Palestrica of the third millennium – Civilization and Sport
Vol. 15, no. 1, January-March 2014, 22–25

Clinical effects of multimodal therapy in patients with knee osteoarthritis

Efectele clinice ale terapiei multimodale la pacienţii cu gonartroză

Rodica Ungur, Viorela Ciortea, Ioan Onac, Teodora Mocan, Laszlo Irsay, Maria Dronca, Şoimiţa Suciu, Ileana Monica Borda
Rehabilitation Department, Iuliu Haţieganu University of Medicine and Pharmacy Cluj-Napoca
Clinical Rehabilitation Hospital

Abstract

Background. Osteoarthritis (OA) is considered to be the most common rheumatologic disease which affects more than 80% of the population above 55 years. Destruction and loss of articular cartilage is a central feature of OA and chronic pain its cardinal symptom, compromising the mobility and the quality of life of those affected. The failure of conventional treatments, analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs) to satisfactorily control OA progression, combined with their frequent adverse side effects, may explain the increasing use of such SYSADOA (Symptomatic Slow-Acting Drugs for Osteoarthritis) therapies as glucosamine sulfate (GS). Physiotherapy is one of the recommended no pharmacological management options in patients with OA

Aims. The aim of the study was to demonstrate effectivness of multimodal therapy for patients with knee OA.

Methods. 30 patients, diagnosed with knee OA according to the American College of Rheumatology, stage 2 or 3 (modified Kellgren-Lawrence classification) on frontal knee radiography, were enrolled in the cohort prospective study and were treated with multimodal therapy: 10 days ultrasound therapy, laser therapy, thermotherapy and physical exercises associated with short periods of NSAID (10 days) and GS 1500 mg daily for six months. Pain on visual analogue scale (VAS) and WOMAC score (WS) were evaluated prior to and at the end of therapy. SPSS software version 17 was used for statistical analysis.

Results. At the end of therapy a statistical significant decrease of pain on VAS (p=0.045) and WS (p=0.007) was observed. No adverse effects were observed.

Conclusions. The multimodal therapy which combines ultrasound therapy, laser therapy, thermotherapy and physical exercises associated with short periods of NSAID (10 days) and GS 1500 mg daily for six months is effective and safe for patients with knee OA.

Key words: osteoarthritis, multimodal therapy, glucosamine, physiotherapy.

Rezumat

Premize. Artroza este considerată cea mai frecventă boală reumatologică, care afectează mai mult de 80% din populaţia de peste 55 de ani. Degenerarea şi mai apoi pierderea cartilajului articular sunt elementele centrale în patogeneza artrozei, iar durerea cronică este simptomul cardinal, care compromite mobilitatea articulară şi calitatea vieţii la cei afectaţi. Eşecul tratamentelor convenţionale, medicamente analgezice sau antiinflamatoare nesteroidiene (AINS), în a controla satisfăcător progresia artrozei, combinat cu efectele lor secundare frecvente, poate explica utilizarea tot mai largă a medicamentelor de tip SYSADOA (Symptomatic slow acting drugs for OA), aşa cum este glucozamina sulfat (GS). Fizioterapia este una dintre cele mai recomandate opţiuni de management nonfarmacologic la pacienţii cu artroză.

Obiective. Scopul studiului a fost de a demonstra eficienţa terapiei multimodale la pacienţii cu gonartroză.

Metode. 30 de pacienţi, diagnosticaţi cu gonartroză conform criteriilor Colegiului American de Reumatologie, grad 2 sau 3 pe scala Kellgren Lawrence modificată, apreciată pe radiografia frontală de genunchi, au fost înrolaţi într-un studiu prospectiv de cohortă şi au fost trataţi printr-un program de terapie multimodală, care a inclus ultrasonoterapie, biostimulare laser, termoterapie şi exerciţii fizice asociate cu AINS, toate administrate timp de 10 zile şi GS 1500 mg/zi administrată timp de şase luni. Durerea pe scara analog vizuală (VAS) şi scorul WOMAC (WS) au fost evaluate înainte şi după terminarea tratamentului. Programul SPSS, versiunea 17, a fost utilizat pentru analiza statistică a datelor.

Rezultate. La sfârşitul tratamentului s-a observat o scădere semnificativă statistic a durerii pe VAS (p=0,045) şi a WS (p=0,007). Nu au fost observate efecte adverse.

Concluzii. Terapia multimodală, care combină ultrasonoterapia, biostimularea laser, termoterapia şi exerciţiile fizice asociate cu perioade scurte de AINS (10 zile) şi GS 1500 mg/zi, timp de şase luni, este eficientă şi sigură pentru pacienţii cu gonartroză.

Cuvinte cheie: artroză, terapie multimodală, glucozamină sulfat, fizioterapie.

Received: 2014, February 15; *Accepted for publication:* 2014, March 3;
Address for correspondence: Clinical Rehabilitation Hospital, Rehabilitation Department, No. 46-50, Viilor St. 400437, Cluj-Napoca
E-mail: viorela.ciortea@yahoo.com, ungurmed@yahoo.com

Copyright © 2010 by "Iuliu Haţieganu" University of Medicine and Pharmacy Publishing

Introduction

Osteoarthritis (OA) is considered to be the most common rheumatologic disease. Destruction and loss of articular cartilage is a central feature of OA and chronic pain is its cardinal symptom, compromising the mobility and the quality of life of the affected subjects. The goal of treatment, therefore, is to help reduce pain, prevent reductions in functional ability and maintain or increase joint mobility (Ng et al., 2010). The failure of conventional treatments, analgesics or non-steroidal anti-inflammatory drugs (NSAIDs), to satisfactorily control OA progression, combined with their frequent adverse effects, may explain the increasing use of SYSADOA (Symptomatic Slow-Acting Drugs for Osteoarthritis) therapies such as glucosamine sulfate (GS) (Calamia et al., 2010). Because no single therapy is adequate in OA, the major clinical guidelines for the management of OA generally agree that therapy should involve a combination of non-pharmacological and pharmacological therapies (i.e., multimodal therapy) (Altman, 2010). The ACR recommendations for hip and knee OA management refer to non-pharmacological therapies as the „cornerstone of OA management," and state that pharmacological therapies should function as add-on therapy to non-pharmacological treatment, the latter of which should be maintained throughout the course of the disease (***, 2000). In accordance with Osteoarthritis Research Society International (OARSI), physiotherapy is one of the recommended non-pharmacological management options in patients with OA. It includes physical exercise (aerobic activity, muscle strengthening, and range-of-motion exercises), local thermotherapy (ice or heat), electrotherapy (TENS) (Zhang et al., 2008). Ultrasound (US) therapy and low-level laser therapy (LLLT) were not included in OARSI recommendations for patients with knee osteoarthritis although, in the last years, many studies have demonstrated clinical (Loyola-Sánchez et al., 2010; Hegedus et al., 2009) and biological (Guo et al., 2011; da Rosa et al., 2012) benefits of these procedures in OA.

Hypothesis

The aim of this study was to evaluate the effects of multimodal therapy, which includes short periods of NSAIDs (10 days) and GS 1500 mg daily for six months, physical exercise, US therapy, LLLT and hot pack, on pain and joint function in patients with knee osteoarthritis.

Material and methods

According to the Helsinki Declaration, the approval of the Ethics Committee of the "Iuliu Hatieganu"University of Medicine and Pharmacy Cluj-Napoca (Romania) regarding research on human subjects was obtained. All study participants gave their written informed consent.

Research protocol

Period and place of the research. The study took place between September 2009 and August 2011 in the outpatient department of the Rehabilitation Hospital Cluj-Napoca.

Subjects and groups. Following a 10 day washout period (NSAIDs or analgesics), 30 patients (aged between 40 and 70 years) from the Rehabilitation Hospital Cluj-Napoca, diagnosed with knee OA according to the American College of Rheumatology criteria, stage 2-3 (modified Kellgren-Lawrence classification) on a frontal knee radiography, with normal values of erythrocyte sedimentation rate and C-reactive protein, were enrolled in a cohort prospective study. The exclusion criteria were: inflammatory rheumatic disease, infectious or endocrine-related arthropathy, gout, chondrocalcinosis, diabetes mellitus, unstable medical illness, any contraindication to physical therapy, lower limb arthroplasty, intra-articular knee injections (viscosupplement or corticosteroids) or physical therapy in the preceding six months. The study was approved by the local Ethics Committee and the informed consent of the patients was obtained.

Interventions. The 30 patients of the experimental group were treated for 10 days by US therapy, LLLT, thermotherapy and physical exercise, associated with NSAIDs and, for six months, with GS (Dona) 1500 mg daily. LLLT was performed with Ga-Al-As diode laser (BTL-Romania), power 50 mW, continuous wave, wavelength 830 nm, 6J/point (8 point).

Continuous ultrasonic waves with 850±5% KHz frequency and 0.5 watt/cm2 power were applied with a transducer that had an effective radiating area of 6.4 cm2 (Misonic 12M, Misonix -Romania), 5 minutes/day. Thermotherapy consisted of wax package at 45 degrees Celsius for 20 minutes/day. Physical exercise was conducted for 20 minutes/day and included range-of-motion exercises, muscle strengthening and aerobic activity. All physical procedures were performed five times a week for two weeks, excluding weekends, for a total of 10 sessions.

Tests applied. Patients were evaluated prior to and at the end of therapy by the visual analogue scale (VAS) and WOMAC score (WS). WS was appreciated on the Likert scale. WOMAC subscores for pain (WSP), stiffness (WSS) and function (WSF) were calculated.

Statistical processing. Prior to the testing of the hypothesis, all variables were tested for the normality of distribution using the Kolmogorov-Smirnov test. For repeateted measurement testing, the Wilcoxon test was used. Data were illustrated using bar charts with error bar marks. For data analysis, the SPSS software version 17 was used. P values < 0.05 were considered statistically significant.

Results

WS presented a significant decrease after multimodal treatment ($p=0.037$) (Table I). Also, the comparison of values recorded prior to and after the end of treatment showed a significant decrease in WSP values immediately after treatment ($p=0.007$). However, the differences between WSS and WSF values recorded prior to and after the end of treatment were not significant (WSS: $p=0.929$, WSF: $p=0.117$ (Table I). Similarly to WS, multimodal treatment induced significant differences in the values of pain on VAS recorded prior to and after the end of treatment ($p=0.045$) (Table I).

Table I
WS and VAS before and after multimodal therapy and statistical differences (p value)

Scores	Recorded values (mean±SD)		Wilcoxon test: p value
	Before multimodal therapy	After multimodal therapy	
WS	37±10.45	29±9.83	0.037*
WSP	8±2.32	4,5±2.75	0.007*
WSS	1±1.83	1±1.32	0.929
WSF	28±7.65	23,5±7.94	0.117
VAS	8±1.50	6,75±1.37	0. 0450*

* = statistically significant

Discussion

OA is the single largest cause of disability in elderly persons. With the acceleration of the ageing processs, the impairment of activities of daily living induced by OA has brought heavy burdens to society, families, and patients (Wei et al., 2012). Even though OA has always been classified as non-inflammatory arthritis, increasing evidence has shown that inflammation occurs as cytokines and metalloproteinases are released into the joint. The main cytokines involved in OA are interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α) (Kapoor et al., 2011). Their synthesis and activation are dependent on nuclear factor-kB (NF-kB) activation. These agents are involved in the excessive matrix degradation that characterizes cartilage degeneration in OA. As OA progresses, the level of proteoglycans drops very low, causing the cartilage to soften and lose elasticity, thereby further compromising joint surface integrity (Lozada, 2012).

NSAIDs are symptom modifying drugs. These treatments have been shown to improve pain and disability effectively. NSAIDs decrease prostaglandin (PG) synthesis by inhibiting cyclooxygenase, the key enzyme required for the conversion of arachidonic acid to PGs (Alvarez-Soria et al., 2006), and have a critical role in many pathophysiological ways, implicated in OA.

The effectiveness of US therapy on pain and functional score improvement immediately after treatment in knee OA was demonstrated both for single treatment (Ozgönenel et al., 2009) and for associated treatment with hot pack therapy and isokinetic exercises (Huang et al., 2005). It was shown that US stimulates chondrocyte metabolic activity (Naito et al., 2010), increases chondrocyte proliferation (Korstjens et al., 2008) and viability (Gurkan et al., 2010), reduces proinflammatory cytokine synthesis in cartilage (Guo et al., 2011) and improves plasma antioxidant capacity in OA patients (Ungur et al., 2011).

For LLLT, previous studies demonstrated the capacity to improve pain and microcirculation in knee OA (Heisel & Kipshoven, 2011). Associated with exercises, LLLT is effective in yielding pain relief, function and activity improvement in patients with knee OA (Alfredo et al., 2012).

GS, which occurs naturally in the body, plays a key role in the construction of cartilage (Rovati et al., 2012). A recent study showed the superiority of the association of NSAIDs and GS compared with GS administered alone (Selvan et al., 2012). GS was shown to inhibit IL-1-induced activation and nuclear translocation of active NF-kB family members in human osteoarthritic chondrocytes (Largo et al., 2003) and to reduce phospholipase A2 activity (Piperno et al., 2000) and PGE2 release from articular cartilage cells (Kapoor et al., 2012). Previous studies demonstrated that GS is effective for WOMAC score improvement after three years of treatment (Reginster et al., 2001).

Our results demonstrated that multimodal therapy associating GS with NSAIDs, continuous US, LLLT, wax package and physical exercise for 10 days relieved pain and improved functional capacity in knee OA patients after only 6 months of therapy. These effects persisted after the cessation of the analgesic effect induced by NSAIDs and physical therapy, suggesting that clinical effects were generated by metabolic and biochemical changes, independently of tissue warming up and analgesia induced by physical therapy.

Although both VAS and WOMAC score found a statistically significant improvement of pain, the measurement of pain on VAS (p=0.045) was different from that on Likert scale (p=0.007), measured for WSP. This aspect was in accordance with other studies (Kersten et al., 2010; Altman & Moskowitz, 1998). Different pain scales measure different aspects of pain experience in knee OA (Creamer et al., 1999). The discrepancy between the self-evaluated pain severity on VAS and WSP suggests that there may be other factors than pain that patients consider when evaluating the severity of their disease (Chan & Chan, 2011).

No stiffness reduction effects suggest that 10 days of physical exercise are insufficient for knee OA patients. No drop out, adverse event, serious adverse event or withdrawal due to adverse events occurred in our study.

The limitations of the study are the absence of a control group and the small number of patients. To our knowledge, this is the first study evaluating multimodal therapy in knee OA.

Conclusion

1. Multimodal therapy, which includes short periods of NSAIDs, physical exercise, US therapy, LLLT and hot pack administered for 10 days and GS 1500 mg daily for six months, is effective for pain relief and safe in knee OA patients.

2. For stiffness reduction and functional improvement, 10 days of physical exercise are insufficient and multimodal therapy must include a more comprehensive program of physical exercise.

3. Pain improvement after multimodal therapy may be an effective method for decreasing NSAIDs administration in knee OA patients.

4. Further studies are necessary to assess multimodal therapy, with an extended period of physical exercise for the improvement of joint stiffness and function of knee in OA patients.

Conflict of interests
Nothing to declare.

Acknowledgements
This work was supported by CNCSIS-UEFISCSU, project number PNII-IDEI code 2623/2008.

References

Alfredo PP, Bjordal JM, Dreyer SH, Meneses SR, Zaguetti G, Ovanessian V, Fukuda TY, Junior WS, Martins RÁ, Casarotto RA, Marques AP. Efficacy of low level laser therapy associated with exercises in knee osteoarthritis: a randomized double-blind study. Clin Rehabil. 2012;26(6):523-533.

Altman RD, Moskowitz R. Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. Hyalgan Study Group. J Rheumatol. 1998;25(11):2203-2212.

Altman RD. Early management of osteoarthritis. Am J Manag Care. 2010;16 Suppl Management:S41-47.

Alvarez-Soria MA, Largo R, Santillana J, Sánchez-Pernaute O, Calvo E, Hernández M, Egido J, Herrero-Beaumont G. Long term NSAID treatment inhibits COX-2 synthesis in the knee synovial membrane of patients with osteoarthritis: differential proinflammatory cytokine profile between celecoxib and aceclofenac. Ann Rheum Dis. 2006;65(8):998-1005.

Calamia V, Ruiz-Romero C, Rocha B, Fernández-Puente P, Mateos J, Montell E, Vergés J, Blanco FJ. Pharmacoproteomic study of the effects of chondroitin and glucosamine sulfate on human articular chondrocytes. Arthritis Res Ther. 2010;12(4):R138.

Chan KKW, Chan LWY. A qualitative study on patients with knee osteoarthritis to evaluate the influence of different pain patterns on patients' quality of life and to find out patients' interpretation and coping strategies for the disease. Rheumatol Reports, 2011; 3(1):9-15.

Creamer P, Lethbridge-Cejku M, Hochberg MC. Determinants of pain severity in knee osteoarthritis: effect of demographic and psychosocial variables using 3 pain measures. J Rheumatol. 1999;26(8):1785-1792.

da Rosa AS, dos Santos AF, da Silva MM, Facco GG, Perreira DM, Alves AC, Leal Piperno M, Reboul P, Hellio Le Graverand MP, Peschard MJ, Annefeld M, Richard M, Vignon E. Glucosamine sulfate modulates dysregulated activities of human osteoarthritic chondrocytes in vitro. Osteoarthritis Cartilage. 2000;8(3):207-212.

da Rosa AS, dos Santos AF, da Silva MM, Facco GG, Perreira DM, Alves AC, Leal Junior EC, de Carvalho Pde T. Effects of low-level laser therapy at wavelengths of 660 and 808 nm in experimental model of osteoarthritis.Photochem Photobiol. 2012;88(1):161-166.

Guo H, Luo Q, Zhang J, Lin H, Xia L, He C. Comparing different physical factors on serum TNF-α levels, chondrocyte apoptosis, caspase-3 and caspase-8 expression in osteoarthritis of the knee in rabbits. Joint Bone Spine. 2011;78(6):604-610.

Gurkan I, Ranganathan A, Yang X, Horton WE Jr, Todman M, Huckle J, Pleshko N, Spencer RG. Modification of osteoarthritis in the guinea pig with pulsed low-intensity ultrasound treatment.Osteoarthritis Cartilage. 2010;18(5):724-733.

Hegedus B, Viharos L, Gervain M, Gálfi M. The effect of low-level laser in knee osteoarthritis: a double-blind, randomized, placebo-controlled trial. Photomed Laser Surg.2009;27(4):577-584.

Heisel J, Kipshoven C. Treatment of osteoarthritis with cristalline glucosamine sulfate. Results of the IDEAL-study. MMW Fortschr Med. 2011; 153 Suppl 3:95-100.

Huang MH, Lin YS, Lee CL, Yang RC. Use of ultrasound to increase effectiveness of isokinetic exercise for knee osteoarthritis. Arch Phys Med Rehabil, 2005; 86(8):1545-1551.

Kapoor M, Martel-Pelletier J, Lajeunesse D, Pelletier JP, Fahmi H. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. Nat Rev Rheumatol. 2011;7(1):33-42.

Kapoor M, Mineau F, Fahmi H, Pelletier JP, Martel-Pelletier J. Glucosamine sulfate reduces prostaglandin E(2) production in osteoarthritic chondrocytes through inhibition of microsomal PGE synthase-1. J Rheumatol. 2012;39(3):635-644.

Kersten P, White PJ, Tennant A. The visual analogue WOMAC 3.0 scale-internal validity and responsiveness of the VAS version. BMC Musculoskelet Disord. 2010;11:80.

Korstjens CM, van der Rijt RH, Albers GH, Semeins CM, Klein-Nulend J. Low-intensity pulsed ultrasound affects human articular chondrocytes in vitro. Med Biol Eng Comput. 2008;46(12):1263-1270.

Largo R, Alvarez-Soria MA, Díez-Ortego I, Calvo E, Sánchez-Pernaute O, Egido J, Herrero-Beaumont G. Glucosamine inhibits IL-1beta-induced NFkappaB activation in human osteoarthritic chondrocytes. Osteoarthritis Cartilage. 2003;11(4):290-298.

Loyola-Sánchez A, Richardson J, MacIntyre NJ. Efficacy of ultrasound therapy for the management of knee osteoarthritis: a systematic review with meta-analysis.Osteoarthritis Cartilage. 2010;18(9):1117-1126.

Lozada CJ. Osteoarthritis[online]. [2012] [cited 2013 december 12] Aviable from: URL: http://emedicine.medscape.com/article/330487

Naito K, Watari T, Muta T, Furuhata A, Iwase H, Igarashi M, Kurosawa H, Nagaoka I, Kaneko K.Low-intensity pulsed ultrasound (LIPUS) increases the articular cartilage type II collagen in a rat osteoarthritis model. J Orthop Res. 2010;28(3):361-369.

Ng NT, Heesch KC, Brown WJ. Efficacy of a progressive walking program and glucosamine sulphate supplementation on osteoarthritic symptoms of the hip and knee: a feasibility trial. Arthritis Res Ther. 2010;12(1):R25.

Ozgönenel L, Aytekin E, Durmuşoglu G. A double-blind trial of clinical effects of therapeutic ultrasound in knee osteoarthritis. Ultrasound Med Biol. 2009;35(1):44-49.

Piperno M, Reboul P, Hellio Le Graverand MP, Peschard MJ, Annefeld M, Richard M, Vignon E. Glucosamine sulfate modulates dysregulated activities of human osteoarthritic chondrocytes in vitro. Osteoarthritis Cartilage. 2000; 8(3):207-212.

Reginster JY, Deroisy R, Rovati LC, Lee RL, Lejeune E, Bruyere O, Giacovelli G, Henrotin Y, Dacre JE, Gossett C.Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. Lancet, 2001; 357(9252):251-256.

Rovati LC, Girolami F, Persiani S. Crystalline glucosamine sulfate in the management of knee osteoarthritis: efficacy, safety, and pharmacokinetic properties. Ther Adv Musculoskelet Dis. 2012; 4(3):167-180.

Selvan T, Rajiah K, Nainar MS, Mathew EM. A clinical study on glucosamine sulfate versus combination of glucosamine sulfate and NSAIDs in mild to moderate knee osteoarthritis. Scientific World J, 2012; 2012:902676.

Ungur R, Dronca M, Crăciun E C, Rusu RL, Văleanu M, Onac I, Borda IM, Irsay L. Improvement of total antioxidant status, a possible bioeffect of the ultrasound therapy - a pilot study. Revista Română de Medicină de Laborator, 2011;19(2):177-183.

Wei ZM, Du XK, Huo TL, Li XB, Quan GN, Li TR, Cheng J, Zhang WT Quantitative T2 mapping evaluation for articular cartilage lesions in a rabbit model of anterior cruciate ligament transection osteoarthritis. Chin Med J (Engl), 2012; 125(5):843-850.

Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage. 2008; 16(2):137-162.

***. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. Arthritis Rheum. 2000; 43(9):1905-1915.