Comparative Study Between The Clinical Effects of Glucosamine/Gingko Biloba & Glucosamine/Chondroitin in Treatment of Knee Osteoarthritis

دراسة مقارنة للتأثيرات ألسريريه لاتحاد والكلوكوزأمين مع الجنكوبايلوبا والكلوكوزأمين مع الكوندروتين في علاج التهاب المفاصل العظمي

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الخلاصة:
الهدف: بحث التأثير ألسريري لاثنين من الادوية المركبة المستخدمة بصورة شائعة لمرضى التهاب المفاصل العظمي وهذان المركبان هما (الكلوكوز آمين مع الكوندرويتين بنسبة 500 مغم الى 400 مغم على التوالي) و (الكلوكوزامين مع الجنكوبايلوبا بنسبة 500 مغم إلى 50 مغم على التوالي) .
المنهجية : تم إعطاء كل مركب لمجموعة من مرضى التهاب المفاصل العضمي(12 ذكور و 17 إناث بالنسبة للمجموعة الأولى و9 ذكور 13 اناث بالنسبة للمجموعة الثانية) لمدة ستة أسابيع . تم قياس تأثير هذه الأدوية على المرضى من خلال الإجابة أسبوعيا على مجموعة من الأسئلة المتعلقة بمكونات الاختبار المسمى (KOOS) والذي يتكون من خمسة محاور، الألم والأعراض والفعالية اليومية والجودة الحياتية والرياضة والمتعة .
النتائج: تم ملاحظة ان كلا المركبين احدثا زيادة معنوية (تحسن) في جميع هذه المحاور ولكن الزيادة التي أحدثها مركب الكلوكوزامين مع الجنكوبايلوبا أدى إلى تغير معنوي أكثر من ذلك الذي أحدثه المركب الأخر.
الاستنتاجات : نستنتج من الدراسة ان اتحاد الكلوكوزامين مع الكوندرويتين احدث تغيرا معنويا في جميع مكونات (KOOS) أكثر من اتحاده مع الجنكوبايلوبا.
التوصيات: يوصى بالحاجة إلى دراسة موسعة للتأكد من هذه الاستنتاجات.

Abstract:
Aim: This study was designed to investigate the effect of two widely used combinations, glucosamine/chondroitin and glucosamine/*ginkgo biloba* on the clinical picture of patient with osteoarthritis(OA).
Methods: Fifty one (51) osteoarthritis patients (21 male and 30 female) were participated in this research depending on certain selection criteria. The selected patient were randomly allocated into two groups: group A includes 22 (9 male and 13 female) patients treated with a combination of glucosamine /*gingko biloba* (500/ 50 mg twice daily) for six weeks whereas group B includes 29 (12 male and 17 female) patients treated with a combination of glucosamine/chondroitin (500/ 400mg twice daily) for six weeks . Effects of drug treatment were assessed each seven days by clinical evaluation and direct interview with patients through a questionnaire method known as Knee Injury and Osteoarthritis Outcome Score (KOOS).
Results: It was found that all components of KOOS including pain score, symptoms score, activity of daily living (ADL), quality of life (QOL) and sport & recreation scores were significantly elevated (improved) in both combinations, however, glucosamine /*gingko biloba* showed a better improvement when statistically compared with the combination of glucosamine/chondroitin.
Conclusions: It is concluded from this study that the glucosamine sulfate is more clinically useful for OA when combined with *gingko biloba* than when it is combined with chondroitin.
Recommendations: A large scale cohort study is recommended to ensure the clinical findings.

Key words: Osteoarthritis, Glucosamine sulfate, Chondroitin sulfate, Gingko biloba, Knee joint and osteoarthritis outcome score

INTRODUCTION:

Osteoarthritis (OA) is the most common joint complaint in the middle aged and older people.[1,2] Its onset is insidious, and its course is mostly progressive and frequently causing pain, loss of function, and disability.[2] It is believed that OA is a disease involving the entire joint, including changes in joint cartilage, bone, synovial membrane, and soft tissues[3]. The disease is characterized by cartilage breakdown, formation of bony tissue at the joint margins (osteophytes), subchondral bone changes (generally referred to as sclerosis), inflammation of the synovial membrane, and

changes (impairment) of the peri-articular soft tissues.[4] OA can occur in every joint in the body, but is most common in the hands, hips, and knees.[2]

Assessing the severity of OA involves assessment of both lesions and patients [5]. This assessment may be done in the clinical setting in support of diagnosis, treatment decision, or evaluation of response to treatment [2]. Clinical examination of the osteoarthritic joints can be helpful in assessing the extent of joint damage, such as deformity and instability, but the reproducibility of findings is low [6]. The pain and inflammatory process involved in OA may be managed by many types of drugs, exemplified by non-steroidal anti-inflammatory agents NSAIDs[7]. However, NSAIDs provoke adverse effects particularly gastrointestinal ulcerations[8]. Furthermore, some of these agents have been reported to disrupt extracellular matrix metabolism, particularly proteoglycans synthesis[9]. Patient with such chronic painful condition always asking for more effective medications with fewer side effects and this is indeed encourage searching for complementary and alternative approaches that has been attracted the interest of both the patients and clinicians[10]. Articular cartilage is made up mostly of extra-cellular matrix that contains giant proteoglycan molecules which are made of a hyaluronic acid backbone to which giant glycosaminoglycan chains (GAGs) are attached. Chondroitin is one type of GAG, and glucosamine is a building block for many different GAGs. Both are thus naturally occurring substrates for the production of articular cartilage[11]. Commercial glucosamine is primarily derived from the shells of crabs and other shellfish while commercial chondroitin is produced primarily from the cartilage of cows[12]. Glucosamine is a small, amino sugar, though easily absorbed, its bioavailability is still less than 20% due to a high first-pass effect in the liver[13]. Chondroitin is a very large, poorly absorbed molecule. Its oral bioavailability is less than 20%. Both glucosamine and chondroitin can stimulate proteoglycan production in vitro.[13] Chondroitin also seems to inhibit the inflammatory enzyme leukocyte elastase, an effect which may provide some analgesia and may contribute to the slowing of cartilage degradation[14]. Extracts of *ginkgo biloba* leaves contain flavonoid glycosides (myricetin and quercetin) and terpenoids (ginkgolides, bilobalides) and have been used pharmaceutically[15]. *Ginkgo biloba* extract has in addition been found to act as a selective 5-HT1A receptor agonist in vivo and was found to decrease the level of some pro- inflammatory cytokines like IL-8 and IL-6 [16]. *Ginkgo biloba* supplements are usually taken in the range of 40–200 mg per day. It was combined with glucosamine sulphate in some pharmaceutical preparations [17]. In this study we tried to evaluate the clinical effect of two widely used combinations, glucosamine plus chondroitin and glucosamine plus *ginkgo biloba* in patients with osteoarthritis.

PATIENTS AND METHOD:

Randomized, double blind clinical study was performed on (51) randomly selected patients (21 males and 30 females) with painful osteoarthritis (OA) of the knee, visiting Out Patients Clinic in Al-Hussein Teaching Hospital, Karbala from November 2012 to April 2013 , with age range 39-72 years (52.07 ± 7.16). All patients have symptomatic and radiological evidence of OA in one or both knee joints; their clinical features were in accordance with the description of OA in UK and North American Clinical Guidelines revised in 1999 by the royal college of physicians[18]. They also show no significant differences in their initial pain, morning stiffness or global assessment. All patients were informed about the nature and the aim of the study. During patient selection certain exclusion criteria were followed, based on the following: 1-Patients with a positive history of allergic reaction to any

one of the used drugs or supplements, 2-Any patient who miss one week of treatment assessment indicated in this study and/or his medication for any reason, 3-Pregnant or lactating female patients, 4-Any patient with renal or hepatic impairment, and those who are on treatment with drugs which could interfere with the tested drugs.

The selected patient were randomly allocated into two groups: Group A includes 22 (9 male and 13 female) patients treated with a combination of Glucosamine /*Gingko Biloba* (500/ 50 mg twice daily) for 6 weeks whereas Group B includes 29 (12 male and 17 female) patients treated with a combination of Glucosamine/Chondroitin (500/ 400mg twice daily) for six weeks . Effects of drug treatment were assessed each seven days by clinical evaluation and direct interview with patients through a questionnaire method known as Knee Injury and Osteoarthritis Outcome Score (KOOS) [19]. The results were expressed as mean ± SEM; paired *t*-test and ANOVA were used to examine the degree of significance; *P* values less than 0.05 were considered significantly different.

RESULTS:

Effect on Pain Score

Before enrolment in the study (zero time), OA patients demonstrated poor pain control with their previous therapy, manifested by low pain score in both groups, which indicate severe or extreme symptoms of pain. Treatment with Glucosamine/*Gingko biloba* resulted in significant increase in pain score started from the first week (111.9%) reaching maximum level after four weeks (183.5%) and remain at this level until the last week of the study (six weeks). Significant improvement in pain score also produced in patients treated with Glucosamine/chondroitin , but the level of improvement was significantly lower than that observed in Glucosamine/*Gingko biloba* treated group, as shown in table (1)

Table 1. Effect of treatment of OA patients with glucosamine/*gingko biloba* or glucosamine/chondroitin on pain score .

	Pain Score			
Duration (Wk.)	Glucosamine/ Chondroitin 500/400mg	Percentage of improvement (from baseline)	Glucosamine/ *Gingko biloba* 500/50mg	Percentage of improvement (from baseline
0	30.7 + 2.7	----------	33.5 ± 1.5	----------
1	36.7 + 2.1[a]	19.5%	71.0 + 3.6[*b]	111.9%
2	48.7 + 1.7[*a]	58.6%	83.7 + 2.9[*b]	149.5%
4	57.8 + 2.8[*a]	88.2%	95.0 + 1.8[*b]	183.5%
6	60.8 + 4.5 [*a]	98.0%	98.9 + 3.1[*b]	194.9%

Data were expressed as mean ± SEM, * significantly different compared to baseline value, values with non-identical superscripts (a,b,) among different groups at the same period are considered significantly different ($P<0.05$).

Effects on Symptom Score

At zero time (before starting treatment), all selected OA patients showed poor management of OA symptoms, manifested by low score of symptoms according to the outcome of KOOS (table 2). Treatment with Glucosamine/Gingko biloba resulted in time-dependent increase in this score, reaching maximum level after 4 weeks (164%) compared to base line level ($P<0.05$), and remain nearly at this value for the remaining period of the study. Treatment with Glucosamine/chondroitin resulted in

significant elevation in symptom score (29.7%), which are significantly lower than those produced by Glucosamine/*Gingko biloba* at the corresponding period(first week of the study).

Table 2. Effect of treatment of OA patients with glucosamine/*gingko biloba* or glucosamine/chondroitin on symptoms score.

	Symptoms Score			
duration (Wk.)	**Glucosamine/ Chondroitin 500/400mg**	**Percentage of improvement (from baseline)**	**Glucosamine/ *Gingko biloba* 500/50mg**	**Percentage of improvement (from baseline)**
0	30.7 + 2.7	----------	35.5 ± 1.3	----------
1	39.7 + 2.1^{*a}	29.7%	73.0 + 1.6^{*b}	111.2%
2	49.1 + 1.9^{*a}	59.9%	80.7 + 2.9^{*b}	127.3%
4	57.8 + 2.8^{*a}	88.2%	94.0 + 1.8^{*b}	164.7%
6	62.8 + 2.5 ^{*a}	104.5%	98.0 + 2.0^{*b}	176.0%

Data were expressed as mean ± SEM, * significantly different compared to baseline value, values with non-identical superscripts (a,b,) among different groups at the same period are considered significantly different (P<0.05).

Effects on Activity of daily living (ADL) Score

In table 3, ADL score was found relatively low before starting treatment in all patients (zero time) enrolled in study. During treatment with Glucosamine/Gingko biloba, ADL score showed time –dependent increase started after 1 week and reaching maximum after 6 weeks (112% and 173% respectively, P<0.05 with respect to baseline value). Table 3 also shows that treatment with Glucosamine/chondroitin resulted in significant elevation in ADL score, started after the second week of treatment (523.%), values which are significantly lower than its counterpart value produced by Glucosamine/Gingko biloba at the same period.

Table 3. Effect of treatment of OA patients with glucosamine/*gingko biloba* or glucosamine/chondroitin on ADL score.

	ADL Score			
Duration (Wk.)	**Glucosamine/ Chondroitin 500/400mg**	**Percentage of improvement (from baseline)**	**Glucosamine/ *Gingko biloba* 500/50mg**	**Percentage of improvement (from baseline)**
0	31.7 + 1.5	----------	39.5 ± 2.6	----------
1	34.7 + 1.1^{a}	9.4%	73.0 + 1.6^{*b}	112.6%
2	48.3 + 1.8^{*a}	52.3%	80.7 + 2.9^{*b}	129.6%
4	59.8 + 1.9^{*a}	91.7%	92.0 + 1.6^{*b}	158.2%
6	67.8 + 2.1 ^{*a}	116.0%	97.9 + 3.1^{*b}	173.1%

Data were expressed as mean ± SEM, * significantly different compared to baseline value, values with non-identical superscripts (a,b,) among different groups at the same period are considered significantly different (P<0.05).

Effects on Sport/Recreation Score

Table 4 revealed low sport/recreation score at zero time levels before starting drug treatment. Treatment with Glucosamine/*Gingko biloba* resulted in significant increase in sport/recreation score started after the first week (140.6%), reaching maximum level after 4 weeks (218.6%) and remain nearly at this level until the end of the study (6 weeks). Table 4 also demonstrated significant improvement in sport/recreation score produced by Glucosamine/chondroitin, but started after the second week of treatment (49.2%). However, the level of improvement that produced by the Glucosamine/chondroitin was significantly lower than that observed due to treatment with Glucosamine/*Gingko biloba*

Table 4. Effect of treatment of OA patients with glucosamine/gingko biloba or glucosamine/chondroitin on sport& recreation score.

	Sport/Recreation Score			
Duration (Wk.)	**Glucosamine/ Chondroitin 500/400mg**	**Percentage of improvement (from baseline)**	**Glucosamine/ *Gingko biloba* 500/50mg**	**Percentage of improvement (from baseline)**
0	32.7 + 3.5	----------	29.5 ± 2.6	----------
1	36.7 + 2.1[a]	12.2%	71.0 + 4.3[*b]	140.6%
2	48.8 + 2.7[*a]	49.2%	82.7 + 3.1[*b]	177.9%
4	58.9 + 3.9[*a]	80.1%	94.0 + 1.8[*b]	218.6%
6	65.8 + 3.5 [*a]	101.2%	96.5 + 3.1[*b]	227.1.9%

Data were expressed as mean ± SEM, * significantly different compared to baseline value, values with non-identical superscripts (a,b,) among different groups at the same period are considered significantly different (P<0.05).

Effects on Quality of Life Score (QOL)

At zero time (before treatment), all patients showed relatively low QOL score, indicating worse consequences of OA on the quality of patients' life (table 5). Treatment with Glucosamine/*Gingko biloba* resulted in time-dependent improvement in QOL score, started after 1 week; of treatment (156%, P<0.05 compared to baseline value), reaching maximum level after 6 weeks (274%) compared to baseline value (P<0.05). Treatment with Glucosamine/chondroitin resulted in significant improvement in the QOL score after 4 weeks of treatment(64.4%), and found significantly (P<0.05) lower than those produced by Glucosamine/*Gingko biloba* within the counterpart study period.

Table 5. Effect of treatment of OA patients with glucosamine/gingko biloba or glucosamine/chondroitin on QoL score.

	QOL Score			
Duration (Wk.)	**Glucosamine/ Chondroitin 500/400mg**	**Percentage of improvement (from baseline)**	**Glucosamine/ *Gingko biloba* 500/50mg**	**Percentage of improvement (from baseline)**
0	34.7 + 3.1	----------	26.5 ± 2.7	----------
1	35.7 + 1.7[a]	2.8%	68.0 + 2.8[*b]	156.9%
2	42.5 + 2.9[*a]	7.8%	84.7 + 2.9[*b]	219.6%
4	51.8 + 3.1[*a]	69.4%	94.0 + 1.8[*b]	254.7%
6	72.1 + 1.6 [*a]	107.7%	98.7 + 3.4[*b]	272.4%

Data were expressed as mean ± SEM, * significantly different compared to baseline value, values with non-identical superscripts (a,b,) among different groups at the same period are considered significantly different (P<0.05).

DISCUSSION:

Knee Injury and Osteoarthritis Outcome Scoring system is intended to evaluate symptoms and functional limitations of people with chronic inflammatory joint diseases and problems from lower extremities. This questionnaire also assesses the sport and recreation function and quality of life domains. Therefore, it can give a more descriptive picture of a subject or a fuller picture of the impact of an intervention[20]. Despite the significant advances in understanding mechanisms of pain, many people with arthritis experience different levels of acute and chronic pain that impair their daytime function[21]. Additionally, unrelieved pain leads to serious negative consequences, like those observed in pain score belongs to OA patients before treatment (table 1), with many other physiological effects associated with increased catabolic demands[22]. Pain with movement is the principle symptom of OA patients; although cartilage tissue contains no pain receptors, sensation of pain likely results from inflammatory mediators, bone edema and mechanoreceptors in the surrounding joints[23]. Patients with OA of the knee often complain of instability or buckling, especially when they are describing stairs or stepping off crumbs, a situation that was clearly revealed by poor pain score according to KOOS results (table 1). Most patients with OA seek medical attention because of pain, and the safest initial approach is to use simple oral analgesics such as acetaminophen.

The combined use of glucosamine sulfate (GS) and chondroitin sulfates (CS) in the treatment of degenerative joint disease has become an extremely popular supplementation protocol. Both GS and CS have been available as supplements for many years, and appear to positively impact symptoms in osteoarthritis; however, their ability to work as a synergistic combination remains open to debate[24]. GS's primary biological role in halting or reversing joint degeneration appears to be directly due to its ability to act as an essential substrate for, and to stimulate the biosynthesis of, the glycosaminoglycans and the hyaluronic acid backbone used in the formation of the proteoglycans found in the structural matrix of joints. CS, whether they are absorbed intact or broken into their constituent components, similarly provide additional substrates for the formation of a healthy joint matrix[24]. In the present study, the reported effect for glucosamine/*gingo biloba* in improving pain score can be explained according to the nature of biological activity of both elements of this combinations, which attributed to many factors. First, quercetin in *gingko biloba*

seems to be one of the most powerful flavonoids for protecting the body against reactive oxygen species, produced during the normal oxygen metabolism or those induced by exogenous damage[25]. Previous studies has reported that quercetin significantly inhibited TNF-α production and gene expression in a dose-dependent manner, [26] which may explain the powerful effect for the combination containing *gingko biloba* compared with glucosamine/chondroitin combination used in this study. A decrease in endogenous TNF- α production in the presence of quercetin indicates that flavonoids have the capacity to modulate the immune response and have potential anti-inflammatory activity which is a validated approach to treat several inflammatory diseases including osteoarthritis[27]. Second, other types of flavonoid present in this plant like luteolin have a well-documented anti-inflammatory and analgesics activities through their inhibitory effects on cyclooxygenase (COX) and lipoxygenase (LOX) that mediate several inflammatory processes[10].

CONCLUSIONS:

It is concluded that the combination of glucosamine/gingko biloba is clinically better than the combination of glucosamine with chondroitin in decreasing the pain and improving other symptoms and has a positive impact on the quality of life of OA patients.

RECOMMENDATIONS:

Based on the results of these study, it is recommended to investigate the effect of these two combinations in a large scale cohort study to ensure these clinical findings.

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