Philippine Clinical Practice Guidelines on the Medical Management of Osteoarthritis of the Knee

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Introduction

Osteoarthritis (OA) is the most common joint disease of man. Consensus definition states that it is a group of diseases resulting from both mechanical and biologic events that destabilize the normal coupling of degradation and synthesis of articular cartilage chondrocytes and extracellular matrix and subchondral bone, and that although they may be initiated by multiple factors, including genetic, developmental, metabolic, and traumatic, OA diseases are manifested by morphologic, biochemical, molecular and biomechanical changes of both cells and matrix which lead to a softening, fibrillation, ulceration, loss of articular cartilage, sclerosis and eburnation of subchondral bone, osteophytes and cysts. When clinically evident, OA diseases is characterized by joint pain, tenderness, limitation of movement, crepitus, occasional effusion and variable degrees of inflammation without systemic effects.[1]

In the Philippines, it ranks second to soft tissue rheumatism as the most common musculoskeletal condition seen in an urban Filipino population[2] and in the rural population[3.] The disease affects the knees, hands, hips, lumbar and cervical spine. It is however most disabling when affecting the knees and hips[4]. The disease has no known cure and becomes symptomatic around 10-15 years after the onset of pathology. This makes diagnosis a rather late phenomenon and reversibility of joint pathology is deemed unachievable.

Treatment of OA is directed at control of pain, retarding disease progression and limiting disability. Almost every other medical community interested in osteoarthritis has developed its own guidelines for treatment of OA[4,5,6,7,8,9, 10]. All these guidelines agree on the importance of non-pharmacologic modalities as the cornerstone of treatment. A large body of information point to the effect of weight control, physical modalities of treatment and exercise in improving pain, gait and stability and confidence of the patients[16]. Drugs and surgical interventions have specific indications in OA.

In the Philippines, treatment is not limited to traditionally accepted therapies but include a wide array of complementary/alternative forms of treatment. Proximity and close sociological ties with China, India, Thailand and other Asian nations have allowed treatment forms like acupuncture, reflexology, herbal concoctions and faith healing, among others to thrive. The use of locally available CAMS is seen in 60% of cases with musculoskeletal diseases (1995, unpublished).

The Philippine Rheumatology Association set out to develop a set of treatment recommendations for knee osteoarthritis that encompass both traditional and alternative methods that are available in the country. The effectiveness of physical modalities of treatment is established and the role of surgical interventions is specific. Physical modalities and surgery are not within the scope of the objectives.

Objective

Develop clinical practice guidelines for all medical practitioners for the medical management of knee osteoarthritis through evidence-based approach.

Questions

What are the effects of the different specified treatment modalities on pain, function in knee osteoarthritis?

What are the adverse effects of these modalities?

Methods

A technical working committee was formed to search for relevant materials from literature. The committee was composed of 14 rheumatologists. The objectives of this working committee were to:

I. Review the current level of evidence attributable to the following:
   A. Non-pharmacologic modalities used in the treatment of knee OA:
      1. Weight reduction
      2. Education
   B. Complementary and alternative modalities (CAMS)
      1. Balneotherapy (Spa)
      2. Massage
      3. Acupuncture
      4. Tai chi, yoga
      5. Herbal preparations
   C. Pharmacologic treatment
      1. Analgesics
         a. Paracetamol
         b. Tramadol
      2. Traditional NSAIDs and Coxibs
      3. Intraarticular agents
         a. Steroids
         b. Hyaluronans
      4. Others
         b. Glucosamine
         c. Chondroitin sulphate
         d. Glucosamine + Chondroitin
         e. Glucosamine + Chondroitin + MSM

II. Produce a list of 15 recommendations for the management of knee OA and to examine the degree to which these recommendations are supported both by research evidence and the consensus of expert opinion

III. Present such recommendations to a panel of experts

IV. Plan for regular review of recommendations and propose amendments

Search Strategy/ Inclusion

PUBMED, OVID and Cochrane databases were searched for meta analyses, systematic reviews, and randomized controlled trials through free text and MESH using the words "osteoarthritis, knee," and "weight loss", "education", "massage", "NSAIDs", "coxibs", "cox2 inhibitors", "analgesics", "paracetamol", "tramadol", "CAMS", "herbals", "intraarticular steroids", "hyaluronic acid", "viscosupplementation", " acupuncture", "Tai chi", glucosamine, chondroitin, MSM from 1966 to Sept 2008 in the English language, for knee osteoarthritis for their effect on pain, function and for their adverse effects. Outcome measures included the WOMAC, Lequesne Index, quality of life measures like HAQ, SF 36, and pain and function measures like Likert Scale and VAS.

Abstracts of publications whose full texts were not available were also appraised. Other search methods were done by hand search. For studies that were available as abstracts only or those where abstracts and full texts were not available, manual search for the title in the available and included studies were done.

Studies on hip and knee OA were included as long as separate analyses of knee outcomes were available. Studies were excluded when the interventions of interest given are for hips and knees combined and no separate analysis of outcomes for the knees are stated.

Modalities of treatment included were selected by virtue of the availability, prevalence of use (when data was available) and by consensus set by the technical working committee.

The scope of recommendations was set to include only medical modalities of treatment that can be used by all medical practitioners without prejudice to surgical and physical therapy modalities and their established use in knee osteoarthritis.

Results and Discussion

1. **Education**

A PUBMED search was done for articles published from 1966 to present using the MeSH terms "osteoarthritis, knee" and "patient education." A total of 56 articles were retrieved. A review of the abstracts of these articles yielded 13 studies for review. In addition, 4 articles were retrieved from

hand search. Of all these, 1 meta-analysis and 3 randomized clinical trials fulfilled the inclusion criteria (population of interest are patients with osteoarthritis alone, presence of a clear control group, intervention was primarily an arthritis self-management programme, and inclusion of pain and disability in the outcomes) and were thus, included for review.

RECOMMENDATION:
Standard clinic encounter, consisting of reading of patient education materials and/or physician's instructions, is recommended based on data showing that this is comparable to structured patient education programmes, particularly arthritis self-management programs.

Level of Evidence: High

Summary of evidence:
Patient education can either be in the form of structured programs or standard clinical practice such as reading of patient education materials or doctors' advice during the clinical encounter. For the purposes of this review, structured programmes are characterized as those having a set curriculum and method of instruction, usually applied in a classroom setting. These interventions are mostly arthritis self-help programmes that can be accessed through various sources including medical organizations.

The meta-analysis and randomized clinical trials reviewed showed a trend towards benefit in terms of pain and function among patients enrolled in arthritis self-management programmes; however, the effect is not clinically significant. Of the 4 studies appraised, only 1 showed possible benefit over time, with 273 patients followed-up at 3 months, and 21 months showing effect size of -0.53 and -0.88, respectively[11]. The metaanalysis by Chosdosh showed <2 mm improvement of pain on the 100 mm VAS or an effect size of -0.06 (0.10 - 0.02).[12] A 2008 RCT by Buszewics with 800 plus subjects showed similar results - no clinically significant difference in outcomes between patients in the structured educational programmes versus those receiving usual care such as reading of patient education materials or instruction in the clinics. Further large scale studies examining this particular intervention may change future recommendations. Thus, although education of patients about their illness is important in the management of knee osteoarthritis, present evidence does not show a clear benefit from structured arthritis self-management programs to justify recruitment of patients for participation in these programs.

2. Weight Loss

A PUBMED search was done for articles published from 1966 to present using the MeSH terms "osteoarthritis, knee" and "weight loss" yielding 33 titles. Review of the abstracts of these articles yielded 13 relevant articles. Of these, 1 meta-analysis and 1 randomized clinical trial fulfilled the inclusion criteria -population of interest are patients with osteoarthritis alone, presence of a control group, intervention was primarily weight loss, and inclusion of pain and disability in the outcomes.

Recommendation
Weight loss is recommended as a core treatment for obese and overweight adults with knee osteoarthritis. Furthermore, it is shown that weight loss of about 5% significantly improves pain and function in knee OA.

Level of Evidence: High

Summary of Evidence:

The meta-analysis (Christensen et al. 2007) compared weight loss with no weight loss in patients with knee osteoarthritis. The meta-analysis included four randomized controlled trials (N=454 participants) which differed with respect to study size, duration of study and intervention (In weight loss method, four randomized controlled trial utilized nutrition class and cognitive-behavioral therapy and one randomized controlled trial utilized Mazindol weight loss drug and low energy diet.). The meta-analysis showed a pooled effect size for pain and disability of 0.20 (95% CI 0 to 0.39) and 0.23 (0.04 to 0.42) at a weight reduction of 6.1 kg (4.7 to 7.6 kg). Meta-regression analysis showed that disability could be significantly improved when weight was reduced over 5.1%, or at the rate of > 0.24% reduction per week. [13]

One randomized controlled trial (Miller, 2006) not included in the Christensen meta-analysis, compared weight loss with no weight loss in N=87 patients with knee osteoarthritis in a 6-month

treatment phase. The study showed that intensive weight loss improves physical function in older obese adults with knee OA with estimated means for sum of WOMAC of 22.6 ± 1.9 units for weight loss and 32.7 ± 2.0 units for weight stable (p=<0.01)

The meta-analysis and randomized clinical trial reviewed suggest that interventions reducing excess load lead to improvement in function provided that the magnitude of weight loss is sufficient.

Complementary and alternative medicine

3. Balneotherapy (Spa therapy)

Twenty-nine (28) titles were reviewed for relevance, 2 of which were systematic reviews and 26 were randomized controlled trials. Both systematic reviews were available but excluded because the populations included in some studies were a mixture of patient with osteoarthritis at different sites. RCTs in which population includes specifically knee osteoarthritis were reviewed. Out of the 26 retrieved RCTs, 21 were obtained as abstract only, 3 with full article and 2 unavailable. Excluded RCTs were eleven (11) for use of foreign language, 5 of which included exercises and 2 because of the mixture of OA of different site. Hence 3 full articles and 3 abstracts were considered relevant and subsequently appraised.

Recommendation:
There is insufficient data to recommend balneotherapy or spa therapy for knee OA.

Level of Evidence: Low

Summary of evidence:

All articles reviewed were of low quality; this included 6 RCTs (3 full articles and 3 abstracts), comparing balneotherapy with different control groups. These studies include patient with moderate and chronic knee pain diagnosed with knee osteoarthritis based on clinical and/or radiographic findings. Almost all studies allowed previous NSAIDs to be continued. Outcomes were measured as short as 2 weeks up to as long as 24 weeks.

Pain was measured using VAS and WOMAC and showed clinically significant reduction in the balneotherapy group as compared to the control group. Function was included as outcome in 3 RCTs using Lequesne and WOMAC, there were also noted clinical significant in the improvement of function in the balneotherapy group as compared to the controls.

Quality of life was the only parameter measured by Yilmaz, et al. (2004) in their study using SF 36 and AIMS 2, and results showed increase in the quality of life patient in spa therapy. Although there is a trend towards decreasing pain and stiffness in knee OA, more high quality studies are needed to form a more definitive recommendation.

4. Massage

There was only one RCT published in 2006, on search for the effects of massage for pain and function in knee OA. Search was done using knee OA and massage (free text and MESH).

Recommendation:
There is insufficient evidence to recommend massage (standard Swedish massage) for the treatment of knee OA.

Level of Evidence: very low

Summary of Evidence:

There is a single small (n=68) randomized placebo-controlled but unblinded trial comparing massage (standardized Swedish massage) with waiting list controls (on pain medications, exercise, or hot/cold compresses). Although there seem to be better pain control with massage, the study has a lot of methodological limitations that affect the validity of the results.

5. Tai c'hi, Iyengar Yoga

Tai c'hi
Pubmed search yielded 7 titles for review, of which all were sought for retrieval. The other 1 article had no English language translation. Of the 4 available articles, 1 article was not reviewed because it did not meet the inclusion criteria. The 3 relevant articles included 1 systematic review which included the other 2 retrieved articles. However, we reviewed the 3 articles since there were scant data for review. These studies were of low quality.

Recommendation:
There is insufficient data to recommend Tai C'hi for knee osteoarthritis.

Level of Evidence: Low

In the systematic review (Soo Lee 2008) which included both the hip and the knee OA, the quality of life was measured using SF 12 and AIMS. The results failed to show a positive effect compared to no treatment.

Iyengar Yoga
There is scarce data to support any recommendation for the use of yoga (Iyengar Yoga) for knee osteoarthritis.

6. Acupuncture

Two hundred eighty one (281) titles were reviewed for relevance and 21 clinical trials and 7 systematic reviews were sought for retrieval. Six systematic reviews were available; 2 were excluded because the outcomes sought for were not expressed numerically and the RCTs included therein were included in the 4 other systematic reviews. Twelve RCTs were retrieved; 2 were excluded (1 studied a mixture of patients with OA at different sites; another was a study on post-operative pain; 8 were studies included in the systematic reviews: 2 were new articles. Hence, these 2 new RCTs and 4 systematic reviews were considered relevant and subsequently appraised.

Recommendation:
Manual or electroacupuncture is recommended as additional therapy to achieve pain relief and improvement of function lasting a few weeks among patients with moderate pain due to knee osteoarthritis. The procedure must be adequate and performed by a trained and experienced acupuncturist.

Level of Evidence: High

Summary of evidence:

Four high quality systematic reviews (which include 16 randomized clinical trials) and 2 recently published clinical trials, with low (Foster 2008) and moderate quality (Jubb 2008), comparing the efficacy and safety of manual or electroacupuncture with various control groups (placebo, usual care, waiting list, or sham acupuncture) were reviewed. These studies included a total of 2,777 patients with moderate and chronic knee pain diagnosed with knee osteoarthritis based on clinical and/or radiographic findings. In almost all studies, previous NSAIDs or analgesics were allowed to be continued. Some studies allowed concomitant physical therapy sessions. There was a lot of variability with regards the particular acupuncture points, how many of these points were used ($\geq$ 4 points), the number of acupuncture sessions ($\geq$6 sessions), and the total duration of the treatment period (2-5 weeks). Outcomes were considered short-term if measured 2-12 weeks after randomization and long-term if beyond 12 weeks.

There was clinically significant greater pain reduction with the acupuncture-treated group over waiting list and usual care controls. There was also greater pain reduction with true acupuncture than with sham acupuncture but the magnitude of the reduction was less than that seen when acupuncture was compared with other kinds of controls. Pain reduction was seen only during short-term measurements. In the study by Foster (low quality), however, both true and sham acupuncture did not have significant pain relief over the control group. This was thought to be due to the effects of an evidence-based exercise package which was allowed as co-intervention for all treatment groups.

Function was included as outcome in 2 of the 4 systematic reviews and in both clinical trials. There was clinically significant improvement in function in the acupuncture group compared with controls but the magnitude of the improvement of true acupuncture versus sham was clinically irrelevant in the systematic review of Manheimer. This improvement in function was sustained up to 6 months in some studies and even up to 52 weeks in 3 studies included in the systematic reviews. However, both recent clinical trials (Jubb and Foster) individually did not show improvement in function. There are many possible explanations for this, including sample size requirements and the effects of co-interventions.

Quality of life was included as an outcome in the study of Jubb. There was no significant difference in EuroQol scores in the true acupuncture group compared with sham.

Adverse events were reported in the reviews of Manheimer and Bjordal and in the trials of Jubb and Foster. Overall, there were no serious AEs that were treatment-related. With acupuncture, there were some small hematomas and transient soreness at the acupuncture points. There are a few case reports of life-threatening complications of acupuncture, including disseminated intravascular coagulation due to staphylococcal septicemia, necrotizing fasciitis, and pseudoaneurysm of the popliteal artery.

7. Herbals

Fifty-four (54) titles were reviewed for relevance, and of these 11 were considered. There were 7 full text and 4 abstracts. Studies reviewed included interventions like comfrey roots, ginger extracts, Chinese herbal recipe, and Chinese pills. Most of the studies included low number of subjects and used diclofenac as comparator drug.

Recommendation:
Among the herbal concoctions reviewed, ginger preparation of *Zinzeber officinale* may be recommended for its small to moderate effects on knee pain.
There is insufficient data on compfrey, Chinese herbal recipe, Chinese pills, rose hip, Devil's claw (Harpagophytum *procumbens*) to recommend their use in knee OA.

Level of Evidence: Moderate

Summary of evidence:

All articles reviewed were of low quality. There were 7 full RCT articles and 4 RCT abstracts, comparing different herbal medicine to different control groups. These studies include patients with moderate and chronic knee pain diagnosed with knee osteoarthritis based on clinical and/or radiographic findings. Outcomes were measured at 2 weeks up to as long as 12 weeks. While most claimed improved effects of the intervention groups, the studies did not fully reveal effect size of the treatment as well as contained many methodological flaws.

Studies on ginger (Zingiberis rhizoma) were of high quality. The larger study by Altman compared 2 ginger species, Zinzeber officinale and Alpinia galangal in patients with knee OA. This was an RTC involving 261 subjects with knee OA, observed for 6 weeks. Outcome of pain was measured by using VAS on reduction in "knee pain on standing," using an intent-to-treat analysis. Results showed improvement in knee pain on standing in the intervention group significantly over control, (63% versus 50%; P = 0.048). Analysis of the secondary efficacy variables revealed a consistently greater response in the ginger extract group compared with the control group, when analyzing mean values: reduction in knee pain on standing (24.5 mm versus 16.4 mm; P = 0.005), reduction in knee pain after walking 50 feet (15.1 mm versus 8.7 mm; P = 0.016), and reduction in the Western Ontario and McMaster Universities osteoarthritis composite index (12.9 mm versus 9.0 mm; P = 0.087). They concluded that the preparation of ginger used had a statistically significant effect on reducing symptoms of OA of the knee. This effect was moderate. There was a good safety profile, with mostly mild GI adverse events in the ginger extract group.

Drugs

8. Analgesics

PUBMED search was utilized using the following MeSH parameters "osteoarthritis" and "analgesics", acetaminophen, tramadol, opioids + RCTs/ Metaanalysis. There were 9 retrievable, and on hand search, 2 more qualified articles. Eleven titles were retrieved for consideration and of these 3 were excluded being studies on topical and disease modifying interventions. Of the 8 studies 4 were used in the final 3 metaanalysis and 1 was not available.

Recommendations:
Paracetamol is recommended in reducing pain for mild knee OA with minimal upper GI side effects at doses of 2 grams or less per day.
Tramadol is recommended for the control of moderate pain and improvement of function of knee OA. It is further recommended that patients be warned of adverse events like dizziness and vomiting.

Level of Evidence. High

Summary of evidence:

The 2006 Cochrane Database Systematic Review of acetaminophen for knee OA involved 15 randomized controlled trials with close to 6,000

patients given the intervention against either placebo or NSAIDs for 6 weeks. It showed acetaminophen superior to placebo (in pain response, physician/ patient global scale and modified HAQ; but not in WOMAC and Lequesne outcomes); with NNT 16 and RR 1.02 for developing AEs. However, NSAIDs was better than acetaminophen especially for moderate to severe pain; RR for overall AEs was 1.04 but RR for GI events was 2.0 with NNH= 12.

In the 2006 Cochrane Database Systematic Review of tramadol for OA of the knees included 11 randomized controlled trials with about 2,000 patients. Tramadol was used alone or in combination with paracetamol and compared with placebo. Results showed better pain control with tramadol alone or in combination [WMD -8.5 (-12.05, -4.9)]. WOMAC and Physician Gobal Assessment likewise showed significant weighted mean difference in the active drug group over placebo.

9. NSAIDs/Coxibs

Oral formulations

Pubmed search resulted in 138 titles for review, out of which 123 were excluded because they did not fulfill inclusion criteria. Fifteen studies were left, with 12 excluded because these were either cited in the selected studies or full text was unavailable. One MA and 2 RCTs were included in the analysis.

Recommendations
Short term use of oral NSAIDS and COXIBs are recommended for their small to moderate effect in reducing exacerbations of knee OA pain and improving function, with no significant adverse events.

Level of evidence Moderate to high

Summary of evidence:

The 2004 metanalysis of Bjorjal et al looked into the efficacy of NSAIDs and coxibs with relevant data in more than 10,000 patients. The study showed the overall change in pain by the VAS pain scale of the WOMAC at 10.1 mm (7.4,12.8). Effect size was small at 0.32 (0.24, 0.39). NSAIDs group showed higher rate of adverse events (9.2%) over placebo. In 2006 study of Svensson and group, effects of naproxen on pain for both knee and hip OA was evaluated in a six-week study in more than 500 patients. Analysis of the patients with knee OA showed that naproxen was more effective than placebo for pain, stiffness and function (effect size 0.48, 0.44, 0.44 respectively). Furthermore, naproxen was seen better for control of knee OA than hip OA. In 2004 study of Schiff and Minic, effects of naproxen and ibuprofen were evaluated in a seven-day study in 461 patients with knee OA. Results showed that naproxen and ibuprofen effectively relieved mild to moderate OA pain with good safety and tolerability. But the level of evidence is moderate because non-compliant patients were excluded in the analysis.

Data showed that in the short term, NSAIDs effect is slightly better than placebo in reducing pain in knee PA. Current analysis do not support long term use of NSAIDs for knee OA. The study of Svensson using naproxen vs. placebo showed a small effect size and concluded that naproxen is better tha placebo in decreasing pain of knee OA using the WOMAC. The study of Schiff et al utilizing naproxen and another study on ibuprofen showed similar beneficial effects for pain in knee OA for both drugs over placebo.

Topical formulations

Pubmed search was done for knee osteaoarthritis and topical NSAIDs. A total of 47 titles were listed and 20 were qualified for inclusion. Fifteen relevant RCTs and 1 meta-analysis were appraised. Trials included were for topical diclofenac gel and solution, ketoprofen, ibuprofen and piroxicam. Most studies compared the drug to placebo or vehicle and 3 were head to head trials with diclofenac and ibuprofen, diclofenac and ketoprofen.

Recommendation for topical NSAIDs is supported by enough evidence. They are beneficial over placebo for the control of symptomatic or acute exacerbation and beneficial effects of function in knee OA, with less systemic effects compared to orally taken preparations.

Level of evidence: High

Summary of Evidence

Most studies dealt with diclofenac and the meta analysis by Towheed analyzed 4 RCTs. The study had a total of of 1412 subjects given topical diclofenac or placebo or comparator drugs for an average duration of 8.5 weeks. The resutls favored topical diclofenac with an effect size of 0.30, 0.33 for WOMAC pain and function scales, respectively. RCTs of other NSAIDs lke ibuprofen, ketoprofen and piroxicam showed similar results favoring topical NSAIDs for symptomatic knee OA.

IA modalities

10. Intraarticular steroids (IA)

A total of 147 titles from the search strategy using the keywords: knee osteoarthritis, intraarticular injection and corticosteroid(s). The safety and efficacy of IA steroids in knee osteoarthritis yielded 20 clinical trials and 2 systematic reviews that are of relevance and were sought for retrieval. All of the 18 RCTs that were retrieved were excluded in the analysis due to differences in assigned outcome measures or are lacking thereof namely: WOMAC, Lequesne Index, quality of life measures (HAQ), pain and function measures (i.e. Likert Scale and VAS). Three of the RCTs utilized histomorphometric techniques as endpoint of their studies. Four RCTs employed unconventional control groups as comparator (orgotein and colchicine) and 2 RCTs labeled anatomy other than the knee as the site of investigation. The remaining excluded RCT's were included in the 2 systematic reviews and were subsequently appraised (Cochrane and Arroll)

Recommendation:
IA steroids administered by experts are recommended for knee OA for its short term (1-3 weeks) effects on pain reduction. To demonstrate long term benefit (16-24 weeks), a dose equivalent to 50 mg of prednisone is recommended.
There is no clear benefit for its effects on function.

Level of Evidence: High

Summary of Evidence:

The validity criteria of both Cochrane and Arroll reviews were met. The evidence for the safety and efficacy of IA steroids in the treatment of knee osteoarthritis from the trials were pooled in the two reviews and was subsequently graded by the review committee. There were clear net benefits seen with IA steroids than harm.

In the systematic review using Cochrane methodology 28 trials (1973 participants) comparing IA corticosteroid against placebo, against IA hyaluronan/hylan (HA products), against joint lavage, and against other IA corticosteroids, were included. IA corticosteroid was more effective than IA placebo for pain reduction (WMD -21.91; 95% confidence interval (CI) -29.93 to -13.89) and patient global assessment (RR of 1.44 (95% CI 1.13 to 1.82)) at one week post injection with an NNT of 3 to 4 for both, based on n=185 for pain on 100 mm visual analogue scale (VAS) and n=158 for patient global assessment. Data on function were sparse at one week post injection and neither statistically significant nor clinically important differences were detected. There was evidence of pain reduction between two weeks (the RR was 1.81 (95% CI 1.09 to 3.00)) to three weeks (the RR was 3.11 (95% CI 1.61 to 6.01), but a lack of evidence for efficacy in functional improvement. At four to 24 weeks post injection, there was lack of evidence of effect on pain and function (small studies showed benefits which did not reach statistical or clinical importance, i.e. less than 20% risk difference). For patient global, there were three studies which consistently showed lack of effect longer than one week post injection. However, all were fairly small sample sizes (less than 50 patients per group). This was supported by another study which did not find statistically significant differences, at any time point, on a continuous measure of patient global assessment (100 mm VAS). In comparisons of corticosteroids and HA products, no statistically significant differences were in general detected at one to four weeks post injection. Between five and 13 weeks post injection, HA products were more effective than corticosteroids for one or more of the following variables: WOMAC OA Index, Lequesne Index, pain, range of motion (flexion), and number of responders. One study showed a difference in function between 14 to 26 weeks, but no differences in efficacy were detected at 45 to 52 weeks. In general, the onset of effect was similar with IA corticosteroids, but was less durable than with HA products. Comparisons of IA corticosteroids showed triamcinolone hexacetonide was superior to betamethasone for number of patients reporting pain reduction up to

four weeks post injection (the RR was 2.00 (95% CI 1.10 to 3.63). Comparisons between IA corticosteroid and joint lavage showed no differences in any of the efficacy or safety outcome measures.

Ten trials met the inclusion criteria in the meta-analysis done by Arroll and Smith. Among the high quality studies, the pooled relative risk for improvement in symptoms of osteoarthritis of the knee at 16-24 weeks after intra-articular corticosteroid injections was 2.09 (95% confidence interval 1.2 to 3.7) and the number needed to treat was 4.4. The pooled relative risk for improvement up to two weeks after injections was 1.66 (1.37 to 2.0). The numbers needed to treat to get one improvement in the statistically significant studies was 1.3 to 3.5 patients.

11. IA Hyaluronan

Pubmed search yielded 606 titles for review, of which 59 were sought for retrieval. The rest of the 606 were either commentaries, or biochemical or animal studies, or had no English language translation. Of the 59, the relevant articles included 4 meta analysis and 2 RCTs which contained 50 of the 59 considered articles. Two of the remaining 57 were abstracts.

Recommendations:
IA hyaluronan, administered by experts in 3-5 injections, is recommended for moderate pain reduction and improvement of function lasting up to 3 months in knee OA.

Level of evidence: Moderate

Summary of evidence:

Four low to moderate quality systematic reviews (which include 104 randomized clinical trials) and 2 recently published clnical trials, comparing the efficacy and safety of intra-articular Hyaluronic acid with placebo (arthrocentesis or saline injection) were reviewed. These studies included a total of 17,841 patients with moderate and chronic knee pain diagnosed with knee osteoarthritis based on clinical and/or radiographic findings. In almost all studies, analgesics were allowed to be continued.

The research evidence on the efficacy of Hyaluronic acid is often difficult to interpret because of confounders including different molecular weights of HA, different injection schedules, poor trial design despite large numbers of studies, for example lack of intention-to-treat analyses, limitations in blinding. On balance, the evidence seems to suggest a benefit for reducing pain up to 3 months after a series of three to five injections. Statistically significant differences were detected between HA and placebo at 1 to 4 weeks (WOMAC pain, pain on weight bearing, pain at rest, WOMAC function, Lequesne Index, flexion), 5 to 13 weeks (pain on weight bearing, WOMAC pain, WOMAC function, Lequesne Index, flexion), and 14 to 26 weeks (pain on weight bearing, WOMAC pain, WOMAC function, flexion) postinjection. Apart from a higher incidence of injection site pain, no statistically significant differences versus placebo were noted in the safety profile variables (Bellamy et al). However, the patients over sixty-five years of age and those with the most advanced radiographic stage of osteoarthritis (complete loss of joint space) were less likely to benefit from intra-articular injection of hyaluronic acid (Wang et al).

Others

12. Glucosamine

A PUBMED search was done for articles published from 1966 to present using the MeSH terms "osteoarthritis, knee" and "glucosamine" yielding 56 studies, of which 31 were meta-analysis and randomized controlled trials.

The meta-analysis by Towheed, et al, as electronically published in the Cochrane Database was used as a start point as most of the randomized trials are contained in this review. In addition, 2 more randomized controlled trials that were published after and hence, not included in the said meta-analysis were reviewed.

Recommendation:
The use of proprietary preparation of oral glucosamine sulfate may be recommended for knee OA on the basis of small benefit over placebo in improving pain and function. There is no evidence that this advantage can be extrapolated to the nutraceutical preparations or other non-bioequivalent formulations.

Level of Evidence: High

Summary of evidence:

The clinical trials for glucosamine have involved the use of different drug preparations, most commonly the sulfated and hydrochloride forms of the drugs. Results from these clinical trials have been varied depending on the form of drug that is administered. This is borne out by the meta-analysis by Towheed, which included information from 20 randomized controlled trials. It showed a small effect size across the different studies (-0.19 (-0.50 - 0.11) for pain and -0.07 (-0.21 - 0.80) for function). However, when per protocol analysis of the different trials using the proprietary sulfated form versus the non-proprietary forms (usually glucosamine hydrochloride) were used, there was an increased effect for the proprietary form of the drug in terms of pain (-1.31 for the proprietary form vs -0.15 for the non-proprietary form) and function (-0.14 for the proprietary form vs 0.3 for the non-proprietary form). The trial by Clegg reinforced this showing no difference in pain and function among patients given the non-proprietary form of glucosamine hydrochloride, whereas the trial by Herrero, involving the proprietory form of the drug, showed a more positive effect. The drug appeared to be safe when compared with placebo.

13. Chondroitin

A PUBMED search was done for articles published from 1966 to present using the MeSH terms "osteoarthritis, knee" and "chondroitin" yielding studies, 19 of which were of interest and were reviewed. Of these studies, 7 were considered for review. The 12 other studies were excluded for the following reasons: use of combination drugs as intervention, non-inclusion of relevant outcome measures (particularly pain and function), use of topical chondroitin as the intervention and inclusion patients with hip osteoarthritis.

Among the five meta-analysis obtained, the one by Reichenbach was used as a start point because it included all the other studies that were reviewed in the previous meta-analyses. Furthermore, it was evaluated to have the highest quality among the different analyses. One meta-analysis combine the results of RCTs on glucosamine with those of chondroitin (Richy, et al). Two other randomized clinical trials not included in the meta-analysis are contained in this review.

Recommendation:
Chondroitin sulfate is not recommended for knee OA.

Level of Evidence: High

Summary of evidence:

To date, the most comprehensive meta-analysis on chondroitin sulfate was carried out by Reichenbach, et al. It included 20 trials involving 3846 patients given chondroitin versus placebo or no treatment in knee osteoarthritis. Pain was the main outcome measure and the meta-analysis showed significant clinical effects (-0.75 (-0.99 - -0.50) equivalent to a change of 1.6 cm on 10 cm VAS scale) when pooled results from all the trials were included. The positive effect of drug is mostly due to the contribution of earlier trials of a proprietary form of chondrotin sulfate. The results of these studies cannot be extrapolated to the nutraceutical preparations or other non-bioequivalent forms of the drugs.

Due to the high degree of heterogeneity of the trials and generally low quality of some of the trials, the authors performed sub-group analysis of the studies that showed large sample sizes and intention-to-treat analysis. In this sub-analysis, covering 40% of the initial population, the effect size on pain was reduced to -0.03 (-0.13, - 0.07) or an equivalent of 0.6 mm change on 10 cm VAS scale, a much less clinically significant finding. Recent trials by Clegg and Mazieres also did not show any statistically significant improvement in pain scales among patients given chondroitin when compared with placebo.

Comparison of studies to show improvement in outcome did not disclose any difference among patients given chondroitin sulfate versus placebo either the study of Clegg or Mazieres (WOMAC score of -235.6 $\pm$ 544.1 for treatment group vs 227.4 $\pm$ 362.7 for the placebo group, p 0.78, and Lequesne Index of -235.6 $\pm$ 544.1 for treatment group vs -227.4 $\pm$ 362.7 for the placebo group, p 0.11, respectively).

Monitoring of adverse events among the studies reviewed did not show a significant increase in the number or severity of adverse events among patients given chondroitin sulfate versus placebo.

14. Combination glucosamine HCL and chondroitin sulphate

A PUBMED search was done for articles published from 1966 to present using the MeSH terms "osteoarthritis, knee", "glucosamine" and "chondroitin" yielding 63 studies, 14 of which were of interest and were reviewed. Of these studies, only 1 randomized controlled trial was found which evaluated the effect of combined glucosamine and chondroitin sulfate in osteoarthritis. One RCT (Messier, 2007) was excluded as the intervention was combined with exercise.

RECOMMENDATION:
In general, the combination of glucosamine HCL and chondroitin sulphate isnot recommended in knee OA. However, based on data from a subgroup analysis, the combination may be recommended for patients with moderate to severe pain.

Level of Evidence: Moderate

Justification:

The GAIT trial unequivocally shows that the combination of glucosamine and chondroitin do not improve pain and function among knee osteoarthritis in general. The mean changes in pain scores did not differ significantly compared to those given placebo (-100.5 ± 112.7 vs –86.1 ± 114.2, respectively). This translates to a 50% decrease in WOMAC pain scores in 46.4% vs. 42.2% in the treatment and control groups. Change in pain scores among patients with mild pain showed a similar trend (-78.8 ± 107.1 vs –75.6 ± 105.6), translating to a 50% decrease in WOMAC pain scores in 44.5% vs. 44.9% in the treatment and control groups. However, there is a significant difference in pain scores in the subset of patients with moderate to severe pain (-117.5 ± 97.8 vs –123.0 ± 134.8) translating to a 50% decrease in WOMAC pain scores in 52.8% vs. 32.9% in the treatment and control groups.

There is also no significant improvement in function among patients given the combination glucosamine and chondroitin in general and among patients with mild pain in particular. Change in WOMAC function scores were -235.6 ± 544.1 vs -227.4 ± 362.7 between patient in the treatment and control groups in general. For patients with mild pain, change in WOMAC function scores were -220.9 ± 345.6 vs –209.2 ± 340.7. However, there is a significant difference in WOMAC function scores in the subset of patients with moderate to severe pain (-473.8 ± 332.7 vs ––291.60 ± 428.1).

Monitoring of adverse events among the studies reviewed did not show a significant increase in the number or severity of adverse events among patients given glucosamine plus chondroitin sulfate versus placebo. There is however one case-report of a patient with asthmatic exacerbations imputed to these drug combination.

15. Glucosamine + Chondroitin + MSM

Pubmed search using the MeSH terms "osteoarthritis", "glucosamine", "chondroitin" and "MSM" did not yield any literature. Likewise a free-hand search on Pubmed for clinical studies involving the combination use of these three drugs was negative. Due to the absence of relevant data, a recommendation on the use of these drugs cannot be made.

Biography

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