

## A Glucosamine-Containing Massage Cream in the Treatment of Knee Osteoarthritis – A Prospective Double-Blind Study

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**Conflict-of-interest statement:** The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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Received: May 8, 2017

Revised: September 22, 2017

Accepted: September 25 2017

Published online: October 28, 2017

### ABSTRACT

**OBJECTIVE:** To assess efficacy of rubbing a glucosamine sulfate containing massage cream as a treatment for pain due to knee osteoarthritis (OA).

**DESIGN:** Eighty patients were randomized to receive treatment by either a Glucosamine Sulfate menthol based rubbing compound or placebo. Patients were required to use the cream at least three times daily over a six-week period. Efficacy was assessed using a Visual Analog Scale (VAS) for pain and the Knee Society Score (KSS).

**RESULTS:** As significant we considered a 20 percent reduction in VAS scores at six weeks following initiation of treatment. 33 of 40

patients in the treatment group improved significantly as compared to 12 of 40 in the placebo group. This difference appears significant when categorized as a categorical parameter ( $p < 0.01$ ). An improvement of 5 points in the KSS score was considered significant. 21 of 40 patients in the treatment group improved significantly as compared to 5 of 40 in the placebo group.

**CONCLUSION:** Our findings suggest a possible positive effect of a Glucosamine Sulfate containing rubbing compound on knee pain due to osteoarthritis, within an six-week treatment period.

**Key words:** Glucosamine; Cream; Knee; Osteoarthritis

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Oron A, Robinson D. A Glucosamine-Containing Massage Cream in the Treatment of Knee Osteoarthritis – A Prospective Double-Blind Study. *International Journal of Orthopaedics* 2017; 4(5): 823-825 Available from: URL: <http://www.ghrnet.org/index.php/ijo/article/view/2067>

### INTRODUCTION

Treatment of osteoarthritis by oral intake of glucosamine sulfate has proven to be both safe and effective<sup>[1,2]</sup>. Glucosamine is possibly a chondroprotective, disease modifying agent in knee osteoarthritis<sup>[3,4,5]</sup>. Some uptake occurs in articular cartilage following oral administration<sup>[6]</sup>. And a possible mechanism of action is reduction of local inflammation as well as decreasing degradation of articular matrix within the osteoarthritic joint<sup>[7]</sup>. Use of glucosamine as a supplement or stand alone therapy for treatment of osteoarthritis has been suggested to be of clinical validity [the GAIT study<sup>[8]</sup>]. Our study was aimed at assessing the efficacy of a glucosamine containing massage cream used TID for a six-week period in the treatment of knee osteoarthritis.

### MATERIALS AND METHODS

#### Study Design

Our study was designed as a single center, double blind, placebo controlled trial. We randomly allocated patients to either a treatment group receiving three times a day (TID) treatment by a menthol based

massage cream containing glucosamine sulfate or a placebo group receiving TID treatment with a menthol based massage cream alone. Patients were randomly assigned to either the treatment or control. Treatment was of six weeks duration. As a primary outcome measure we used subjective pain as assessed using a VAS. The secondary outcome measure utilized was the modified functional domain of the Knee Society Score (KSS)<sup>[9]</sup>. The trial was approved by the Assaf Harofeh Medical Center local Helsinki committee.

**Participants**

Subjects were recruited from the community from the office of one of the authors (D.R.). Subjects were initially screened by the referring physicians as to their health status and stage of osteoarthritic changes in the knees.

**Inclusion Criteria**

Patients randomized to either group were over the age of forty, had a history of knee pain of at least 3 months duration, radiological changes of the symptomatic knee correlated with an Ahlbeck grade 2-3 staging of osteoarthritic changes at the knee joint, and patients were physically able and testified as willing to use the assigned topical formulation three times daily for a six week period.

**Exclusion Criteria**

Patients suffering from knee pain with concomitant inflammatory disease or previous trauma resulting in a fracture within the vicinity of the knee were excluded from participating in the study. Patients knees defined as Ahlbeck grade 4 on radiological assessment. Patients with VAS responses under a score of 4 for subjective pain. A skin disease within the vicinity of the knee prohibiting localized rubbing. Allergy to sulpham or to celecoxib (as this is the designated rescue medication).

**Interventions**

The active preparation contained glucosamine (180 mg/g) emulsified in a water soluble base which contained peppermint oil (menthol). The base which was used as the emulsifying agent was a simple cosmetic cream that used conventional skin emollients, petrolatum and mineral oil. This base was utilized as the placebo treatment, though without enrichment with glucosamine. The creams were produced by Manon Pharmaceuticals Ltd. Subjects were instructed to clean the skin adjacent to their aching knee and apply the cream at least three times daily.

**Randomization and Blinding**

Subjects who successfully fulfilled all inclusion criteria and none of the exclusion criteria were enrolled in the study. Subject randomization was performed by using a box full of opaque envelopes shuffled ahead of time. The envelopes and corresponding cream filled containers were administered by an independent study coordinator, while the investigators were blinded to which group the patients were assigned to. Patients were asked not to bring their cream to the follow-up visits. No breakings of code or contamination were recorded within the scope of this study.

**Rescue medication**

Patients were allowed use of celcoxib 100 mg daily as a rescue medication. Amount of tablets used was recorded per anamnesis.

**Outcome measures**

VAS scores were rendered the primary outcome measure, where

an improvement of at least 20% was considered significant improvement. A questionnaire with a VAS of 100 mm in length was administered at initiation of the study and at its closing 6 weeks later. As a secondary outcome measure we used the KSS score, as calculated from a questionnaire administered at initiation and at the termination of the study. All patients were asked to report any adverse events to the physicians involved in the study on a real-time basis using their cellular phones as a direct means of communication.

**Statistical Analysis**

Continuous variables were evaluated using the t-test for un-paired samples with similar variance. A significant inter-group difference was considered as a *p*-value less than 0.05. Group size was calculated on the assumption of a 20% self-improval in osteoarthritic symptoms during the study period in the control group versus a 50% improval in the treatment group [standard deviation was assumed to be equal in both groups and not higher than 20%]. For a two-tailed alpha error of 5% and power of 80%, we estimated that at least 35 patients were required in each group.

**RESULTS**

80 patients were enrolled in the study. All patients enrolled in the study, were randomized to either group. There were no drop-outs from the study.

Data from all 80 subjects was input to Excel workbook and statistical analysis was performed using the Analyze-It add-in (Analyze-it Software Ltd, 2003). The 2 groups were similar in their demographic disposition and illness conditions (Table 1). All participants had knee pain with radiographic changes in both knees not exceeding Ahlbeck grade 3. Severity of osteoarthritic changes was similar in both groups averaging 2.1 ± 0.6 in the treatment group and 2 ± 0.5 in the control group (Mann-Whitney U Statistic 817.5, 2-tailed *p* value > 0.8).

**Table 1** Demographic characteristics of study participants.

Variable	Treatment Group	Control Group	Significance
Age (years)	64 ± 7 years	65 ± 5 years	n.s. ( <i>p</i> > 0.6)
BMI (kg/m <sup>2</sup> )	37 ± 5 kg/m <sup>2</sup>	34 ± 7 kg/m <sup>2</sup>	n.s. ( <i>p</i> > 0.8)
SEX (M/F)	35% male	38% male	n.s. ( <i>p</i> > 0.8)
Renal Disease	2.50%	6.50%	n.s. ( <i>p</i> > 0.3)
Ischemic Heart Disease	58%	52%	n.s. ( <i>p</i> > 0.6)
Hypertension	65%	68%	n.s. ( <i>p</i> > 0.7)
Diabetes	17%	25%	n.s. ( <i>p</i> > 0.2)

expressed as average ± standard deviation. Significance expressed as *p*-value, derived from t-test for unpaired groups for continuous variables and from Mann-Whitney test for non-continuous variables.

**Table 2** Study results variables.

Variable	Treatment Group	Control Group	Significance
Pre-treatment VAS (scale 0-100)	70 ± 15	63 ± 12	n.s. ( <i>p</i> > 0.2)
Post-Treatment VAS (scale 0-100)	92 ± 10	75 ± 7	Significant. ( <i>p</i> > 0.05)
Post to Pre Treatment VAS Difference (scale 0-100)	22 ± 7	12 ± 9	Significant ( <i>p</i> > 0.05)
Pre-treatment KSS	38 ± 14	35 ± 10	n.s. ( <i>p</i> > 0.5)
Post-treatment KSS	40 ± 13	40 ± 5	n.s. ( <i>p</i> > 0.3)
Post to Pre Treatment KSS Difference	2 ± 4	5 ± 6	n.s. ( <i>p</i> > 0.1) difference is trending toward significance

Pretreatment VAS values averaged  $63 \pm 12$  in the control group versus  $70 \pm 15$  in the treatment group (the difference is not significant, *t*-test,  $p < 0.2$ ). Pretreatment functional Knee Society Score (KSS) averaged  $38 \pm 14$  in the control group versus  $35 \pm 10$  in the treatment group (the difference is not significant, *t*-test,  $p > 0.3$ ).

The change in VAS scores were  $12 \pm 9$  in the control group versus  $22 \pm 7$  in the treatment group (the difference is highly significant, *t*-test,  $p < 0.001$ ). The change in functional KSS score averaged  $2 \pm 4$  points in the control group versus  $5 \pm 6$  points in the treatment group (there was a tendency toward significance that did not reach a significant level, *t*-test,  $p < 0.065$ ).

Another manner of calculating an improvement in the VAS scores, is to consider an improvement of 20 points or more, as a positive response. When employing this criteria 30% (12/40) of the control group and 82.5% (33/40) of the treatment group improved (this difference was significant, Mann-Whitney test,  $p < 0.01$ ).

A similar criteria was used regarding the functional KSS value. An improvement of more than 5 points was considered as an improvement. Using this criteria, 10% (4/40) patients in the control group improved versus 53% (21/40) in the treatment group.

Rescue medication usage was similar in both groups ( $21 \pm 11$ ) tablets in the control group versus  $26 \pm 10$  in the treatment group (the difference was not significant,  $p > 0.1$ ).

No complications were observed in any of the patients, either in the control or in the treatment group. No patients withdrew from the study.

## DISCUSSION

The current study attempted to evaluate the potential effect of a glucosamine containing cream on symptoms related to knee osteoarthritis. The study design was a placebo-controlled trial, in which a menthol-cream served as a placebo. While menthol-based creams are marketed as soothing creams for various malaises, they have not been proven superior to placebo for the treatment of osteoarthritis of the knee. The results of the current study appears to indicate that use of a glucosamine cream leads to a minor improvement in pain symptoms as measured by the VAS and in the functional KSS score in patients with moderate osteoarthritis of the knee. As in other glucosamine trials for knee osteoarthritis, the treatment effect is small<sup>[1]</sup>.

It is somewhat difficult to explain the possible mechanism of action. Other authors have documented an ameliorative effect of a glucosamine containing cream on knee osteoarthritis<sup>[10,11]</sup>. However, glucosamine is a fairly large molecule that does not easily penetrates the skin. Little if any data in the literature indicates what proportion of the compound actually penetrates into the joint following topical application. However previous authors have suggested that a 30% skin-penetration of the total amount applied, can be expected using a glucosamine group<sup>[10,11]</sup>.

A placebo effect is common in clinical trials of osteoarthritis, with mild pain reduction in the control group as well. This improvement is presumably due to the cyclical nature of osteoarthritis symptomatology<sup>[12]</sup>. The study design employed celecoxib as a rescue medication and drug consumption appears to be similar in both groups. However, it should be noted that the tablets used were estimated by

the patients and not supplied as part of the study. Thus, it is possible that some reporting bias by the patients occurred. As groups were demographically similar, it is the authors opinion that any reporting bias that possibly exists is similar in both groups and thus should not influence the interpretation of study results.

In summary, it appears that glucosamine-containing cream is a possibly useful additive to the armamentarium of conservative treatment of knee osteoarthritis.

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Peer Reviewer: Ahmet Eroglu