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Are curcuminoids effective in improving physical function in patients with knee osteoarthritis?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
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Abstract

Objective: The objective of this selective EBM review is to determine whether or not curcuminoids are effective in improving physical function in patients with knee osteoarthritis.

Study Design: Review of a double-blind randomized control trial, a randomized control trial, and a randomized single-blind placebo-controlled trial.

Data Sources: The articles were found on PubMed and selected based on the relevance to the clinical question and if they were focused on patient-oriented evidence that matters (POEM).

Outcomes Measured: The outcomes were based solely on function measures using a patient rated WOMAC scale (WOMAC function) (patient satisfaction of treatment on a 5-category scale (high, moderate, little, same, or dissatisfaction), an investigator based Clinician Global Impression of Change (CGIC), a 6-minute walk distance), and time spent during a 100-meter walk and going up and down a flight of stairs. This study focuses on the WOMAC scale and time spent during a 100-meter walk.

Results: Kuptniratsaikul, et. al (2014) found that *C. domestica* extracts were just as effective as Ibuprofen in treating knee OA and had a similar side effect profile, with less GI side effects than ibuprofen. Kuptniratsaikul, et. al (2009) also found that *C. domestica* extracts seemed just as effective and safe at treating knee OA as ibuprofen, but was not statistically different enough to be definitive. Madhu, et. al found NR-INF-02 to be an acceptable and tolerable option in the treatment of knee OA.

Conclusions: Based on these three randomized, controlled clinical trials, the efficacy of curcuminoids on knee osteoarthritis is likely to be an effective alternative treatment method to improve functionality. The populations studied in these trials were not large and should be considered and addressed in future studies.

Key Words: Turmeric, arthritis, randomized controlled trial

Introduction

Worldwide, knee osteoarthritis (OA) is a major public health concern, being the most common degenerative joint disorder in the elderly.[1] In osteoarthritis, cartilage between the bones begins to break down leading to pain, swelling, and difficulty moving the effected joint.[2] Over time, OA worsens causing bony spur formation, pieces of broken off bone or cartilage to float in the joint space, and inflammation.[2] This inflammation further damages the cartilage.[2] In the final stages of OA, the cartilage has been completely worn out which causes bone to rub against bone resulting in increased pain, inflammation, and damage, and decreased joint function.[2]

The symptoms of knee OA are secondary to the degradation of collagen and include a gradual onset of pain and stiffness in the joint, most likely occurring first thing in the morning or soon after resting.[2] Symptoms also include swelling that gets worse with extended activity, limited ROM that increases after movement, pain that can worsen at the end of the day, and crepitation that occurs when joint is bent.[2] There are many different causes and risk factors of OA. The first is an increased weight/BMI that can cause cartilage cushions to break down faster.[2] Injury or overuse of a joint can also cause OA.[2] Although the exact genetic cause is unknown, scientists believe that there is a rare defect in the production of collagen or a defect in the way bones fit together.[2]

Knee OA is a common joint disorder affecting many people and incurring increasingly high healthcare costs every year. It affects approximately 30.8 million Americans.[3] It is also estimated that 1 in 2 people in the US, at some point in their lives, will develop knee OA symptoms.[4] Most patients spend approximately 13 years with symptomatic knee OA before receiving a total knee arthroplasty (TKA), instead supplementing with pharmacologics.[4] These patients had an average of 6 more yearly MD visits and 3.8 more non-MD visits than patients

without knee OA.[5] Eventually, most patients with knee OA will need to receive a TKA, with an average of 658,000 Americans receiving one every year resulting in a 28% increase in hospital stays.[4,5] As a result of increased visits, pharmacologic supplementation, TKAs, and associated hospital stays, it is estimated that knee OA contributes in excess of 27 billion dollars in healthcare costs every year.[4] In 2011 alone, Medicare reimbursed healthcare systems 3.5 billion dollars for TKAs, which is a higher cost than heart failure, spinal fusions, or coronary stents.[4]

There are various treatment methods that can be used to increase functionality in patients with knee osteoarthritis. Non-pharmacologic methods include weight management, stretching, PT/OT, and assistive devices.[2] Furthermore, you can do various physical activities, including strengthening, ROM exercises, and aerobic exercises.[2] Pharmacologic treatments can include pain and anti-inflammatory medications like analgesics, NSAIDs, corticosteroids, or hyaluronic acid.[2] It can also include natural and alternative methods like supplements, acupuncture, acupressure, and massage.[2] Most patients will need a TKA at some point in their struggle with knee OA.[2]

Although there are many different treatment options available to treat the decreased functionality that comes with knee OA, some of the treatment options have increased side effect profiles. Also, some patients are not able to implement available treatment modalities due to other comorbid conditions and the effects certain medications might have on them. 60-90% of patients with knee OA are interested in alternative methods of medicine, and curcuminoids fall into that category in the treatment of knee OA.[4] Curcuminoids inhibit the effect of substances found in the inhibitory pathway (lipoxygenase, cyclooxygenase, phospholipase, etc.) and pro-inflammatory cytokines (IL-1 beta, IL-8, TNF-alpha, etc.).[1]

Objective

The objective of this selective EBM review is to determine whether curcuminoids are effective in improving physical function in patients with knee osteoarthritis.

Methods

Criteria used for selection of studies for this systematic review is based on specific populations, interventions, comparisons, outcomes measured, and the type of study that was done. The population studied was any patient, male or female, greater than 40 years of age with knee osteoarthritis. None of the patients had an allergy to curcuminoids or co-existing conditions that could impede the success of the trial. The interventions studied were the use of curcuminoids versus a placebo, ibuprofen, or glucosamine sulfate when comparing the effective treatment of knee OA. The outcome measured was the improvement of physical function with the use of curcuminoids using methods that centered around patient-oriented evidence that matters (POEM). The studies used in this systematic review include a double-blind randomized control trial, a randomized control trial, and a randomized single-bind placebo-controlled trial.

Research for this systematic review was found using PubMed. The studies were randomized controlled trials and the articles were published in peer-reviewed journals within the last 10 years. All articles were written in the English language. The keywords used when searching for these articles were “turmeric”, “arthritis”, and “randomized controlled trial”. The articles were selected for this systematic review based on the relevance to the objective. This includes patients that were greater than 40 years old who had been diagnosed knee OA and whether or not the articles’ outcomes were based on patient-oriented evidence that matters. The exclusion criteria excluded papers that included patients less than 40 years old, studies that were not randomized or controlled, and studies that had outcomes that were not based on patient-

oriented evidence that matters. The statistics used or reported in these studies were change in the mean baseline. The data from the articles was analyzed using p-values and Confidence Intervals using continuous data to analyze the efficacy of curcuminoids in improving physical function in patients with knee osteoarthritis compared to placebos or alternative treatment methods.

Outcomes Measured

The outcome that was measured in these studies was a change in physical function in patients with knee osteoarthritis. Kuptniratsaikul et. al (2014) assessed physical function in the patients using a modified Thai version of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale, with a focus on the WOMAC function subscale.[1] The scale has a range from 0 to 10, with a higher score representing worse knee function.[1] They also used a 6-minute walk distance to evaluate function.[1] These assessments were completed at weeks 2 and 4 during treatment follow-up.[1] At the end of the trial, patients were asked to complete a global assessment and satisfaction survey.[1] The patients were also asked to report any adverse events that occurred throughout the study, recorded as any new symptoms the patients experienced.[1]

Kuptniratsaikul, et. al (2009) assessed physical function in the patients based on time spent on a 100-meter walk and time spent going up and down a flight of stairs (10 steps).[6] For both exercises, the time was measured using a digital stopwatch that had a resolution within 0.001 seconds.[6] Each participant was analyzed by the same assessor at every visit, and all patients completed the exercises at the same location.[6] The patients were assessed at weeks 2, 4, and 6.[6] Throughout the study, patients reported any adverse events as either new symptoms experienced or a change in lab profiles completed at week 0 and week 6 that included a complete blood count, liver function, and renal function.[6] At the end of the trial during the 6 week follow-

up, patients were asked to complete a patient satisfaction survey evaluated by a 5-category scale: high, moderate, little, same, or dissatisfaction.[6]

Madhu, et. al assessed physical function in the patients based on the Likert Version-3.0 of the WOMAC, which was modified for Indian use.[4] The WOMAC scale had 24 questions, with questions 8-24 focusing on physical functional difficulty.[4] The responses were quantitative: 0 being none, 1 being mild, 2 being moderate, 3 being severe, and 4 being extreme.[4] The highest score possible was a 96.[4] This was completed on days 0, 21, and 42.[4] The Clinician Global Impression of Change (CGIC) was assessed by clinical examination by a designated orthopedic consultant and had an emphasis on the presence or absence of the limitation of movement, crepitus, muscle wasting, and subluxation of joint.[4] This was completed on days 21 and 42 of trial follow-up.[4] At the end of the trial, the acceptability of medications by study patients wherever available was evaluated as 0-3: 0 being not acceptable, 1 being good, 2 being better, and 3 being best.[4] Patients were also asked to report any adverse events throughout the trial.[4] Three articles were chosen for this systematic review. Table 1 represents the demographics and characteristics of each study that was selected.

Results

Three randomized, controlled trials were chosen for this systematic review to determine the efficacy and safety of curcuminoids for the improvement of function in patients with knee osteoarthritis. The Kuptniratsaikul, et. al (2014) study used continuous data that was not convertible into dichotomous form.[1] The data was analyzed using a per-protocol analysis.[1] The Kuptniratsaikul, et. al (2009) study also used continuous data that was not convertible into dichotomous data.[6] Like the previous study, the data was not based on an intention-to-treat-analysis, but instead it was based on a per-protocol analysis.[6] The Madhu, et. al study also used

Table 1: Demographics & Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Kuptnir-atsikul, 2014	RCT	367	≥ 50	Pts who had primary knee OA with a numerical pain scale >5/10 and ≥50 y.o.	Pts who had abnormal liver or kidney function, history of peptic ulcer, allergy to curcumin or ibuprofen, or unable to walk	36	*C. domestica* extracts 1,500 mg/day VS. Ibuprofen 1,200 mg/day
Kuptnir-atsikul, 2009	RCT	107	> 50	Pts who had primary knee OA, knee pain, radiographic osteophytes and 1 of the following: 1) age > 50 years, 2) morning stiffness 30 mins in duration, 3) and crepitus on motion	Pts who had peptic ulcers, hepatobiliary tract disease, or known allergy to curcumin or ibuprofen	16	*C. domestica* extracts 2 g/day VS. Ibuprofen 800 mg/day
Madhu, 2013	RCT	120	> 40	Pts who were either gender, > 40 y.o., clinical evidence confirming diagnosis of knee OA, duration of pain at least 6 months on majority of days during preceding months, and showing radiological evidence of knee OA Grade 2 or Grade 3	Pts who had medical or arthritic conditions confounding evaluation of knee OA, Primary predominant patella-femoral disease, history of clinically significant trauma/surgery to affected knee, and co-existing disease that could preclude the successful completion of the trial	10	NF-INF-02 500 mg BID VS. Glucosamine Sulfate (GS) 750 mg BID VS. Combo of NF-INF-02 and GS VS. Placebo 400 mg BID

continuous data that was not convertible into dichotomous data; however, it was based on an intention-to-treat analysis.[4] All three studies analyzed the measured outcomes based on change in mean baseline of improvement of physical function of the patients.

In the Kuptniratsaikul, et. al (2014) study, 367 patients were initially included in the study based on inclusion and exclusion criteria. 331 patients were able to finish the study with 36 lost to follow-up (Table 1). This meant that 171 patients were left in the *C. domestica* extracts group and 160 were left in the ibuprofen group.[1] The patients either received 1,500 mg/day of *C. domestica* or 1,200 mg/day of ibuprofen, with both treatment options being made to look identical.[1] Patients were asked to take 2 capsules after meals three times a day for 4 weeks and to not use any other medications during the study, except recorded Tramadol as a rescue medication for severe pain.[1] The outcomes were evaluated at weeks 2 and 4 by the same assessor at each site.[1] At week 4, the WOMAC function scale showed a non-inferiority of *C. domestica* extract as a treatment when compared to ibuprofen (p-value = 0.010) (Table 2).[1] The baseline WOMAC function score was not significantly different between the two groups at the beginning of the study (Table 2).[1] One hundred and twenty patients (29.7% in the *C. domestica* group and 35.7% in the ibuprofen group) reported adverse events including dyspepsia, abdominal pain, nausea, loose stools, and pitting edema.[1] *C. domestica* had lower GI side effects overall than ibuprofen.[1]

Table 2: Mean WOMAC Function Score at the Beginning and End of Treatment[1]

	***C. domestica* extracts (n=171)**	**Ibuprofen (n=160)**	**P-value**
WOMAC functions (beginning)	5.3±2.0	5.1±1.8	0.440
WOMAC function (end, adjusted by week 0)	3.41±2.09	3.26±2.05	0.010

When looking at the WOMAC function score, the change from week 0 to week 4 was an improvement of 3.41±2.09. This is a large improvement since the scale was based on a 0-10

measure, despite the standard deviation being wide. The confidence interval was at 95% and the p-value was ≤ 0.05 at 0.01. Keeping these statistics in mind, it can be confidently said that *C. domestica* is a statistically significant treatment and would be a non-inferior treatment in a large population.

In the Kuptniratsaikul, et. al (2009) study, 107 patients were initially included in the study based on inclusion and exclusion criteria. 91 patients were able to finish the study with 16 lost to follow-up (Table 1). This meant that 45 patients were left in the *C. domestica* extracts group and 46 were left in the ibuprofen group.[6] The patients either received 500 mg four times a day of *C. domestica* extracts or 400 mg twice a day of ibuprofen, with instructions not to use any other medicines or herbs.[6] The outcomes were evaluated at weeks 0, 2, 4, and 6 by the same assessor at each site.[6] At week 6, the time spent on a 100-meter walk suggests that *C. domestica* extracts might be as effective as ibuprofen in improving function, but the values were not statistically different (p-value = 0.16) (Table 3).[6] Thirty-nine patients (16 in the *C. domestica* group and 23 in the ibuprofen group) reported adverse events including dyspepsia, dizziness, nausea and vomiting, and loose stools.[6] *C. domestica* had lower GI side effects overall than ibuprofen.[6]

Table 3: Change in Time Spent Walking 100-meters Between the Beginning and End of Treatment[6]

	***C. domestica* extracts (n=45)**	**Ibuprofen (n=46)**	**Difference of Change Score (95% CI)**	**P-value**
Change Score (sec)	10.1±16.8	5.0±16.9	5.07 (-2.09 to 12.23)	0.16

When looking at the time spent walking 100-meters, the difference in mean change scores from week 0 to week 6 was a difference of 5.07 seconds with a 95% confidence interval between -2.09 and 12.23. This is a small improvement since the *C. domestica* group only

improved 5 seconds more than the ibuprofen group and the confidence interval is wide. If the confidence interval was narrowed and the difference in change score had increased, it would be a large improvement. The confidence interval was at 95% and the p-value was > 0.05 at 0.16. When interpreting the statistics, it can be confidently said that the treatment was not statistically significant and may not be a good treatment option in a large population.

In the Madhu, et. al study, 120 patients were initially included in the study based on inclusion and exclusion criteria. 110 patients were able to finish the study with 10 lost to follow-up (Table 1). This meant that 29 patients were left in the NR-INF-02 group, 28 in the glucosamine sulfate (GS) group, 24 in the NR-INF-02 + GS group, and 29 in the placebo group.[4] The NR-INF-02 group received one 500 mg capsule twice a day, the GS group received two 375 mg capsules twice a day, the NR-INF-02 + GS received one 500 mg capsule twice a day and two 375 mg capsules twice a day (respectively), and the placebo group received one 400 mg capsule twice a day.[4] The outcomes were evaluated at days 0, 21, and 42.[4] Acetaminophen tablets 2,000-4,000 mg per day were allowed as a rescue medication, except 24 hours before clinical examination of the knee joint.[4] At day 42, the WOMAC score showed a significantly higher reduction in the NR-INF-02 groups when compared to the placebo and NS-INR02 + GS group (p-value < 0.05); however, there were so significant difference when compared to the GS group (Table 4).[4] The baseline WOMAC function score was not significantly different between the four groups at the beginning of the study (Table 4).[4] Thirteen patients (2 in the NR-INF-02 group, 5 in the GS group, 4 in the NR-INF-02 + GS group, and 2 in the placebo group) reported adverse events including dyspepsia, fever, sore throat, pedal edema, generalized body pain, and cough.[4] NR-INF-02 had the least number of adverse events during the trial.[4]

Table 4: Effect of Treatment on WOMAC over 21st Day and 42nd Day Follow-Up

	NR-INF-02 (n=29)	Glucosamine (n=24)	NR-INF-02 +GS (n=24)	Placebo (n=29)
Baseline	54.97±9.85	58.30±12.73	60.73±11.47	57.23±9.63
21st Day[1]	36.67±16.08[a,b]	44.17±15.77	47.31±19.16	52.23±9.63
42nd Day[2]	27.14±16.13[a, b]	34.92±19.48	36.21±24.74	47.90±12.59

[1] Significantly different from baseline to first follow-up ($p < 0.01$); [2] Significantly different from baseline to second follow-up ($p < 0.01$); [a] Significantly different from Placebo ($p < 0.05$); [b] Significantly different from NR-INF-02 + GS ($p < 0.05$)

When looking at the WOMAC score, the score was significantly different on day 42 than when compared to the baseline (p-value < 0.01). The confidence interval was not given, but the p-value was < 0.01 and was significantly different than the NR-INF-02 + GS and placebo groups with a p-value of < 0.05. Keeping these statistics in mind, it can be confidently said that NF-INR-02 is a statistically significant treatment and would be an acceptable and tolerable treatment option in a large population.

Discussion

This systematic review compares three randomized, controlled clinical trials, and two out of three of them found that curcuminoids are statistically effective at improving physical function in people with knee osteoarthritis.[1, 4, 6] Kuptniratsaikul, et. al (2014) found significant improvement in the WOMAC function subscale.[1] Kuptniratsaikul, et. al (2009) did not find significant improvement in the time it took to walk 100-meters.[6] Madhu, et. al found significant improvement in the WOMAC score.[4]

For a long time, curcumin has been used as a spice and coloring agent in Thai curry powders.[1] In Ayurvedic and Chinese medicine, it has been used as an anti-oxidant, for its anti-inflammatory properties, to aid in digestion, to treat liver problems and skin disease, and to aid in wound healing.[7] In food, curcumin is considered safe; however, large amounts for long periods of time can cause stomach upset and ulcers.[7] It can also lower blood sugars, so should be used with caution in diabetics.[7] Furthermore, it can cause blood thinning, so it should be discontinued

at least two weeks before a planned surgery.[7] It should be used with caution if one is taking: blood thinners, diabetic medicines, proton pump inhibitors, or antacids/antihistamines.[7]

Kuptniratsaikul, et. al (2014) mentioned that they were concerned about the dosage of ibuprofen used in the active control group.[1] They chose a 1,200-mg dosage instead of a higher dosage of 1,800 mg at the recommendation of a rheumatologist due to the smaller body habitus of the Thai population.[1] Kuptniratsaikul, et. al (2009) mentioned that the wide range of 95% CI indicated that their study had an inadequate sample size.[6] They also had concerns about the amount of *C. domestica* dosages needed throughout the day and the low dosage of ibuprofen used, which was 400 mg twice daily.[6] They suggested another study with a bigger sample size and increased dosage of ibuprofen.[6] Madhu, et. al considered a few limitations in their study including: 1) small sample size; 2) study being single blind; 3) short duration of treatment; and 4) subjective scales.[4] They suggested that future studies should include a large sample group and a longer duration of treatment.[4]

Conclusion

Based on these three randomized, controlled trials, the efficacy of curcuminoids is inconclusive, with only two out of the three studies finding statistically significant improvement in physical function when using curcuminoids as treatment.[1, 4, 6] In future studies, it would be appropriate to have larger sample sizes and longer duration of studies. If researchers focused on these two areas, they would give a more accurate portrayal of and validate the efficacy of curcuminoids in improving physical function in the general population of patients with knee osteoarthritis.

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