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RESEARCH ARTICLE

Current status of glucosamine and chondroitintherapy in osteoarthritis.

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Abstract

Osteoarthritis is one of the common disabling chronic disorder in geriatrics. Its chronic nature makes it difficult to conduct clinical trials. With the available evidence, the usage of glucosamine and chondroitin in osteoarthritis (OA) is controversial. With the view of keeping update on the use of these products, various standard guidelines were reviewed to find the current status of glucosamine(G) and chondroitin(C) in OA. Incongruity was noted in different guidelines and no confirmatory evidence was available from the analysis of latest clinical trials. Some of the studies has found its beneficial effects in reducing only symptoms but others found no definite evidence for its use in OA. However, none of the studies found the drugs as unsafe when used in OA. Hence, we conclude that it is prudent to use the combination(G and C) for a trial run of 2-3 months, as they are slowly acting agents and patient centered approach should be considered after a trial run period for its continual as a therapy in OA.

INTRODUCTION

Osteoarthritis is a commonest cause of arthritis and a leading cause of pain and disability worldwide (Arden and Nevitt, 2006). Osteoarthritis (OA) accounts for 15% of all musculoskeletal disorders in patients aged 45 years and over in primary care(National Collaborating Centre for Chronic Conditions, 2008).This degenerative articular disease predominantly affects the knees, hips, hands and feet.

Glucosamine is a component of all human tissues, but concentrated in connective tissues and in cartilage. Glucosamine is a natural aminomonosaccharide and a component of the glycosaminoglycan chains in aggrecan and other proteoglycans found in the synovial fluid as well as articular cartilage of joints (Tabassi and Garnero, 2007). Aggrecan and other proteoglycans trap water in the matrix of cartilage, provides resilience for joint function(Sanders and Grundmann, 2011). In vitro experiments of chondrocyte cultures show addition of glucosamine increases aggrecan synthesis, suggesting glucosamine's major role in increasing synovial fluid availability and maintaining joint lubrication(Dodge and Jimenez, 2003, Uitterlinden et at., 2006 and Barclay et al., 1998).

The protective effect of glucosamine on chondrocyte include direct stimulation, integration of sulfur into cartilage, and protection against degradative processes by altered gene expression (Setnikar et al., 1993, Reichelt et al., 1994 andAmbrosio et al., 1981). The exact mechanism and effectiveness of glucosamine in OA is still a controversy.This review was an effort to know the current status of these two products in OA by critically analyzing the latest standard guidelines and clinical studies.

CLINICAL EVIDENCE OF GLUCOSAMINE AND CHONDROITIN IN OA

Wandel et al., 2010, analyzed over 10 trials in 3803 patients with main outcome measure being pain intensity and change in minimal width of joint space. The study concluded that compared with placebo, glucosamine, chondroitin, and their combination do not reduce joint pain or have an impact on narrowing of joint space.

On the contrary more recent studies (Fransen et al., 2014) concludes that glucosamine sulfate(Gs) and chondroitin sulfate(Cs) is beneficial when given for a long duration of 2yr.

Glucosamine/ Chondroitin Arthritis Intervention Trial (GAIT), which included more than 1,500 patients, was one of the most popular trial done in large number of patients. The trial had five arms comparing glucosamine alone, chondroitin alone, a combination of glucosamine and chondroitin, celecoxib, and placebo. The results were favorable only for the combination of glucosamine and chondroitin, which appeared to be effective for moderate to severe osteoarthritis of the knee. Chondroitin alone did not show benefit for osteoarthritis of the knee or hip in a meta-analysis. Finally GAIT- concluded that combination of Gs+Cs is beneficial in moderate to severe OA and recommends a trial period of 3 months for the treatment and then discontinue if there is no satisfactory response. (Sinusas, 2012).Similarly **(**Van Manen et al., 2012 and Sinusas, 2012) reiterated the usage of glucosamine for a trial period and the decision to continue is made only after interaction with patient about its benefit during the trial period.

Conflict is also noted against the glucosamine formulations. Studies have concluded that, formulation glucosamine hydrochloride (GHCL) is ineffective but Glucosamine sulfate(Gs) given for longer period has shown its clinical benefits in knee OA(Wu et al., 2013 and Kwoh et al., 2014). However a study performed in China establishes that glucosamine hydrochloride and glucosamine sulfate are equally effective. (Qiu et al., 2005) Another study, concludes that regardless of the formulation used, the reason for no or marginal beneficial effects observed with glucosamine is because of the under dosing which stems from low bioavailability at the commonly calculated dose of 1.5g/d doses in humans. (Habashi and Jamali, 2011).

It is observed from above discussion that the incessant question on the usage of Gs and Cs as therapeutic agents in OA remains unanswered by these clinical studies. The potential hurdles that have led to the inconclusive results of the efficacy of Gs and Cs in osteoarthritis is summarized by Hunter and Matthews, 2011.

1) Target selection and validation has been challenging because the specific cause of OA is relatively unknown.

2)Though there is no shortage of in vitro and in vivo models, establishing the validity and utility of these models for ready translation into the human model in the face of a paucity of successful candidates is challenging.

3) The third reason being trial endpoints. Pain trials generally use subjective patient reported outcomes. Placebo effects in OA trials can be high and persist over several months. A total of 97 structure modification trials are hindered by a combination of slow and unpredictable disease progression and relatively insensitive detection tools (imaging, biochemical biomarkers). This combination of factors often led to inconclusive trials. Hence, it is important that the future research should focus on performing long term clinical trials in large number of patients with these products.

A BIRD'S-EYE VIEW OF DIFFERENT RECOMMENDATIONS

European League against rheumatism (Eular) recommendation:

Eular recommendation on hip OA concludes that there is no direct evidence to support the clinical benefits (pain relief and functional improvement) of glucosamine sulfate (Gs) in hip OA, and there is Ib evidence for chondroitin sulfate (Cs). Category Ib, is the evidence based on only one RCT (randomized controlled trials) (Zhang et al., 2005). Recommendations for knee OA support the use of both Gs and Cs for their symptomatic effects. The level of evidence for both glucosamine sulphate and chondroitin sulphate is Ia for knee OA. Category Ia indicates evidence by meta-analysis of many randomized controlled trials (Jordan et al., 2003**).**

Osteoarthritis Research Society International (OARSI):

Glucosamine and chondroitin were both found to be "not appropriate" for all patients when used for disease modification and "uncertain" for all patients when used for symptom relief. Quality of evidence was found to be good for both the products.(OARSI guidelines. 2010)

Meta-analyses and SRs were assigned a quality rating of "Good", "Fair", or "Poor" using the Assessment of Multiple Systematic Reviews Tool (AMSTAR). The Cochrane Risk of Bias Assessment Method was used to rate RCTs.(McAlindon et al., 2014)Voting and scoring was done according to the RAND/UCLA Appropriateness Method, the panelists ranked the appropriateness of each treatment on a ninepoint scale, in which a score in the range 1-3 is considered 'inappropriate', 4-6 'uncertain', and 7-9 'appropriate'. (Fitch et al.,2001).

Score between 3 and 6, or a treatment with disagreement, was classified as "uncertain". An "uncertain" recommendation can reflect either the ambiguous state of current evidence or equivocal appropriateness either due to a moderately unfavorable risk profile or to limited efficacy. However, the 'uncertain' classification is not intended to be a negative recommendation or preclude use of that therapy. Rather it indicates a role for physician patient interaction in determining whether this treatment may have merit in the context of their individual characteristics, co-morbidities and preferences.

American academy of orthopaedic surgeons (AAOS) recommendations:(Treatment of osteoarthritis of the knee. 2013)

Donot recommend using glucosamine and chondroitin for patients with symptomatic osteoarthritis of the knee.
Strength of Recommendation: Strong
Description: A Strong recommendation means that the quality of the supporting evidence is high
Implications: Practitioners should follow a Strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Level of evidence: High

American college of rheumatology (ACR) Guidelines: (Marc et al., 2012**)**

Conditionally recommend that patients with knee/hip OA should not use the following:
Chondroitin sulfate
Glucosamine

National Institute for Health and Care Excellence (NICE) Guidelines

Do not offer glucosamine or chondroitin products for the management of osteoarthritis. (National Institute for Health and Care Excellence2014). The outcomes that were considered by guideline development group (GDG) for decision making were pain, function, structure modification and adverse events profile. The GDG reviewed the evidence for the use of glucosamine and chondroitin as separate agents and in combination in joints such as hip, knee and hand. After reviewing the clinical evidence, the GDG concluded that the symptom modifying data (e.g. improvement in pain or function) were not positive to permit their use in OA.

Economic consideration: By looking at the results of the clinical review the GDG considered the increase in effectiveness observed with glucosamine was not clinically important and therefore considered the results of the cost-effectiveness analyses as negligible and non-significant. GDG also suggested interventions should first be proven effective (compared to placebo) before considering cost effectiveness and noted insufficient clinical data on structural modification.

SUMMERY AND CONCLUSION

Inconsistency is noted from the overall critical analysis of the different guidelines. The three international guidelines AAOS, ACR and NICE donot recommend both the products for OA. However, EULAR provides RCT evidence (Ia) for using both of them in knee OA (not in other joints) but OARSI concludes as “uncertain” for symptom relief and “inappropriate” for disease modification of all patients with OA. Some clinical studies show positive results and others reveal negative results, but none of the studies till date showed it as unsafe. In conclusion, the mystery continues for Gs and Cs usage in OA. Nonetheless, in the lights of the fact that some countries like North America already recommends it to be used as dietary supplements, it is justifiable to use it in all cases of OA as an alternative treatment. Gs in combination with Cs should be considered as a viable option. It is prudent to use the combination for a trial run of 2-3 months as they are slowly acting agents and patient centered approach should be considered after a trial run period for its continual as treatment in OA.

PROSPECTIVE

Long term studies in large number of patients for safety and efficacy and also, studies to evaluate its potential use as a preventive or delaying strategy in osteoarthritis will give us the more confirmatory evidence for its inclusion as one of the independent therapeutic option in OA.

CONFLICT OF INTEREST: None

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