Randomized observational multicenter study to assess the efficacy and safety of the association of Fortigel (10 Gr) and Fucoidan (100 Mg) in patients with Gonarthrosis

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Abstract

Purpose: In order to further elucidate the efficacy and safety of some nutritional supplements on gonarthrosis, we have conducted a preliminary randomized multicenter (n=9) observational study comparing the effects of an association of Fortigel® (10 gr) and Fucoidan (100 mg) (ACTEN®) versus another commonly therapeutically used formulation based on Glucosamine (500 mg), Chondroitin Sulfate (400mg) hyaluronic Acid (50 mg) and Vitamin C (100 mg) (COMBIART).

Patients and methods: The protocol was administered over a 12-weeks period in a population (n=126) aged 40-65 years, with diagnosed mild-to-moderate osteoarthritis (OA) of the knee (grade 2-3 of Kellgren Lawrence grading scale). Safety was measured by closely monitoring adverse events. Efficacy was measured by grading evaluations, at basal, 1 month and 3 months controls, of the Visual Analog Scale (VAS) and the Lequesne algofunctional index for severity of osteoarthritis (LAI) for articular functionality.

Results: Both groups showed an important reduction (P < 0.0001) in the mean visual analog scale values at T1 (28.5% ACTEN®, 21.3% COMBIART at 1 month) and T3 (49.4% ACTEN®, 40.1% COMBIART at 3 months), as well as a marked reduction in the Lequesne algofunctional index means (P < 0.0001) (ACTEN® 28.9% T1 44.9% T3, COMBIART T1 21.3% T3 37%). The effect seems to be time dependent, as the mean values decrease further for both parameters from T1 to T2 (P < 0.0001, for VAS for both groups; P 0.0011 for ACTEN® group, P 0.0064 Control group for LAI). No statistically significant difference was found between the ACTEN® group and the COMBIART group at time T1 or T3. These interesting preliminary data will be further investigated on a larger scale.

Conclusions: Fortigel® (10gr) and Fucoidan (100 mg) (ACTEN®) taken as oral nutritional supplements have a significant impact as therapeutic intervention for knee osteoarthritis as indicated by the marked decrease in VAS and LAI values over the course of the treatment. A similar effect, as expected, has been confirmed in the COMBIART group, and no statistically significant difference has been detected between the two groups.
Clinical management of pain and structural improvements [19]. Chondroitin sulfate coupled to Glucosamine, or by itself, has been the center of significant studies [20], but many other compounds synthetic or natural have been investigated, including Vitamin C [21–25]. Particular interest has been paid to Collagen hydrolysates (CHs) and Fucoidans [26–44]. CH is obtained by the enzymatic hydrolysis of collagenous tissues from mammals. The main characteristic of CH is its amino acid composition, which is identical to type II collagen, thus providing high levels of glycine and proline, essential amino acids for the stability and regeneration of cartilage [28]. This product is recognized as a safe food ingredient by regulatory agencies. CH is well digested and is preferentially accumulated in cartilage [29]. Clinical use of CH has not been associated with adverse effects, aside some gastrointestinal side effects, such as fullness or unpleasant taste.

Fucoidans, on the other side, are a class of sulfated, fucose-rich polymers found in several types of brown macroalgae [41,42] used in a variety of different medical conditions [38]. Several recent studies indicate a role of fucoidan in addressing the symptoms of osteoarthritis. Animal models of collagen induced arthritides showed that orally administered fucoidans successfully inhibited pain [39]. In a small human clinical study osteoarthritis symptoms were inhibited by 12 weeks oral administration of fucoidan rich seaweed extracts by 52% [40]. There was no reduction in TNF alpha as inflammation marker, but an accompanying study in healthy volunteers showed a decrease in Interleukin 6, a marker for chronic inflammation [43]. Fucoidan’s effect on pain has been linked to its selective blockade on neutrophils accumulation [44,45].

In order to test the clinical efficacy of the combined use of these compounds, CH (Fortigel® 10 gr.) and Fucoidan (100 mg) (ACTEN®), we have designed a preliminary multicenter randomized clinical trial. Testing its clinical efficacy against another formulation used in clinical practice, based on well-known substances: Glucosamine (500 mg), Chondroitin Sulfate (400 mg) hyaluronic Acid (50 mg) and Vitamin C (100 mg) (COMBIART).

Material and methods

This trial was designed as a randomized preliminary study. It was conducted over 12 weeks (84 days) by a single research group in nine centers (Lazio and Sardinia regions, in Italy) between Oct 2015 and May 2016 and involved 126 participants aged 40-65 years, with mild-to-moderate osteoarthritis (OA) of the knee (grade 2-3 of Kellgren Lawrence grading scale).

Individuals were excluded from the study if they 1) were aged 39 years or younger at the start of the study; 2) had rheumatoid or other forms of arthritis; 3) had joint pain as a result of nerve or muscle damage, accidents, falls, trauma, etc. (4) had comorbidities often associated with osteoarthritis, such as diabetes, cardiovascular disease, elevated cholesterol requiring medical intervention, renal insufficiencies, asthma, or hypertension requiring medical intervention; 5) had cancer within the prior 5 years; 6) were taking any other herbal product or other supplement for pain or inflammation of joints health, such as glucosamine/chondroitin/methylsulfonylmethane, S-adenosylmethionine, or omega-3; 7) were smokers; 8) were heavy alcohol consumers; 9) were pregnant or nursing women; 10) had shellfish allergies; and 11) had a BMI lower than 18.5 (underweight) or greater than 40.0 (morbidly obese) or a body weight exceeding 225 lbs (102 kg). The demographics of the patient population are listed in Table 1.

Intervention

Participants underwent a 4-week washout period during which they stopped taking all dietary supplements for bones, joints, and inflammation as well as non-prescription drugs.

Prescription drugs that were not related to joint health were allowed, as was OTC rescue medication that was taken only on an as-needed basis. Participating individuals were also asked not to change any aspects of their lives during the 4-week trial. Lifestyle variables were unaltered, including but not limited to diet, fitness regimens, work and family-related tasks.

Participants who passed the initial screening at the baseline appointment were provided with one of the two randomly assigned nutritional supplements (ACTEN® or COMBIART), paper copies of a visual analog scale (VAS) questionnaire and the Lequesne algo-functional index (LAI). Each participant was asked to fill out the baseline VAS and LAI questionnaire and return it to the investigator before beginning to take the supplements. The supplements were consumed daily for both groups for the first month. The remaining eight weeks ACTEN® group used the supplement every other day, while COMBIART continued on a daily basis.

Data were collected again at 1 month and 3 months (12 weeks). This approach was chosen to reflect the higher absorption of gel (ACTEN®) compared to capsules (COMBIART) [46].

Outcome measures

A VAS scale of 0 to 10 for pain, and the LAI scale of 0 to 24 for pain and functionality were employed to evaluate the 2 measures before and after 4 and 12 weeks of supplementation. VAS scores were reported by asking the participants to mark responses on a 10-cm line. The line contained both end anchor points and 3 additional descriptors that were evenly spaced along the VAS scale at 2.5-cm intervals to help orient the participant. Definitions for the descriptors for each scale are listed in Table 2.

At baseline evaluation, participants were told to notify the research team immediately if any mild, moderate, or severe adverse events occurred during the period of supplementation. During the 1 month follow-up, and again at 3 months participants were once again asked whether they had experienced any adverse events or required any form of rescue treatment (pain or anti-inflammatory drugs) during the supplementation period. No complaints were reported.

| VAS Value (cm) | Pain Level |
|---------------|------------|
| 0             | None       |
| 2.5           | Mild       |
| 5             | Moderate   |
| 7.5           | Severe     |
| 10            | Worst possible |

| Population | Age | SD |
|------------|-----|----|
| Men        | 57.10 | 8.04 |
| Women      | 48   |    |
| VAS cm     | Mean 6.595 | SD 1.318 |
| LAI (Lequesne index) | Mean 10.595 | SD 3.519 |
The criteria for mild, moderate, and severe adverse events were as follows: (1) mild: an adverse event that does not interfere with usual day-to-day activities and requires no special intervention or treatment; (2) moderate: an adverse event that can affect usual daily activities and that can be addressed with simple therapeutic treatments; (3) severe: an adverse event that requires therapeutic intervention.

Statistical analysis

Data gathered from the VAS and LAI questionnaires underwent statistical analysis using a 2-tailed, paired t test to test baseline versus T1 (1 month) and T2 (3 months) for both treatments. Data were cross-analyzed using a 2-tailed non-paired t test to compare efficacies. The analyses were performed with the Graphpad PRISM statistical analysis software, version 5.0 (La Jolla, CA, USA). The alpha that was used for statistical significance was 0.05.

Results

Of the 126 participants enrolled in the study, none withdrew or were removed due to medical complications or lack of compliance with the study’s protocol. In comparison with baseline, the results for all participants at the end of the 4/12 weeks for all measures were statistically significant. The ACTEN® group showed a 28.5% decrease in joint pain at 1 month (T1), from a mean VAS score of 6.68 (1.38SD) at baseline to 4.77 (1.98SD) ($P = 0.0001$; 95% CI, 1.57, 2.25) and a -49.4% at T3, mean VAS 3.38 (1.78SD) ($P = 0.0001$; 95% CI, 2.95, 3.65). LAI was also reduced by -28.9% at T1, from a mean baseline of 11.28 (3.69SD) to 8.01 ($P = 0.0001$; 95% CI, 2.72, 3.82) and by -44.9% at T3 mean LAI 6.21 (3.01SD) ($P = 0.0001$; 95% CI, 4.42, 5.71).

The COMBIART group showed a 21.3% decrease in joint pain, from a mean VAS score of 6.5 (1.25SD) at baseline to 5.11 (1.53SD) at T1 ($P = 0.0001$; 95% CI, 1.09, 1.69) and a -40.1% at T3 mean VAS 3.89 (1.81SD) ($P = 0.0001$; 95% CI, 2.97, 4.33). LAI is again reduced by -21.3% at T1 from a mean baseline of 9.84 (3.18 SD) to 7.74 (3.08 SD) ($P = 0.0001$; 95% CI, 1.63, 2.57) and by -37% at T3, mean LAI 6.19 (3.04 SD) ($P = 0.0001$; 95% CI, 2.97, 4.33).

The ACTEN® group seems to work more efficiently than the COMBIART group (VAS T3 means -49.4%/-40.1%; LAI T3 means -44.9%/-37%), but no statistically relevant significance has been detected comparing the two groups [Figure 1-4].

Summary of adverse effects

No adverse effects were reported during the study.

Discussion

Osteoarthritis is the most common form of arthritis in Italy and in the USA [47]. Glucosamine and chondroitin sulfate and hyaluronic acid are natural substances present in and around cartilage cells and, as such, are the most commonly used natural supplements for OA and joint pain. Previous studies have found them to be effective and safe for addressing the symptoms of OA [48,49]. In particular, the Glucosamine/Chondroitin Arthritis Intervention Trial in 2006, sponsored by the National Institutes of Health (NIH), found that glucosamine combined with chondroitin sulfate provided statistically significant pain relief for a subset of participants in comparison with a placebo [20].

In this study we have evaluated the clinical safety and efficacy of ACTEN® (CH 10gr and Fucose 100 mg) and compared it with a supplement (COMBIART) based on the well-studied effects: glucosamine, chondroitin sulfate, hyaluronic acid and the added value of Vitamin C [21]. As expected the COMBIART group showed a
marked reduction in pain and functionality indexes. The decrease in pain and functionality is established in the first 4 weeks of treatment (-21.3% for both VAS and LAI) and is further increased in the following weeks, up to a -40.1% in VAS and -37% in LAI at T3 (12 weeks). ACTEN® showed similar results, with a reduction in VAS and LAI at T1 of 28.5% and 28.9% respectively. Again, the highest efficacy is reached with prolonged exposure, reaching a -49.4% in VAS and -44.9% in LAI at T3. Notably the ACTEN® group in the last 8 weeks only assumed the nutritional supplement once every other day, without any loss of efficacy. No statistically relevant difference has been found between the two groups, but larger numbers or prolonged exposures to the supplements might uncover subtler differences.

It has to be taken in consideration that, a daily regimen of ACTEN®, instead of every other day regimen as used in this trial, it is likely to produce further benefits, and it should be investigated.

Conclusions

Both nutritional supplements (ACTEN® and COMBIART™) are safe, well tolerated, and able to exert an important pain reduction and improved functionality in the OA of the knee. Further studies are required to establish pathways for the shown efficacy in pain reduction and radiological studies to check on the structural changes behind the improved functionality of the articulation.

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