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The effect of niacinamide on osteoarthritis: A pilot study

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Abstract. *Objective*: To evaluate the effect of niacinamide, on selected parameters of osteoarthritis using a double-blind, placebo controlled study design.
Methods: Seventy two patients with osteoarthritis were randomized for treatment with niacinamide or an identical placebo for 12 weeks. Outcome measures included global arthritis impact and pain, joint range of motion and flexibility, erythrocyte sedimentation rate, complete blood count, liver function tests, cholesterol, uric acid, and fasting blood sugar. Compliance was monitored with a pill record sheet and interview.
Results: Global arthritis impact improved by 29% (95% confidence interval [CI] 6, 46) in subjects on niacinamide and worsened by 10% in placebo subjects ($p = 0.04$). Pain levels did not change but those on niacinamide reduced their anti-inflammatory medications by 13% (95% CI 9, 94; $p = 0.01$). Niacinamide reduced erythrocyte sedimentation rate by 22% (95% CI 6, 51; $p < 0.005$) and increased joint mobility by 4.5 degrees over controls (8 degrees vs. 3.5 degrees; $p = 0.04$). Side effects were mild but higher in the niacinamide group (40% vs 27%, $p = 0.003$).
Conclusion: This study indicates that niacinamide may have a role in the treatment of osteoarthritis. Niacinamide improved the global impact of osteoarthritis, improved joint flexibility, reduced inflammation, and allowed for reduction in standard anti-inflammatory medications when compared to placebo. More extensive evaluation of niacinamide in arthritis is warranted.

Keywords: Niacinamide – Randomized controlled trial – Osteoarthritis

Introduction

Osteoarthritis (OA) is one of the most common and debilitating diseases in developed countries and is increasing in importance as the population ages. Despite a growing interest in uncovering the basic mechanisms of osteoarthritis, medical treatment remains symptomatic involving non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, anti-spasmotics, and occasionally steroids. Current medical treatments do not halt the long-term progression of the disease [1] and research on OA is disproportionately directed toward the use of NSAIDs for short-term symptomatic treatment [2].

In the 1940's and 50's, William Kaufman, M.D., Ph.D., a Connecticut physician, did detailed evaluations of several hundred patients with both osteo and rheumatoid arthritis treated with large doses of niacinamide, a form of vitamin B_3 [3, 4]. He documented improvements in joint function, range of motion, increased muscle strength and endurance, and reduction in sedimentation rate over long periods in these patients. Reported effects began after one to three months on niacinamide and reaching their peak between one and three years. He claimed that improvements occurred not because of specific, direct anti-inflammatory effect of niacinamide, but because of increased mobility and flexibility in all aging joints. His studies, as well as similar reports by others [5], however, involved only uncontrolled series of patients [6].

If effective, niacinamide would provide an alternative or complementary treatment to those currently available for osteoarthritis. In order to evaluate whether niacinamide has any specific effect on osteoarthritis over-and-above that obtained from standard treatment, we conducted a three month study using a randomized, double-blind, placebo-controlled design on patients who had been clinically diagnosed and had been under conventional treatment for OA chronically.

Materials and methods

Population

Seventy-two patients, referred from the general outpatient clinics of orthopedics, internal medicine, and family practice at a small community hospital were entered into the study. All subjects had clinical and radiological evidence of osteoarthritis and required

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daily use of anti-inflammatory medications for control of pain and swelling. Inclusion criteria were: 1) over 40 years of age; 2) a diagnosis of idiopathic osteoarthritis by a licensed, orthopedic, internal medicine, or family physician; 3) symptomatic disease for at least 5 years duration; 4) radiological evidence of OA in at least two effected joints demonstrating either localized loss of joint space, osteophyte formation, subchondral cysts, bony collapse, or intra-articular osseous bodies; and, 5) joint pain requiring daily use of NSAIDs for pain control. Exclusion criteria were: 1) being under 40 years of age; 2) pregnant; 3) increased morning joint stiffness lasting over 30 minutes; 4) palpable warmth of the affected joints; 5) severe liver disease (chronic active hepatitis or advanced cirrhosis) [7]; 6) diabetes requiring insulin; 7) active gout; 8) active peptic or gastric ulcers [8]; 9) those taking corticosteroid medications; or, 10) an inability to comprehend or adequately complete the initial history, physical examination, questionnaires, and a two week compliance screening (run-in) period prior to joint evaluation. Subjects met the American Rheumatism Association's criteria (and the referring physician's clinical impression) of OA except for age over 50 in all cases [9].

Randomization and blinding

Subjects were assigned to either treatment or control groups in a blind fashion using a table of random numbers in the hospital pharmacy by a single individual not otherwise involved in the trial. Codes for niacinamide or placebo were kept in a locked drawer in the pharmacy until the end of the study. Niacinamide (500 mg/tablet) and an identical appearing, coated, placebo tablet were manufactured specifically for this study (Bronson Pharmaceuticals, LaCanada, CA). Tablets were coated with a paraffin layer to prevent detection of the bitter taste of niacinamide and all patients were instructed not to bite or chew the tablets as they might find them unpleasant.

Treatment and compliance

Dosage was one tablet six times daily for 12 weeks (a total of 3000 mg/day). Subjects were required to return their bottles at 6 and 12 weeks for a pill count and refill before completing final evaluations. Subjects were allowed to continue their regular arthritis medications for pain and to adjust the dosage as needed during the course of the study. Pill sheets were completed daily to assist subjects in taking the tablets regularly, recording the number and amount of other arthritis medications taken, and estimating non-compliance. Subjects who could not complete the evaluation procedures or comply with the pill frequency during a two week run-in period before initial joint evaluations were not entered into the study.

Baseline and outcome evaluations

Evaluations were done on entry into the study and at 6 and 12 weeks. Once entered into the study, all follow up evaluations were done by the same physician and joint mobility was measured by the same physical therapist. Baseline and outcome evaluations included the following:

1) A complete history and physical by a study physician.

2) Joint evaluation including range of motion as determined by goniometric measurements taken in quadruplicate for 16 pre-determined joints (all metacarpophalangeals, shoulders, knees, hips) using previously established and reliable measurement methods [10]. These measurements were then averaged to produce an overall estimate of joint flexibility called a Joint Range Index (JRI). Correlation coefficients for repeated joint range measurement was high (overall Pearson and Spearman correlation coefficients both greater than 0.98 for repeated measures on the same joints) demonstrating low intra-observer error. In addition subjects were assessed for joint swelling, crepitation, and tenderness by exam. To increase reliability, all joint evaluations were done by a single physical therapist (CP) who was otherwise not involved in the design or execution of the study. In this way joint measurement variability was both reduced and randomization distributed any measurement errors equally between the niacinamide and placebo groups.

3) Arthritis impact was measured using the Arthritis Impact Measurement Scale (AIMS), a validated and extensively used questionnaire for evaluating arthritis [11]. Global arthritis impact and pain were the two predetermined main outcome assessments evaluated from this scale and the variables upon which power calculations were made.

4) The use of other arthritis medications was assessed by a daily pill sheet on which subjects recorded any other medications taken for arthritis. These medications were converted into standard pill/equivalents using established dosage comparisons [12].

5) Laboratory tests included complete blood count (CBC), erythrocyte sedimentation rate (ESR), urinalysis, fasting blood sugar (FBS), total cholesterol, triglycerides, uric acid, total bilirubin (TB), alkaline phosphatase (AP), and serum glutamic oxaloacetic transaminase (SGOT).

6) Baseline nutrient and B_3 intakes were estimated from all sources with a dietary food frequency questionnaire (DFFQ) and nutritional analysis software (FoodProcessor II; Salem, Oregon). All subjects were asked to stop vitamin supplements during the course of the study except those medically prescribed.

7) Side effects were evaluated by history, a pre-determined symptom checklist administered at each visit, and selected laboratory evaluations. Subjects were encouraged to call about any significant unexplained symptoms during the study period.

Power and statistical analysis

We estimated that a placebo response rate of 40% would require approximately 65 patients to detect a 25% improvement in the experimental over control group (alpha = 0.05, 1-tailed) [13]. The two, pre-established main outcome criteria upon which power was calculated were global arthritis impact and pain. Secondary outcome criteria were joint range of motion and medication use. Age, sex, weight, duration of arthritis, health habits, laboratory studies, change in NSAIDs, and compliance measures (pills missed per month) were evaluated by Student's t-test. AIMS scores for

Table 1. Characteristics of study groups*.

Characteristic	Group	
	niacinamide mean (SD)	placebo mean (SD)
Number	31	29
Age	64 (6.4)	65 (8.9)
Weight (lbs.)	162 (30.1)	164 (31.8)
Females	22	17
Males	9	14
Arthritis duration (years)	15 (9.7)	16 (10.5)
Arthritis severity (AIMS score)	2.7 (1.4)	3.6 (1.3)
NSAIDs use (pill-equivalents/mo.)	50.8 (67.8)	46.3 (54.6)
Vitamin B_3 intake (pre-study mg/day)	55	49
Compliance (pills missed/month)	31 (43.6)	20 (28.4)
Drop outs	5	7

* All p values >0.05.

Table 2. Drop-outs.

Group/Period		Number	Reason(s)
During 2-week run in		13	• incorrect forms – 5 • traveling/changed mind – 3 • too many pills – 4
During study period (total)		12	
Treatment group	treatment related	3	• nausea – 1 • heartburn – 1 • skin rash – 1
	not treatment related	1	• endarterectomy – 1 • severe sciatica – 1
Placebo group	treatment related	1	• too many pills – 1
	not treatment related	6	• aneurysm repair – 1 • bladder surgery – 1 • bnee surgery – 1 • COPD flare – 1 • wife got cancer – 1 • no followup, no phone – 1

overall impact, pain, and JRI differences, were evaluated using the Wilcoxon's rank sum test. Side effect rates were evaluated by the Chi square method, p values less than 0.05 were considered significant.

Results

Randomization and blinding

No significant differences were found between experimental and control groups when compared by age, sex, height, weight, health habits, duration of arthritis, amount of baseline NSAIDs taken at the beginning of the study, or initial global arthritis impact (Table 1). Thirty subjects were taking vitamin supplements (including vitamin B_3) prior to entry into the study (17 in the treatment and 13 in the placebo group). Average B_3 intake from combined food and supplement sources prior to start of the study was calculated at 55 mg/day in the treatment and 49 mg/day in the placebo group. At the end of the study neither subjects nor physicians could correctly predict which group they were in, indicating that blinding remained successful throughout the study and that the effects were not sudden or dramatic.

Drop outs and compliance

Thirteen subjects failed to properly complete either the baseline evaluations or the two week run-in period and were not entered into the study. Sixty subjects (83% of those entered) completed all three month follow-up evaluations. Eight subjects dropped out of the study for personal or medical reasons unrelated to the therapy. Three individuals on niacinamide stopped the study because of side effects, two for GI upset and one because of a rash on the hands. One subject on placebo stopped because she was "tired of taking pills" and one failed to return for the final evaluation and could not be contacted (Table 2).

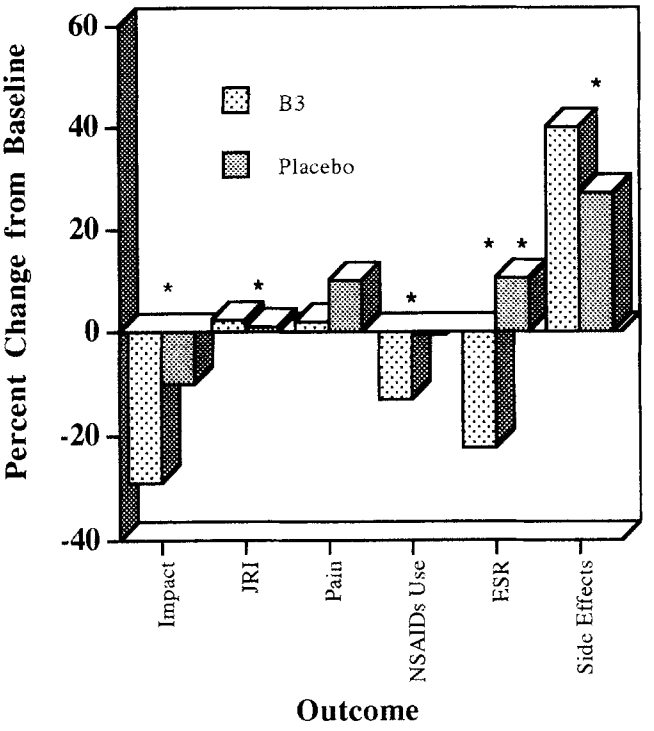

Fig. 1. Percent change from baseline to twelve weeks of main outcome parameters in niacinamide and placebo groups. "Impact" refers to AIMS arthritis impact scale score, "JRI" = Joint Range Index, "Pain" is from AIMS pain scale, "ESR" = erythrocyte sedimentation rate, "Side Effects" refers to the percent of subjects in each group who reported side effects of any kind after starting the medication. *indicates p value less than 0.05, **p less than 0.005.

Outcomes

Global arthritis impact, as measured by the AIMS 100 mm visual analog scale (VAS), improved by 29% (95% confidence interval [CI] 6, 46) in subjects on niacinamide compared to a 10% worsening in those on placebo (mean VAS score, $B_3 = -5.9$ mm; vs. c = +2.7 mm; p = 0.036). While pain levels were no different in the two groups, those on niacinamide reduced their adjusted, anti-inflammatory medication dosage (all NSAIDs) by 13% (95% CI 9, 94) compared to a slight increase in pain medication use by the placebo group ($B_3 = -6.7$ pill/equivalents/month; vs. c = +0.25/month; p = 0.014). Average joint mobility as measured by the JRI increased by 8 degrees in the niacinamide group and 3.5 degrees in the placebo group a 2.8% (95% CI 0.4, 3.9) increase in joint mobility in the experimental subjects (p = 0.044) (Table 3).

Inflammation (as measured by ESR) was reduced by 22% (95% CI 6, 51) in the niacinamide group over controls ($B_3 = -6.4$ mm/hr. vs. c = +3.3 mm/hr.; p = 0.004) (Table 3). Total cholesterol decreased by 14.6 mg/dl (95% CI 7.0, 22.1) in the placebo group (an unexplained finding) and by 0.85 mg/dl in the treatment group (p = 0.004). SGOT rose by 3.1 u/L (95% CI 0.1,

Table 3. Main Outcomes, baseline vs. week twelve.

Outcome	Group		% Change (95% CI)	p value
	niacinamide	placebo	treatment group	
Arthritis impact (AIMS score)	−5.9	+2.7	−29 (6, 46)	0.04
Joint range index (degrees)	+8	+1.4	+2.8 (0.4, 3.9)	0.04
Pain (AIMS score)	+0.10	+0.82	+2 (−0.2, 23.8)	0.1
NSAIDs intake (pill-equivalents/mo.)	−6.7	+0.25	−13 (9, 94)	0.01
ESR (mm/hr.)	−6.4	+3.3	−22 (6, 51)	0.004
Side effects (no. subjects with)	12	8	40	0.03

6.1) in the niacinamide group, a 20% change over baseline ($p = 0.04$). None rose to a dangerous or concerning level. No other laboratory tests showed significant differences between groups.

Side effects were mild and due almost exclusively to gastrointestinal (GI) disturbances such as eructations, nausea, or loose stools and were managed by having subjects take the medicine with food or extra fluids. Twelve subjects (40%) in the niacinamide group reported side effects compared to eight (27%) of those on placebo ($X_2 = 4.48$; $p = 0.034$) (Table 3, Fig. 1). Eleven subjects on niacinamide and two on placebo experienced nausea or heartburn. One subject had an upper GI bleed requiring hospitalization. She was on placebo. Endoscopy of this patient showed gastric erosion attributed to NSAIDs use.

Compliance was excellent although three individuals found that taking a tablet six times a day was not possible. Five subjects reported that they took two tablets three times a day. Based on pill sheets, subjects missed only about 5% of their medications. There was no significant difference in compliance rates between the groups ($p = 0.16$), (Table 1).

Discussion

This study indicates that niacinamide may have a role in the treatment of osteoarthritis. Niacinamide improved the global impact of osteoarthritis, improved joint flexibility, reduced ESR, and allowed for reduction in anti-inflammatory medications when compared to placebo. Kaufman reported that between one and three months was the minimum amount of time needed to see improvement in joint function while on niacinamide which then reached its maximum effect in one to three years. If niacinamide works by improving cartilage repair mechanisms, as discussed below, this study was not long enough to detect evidence for this.

Niacinamide appears to be a safe medication when taken at this dosage level. Side effects were mild and mostly limited to GI symptoms could be managed by taking the medication with food or fluids. Comparable and higher doses of niacin (the nicotinic acid form of vitamin B_3) are currently used for the treatment of hypercholesterolemia. Niacinamide does not cause the flushing and pruritus found with niacin and appears to be better tolerated. This study found no evidence that niacinamide effected blood glucose levels, uric acid, cholesterol, or hematological values significantly. SGOT levels were slightly elevated and warrant following in patients on this medication [8]. The dosage frequency of one tablet six times per day as recommended by Kaufman was difficult for a number of patients and future studies should explore whether reduction in pill frequency will produce similar effects on joint symptoms and function. Kaufman also reviewed the joint range of motion score for this study and felt that it was less sensitive than his and may not have picked up important changes. Range of motion, however (especially at only the 8% improvement level) may not be so important as more clinically relevant factors such as arthritis impact, function, pain and medication use.

Large amounts of extracellular niacinamide might work by increasing levels of the coenzymes niacinamide adenine dinucleotide (NAD) and niacinamide adenine dinucleotide phosphate (NADP) in synovial fluid and, via diffusion, into the cartilage matrix itself [7]. This would provide energy and nucleic acids through non-oxidative mechanisms (i.e. via the pentose shunt, bypassing the tricyclic acid and glycolytic sequences) so important for cartilage repair in the deeper layers of the matrix [14,15]. This effect could increase cartilage repair rates and so complement the anti-inflammatory and anti-cytokine effect of NSAIDs [16].

This study showed a positive effect of niacinamide on some of the more common manifestations of osteoarthritis. More extensive evaluation of niacinamide in a larger population is warranted.

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