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Methylsulfonylmethane and boswellic acids versus glucosamine sulfate in the treatment of knee arthritis: Randomized trial

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Abstract

Until now glucosamine sulfate (GS) has been the most widely used supplement and has been shown to be efficacious in the treatment of osteoarthritis (OA). Methylsulfonylmethane (MSM) and boswellic acids (BA) are new effective supplements for the management of inflammation and joint degeneration, according to previous experimental studies. The aim of our study is to test the effectiveness of association of MSM and BA in comparison with GS in knee arthritis.

In this prospective randomized clinical trial, MEBAGA (Methylsulfonylmethane and Boswellic Acids versus Glucosamine sulfate in the treatment of knee Arthritis), 120 participants affected by arthritis of the knee were randomly assigned to an experimental group (MB group) or a control group (GS group) treated for 60 days with 5 g of MSM and 7.2 mg of BA or with 1500 mg of GS daily, respectively. At the 2-month (T1) and 6-months (T2) follow-up , the efficacy of these two nutraceuticals was assessed using the visual analog pain scale (VAS) and the Lequesne Index (LI) for joint function, along with the use of anti-inflammatory drugs (non-steroidal anti-inflammatory drugs and anti-cyclooxygenase-2).

The repeated measures ANOVA analysis shows that for VAS, LI, and the use of anti-inflammatory drugs scores there are improvements due to the time in the two groups (respectively, $F = 26.0$; $P < 0.0001$; $F = 4.15$; $P = 0.02$; $F = 3.38$; $P = 0.04$), with a tendency to better values for the MB group at T2.

On the basis of these preliminary data, we could support the efficacy of the MSM in association with BA in the treatment of OA. These results are consistent with the anti-inflammatory and chondroprotective effects previously occurred in experimental studies. This new combination of integration (MSM and BS) has presented good results and satisfactory in comparison with GS, until now the cornerstone of the treatment of arthritis in according to guidelines.

Keywords

boswellic acid, glucosamine, knee, methylsulfonylmethane, osteoarthritis

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Introduction

Osteoarthritis (OA) is the most common disease affecting the joints. It is a chronic degenerative disease originated from imbalance of catabolic and anabolic phenomena in cartilage tissue and it is characterized by periods of remission and inflammation.[1] Therapy should be anti-inflammatory and aim at cartilage protection. This could include: lifestyle modification, pharmacological treatment, physical therapy, and surgery.[2] Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to control OA symptoms. However, they are associated with gastro-intestinal and cardiovascular side effects, and other adverse health effects.[3] Due to safety concerns related to these drugs, patients have turned to dietary supplements that claim to be safer in the long-term treatment of OA.[4] Among biological agents, glucosamine sulfate (GS) seems to be most promising.[5] Glucosamine scored the highest level of evidence and strength of recommendation for knee OA symptoms in the current European League Against Rheumatism (EULAR) practice guidelines,[6] and it is recommended by the latest Osteoarthritis Research Society International (OARSI) guidelines.[7]

In clinical practice, other nutraceuticals are administrated in the management of OA. These include methylsulfonylmethane (MSM) and boswellic acids (BA), both of which have been examined in previous studies.[8–14] Until now no clinical studies have been made to compare the clinical efficacy of MSM and BA versus GS in knees OA. The aim of the present investigation is to characterize better the symptomatic activity of MSM and BA in patients with OA of the knee, in comparison with the commonly prescribed GS.

Materials and methods

This prospective, randomized controlled trial, MEBAGA (for "Methylsulfonylmethane and Boswellic Acids vs. Glucosamine Sulfate in the Treatment of knee Arthritis") was aimed at assessing the comparative effect of 5 g of MSM and 7.2 mg of BA, administered in the commercial formulae Lignisul® and Triterpenol® (Artrosulfur C, Laborest Italia S.p.A., Nerviano, Milan, Italy) twice a day, respectively, versus 1500 mg of GS (Dona, sachets 1500 mg, Glucosamine sulfate, Rottapharm Ltd., Ireland) once a day. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of General Hospital of Bari (authorization no. 104/C.E. of 4 February 2013). Informed consent to take part was given by all participants. The knee was the chosen anatomical site to assess the efficacy of the active ingredients administered.

The inclusion criteria were as follows:

- a diagnosis of OA of the knee according to the criteria of the American College of Rheumatology;[15]
- grade 3 Kellgren and Lawrence radiographic staging,[16] in which the severity of the arthritis is assessed on a scale in the range of 0–4, hypothesizing a sequential evolution from the manifestation of osteophytes through a reduction in the width of the joint space, to subchondral sclerosis and finally the formation of cysts;
- frequent joint pain (several days a week) for at least 6 months before recruitment;
- pain in the knee, scored at least 4 cm on a 10 centimetric visual analogic scale (VAS) (from moderate to severe pain), where 0 means no pain and 10 is the worst pain possible;[17]
- a score of >2 on the Lequesne pain-function index (LI).[18] The LI is an OA-specific validated questionnaire that poses a series of questions about pain in the knee (five questions on a scale from 0 to 2, where 0 indicates no pain and 2 intense pain), functional limitation (four questions, using the same scale), and maximum walking distance (one question, with a score from 0 to 6, where 0 indicates the ability to walk for an unlimited distance and 6, the inability to cover 100 m). The maximum worst final score is 24.

Lack of symptoms in other joints was not taken into consideration.

The exclusion criteria were as follows:

- previous surgery of the affected knee;
- disease processes such as rheumatoid arthritis, autoimmune diseases, systemic diseases, and tumors;
- severe obesity (BMI >40 kg/m^2);
- meniscal or ligament injuries;
- allergy to shellfish;

- altered blood chemistry and kidney, liver, and metabolic (diabetes mellitus) function;
- intra-articular hyaluronic acid/cortisone infiltrations to the affected knee within 3 months before the start of the study;
- systemic cortisone treatment taken within 3 months before the start of the study;
- supplements (glucosamine, chondroitin sulfate, bromeline, etc.) taken within 3 months before the start of the study (patients were also informed that they were not to be taken for the following 6 months).

A 7-day wash-out period for anti-inflammatory drugs was stipulated before the first recruitment visit.

Recruitment and randomization

The required study population was 120 patients affected by gonarthrosis. The participants were enrolled from the University Hospital of Bari. Patients were randomized into two groups; the first taking the MSM and BA (MB group) and the second taking the GS (GS group), each consisting of 60 patients. Considering that advanced age, female gender, and smoking are negative prognostic factors for OA, we adopted the following randomization criteria: sex (female/male), age (</=60 and >60 years), smoker (yes/no). The clinician (VP) who conducted the patients' recruitment and monitoring processes was blinded to the treatment administered (MB or GS), as the randomization was performed by a different physician (AN). At recruitment, two homogeneous groups (determined by sex, age, and smoking habit) were randomly created. All patients had a clinical examination performed by an experienced knee surgeon, a specialist in general orthopedics, and a fourth-year resident. A 40 cm, 360° goniometer was used, marked in 1° increments, with two adjustable overlapping arms.

Study protocol

The study protocol included a clinical visit, medical history, and assessment using the VAS and LI at the time of recruitment (T0) and at the two follow-up visits, at 2 months (T1) and 6 months (T2). If the patients complained of pain, they were allowed to take 500 mg of paracetamol, 20 mg of pyroxicam, or 50 mg of diclofenac, and the investigator postponed the clinical evaluation after a period of at least five times the half-life of the drug. Patients were asked to write down their use of NSAIDs and anti-COX-2 in a diary; the mean quantity of anti-inflammatory drug tablets/day was evaluated.

Pharmacological treatment

The patients were divided into two groups. The first group (MB group; 60 patients) was treated with two daily sachets containing 2.5 g of MSM, 3.6 mg of titered BA, and vitamin C. The active ingredient has been commercially available since 2013 (Artrosulfur C®, Laborest Italia S.p.A.). The purity of MSM was estimated by high resolution gas chromatography to be 99.9%.[19] The alpha and beta BAs were obtained by electromagnetic field extraction, resulting in the formation of free-form synergic macromolecular triterpene complexes. In the second group (GS group; 60 patients) the patients were treated with 1500 mg of glucosamine sulfate (Dona sachets 1500 mg Glucosamine sulfate, Rottapharm Ltd., Ireland) once a day. The possible side effects of GS, MSM, and BA are gastrointestinal disorders, skin rash, and hypersensitivity reactions in allergic individuals. All participants were asked to take the treatment for 60 days.

Outcomes measures

The primary outcome measure was the response to treatment, defined as a decrease of pain on the VAS and an improvement in the patient's global assessment score on the LI from baseline at the first follow-up, and last follow-up at 6 months. The secondary endpoint was a reduction in the patients' need to take anti-inflammatory drugs. All analyses were performed at each follow-up, comparing results within each group and between the two groups. Because the randomization had taken into account only age, sex, and smoking habit, it was hypothesized that at subsequent follow-ups there might be a post-randomization imbalance in the clinical evaluations between the two groups.

Sample size

The sample analysis of the study was conducted on the primary outcome of the study, i.e. the pain, expressed as VAS, given the presence in literature of previous studies on the therapeutic effect of

Boswellia serrata and MSM on knee arthritis.[9–14,19,20] Starting from two homogeneous groups determined by the mean value of VAS at baseline, we hypothesized a difference of two units, with ± standard deviation (SD) of two units, in the mean VAS value between the two groups, at T1. We established a margin of error of 5% and confidence intervals (CIs) of 95%; power calculation was carried out with the Raosoft sample size calculator. This yielded a minimum number of participants per group of 26.

Statistical analysis

For each participant enrolled we completed a file where we put in anagraphic variables and results at the different follow-ups. The files were then put in a database using File Maker Pro and we used STATA MP11 software to analyses the data. Continuous variables are expressed as means and SDs, and categorical variables as proportions and 95% CIs. The chi-square test was used to compare categorical variables.

The means of the LI and VAS scores within the two groups were compared by student's t-test for independent samples. To compare mean LI and VAS values in the two groups at recruitment and the different follow-ups, student's t-test for paired samples was employed. In order to evaluate the differences between T0, T1, and T2 in each group, the ANOVA model for repeated measures was performed. To evaluate confusion factor linked to gender, age, weight, group, laterality, manual work, smoking habit, value of variable measured at T0, T1, and T2 a multivariable regression model and a multiple logistic regression model (with reference to NSAIDS and anti-COX-2 administration) were built.

Given the relatively small sample size, we also relied on Cohen's d, a measure of effect size, to describe differences between the groups. We considered a range of 0.20–0.40 a small effect, a range of 0.40–0.80 a medium effect, and >0.80 a large effect. Significance was set at a value of $P < 0.05$.

Results

Of the 120 participants recruited into the study, 112 (n = 54 MB group and n = 58 GS group) completed all aspects of the study. Participants dropping out of the study (n = 6 from MB group; n = 2 from GS group) cited health issues (n = 6) or not liking the supplementation regimen (n = 2). Compliance for both treatments was good. All 112 patients have completed treatment. The detailed demographic and baseline clinical characteristics between the two groups is shown in Table 1. There were no significant differences between the two groups. Patient characteristics are compared between groups in Table 1, with no significant group differences measured. There were no harms or unintended effects in each group.

For the primary outcomes the pain severity (VAS score) was significantly reduced in the two groups at the follow-ups (F = 26.0; $P < 0.0001$), with a tendency to a better value for the MB group at T2 (F = 3.19; $P = 0.08$) (Table 2). Comparison between the VAS scores at T0 and T1 showed worse mean value in MB group (respectively, d = 0.76, d = 0.44, medium effect size). By contrast, at 6-month follow-up a better mean value was recorded in the MB group (d = −0.20, small effect size). The multivariable regression model showed that VAS value at T2 was linked to VAS at T1 (coef = 0.99; t = 5.17; $P < 0.0001$) and to the right side (coef = 1.55; t = 2.2; $P = 0.034$).

The Lequesne Index total was significantly reduced in the two groups at the follow-ups (F = 1.05; $P = 0.31$), with a tendency to a better value for the MB group at T2 (F = 1.05; $P = 0.31$) (Table 2). Comparison between the Lequense Index at recruitment (T0) showed a worse mean in the MB group (d = −0.38, small effect size). At 2 months (T1) no difference was found between the two groups (d = −0.19, negligible effect size). At the end of the study (T2) the MB group showed better values than the GS group (d = −0.5, medium effect size).

The pain or discomfort (Lequesne Index I, LI-I) was significantly reduced in the two groups at the follow-ups, without differences between the two groups (ANOVA for repeated measures; group F = 0.55; $P = 0.46$; time F = 4.68; $P = 0.0112$). The multivariable regression model showed that the LI-I value at T2 was linked to male gender (coef = 1.23; t = 2.05; $P = 0.047$) and LI-I at T1 (coef = 0.69; t = 5.67; $P < 0.0001$).

The maximum distance walked (Lequesne Index II, LI-II) improved in the two groups at the follow-ups, without statistically significant differences (ANOVA for repeated measures; group F = 0.29; $P = 0.59$; time F = 0.65; $P = 0.76$). The multivariable regression model showed that the LI-II value at T2

Table 1. Demographic and clinical characteristics of the participants at recruitment.

Variable	All population	MB group	GS group	*P* value (t-test or ANOVA)
Female (n)	80	38	42	Chi-square = 0.03; *P* = 0.87
Male (n)	32	17	15	
Age (years) (mean ± standard deviation)	59.2 ± 13	58.7 ± 12.5	59.5 ± 13.7	t = 0.21; *P* = 0.4
Height (cm) (mean ± standard deviation)	163.4 ± 7.9	163.4 ± 8.5	162.7 ± 7.4	t = 0.32; *P* = 0.37
Body mass (kg) (mean ± standard deviation)	79.8 ± 15.1	80 ± 14.1	76.1 ± 16	t = 0.1; *P* = 0.46
BMI (kg/cm^2) (mean ± standard deviation)	29.9 ± 4.7	30.0 ± 1.0	29.9 ± 0.8	t = 0.08; *P* = 0.46
Smoking (n)	10	6	4	Chi-square = 0.12; *P* = 0.7
Manual occupation (n)	30	16	14	Chi-quadro = 0.21; *P* = 0.64
Right side (n)	96	48	48	Chi-square = 0.43; *P* = 0.512
Left side (n)	92	44	48	Chi-square = 0.01; *P* = 0.90
Bilateral side (n)	76	38	38	Chi-square = 0.15; *P* = 0.70
Range of motion (ROM) of knee flexion (mean ± standard deviation)	112.6 ± 16.4	113.9 ± 15.5	111.4 ± 17.4	t = −0.57; *P* = 0.29

Statistical analysis of the differences between the two groups.
Significance value of *P* <0.05.

was linked to LI-II at T0 (coef = 0.49; t = 3.03; *P* = 0.004) and T1 (coef = 0.45; t = 3.17; *P* = 0.003).

The activities of daily living (Lequesne Index III, LI-III) was significantly reduced in the two groups at the follow-ups, without difference between the two groups (ANOVA for repeated measures; group F = 1.46; *P* = 0.23; time F = 4.23; *P* = 0.02). The multivariable regression model showed that LI-III value at T2 was linked to LI-III at T0 (coef = 0.43; t = 2.39; *P* = 0.022) and T1 (coef = 0.45; t = 3.26; *P* = 0.002).

For the secondary outcome, the taking of NSAIDS and anti-COX-2 was reduced at the follow-ups, with a tendency to better value for the MB group at the last follow-up (Table 3). The taking of NSAIDS and anti-COX-2 at T1 was related to taking NSAIDS and ANTI-COX-2 at T2 (OR = 68.5; 95% CI = 3.8–1246.1; z = 2.86; *P* = 0.004). The mean administration of NSAIDS and anti-COX-2 was significantly decreased at T1 and T2 without differences between the two groups (ANOVA for repeated measures; group F = 0.00; *P* = 0.99; time F = 3.38; *P* = 0.04) (Table 4). The multivariable regression model showed that value of frequency at T2 was linked to the value of frequency at T0 (coef = 0.31; t = 2.83; *P* = 0.007) and T1 (coef = 0.31; t = 2.14; *P* = 0.04).

Discussion

In our study the two treatments led to a significant improvement in VAS and LI compared with baseline at the two follow-ups. We verified a tendency to better values for participants receiving the formulation of MSM and BA. Analyzing sub-categories of the Lequesne Index, the improvements were significant regarding sub-category I, which measures pain, and sub-category III, which measures function. Sub-category II, which evaluates maximum distance walked, showed a tendency toward improvement. The participants did not present any serious functional limitation that would compromise normal walking and this explains the limited improvements.[21]

The secondary aim of the study is to evaluate the use of anti-inflammatory drugs. Both treatments permitted a significant reduction in the need of anti-inflammatory drugs with a tendency to better results for MSM and BA at 6 months. It is interesting to note that the benefits are persistent 4 months after the suspension. The multiple regression model showed for both integrators the influence of T1 values for all examined aspects and these results confirm that the two integrators, even though their action may be slow, induce clinical effects that persist after suspension. Instead we verified the influence of corresponding values at recruitment only for sub-categories II and III for the Lequesne Index and frequency of NSAIDS and ANTI-COX-2 administration. Some epidemiological characteristics, such as male gender (for LI-I) and the right side (for VAS), are associated with the worst end.

One limitation was the lack of blinded administration of the two integrators. Moreover, the present trial explored the effects on patients with knee arthritis using clinical and functional scales, but

Table 2. Primary outcomes.

Score	MB group	GS group	Comparison between two groups (ANOVA)
VAS			
T0	7.7 ± 1.5	6.4 ± 1.8	
T1	6 ± 1.6	5.3 ± 1.7	
T2	4.6 ± 2.6	4.9 ± 1.6	F = 3.19; *P* = 0.08
Comparison of the three times (ANOVA)	F = 26.0; *P* <0.0001		
Lequesne total (I+II+III)			
T0	10.5 ± 1.0	8.8 ± 0.8	F = 4.15; *P* = 0.02
T1	8.3 ± 1.1	7.4 ± 0.8	
T2	7.1 ± 1.0	7.4 ± 1.0	
Comparison of the three times (ANOVA)	F = 1.05; *P* = 0.31		–
Lequ_I (pain or discomfort)			
T0	4.4 ± 2.5	3.4 ± 1.9	
T1	3.0 ± 2.5	3.0 ± 2.5	
T2	2.7 ± 2.3	2.7 ± 2.3	F = 0.55; *P* = 0.46
Comparison of the three times (ANOVA)	F = 4.68; *P* = 0.0112		
Lequ_II (maximum distance walked)			
T0	1.9 ± 1.7	1.9 ± 1.2	
T1	1.7 ± 1.7	1.6 ± 1.3	
T2	1.8 ± 1.8	1.4 ± 1.3	F = 0.29; *P* = 0.59
Comparison of the three times (ANOVA)	F = 0.65; *P* = 0.76		
Lequ_III (activities of daily living)			
T0	4.3 ± 1.7	3.5 ±.1.8	
T1	3.6 ± 2.3	2.7 ± 2.0	
T2	2.8 ± 2.5	3.0 ± 1.8	F = 1.46; *P* = 0.23
Comparison of the three times (ANOVA)	F = 4.23; *P* = 0.02		

Mean values ± standard deviation of the two groups and statistical comparison at T0 (recruitment), T1 (2 months), and T2 (6 months).
Significance value of *P* <0.05.

Table 3. Secondary outcome: the participants who were taking NSAIDS and anti-COX-2 drugs.

Intake of NSAIDS and ANTI-COX-2 drugs per day	T0	T1	T2
MB group	26	18	16
GS group	24	14	14
Chi-square	0.26	0.58	0.21
P	0.61	0.447	0.643

No significant differences in the groups at the time of measurement.
The statistic comparison between the two groups at three different follow-ups (T0 = recruitment; T1 = 2 months; T2 = 6 months).
Significance value of *P* <0.05.

Table 4. Secondary outcome: the average of daily dose of NSAIDS and anti-COX-2 drugs.

Intake of NSAIDS and ANTI-COX-2 drugs per day	T0	T1	T2
MB group	0.17 ± 0.29	0.1 ± 0.2	0.05 ± 0.2
GS group	0.14 ± 0.22	0.1 ± 0.2	0.1 ± 0.2

ANOVA for repeated measures; group F = 0.00; *P* = 0.99;
time F = 3.38; *P* = 0.04.
The average values ± standard deviation and statistic comparison between the two groups at three different follow-ups (T0 = recruitment; T1 = 2 months; T2 = 6 months).
Significance value of *P* <0.05.

not diagnostic imaging. In future studies, an imaging (MRI) evaluation would have been useful to confirm results.

This study suggests the potential effects of MSM and BA in knee OA patients in pain management, functional recovery, and the reduction of intake of anti-inflammatory drugs. The point that this new combination of integration (MSM and BA) has presented results comparable with GS could confirm validity in the treatment of OA. Further research is necessary to clarify the effects of long-term administration of MSM and BA for the planning of treatment cycles.

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Declaration of conflicting interest

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