General, systemic & local examination of knee joint done.

➢ Laboratory investigations done.

➢ X ray knee joint - Anteroposterior & Lateral view taken

VISIT 1 (Baseline):

➢ Randomization done.

➢ Vital signs recorded.

➢ Pain assessment done by Visual analogue scale.

➢ Osteoarthritis index assessment done by WOMAC index.

> Study drugs were issued for 2 weeks to respective groups.

> Instructed to return the empty strips during subsequent visit.

> Patients were instructed to report if any adverse events occur.

VISIT 2 (end of 2 weeks)

> Vital signs recorded.

> Patients were asked to return empty strips to check compliance.

> Clinical examination of knee joint was done.

> Adverse events monitored.

> Pain assessment done by Visual analogue scale.

> Osteoarthritis index assessment done by WOMAC index.

> Study medication issued for subsequent 2 weeks.

VISIT 3 (end of 4 weeks)

> Vital signs recorded.

> Patients were asked to return empty strips to check compliance.

> Clinical examination of knee joint was done.

> Adverse events monitored.

- ➢ Pain assessment done by Visual analogue scale.

- ➢ Osteoarthritis index assessment done by WOMAC index.

- ➢ Study medication issued for subsequent 2 weeks.

VISIT 4 (end of 6 weeks)

- ➢ Vital signs recorded.

- ➢ Patients were asked to return empty strips to check compliance.

- ➢ Clinical examination of knee joint was done.

- ➢ Adverse events monitored.

- ➢ Pain assessment done by Visual analogue scale.

- ➢ Osteoarthritis index assessment done by WOMAC index.

- ➢ Study medication issued for subsequent 2 weeks.

VISIT 5 (end of 8 weeks)

- ➢ Vital signs recorded.

- ➢ Patients were asked to return empty strips to check compliance.

- ➢ Clinical examination of knee joint was done.

- ➢ Adverse events monitored.

- ➢ Pain assessment done by Visual analogue scale.

- ➢ Osteoarthritis index assessment done by WOMAC index.

- ➢ Study medication issued for subsequent 2 weeks.

VISIT 6 (end of 10 weeks)

- ➢ Vital signs recorded.

- ➢ Patients were asked to return empty strips to check compliance.

- ➢ Clinical examination of knee joint was done.

- ➢ Adverse events monitored.

- ➢ Pain assessment done by Visual analogue scale.

- ➢ Osteoarthritis index assessment done by WOMAC index.

- ➢ Study medication issued for subsequent 2 weeks.

VISIT 7 (end of 12 weeks)

- ➢ Vital signs recorded.

- ➢ Patients were asked to return empty strips to check compliance.

- ➢ Clinical examination of knee joint was done.

- ➢ Adverse events monitored.

- ➢ Pain assessment done by Visual analogue scale.

> Osteoarthritis index assessment done by WOMAC index.

> Laboratory investigations done.

> X ray knee joint - Anteroposterior & Lateral view taken.

VISIT 8 (end of 16 weeks)

> Vital signs recorded.

> Clinical examination of knee joint was done

> Pain assessment done by Visual analogue scale.

> Osteoarthritis index assessment done by WOMAC index.

Lab investigations:

The following laboratory investigations and assessment of symptoms were performed in the patients on screening and at the end of 12 weeks.

- Haematology - Haemoglobin, Total leucocyte count, Differential count, Platelet count, ESR
- Blood glucose
- Blood urea
- Serum creatinine
- Liver function test (SGOT, SGPT)
- X ray – chest PA view
- X ray – knee AP & Lateral view on standing

- ECG all leads

Follow up:

The patients were followed up for a post treatment period of 4 weeks, without the study drug for the assessment of symptoms of osteoarthritis.

After the completion of 16 weeks of study period, the patients were provided appropriate medical care at Institute of Orthopaedics, Rajiv Gandhi Government General Hospital, Chennai.

Adverse events:

Any adverse event reported by the patient or observed by the physician during the study was recorded. The onset of adverse event, causal relationship to the study drug and action taken will be recorded. Appropriate medical care was provided.

Withdrawal:

During the study period the subject was allowed to withdraw his/her voluntary consent and opt out of study. Similarly at the discretion of the investigator, the subjects

were withdrawn from the study if any serious adverse event reported by the patient or observed by the physician.

Statistical analysis:

The obtained data was analyzed statistically.

Distribution of age was analyzed using one way ANOVA and Sex distribution was analyzed by Pearson chi- square test.

The biochemical investigations were performed at baseline and at the end of 12 weeks. The differences within the groups before and after treatment were analyzed using student's paired t- test.

The difference within the groups in pain assessment score and WOMAC Osteoarthritis index score was analyzed using students paired t-test. Similarly the difference between the control and test groups was analyzed using independent t-test.

Statistical analysis was done by using SPSS software.

p value <0.05 was considered to be statistically significant

RESULTS

RESULTS

This study was conducted to evaluate the efficacy and safety of collagen peptide as add on therapy to Standard treatment in comparison with standard therapy alone in patients with Knee joint Osteoarthritis.

126 patients were screened, of which 58 patients were excluded from the study based on exclusion criteria and 8 patients who were eligible for the study were not willing to participate.

Thereby 60 patients were enrolled in this study and were randomized into either of the 2 groups: Control group [Standard therapy] and Test group [Collagen peptide along with Standard therapy]. Each group consisted of 30 patients. All the enrolled patients completed the study.
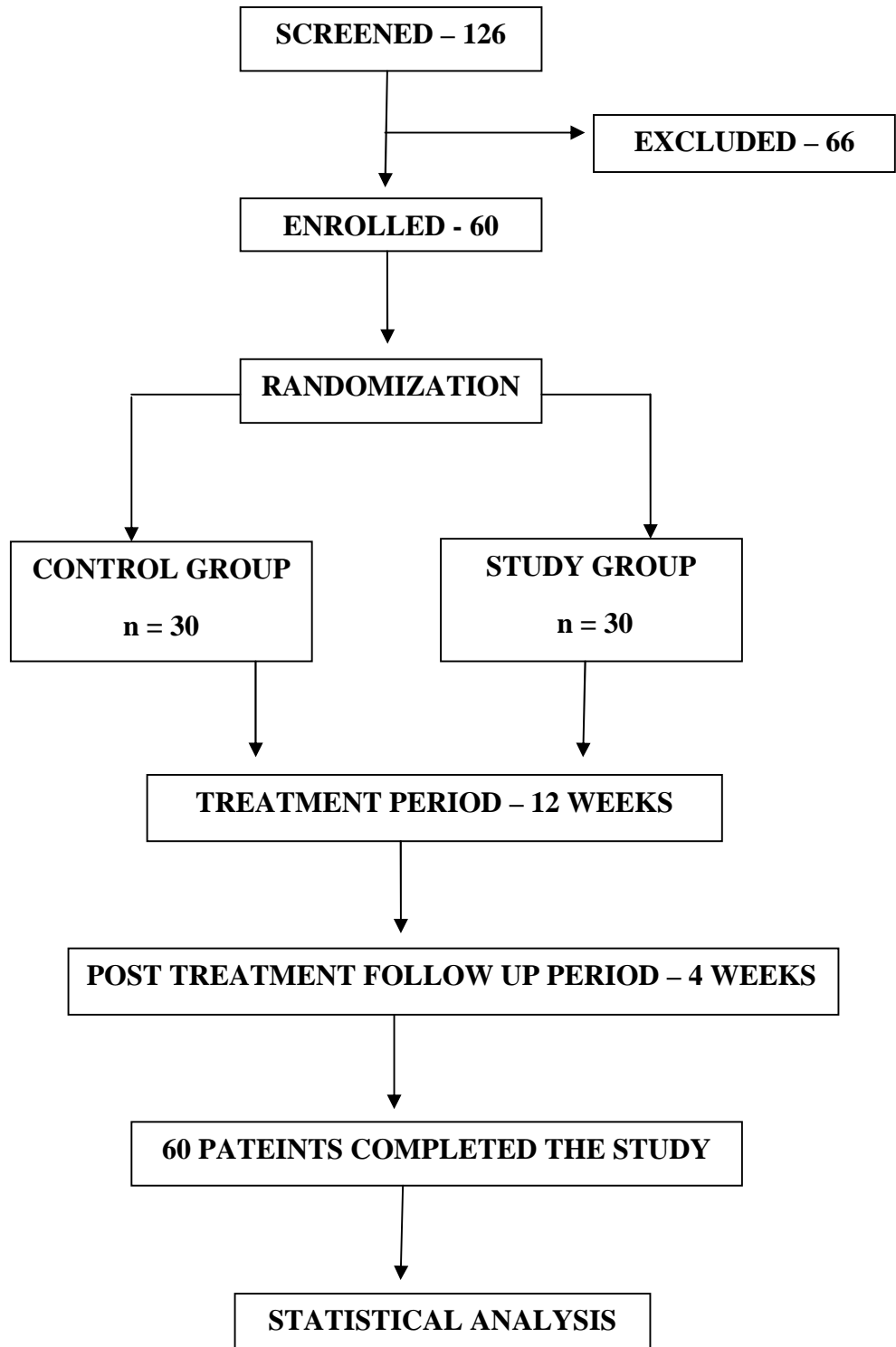
STUDY FLOW CHART

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                    ┌─────────────────────┐
                    │  SCREENED – 126     │
                    └─────────────────────┘
                              │
                              │────────────────►  ┌──────────────────┐
                              │                   │  EXCLUDED – 66   │
                              ▼                   └──────────────────┘
                    ┌─────────────────────┐
                    │   ENROLLED - 60     │
                    └─────────────────────┘
                              │
                              ▼
                    ┌─────────────────────┐
                    │   RANDOMIZATION     │
                    └─────────────────────┘
              ┌───────────────┴───────────────┐
              ▼                               ▼
    ┌───────────────────┐           ┌───────────────────┐
    │  CONTROL GROUP    │           │   STUDY GROUP     │
    │                   │           │                   │
    │     n = 30        │           │     n = 30        │
    └───────────────────┘           └───────────────────┘
              │                               │
              ▼                               ▼
    ┌─────────────────────────────────────────────────┐
    │      TREATMENT PERIOD – 12 WEEKS                 │
    └─────────────────────────────────────────────────┘
                              │
                              ▼
    ┌─────────────────────────────────────────────────┐
    │  POST TREATMENT FOLLOW UP PERIOD – 4 WEEKS       │
    └─────────────────────────────────────────────────┘
                              │
                              ▼
    ┌─────────────────────────────────────────────────┐
    │     60 PATEINTS COMPLETED THE STUDY             │
    └─────────────────────────────────────────────────┘
                              │
                              ▼
                    ┌─────────────────────┐
                    │ STATISTICAL ANALYSIS│
                    └─────────────────────┘
```

TABLE-1: AGE DISTRIBUTION

AGE(YEARS)	CONTROL	STUDY
≤50	11	8
51-60	15	18
61-70	4	4
TOTAL	30	30

Table-1 shows the age distribution of patients among the control and study groups.

More number of patients were in the age group of 51 to 60 years in both the groups.
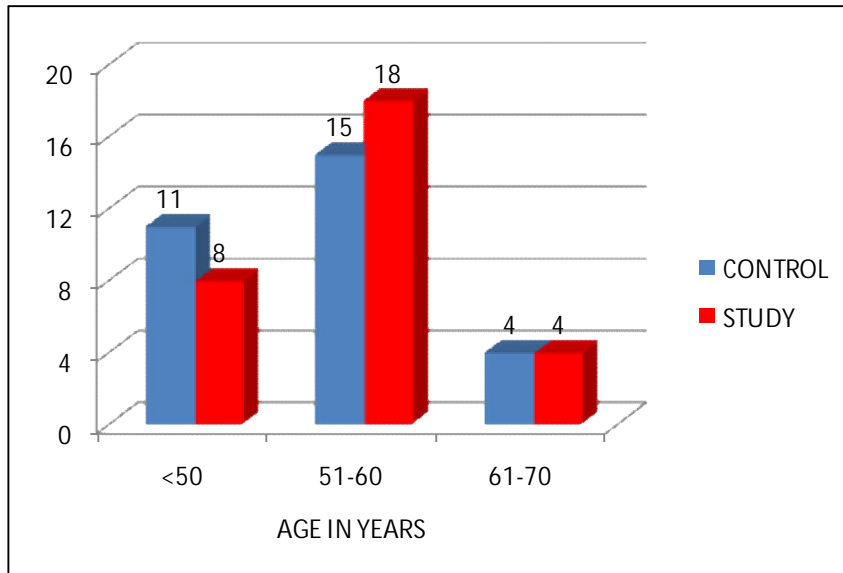
FIGURE-1: AGE DISTRIBUTION

Figure-1 is the graphical representation of table-1

GROUP	NO. OF PATIENTS (n)	MEAN AGE IN YEARS	S.D
CONTROL	30	54.36	4.64
STUDY	30	54.43	5.37
p-VALUE	p = 0.43		

Table-2 shows the Mean Age Distribution of patients among the control and study groups

The mean age of patients in control group was 54.36 and in the study group was 54.43.

There was no statistically significant difference in mean age between control and study groups.

FIGURE -2 MEAN AGE DISTRIBUTION
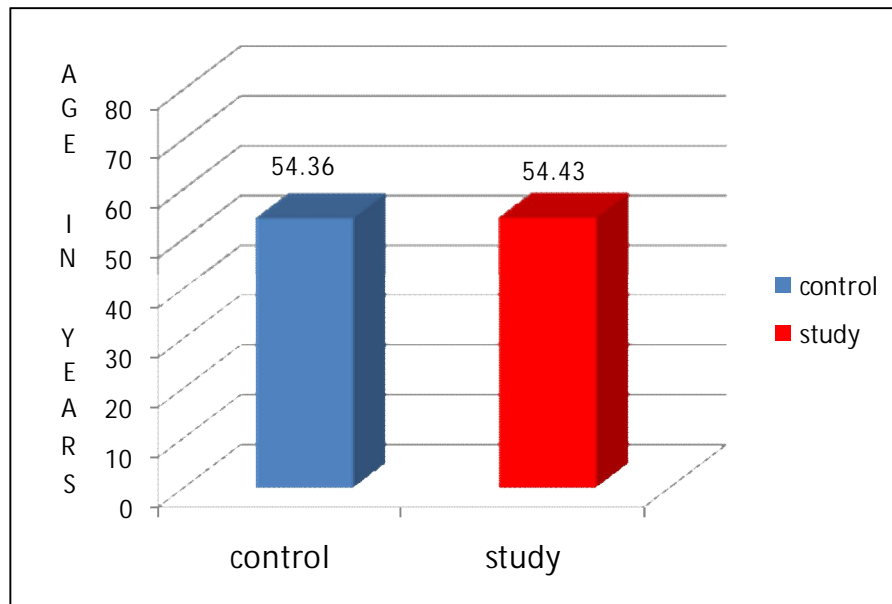
Figure-2 indicates the Mean Age Distribution of patients among control and study groups

<p style="text-align:center"><u>TABLE-3: GENDER DISTRIBUTION</u></p>

GROUP	MALE		FEMALE		TOTAL	
	N	%	n	%	N	%
CONTROL	12	40	18	60	30	100
STUDY	10	33	20	67	30	100
p-VALUE	p = 0.61					

Table 3 shows the distribution of sex in the control and study groups.

Percentage of females was higher than males.

There was no statistically significant difference between the groups.

<p style="text-align:center"><u>FIGURE-3: GENDER DISTRIBUTION</u></p>
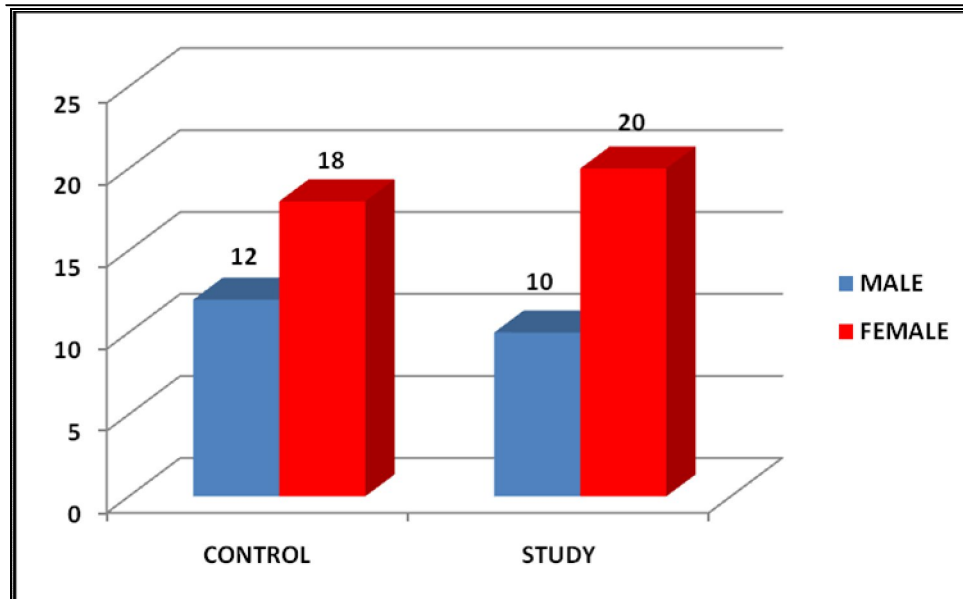
<p style="text-align:center">Figure-3 is the graphical representation of table-3</p>

TABLE-4: NUMBER OF KNEE JOINT INVOLVEMENT

GROUP	UNILATERAL	BILATERAL	TOTAL
CONTROL	21	9	30
STUDY	23	7	30
p-VALUE	p = 0.57		

Table-4 shows the number of knee joint involvement in both the control and study groups.

More number of patients were having single joint involvement in both the groups.

There was no statistically significant difference between the groups.

FIGURE-4: NUMBER OF KNEE JOINT INVOLVEMENT
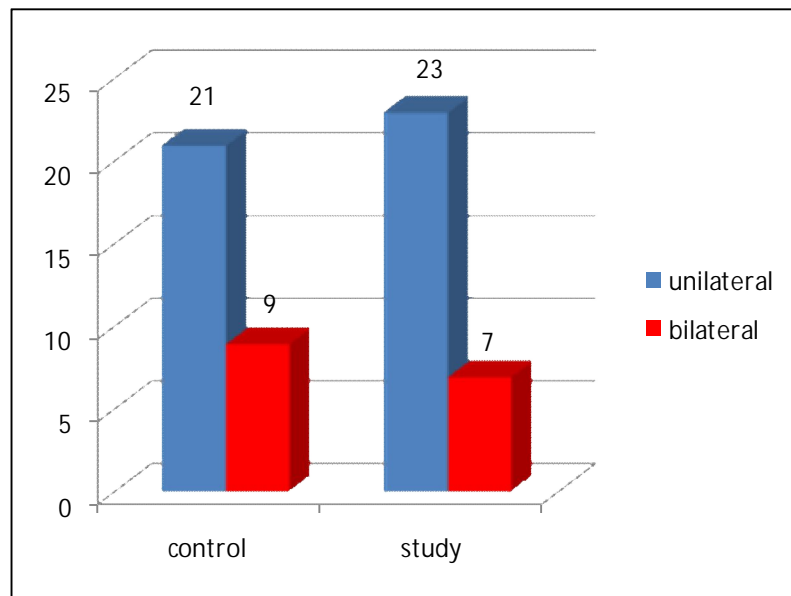
Figure-4 is the graphical representation of table-4

TABLE-5: X RAY GRADING

GROUP	GRADE 1		GRADE 2		TOTAL		p-VALUE
	n	%	n	%	n	%	
CONTROL	21	70	9	30	30	100	0.59
STUDY	19	63	11	37	30	100	

Table-5 shows the baseline x ray grading of knee joint involvement in both the control and study groups.

In both the groups, grade 1 changes were present in more number of patients.

There was no significant difference between the groups.

Repeat x ray grading at the end of the study period in both the groups also showed same results.

FIGURE-5: X RAY GRADING
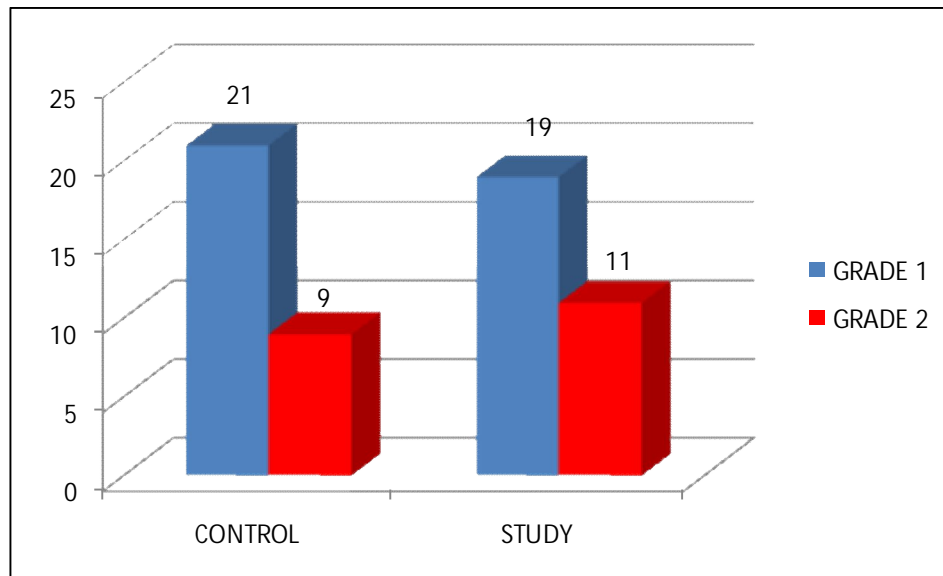
Figure-5 is the graphical representation of table-5.

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TABLE-6: VAS PAIN SCORE:

	CONTROL GROUP		STUDY GROUP		INDEPENDENT T-TEST
	MEAN	SD	MEAN	SD	
BASELINE	7.63	0.54	7.7	0.45	p=0.62
WEEK 2	6.76	0.66	6.53	0.71	p=0.21
WEEK 4	6.36	0.79	6.13	0.88	p=0.29
WEEK 6	6.03	0.60	5.8	0.74	p=0.19
WEEK 8	5.76	0.76	5.33	0.74	p=0.03
WEEK 10	5.66	0.69	4.5	0.56	p<0.01
WEEK 12	5.53	0.56	3.8	0.65	p<0.01
WEEK 16	5.43	0.55	3.66	0.53	p<0.01
p-VALUE	p<0.01		p<0.01		

Table-6 shows mean pain score in both the groups by visual analogue pain scale from baseline to week 16.

Statistical analysis within the group showed a significant decrease in mean pain score in both the control and study groups.

Comparison between the groups showed statistically significant decrease in mean pain score from week 8 onwards.

Post treatment follow up period at week 16 showed less pain score in the study group than the control group.
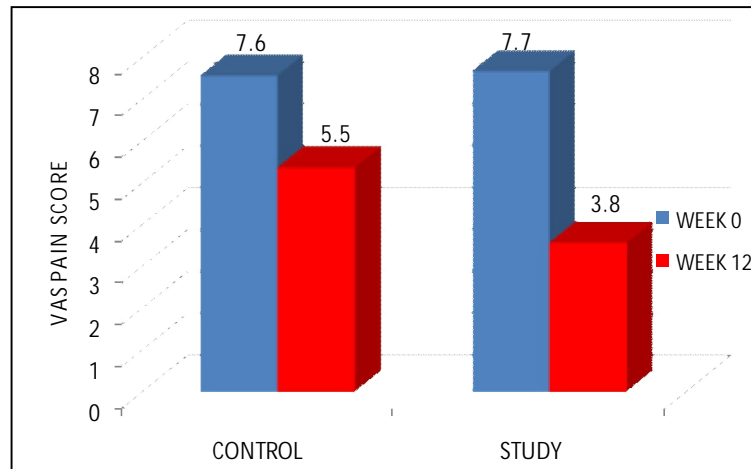
FIGURE-6: VAS PAIN SCORE
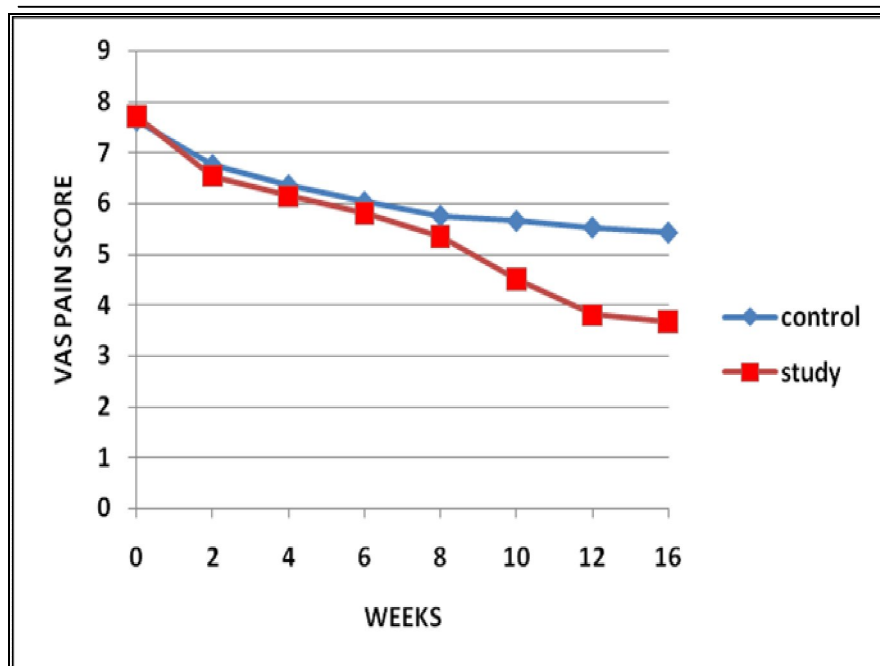
Figure-6 is the graphical representation of table-6.

TABLE-6A: VAS PAIN SCORE - TREATMENT PERIOD

BASELINE vs 12 WEEKS

	CONTROL GROUP	STUDY GROUP	p-VALUE
BASELINE	7.63	7.7	
12 WEEKS	5.53	3.8	<0.01

Table-6A shows mean pain score in both the groups by visual analogue pain scale at baseline and week 12.

Comparison between the groups showed a statistically significant decrease in mean pain score.

FIGURE-6A: VAS PAIN SCORE

BASELINE vs. 12 WEEKS

Figure-6A is the graphical representation of table-6A.

TABLE-6B: VAS PAIN SCORE

POST TREATMENT FOLLOW UP PERIOD

12 WEEKS vs 16 WEEKS

	CONTROL GROUP	STUDY GROUP	p-VALUE
12 WEEKS	5.53	3.8	<0.01
16 WEEKS	5.43	3.66	<0.01

Table-6B shows mean pain score in both the control and study groups by visual analogue pain scale during post treatment follow up period at week 12 and week 16.

During this follow up period, control group patients continued Tab.Diclofenac and study group patients were without any drug.

Comparison between the groups showed that statistically significant decrease in mean pain score was maintained in the study group even without analgesics at week 16.

FIGURE-6B: VAS PAIN SCORE

12 WEEKS vs 16 WEEKS
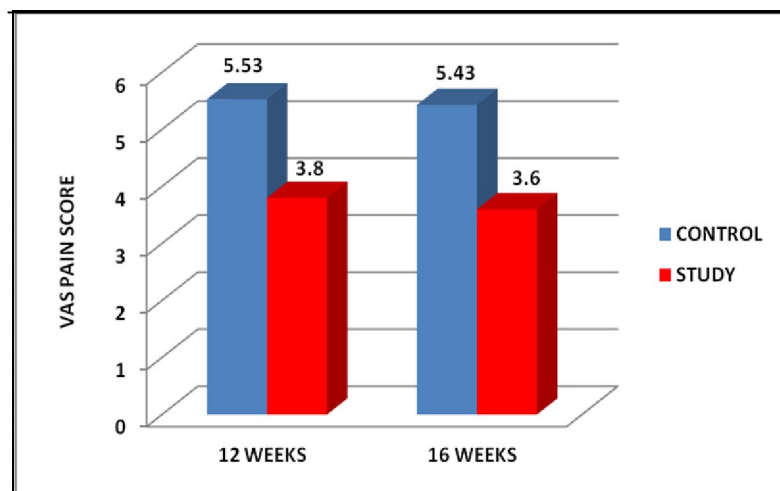
Figure-6B is the graphical representation of table-6B.

TABLE-7: WOMAC PAIN SCORE:

	CONTROL GROUP		STUDY GROUP		INDEPENDENT T-TEST
	MEAN	SD	MEAN	SD	
BASELINE	14.13	0.61	14.46	0.80	p=0.08
WEEK 2	13.8	0.79	13.73	0.81	p=0.75
WEEK 4	12.5	0.67	12.23	0.66	p=0.13
WEEK 6	11.73	0.51	11.5	0.56	p=0.11
WEEK 8	11.06	0.89	9.93	1.36	p<0.01
WEEK 10	10.9	0.86	8.86	1.49	p<0.01
WEEK 12	10.63	0.83	7.13	0.80	p<0.01
WEEK 16	10.53	0.92	7.1	0.86	p<0.01
p-VALUE	p<0.01		p<0.01		

Table-7 shows mean pain score in both the groups by WOMAC pain subscale from baseline to week 16.

Statistical analysis within the group showed a significant decrease in pain score in both the control and study groups.

Comparison between the groups showed statistically significant decrease in pain score from week 8 onwards.

Post treatment follow up period at week 16 showed less pain score in the study group than the control group.
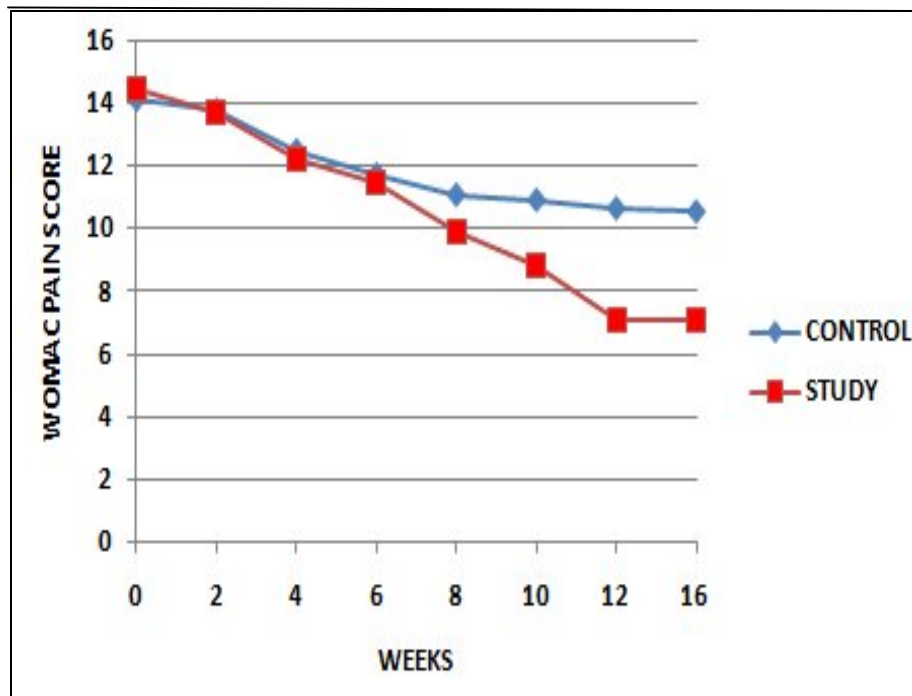
.

FIGURE-7: WOMAC PAIN SCORE

Figure-7 is the graphical representation of table-7.

	CONTROL GROUP	STUDY GROUP	p-VALUE
BASELINE	14.13	14.46	
12 WEEKS	10.63	7.13	<0.01

Table-7A shows mean pain score in both the groups by WOMAC pain subscale at baseline and week 12.

Comparison between the groups showed a statistically significant decrease in mean pain score.
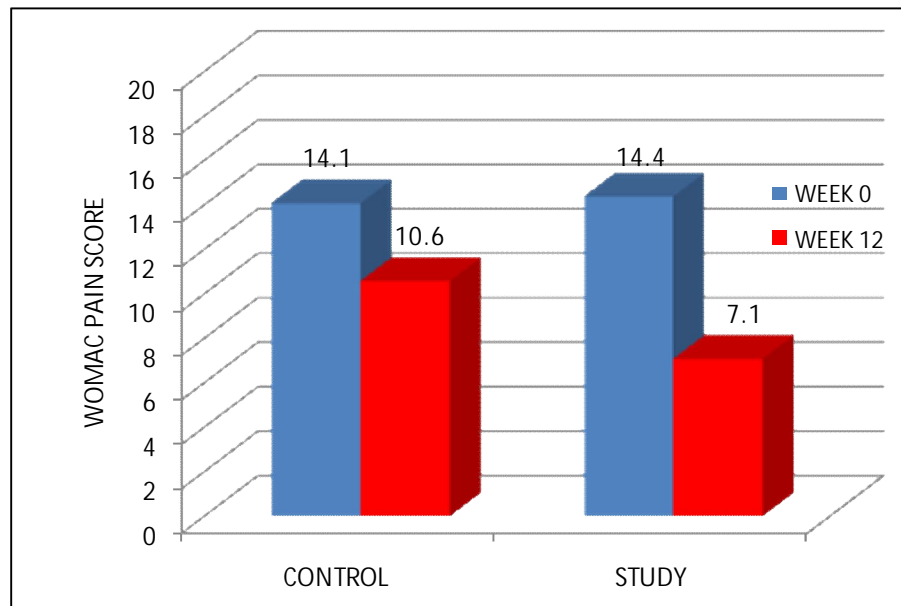
FIGURE-7A: WOMAC PAIN SCORE

BASELINE vs 12 WEEKS

Figure-7A is the graphical representation of table-7A.

POST TREATMENT FOLLOW UP PERIOD

12 WEEKS vs 16 WEEKS

	CONTROL GROUP	STUDY GROUP	p-VALUE
12 WEEKS	10.63	7.13	<0.01
16 WEEKS	10.53	7.1	<0.01

Table-7B shows mean pain score in both the groups by WOMAC pain subscale at week 12 and week 16.

During this follow up period, control group patients continued Tab.Diclofenac and study group patients were without any drug.

Comparison between the groups showed that statistically significant decrease in mean pain score was maintained in the study group even without analgesics at week 16.

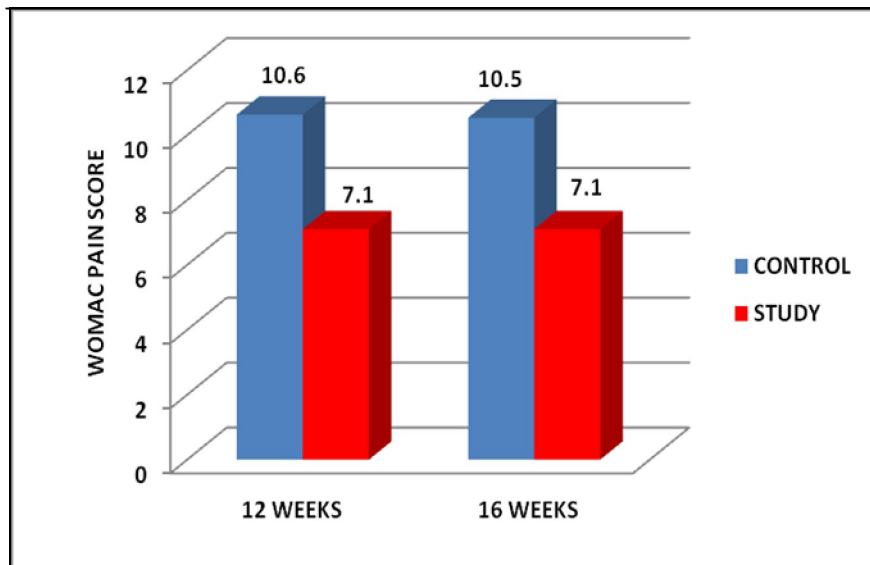FIGURE-7B: WOMAC PAIN SCORE

12 WEEKS vs 16 WEEKS

Figure-7B is the graphical representation of table-7B.

TABLE- 8: WOMAC STIFFNESS SCORE

	CONTROL GROUP		STUDY GROUP		INDEPENDENT T-TEST
	MEAN	SD	MEAN	SD	
BASELINE	5.43	0.49	5.36	0.60	p=0.64
WEEK 2	4.93	0.57	4.83	0.58	p=0.51
WEEK 4	4.33	0.47	4.26	0.51	p=0.61
WEEK 6	4.13	0.56	4.03	0.60	p=0.52
WEEK 8	4.03	0.54	3.63	0.48	p=0.02
WEEK 10	3.96	0.54	2.86	0.61	p<0.01
WEEK 12	3.76	0.61	2.33	0.59	p<0.01
WEEK 16	3.63	0.54	2.2	0.47	p<0.01
p-VALUE	p<0.01		p<0.01		

Table-8 shows mean stiffness score in both the groups by WOMAC stiffness subscale from baseline to week 16.

Statistical analysis within the group showed a significant decrease in stiffness score in both the control and study groups.

Comparison between the groups showed statistically significant decrease in stiffness score from week 8 onwards.

Post treatment follow up period at week 16 showed less stiffness score in the study group than the control group.
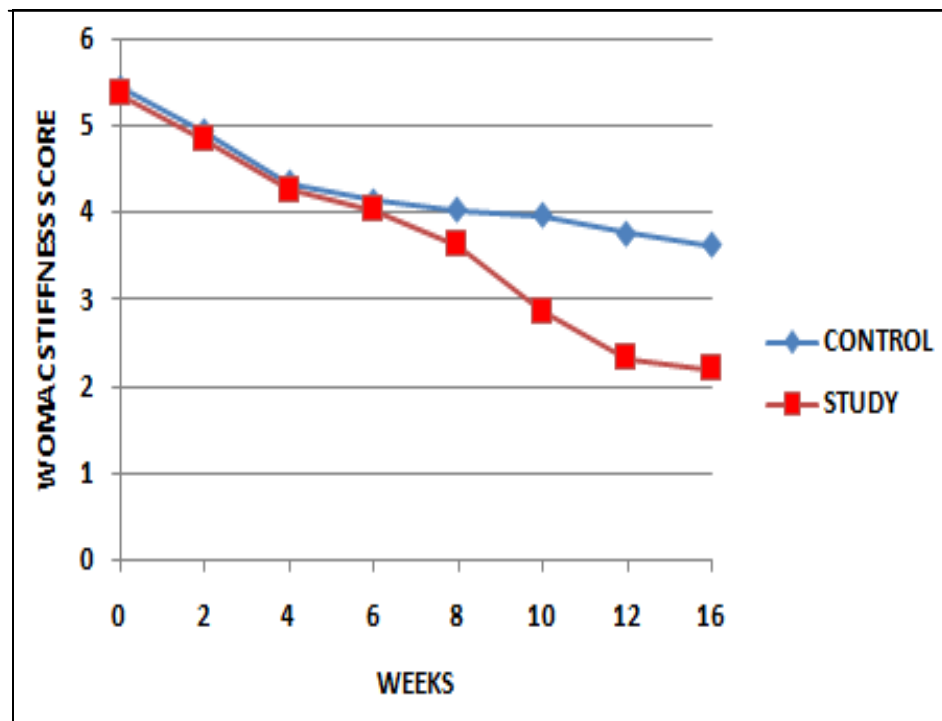
FIGURE-8: WOMAC STIFFNESS SCORE

Figure-8 is the graphical representation of table-8.

TABLE-8A: WOMAC STIFFNESS SCORE – TREATMENT PERIOD

BASELINE vs 12 WEEKS

	CONTROL GROUP	STUDY GROUP	p-VALUE
BASELINE	5.43	5.36	
12 WEEKS	3.76	2.33	<0.01

Table-8A shows mean stiffness score in both the groups by WOMAC stiffness subscale at baseline and week 12.

Comparison between the groups showed a statistically significant decrease in mean stiffness score.

FIGURE-8A: WOMAC STIFFNESS SCORE
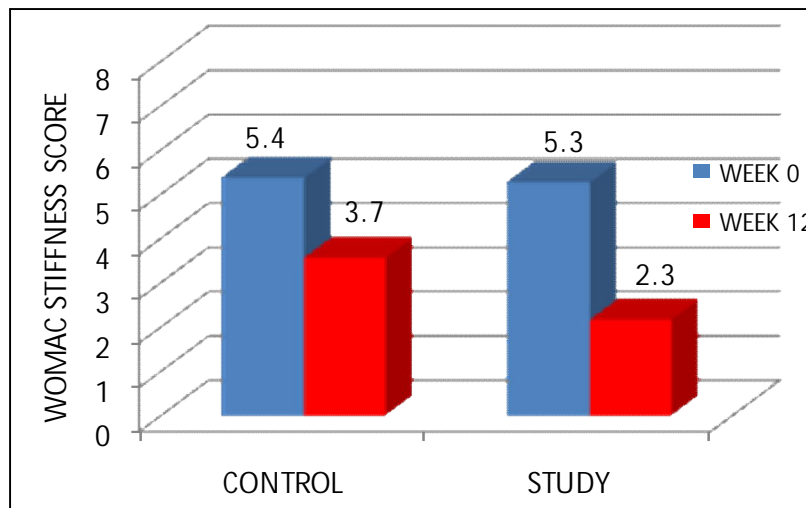
BASELINE vs 12 WEEKS

Figure-8A is the graphical representation of table-8A

TABLE-8B: WOMAC STIFFNESS SCORE

POST TREATMENT FOLLOW UP PERIOD

12 WEEKS vs 16 WEEKS

	CONTROL GROUP	STUDY GROUP	p-VALUE
12 WEEKS	3.76	2.33	<0.01
16 WEEKS	3.63	2.2	<0.01

Table-8B shows mean stiffness score in both the groups by WOMAC stiffness subscale at week 12 and week 16.

During this follow up period, control group patients continued Tab.Diclofenac and study group patients were without any drug.

Comparison between the groups showed that statistically significant decrease in mean stiffness score was maintained in the study group even without analgesics at week 16.

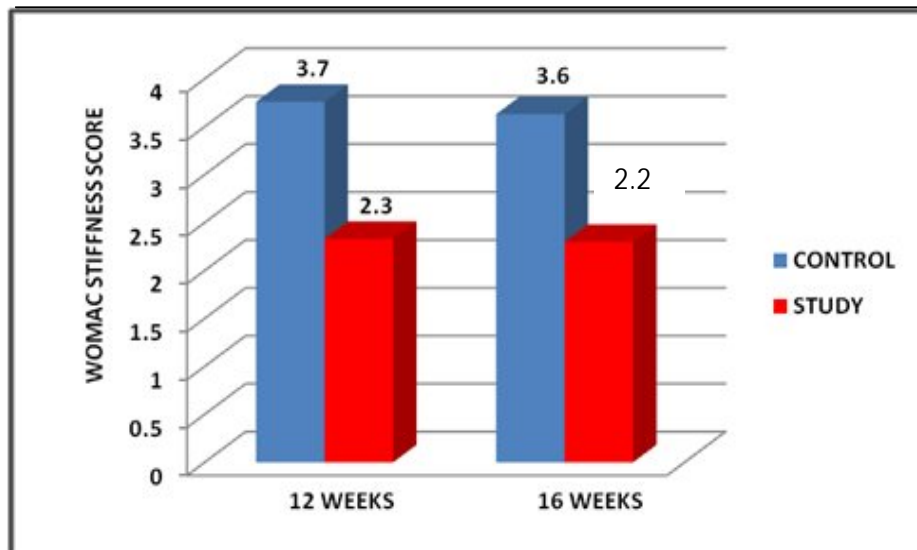## FIGURE-8B: WOMAC STIFFNESS SCORE

12 WEEKS vs 16 WEEKS

Figure-8B is the graphical representation of table-8B.

TABLE-9: WOMAC DISABILITY SCORE

	CONTROL GROUP		STUDY GROUP		INDEPENDENT T-TEST
	MEAN	SD	MEAN	SD	
BASELINE	45.43	2.71	46.33	1.84	p=0.15
WEEK 2	42.53	2.67	41.86	1.97	p=0.29
WEEK 4	38.8	2.57	38.13	2.20	p=0.29
WEEK 6	35.33	2.82	33.7	1.93	p=0.21
WEEK 8	34.43	2.85	29.3	2.22	p=0.02
WEEK 10	34.13	2.76	26.0	2.51	p<0.01
WEEK 12	33.1	2.85	23.23	2.61	p<0.01
WEEK 16	32.23	2.70	23.16	2.57	p<0.01
p-VALUE	p<0.01		p<0.01		

Table-9 shows mean disability score in both the groups by WOMAC disability subscale from baseline to week 16.

Statistical analysis within the group showed a significant decrease in disability score using WOMAC disability subscale in both the control and study groups.

Comparison between the groups showed statistically significant decrease in disability score from week 8 onwards.

Post treatment follow up period at week 16 showed less disability score in the study group than the control group.
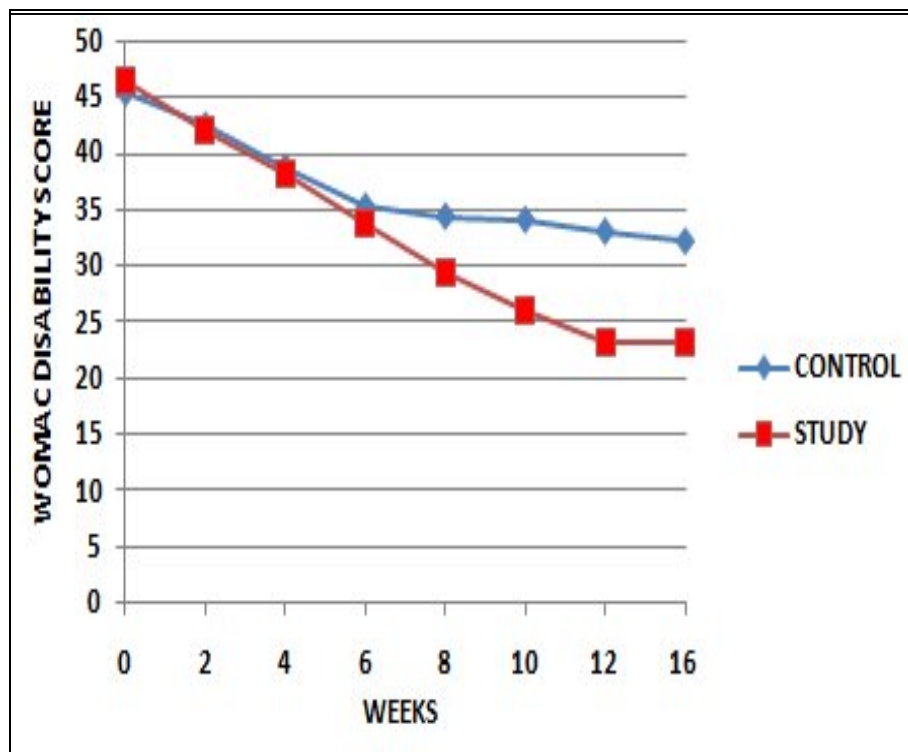
FIGURE-9: WOMAC DISABILITY SCORE:

Figure-9 is the graphical representation of table-9.

TABLE-9A: WOMAC DISABILITY SCORE – TREATMENT PERIOD

BASELINE vs 12 WEEKS

	CONTROL GROUP	STUDY GROUP	p-VALUE
BASELINE	45.43	46.33	
12 WEEKS	33.1	23.23	<0.01

Table-9A shows mean disability score in both the groups by WOMAC disability subscale at baseline and week 12.

Comparison between the groups showed statistically significant decrease in mean disability score.

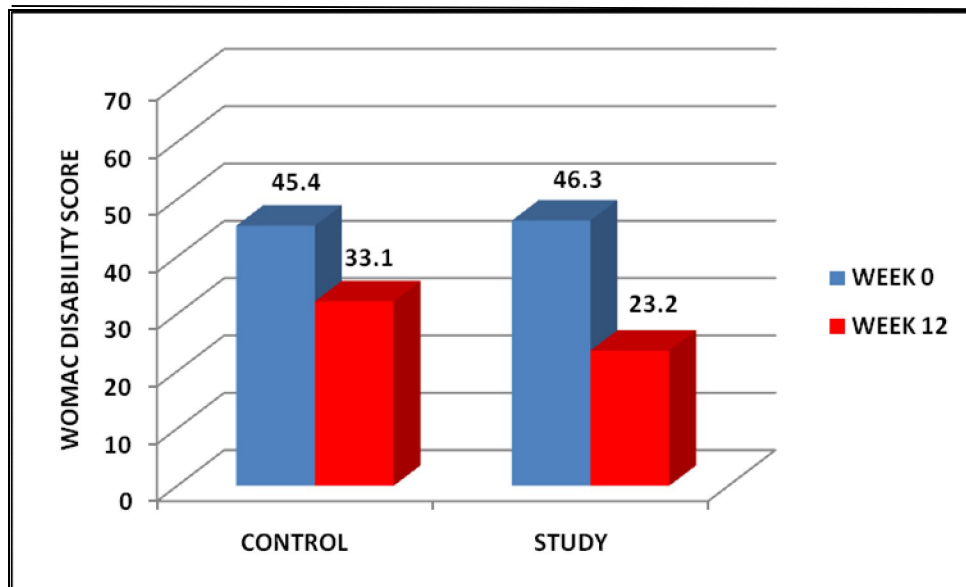## FIGURE-9A: WOMAC DISABILITY SCORE

BASELINE vs 12 WEEKS

Figure-9A is the graphical representation of table-9A.

TABLE-9B: WOMAC DISABILITY SCORE

POST TREATMENT FOLLOW UP PERIOD

12 WEEKS vs 16 WEEKS

	CONTROL GROUP	**STUDY GROUP**	**p-VALUE**
WEEK 12	33.1	23.23	<0.01
WEEK 16	32.23	23.16	<0.01

Table-9B shows mean disability score in both the groups by WOMAC disability subscale at week 12 and week 16.

During this follow up period, control group patients continued Tab.Diclofenac and study group patients were without any drug.

Comparison between the groups showed that statistically significant decrease in mean disability score was maintained in the study group even without analgesics at week 16.

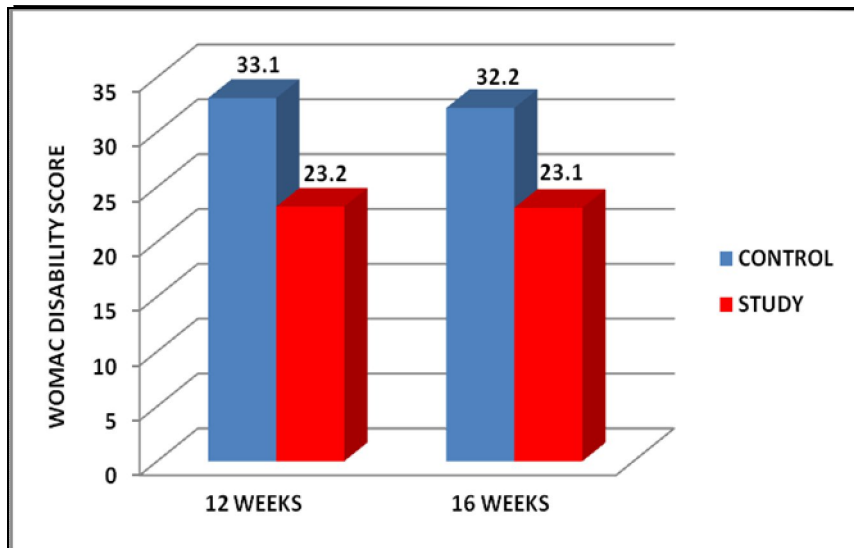**FIGURE-9B: WOMAC DISABILITY SCORE**

12 WEEKS vs 16 WEEKS

Figure-9B is the graphical representation of table-9B.

TABLE-10: ANALGESIC NEEDED DURING

POST TREATMENT FOLLOW UP PERIOD

	CONTROL GROUP	STUDY GROUP	p-VALUE
Analgesic needed (n)	30	8	<0.001

Table-10 shows analgesic needed in both the groups during the post treatment follow up period from week 12 to week 16.

During this follow up period, analgesic was needed in all the 30 patients in the control group.

In the study group, only 8 patients needed analgesics as and when required (less than 5 days).

Statistical analysis showed that the difference between the groups is statistically significant.

FIGURE-10: ANALGESIC NEEDED DURING
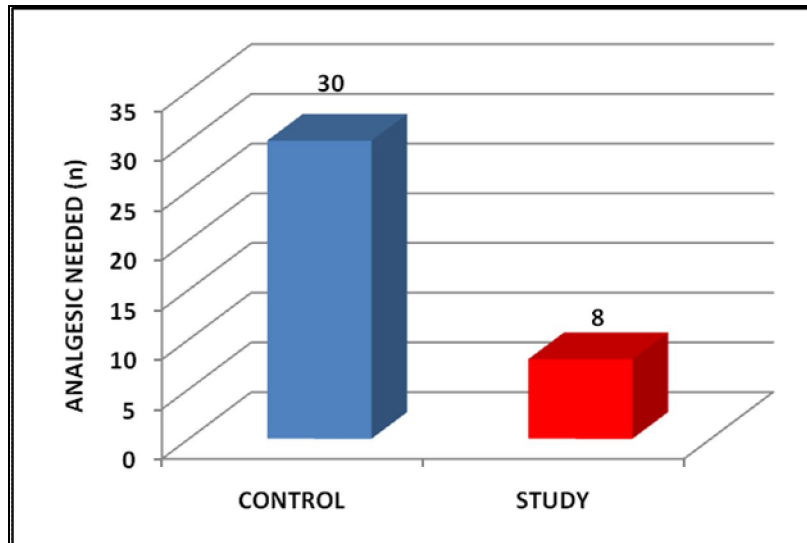
POST TREATMENT FOLLOW UP PERIOD

Figure-10 is the graphical representation of table-10.

TABLE-11 A: BIOCHEMICAL INVESTIGATIONS (CONTROL GROUP)

INVESTIGATIONS	CONTROL GROUP		p-VALUE
	BASELINE	12 WEEKS	
HEMOGLOBIN (g%)	11.3	11.8	0.42
TOTAL WBC COUNT (cells/mm3)	9642	9234	0.34
BLOOD SUGAR (mg/dl)	104	110	0.88
BLOOD UREA (mg/dl)	23.2	24.6	0.41
SERUM CREATININE (mg/dl)	0.88	0.91	0.78
SGOT (IU/L)	32	35	0.46
SGPT (IU/L)	38	36	0.84

Table 11A shows the biochemical investigations mean values done in the control group at baseline and 12 weeks.

Comparison showed that there was no statistically significant difference in the biochemical investigation mean values.

TABLE-11 B: BIOCHEMICAL INVESTIGATIONS (STUDY GROUP)

INVESTIGATIONS	STUDY GROUP		p-VALUE
	BASELINE	12 WEEKS	
HEMOGLOBIN (g%)	11.8	12.1	0.71
TOTAL WBC COUNT (cells/mm3)	8953	9178	0.81
BLOOD SUGAR (mg/dl)	109	105	0.84
BLOOD UREA (mg/dl)	24.1	23.4	0.62
SERUM CREATININE (mg/dl)	0.82	0.86	0.46
SGOT (IU/L)	36	35	0.72
SGPT (IU/L)	40	37	0.54

Table 11B shows the biochemical investigations mean values done in the study group at baseline and 12 weeks.

Comparison showed that there was no statistically significant difference in the biochemical investigation mean values.
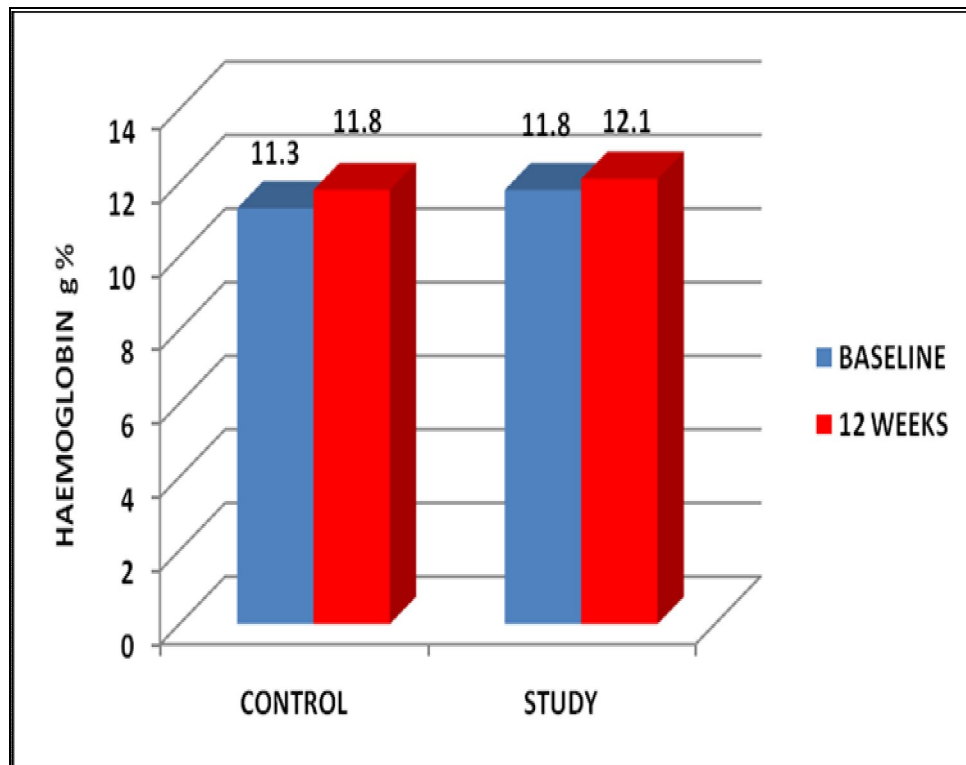
FIGURE-11A: HAEMOGLOBIN

Figure-11A shows the mean haemoglobin value in control and study groups at baseline and 12 weeks
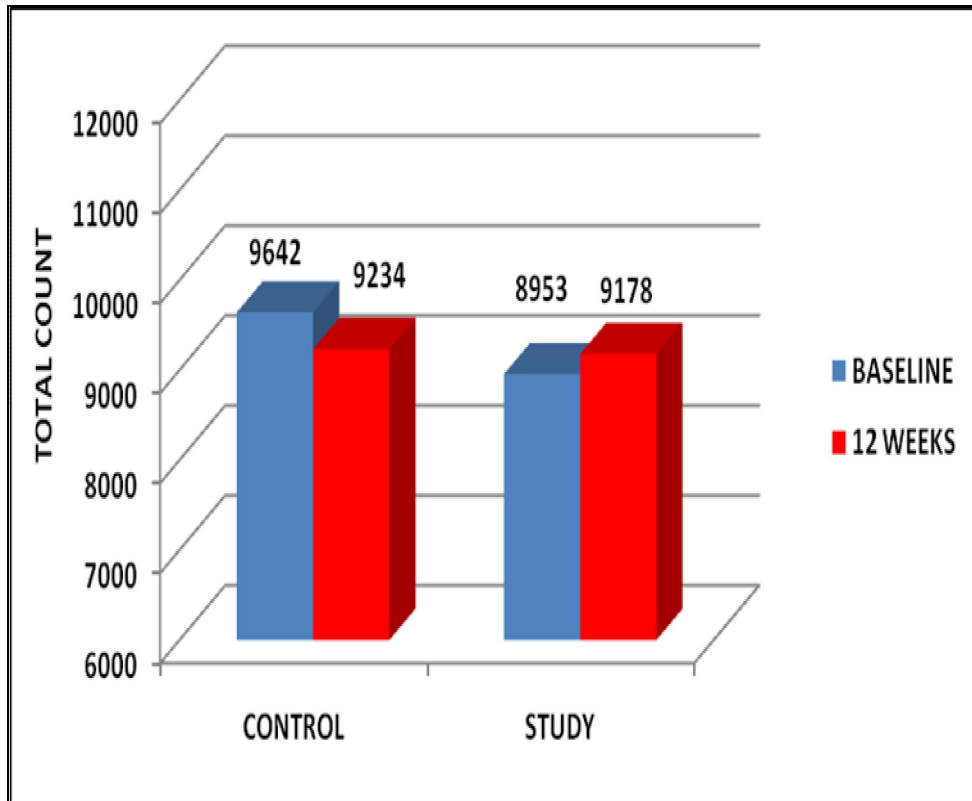
FIGURE-11B: TOTAL COUNT

Figure-11B shows the mean total count value in control and study groups at baseline and 12 weeks

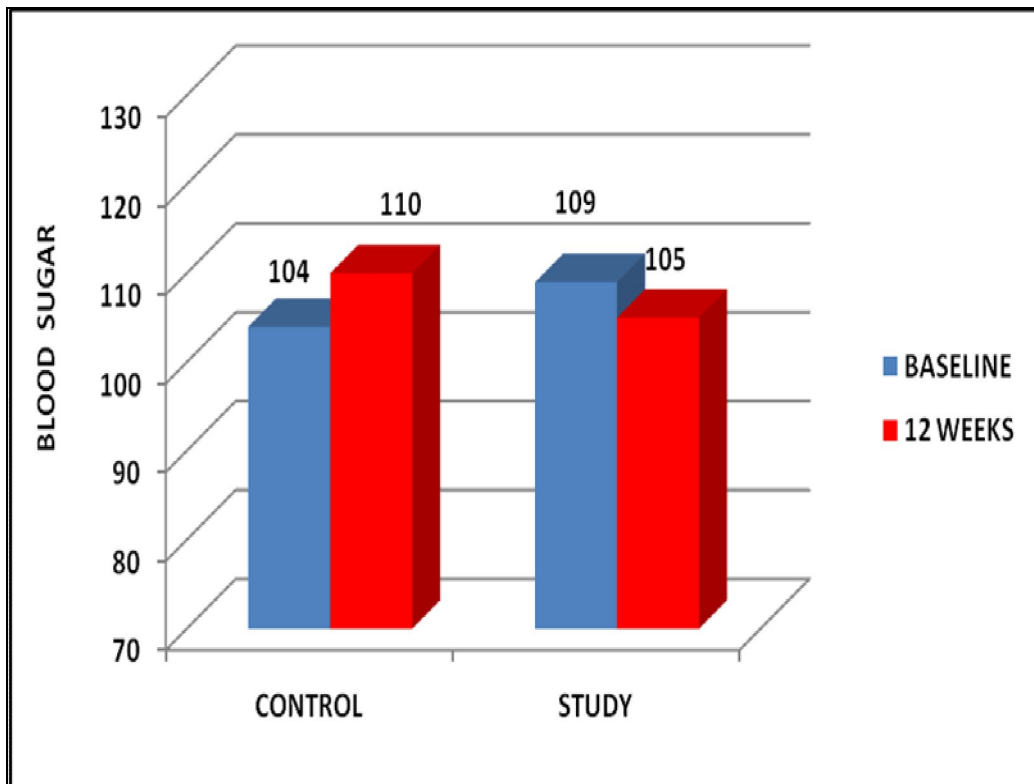## FIGURE-11C: BLOOD SUGAR

Figure-11C shows the mean blood sugar value in control and study groups at baseline and 12 weeks

FIGURE-11D: BLOOD UREA

Figure-11D shows the mean blood urea value in control and study groups at baseline and 12 weeks

FIGURE-11E: SERUM CREATININE

Figure-11E shows the mean serum creatinine value in control and study groups at baseline and 12 weeks

FIGURE-11F: SGOT

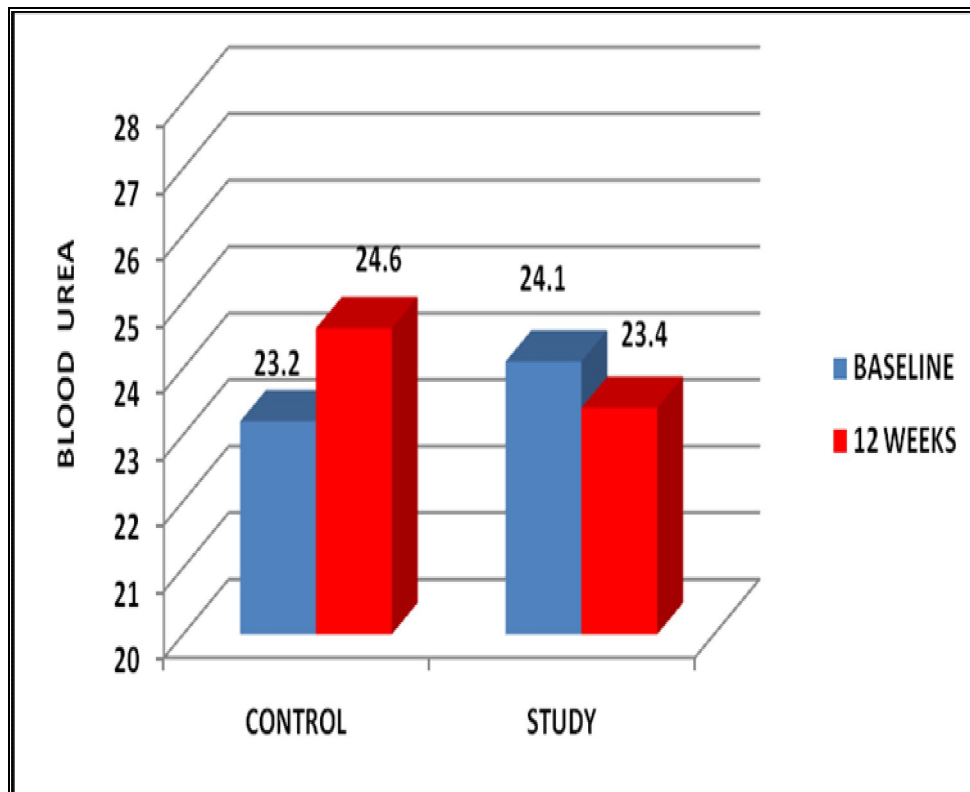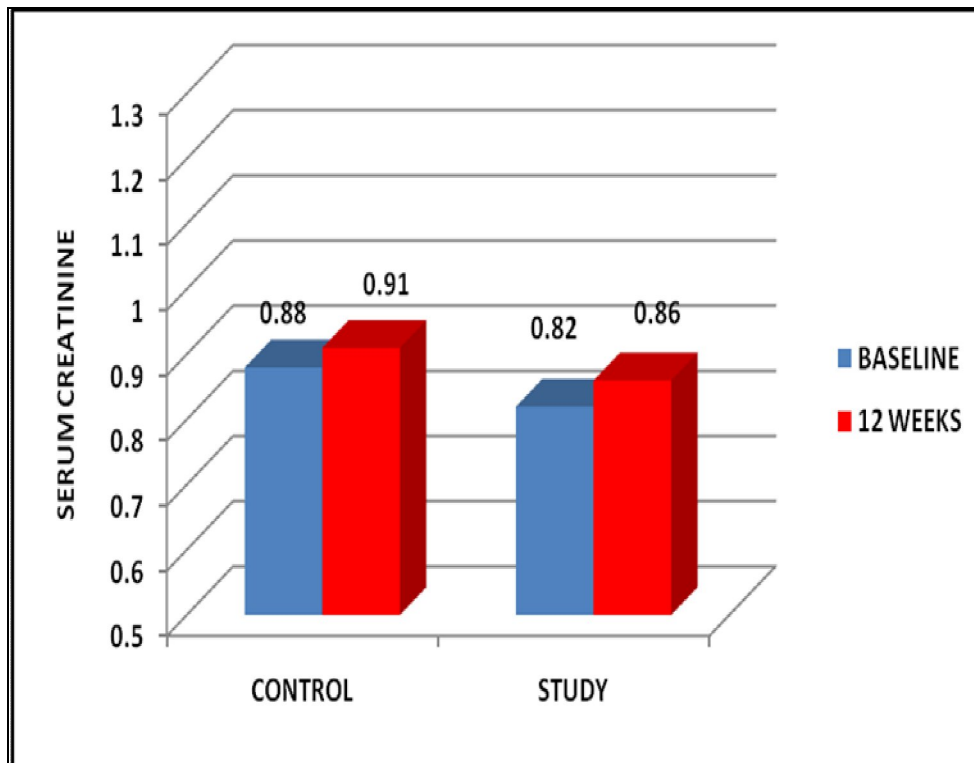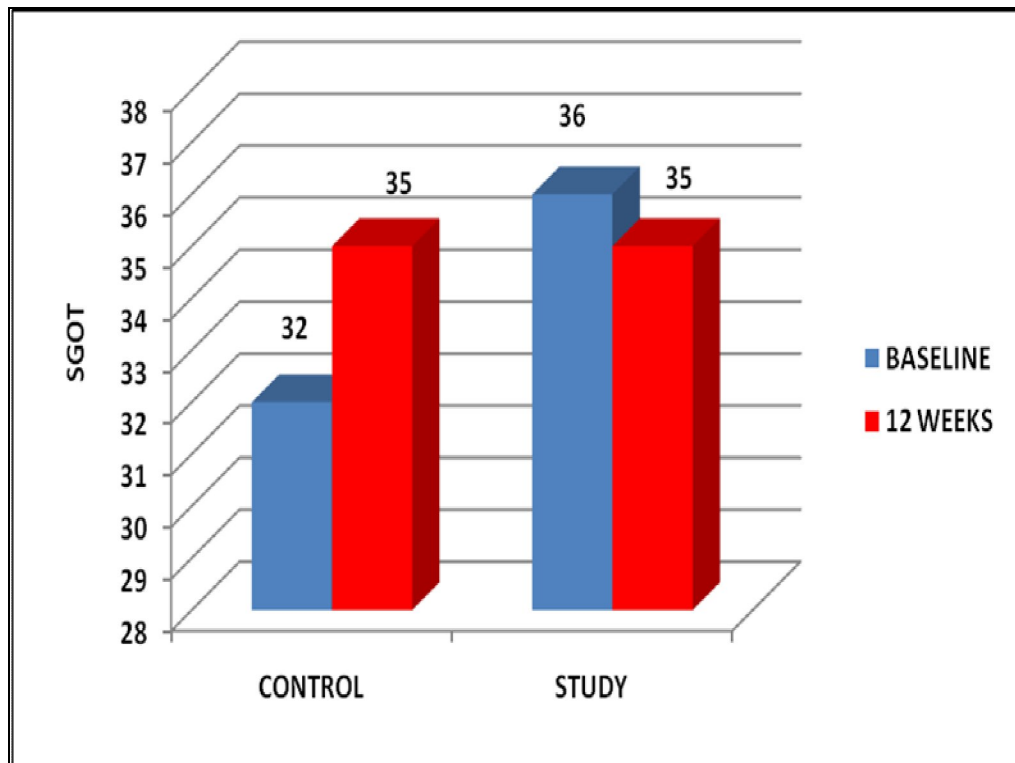**Figure-11F** shows the mean SGOT value in control and study groups at baseline and 12 weeks

FIGURE-11G: SGPT
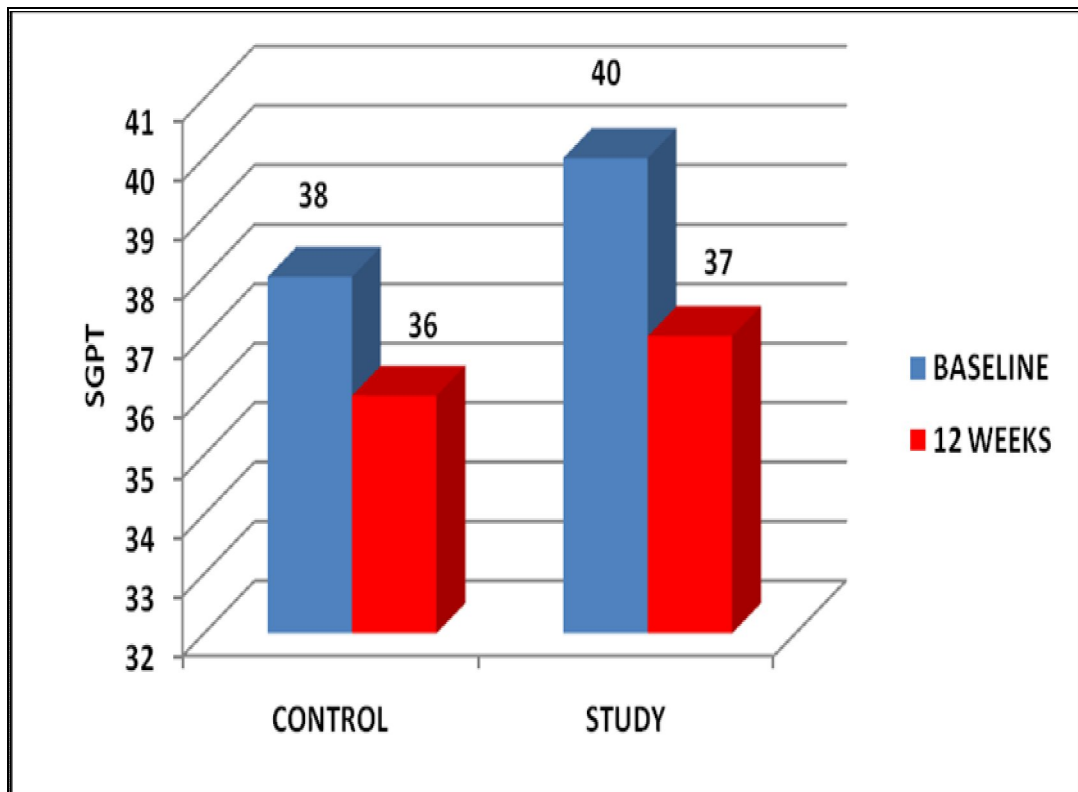
Figure-11G shows the mean SGPT value in control and study groups at baseline and 12 weeks

TABLE-12: ADVERSE EVENTS

ADVERSE EVENTS	CONTROL GROUP	STUDY GROUP
NAUSEA	3	4
VOMITING	2	2
ABDOMEN PAIN	7	6
DIARRHOEA	1	0
HEAD ACHE	1	1

Table-12 shows the adverse events noted in both control and study groups.

Nausea and abdomen pain were the common adverse events noted during the study.

Other adverse events noted were vomiting, diarrhoea and headache.

No significant difference was noted in the adverse events between the control and study groups.

FIGURE-12: ADVERSE EVENTS

Figure-12 shows the adverse events noted during the study in graphical representation

DISCUSSION

DISCUSSION

Ostaoarthritis is the most common musculoskeletal disorder affecting elderly people resulting in pain, stiffness and functional disability. The loss of articular cartilage is responsible for the pain experienced during movements of the joint. This leads to restriction of movements resulting in severe disability.
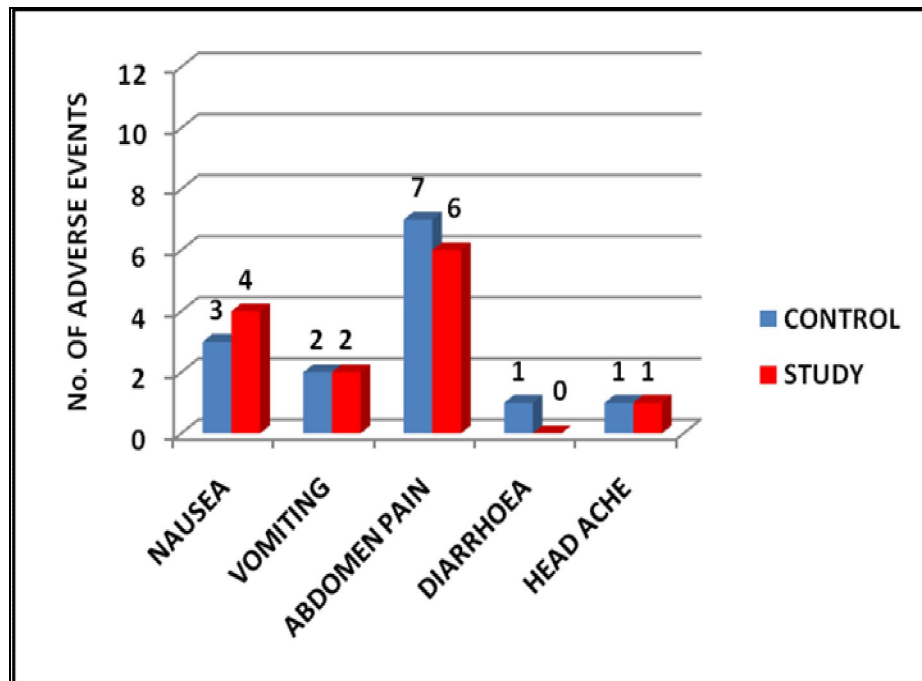
Standard treatment with NSAIDs and physiotherapy, used at present provides symptomatic relief by decreasing the pain and improves the functional mobility. This treatment should be continued for prolonged period of time. This may lead to many significant immediate and late adverse reactions.

Collagen peptide contains predominantly aminoacids - glycine, proline and hydroxyproline. When ingested orally, it accumulates in the cartilage and stimulates production of collagen and proteoglycans by the chondrocytes. This slows the progression of disease and improves the symptoms in patients with osteoarthritis. Addition of collagen peptide with standard treatment is aimed at reduction of the symptoms in osteoarthritis.

This study was done in the Institute of Pharmacology, Madras Medical College, Chennai in collaboration with Institute of Orthopaedics, Rajiv Gandhi Government General Hospital, Chennai. 126 patients were screened and 60 patients who fulfilled the inclusion and exclusion criteria were enrolled for the study. They were randomized into 2 groups of 30 patients each.

Patients in the control group received the standard treatment with Tab.Diclofenac 50 mg twice daily and Tab.Ranitidine 150 mg twice daily along with physiotherapy. Tab.Diclofenac and Tab.Ranitidine were given initially for a period of 2 weeks. Then depending on the pain assessment every 2 weeks, these drugs were continued during the study period of 12 weeks.

Patients in the study group received collagen peptide powder 10g once daily orally in addition to the standard treatment for a period of 12 weeks.

The efficacy of the treatment was assessed every 2 weeks by using VISUAL ANALOGUE SCALE for pain assessment and WOMAC OSTEOARTHRITIS INDEX for improvement in joint mobility.

X ray knee joint was taken at the beginning and at the end of the study period and was used for comparing the efficacy of treatment groups.

Tolerability of the drugs was assessed by laboratory investigations and monitoring of adverse events during the study period. Post treatment follow up was done for a period of 4 weeks. The data were collected and the results were analysed statistically.

There was no significant difference in the mean age and sex distribution in both the control and the study groups. The mean age distribution in both the groups was 54. More number of female patients were in both the groups.

The number of knee joint involvement was also equally distributed in both the groups. There was no significant difference in Xray grading in both the groups. Grade 1 Xray changes were present in more number of patients in both groups.

In this study, **pain assessment with visual analogue scale** showed a statistically significant decrease in mean pain score (p<0.01) at the end of 12 weeks in both the control and study groups. **Comparison between the groups showed a statistically significant (p<0.01) improvement in the study group than the control group from week 8 onwards.**

Since pain was very much reduced in the study group patients (mean pain score of 3.8) at the end of 12 weeks, Tab.Diclofenac was stopped in all the patients in the study group. But in the control group patients (mean pain score of 5.5), Tab.Diclofenac was continued. The patients in both the groups were then assessed after the post treatment follow up period of 4 weeks.

During the **post treatment follow up period**, the need for analgesics was drastically reduced in the study group patients. Only 8 patients needed analgesics as and when required (less than 5 days). But in the control group, the need for analgesics was there and continued in all the 30 patients. Statistical analysis showed that the difference between the groups is statistically significant (p<0.001).

Comparison between the groups at the end of post treatment follow up period at week 16 showed that the statistically significant reduction in mean pain score was maintained in the study group even without analgesics. **This shows that collagen peptide when used for a period of 12 weeks retards the disease progression and decreases the requirement of analgesics.** This was similar to the placebo controlled study done by Jian-Xin Jiang et al (2012),[84] and O.Bruyere et al (2012)[85] which also showed a statistically significant reduction in VAS pain score and significant decrease in analgesic requirement

with the use of collagen peptide. A study done in athletes by Clark KL et al (2008)[86] also showed a statistically significant reduction in pain score and decreased requirement of analgesics with collagen peptide.

Our study showed a statistically significant decrease (p<0.01) in mean pain score, mean stiffness score, mean disability score at the end of 12 weeks assessed by **WOMAC index** in both the control and study groups. Comparison between the groups showed a statistically significant (p<0.01) improvement in the study group than the control group from week 8 onwards.

Addition of collagen peptide to standard treatment showed a statistically significant reduction in mean pain score (51% vs 25%), mean stiffness score (59% vs 33%) and mean disability score (50% vs 30%) when compared to standard treatment alone. This correlates well with the placebo controlled studies conducted by Benito Ruiz et al (2009)[87] and Kumar S et al (2014)[88] which also showed a statistically significant reduction in VAS pain score and WOMAC subscales score with the use of collagen peptide.

Post treatment follow up period at week 16 also showed that the statistically significant reduction in mean pain score, mean stiffness score and mean disability score was maintained in the study group even without analgesics. There was no change in X ray knee joint grading at the end of study period in both the control and study groups.

This study showed that the addition of collagen peptide to standard treatment in the management of patients with knee joint osteoarthritis significantly reduces the symptoms and improves the joint functional mobility.

There was no statistically significant difference in the biochemical parameters like Hemoglobin, Total WBC count, Blood Sugar, Blood Urea, Serum Creatinine, Serum SGOT, Serum SGPT in both the control and study groups at the end of treatment period when compared with the baseline. This study showed that collagen peptide does not affect the haematological and biochemical lab parameters and has no significant adverse effect on hepatic and renal functions.

No serious adverse events were reported in our study. Abdomen pain and Nausea were the common adverse events reported during the study period in both the groups. Other adverse events noted were vomiting, diarrhea, and headache. Abdomen pain, when reported was treated with Tab.Pantoprazole 40mg once daily. Tab.Diclofenac was stopped temporarily for 3 days and patient was advised to apply topical Diclofenac ointment locally. Then after 3 days as pain subsided, Tab.Diclofenac was continued with Tab.Pantoprazole with careful monitoring. Other adverse events were managed symptomatically with standard care**. There was no significant difference in the occurrence of adverse events between the two groups.**

This suggests that addition of collagen peptide is not associated with increase in incidence of any adverse events, thereby showing the safety of collagen peptide. Similarly the safety of collagen peptide was also well established in a study done by Moskowitz RW (2000).[89]

Thus collagen peptide can be used in patients with osteoarthritis and its use can decrease the requirement of analgesics. Collagen peptide was not associated with any serious adverse effects and hence can be safely used in the management of osteoarthritis.

CONCLUSION

CONCLUSION

From this study, we conclude that

- Collagen peptide when added to standard treatment is more effective in symptomatic improvement in patients with knee joint osteoarthritis.

- Treatment with Collagen peptide decreases the requirement of analgesics.

- Collagen peptide is well tolerated and is not associated with serious adverse events.

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APPENDICES

APPENDIX -1

LIST OF ABBREVIATIONS USED

ACE   –   Angiotensin Converting Enzyme.

ACR   –   American College ofRheumatology.

ADAMTS   –   A Disintegrin and Metalloproteinase with Thrombospondin Motifs.

ANOVA   –   Analysis of Variance.

COX   –   Cycloxygenaseenzyme.

ESR   –   Erythrocyte Sedimentation Rate.

GAGPS   –   Glycosaminoglycan polysulfuricacid .

GC-P   –   Glycosaminoglycan peptide complex.

GI   –   GastroIntestinal.

IL   –   Interleukin.

MMP   –   MatrixMetalloProteinase.

MRI   –   Magnetic Resonance Imaging.

NSAID   –   Non Steroidal Anti Inflammatory Drug.

OA   –   Osteoarthritis.

PUFA   –   Poly Unsaturated Fatty Acid.

SGOT   –   Serum Glutamate OxaloacetateTransaminase.

SGPT   –   Serum Glutamate Pyruvate Transaminase.

TGF   –   Transforming Growth Factor.

TNF   –   Tumor Necrosis Factor.

VAS   –   VisualAnalogue Scale.

WOMAC   –   Western Ontario and McMaster Universities Osteoarthritis Index.

APPENDIX -1I

THE EVALUATION OF SAFETY AND EFFICACY OF COLLAGEN PEPTIDE AS AN ADD ON THERAPY TO STANDARD TREATMENT IN COMPARISON WITH THE STANDARD TREATMENT ALONE IN THE MANAGEMENT OF PATIENTS WITH KNEE JOINT OSTEOARTHRITIS

CASE REPORT FORM

NAME: AGE/SEX   :   PLACE:

OP No: DIAGNOSIS:

Inclusion criteria: **YES/NO**

- ❖ Age - 40 years to 70 years

- ❖ Sex - both genders

- ❖ Patients with primary osteoarthritis of knee joint diagnosed less than 1 year

- ❖ Patients willing to give written informed consent.

Exclusion criteria: **YES/NO**

- ❖ Patients with secondary osteoarthritis.

- ❖ Patients with genu varum, genu valgum, gouty arthritis, rheumatoid arthritis.

- ❖ Patients with known hypersensitivity to NSAIDs, collagen peptide.

- ❖ Patients on oral or parenteral corticosteroid therapy

- ❖ Patients with chronic systemic illness of liver, heart, kidney, gastrointestinal tract etc.

- ❖ Patients who had taken other osteoarthritis treatment (glucosamine sulphate, chondroitin sulphate, diacerin, hyaluronic acid) within past 1 month.

- ❖ Pregnant and lactating women

Subject initials: Subject number:

Subject : Included/Excluded   Reason if excluded:

Informed Consent Obtained: Yes/No

CONTROL/ TEST

Subject initials:

 Subject number:

Signature of principal investigator

VISIT 1

1. Vitals:

2. Medical History:

3. General /systemic examination:

4. Investigations:

    Haematology:

    Hb: Total WBC count:

    Blood Urea: Blood sugar: Serumcreatinine:

    SGPT: SGOT:

    ECG:

    X-ray knee joint AP & Lateral view:

    X-ray chest PA view:

    Urine routine:

5. Visual analogue pain scale:
6. WOMAC Osteoarthritis index.

VISIT 2

1. Vitals:

2. Visual analogue pain scale:

3. WOMAC Osteoarthritis index:

4. Adverse Events:

VISIT 3

1. Vitals:

2. Visual analogue pain scale:

3. WOMAC Osteoarthritis index:

4. Adverse Events:

VISIT 4

1. Vitals:

2. Visual analogue pain scale:

3. WOMAC Osteoarthritis index:

4. Adverse Events

VISIT 5

1. Vitals:

2. Visual analogue pain scale:

3. WOMAC Osteoarthritis index:

4. Adverse Events:

VISIT 6

1. Vitals:

2. Visual analogue pain scale:

3. WOMAC Osteoarthritis index:

4. Adverse Events:

VISIT 7

1. Vitals:

2. Visual analogue pain scale:

3. WOMAC Osteoarthritis index:

4. Adverse Events:

5. Investigations:

   Haematology:

   Blood Urea: Blood sugar: Serum creatinine:

   SGPT: SGOT:

6. X-ray knee joint AP & Lateral view:

VISIT 8

1. Vitals:

2. Visual analogue pain scale:

3. WOMAC Osteoarthritis index:

PATIENT INFORMATION SHEET

Title: **THE EVALUATION OF SAFETY AND EFFICACY OF COLLAGEN PEPTIDE AS AN ADD ON THERAPY TO STANDARD TREATMENT IN COMPARISON WITH THE STANDARD TREATMENT ALONE IN THE MANAGEMENT OF PATIENTS WITH KNEE JOINT OSTEOARTHRITIS**

Investigator:

Name of Participant:

This study is conducted in Rajiv Gandhi Govt. General Hospital, Chennai. You are invited to take part in this study. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

What is the purpose of this study?

Osteoarthritis is the most common form of arthritis characterized by progressive destruction of articular cartilage leading to disability. It usually presents as joint pain and joint stiffness and gradually worsens with time. We want to test the efficacy and safety of collagen peptide powder in this condition. We have obtained permission from the Institutional Ethics Committee.

The study design

All patients in the study will be divided into 2 groups A & B. You will be assigned to either of the groups. Group A receives standard treatment & Group B receives standard treatment + collagen peptide powder.

Study Procedures

The study involves evaluation of improvement in your symptoms and reduction in stiffness. The planned scheduled visits involve visits at 2^{nd}, 4^{th}, 6^{th}, 8^{th}, 10^{th}, and 12^{th} weeks after your initial visit. You will be required to visit the hospital 6 times during the study. At each visit, the study physician will examine you. Blood tests will be carried out twice during the study and each time about 15 ml blood will be collected. These tests are essential to monitor your condition, and to assess the safety and efficacy of the treatment given to you.In addition, if you notice any adverse events, you have to report it. You will be required to return unused study medicines when you report for your scheduled visits. This will enable correct assessment of the study results.

Possible benefits to you – collagen peptide along with standard treatment will cause reduction in your joint pain and stiffness

Possible benefits to other people - The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, Institutional Ethics Committee and any person or agency required by law like the Drug Controller General of India to view your data, if required.The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. You will be taken care of and you will not loose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc.The results of this study will be informed to you at the end of the study.

Signature of Investigator   Signature of Participant

Date   Date

INFORMED CONSENT FORM

Title: THE EVALUATION OF SAFETY AND EFFICACY OF COLLAGEN PEPTIDE AS AN ADD ON THERAPY TO STANDARD TREATMENT IN COMPARISON WITH THE STANDARD TREATMENT ALONE IN THE MANAGEMENT OF PATIENTS WITH KNEE JOINT OSTEOARTHRITIS

Name of the Participant:

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in this study.

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I am aware of the fact that I can opt out of the study at any time without having to give any reasonand this will not affect my future treatment in this hospital.
6. I hereby give permission to the investigators to release the information obtained from me as resultof participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC.Iunderstand that they are publicly presented.
7. I have understand that my identity will be kept confidential if my data are publicly presented
8. I have had my questions answered to my satisfaction.
9. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signingthis consent form I attest that the information given in this document has been clearly explained to meand understood by me, I will be given a copy of this consent document.

Name and signature / thumb impression of the participant (or legal representative if participantincompetent)
Name _____ Signature_____ Date_____

Name and Signature of impartial witness (required for illiterate patients):
Name _____ Signature_____ Date_____
Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent:
Name _____ Signature_____ Date_____