Efficacy and Safety of Natural Eggshell Membrane (NEM®) in Patients with Grade 2/3 Knee Osteoarthritis: A Multi-Center, Randomized, Double-blind, Placebo-Controlled, Single-crossover Clinical Study

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Abstract

Objective: To evaluate the efficacy and safety of NEM® (natural eggshell membrane), in patients with grades 2 and 3 knee osteoarthritis (OA) having significant joint pain and stiffness, in a large, multi-center clinical trial.

Subjects and methods: This study was a randomized, double-blind, placebo-controlled, multi-center, single-crossover design. One-hundred sixty subjects (male, 32; females, 134; age ≥ 40 years) with grade 2 or 3 knee OA for 1-5 years were randomized to either NEM (n=83) 500 mg once daily or placebo (n=83) for 30 days. Osteoarthritis was evaluated using the Western Ontario and McMaster Universities OA index. NEM and placebo groups were compared at baseline, day 7, and day 30. After 30 days on placebo, the placebo group crossed over while remaining blinded and was provided with NEM (500 mg) for an additional 60 days.

Results: In NEM-treated subjects, WOMAC-stiffness was reduced at day 7 (P=0.034 vs. placebo), and WOMAC-total (P=0.004), WOMAC-pain (P=0.023), WOMAC-stiffness (P=0.001), and WOMAC-function (P=0.001) were reduced at day 30 (vs. placebo). The number of subjects experiencing greater decreases (≥ 20%) in WOMAC-pain was significantly greater in the 90-day NEM group (48%, P=0.022), compared to the 60-day NEM group (30%). No serious adverse events (AE) were observed in the NEM group, and there was no significant between-group difference in the total number of AEs reported (NEM, n=8; placebo, n=15).

Conclusion: In this large, multi-center study in subjects with grade 2 and 3 knee OA, NEM reduced pain and stiffness within 7-30 days, and these clinically meaningful benefits persisted for 90 days. NEM can be considered as a safe, natural intervention for inclusion as part of a comprehensive clinical protocol in the management of knee OA.

Keywords: Arthritis; Complementary therapy; Nutraceuticals; Pain; WOMAC

Abbreviations: AE(s): Adverse Events(s); NEM: Natural Eggshell Membrane; OA: Osteoarthritis; RCT: Randomized Controlled Trial; ROM: Range of Motion; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Introduction

Joint and connective tissue disorders are among the most common and important chronic diseases that unfavorably influence the quality of life of those afflicted. In 2010, it was estimated that osteoarthritis (OA) and rheumatoid arthritis (RA), the two most prevalent chronic rheumatic diseases, affected 3.8% and 0.24% of the global population, respectively [1]. This equates to more than 290 million people combined worldwide.

Symptomatic knee OA including knee pain and stiffness, occurs to a greater degree in females and in individuals over the age of 50 years. The incidence of OA increases with age and 50% of those 60 years and older report having chronic knee pain [2]. A gradual increase is expected in the future prevalence of OA due to the increasing elderly population and obesity rates throughout the world. A recent study of the prevalence of symptomatic knee OA in the Izmir region in Turkey found that 20.9% of those aged 40 and over were afflicted [3].

For these reasons, there is an increasing interest in studies focusing on the treatment of OA [4]. The main goal of OA treatment is to relieve the pain and other symptoms of patients, and to enhance their functional capacities. There are a variety of prescription drugs and biologicals approved for use for OA, but these options are often associated with significant side effects and are costly. Traditional pharmacological therapies include analgesics (e.g. paracetamol, oxycodone, propoxyphene, etc.) and/or non-steroidal anti-inflammatory drugs (NSAIDs) (e.g. ibuprofen, diclofenac, celecoxib), either alone or in combination [5-7]. However, these treatments are frequently associated with adverse health concerns including cardiac

risks [8,9], gastrointestinal problems [10,11], and addiction issues associated with long-term use of pain-relieving narcotics [12,13].

For OA (and many other conditions), natural, non-prescription interventions (i.e. integrative approaches including nutraceuticals, dietary supplements, functional foods) are preferred by many patients due to their reduced potential for side effects and generally lower cost. The most intensively investigated natural products in the context of OA are glucosamine and chondroitin sulfate [14,15]. Although less costly and having an improved side effect profile compared to prescription therapies, their overall efficacy is mild with borderline clinical significance. Clearly, there remains an unmet need for additional safe and efficacious non-prescription treatment options.

Natural eggshell membrane [NEM; commercially available in the USA as NEM®] is a non-prescription, natural source of immune-modulating bioactives [16,17]. NEM has demonstrated safety and efficacy in multiple, clinical trials in relieving joint pain and stiffness in individuals with OA [18-21]. In addition, NEM has also been reported efficacious in various animal species, including rat models of OA and RA [17,22-26]. The current study was performed to confirm the efficacy and safety of NEM in a large, multi-center trial in a new geographic population of subjects with diagnosed grades 2 and 3 OA of the knee.

Subjects and Methods

Study design

This study was a randomized, double-blind, placebo-controlled, multi-center, single-crossover study conducted in accordance with local regulations, the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP), and the Declaration of Helsinki at the following eight study sites: Istanbul University (Istanbul and Cerrahpaşa Schools of Medicine, (Istanbul, Turkey; sites 1 and 2, respectively); Ataturk University School of Medicine (Erzurum, Turkey; site 3); Ordu University School of Medicine (Ordu, Turkey; site 4); Adnan Menderes University School of Medicine (Aydın, Turkey; site 5); Marmara University School of Medicine, Pendik Training and Research Hospital (Istanbul, Turkey; site 6); Akdeniz University School of Medicine (Antalya, Turkey; site 7); Uludag University School of Medicine (Bursa, Turkey; site 8). Ethical approval was obtained from the respective Institutional Review Board at each study site. The study was registered at ClinicalTrials.gov (Identifier # NCT02291757). The subjects were recruited as they sought treatment at one of the participating medical centers. Written, informed consent was obtained from all participants before any study-related activities. Recruitment began in October, 2013 and was completed in May, 2015.

For the initial 30-day intervention, subjects were provided with either NEM (treatment group) or placebo. After the assessment on day 30, the placebo group was switched to NEM (single-crossover, also known as a wash-in design). At the end of 90 days, clinical evaluations were performed on two groups: one of which received NEM for 60 days (60-day treatment group, former placebo group) and the other of which received NEM for 90 days (90-day treatment group, original NEM treatment group).

Subjects

The study enrolled patients aged ≥ 40 years who were admitted to the Physical Therapy and Rehabilitation Clinics with the complaint of knee pain, had OA complaints lasting for 1-5 years, were diagnosed with knee OA according to the 2010 American College of Rheumatology and the European League against Rheumatism (ACR/EULAR) Classification criteria, and had grade 2 or grade 3 knee OA according to the Kellgren and Lawrence classification [27].

The following were the main exclusion criteria for this study: BMI > 35 kg/m²; diagnosed inflammatory syndromes such as rheumatoid arthritis, gout, pseudogout, Paget's disease, or chronic pain syndrome; severe chronic joint pain lasting for at least 3 months with a score of ≥ 80 according to the Western Ontario and McMaster Universities Osteoarthritis (WOMAC 3.1) Index [28]; known allergy to eggs or egg products; prior enrollment in any clinical study for the treatment of joint and/or connective tissue disorders in the previous 6 months; those who received any new study product in the previous 30 days; pregnant women or breastfeeding women. Patients who agreed to participate in the study but were receiving exclusionary drugs were deemed eligible to be included in the study following a 7-day wash-out period for analgesics and NSAIDs, and a 90-day wash-out period for steroids and nutraceuticals used for the treatment of joint and connective tissue disorders (e.g. glucosamine, chondroitin, methylsulfonylmethane, etc.). Only paracetamol was allowed for pain use during the study and was provided and tracked in the same manner as treatment capsules. All other pain treatments were excluded during the study period.

Randomization

The patients were randomly assigned to either the NEM or placebo groups, and were randomized centrally, according to their registration order, using a permuted-block randomization table consisting of 4 subjects per block with a constant ratio of 1:1 among all centers. The principal investigator, co-investigators, study personnel, study participants, and statisticians were blinded to the treatment until the completion of the 90-day study.

Study intervention

Natural eggshell membrane (NEM®) is produced by mechanical separation of the eggshell membrane from the eggshell of chickens, partially hydrolyzed, dry-blended, and ground to its final particle size. NEM is primarily composed of type I collagen fibrous proteins [29] and also contains glycosaminoglycans such as dermatan sulfate and chondroitin sulfate [30,31], hexosamines such as glucosamine, hexoses and fucose [32], and a substantial amount of hyaluronic acid [31]. Other constituents of eggshell membrane include sialic acid [31], desmosine and isodesmosine [33], ovotransferrin [34], lysyl oxidase [35], and lysozyme [36]. In addition, eggshell membrane has a high potential to contain bioactive peptides (or to produce them by selective hydrolysis), as it contains a considerable amount of protein.

NEM was administered in vegetarian capsules (500 mg, once daily po). Previous studies evaluating NEM in adult subjects with osteoarthritis established that the efficacious daily dose is 500 mg [19-21]. The placebo was provided in identical vegetarian capsules containing 500 mg of a comparable but inactive substance that was identical in appearance and other qualities to the NEM capsules. The patients were instructed to ingest the study capsules with water at breakfast. Treatment compliance was evaluated at clinic visits by counting any unused capsules. Paracetamol was allowed as rescue medication and was provided as part of the study. NEM ingredient was provided by ESM Technologies, LLC (Carthage, MO USA) without cost.

Clinical assessments

In addition to the demographic characteristics of the patients, their medical histories including current medications and physical

examination findings (i.e. general health, heart rate, respiration rate, blood pressure) were also recorded. The clinical assessment of OA was performed using the Likert version of the Western Ontario and McMaster Universities Osteoarthritis Index ((WOMAC; v LK3.1: Turkish language translation) and the measurement of joint range of motion (ROM) at baseline and on days 7, 30, and 90 of treatment. The WOMAC questionnaire consists of 24 questions divided into 3 subscales, Pain (5 questions, 0-20 total points), Stiffness (2 questions, 0-8 total points), and Function (17 questions, 0-68 points). The WOMAC sub-scores were summed to produce the WOMAC-total score (0-96 points). A lower score on any WOMAC scale denotes a better outcome. The patients were also questioned at each clinic visit about any adverse events that they may have had. All clinic assessments were performed a minimum of 24 hours following the most recent paracetamol dose, if applicable. The NEM and placebo groups were compared in terms of the findings on days 7 and 30. In the evaluations performed on day 90, the 60-day NEM treatment group was compared with the 90-day NEM treatment group.

Sample size estimation, statistical analyses and outcome measures

The primary end point was the difference between the NEM group vs. placebo group in the WOMAC-total score, assessed on day 30. To detect a 15% treatment effect (vs. placebo), we estimated that a sample size of 156 patients would be required to provide a statistical power of 80%, assuming a response rate of 20% in the treatment group and response rate of 5% in the placebo group, with a 5% dropout rate. Data analyses were performed using the IBM SPSS Statistics for Windows version 22.0 (IBM Corp, Armonk, NY USA). Descriptive statistics were expressed as a number and percentage for categorical variables, and as mean ± standard deviation (SD) for numerical variables. The Wilcoxon signed-rank test was used for normally distributed two group comparisons, whereas the Mann-Whitney U test was performed for two group comparisons for non-normally distributed variables. A P value of < 0.05 was considered statistically significant. To minimize missing data points due to dropouts for statistical calculations, the last observation carried forward (LOCF) approach was used for subjects for which at least one evaluation following the baseline visit was conducted.

Results

The trial enrollment flow diagram shows the assignment and progress of subjects during the study (Figure 1). A total of 208 candidates were assessed for eligibility by the 8 clinical sites, and 42 candidates were excluded. One-hundred-sixty-six (166) individuals qualified for randomization, with 83 assigned to the NEM group and 83 assigned to the placebo group. The distribution of the enrolled
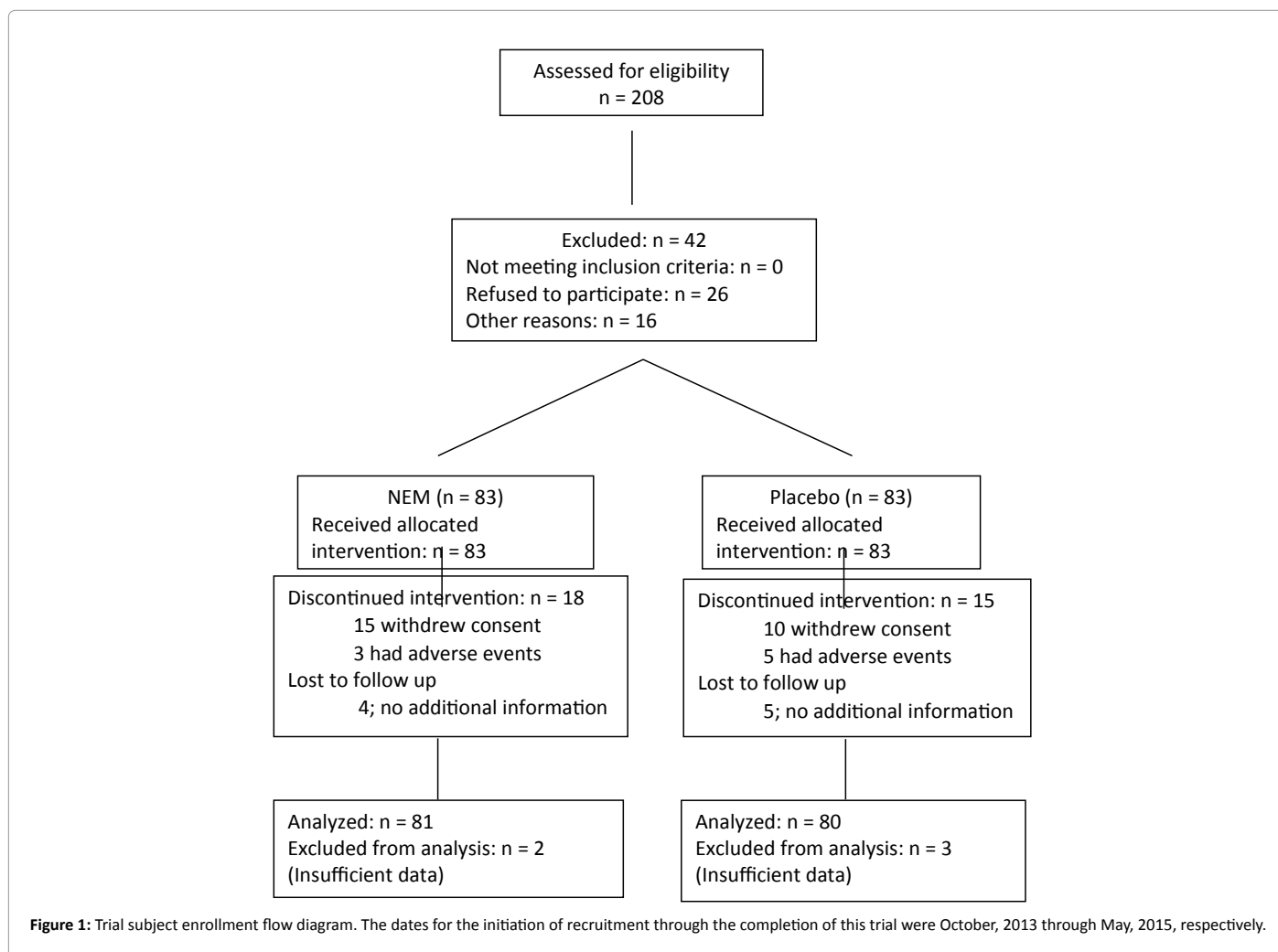

Figure 1: Trial subject enrollment flow diagram. The dates for the initiation of recruitment through the completion of this trial were October, 2013 through May, 2015, respectively.

subjects among the study sites was as follows: 16 (10%) were from site 1, 31 (19%) were from site 2, 22 (13%) were from site 3, 11 (7%) were from site 4, 16 (10%) were from site 5, 11 (7%) were from site 6, 22 (13%) were from site 7, 37 (22%) were from site 8. No serious adverse events were observed in the NEM treatment group, and there was no significant between-group difference in the number of adverse events reported (NEM, n=8; placebo, n=15). Thirty-four of the original 166 enrolled subjects dropped out during the study for unanticipated personal reasons (NEM, n=19; placebo, n=15), and 9 subjects were lost to follow-up (NEM, n=4; placebo, n=5). Table 1 shows the baseline demographic data for the enrolled subjects and indicates that both groups were statistically similar.

All clinical indices of OA were similar between the 2 groups at baseline (Table 2). The WOMAC-stiffness score at the end of the 7-day treatment period in the NEM group improved by approximately 24% from baseline (3.4 ± 1.7; within group P=0.004) and was significantly lower compared to the placebo group (NEM 2.6 ± 1.8; placebo 3.4 ± 2.0; P=0.034). Similarly, the WOMAC-pain score at the end of the 7-day treatment period in the NEM group improved by approximately 22% from baseline (10.1 ± 4.1; within group P=0.001). No between-group differences were observed in this or the other clinical indices.

After 30 days, WOMAC-pain and WOMAC-stiffness in the NEM group had improved from baseline by 33% and 35%, respectively (within group P both<0.001). All WOMAC-based indices, including the primary outcome measure (WOMAC-total) were significantly lower in the NEM group compared to placebo: WOMAC-total (Absolute Treatment Effect 14.9%, P=0.004); WOMAC-pain (Absolute Treatment Effect 12.3%, P=0.023); WOMAC-stiffness (Absolute Treatment Effect 18.2%, P=0.001); WOMAC-function (Absolute Treatment Effect 15.2%, P=0.001) (Table 2). No between-group differences were observed for range of motion (angles of flexion or extension).

After 90 days, final clinical assessments were performed on the original NEM group (90-day NEM) and the original placebo group (60-

Parameter	NEM (n=83)	Placebo (n=83)	P
Age, years	55.9 ± 11.9	58.5 ± 9.7	0.156
Gender			
Male (%)	12 (14.5)	20 (24.1)	0.168
Female (%)	71 (85.5)	63 (75.9)	
Race			
Caucasian (%)	83 (100)	83 (100)	-
Weight (kg)	76.9 ± 11.4	78.0 ± 11.2	0.531
Height (m)	1.6 ± 0.1	1.6 ± 0.1	0.734
BMI, kg/m2	29.4 ± 3.7	29.5 ± 3.3	0.668
Smoking			
Present (%)	30 (36.1)	32 (38.6)	0.873
Absent (%)	53 (63.9)	51 (61.4)	
Alcohol consumption			
Present (%)	1 (1.2)	1 (1.2)	1
Absent (%)	81 (98.8)	81 (98.8)	
Blood Pressure (mm Hg) systolic /	127.1 ± 12.4 /	127.4 ± 16.4 /	0.133
Diastolic	80.9 ± 14.3	79.9 ± 8.9	0.782
Heart Rate (beats per minute)	78.3 ± 7.7	80.2 ± 8.3	0.135
Respirations (breaths per minute)	16.5 ± 3.3	16.4 ± 2.9	0.919
Oral Temperature (°C)	36.7 ±0.6	36.7 ± 0.5	0.398

Data are presented as the actual number (% total number) or mean ± standard deviation, where appropriate. Abbreviations: BMI: Body Mass Index; calculated as weight in kilograms divided by the square of height in meters

Table 1: Baseline demographic characteristics of enrolled subjects.

Time Index	NEM	Placebo	P
Baseline	**(n=83)**	**(n=83)**	
WOMAC-total	42.4 ± 20.0	47.7 ± 23.9	0.123
WOMAC-pain	10.1 ± 4.1	10.8 ± 5.2	0.551
WOMAC-stiffness	3.4 ± 1.7	4.1 ± 2.0	0.105
WOMAC-function	28.9 ± 14.2	32.8 ± 16.7	0.107
Angle of flexion	127.2 ± 12.1	125.1 ± 14.1	0.481
Angle of extension	0.2 ± 3.7	2.2 ± 21.7	0.643
Day 30	(n=81)	(n=80)	
WOMAC-total	32.8 ± 18.7	44.0 ± 22.8	0.004
WOMAC-pain	6.8 ± 4.0	8.6 ± 5.0	0.023
WOMAC-stiffness	2.2 ± 1 .7	3.4 ± 2.1	0.001
WOMAC-function	23.8 ± 13.0	32.0 ± 15.7	0.001
Angle of flexion	128.7 ± 10.7	126.6 ± 12.7	0.529
Angle of extension	2.5 ± 22.6	2.7 ± 22.6	0.811

Data are presented as mean ± standard deviation. Abbreviations: WOMAC: The Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2: Clinical Indices of OA in NEM and Placebo Groups at Baseline and Day 30.

day NEM). Addition of NEM to the original placebo group resulted in a marked clinical improvement, as judged by the lack of between-group statistical significance in the WOMAC-total, WOMAC-pain, and WOMAC-stiffness scores (P=0.193, P=0.140, P=0.079, respectively). This difference was due to improved WOMAC scores in the original placebo group, and not due to any apparent reduction in efficacy in the original NEM group. The difference in WOMAC-function score remained statistically different between the original NEM group and the original placebo group (P=0.002). No between-group differences were observed for the range of motion.

A responder analysis was performed in the two groups. Interestingly, the number of patients having at least a 15% decrease in WOMAC-pain score was greater in the 90-day NEM group (71% of subjects) compared to the 60-day NEM group (53% of subjects; P=0.025). Similarly, the number of patients having at least a 20% decrease in WOMAC-stiffness score was greater in the 90-day NEM group (48% of subjects) compared to the 60-day NEM group (30% of subjects; P=0.022).

Safety and tolerability

Overall, the treatment was well tolerated by the patients, with no between-group statistical difference in adverse events. There was a total of 8 (9.6%) adverse events (AEs) reported in the NEM group, and none were deemed serious by study investigators. Three AEs (i.e. rash, nausea) were judged to be related to the study material, perhaps due to undiagnosed egg allergy. There were a total of 15 (18.1%) AEs reported in the placebo group; 3 of these were serious AEs. Three AEs in the placebo group were believed to be related to the study material. Rescue medication (paracetamol) use was comparable (~50.0% utilization rate) between the two groups. Treatment compliance was excellent, as judged by approximately 92% of the original NEM group and 88% of the original placebo group returning fewer than 10 of the allocated capsules.
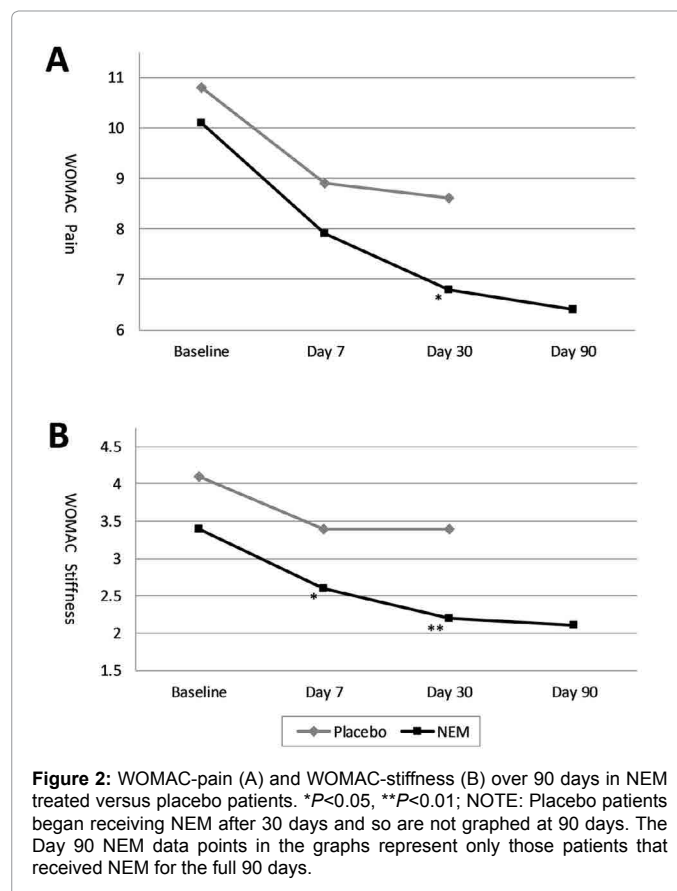
Discussion

NEM was used at a dose of 500 mg/day to assess its efficacy and safety in patients with grade 2 and grade 3 knee OA. The principal finding of this study was the rapid (7 days) and persistent (through day 90) clinically meaningful improvement in validated indices (WOMAC scores) of OA, in subjects with moderate-to-severe OA of the knee who

were taking NEM (compared to placebo). Specifically, in the NEM group, the WOMAC-stiffness score was significantly reduced at day 7 and, by day 30, all major WOMAC indices (total, pain, stiffness, and function) including the primary outcome measure (WOMAC-total) were significantly improved. As has been reported previously [19], continuation on the NEM regimen increases the number of responders along with the overall magnitude of the clinical improvement. In this study, the percentage subjects experiencing greater percent decreases in the WOMAC-pain score was significantly greater in the 90-day NEM group compared to those in the 60-day NEM group. Thus, there appears to be a positive correlation between the duration of exposure to NEM, the number of responders, and the overall magnitude of effect.

Despite a significant within-group improvement at 7 days in the NEM treatment group for WOMAC-pain (-22% from baseline), there was no difference when compared to placebo. There have been a number of prior open-label clinical studies evaluating NEM in subjects with various joint and connective tissue disorders: two in the United States (U.S.) (n=11; n=28) [18], one in Germany (n=44) [20], and one in Italy (n=25) [21]. There has also been an RCT evaluating knee OA in the U.S. (n=67) [19]. These prior studies reported significant clinical improvements within 7-10 days with regard to reducing joint pain, ranging from 15.9% to 40.6%. Although the present study had a similar treatment effect size, rapid results may have been obscured by the greater severity of knee OA in our study. This is supported by the fact that WOMAC-stiffness had a similarly sized within-group treatment effect (-24% from baseline) that was also significantly different from placebo (P=0.034). It is mechanistically consistent that stiffness would be affected earlier than pain, as the swelling from localized inflammation is reduced. The prostaglandins that are involved in pain sensation are produced as a result of inflammation and so would take more time to resolve once inflammation diminishes. So it may be that WOMAC-pain would have reached statistical significance by 10 days as was seen in a number of the previous clinical trials mentioned above.

At the end of the placebo-controlled portion of the trial (Day 30), there was a marked difference in improvement in pain and stiffness, two symptoms of OA critically important to treat. NEM improved WOMAC-pain and WOMAC-stiffness by absolute treatment effects of 12.3% and 18.2%, respectively. These results are very consistent with 30-day absolute treatment effects found in a prior randomized controlled trial (RCT) of 67 subjects conducted in the United States (pain 10.3%; stiffness 16.8%) [19]. Our results from this much larger, multi-center study now confirm the results found previously with NEM, despite the fact that we included patients with moderate to severe knee OA. Treatment options are limited for Grade 2/3 OA, so the results presented here for a natural, non-prescription intervention like NEM are quite remarkable.

Comparison of the subjects receiving NEM for 60 versus 90 days revealed a number of noteworthy items. Of greatest importance is that NEM continued to improve WOMAC-pain and WOMAC-stiffness in the group that received NEM continuously for 90 days (Figure 2A and 2B), albeit at a reduced rate of improvement compared to earlier in the trial. The majority of symptomatic (pain & stiffness) improvement appeared to occur within the first 30 days of treatment; however, symptoms continued to improve through 90 days of treatment. This is the first RCT to evaluate NEM for this length of time and it would appear that maximal efficacy for NEM is reached around 3 months of use. Secondly, the crossover of the placebo group to NEM treatment after 30 days served as an internal check on the validity of NEM's efficacy beyond that of the placebo effect. That is, the fact that there

Figure 2: WOMAC-pain (A) and WOMAC-stiffness (B) over 90 days in NEM treated versus placebo patients. *P<0.05, **P<0.01; NOTE: Placebo patients began receiving NEM after 30 days and so are not graphed at 90 days. The Day 90 NEM data points in the graphs represent only those patients that received NEM for the full 90 days.

was a statistically significant difference between subjects taking NEM for 60 days versus those taking NEM for 90 days supports that the improvements from NEM are real, as surely the placebo effect would have diminished substantially if not completely after 4 weeks in patients with moderate to severe OA.

No improvement in either flexion or extension range of motion evaluation was observed in this study. Within the context of significant reductions in both pain and stiffness, it is reasonable to have expected a concomitant improvement in joint flexibility. Yet this was not the case. This might be attributable to the more severe OA burden in theses study patients, the evaluation of only the knee in this study vs. other joints in the previous open-label study [18], or possibly due to a difference(s) in how range of motion was measured in the current vs. previous studies.

As has been reported in previous clinical studies [18-21], NEM was safe and well tolerated in the current study with no occurrence of serious adverse events or any observed difference in total number of between-group AEs. This confirms in humans what had previously been reported through *in vitro* and *in vivo* toxicity studies [37]. From a regulatory perspective in the U.S., NEM is generally recognized as safe (GRAS), with an allowable daily intake of up to 14 grams, enabling its inclusion in multiple delivery formats for foods, beverages, and dietary supplements.

The overall drop-out rate (25.3%) was greater than estimated (5%) in the sample size calculation. However, trial recruitment (166) exceeded the calculated sample size (156) by 6% and the estimated net treatment effect (15%) used in the sample size calculation was similar to the actual net treatment effect for WOMAC-pain (12%) and was

exceeded for WOMAC-stiffness (18%). These facts likely helped to mitigate the increased dropout rate and may partially explain why a treatment effect for WOMAC-stiffness was able to be detected at just 7 days. Dropouts were evenly distributed between the NEM group (n=22; 26%) and the placebo group (n=20; 24%) with no obvious differences in the reason for dropping out. Many of the patients had to travel a fair distance to the regional medical centers to participate in the study and there were 6 clinical visits, so this may have contributed appreciably to the increased drop-out rate.

The present study had a number of strengths and limitations. Major strengths of the study include the use of a large number of subjects (n=83 per group) with well-characterized OA of the knee, thus affording the appropriate statistical power. The use of a placebo group for the initial 30-day evaluation period along with the utilization of 8 individual study centers substantially minimized the possibility for experimental bias in evaluating the potential clinical benefit for NEM. Another strength of this study was the use of a well-validated clinical index of OA, namely the WOMAC index [38]. There are over 200 citations (primary studies, reviews, etc.) reporting the successful use of this self-reported health questionnaire in multiple clinical settings including OA. The major limitations of this study were the failure to include a third arm of the study evaluating a reference intervention (e.g. standard of care) for comparison, or any serum/urinary biomarker(s) of cartilage metabolism. However, these added features of the study were beyond the scope of this particular study, which was simply to evaluate NEM in a well-defined clinical population, using a large sample size spread across multiple study centers.

Conclusions

This is now the sixth clinical trial involving NEM and the largest trial to date. The therapeutic benefits reported in each of these geographically-diverse trials, including the present study, have been consistent and reproducible. Taken together, the use of NEM in the context of OA consistently yields statistically significant and clinically meaningful results. The combination of quick symptom relief (7 days) coupled with continuing long-term relief (90 days) is impressive from a food-based ingredient, and should be clinically beneficial for those suffering from OA. NEM can be considered as a safe, cost-effective, natural intervention for inclusion as part of comprehensive clinical protocol in the management of patients with knee OA, even in patients with more severe grade 2 and 3 OA.

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