Review article

Non-operative management of osteoarthritis of the knee joint

Raju Vaishya^{*}, Godfrey B. Pariyo, Amit Kumar Agarwal¹, Vipul Vijay

Department of Orthopaedics, Indraprastha Apollo Hospital, Sarita Vihar, Mathura Road, New Delhi 110076, India

ARTICLE INFO

Article history:

Received 20 April 2016

Accepted 14 May 2016

Available online 28 June 2016

Keywords:

Osteoarthritis

Knee

Non-operative treatment

Operative treatment

Drugs

ABSTRACT

Osteoarthritis is a chronic disorder of synovial joints in which there is progressive softening and disintegration of articular cartilage accompanied by the growth of osteophytes. Treatment designed for osteoarthritis should aim at reducing pain, improve joint mobility, and limit functional impairment. It can be achieved by pharmacological and non-pharmacological means. Non-operative treatment of OA is useful for patients with KL grade 1–3, which are early stages of OA. However, in an advanced stage of OA (KL grade 4), surgical treatment is needed as definitive treatment.

© 2016

1. Introduction

Osteoarthritis (OA) is a chronic disorder of synovial joints in which there is progressive softening and disintegration of articular cartilage accompanied by a growth of osteophytes, cyst formation, and subchondral sclerosis.¹ By the age of 65, approximately 80% of the US population is affected.² More than half of those with arthritis are relatively young and are under 65 years of age. Indian data in this regard is lacking, but it is estimated that it is the most frequent joint disease with a prevalence of up to 22–39%. The OA of knee joint contributes to nearly 80% of total OA burden.¹

2. Risk factors for knee osteoarthritis

The systemic risk factors for knee OA are age, gender, race, genetic and dietary factors, smoking, bone density, estrogen deficiency, etc. which influence susceptibility to the disease. The local factors include obesity, knee alignment, proprioception, laxity, physical activity, periarticular muscle weakness, occupational stress, injury, etc., which affect the distribution of the load across the knee joint (Table 1).

Management of OA knee largely depends on clinical symptoms as well as on radiological grading. Kellgren–Lawrence (KL) grading system (Table 2) for knee OA is the most commonly used grading system and is based on a weight-bearing anteroposterior (AP)

radiograph of both knees. The higher grades indicate more severe signs of OA and need for surgical intervention.

3. Non-operative management of OA

Although there is no known cure for OA, treatment designed for the individual patient can reduce pain, improve joint mobility, and limit functional impairment.¹ The management of knee OA includes both surgical as well as conservative options. Surgical modalities include various types of the osteotomy, arthroscopic interventions, and knee arthroplasty. The wide range of non-operative treatment options for OA requires a multidisciplinary approach. The non-operative treatment is usually useful for patients with KL grade 1–3. The aim of this article is to explore the literature on how conservative treatment of OA has evolved over time and to discuss the pros and cons of various conservative modalities.

3.1. Choices of non-operative treatment of OA

I. Pharmacological

II. Non-pharmacological

- Use of orthosis (braces and other mobility aids)
- Physical therapy/yoga
- Lifestyle modification

3.1.1. Pharmacological treatment of OA

Pain relief is important in the treatment of OA but not all patients require drug therapy, and those who do may not need it all the time.

^{*} Corresponding author. Tel.: +91 1129871210.

E-mail addresses: raju.vaishya@gmail.com (R. Vaishya), pariyobonane@yahoo.com (G.B. Pariyo), amitorthopgi@yahoo.co.in (A.K. Agarwal), dr_vipulvijay@yahoo.com (V. Vijay).

¹ Tel.: +91 9968578514.

Table 1

Risk factors for knee osteoarthritis.

Systemic risk factors	Local risk factors
Age	Obesity
Gender	Joint mechanics (alignment, proprioception, laxity)
Race/ethnicity	Muscle weakness (quadriceps)
Genetic factors	Occupational stress
Dietary factors (?)	Physical activity
Smoking (?)	Knee injury
Estrogen deficiency	

Table 2

Kellgren–Lawrence (KL) grading system for knee osteoarthritis.

Grade	Radiological findings
0	Normal, no features
1	Questionable presence of osteophytes/joint space narrowing or both
2	Definite presence of osteophytes with possible joint space narrowing or definite mild joint space narrowing
3	Definite moderate joint space narrowing (at least 50%) osteophytes usually present, cysts/sclerosis may be present
4	Severe joint space narrowing with subchondral bone sclerosis and possible deformity of bone ends

3.2. Non-steroidal anti-inflammatory drugs (NSAIDs)

There are various types of analgesics used, and the choice of its use is multifactorial. All NSAIDs are chemically heterogeneous group of compounds often chemically unrelated but share certain therapeutic actions and adverse effects. They act by inhibition of prostaglandin biosynthesis, which is the first step in all inflammatory disorders. The first step enzyme in the prostaglandin synthetic pathway is prostaglandin G/H synthase, also known as cyclooxygenase or Cox. This enzyme converts arachidonic acid (AA) to unstable intermediated PGG₂ and PGH₂ and leads to the production of thromboxane A₂ (TXA₂) and a variety of prostaglandins. There are two forms of cyclooxygenase enzymes, cyclooxygenase-I (Cox-I) and cyclooxygenase II (Cox-II). Cox-I is a primary constitutive isoform found in most normal cells and tissues while cytokines and inflammatory mediators that accompany inflammation induce Cox-II production. However, Cox-II is constitutively expressed in certain areas of kidney and brain and is induced in endothelial cells by laminar shear forces.³ Therapeutic doses of NSAIDs reduce prostaglandin biosynthesis by inhibiting the actions of cyclooxygenase enzyme.

3.3. Non-specific cyclooxygenase inhibitors

The non-specific Cox-inhibitors (e.g. Ibuprofen, Diclofenac, Meloxicam, Aspirin, etc.) inhibit both Cox-I and Cox-II with little selectivity to slow down prostaglandin synthesis (Table 3).

Table 3

Summary of NSAIDs used for knee OA.

Type of NSAID	Examples	Mechanism of action	Side effects
Non-specific Cox inhibitors	Ibuprofen, Diclofenac, Meloxicam, Aspirin	Inhibit Cox I and Cox II	GIT, CVS, bleeding, renal
Selective Cox II inhibitors	Celecoxib, Refecoxib, Valdecoxib	Inhibits Cox II	CVS, stroke

Table 4

Opioid painkillers used for knee OA.

Type of opioid	Examples	Mechanism of action	Side effects
Short acting	Hydrocodone, Oxycodone, Codein	Inhibit ascending transmission of nerve impulses	Respiratory depression, addiction
Long acting	Morphine, Methadone, Fentanyl	Same	Constipation
Partial agonists	Tramadol, Nalbuphine, Buprenorphine	Same	Same

3.4. Selective Cox-II inhibitors

The selective Cox-II inhibitors (e.g. Celecoxib, Rofecoxib, and Valdecoxib) have a high predilection for Cox-2, and they gained approval based on superior side effect profile in GIT endoscopy studies when compared with NSAID.³ They have been found to relieve pain due to osteoarthritis and have less GIT related side effects compared with other NSAIDs.

There exists a high-quality data that supports the use of NSAIDs in OA. On efficacy, the results are consistent, with good quality patient-oriented evidence. However, there may be side effects related to gastrointestinal, renal, and cardiovascular systems to consider that may offset their place in OA therapy. The literature supports the use of Paracetamol in OA (level A), but NSAIDs are more effective than Paracetamol in pain relief.⁴

3.5. Opiates

Opiates are the drugs derived from opium, and they include the natural products of morphine, codeine, and many semi-synthetic derivatives. The analgesic effect of opioids arises from their ability to directly inhibit the ascending transmission of nociceptive information from the spinal cord dorsal horn and to activate pain control circuits that descend from the midbrain via the rostral ventromedial medullary tract to the spinal cord dorsal horn. Opiates can be classified into short acting, long acting and partial agonist (Table 4). Both short and long acting opiates and partial agonists have been found to be effective in pain relief and have level 3 evidence in their support. However, the pain relief is limited and in long-term use, these drugs are associated with frequent and sometimes severe side effects.³ Repeated daily administration of opioid analgesics eventually will produce tolerance and some degree of physical dependence. The extent of physical dependence will depend on the particular drug, the frequency of administration, and the quality administered. When pain is due to a chronic condition like OA, measures other than opioid drugs should be employed to relieve pain if they are efficient and available.

3.6. Other non-opioid oral analgesics

3.6.1. Acetaminophen (Paracetamol)

Acetaminophen (Paracetamol) is an active metabolite of Phenacetin; it is effective in pain relief among patients with inflammatory osteoarthritis but less efficient than NSAIDs in the treatment of inflammatory arthritis. It is well tolerated and has a lower incidence of GIT side effects compared to the non-specific NSAIDs (Table 5).

3.6.2. Antidepressants

Tricyclic antidepressants actions (Table 5) have the positive analgesic effect to chronic pain.³ Literature searches in Pub Med

Table 5

Details of other analgesics used for knee OA.

Category of drug	Examples	Mechanism of action	Side effects
Acetaminophen	Paracetamol	Block nerve impulse transmission	Hepatotoxicity
Tricyclic antidepressants	Antidepressants, Amitriptyline, Fluoxetine	Block nerve impulse transmission	Sedation, weight gain
Diacerin	Oral diacerin	Short acting interleukin inhibitor, slows down break down of cartilage	Diarrhea
Nutraceuticals	Glucosamine	Improves cartilage regeneration, inhibits inflammation, analgesic effect	Diarrhea and constipation, nausea
	Chondroitin	Improves cartilage regeneration, anti inflammatory, analgesic	Diarrhea and constipation, nausea
	Collagen hydrolysates	Stimulates collagen synthesis	Hair loss, visual problems, anaemia
	Ovaco soya bean unsaponified	Anti-inflammatory	None

and Cochrane do not show sufficient evidence on their use in the treatment of OA.

3.6.3. Nutraceuticals

In the recent past, interest has developed in the role of nutritional supplements (nutraceuticals) in the management of OA, on the presumption that they may have a specific effect on disease pathophysiology and hence can be used as disease-modifying agents. However, their mechanism of actions and efficacy remains unclear.

3.6.4. Glucosamine

Glucosamine Sulfate (GS) is a natural substance which is building block for proteoglycans. It normalizes articular cartilage metabolism and also is reported to have mild anti-inflammatory property. As per a Cochrane Review (2008), it produced a reduction of pain by 21% and an increase in function by 11%. Hughes et al. did a randomized, double-blind placebo-controlled trial of GS but did not find any difference between placebo and GS in the management of pain in OA of the knee.⁶ Therefore, neither placebo nor GS is recommended in the treatment of OA of the knee.

3.6.5. Chondroitin

It is found naturally in human cartilage, bone, cornea, skin, arteries. As Chondroitin sulfate (CS), it decreases expression of cytokines and proteases. It leads to mild improvement in pain and function (6–10% absolute change). The CS may also slow down the progression of OA on X-ray. Clegg et al. did a multicentric double blind placebo and Celecoxib-controlled Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) to evaluate their efficacy and safety as a treatment option for OA knee pain. In this study, it was found that GS and CS alone or in combination did not reduce pain effectively in the overall group of patients with OA of the knee.⁷

3.6.6. Methylsulfonylmethane (MSM)

It is naturally present in human body. Its mechanism in OA is unclear. It may be associated with decreased inflammatory markers in vitro. It is known to cause a significant reduction in pain and increase in function but is inferior to NSAIDs.

3.6.7. Collagen hydrolysates (CHs)

Collagen hydrolysates (CHs) are reported to have the beneficial effect in the improvement of OA, as demonstrated in several investigations. However, the therapeutic mechanism remains unsolved. It has the potential to rebuild some of the cartilage that may be lost during the osteoarthritic process by the stimulation of chondrocytes and the increased synthesis of extracellular matrix.⁸ This action of CH counteracts the degenerative process and may prevent degenerative OA. Pharmaceutical grade collagen hydrolysate (PCH) is obtained by hydrolysis of pharmaceutical gelatin.

Clinical studies suggest that ingestion of 10 g of PCH daily reduces pain in patients with OA of the knee.⁸ The clinical use of PCH is associated minimal adverse effects mainly gastrointestinal, characterized by fullness or unpleasant taste. The high level of safety of CH makes it attractive as an agent for long-term use in chronic disorders like knee OA. Pramitt et al. found CH to be highly effective in improving joint function on WOMAC score values.⁹

3.6.8. Diacerin

An oral interleukin-1 inhibitor, it is reported to be slow-acting, but persistent, symptomatic relief in patients with OA. Jat Upon et al. in a meta-analysis concerning Diacerin showed that it may be an alternative therapy for OA in patients who cannot take Paracetamol.^{10,11}

3.7. Intraarticular injections and other forms of parental treatment

Intraarticular injections are recommended in situations where the patient has not responded to the simpler analgesics. These are reserved for stages 2 to 3 OA (Table 6).

3.7.1. Corticosteroids

Their mechanism of action in vitro is due to a reduction in prostaglandins, bradykinin, and histamine. They may also alter pain reception. Various steroid-based injectable formulations have been employed such as Triamcinolone acetonide, Methylprednisolone acetate, Dexamethasone Sodium Phosphate (Table 6). On efficacy, the results are consistent, with good quality patient-oriented evidence (level A). Short-term benefit of significant improvement has been seen, when compared to placebo. However, the repeated use of corticosteroids could facilitate tissue atrophy, joint destruction, or cartilage degeneration. Oral steroids are not recommended for the treatment of OA because of their modest benefit and high rate of adverse effects.

3.7.2. Hyaluronic acid derivatives

Their mechanism of action is the restoration of the normal intraarticular level of HA since joints with OA are deficient in HA. They may also have either antinociceptive or antiinflammatory effects. Formulations of various densities and compositions of HA are available. Peak effectiveness is seen 5–13 weeks after treatment. They are inferior to steroids in short-term duration, but with likely improved benefit in longer term results.

3.7.3. Platelet-rich plasma (PRP)

Platelet-rich plasma (PRP) is being considered as an innovative and promising tool to stimulate repair of the damaged cartilage. The PRP is an autologous concentration of human platelets in a small pool of plasma and consists of many growth factors proved to be actively secreted by platelets to initiate mesenchymal tissue healing. It may help in the treatment of degenerative lesions of articular cartilage and OA.

Table 6

Intraarticular injections and other forms of parental treatment for knee OA.

Drug name	Examples	Mechanism of action	Side effects
Corticosteroids	Methyl prednisolone, Dexamethazone	Inhibits inflammation, analgesic effect	Skin discoloration, allergic reactions, facial flushing
Hyaluronic acid derivatives	Sodium hyaluronate	Inhibits inflammation, cartilage regeneration, analgesic effect, restores HA levels in joints	Agony, swelling hypersensitivity
Autologous blood products	Platelet rich plasma (PRP)	Growth induction, cartilage regeneration, anti-inflammatory effect	None
	Whole blood	Unknown	Transfusion reactions
	Stem cell therapy	Unknown	Transfusion reactions
Other forms of parental treatment			
Prolotherapy	Various formulations containing 15–23% dextrose	Collagen strengthening, induction of inflammation of weak soft tissues, analgesic effect	None
Anti nerve growth factor	Tanezumab, IV, IM, Oral	Blocks interaction of nerve growth factor with its receptors	Headache, paraesthesia, upper respiratory tract infections

Several studies have compared the efficacy of various techniques of intraarticular injections for knee OA. Carlos et al. in a systematic review compared hyaluronic acid (HA) and corticosteroids in painful knee OA. He found that HA was more effective in pain reduction than corticosteroid because 3–5 weekly injections of HA had 5–13 week effect on pain reduction post-injection compared to 2–3 weeks effect for corticosteroids.¹¹ Ahmed et al. in a randomized clinical trial evaluated the long-term effect of IA injection of platelet-rich plasma (PRP) and HA on clinical outcomes and quality of life of patients with knee OA. At 12 months follow-up, WOMAC pain score and bodily pain significantly improved in both groups; however, better results were determined in the PRP group compared to the HA group (p -value: <0.001) particularly in Kellgren stages 1 and 2. This study shows that PRP is more efficacious in reducing symptoms among patients with OA.² However, HA can still be used for the treatment of OA because it is superior to steroids and NSAIDs. Ilhanli et al. in a randomized study compared the effectiveness of IA injections of PRP with physical therapy in the treatment of OA of the knee. At the end of the treatment and 3 months after the end of therapy, significant improvement in ROM was detected in both groups. The pain was reduced significantly in both the groups, and when WOMAC scores were compared, the improvement was observed in both groups. However, in comparison to the second and third evaluation steps, improvement in the WOMAC scores of PRP was significantly better than the physical therapy group.¹² This study shows that in the long run PRP is a better treatment option than physical therapy.

3.7.4. Stem cell therapy

The aim in using stem cell is to support the self-healing process of knee joint cartilage which results from OA symptoms. The fluid inside the joint contains mesenchymal cells (MCS) which can differentiate into chondrocytes. In stem cell therapy, MCS and platelet-rich plasma are harvested from the patient to be treated. This process includes separation of the MSC by centrifugation and other purification steps with the aim of increasing cartilage buildup. There is still no sufficient amount of clinical data on the effectiveness of stem cell therapy when compared with pharmacological treatments for OA. Based on the current status of clinical investigations regarding autologous stem cell therapy for OA of the knee, some authors have expressed concerns about the issues of dosing, timing of intervention, type of MSC, mode, and route of delivery of MSC in clinical studies.¹³

3.8. Non-intraarticular parental forms of treatment

3.8.1. Prolotherapy

Prolotherapy or proliferation therapy is the non-surgical treatment with the injection of an irritant solution to stimulate

healing. It works by stimulating the body's natural healing mechanisms to repair injured musculoskeletal tissue. Their mechanism of action is stimulation of growth factors (platelet derived GF, ILGF, transforming growth factor β), which in turn stimulates expression of type I and III collagens. The synovial tissue exposed to glucose increases HA production (see Table 6). Various formulations containing 15–25% Dextrose are available. Multiple injections^{3–5} separated by 1–4 weeks. Relative rest is given for 2–3 days with the resumption of normal activity over 4 weeks. Masoud et al. in an RCT compared prolotherapy with hypertonic dextrose versus prozone (intra-articular ozone) and found prolotherapy with dextrose and with prolozone result in same pain relief on WOMAC score among patients with mild to moderate OA of the knee joint.¹⁴

3.8.2. Anti-nerve growth factor (e.g. Tanezumab)

Exogenous nerve growth factor increases pain either locally or systemically depending on the dose and the route of administration. Increased expression of nerve growth factor is found in inflamed tissues obtained from patients with conditions such as arthritis.¹⁵ Therefore, pharmacological inhibition of the activity of nerve growth factor reduces or blocks signs of pain. Tanezumab is a monoclonal antibody used as biological agents in patients with pain. It binds and inhibits nerve growth factor, and appears to relieve joint pain enough to improve function in patients with moderate-to-severe knee OA (Table 6). Osteonecrosis may be a serious side-effect following its use. Nancy et al. in a randomized placebo control trial reported a reduction in joint pain and improvement in function with mild and moderate side effects with the use of Tanezumab.¹⁵ However, longer trials involving larger samples are needed to understand better safety and tolerability issues and explore the clinical potential of its use as an alternative to current pharmacological treatments.

3.9. Topical treatment for knee osteoarthritis

The use of topical creams for the relief of knee pain in OA is popular amongst the patients. The efficacy of this treatment in relieving pain has been evaluated. Hasel et al. in a randomized, double-blind study compared homeopathic gel versus Piroxicam gel in the treatment of painful arthritis of the knee joint and found that homeopathic gel was as effective as Piroxicam gel, and the two can be used for short-term management of OA.¹⁶ Bruhlmann et al. reported from a randomized, double-blind controlled study that Diclofenac hydroxyl ethyl pyrrolidine (DHEP) patch to be an efficient and safe treatment for patients suffering from symptomatic knee OA.¹⁷ The local burning sensation and dry skin are known side effects of NSAID topical use.

4. Non-pharmacologic and alternative medicine

4.1. Lifestyle modification

Lifestyle modifications include losing weight, switching from running or jumping exercises to swimming or cycling, and minimizing activities that aggravate the condition, such as climbing stairs. It is known that obesity is a major risk factor for developing knee OA. Weight reduction is very useful for patients suffering from obesity since it has shown significant benefits in improving the symptoms and progression of arthritis. It reduces the pain and improves physical function. This can be accomplished through an intensive low-calorie diet program. These lifestyle changes must be continued throughout life. Christensen et al. did an RCT and reported weight reduction of 10% improved function by 28%.¹⁸

4.2. Physical therapy

Physical therapy is aimed at maintaining joint mobility and improving muscle strength. Water or land-based exercise, aerobic

walking, quadriceps strengthening, resistance exercise, and tai chi reduce pain and disability from knee OA. Page et al. in a meta-analysis found that physiotherapy interventions can reduce pain and improve function in as a short-term treatment of OA of the knee joint.¹⁹ Physiotherapy benefits appear to be additive when exercise is delivered with accompanying weight loss. Yoga also plays a significant role in the management of knee OA and is based on the following assumption: complexity and multi-dimensionality, various positive influences on an individual's wholeness through the mind, body, and the relationship between them. Ebenezer et al. in a prospective randomized active controlled trial reported better improvements in yoga than control groups regarding improvement in walking pain, the range of knee flexion, walking time, tenderness, swelling, crepitus, and knee disability in patients with OA of knees.²⁰ Punee et al. in an RCT investigated the effectiveness of a class and home-based exercise with massage between Thai traditional (TPT) and standardized physical therapy (SPT) in older people with knee OA.²¹ They found significant improvement in both groups, but the improvement of the TPT group was greater.

Fig. 1. OARSI guidelines for the non-surgical management of knee osteoarthritis.

Physiotherapy modalities like transcutaneous electrical nerve stimulation (TENS), interferential current stimulation, and pulsed electro stimulation have been used for a few decades to treat OA in the knee. TENS uses electrical currents applied to the skin surrounding the knee. Treatment efficacy of these physical agents in painful OA of the knee has largely been unknown. Bjordal et al. in a recent meta-analysis indicates that electro stimulation seemed to have a large effect on pain relief, moderate improvement in function, and with no evidence that it is unsafe.²² Therapeutic ultrasound is widely used for its potential benefits on both knee pain and function, which may be clinically relevant. Therapeutic ultrasound may be beneficial for patients with OA of the knee. Low-level laser therapy is considered useful in yielding pain relief and function due to its photochemical effect.

4.3. Acupuncture

The mechanism of pain relief in OA with acupuncture is unclear. It is possibly associated with changes in neurotransmitters involved in pain. At least 4 weeks of treatment is advised. Many authors recommend > 10 sessions. Manyanga et al. found that with acupuncture, there was a significant reduction of pain and increased functional mobility with minimal side effects.²³ Some controlled trials show statistically significant benefits. However, these benefits are small, do not meet predefined thresholds for clinical relevance, and are probably due at least partially to placebo effects from incomplete blinding. Waiting list-controlled trials of acupuncture for peripheral joint OA suggest statistically significant and clinically relevant benefits, much of which may be due to expectation or placebo effects.

4.4. Bracing and orthoses

Bracing of the knee or the foot can be a useful non-operative and non-pharmacologic treatment for persons with OA that predominantly involves either the medial or lateral tibiofemoral compartment. Raja et al. and Mokhtar et al.^{24,25} reported that knee braces and foot orthoses are effective in decreasing pain and joint stiffness. The Osteoarthritis Research Society International and the American College of Rheumatology also recommend the use of laterally wedged insoles for medial compartment knee OA. Knee sleeves provide warmth and mild compression and are useful in early knee OA. These do not enhance joint stability. Corrective or realignment braces are more effective in moderate or severe OA. These have greater benefits and reduce compressive loading of the more affected joint compartment. These also improved proprioception and quadriceps strength. Contraindications to bracing include flexion contracture of more than 10°, peripheral vascular disease, or intractable contact dermatitis.

Non-medical therapies like hydrotherapy, mud pack therapy, balneotherapy (with mineral bath) have been used as an alternative mean of relieving joint pain in knee OA. Studies with better methodology are needed to prove their scope.

In the management of OA, the osteoarthritis research Society International (OARSI) guidelines for the non-surgical management of knee osteoarthritis can be a good reference source for the treating doctors (Fig. 1).

5. Conclusion

The main goal of non-operative treatment of OA of the knee is to reduce pain, restore function, improve the quality of life, and limit disease progression. This can be achieved through pharmacological and non-pharmacological means. The treatment given depends on the severity of the disease. Lifestyle modification is an important tool for pain relief and control of disease progress in OA.

Non-pharmacological measures, oral and topical analgesics are useful for short-term treatment while IA injections are beneficial for longer-term treatment. The non-pharmacological options can be used concurrently with pharmacological modalities. The painkillers like NSAIDs are still the most commonly used drugs in the management of pain related to OA. However, the long-term uses of these drugs are associated with significant side effects and hence they must only be used with extreme caution and medical supervision. The 'disease modifying agents' for OA are mostly in the form of nutraceuticals like Glucosamine, Chondroitin, etc. However, the efficacy of these agents is not universally predictable, and some studies have not found these to be any better than placebo. Recently, agents like bioactive collagen peptide have been used to retard the progress of OA and seem to be showing promising results. These non-operative treatment measures are quite effective in the early course of knee OA (KL grades 1, 2, 3). However, in the advanced stages of knee OA (KL grade 4), surgical treatments like arthroplasty, osteotomy, etc. are needed as a definitive treatment.

Conflicts of interest

The authors have none to declare.

References

- Solomon L, Warwick D, Nayagam S. *Apley's System of Orthopaedics and Fractures*. 9th ed. 2010:85–86.
- Raeissadat SA, Rayegai SM, Hassanbadi H, Fathi M. Knee osteoarthritis injection choices, platelet-rich plasma (PRP) versus hyaluronic acid (a one year randomized clinical trial). *Clin Med Insights Arthritis Musculoskelet Disord*. 2015;8:1–8. <http://dx.doi.org/10.4137/CMAMD.517894>.
- Bruton LL, Lazo J, Parker KL. *The Pharmacological Basis of Therapeutics*. 11th ed. Goodman & Gilman; 2005:438–440.
- Bradley JD, Brandt KD, Katz BP. Comparison of an anti-inflammatory dose of Ibuprofen, an analgesic dose of Ibuprofen and Acetaminophen in the treatment of patients with osteoarthritis of the knee. *N Engl J Med*. 1991;325:87–91.
- Hochberg MC, Pelletier JM, Manjot J. Combined chondroitin sulphate and glucosamine for painful arthritis: a multicentre, randomized double blind, non inferiority trial versus celecoxib. *Ann Rheum Dis*. 2016;75:37–44.
- Hughes R, Carr A. A randomized double blind placebo, controlled trial of glucosamine sulphate as an analgesic in osteoarthritis of the knee. *Rheumatology*. 2002;41:279–328.
- Clegg DO. Efficacy and safety of placebo and celecoxib controlled glucosamine/chondroitin in the treatment of painful arthritis of the knee. *N Engl J Med*. 2006;354(8):795–808.
- Moskowitz R. Role of collagen hydrolysate in bone and joint disease. *Semin Arthritis Rheum*. 2000;30:87–99.
- Pramitt J. Role of peptan a collagen peptide in knee joint pain and function: randomized double blind, placebo controlled study. *Agro Foods J*. 2014.
- Rongtharvongsul JU, Anothaisintawee T, Evoy MM, Attia J, Warantantare P, Thakkistian A. Efficacy and safety of glucosamine, diacerein and NSAIDs in osteoarthritis of the knee, a systematic review and metaanalysis. *Eur J Med Res*. 2015;20:24. <http://dx.doi.org/10.1186/s40001-015-0115-7>.
- Rodriguez-Maerchan EC. Intra articular injection of hyaluronic acid and other drugs in knee joint. *HSSJ*. 2013;9:180–182.
- Ilhanli I, Guder N, Esin AVCI. *Unified J Med Med Sci*. 2015;1(1):001–005.
- Uth K, Trifonov D. Stem cell application for osteoarthritis in knee joint. A mini review. *World J Stem cells*. 2014;6(5):629–636.
- Hashein M, Jalil P, Mennati S, et al. Randomized clinical trial to assess the effects of prolotherapy with hypertonic dextrose versus prolozone on pain intensity in osteoarthritic knee joint. *Anesth Pain Med*. 2015;5(October (5)):e 27585.
- Lane NE, Schnitzer TJ, Bribara CA, et al. *N Engl J Med*. 2010;263:1521–1531.
- Van Hasel RA, Fisser PAG. Efficacy and safety of a homeopathic gel versus NSAID (piroxicam) gel in the treatment of osteoarthritis of the knee. *Rheumatology*. 2000;39:71–719.
- Bruhlmann P, Micheal BA. Topical diclofenac patch in patients with knee osteoarthritis. *Clin Exp Rheumatol*. 2003;21:193–198.
- Christensen R, Astrup A, Bliddal H. Weight loss; treatment of choice for knee osteoarthritis. *Osteoarthr Cartil*. 2005;13:20–27.
- Page CJ, Hinman RS, Bennell KL. Short term beneficial effects of exercise on pain and function. *Int J Rheum Dis*. 2011;14(2):145–151.
- Ebenezer J, Nagarathma R, Yogitha B, Nagendra R. Effect of integrated approach of hatha yoga therapy on functional disability, pain and flexibility in osteoarthritis of knee joint. A randomized control study. *J Altern Complement Med*. 2012;18(5):463–472.
- Peungsuwan P, Sermchap P, Hanmontree P, Eungpinichpong W, Puntumetaka R, Chatchowan U. The effectiveness of Thai exercise with traditional massage on the

- pain, walking ability and quality of life of older people with knee osteoarthritis. A randomized controlled trial in the community. *Phys Ther Sci.* 2014;26:139–141.
22. Bjordal JM, Johnson MI, Lopes Martins RAB, Bogen B, Clow R, Ljuggren AE. Short term efficacy of physical interventions in osteoartritic knee pain. Systematic review and metaanalysis of randomized placebo-controlled trials. *BMC Musculoskelet Disord.* 2007;8:51. <http://dx.doi.org/10.1186/171-271/8/51>.
23. Manyanga B, Froese M, Zarychanski R, et al. Pain management with acupuncture in osteoarthritis: a systematic review and metaanalysis. *BMC Complement Altern Med.* 2014;1:312.
24. Raja Kavitha MS, Dewan PT, Deha M. Efficacy of knee braces and foot orthoses in conservative management of knee osteoarthritis. A systematic review. *Am J Phys Med Rehabil.* 2011;90(3):27–262.
25. Arazpour M, Bani MA, Malekil M, Ghomshel FT, Kanshani RV, Hutchins SW. Comparison of the efficacy of laterally wedged insoles and bespoke unloader knee orthoses in treating medial compartment knee osteoarthritis. *Prosthet Orthot Int.* 2013;37(1):50–57.