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EFFECTS OF GALLIUM NITRATE PERCUTANEOUS APPLICATIONS IN PATIENTS WITH KNEE ARTHRITIS

***Diogo Muniz de Albuquerque, Petr Melnikov, Albert Schiaveto Souza and Joel Saraiva Ferreira**

Federal University of Mato Grosso do Sul, Campo Grande, Brazil, ZIP CODE 79080-680

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ABSTRACT

In this study, 35 patients with knee arthritis were evaluated, of whom 18 were treated with gallium nitrate and 17 with saline solution by means of the percutaneous application on the joint surface. The patients were evaluated according to the protocol specially prepared for this study by the research group. No allergic or other adverse reactions were observed during the applications or later. With regard to the assessment of joint pain and the dynamics of physical capabilities, the Lysholm scale was shown to be an adequate statistical tool. A comparison was made among the data obtained at the starting point and those recorded each month during the four consecutive months. It was shown that at all moments after treatment the group of patients treated with gallium nitrate presented gains in quality of life significantly higher than those in the group of patients treated with saline solution. The participants perceived the improvement of their symptoms in terms of pain, the reduction of phlogistic signs and the recovery of general well-being. Earnings perceived by participants in quality of life remained constant during subsequent evaluations, demonstrating a clinically long lasting effect with the use of gallium nitrate.

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INTRODUCTION

Arthritis includes more than 100 diseases and conditions that affect joints, the tissues that surround them, as well as different types of connective tissue proper. Symptoms may vary, depending on the specific form of the underlying disease, but typically include pain and stiffness in and around one or more joints (Center for Disease Control and Prevention (US), 2017). The high prevalence of rheumatic diseases in the adult population represents a significant cause of morbidity in developed countries. An estimated 10% of the population is afflicted with some form of rheumatic illness, and this frequency is estimated to grow to 22% in individuals over 16 years of age (Senna *et al*., 2004). In the U.S. and other developed countries about 55% of individuals aged 65 and older report having arthritis or chronic joint symptoms. Due to the increasing number of older adults in many countries, the prevalence of arthritis is expected to rise dramatically. These estimates portend a mounting public health burden (Dominick *et al.,* 2004). All articular tissues, including cartilage, subchondral bone, synovium, intra-articular fat, meniscus, ligaments and periarticular muscles can be affected (Malfait, 2016). The definition of the disease can be based on clinical or radiographic criteria (Corti and Rigon, 2003). Despite the great variety of manifestations of arthritis, with different etiologies, acute or chronic evolution and affected joints, the types of treatments converge to relieve symptoms, especially pain and edema and prevent the transformation of these conditions into arthrosis, a final stage that orthopedists are directly dealing with. Therapy for rheumatic diseases may be classified as immunosuppressive agents, synthetic chemical compound disease-modifying anti-rheumatic drugs or biologic disease-modifying anti-rheumatic drugs. The improved quality of life, reduced morbidity and mortality, of patients with rheumatic disease validates the efficacy of these agents (El Miedany, 2017). Therefore, there is a special interest in the new methodologies using transition metal compounds, for example gallium, which in recent decades has shown promising activity in the treatment of bone diseases. The least studied treatment option is the percutaneous application of gallium nitrate, compound abbreviated as GaNit in the literature. Its properties were accidentally discovered by the staff of the veterinary clinic that treated horses with arthrosis, observing that after

Corresponding author:* **Diogo Muniz de Albuquerque,
Federal University of Mato Grosso do Sul, Campo Grande, Brazil, ZIP CODE 79080-680.

soaking hands in gallium nitrate solution at 14% the arthritis pain in their fingers was over and did no returned at least for 2 years (Eby, 2005). It was known that after being taken orally or in the form of injections, GaNit acts on cancer-related hypercalcemia, inhibits bone resorption even at low doses, and leads to improved bone mineralization without any apparent cytotoxic effects on bone cells. Organic compounds containing this element seem to have promising results in the treatment of osteoporosis and do present neither chronic, nor acute toxicity. (Dermience *et al.,* 2015; Chitambar, 2010) As the most important carriers of iron, transferrin and lactoferrin, do not distinguish gallium from iron, all gallium in blood is present in plasma as complexes with these proteins (Melnikov, 2008; Bernstein, 1998). The accumulation of Ga-compounds within bone tumors and their favorable antitumor properties are probably a consequence of the large expression of transferrin in tumor cell (Harris and Messori, 2002; Apseloff, 1999). It was shown that gallium concentrates on inflammation and infection foci including those of granulomatous origin and synovitis associated with rheumatoid arthritis, particularly in granular neutrophils and polymorphonuclear leukocytes (Bernstein, 1998). The possibility of using gallium compounds for topical treatments and coating of biomaterials and implants is also a perspective (Menandri *et al.*, 2014).Some gallium derivatives can be used as diagnostic and therapeutic agents in medicine, especially in the areas of metabolic disease of bone, cancer, and infectious diseases (Chitambar, 2010). It has been observed that they also have significant immunosuppressive effects (Choi *et al*, 2014). GaNit demonstrated effects on macrophage activity, inhibition of inflammatory cytokines and NO secretion by murine RAW 264-activated murine macrophages (Bernstein, 2013). Clinical trials have demonstrated GaNit efficacy in bone diseases and activity against some types of malignancies, including ovarian epithelial carcinoma, non-squamous cell carcinoma of the cervix, bladder cancer, non-Hodgkin's lymphoma and Paget's disease (Apseloff, 1999; Drobyski *et al*., 1996). With regard to the assessment of joint pain and the dynamics of physical capabilities, the Lysholm scale appears to be an adequate statistical tool. It was successfully applied for the evaluation of knee injuries, such as ligament and meniscal lesions, surgical corrections and therapeutic exercises (Collins *et al*., 2011). .An important characteristic of this scale is that the age of the patients does not seem to represent a limiting factor for its application (Metsavath *et al*., 2011). The aim of this research is to evaluate the effect of GaNit on symptomatic knee arthritis, as compared with placebo.

MATERIALS AND METHODS

This prospective, randomized placebo controlled study was approved by the Ethics Committee of the Federal University of Mato Grosso do Sul, number CAAE 5021.4215.8.0000.0021. The Free and Informed Consent Form was signed by all the participants of the trial after a joint reading with the researcher. All doubts regarding the study were clarified before signing the Form. Before starting the survey, participants were screened to assess whether they met the pre-established inclusion and exclusion criteria. Eligible persons met all of the following criteria:participants with arthritis of the knee of both sexes at the age of 18 and over, from the outpatient clinics of the Federal University of Mato Grosso do Sul, Brazil, with inflammatory, post-traumatic and degenerative arthritis who presented complaints of articular alterations. Exclusion criteria included the presence of autoimmune diseases with cutaneous involvement, dermatological alterations that prevented drug application, history of drug hypersensitivity and pregnant women. The following protocol was specially elaborated for this study. The Medical School of the Federal University of Mato Grosso do Sul generated a random allocation sequence and provided identically looking receptacles. The latter were consequently labelled with study identification number. Eighteen contained active medication (GaNit solution, 14%) and the rest contained placebo (isotonic saline). The patients were consequently assigned the next available identification number. The procedure was performed as follows. A high quality filter paper disk was wetted with 5 ml of GaNit/saline solution, and placed on the front surface of the right knee. The patient was previously informed that the local feeling of warmth that may arise at the beginning is normal. This technique was repeated after 15 days. Each application lasted thirty minutes and when there were no adverse events such as erythema or pruritus, the patient removed the disc at home after 8 hours. The solution of gallium used percutaneously has no toxicity, so the filters can be thrown away into the common waste. The comparison between the treatments in relation to the Lysholm scale, as well as gain on the same scale, was performed using the non-parametric Mann-Whitney test, since the data samples did not pass the Shapiro-Wilk normality test. The comparison between the moments of evaluation in relation to the score on the Lysholm scale, as well as the gain on the same scale, was performed using the non-parametric Friedman test, followed by the Dunn post-test. The remaining results of this study were presented as descriptive statistics or in the form of tables and graphs. Statistical analysis was performed using the program SigmaPlot, version 12.5 or SPSS, version 23.0, considering a level of significance of 5%

RESULTS AND DISCUSSION

In this study, 35 patients with arthritis were evaluated, of whom 18 were treated with GaNit and 17 with saline solution. No patient reported allergy or other adverse reaction during the applications or later. Osteoarthritis, the most common type of arthritis, has an increased prevalence with age and affects the hands and knees of women more frequently than men (Hochberg *et al*., 2012). Our results are compatible with these data, showing that the majority of participants were female and over 50 years old. In relation to gender, there were 7 male patients and 28 female, 20% and 80%, respectively. The mean age of the participants was 61.7 years, with a minimum of 33 years and a maximum of 94 years old. They were concentrated in the age groups of 51 to 60 and 61 to 70 years. Studies report the prevalence of arthritis in more advanced age groups, with half of adults aged 65 years being affected. Almost two-thirds of adults who reported diagnosed arthritis were less than 65 years of age and more than 60% of them were women (Barbour *et al*., 2013).The prevalence of age-adjusted arthritis, by separating the participants of this study by age group, was higher for women than for men (24% *vs* 18%). Table 1 presents the quality of life scores based on the patients reports of their experience with illness, evaluation being performed by the Lysholm scale. The results are given in mediana (minimum – maximum).

Letters *a* and *b* in the column referring to GaNit mean that there is a significant difference between the pre-treatment moments to the moments after treatment (Dunn post-test, $p < 0.05$). In the column of the saline there is no significant differences.

Table 1. Quality of life scores of the patients treated with GaNit/saline solution as referred to each moment of evaluation

Moments	Applications		p*)value
	GaNit (n=18)	Saline (n=17)	
Pre-treatment	30.5 (11 – 69)*b*	43.0 (18 – 66)*a*	0.092
1 month	54.5 (27 – 95)*a*	43.0 (18 – 66)*a*	0.137
2 months	53.0 (27 – 95)*a*	43.0 (18 – 66)*a*	0.203
3 months	53.0 (27 – 95)*a*	43.0 (18 – 66)*a*	0.176
4 months	51.5 (27 – 95)*a*	43.0 (18 – 66)*a*	0.248
p** values	<0.001	0.017	

*)p value according to the Mann-Whitney test,
**)p value according to the Friedman test.

Table 2. Life score quality gain in relation to pre-treatment of patients treated with GaNit /saline solution as referred to each moment of evaluation

Moments	Applications		p*) values
	GaNit (n=18)	Saline (n=17)	
1 month	22.5 (2 – 35)*a*	0 (0 – 9)*a*	<0.001
2 months	21.0 (0 – 35)*a*	0 (0 – 9)*a*	<0.001
3 months	18.5 (0 – 35)*a*	0 (0 – 9)*a*	<0.001
4 months	18.5 (0 – 31)*a*	0 (0 – 9)*a*	<0.001
p**)value	0.015	0.392	

*)p value according to the Mann-Whitney test,
**) p value according to the Friedman test.

In none of the evaluated moments there was a difference between the treatments in relation to the quality of life, as measured by the Lysholm score (Mann-Whitney test, p-value ranging from 0.092 to 0.248). On the other hand, there was a sharp difference between the moments of evaluation for both patients treated with GaNit ($p < 0.001$) and those treated with saline solution (Friedman test, $p = 0.017$). However, in the multiple-comparison test, the difference between moments was only significant in patients treated with GaNit, where, at all moments after treatment (1 to 4 months), the Lysholm score was higher than that observed at the time of pre-treatment (Dunn post-test, $p < 0.05$). Regarding the gain in the Lysholm score, at all moments after treatment (1 to 4 months), the group of patients treated with GaNit presented gains in quality of life significantly higher than those in the group of patients treated with saline solution (Mann-Whitney test, $p < 0.001$). Moreover, in the comparison between the moments of analysis for the group of patients treated with GNit, there was a difference between them in relation to the gain in the Lysholm score (Friedman test, $p = 0.015$). However, in the test of multiple comparisons, comparing two to two moments, there was no significant difference between them (Dunn post-test, $p > 0.05$). Earnings perceived by participants in quality of life remained constant during subsequent evaluations, demonstrating a clinically long lasting effect with the use of gallium. These results are presented in Table 2.

Three forms of arthritis were diagnosed in the participants. Thirty of these last reported the idiopathic cause, four had a post-traumatic history and one case was of inflammatory etiology. Each of them has tried at least one type of previous treatment, but, so far, did not receive specific guidance on the best option to deal with the disease. The practice of orthopedics has been tremendously modified over the past 10–15 years. Fifteen years ago, the relative lack of effective treatments and treatment strategies meant that the therapist was mainly managing the disease and its consequences on the patient's life, sometimes even "running after" the inflammatory process rather than controlling it (El Mediany, 2017; Ammar *et al*., 2015; Fallopa and Belloti, 2006). Today, thanks to new management strategies, more tight control, and more effective treatments, the prognosis of this disorders and in particular inflammatory disorders has been profoundly improved. It is in this context that a focus on conservative simple techniques treatments should be made. There is a possibility of using gallium compounds because of their remarkable activity against bone resorption. When comparing the protocol adopted for the topical application of GaNit with the existing treatments, it can be considered a therapy of low complexity, low cost and easy to perform for arthritis in the outpatients' clinic. In countries with a large number of poor and unattended patients, it can turn a life of limitations into a possibility of well-being and relief for the afflictions of those suffering from arthritis.

Conclusion

At all moments after treatment the group of patients treated with GaNit presented gains in quality of life significantly higher than those in the group of patients treated with saline solution. In particular, the participants perceived the improvement of symptoms, especially pain, reduction of phlogistic signs and recovery of general well-being. Earnings perceived by participants in quality of life remained constant during subsequent evaluations, demonstrating a clinically long lasting effect with the use of GaNit. This treatment can be recommended to relieve the manifestation of arthritis in orthopedic patients.

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