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ORIGINAL ARTICLE

Combined glucosamine and chondroitin sulfate, once or three times daily, provides clinically relevant analgesia in knee osteoarthritis

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Abstract We compared the analgesic efficacy and safety of glucosamine sulfate (GS) and chondroitin sulfate (CS) capsules or sachet preparations with glucosamine hydrochloride (GH) and CS capsules in knee osteoarthritis (OA) patients. 1,120 subjects with radiographic knee OA (Kellgren/Lawrence 2–3) were randomized (1:1:1) at 16 centers to receive GS 500 mg/CS 400 mg three times daily capsules (GI) or once daily sachet (GII) or GH 500 mg/CS 400 mg three times daily (GIII) for a 16-week trial. Primary outcome, intention-to-treat (ITT) was change from baseline of patient reported pain intensity (0–100 mm visual analogue scale) in the affected knee and variation of Lequesne's index (LI). Monthly secondary outcomes were changes from baseline in patient reported pain and LI, patient and physician global assessments of disease activity, acetaminophen consumption, and adherence. ITT population comprised 302, 301, and 306 patients in GI, GII, and GIII. Pain significantly decreased (GI=−30.9±1.5; GII=−28.7±1.5; GIII=−29.7±1.5 mm) in all groups ($P<0.001$) as well as LI (GI=−3.8±0.2; GII=−3.7±0.2; GIII=−3.9±0.2; $P<0.001$). All secondary outcomes improved ($P<0.005$) for all groups. Patients that did not complete the study were 77 (44.8 %) for lack of adherence, 16 (9.3 %) consent withdrawal, 11 (6.4 %) adverse events, eight (4.7 %) lost to follow-up, and 17 (9.9 %) for other causes. Non-inferiority analysis found no differences among groups. This is a large study showing that GS/CS and GH/CS provide clinically meaningful and sustained analgesia in knee OA regardless of dose fractionation and capsule or sachet formulations.

Keywords Chondroitin · Glucosamine · Knee · Lequesne · Osteoarthritis · Pain

Introduction

Osteoarthritis (OA) is the most common cause of joint disability in the elderly. In developing countries, the increase in life expectancy will probably raise the numbers of affected individuals. However, disease modifying treatments to OA are still an unmet need. Additionally, symptom relief provided by analgesics such as acetaminophen, opioids, and nonsteroidal anti-inflammatory drugs (NSAIDs) is suboptimal besides provoking concerns regarding safety related to gastrointestinal and cardiovascular risks [1, 2].

The use of glucosamine and chondroitin sulfate, either alone or combined, to treat OA has gained wide acceptance among patients. There is controversy as to whether glucosamine sulfate and/or chondroitin sulfate reduce radiographic progression of OA [3]. Based on the available literature, the updated 2010 OARSI recommendations have maintained the

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decision made in 2008 stating that glucosamine and/or chondroitin sulfate may provide symptomatic relief in knee OA with possible structure-modifying effects. However, concerns on the effect size of these treatments, publication bias, and paucity of adequately controlled trials were raised [1]. In fact, a recent review on this subject considered that OA studies with fewer than 100 patients per treatment arm are more prone to methodological deficiencies and reporting biases [4]. Despite being considered small in most studies, the symptomatic effect size provided by glucosamine/chondroitin sulfate is at least comparable to that achieved by commonly prescribed NSAIDS, opioids and acetaminophen [5]. However, these latter compounds, including acetaminophen, are not devoid of toxicity, especially in elderly patients, which are more prone to have OA [6]. Considering the favorable toxicity profile, the utility of glucosamine/chondroitin sulfate in the OA treatment armamentarium even as a symptom-relieving agent could then be justifiable [4, 7].

We have previously shown that a commercially available drug formulation of glucosamine/chondroitin sulfate capsules given to rats subjected to a surgically induced experimental OA model decreased the hypernociceptive response. Additionally, chronic administration led to improvement of structural joint damage. Though experimental, that is one of the few in vivo studies reinforcing the symptomatic relief and possible disease modifying effects of the combined use of glucosamine sulfate and chondroitin sulfate association in a classical experimental OA model [8].

Commercially available oral glucosamine preparations can be found as glucosamine hydrochloride and cocrystals or coprecipitates of glucosamine sulfate with sodium chloride [3]. Apparently, pharmacological effects of both formulations do not differ, since dissociation in the acid milieu of the stomach releases glucosamine [9]. Capsule or soluble powdered (sachet) glucosamine/chondroitin formulations are found in Brazil, and dosing can be either once (sachet) or three times daily (capsules) [10]. However, there are no studies addressing the issue of dose fractionation as well as efficacy of these two formulations in pain relief in OA. Notwithstanding this, there are concerns on the purity of glucosamine/chondroitin preparations sold as dietary supplements, as compared to marketed drug formulations that have to meet stringent efficacy and safety thresholds [11].

We conducted a randomized trial comparing the efficacy and safety of three different glucosamine preparations, specifically aiming to demonstrate whether two glucosamine/chondroitin sulfate preparations were non-inferior to a glucosamine hydrochloride/chondroitin sulfate formula in achieving the primary outcome. Special attention was paid to adequately include a significant number of participants in each arm so that more than 1,100 patients were screened, rendering more than 300 patients/arm that were evaluated in an intention-to-treat (ITT) analysis.

Methods

Study design

This was an open-label, prospective, multi-center, randomized controlled trial examining the comparative efficacy and safety of three oral preparations of glucosamine and chondroitin sulfate in patients with symptomatic knee OA. Groups I and II received 500 mg glucosamine sulfate/400 mg chondroitin sulfate either as capsules (Artrolive™; Aché Laboratórios Farmacêuticos S.A.) three times daily or as a sachet preparation once daily, respectively. Group III received 500 mg glucosamine hydrochloride/400 mg chondroitin sulfate capsules (Cosamin DS™; Nutramax Laboratories, Inc., Baltimore, MD, USA) three times daily. The protocol was conducted from February 2009 to December 2010 (last patient visit) at 16 sites in Brazil in accordance with good clinical practices. The protocol was approved by the Committee on Ethics in Clinical Research of the Pontifícia Universidade Católica of Campinas, SP, Brazil, which follows the rules of the Brazilian National Council on Ethics in Clinical Research (CONEP – protocol 348/08). All patients had to sign an informed consent prior to any intervention. A central randomization system, by means of sealed envelopes, was used to consecutively assign patients to the three groups in a 1:1:1 ratio. Clinical and laboratory evaluation was done at least 1 week prior to randomization in order to check for the inclusion criteria. Follow-up visits assessed safety and clinical benefit at weeks 4, 8, 12 and 16 after randomization. Acetaminophen (up to 3,750 mg/day) was provided as rescue medication.

Clinical protocol

Patients were older than 40 years, with knee OA and pain in the affected knee for at least 6 months prior to randomization; Kellgren–Lawrence (K-L) [12] grade 2–3 by X-ray in the affected knee and presence of at least one osteophyte (>1 mm) were part of the inclusion criteria; patients had to report pain on movement of the affected knee for more than 15 days in the previous month with at least partial relief at rest; following screening, prior NSAIDs users discontinued treatment to allow for washout; those on acetaminophen less than 750 mg daily remained on treatment. Patients were excluded from study participation based on the following: K-L grade 4 of both knees, inflammatory diseases of the knee other than OA, use of glucosamine and/or chondroitin sulfate 3 and 6 months prior to study entry, respectively; oral or intramuscular corticosteroids 4 weeks prior to study entry; history of knee surgery in the previous 6 months, arthroscopy of the study knee within 6 months, intra-articular injections with corticosteroids into the study knee within the past 3 months and in any other joint within the past 4 weeks; intra-articular injections of hyaluronic acid within the past 12 months;

alcohol intake (>3 doses/day); diabetes, serum creatinine >1.8 mg/dl; use of topical NSAID and/or capsaicin 2 weeks prior to randomization; use of warfarin, heparin and vitamin D >800 IU/day; allergy or history of allergy to acetaminophen, glucosamine sulfate or chondroitin sulfate and sulfonamides; use of nonprescription herbal therapies and tetracycline. Women in child-bearing age were advised to use proper contraceptive methods. Patients were not permitted to initiate physical therapy 2 months prior to the study period. Low-dose aspirin (325 mg or less, once daily) was allowed for cardio-protective benefit. Presence of any serious disease that could compromise the study at investigator discretion would also lead to exclusion from study entry.

Outcome measures

The primary outcome measures of effectiveness were the change from baseline of patient reported pain intensity in the affected knee by a visual analogue scale (VAS; 0–100 mm) and variation of the Lequesne's index (LI; 0–24) [13] both at 16 weeks following study entry. The LI questionnaire has been translated and validated to be applied to Brazilian patients [14]. Secondary outcome measures, recorded at each visit, included mean changes from baseline in patient reported pain in the affected knee, mean change of the LI, patient and physician global assessments of disease activity by VAS, acetaminophen consumption, and adherence to treatment, by counting the returned number of capsules and sachets at each visit. A non-inferiority evaluation was done allowing a difference of less than 1.7 points in the LI and a decrease of pain intensity by VAS less than 18 mm in Groups I and II, as compared to Group III. Safety evaluations included adverse events coded by the Medical Dictionary for Regulatory Activities (MedDRA Ver. 12.2) and examination of the affected knee at each visit. Peripheral blood cell counting and serum chemistries were assessed at screening and after 8 and 16 weeks. Any clinically or laboratory relevant abnormalities were collected as adverse events during the study.

Statistical methods

The sample size was based on the requirement to show the non-inferiority of 500 mg glucosamine sulfate/400 mg chondroitin sulfate either as capsules three times daily (Artrolive™) or as a sachet preparation once daily versus 500 mg glucosamine hydrochloride/400 mg chondroitin sulfate capsules three times daily (Cosamin DS™) in relation to the primary efficacy variables. Sample size calculations were determined based on the following assumptions: (1) 90 % two-sided confidence intervals (CI); (2) a mean difference between each of the test groups and the comparator in VAS pain of 15±2.0 mm and a non-inferiority margin of 18 mm; (3) a mean difference between each of the test groups and the comparator in LI of 1.1±3.8 points and a non-inferiority margin of 1.7 points; (4) a 15 % drop-out rate per group was allowed. The non-inferiority margins were established based on previous results using VAS for pain [15, 16] and LI [17]. The total sample size required to establish the non-inferiority of the test groups compared with the comparator using a two-sided 90 % CI was 828 patients (276 per study group). All efficacy measures were analyzed using the ITT population, consisting of all randomized subjects who took at least one dose of study medication and had at least one post-baseline primary efficacy assessment. Ninety percent CIs (90 % CIs) were calculated for the least square mean treatment difference between each one of the test groups and the comparator group using analysis of covariance (ANCOVA) with treatment group as factor, and the baseline value and center fitted as covariates. The non-inferiority was assessed by comparing the upper limit of the 90 % CI for the mean treatment difference (test group minus the comparator group) to 18 mm and 1.7 points for VAS pain and LI, respectively.

Repeated measurement analysis was used to analyze the secondary variables overtime. A linear model with treatment group and time as fixed effect, center, and baseline score (only for OA pain VAS and LI) as covariates and the group by time interaction was employed. Treatment groups were compared in relation to acetaminophen consumption in the periods week −1 to week 0 and week 0 to week 16. The number of tablets per week was fitted by a GEE (Generalized Estimating Equations) model considering negative binomial distribution, treatment group, and period as fixed factors, center as a covariate and the group by period interaction.

The compliance to the treatment was assessed by counting the returned medication. A patient was classified as being compliant when he/she had taken 80 % to 120 % of the study drug amount over the treatment period. A generalized linear model was used to compare the treatment groups, considering binomial distribution, group as a fixed effect and center as a covariate.

The safety population included all randomized patients who took at least one dose of study medication. All adverse events terms were coded by MedDRA. Standard summaries of adverse events by treatment group, treatment discontinuations, laboratory data, and concomitant medications were generated for the safety. The Statistical Analysis System™ version 9.1 was used.

Results

As shown in Fig. 1, a total of 922 out of 1,120 screened patients met eligibility criteria and were randomized to treatment; the ITT population consisted of 909 patients, comprising 302, 301, and 306 in Groups I, II, and III, respectively.

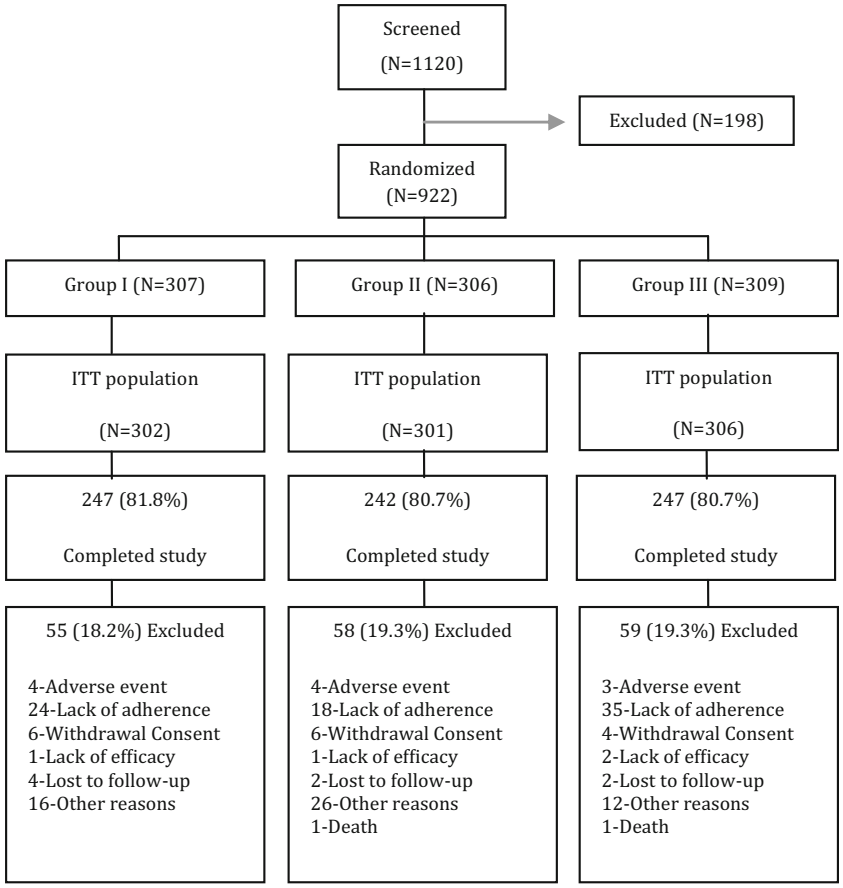

Fig. 1 Flow and outcome of patients. Groups I and II received 500 mg glucosamine sulfate/ 400 mg chondroitin sulfate capsules or sachet, respectively. Group III received 500 mg glucosamine hydrochloride/ 400 mg chondroitin sulfate capsules

Safety analysis was done in 911 patients. The most common reason for exclusion post-screening was inability to meet the X-ray criteria. Baseline demographics and clinical data are shown in Table 1. There were no differences among the three treatment arms regarding baseline evaluation. The majority of patients of the ITT population were women, with 795 (87.4 %), and the mean age was 61.6±8.6 years. The number of patients was well balanced among the three study groups and the withdrawal rate was 18.2 %, 19.3 %, and 19.3 % for Groups I, II, and III, respectively. Table 1 also displays baseline characteristics regarding pain evaluated using VAS and the LI, as well as patients and physician global assessments, of the three study groups. Adherence to treatment, considering the number of patients in each group that took at least 80 % of the study medication, was 91.0 %, 93.6 %, and 86.9 % of the ITT population in Groups I, II, and III, respectively. There was a mild although statistically significant difference among patients from Groups II and III, in favor of Group II, with respect to compliance to treatment. There were 172 (18.9 %) patients that did not complete the study, equally distributed among the three study groups, as shown in Fig. 1. Reasons for exclusion were 77 (44.8 %) for lack of adherence, 43 (25 %) for use of non-permitted medications, 16 (9.3 %) for withdrawal of consent, 11 (6.4 %) for adverse events including two deaths, eight (4.7 %) lost to follow-up, and 17 (9.9 %) for other causes.

Clinical protocol outcomes

Table 2 shows the results for pain intensity, LI, as well as patient and physician global assessment for the three groups. At 16 weeks, pain reduction, as compared to baseline (GI= −30.9±1.5; GII=−28.7±1.5; GIII=−29.7±1.5 mm) was significant for all groups ($P<0.001$). Values for the LI were also significantly reduced for all groups (GI=−3.8±0.2; GII=−3.7 ±0.2; GIII=−3.9±0.2; $P<0.001$). Monthly assessed secondary outcomes, specifically changes from baseline in pain in the affected knee and LI as well as in patient and physician global assessments of disease activity by VAS did also significantly improve ($P<0.005$) for all groups with no difference among them (Table 2).

Acetaminophen consumption was also significantly and similarly reduced ($P<0.005$) in all groups (GI=−5; GII=−3; GIII=−5) (Table 3). The estimated average number of tablets used per week during pre-treatment was 9.7, 10, and 10.5 for GI, GII, and GIII, respectively and dropped to a mean of 4.8, 5.3, and 5.3 after treatment in GI, GII, and GIII, respectively. These results indicate a statistically significant 1.96 times drop

Table 1 Baseline features of patients with knee osteoarthritis

Feature	Artrolive™ Capsules (*N*=302)	Artrolive™ Sachet (*N*=301)	CosaminDS™ Capsules (*N*=306)
Age (years)	61.2±8.6	61.9±8.7	61.71±8.59
Female gender	266 (88)	257 (85.3)	272 (88.8)
Ethnicity			
White	209 (69.2)	223 (74)	203 (66.3)
Non-white	92 (10.1)	75 (8.2)	100 (11)
Other	1 (0.001)	3 (0.003)	3 (0.003)
Pain intensity (VAS; 0–100 mm)	62.3±24.2	62.1±24.9	64.4±23.7
Lequesne's Index (0–24)	11.1±3.3	11.0±3.5	11.0±3.2
Patient Global Assessment (0–100 mm)	46.2±29.7	41.9±28.0	47.8±28.3
Physician Global Assessment (0–100 mm)	42±26.2	39.7±24.2	41.4±25.3
Acetaminophen tablets/day (median)	9.7 (8.8–10.8)	10 (9.1–11)	10.5 (9.6–11.5)

Data represent mean±SD or median (range), as indicated. *VAS* visual analogue scale; *N* numbers (%)

in acetaminophen use observed post-treatment (95 % CI, 1.85–2.08; $P<0.0001$) (Table 3).

Non-inferiority analysis was done for the primary outcome variables, as shown in Fig. 2. The data confirm that the results were absolutely similar among the three groups indicating that there were no significant differences concerning efficacy to achieve the primary outcomes between the three treatment groups.

Safety

At least one adverse event was reported from 604 (66.3 %) out of the 911 patients included in the safety analysis, equally distributed among groups, comprising 199 (65.7 %), 205 (67.9 %), and 200 (65.4 %) in GI, GII, and GIII, respectively. There were 1,824 reported adverse events evenly distributed that were generally considered mild corresponding to 619,

Table 2 Improvements from baseline in pain intensity, functional score, patient and physician global assessments in Groups I, II, and GIII

		Group I		Group II		Group III	
		N	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)
Pain intensity (VAS, mm)	Baseline	302	62.3 (24.2)	301	62.1 (24.9)	306	64.4 (23.7)
	Week 4	302	48.1 (26.0)	301	50.5 (24.0)	306	52.0 (23.8)
	Week 8	272	42.4 (25.7)	279	45.2 (24.9)	273	43.6 (24.4)
	Week 12	260	36.3 (25.0)	262	40.7 (25.2)	258	39.0 (23.8)
	Week 16	249	32.2 (25.0)	246	34.1 (24.3)	248	34.7 (24.9)
Lequesne's index	Baseline	299	11.1 (3.3)	297	11.0 (3.5)	304	11.0 (3.2)
	Week 4	300	9.3 (3.9)	294	9.3 (3.9)	305	9.6 (3.6)
	Week 8	272	8.5 (4.1)	278	8.6 (3.9)	270	8.4 (3.8)
	Week 12	255	7.5 (4.2)	261	7.6 (4.2)	255	7.6 (4.0)
	Week 16	244	6.8 (4.3)	244	7.0 (4.0)	244	7.0 (4.1)
Patient global assessment (VAS, mm)	Week 4	302	46.2 (29.7)	301	41.9 (28.0)	306	47.8 (28.3)
	Week 8	272	53.9 (28.8)	279	51.9 (26.3)	273	54.4 (27.2)
	Week 12	260	62.4 (26.2)	262	58.9 (26.7)	258	59.7 (25.9)
	Week 16	249	69.1 (25.4)	246	66.5 (25.1)	248	68.2 (25.4)
Physician's global assessment (VAS, mm)	Week 4	300	42.0 (26.2)	301	39.7 (24.2)	306	41.4 (25.3)
	Week 8	270	48.4 (26.7)	279	47.1 (23.7)	273	49.2 (26.5)
	Week 12	258	52.2 (27.4)	262	49.0 (27.7)	258	52.5 (27.0)
	Week 16	247	61.9 (25.0)	246	59.7 (24.9)	248	60.3 (27.1)

Groups I and II received 500 mg glucosamine sulfate/400 mg chondroitin sulfate capsules or sachet, respectively. Group III received 500 mg glucosamine hydrochloride/400 mg chondroitin sulfate capsules

Table 3 Compliance to study and rescue medications between Groups I, II, and GIII

Compliance to treatment[a]	Odds ratio (90 % CI)	Group I vs. Group III	1.6 (0.9; 2.6)	P=0.0891
		Group II vs. Group III	2.3 (1.3; 4.0)	P=0.0055
		Group I vs. Group II	1.4 (0.8; 2.7)	P=0.2458
Acetaminophen consumption[b]	LS means (90 % CI) tablets/week	I — week −1 to week 0	9.7 (8.8;10.8)	P=0.3142
				P<0.0001
		I — week 0 to week 16	4.8 (4.3; 5.4)	
		II — week −1 to week 0	10 (9.1; 11.0)	
		II — week −1 to week 16	5.3 (4.8; 5.9)	
		III — week −1 to week 0	10.5 (9.6; 11.5)	
		III — week −1 to week 16	5.3 (4.8; 5.8)	

[a] Odds ratio and 90 % confidence interval of being compliant to treatment (intake 80 % to 120 % of the study medication). P value for the difference between treatment groups

[b] Least square (LS) means and 90 % confidence interval for the number of tablets/week of acetaminophen in the periods week −1 to week 0 and week 0 to week 16. There was no treatment effect (P=0.3142) and there is a statistically significant reduction (P<0.0001) post-treatment

589, and 616 in GI, GII, and GIII, respectively. All but one of the seven (0.38 %) reported serious adverse events were considered as not related to study medications, as follows: one hypertensive crisis in GI; mesenteric occlusion, breast cancer, and indication of retrograde endoscopic colangiopancreatography, one each, in GII; transient ischemic attack, lower limb fracture, and acute myocardial infarction, one each, in GIII. Two out of these adverse events were fatal, both in males, so that the acute myocardial infarction was considered as not related to study drug whereas the mesenteric occlusion was considered possibly related to study drug. There were no significant alterations in laboratory values during the whole study, including fasting glycemia (data not shown).

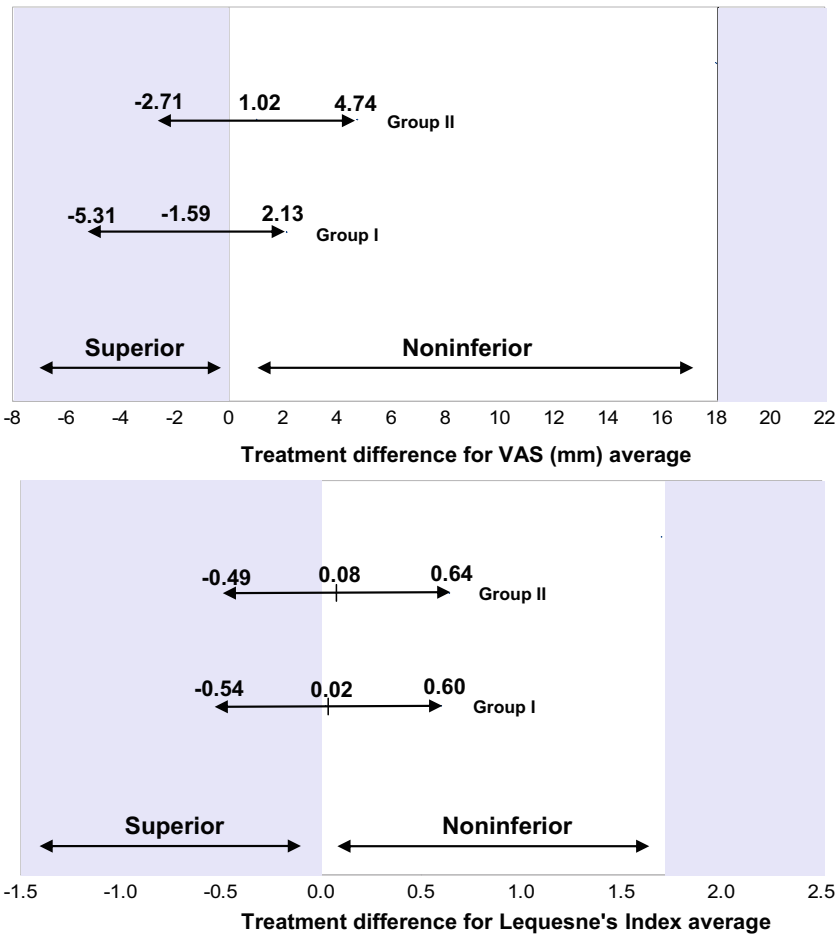

Fig. 2 Groups I and II received 500 mg glucosamine sulfate/400 mg chondroitin sulfate capsules or sachet, respectively. Group III received 500 mg glucosamine hydrochloride/400 mg chondroitin sulfate capsules. Treatment effect according to pain intensity (VAS; 0–100 mm) and Lequesne's index at the end of treatment. Point estimates and 95.0 % two-sided CIs are shown for the treatment effect, defined as the mean difference between the treatments groups I and III and II and III. The margin of non-inferiority was defined as 18 mm for VAS and 1.7 for Lequesne's index

Discussion

The present study reports the first randomized controlled trial on the efficacy of three different formulations of combined glucosamine and chondroitin in knee OA pain. In addition to being the first study to compare glucosamine sulfate/chondroitin sulfate to a glucosamine hydrochloride/chondroitin sulfate formulation, we do also show that dose fractionation does not affect efficacy and that a once daily powdered sachet glucosamine sulfate/chondroitin sulfate preparation leads to a mild though significantly increase in patient compliance as compared to three daily capsules. It is worth mentioning that we had no access to a glucosamine hydrochloride/chondroitin sulfate capsule preparation at the time of this protocol.

Since this study had regulatory purposes, a placebo group was not permitted for comparison. However, the results achieved by any of the three formulations clearly show a statistically significant and clinically relevant reduction in pain and functional domains, measured using the VAS and the LI. We should also stress that the 16 weeks' duration of the protocol and the number of patients included (more than 300 per arm) represent the largest conducted trial comparing these formulations and administration schedules while demonstrating a sustained efficacy of the compounds in pain relief in those knee OA patients. The issue of the relevant differences among the hydrochloride and sulfate preparations of glucosamine is still on debate [7]. However, our data add to the relevant literature since the non-inferiority analysis, evaluating the primary outcomes, was absolutely clear in showing the similar efficacy among the three randomly assigned groups. Moreover, as for the secondary outcomes, both the reduction in acetaminophen consumption and the number of reported adverse events were similar among the three groups. As mentioned in the Introduction section, these results could be anticipated since both hydrochloride and stabilized glucosamine formulations lead to the release of glucosamine in the stomach [3]. However, there are claims that the association of chondroitin sulfate decreases the blood levels of glucosamine [18]. Although we did not measure glucosamine or chondroitin serum levels, the fact that we could not detect a difference among the three formulations in a study specifically powered to that purpose makes the clinical relevance of this possible alteration unlikely.

We have to stress that, in addition to being a large and adequately prolonged protocol to evaluated knee OA pain and function, the trial was designed to include patients with mild to moderate radiological disease, with moderate pain in the index joint. Prior to entering, the wash-out of pain killers had the intention to avoid interference with study medication. The provision of acetaminophen by the sponsor as a rescue medication probably reduced the risk of self-medication for pain relief.

In the largest published study to date comparing glucosamine hydrochloride combined to chondroitin sulfate, glucosamine sulfate or chondroitin sulfate isolated and celecoxib to placebo (the GAIT trial), no significant differences were detected among any of the groups. However, the patients were considered as presenting relatively mild pain at baseline, which might have influenced the relatively high placebo response achieved in that study [19]. Sub-analysis of the patients with moderate to severe pain in that same study showed a difference favoring the combination therapy, as compared to placebo [19]. In the present study, we included patients with moderate pain that had to report pain in the majority of the days in the month prior to screening. Additionally, those on NSAIDs had to stop the medication. Therefore, our strategy probably selected patients more prone to have pain-relief benefit from the medication.

Worries about the quality of glucosamine and chondroitin formulations sold as supplements are also relevant in our country. Therefore, choosing regularly registered medications, as done in the present study, probably have accounted for demonstrating both efficacy and non-inferiority among the formulations used.

OA patients are usually represented by elderly people. Therefore, it is not uncommon for those patients to also have comorbidities that render then more susceptible to adverse events when taking several medications. NSAIDs are well known for the gastrointestinal and cardiovascular side effects associated to their use, especially for long periods, as it happens in OA patients [6]. Acetaminophen and opioids are currently recommended by the Osteoarthritis Research Society International as options to be used as painkillers in OA patients [1]. However, in addition to concerns regarding adverse events linked to the central nervous system and constipation with the use of opioids, recent data reported an increase in fractures and overall mortality associated to opioids use, as compared to NSAIDs [20]. With regard to acetaminophen, the dosages usually assumed to be effective in providing symptom relief in OA range from 3 to 4 g/day [1]. However, apart from its potential hepatotoxicity, acetaminophen has been recently shown to increase intestinal blood loss, especially if combined to low-dose ibuprofen [2]. Therefore, our present data, showing that combined glucosamine/chondroitin preparations provide significant and sustained pain relief in knee OA coupled to a significant reduction in acetaminophen consumption are clinically relevant. Criticism about the effect size of the pain relief provided has to bear in mind that the reduction achieved is similar to that reported with other pain killers. Clinical relevance of the effect achieved can be estimated using minimal clinically important differences (MCID). For the pain component, using a 0–100 mm VAS, a decrease of at least 19.9 mm or a 40.8 % reduction of baseline levels has been proposed as MCID in knee OA [21]. Actually, patients achieved more than 45 % reduction of baseline pain levels,

with a slight though not significant better result in the group that received glucosamine sulfate/chondrotin sulfate capsules.

Our study has several limitations, and the major one is probably the lack of a placebo arm. Being an open-label study could also have influenced the results. However, the need to demonstrate the non-inferiority between the three groups, as requested by the regulatory agency, precluded such a design because of the major increase in the number of patients needed. In order to minimize these possible influences, a diary kept by the patient was used for recording of the number of acetaminophen tablets consumed and main outcomes, represented by the VAS pain analysis and LI, were filled by the patient. Identifications were blinded to the people managing data analysis, hoping to avoid bias when interpreting.

In conclusion, this is the largest study reporting the efficacy of three different formulations of combined glucosamine sulfate or hydrochloride with chondroitin sulfate in patients with knee OA. We have provided data showing that these compounds are non-inferior with regard to efficacy in relieving OA symptoms and are equally similar with regard to safety.

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