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Fast Improvements of Acute Inflammatory Symptomatology in Patients With Hand Osteoarthritis With the Use of Doxycycline.

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Abstract

Background: Osteoarthritis (OA) presents the high activity of free radicals and proteolytic enzymes which were inhibited by Doxycycline (DOX).

Objective: To search the efficacy, safety, and fastness for the improvement of inflammatory signs in patients with Hand Osteoarthritis (HOA).

Methodology: Randomized, placebo-controlled trial during four weeks with two groups of patients: DOX group using one tablet of 100 mg *bid per os;* control group using paracetamol *bid per os*; the data were obtained through Visual Analog Scale (VAS) evaluation for pain, flushing/edema by the patient and the examiner; the primary outcome was the improvement greater than 50% from the basal values after four weeks**.**

Results: Thirty-eight female patients with HOA after menopause were allocated: 20 in the DOX group and 18 in the control group. The results showed that the DOX group presented a significant improvement in 75% of patients compared to the control group ($p < 0.00000$), which started after 6.05 ± 3.7 days of treatment; and mild adverse effects in 20% of the sample - gastric pain, nausea, vomiting after 9.0 ± 5.2 days without any removal from the trial. Compared to the baseline and the control group results, was observed a significant improvement in pain ($p < 0.00000$) and edema/flushing ($p<0.00000$) demonstrated the efficacy of inflammation; no abnormality was seen on the blood analysis, and no hematological, renal, cardiologic and hepatic commitment.

Conclusion: Doxycycline by a short length of time was safe and improved the pain and inflammatory signs of HOA.

Introduction

A specific type of Osteoarthritis (OA) is Hands Osteoarthritis (HOA), which evolves with poliarticular inflammatory signs, enthesitis, deformity, and functional impairment of interphalangeal and metacarpophalangeal joints, increased frequency in females, associated with menopause, hereditary profiles and none relationship with trauma (1, 2, 3, 4). HOA and OA develop with the production of harmful molecules to the cartilage-like cytokines as interleukin 1(IL1), tumor necrosis factor alpha (TNFα), interferon, transforming growth factor beta (TGFβ), platelet derived growth factor (PDGF), metalloproteinase (MMP), cyclooxygenase (COX), induced nitric oxide synthase (iNOS), superoxides, free radicals, free oxygen, hydroxyl ions which contributes to an inflammatory process without systemic manifestations (5, 6, 7, 8). With many characteristics and different targets, the treatment of OA must have a systemic approach and act at intracellular levels to modify the degenerative process. Based on this rationale, Doxycycline (DOX) is a broad-spectrum tetracycline with intracellular, anti-inflammatory, and immune actions, even with low daily doses, and can treat infectious and inflammatory diseases (8, 9, 10). Many studies on the control of inflammation and degenerative diseases demonstrated its efficacy in decreasing inflammation and enzymatic activities induced by lipopolysaccharides and mediated by IL 1,

IL 6, IL 8, TNFα, interferon through modifying inflammatory pathways of macrophages and neutrophils (8, 9). The DOX also inhibits relevant factors to the tissue damage, restricting the synthesis of MMP, gelatinase, collagenase, hydrolase, amylase, stromelysin, phospholipase A2, cyclooxygenases (COX), free radicals, NO (nitric oxide) and leukotrienes (10, 11, 12). These reasons can justify the use of DOX in HOA treatment, a hardly controlled disease, but several studies failed to demonstrate good results in treating knee and hip osteoarthritis possibly related to repeated articular trauma (10, 13, 14). In HOA the joints do not support repetitive trauma and the symptoms have a spontaneous beginning which provide a relevant model to evaluate the DOX action at cellular levels. The treatment of HOA is limited, and every attempt, even with modifying drugs, did not obtain significant effects on the disease evolution and symptomatology control. This research aims to search the clinical effectiveness of the use of DOX for four weeks in climacteric females with idiopathic HOA on the management of pain and inflammatory signs and compared to a controlled placebo group.

Methods

Trial design. Retrospective, randomized, observational, placebo-controlled clinical trial to evaluate the efficacy of DOX in treating idiopathic HOA and randomized from 1:1 patients for DOX and placebo groups, and performed in the outpatient unit of the Rheumatological Service, Universidade Federal do Rio de Janeiro, Brazil; all patients provided written informed consent terms, and The study conduct followed the ethical standards outlined in the Declaration of Helsinki; the trial has the registration number 144/2010, approved by the Institutional Research Board and Ethics Committee / Hospital Universitário Clementino Fraga Filho/ Universidade Federal do Rio de Janeiro, RJ, Brazil, under the Research Line - Pathophysiology of Rheumatic Diseases - Rheumatic Arthritis.

Intervention.

Randomization. The randomized patients were divided into two groups and followed for four weeks: DOX Group only treated with Doxycycline 100 mg bid *per os*; Control Group using paracetamol tablets 500 mg bid *per os* as a placebo drug.

Intervention. The DOX schedule of 100 mg tablets *bid per os* was similar to the safe and effective dose used for the treatment of Reactive Arthritis (ReA) and Lyme's Disease without any direct analgesic effect (15). The placebo group received paracetamol and it was selected by the safety and efficacy on pain control without inflammatory action.

Patient criteria. The patients must live in the same city from the same social group and follow a randomized sequence based on the study criteria.

Inclusion Criteria: Patients with acute idiopathic HOA filling the diagnostic criteria of the American College of Rheumatology 2, with the start of symptoms at the menopause period, amenorrhea for more than a year, and presence of inflammatory symptoms at hand's interphalangeal and carpal-metacarpal joints. To be included, the patient must have more than five centimeters (cm), or five points, obtained with the

Visual Analog Scale (VAS) at the basal intensity measurement of pain by the patient and for inflammatory signs and symptoms by the physician and patient. The criteria for analyzing inflammatory signals on compromised joints were as signals of vascular commitment: swelling for soft tissue enlargement and erythema. Previous treatment with glucosamine, chondroitin sulfate, diacerein, soy/avocado derivative drugs, anti-malarial drugs, non-steroidal anti-inflammatory drugs, and corticosteroids are accepted.

Exclusion Criteria: Patients with inflammatory connective tissue diseases, spondyloarthropathy, osteometabolic diseases, microcrystalline diseases, dermatological diseases, trauma, infection, diabetes, primary endocrinological disease, renal diseases, heart disease, neuropathies, lung disease, psychiatric diseases, fibromyalgia, genetic diseases, inflammatory bowel diseases, liver disease, esophagitis, active gastroesophageal reflux, peptic ulcers; concomitant use of glucosamine, chondroitin sulfate, diacerein, soy/avocado derivative drugs, anti-malarial drugs, non-steroidal anti-inflammatory drugs, corticosteroids, chemotherapy drugs; and allergies to the observational components of the drugs.

Sample size. In the early phase, the idiopathic HOA presents pain and inflammatory signs such as erythema, heat, swelling, and hypersensitivity and occurs predominantly in females with an essential relationship with menopause and age group (15, 16, 17). The sample size depends upon the inclusion and exclusion criteria and the results from several research which demonstrated the relationship with spontaneous menopause, and age between 49 to 54 years old, a populational frequency of 18%, risk 0.23, and chance 0.25 (15, 16,17). The total population is composed of 2126 rheumatic patients; the clinical inclusion and exclusion criteria filled by 1232 patients: female 92% (1134); degenerative disease 75% (858); no inflammatory disease 25% (556); degenerative disease and menopause 50% (278); and diagnose of idiopathic HOA 7% (39). The statistical calculation showed the accepted sample size of 18 patients (95% CI 11 - 27) in each group with a confidence level of 95%, statistical significance $p < 0.05$, and a beta error of 20%.

Setting. The study made in six weeks, with four weeks of effective use of drugs and clinical and data collection every two weeks. At first, the patient was submitted to clinical and rheumatological evaluation and sent to perform the tests for hematologic, cardiologic, metabolic, hepatic, renal control, and radiographic examination of the hands. At the second evaluation, after two weeks, the basal VAS' inquired and started the use of the medications; after two weeks, at the third evaluation, were submitted to clinical and rheumatologic evaluations and VAS measurement; at the fourth evaluation, after two weeks, performed the final VAS' measurement, clinical and rheumatologic examination, and actualized laboratory tests. The patients present questions and complaints to the clinical staff through telephone or personal contact.

Patients, measures, outcomes, objectives, and primary endpoints.

Patient. Selected following a randomized sequence and to be included in the trial, the intensity of signal and symptoms should be greater than five (05) centimeters (cm) measured through a VAS ruler graded from 0 to 10 cm.

*Measures. T*he intensity of local signs and symptoms is graded by the patient and physician's measurement of pain to evaluate the nociception and the articular soft enlargement (swelling) and erythema to characterize local inflammation, and the drug efficacy quantifies through the difference between final and basal values. The quantitative and qualitative data measure the intensity of the signals and symptoms obtained by VAS, with zero (0) cm for the absence of signs and symptoms and 10 cm representing the highest intensity. Only the patients defined the pain data, and patient and physicians evaluate swelling/erythema.

Criteria to grade the intensity of signs and symptoms through the patient and physician VAS measurements. Pain: 0 cm - no symptom; 1cm to 2.5cm, low; 2.6 cm to 5.0 cm, mild; 5.1 cm to 7.5 cm, moderate; 7.6 cm to 10.0 cm, marked intensity. Swelling and erythema: 0 cm - no signals; 1cm to 2.5 cm, low; 2.6cm to 5.0 cm, mild; 5.1 cm to 7.5 cm, moderate; 7.6 cm to 10.0 cm, marked intensity.

Criteria to grade the intensity of improvement obtained with the treatments. From 0 cm to 2.5 cm, poor or no response with less than 25%; 2.6 cm to 5.0 cm, regular response with more than 25% and less than 50%; 5.1 cm to 7.5 cm, good response with more than 50% and less than 75%; 7.6 cm to 10.0 cm, excellent response with more than 75% of improvement.

Outcomes. The use of the medications must produce at the final evaluation the improvement of pain and inflammatory signals bigger than 50% from the basal values, and no responders who present less than 25%.

Objectives.

Primary objective: To evaluate if the use of DOX in a short time improves the pain and inflammatory symptoms of the HOA.

Secondary objectives: To evaluate the efficacy and safety of the use of DOX compared to the placebo group, the time for the beginning of improvements, the presence of adverse effects, and the presence of laboratory changes.

Adverse effects and removal from the trial. Patients who presented adverse effects stopped using the trial medications, and only after a total clinical resolution could they return to complete the four weeks of observation. After the return adverse event continued or repeated, the patient was retired from the trial.

Statistical analysis.

The descriptive analysis measures the central tendency and dispersion. The VAS' mean and sd of the basal and final intensity of the signs and symptoms are evaluated through the VAS' mean, and standard deviation (sd) for pain and swelling/erythema obtained from the patient and examiner analyzed using a t-test. The chi-square test analyzed the quantitative data for improvement. The significance level assumed was $p < 0.05$, with a 95% confidence interval.

Results

Observed thirty- eight females with HOA sequentially randomized into two groups: 20 patients assigned to the DOX group and 18 patients to the placebo/control group. The groups were homogeneous, with similar clinical and demographic characteristics, and without black patients. All patients improved, and the DOX group presented good improvement in 75% of the sample and mild improvement in 25%, with significant differences when compared to baseline ($p < 0.0000$) and to the control group, which obtained improvement lesser than 25% ($p < 0.0000$). The percentage of progress in the DOX group was significantly more significant than 50% compared to the basal values and the control group ($p= 0.00000$). The DOX's group improvements started after 6.05 sd 3.7 days. Five patients (20%) presented adverse effects after 9.0 sd 5.2 days of treatment. They were diagnosed with gastric pain in 03 patients and nausea and vomiting in 01 patient each; the medication was avoided by 4.5 sd 3.5 days, and with rescue therapy, all these patients returned to the research and the trial's final evaluation with no laboratory changes.

At baseline, the intensity of the signals and symptoms presented by the groups is homogeneous. After four weeks, the final evaluation demonstrated that all patients in both groups improved. Still, the DOX group showed less intensity than the control group, with lower intensity of pain ($p=0.002$) and edema/flushing (by patients $p=0.00005$ / physicians $p=0.00002$) than the control group ($p<0.0000$).

The data demonstrated that all patients improved with significant differences from basal values related to pain and swelling/erythema. The evaluation between basal and final results demonstrated that the DOX group presented improvement of 62,5% for pain, 75% for swelling, 68.4% for erythema and significantly greater than the obtained on the control group.

Discussion

The demographic results showed that this miscigenated sample presented a preponderance of white ethnicity, as had been indirectly demonstrated by the study of Pishgar F et al. (2020) about the HOA's frequency in black Africans. The groups were homogeneous, and the findings related to race, age at menopause, age on onset, and time of disease with no difference to the results from previous studies (17, 18, 19, 20, 21). After four weeks of treatments, all patients improved, but the control group presented poor results (<25%) compared to the DOX group, where all patients showed good (15/75%) or mild (05/25%) improvements starting after 6.05 sd 3.7 days. These data are relevant because several studies to control HOA with colchicine, methotrexate, hydroxychloroquine, and biological therapies didn't present these results except for the trial about the use of DOX (2015) performed by Ma J et al. (21, 22, 23, 24, 25, 26). All the DOX patients had significant and fast improvement of the VAS values related to pain intensity and inflammatory signs compared with baseline ($p = 0.000001$) and control group ($p=0.002$). At the final evaluation, the DOX group presented a reduction more significant than 50% related to pain and inflammatory signs, and in the control group, the obtained value was less than 25%. Side effects were observed in five patients (20%) in the DOX group after 9.0 sd 5.2 days of treatment, all related to

gastrointestinal complaints which resolved after 4.5 sd 3.5 days without the drug, and the patients completed the trial; the control group didn't present adverse effects. The groups didn't show laboratory abnormalities. These results demonstrated that the treatment of HOA with DOX was fast, effective, safe in the control of inflammatory symptoms, and significantly better than the placebo, and the improvements depend on its pharmacological characteristics, such as rapid absorption, tissue distribution, and action on the intracellular environment.

The HOA symptomatology depends on stimulating factors produced by cellular activities related to predisposing, precipitant, etiologic, pathogenic, and harmful factors. The results showed that the obtained modification with DOX treatment depended on its specific therapeutic interference on these factors restricting the activity of several reactive molecules. In females, HOA presents a clinical relationship with hormonal misbalance characterized by the beginning at menopause, higher frequency in patients who evolved with high levels of estrogen acting as a predisposing factor, and after the abrupt hormonal failure at menopause, as a precipitant factor, occurs increased production of harmful inflammatory molecules which participates to the development of this disease without systemic manifestations (3). The tissular commitment, clinically characterized by pain and inflammatory signals, begins after cellular stress stimulation, even by estrogen misbalance, in the cellular microenvironment and is clinically characterized by pain and inflammatory signals, intensified production of IL1, TNFα, interferon, enzymes (MMP1 / 3 and COX) which induce neural degeneration, and nociception pathways, and local pain perception (3,12, 27, 28, 29). The trial's results demonstrated that DOX had reduced pain intensity, probably obtained through an indirect action modifying the intra-cellular environment and the production of aggressive molecules.

The articular inflammatory signals depend on exacerbated vascular permeability and angiogenesis, also stimulated by GTPCH activity intensifying the cellular production of reactive oxygen derivates, and this signaling pathway is inhibited by DOX and explaining the improvements obtained on the inflammatory articular signals (10, 11, 12, 27, 28). This inhibitory action protects the cartilage health through the intensification of cartilage remodeling and the chondrogenesis dependent on mesenchymal stem cells (17, 29, 30, 31).These characteristics are produced by harmful molecules, dependent on cellular stress and consequent stimulation of intracellular catabolic pathways of the activity of tumor cell primers intensifying the mitochondrial oxidative and glycolytic activities, and dependent on NOTCH, WNR, TGFβ Transforming Growth Factor beta (TGFβ) signaling, which stimulates the production of IL1, TNFα, IL6 and TGFβ and as had been demonstrated that DOX inhibits the tumor cells primers activity and restricts the inflammatory reaction (32,33). The growth factors maintain the cartilage integrity, and TGFβ is the principal cartilage activator but presents an antagonistic behavior: acts as an anabolic growth factor inducing mesenchymal cell proliferation and improving cartilage repair and inhibiting osteophyte formation or like a catabolic factor, dependent on the mutation of the SMAD 3 molecule, modifying the fibroblast-myofibroblast transformation and the mesenchymal-epithelial transition, which compromises the integrity of the extracellular matrix (ECM) (33, 34, 35). This anabolic/catabolic balance depends on hormonal stimulus linked to the estrogen profile and the production of inflammatory agents: a high hormone level has anabolic activity, and a low level, as induced by menopause, promotes TGFβ catabolic

action and the release of harmful cytokines as IL1, IL6, and TNFα (36). The persistent inflammation presented on HOA also depends of inflammasome participation, a cytosolic protein complex NLRP3 (NOD-like receptor pyrin domain containing 3) produced by microbial or cellular stimulation by lipopolysaccharides(LPS) and adenosine triphosphate (ATP), which mediates caspase one activation and stimulates the production of IL1β, TNFα, metalloproteinase (36,37,38). There is a relationship between inflammasome activity and the estrogen profile, where normal or high hormone levels inhibit the action of NLRP3 inflammasome in fibroblast-like synoviocytes and protect the cartilage; low levels of estrogen, as occurs after menopause, activate the NLRP3 production and increase the production of IL1β by fibroblast-like synoviocytes; and previous studies demonstrated that DOX, in addition to the inhibition the growth of cancer cells, acts as modulator agent and suppress the NLRP3 activation, restricting IL1β production which protects the cartilage by the similar way obtained with the inhibition of IL1β activity by biologic anti IL1 specific therapy which improved knee OA symptomatology (39,40, 41).

HOA has specific relationships with hereditary profiles, patient development evolutes with high estrogen levels, menopause and with the abrupt fall of estrogen production. The initial symptomatology is a localized inflammation of the hand's joints, without systemic commitment, and dependent on high local production of harmful molecules, evolving into hypertrophic deformities. This specific process depends on genetic characteristics and the production of abnormal local tissue cellular specific components, which stimulated by any cellular stress, complicate the control of articular disease and unsuccessful therapeutic approaches failed, even associated with hormonal targets and disease-modifying drugs, except with the use of specific biological anti-IL1 on treatment of OA of the hip and knee (41). The results demonstrated the efficacy of DOX on the treatment of HOA's local and persistent inflammatory signs, through direct or indirect actions, with fast improvement, few side effects, no laboratory commitments, and better than placebo in the control of the inflammatory symptomatology, and perhaps retard the progression of the disease and be used as adjuvant therapy as had been demonstrated on oncologic, in inflammatory and infectious diseases used on the control of acute or chronic diseases (33, 42). The trial presents some limitations as the small sample size, the lack of HOA's evaluation protocols, and more studies are necessary to confirm these results over a long space of time, evaluate the use of recurrent flares, and establish the hormonal relationship and the action of DOX on cellular microenvironment.

Conclusion

The use of DOX in patients with HOA presented fast, safe, and significant improvement of articular pain and inflammatory signs, better than the placebo, with few side effects and no laboratory change.

Declarations

Ethical approval and consent to participate. The study is a retrospective trial was conduct following international and local ethical standards and regulations protocol and approved by the Ethics Committee of the participating institution. All participants signed an Informed Consent Form which was previously approved by the local Research Ethics Committee.

Consent for publication. The author gave the consent for publication.

Availability of data and materials. The data of the study and the results are available on request for the corresponding author who is the responsible for the data and materials of the research.

Competing interests. The author declare that don't have any competing interests.

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Author´s contibuitions. The author made substantial contributions to conception and design, as well as acquisition, synthesis, and interpretations of data, and were also involved in writing the manuscript and given final approval of the version to be published. The author agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The authors approved the manuscript for submission.

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Tables

Tables 1 to 3 are available in the Supplementary Files section.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.docx