Prospective Study on Functional Outcome of Intra Articular Hyaluronic Acid with Oral Glucosamine and Chondroitin Sulfate Compared to Intra Articular Hyaluronic Acid Alone for Treatment of Osteoarthritis of Knee Joint

Ahmed Alkhuzai, Seerwan Hama Shareef, and Zeyad Mustafa
Sulaimaniyah University.

Received 5/5/2010 – Accepted 5/10/2010

الخلاصة

يستخدم الحقن المفصلي للركبة بمادة هايلورونيك اسيد، اقراص كلوكوز امين و كوندرويتن سلفيت فى معالجة مرضى سوفان الركبة. فى هذا البحث قمنا بتحديد مدى الاستفادة و تأثيرات استخدام الحقن المفصلى لهايلورونيك اسيد مع حبة كلوكوز امين و كوندروتين سلفيت مقارنة باستخدام حقنة المفصلى لهايلورونيك اسيد فقط فى معالجة مرض سوفان الركبة. تم اختيار 104 عينة من المرضى يعانون من مرض سوفان الركبة.و تم تقسيمهم الى مجموعتين عشوائيا بعد تحديد مرضى السوفان فقط.

المجموعة أ : تتكون من 55عينة يعانون من التصنيف الثانى و الثالث لسوفان الركبة طبقا لتصنيف (kellgren) .ان هذه المجموعة كانت تخضع لعلاج الحقن المفصلى لهايلورونيك اسيد 25 ملغم اسبوعيا و لمدة خمسة اسابيع مع عقاري كلوكوز امين 1500 ملغم و كوندروتين سلفيت 645 ملغم يوميا عن طريق الفم لمدة سنة واحدة.

المجموعة ب : تتكون من 49 عينة يعانون من التصنيف الثانى و الثالث لسوفان الركبة .ان هذه المجموعة كانت تخضع لعلاج الحقن المفصلى هايلورونيك اسيد 25 ملغم اسبوعيا و لمدة خمسة اسابيع فقط.

تم متابعة المجموعتين لمدة اثنا عشر شهرا، و كانت متابعة المرضى و استجابتهم للعلالج تستند على تصنيفى WOMAC و Lequesne's وكانت المتابعة قد اعتمدت على اخذ البيانات الاولية و عند الشهر الاول ،الثالث،السادس و الشهر الثانى عشر.

ان عدد مرضى المجموعة (أ) والتى اكملت المتابعة فى دراسة البحث كانت 55 مريضا فقط. ان معدل العمر ضمن هذه المجموعة كان 61 سنة. اما عدد مرضى المجموعة (ب) والتى اكملت المتابعة كان 49 مريضا فقط و كان معدل العمر ضمن هذه المجموعة 60 سنة .

فى كلتا المجموعتين و خلال المتابعة فى البحث كان هناك انخفاض واضح ومهم فى المعدل الوسطى طبقا لتصنيفى WOMACو Lequesne's. (فى بداية الدراسة كان المعدل الوسطي لتصنيف Lequesne's للمجموعة أ 14.4 ومجموعة ب كان 13.8 و المعدل الوسطي لتصنيف WOMAC للمجموعة أ كان 35.9 ومجموعة ب كان 34.7 . و قد لوحظ تغييرا فى المعدل الوسطي خلال مدة البحث. كان المعدل الوسطي فى الشهر الثانى عشر لتصنيف Lequesne's للمجموعة أ 9.2 ومجموعة ب كان 11.8 و المعدل الوسطي لتصنيفWOMAC للمجموعة أ 22 ومجموعة ب كان 29.6) 0.0001> (p-value)

و ايضا كان هناك فرقا احصائيا مهما فى الشهر الثانى عشر لتصنيفى WOMACو Lequesne's بين المجموعتين أ و ب.(p-value < 0.0001) .لم يتم تسجيل اى عوارض جانبية شديدة خلال مدة البحث.

من خلال دراستنا فى هذا البحث استنتجنا ان استخدام الحقن المفصلى لهايلورونيك اسيد 25 ملغم اسبوعيا و لمدة خمسة اسابيع مع عقاري كلوكوز امين 1500 ملغم و كوندروتين سلفيت 645 ملغم يوميا عن طريق الفم لمدة سنة واحدة كانت نتائجه افضل من استخدام الحقن المفصلى لهايلورونيك اسيد 25 ملغم اسبوعيا و لمدة خمسة اسابيع فقط.ان هذا المزيج الدوائى كان افضلا فى تخفيف الام مفصل الركبة و تحسين اداء وظيفة المفصل ومن ثم اداء المريض و لفترة اطول للمرضى الذين يعانون من التصنيف الثانى و الثالث لسوفان الركبة .

ABSTRACT

We studied the effect of combination of intra articular injection of hyaluronic acid plus oral glucosamine and chondroitin sulfate compared to intra articular injection of hyaluronic acid alone in treatment of knee osteoarthritis.

In prospective comparative study 104 patients with knee osteoarthritis were randomized according to inclusion exclusion criteria into two groups to receive either, intra-articular injections of hyaluronic acid 25 mg plus oral combination of glucosamine 1500mg and chondroitin sulfate 645 mg daily for 1 year, or receive intra-articular injection of hyaluronic acid 25 mg alone. The patients were followed up for 12 months period. The primary outcome measurements were according to Lequesne's and WOMAC scores.

In both group A and B significant reduction in the mean of both Lequesne's and WOMAC scores from baseline were seen at all follow up visit for 12 months. Also there were significant statistical differences at 12 months for both Lequesne's and WOMAC scores between group A and group B (p-value < 0.0001). No severe adverse events related to drugs were observed.

We concluded that intra-articular injections of hyaluronic acid plus oral combination of glucosamine and chondroitin sulfate for 1 year are superior to intra-articular injections of hyaluronic acid alone.

Key words: ***OA*** *osteoarthritis,* ***HA*** *hyaluronic acid, GS glucosamine, CS chondroitin sulfate, IA Intraarticular.*

INTRODUCTION

Osteoarthritis is the most common cause of musculoskeletal disability in elderly. (1) Osteoarthritis can arise in any synovial joint in the body (2) The important risk factors for OA are obesity, previous knee injury, selected physical activity.(3, 4) . Other risk factors are torn meniscus, ligament instability. (5) The articular surface is lubricated by a viscous fluid called synovial fluid. It is produced by synovial membrane. (6) The cartilage consists of 70% water, collagen with proteoglycans and glycosaminoglycans (consisting mainly of aggrecan and chondroitin) produced by chondrocytes. (7) Hyaluronic acid is one of the most important components of synovial fluid. It is usually accepted as protector of articular cartilage. (8)

The HA was discovered by Meyer and Palmer in 1934 in the vitreous humor of cattle eyes. (9) The concept of Viscosupplementation for the joint was developed by Endre A. Balazs and his co-worker in 1960s. Hylan is an easily deformable gel with fluid like property. In that time, the development of hyaluronan, derived from human umbilical cord and rooster comb, for the medical use was begun. (8)

Viscosupplementation came into clinical use in Japan and Italy in 1987, in Canada in 1992, in Europe in 1995 and in the United States in 1997. (10) At present, multiple Viscosupplementation products from various sources, with different degree of purity and different molecular weights,

are available for medical applications (11) Hyaluronan is a large, polydisperse, linear glycosaminoglycan. The synoviocytes, fibroblasts and chondrocytes all synthesize HA. In normal human synovial fluid the MW of HA is 6-7 x 10 6 Da. (12) the actual period that the hyaluronan stays with in joint space is in the order of hours to days, but the time of clinical efficacy is often in the order of months. (11) When the fluid accumulates in joint due to any pathology, the concentration of HA will decrease, which leads to a viscous circle. In arthragia due to pain and increase in fluid volume, the joint movement decrease. In such situation the injected HA restores the theological properties of synovial fluid. (8) Glucosamine and chondroitin sulfate are symptomatic slow-acting drugs for osteoarthritis (SYSADOA). These substances are characterized by both a several week delay in improvement of OA symptoms. . (13) The rationale for their usage is based on a general belief that osteoarthritis is associated with a local deficiency in some key natural substances. Therefore, it is assumed that they work as a "building box" for cartilage extracellular matrix repair. (14)

PATIENTS AND METHODS

This study was prospective comparative clinical trail. From November 2008 to November 2009 one hundred twelve patients attending private out patient clinic in Sulaimaniyah city with a diagnosis of OA of one or both knee joints according to the American College of Rheumatology Criteria were included. All patients had x ray of knee with kellgren and Lawrence grade two or three and hematological investigation prior to study entry.

Inclusion criteria are adult of both genders with a minimum age of 45 years. OA of one or both knee joint, radiographic changes equivalent to kellgren stage II and III, and dissatisfaction with prior attempt at non operative treatment as NSAID, physiotherapy.

The most widely used classification schemes for OA are based on the Radiological appearance of the joint Severity may be graded based on the 0-4 scale developed by:

Kellgren and Lawrence (15);

- Grade 1; doubtful narrowing of joint space and possible osteophyte lipping.
- Grade 2; definite osteophyte and possible narrowing of joint space.
- Grade 3; moderate multiple osteophytes, definite narrowing of joint space, some sclerosis and possible deformity of bone ends.
- Grade 4; large osteophytes, marked narrowing of joint space, sclerosis

Exclusion criteria are; Kellgren grade 1 and grade 4 OA of knee. Allergy to egg protein, any systemic active inflammatory condition such as Rheumatoid arthritis, gout, pseudo gout, ankylosing spondylitis, or infection as septic arthritis. Meniscal diseases, ligament and Meniscal injuries.

As our study is an Intraarticular injection of HA plus combination of oral GS and CS compared to Intraarticular injection of HA alone, Following initial screening, patients who fulfilled the entry criteria were admitted to the trial. We divided randomly the patients into two groups. Group A were 55 patients who received IA injection of HA and oral GS and CS and group B were 49 patients who received injection of HA alone to one or both knee joint.

For assessment of pain and function of knee joint we used both WOMAC and Lequesne's indices to know the effect of treatment on pain and functional outcome of this new line of treatment of OA. The patients were asked at the end of treatment about the satisfaction and any adverse events during follow up period. The WOMAC and Lequesne’s indices were used for assessments.

Figure -1: intra articular injection of HA into knee joint.

Patient's Full Name: _____ **Date:**
_____/_____/_____

Month Day Year

WOMAC OSTEOARTHRITIS INDEX [21]

1. The following questions concern the amount of pain you are currently experiencing in the knees. For each situation, the amount of pain in the past 48 hours.

		None	mild	moderate	severe	extreme
A. Walking on a flat surface	A.	☐	☐	☐	☐	☐
B. Going up or down stairs	B.	☐	☐	☐	☐	☐
C. At night while in bed	C.	☐	☐	☐	☐	☐
D. Sitting or lying	D.	☐	☐	☐	☐	☐
E. Standing upright	E.	☐	☐	☐	☐	☐

2. The level of pain experienced in the past 48 hours for each one of your knees.

		None	mild	moderate	severe	extreme
A. Right knee	A.	☐	☐	☐	☐	☐
B. Left knee	B.	☐	☐	☐	☐	☐

3. How severe is stiffness after first awakening in the morning?

None	mild	moderate	severe	extreme
☐	☐	☐	☐	☐

4. How severe is stiffness after sitting, lying, or resting later in the day?

None	mild	moderate	severe	extreme
☐	☐	☐	☐	☐

5. The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities, please indicate the degree of difficulty experienced in the last 48 hours, in your knees.

What degree of difficulty do you have with?

		None	mild	moderate	severe	extreme
A. Descending (going down) stairs	A.	☐	☐	☐	☐	☐
B. Ascending (going up) stairs	B.	☐	☐	☐	☐	☐
C. Rising from sitting	C.	☐	☐	☐	☐	☐
D. Standing	D.	☐	☐	☐	☐	☐
E. Bending to floor	E.	☐	☐	☐	☐	☐
F. Walking on a flat surface	F.	☐	☐	☐	☐	☐
G. Getting in/out of car	G.	☐	☐	☐	☐	☐
H. Going shopping	H.	☐	☐	☐	☐	☐
I. Putting on socks/stockings	I.	☐	☐	☐	☐	☐
J. Rising from bed	J.	☐	☐	☐	☐	☐
K. Taking off socks/stockings	K.	☐	☐	☐	☐	☐
L. Lying in bed	L.	☐	☐	☐	☐	☐
M. Getting in/out of bath	M.	☐	☐	☐	☐	☐
N. Sitting	N.	☐	☐	☐	☐	☐
O. Getting on/off toile	O.	☐	☐	☐	☐	☐
P. Heavy domestic duties (mowing the lawn, lifting heavy grocery bags)	P.	☐	☐	☐	☐	☐
Q. Light domestic duties (such as tidying a room, dusting, cooking)	Q.	☐	☐	☐	☐	☐

7

Patient's full name ----------

Lequesne's index [18]

Pain or discomfort

1. During nocturnal bed rest:
   - non or insignificant 0
   - only on movement or in certain position 1
   - with no movement 2

2. Morning stiffness or regressive pain after rising
   - one minute or less 0
   - more than 1 minute but less than 15 min 1
   - 15 minutes or more 2

3. after standing for 30 minutes 0 -- 1 ☐

4. While ambulating
   - None 0
   - Only after ambulating some distance 1
   - After initial ambulation and increasing with continued ambulation 2
   - After initial ambulation not increasing With continued ambulation 1

5. While getting up from sitting with out the help of arms 0 – 1 ☐

6. Maximum distance walked (may walk with pain)
   - Unlimited 0
   - More than 1 km, but limited 1
   - About a km in about 15 min 2
   - From 500 to 900 m about 15 min 3
   - From 300 to 500 m 4
   - From 100 to 300 m 5
   - Less than 100m 6
   - With one walking stick or crutch 1
   - With two walking sticks or crutches 2

7. Activity of daily living

• Able to climb up a standard flight of stairs 0 -- 0.5 -- 1 -- 1.5 -- 2	☐	☐	☐	☐	☐
• Able to climb down a standard flight of stairs 0 -- 0.5 -- 1 -- 1.5 -- 2	☐	☐	☐	☐	☐
• Able to squat or bend on the knees 0 -- 0.5 -- 1 -- 1.5 -- 2	☐	☐	☐	☐	☐
• Able to walk on uneven ground 0-- 0.5 -- 1 -- 1.5 -- 2	☐	☐	☐	☐	☐

Without Difficulty: 0
With Small Difficulty: 0.5
Moderate: 1
Important Difficulty: 1.5
Unable: 2.

Statistical package for social science (SPSS) version 16 was used for data analysis. ANOVA test was used to compare the means within group A and B separately for both indices at different period of follow up. T-test was used to compare the means of both indices between the two groups at the baseline and at twelve month period. Level of significance was regarded to be <0.05.

RESULTS AND DISCUSSION

Total Number of patients was 104 in the study. 55 patients in group A, and the number of patients in group B were 49 patients.
The base line characteristic features are shown in table 1.

Table -1:Baseline features of patients of both groups

Characters of patients		Group A	Group B
Mean of age		*61 years*	*60 years*
Female to male ratio		*3.6:1*	*3.1:1*
Duration of OA		*27 months*	*24 months*
Right side OA	*Grade 2*	*24*	*22*
	Grade 3	*27*	*17*
Left side OA	*Grade 2*	*23*	*25*
	Grade 3	*27*	*19*
Mean of Lequesne's score		*14.4*	*13.8*
Mean of WOMAC score		*35.9*	*34.7*

From the analysis of data, both groups showed a decline in Lequesne's and WOMAC knee OA scores, also there were significant decreases in Lequesne's and WOMAC knee OA scores in group A, compared to group B. In figure (2) and figure (3).

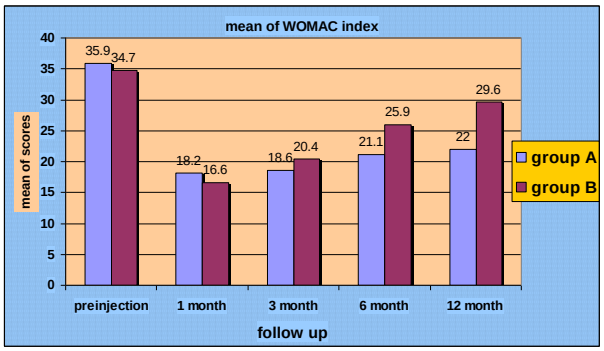

Figure -2:shows the means of knee OA scores over 12 Months of follow up period for Lequesne's score.

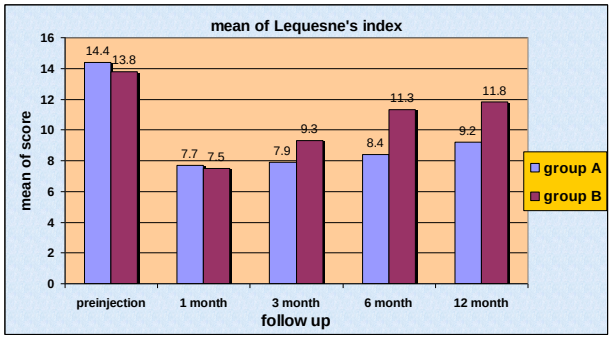

Figure -3: shows the means of knee OA scores over 12 Months of follow up period for WOMAC score.

The statistical analysis done for means in each groups separately .In group A there was a significant statistical difference among the means of both scores (Lequesne's and WOMAC) of the different period of follow up (P value < 0.0001).

Also in the group B there was significant statistical difference among the means of both scores (Lequesne's and WOMAC) of the different period of follow up (P value < 0.0001). The statistical analysis done for the means of scores of both (Lequesne's and WOMAC) between group A and group B at baseline and at 12 month of follow up, there was no significant statistical difference between the means of scores of (Lequesne's and WOMAC) at baseline (P value = 0.232 for Lequesne's index ,P value = 0.406 for WOMAC index)

But there was a significant statistical difference of the means of scores of both (Lequesne's and WOMAC) between group A and group B at the 12 months of follow up (P value = 0.001 for Lequesne's index, P value = 0.001 for WOMAC index).The adverse events that happened during follow up period is minimal and mostly related to local adverse event mostly pain at injection site and swelling of knee joint.

In the recent years the use of Viscosupplementation becomes widely used for knee OA. In a study in United Kingdom which was done by E. C. Huskisson and S. Donnelly (16), they examined the efficacy, safety and patient satisfaction with 5 weekly intra articular injection of HA (10mg/ml) to knee joint in 100 patients. They were found that intra articular HA was superior in first few months to placebo but at 6th month their Lequesne's scores is elevated as the patients were starting to complain of symptoms of OA. The mean of Lequesne's score at base

line was (13.4) and at 6 months was (11.2) in HA treated group. In our study the mean of Lequesne's score at base line in group A was (14.4), at month 6 was (8.4) and at month 12 was (9.2). In group B of our study which they were received HA injection alone; the mean of Lequesne's score at base line was (13.8), at month 6 was (11.3) and at month 12 was (11.8). The reported adverse events during their study in HA treated group were few and mostly related to local reaction at injection site, flare at knee and effusion. While in our study the adverse events were injection site pain more than 1 day (11%, 10%) and swelling of knee joint (14%, 13%) in group A and B respectively.

A study done in Taiwan (Shu-Fen Sun et al) [17], they also used HA for treatment of osteoarthritis in a prospective study The assessment of out come in their study was by Lequesne's index alone as they found Lequesne's score changed from 10.3 at baseline to 5.7 at 6 months, while in our study we used both Lequesne's and WOMAC indices. Their result supported our study. The score of Lequesne's was lower than our result at baseline and at 6 months, this is probably because of our patients were grade 2 and 3 kellgren and Laurence knee osteoarthritis and follow up for 12 months. From the above 2 studies in comparism to our results in group B (injection alone) we concluded that Intraarticular injections of HA is effective up to 6 months. The complication of injection of HA was local and transient with no systemic adverse events.

Regarding the effect of glucosamine and chondroitin sulfate, there were variable effects of these drugs on knee osteoarthritis. In a study done by Sudha et al in India (18). They used Lequesne's index as changed from (11.5) at baseline to (8) at 12 weeks. In our study the group who used combined injection and oral combination of glucosamine and chondroitin sulfate, the mean of Lequesne's score were changed from (14.4) at baseline to (7.9) at 3 months. This explains that the Lequesne's scores were more dropped in our patient in comparism to that study in 3 months.

Other studies had used chondroitin sulfate or glucosamine alone. As a study was done by Bernard et al (19) on efficacy and tolerability of chondroitin sulfate in 307 patients and Gabriel et al (20) compared the use of oral glucosamine in dose of 1500 mg daily to placebo and acetaminophen. both studies showed effectiveness of these drugs the

scores is less decreased compared to our results. In there study no severe adverse events were recorded.

The above studies on both glucosamine and chondroitin sulfate is explaining that both drugs were effective in treatment of osteoarthritis but in comparism to our result there was more response to treatment if these drugs combined with intra articular injection of HA and prolong their effect on knee joint for patients with knee OA grade 2 and 3, who do not get benefit from NSAIDs and non pharmacological therapies.

We concluded from this study that the combination of intra articular injection of Hyaluronic acid 5 weekly injections, plus oral glucosamine and chondroitin sulfate for 1 year was effective in reducing pain and increasing functional outcome of patient with knee OA with kellgren grade 2 and 3.

REFERENCES

1. Yuanyuan Wang, Louise F Prentice, Luis Vitetta, Anita E Wluka, Flavia M Cicuttini. The effect of nutritional supplements on osteoarthritis. Alternative Medicine Review; 9(3):275-96(2004).
2. David Borenstein, Shari Diamond. Arthritis In: Jeffry S Fischgrund. Orthopedic Knowledge Update 9. American academy of orthopedic surgeons: p. 227-9(2008).
3. Cyrus Cooper, Shelagh Snow, Timothy E MCAlindon, Samantha Kellingray, Brenda Stuart, David Coggon, et al. Risk factors for the incidence and progression of radiographic knee osteoarthritis. Arthritis and Rheumatism; 43 (5):995-1000(2000).
4. Helga Lorenz, Wiltrud Richter. Osteoarthritis: Cellular and molecular changes in degenerating cartilage. Progress in Histochemistry and Cytochemistry; 40:135–63(2006).
5. Osteoarthritis In: Louis Solomon, David J Warwick, Selvaduria Nayagam. Apley's System of Orthopedic and Fracture. 8th ed. Arnold; P 77-86,472-3(2001).
6. Disease of articular tissue. Nicholas A Athanasou In: Pathological Basis of Orthopedic and Rheumatic disease. 1st ed. Arnold. p 156-60(2001).

7. Megumi Hashimoto, Tomoyuki Nakasa, Tomohiro Hikata, Hiroshi Asahara. Molecular Network of Cartilage Homeostasis and Osteoarthritis. Medical Research Review; 28 (3):464-81(2008).
8. Sureshwar pandey, Anil kumar pandey. Intra-articular hyaluronic acid In: Sureshwar pandey, Anil kumar pandey Intra-articular and allied injection. 2nd edition. Jaypee Brother; p 18-21(2005).
9. Kazuaki Kakehi, Mitsuhiro Kinoshita, Shin-ichi Yasueda. Hyaluronic acid: separation and biological implications. Journal of Chromatography; 797:347–55(2003).
10. Dennis Y Wen. Intra-articular Hyaluronic Acid Injections for Knee Osteoarthritis. American Family Physician; vol.62/No.3(2000).
11. E J P Jansen, P J Emans, C M Douw, N A Guldemond, L W Van Rhijn, S.K. Bulstra, et al. One intra articular injection of hyaluronan prevents cell death and improves cell metabolism in a model of injured articular cartilage in rabbit. Journal of Orthopaedic Research; 26(5):624-30(2008).
12. Kenneth D Brandt, Gerald N Smith, and Lee S Simon. Intra articular injection of hyaluronan as treatment for knee osteoarthritis. Arthritis and Rheumatism; 43(6):1192–203(2000).
13. Fajardo M, Di Cesare PE. Disease-modifying therapies for osteoarthritis: current status. Drugs Aging; 22:141–61(2005).
14. Tiraloche G, Girard C, Chouinard L, Sampalis J, Moquin L, Ionescu M, et al. Effect of oral glucosamine on cartilage degradation in a rabbit model of osteoarthritis. Arthritis Rheum; 52:1118–28(2005).
15. J H Kellgren, J S Lawrence. Radiological assessment of osteo-arthrosis. Ann Rheum Dis; 16:494-502(1957).
16. E C Huskisson and S Donelly. Hyaluronic acid in the treatment of osteoarthritis of the knee. Rheumatology; 38; 602-07(1999).
17. Shu-Fen, Chien Wei Hsu, Chiao-Wen Hwang, Pei-Te Hsu, Jue-Long Wang, Shin-Lung Tsai, et al. Hyaluronate improves pain, physical function and balance in the geriatric osteoarthritis knee: a 6 month follow-up study using clinical tests. Osteoarthritis and Cartilage; 14:696-701(2006).
18. Sudha V, Prabhu M, U Shashikiran, Adiga Sachidananda, Sharath Rao, K Laxminarayana Bairy et al. Efficacy and tolerability of Glucosamine - Chondroitin sulfate - Methylsulfonylmethane (MSM)

in osteoarthritis of knee in Indian patients. Iranian journal of Pharmacology and Therapeutics; 3(2):61-5(2004).

19. Bernard Mazieres, Michel Hucher, Mohammed Zaim, Patrick Garnero. Effect of chondroitin sulphate in symptomatic kneeosteoarthritis: a multicentre, randomised, double-blind, placebo-controlled study. Ann Rheum Dis; 66:639–45(2007).
20. Gabriel Herrero, Jose Andres, Maria del ,Francisco Jvier , Pere Benito, Emilio Martin-Mola et al. Glucosamine sulfate in treatment of knee osteoarthritis symptoms. Arthritis and Rheumatism; 56 (2):555-67(2007).
21. Bellamy N. WOMAC: a 20-year experiential review of a patient-centered self-reported health status questionnaire. Journal of Rheumatology; 29:2473-6(2002).