Colchicine in the treatment of the inflammatory phase of Graves' ophthalmopathy: a prospective and randomized trial with prednisone

Colchicina no tratamento da fase inflamatória da oftalmopatia de Graves: um estudo prospectivo e randomizado com prednisona

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ABSTRACT

Purpose: To investigate if colchicine is valuable in the treatment of Graves' ophthalmopathy (GO), we compared its effect with prednisone in 22 patients during the inflammatory phase of GO. **Methods:** All patients, similar in age, sex and smoking habits, were euthyroid for at least 3 months and randomly divided into two groups, one treated with colchicine (1.5 mg/day) and the other treated with prednisone (0.75 mg/kg/day). They were monitored with ophthalmologic assessment (clinical activity score-CAS) and magnetic resonance imaging, using a signal intensity ratio (SIR) of the recti muscles in comparison to the cerebral substantia alba. **Results:** Amelioration of CAS was seen in 68% of the orbits in both groups. SIR also had a significant reduction after treatment: the initial median of 1.14 in G1 and 1.27 in G2, evolved, after treatment, to 1.07 in G1 and 0.69 in G2. The variation between both groups after treatment was not significant (p=0.22). None of the patients treated with colchicine had side effects; on the other hand, side effects in G2 were weight gain, edema, gastric complaints, hirsutism, weakness, depression, and alterations in blood pressure. **Conclusion:** Colchicine had a beneficial effect on the inflammatory phase of GO without the side effects of prednisone.

Keywords: Graves ophthalmopathy/drug therapy; Colchicine/therapeutic use; Prednisone/adverse effects; Smoking; Prospective studies

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INTRODUCTION

Graves' ophthalmopathy (GO) is a chronic autoimmune process that affects the orbital tissues and it is generally associated with Graves' thyroid disease. As other autoimmune diseases, GO is multifactorial and dependent upon the interaction among environmental, genetic and endogenous factors[1-2]. Smoking is the most clearly identified risk factor, and there is an association between the severity of the disease and the amount of smoked cigarettes[1-2]. During the inflammatory stage of the disease, there is an infiltration of the orbital tissues by lymphocytes and macrophages[1-3], with release of several cytokines, mostly interleukin 1 (IL-1), tumor necrosis factor-α (TNF-α) and inte-γ (IFN-γ), that induces the production of glycosaminoglycans by fibroblasts. In later stages, fibrosis with restriction and atrophy of the extraocular muscles accounts for the clinical dysfunction[1].

Colchicine is an alkaloid that has been used for an increasing number of diseases due to its anti-inflammatory effects[4-5]; it reduces motility, chemo-

taxis, phagocytosis and adhesiveness of polymorphonuclear cells, as well as the activity of proinflammatory enzymes[6-9]. In addition, it decreases the production of TNF-α and TNF-α mRNA levels, the expression of adhesion molecules and IL-2 receptors and the synthesis of IL-6[10-14]. Furthermore, it inhibits the production of IL-1 by neutrophils and induces an increased IL-1 production by macrophages[15-16]. It is also a potent inhibitor of fibroblast and lymphocyte functions and proliferation[14].

Corticosteroids are the first-choice immunosuppressive treatment for GO, but cause important side effects[17]. To investigate if colchicine could be an appropriate therapy for patients with inflammatory GO due to its good tolerability and possible action on GO etiological factors, we performed this prospective and randomized study to compare its efficacy and side effects with those of oral prednisone.

METHODS

Patients

Twenty-five patients with untreated and active inflammatory stage of the eye disease, GO classes II-IV[18], 16 females and 9 males aged 23 to 66 years (median 41 years) were admitted to the Orbital Center of "Hospital São Paulo", a teaching hospital of the Federal University of São Paulo, in São Paulo, Brazil from 1999 to 2000. All patients had GO of less than 18 months of duration and were euthyroid for at least 3 months (independently of the type of treatment for the thyroid disease - Table 1), as indicated by physical examination and normal values of serum free thyroxine (fT4: 0.6-1.5 ng/dL; Delfia fluoroimmunoassay - IFMA) and thyrotropin (TSH: 0.3-5 mU/L; IFMA).

Methods

Ophthalmologic evaluation and magnetic resonance imaging (MRI).

The GO activity was evaluated by the clinical activity score (CAS) suggested by Mourits et al.[19], and by the signal intensity of the extraocular muscles (superior, medial, inferior and lateral) on MRI. This signal intensity was measured and expressed as a ratio (SIR) between extraocular muscles and cerebral substantia alba[20-21]. MRI was performed in coronal planes T2 using a 1.0 T superconducting MR unit gyroscan T10-NT (Philips). To evaluate the results obtained after treatment we have chosen the two more involved muscles. Patients and physicians who assigned the pre- and post-treatment CAS and MRI scans were blinded regarding the treatment group. Patients with optic neuropathy, diabetes mellitus, hypertension, hepatic and kidney disease, or gastrointestinal complaints were not included. Patients with insufficient follow-up, or who developed abnormal thyroid function during the study were excluded. The trial was approved by the Committee of Medical Ethics of our institution and a written informed consent was obtained from all patients.

Treatment and follow-up

Patients were randomized by random permuted blocks (blocking) in two groups[22-23]. Group 1 (G1, n=12) was treated with a single oral dose of colchicine 1.5 mg/day for 1 month and thereafter with a dose of 1.0 mg/day for 2 more months. Group 2 (G2, n=13) received oral prednisone 0.75 mg/kg/day for 1 month and, subsequently, decreasing doses for 2 more months. Both groups were similar regarding age, sex and smoking habits (Table 1). Both drugs were supplied to the patients to obtain better compliance. Follow-up examinations were performed at the beginning of the treatment and 1 and 3 months after. Routine laboratory tests were performed monthly. One patient in G1 was excluded due to the development of hypothyroidism during the period of the study. Two patients in G2 were excluded due to side effects of prednisone (hypertension, weight gain and edema).

To assess the efficacy of both forms of treatment the patients were evaluated by measuring CAS and MRI before and three months after the therapy. The success of each form of treatment was defined as a decrease in CAS from inflammatory (≥ 4) to stable (≤ 3) and a reduction of the signal intensity ratio on MRI.

Statistical analysis

The CAS and SIR results were analyzed with the GraphPad InStat (Instat Inc., USA) software package V2.02. For sta-

Table 1. Characteristics of patients with Graves' ophthalmopathy that received colchicine or prednisone

Patient	Age	Sex	Treatment for thyroid disease	Smoking habits
Group 1 - Colchicine				
1	41	Female	Metimazole + l-thyroxine	Yes
2	25	Male	Radioiodine	No
3	40	Male	l-thyroxine after Radioiodine	No
4	35	Male	l-thyroxine after Radioiodine	No
5	42	Male	Euthyroidism	Yes
6	48	Female	Metimazole	Yes
7	58	Female	Remission of hyperthyroidism	No
8	58	Female	Metimazole	Yes
9	66	Male	Propiltiouracil + l-thyroxine	No
10	44	Female	Remission of hyperthyroidism	Yes
11	51	Female	L-thyroxine after thyroidectomy	Yes
Group 2 - Prednisone				
12	49	Female	Remission of hyperthyroidism	Yes
13	53	Female	l-thyroxine after thyroidectomy	No
14	31	Female	Euthyroidism	Yes
15	32	Female	l-thyroxine after Radioiodine	Yes
16	55	Male	Metimazole	No
17	35	Female	Euthyroidism	Yes
18	31	Female	l-thyroxin after Metimazole	Yes
19	43	Female	l-thyroxin after thyroidectomy	No
20	52	Female	Euthyroidism	No
21	23	Male	l-thyroxine after thyroidectomy	No
22	24	Male	Euthyroidism	No

tistical analysis of the treatment outcome by CAS, only data of inflamed orbits (CAS ≥ 4) were considered. For the SIR evaluation we selected the two more inflamed muscles. The Mann-Whitney test was used for comparison between groups and between smokers and non-smokers before treatment. Pre- and post-treatment values were compared by the one-tailed Wilcoxon rank sum test. Fisher's exact probability test was used for the analysis of effectiveness between groups. To compare the percentage of variation we used the one-tailed Mann-Whitney test. For all tests p≤0.05 was considered significant.

RESULTS

All 22 patients remained euthyroid during the study showing normal values of serum fT4 and TSH. At the end of the treatment all of them showed symptomatic relief and improvement in appearance.

The initial median CAS in G1 was 5.0 and, after treatment, was altered to 3.0. Similarly, in G2, the initial median CAS was 4.0 and, after treatment, was changed to 1.0. Therefore, under both treatments, a significant reduction in CAS was observed (p<0.0001 for G1 and p=0.0003 for G2, Table 2 and Figure 1). After 3 months the therapeutic effect was similar in both groups, with 13 of 18 orbits (72%) with inflammatory disease in G1 responding to colchicine and 16 of 17 orbits (94%) in G2 responding to prednisone (p=0.12). When we considered a more strict outcome, the improvement of at least 2 points in CAS of all orbits, 15 orbits in G1 (68%) and 15 orbits in G2 (68%) showed amelioration of disease activity and, again, the therapeutic effect was identical in both groups.

The evaluation of SIR revealed a significant reduction after treatment in both groups (Table 2 and Figure 2). Thus, the initial median SIR in G1 was 1.14 and, after treatment, changed to 1.07 (p=0.01). The initial median in G2 was 1.27 and, after treatment, was modified to 0.67 (p=0.01). There was no statistical difference in the initial SIR between both groups (p=0.80). In addition, the percentage of variation between groups was also not significant, G1=0.16 and G2=0.38 (p=0.22).

None of the patients in G1 had side effects with the employed dose of colchicine. On the other hand, in G2, besides

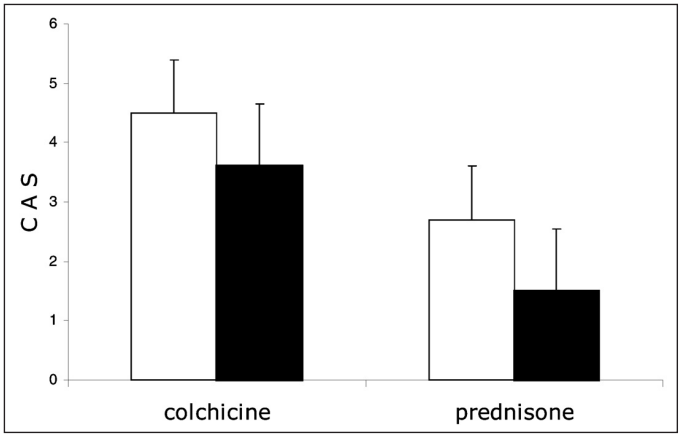

Figure 1 - Comparison of the clinical activity score (CAS) of patients with Graves' ophthalmopathy before (white bars) and after treatment (black bars) with colchicine (n=11) or prednisone (n=11); under both treatments, a significant reduction in CAS was observed (p<0.0001 for G1* and p=0.0003 for G2)**

Table 2. Clinical activity score (CAS) and mean signal intensity ratio (SIR) of the two more inflamed muscles of patients with Graves' ophthalmopathy before and after treatment with colchicine or prednisone

Patient	Orbit	CAS before treatment	CAS after treatment	SIR before treatment	SIR after treatment
		Group 1 - Colchicine			
1	Right	6	3	1.13	0.74
	Left	2	1	0.98	0.49
2	Right	4	2	1.15	0.94
	Left	5	3	0.99	1.05
3	Right	4	0	0.88	0.77
	Left	0	0	0.79	0.75
4	Right	5	2		
	Left	5	3		
5	Right	5	2	1.27	1.04
	Left	8	5	1.29	1.08
6	Right	4	3	1.10	1.14
	Left	5	3	1.23	1.31
7	Right	5	3	1.98	1.68
	Left	4	3	2.09	1.74
8	Right	6	5	1.62	1.60
	Left	6	4	1.53	1.31
9	Right	5	2		
	Left	3	2		
10	Right	7	4	1.02	1.18
	Left	7	5	0.83	0.93
11	Right	3	2		
	Left	4	2		
		Group 2 - Prednisone			
12	Right	5	1	1.14	0.69
	Left	2	1	0.80	1.09
13	Right	4	1	1.39	0.50
	Left	4	1	1.39	0.36
14	Right	4	1		
	Left	0	0		
15	Right	3	2	0.74	0.58
	Left	4	1	0.69	0.77
16	Right	5	3	1.91	1.59
	Left	4	2	1.74	1.20
17	Right	4	1		
	Left	1	0		
18	Right	5	3		
	Left	5	3		
19	Right	4	1	2.03	0.62
	Left	4	1	1.95	0.64
20	Right	5	2		
	Left	4	4		
21	Right	3	2	0.43	0.63
	Left	4	1	0.69	0.74
22	Right	5	3		
	Left	0	0		

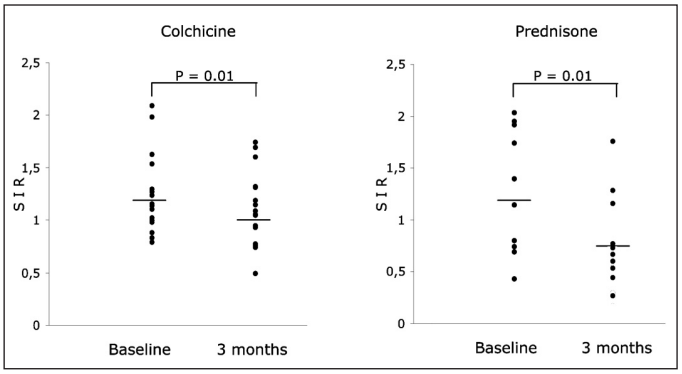

Figure 2 - Comparison of the signal intensity ratio (SIR) of the two more inflamed orbital muscles of patients with Graves' ophthalmopathy before and after treatment with colchicine (G1) or prednisone (G2); under both treatments a significant reduction of SIR was observed (p=0.01 for colchicine-treated group and p=0.01 for prednisone-treated group)

those 2 patients excluded due to adverse reactions, there were additional side effects related to prednisone, as weight gain (3 patients), edema (3 patients), gastric complaints (2 patients), hirsutism (1 patient), weakness (1 patient), depression (1 patient), and hypertension (4 patients).

On comparison between smokers and nonsmokers, independently of the treatment, there was a tendency for nonsmokers to present lower values of initial CAS (p=0.08). Additionally, 10 of 15 orbits with inflammatory disease in smokers (66%) responded to treatment, when compared with 18 of 19 orbits of nonsmokers (94%), but this is not statistically significant (p=0.06).

DISCUSSION

Graves' ophthalmopathy can be an incapacitating eye disease in the most severe cases, causing disfiguring proptosis, pain, redness, swelling of the eyelids, grittiness of the eyes, diplopia, and even blindness[1,24]. In the active phase, lymphocytic infiltration and secretion of various cytokines induce glycosaminoglycan (GAG) production by fibroblasts[25-26]. Due to their hydrophilic nature, GAG contribute to interstitial edema and swelling of the orbital tissue in GO, leading to the clinical expression of the disease[27].

Anti-inflammatory treatment can be applied in the active stage. The most used treatments are corticosteroids, radiotherapy or a combination of both. The success rate of corticosteroid therapy is 65%, but this is achieved at the cost of significant morbidity. Almost one-third of the patients will experience the well-known and frequent side effects of this kind of treatment; and exacerbation following withdrawal is frequent[17,28]. Radiotherapy appears to be effective in some centers[29], but without beneficial therapeutic effect in others[30-31]. There are other options for the treatment of GO, with similar response rates, but seldomly indicated, as immunoglobulins, cyclosporine A, octreotide, azathioprine, cyclophosphamide and pentoxyfylline[2,28,32]. Another suggestion is the use of antagonists of cytokines[26,33-36], since there is evidence that citokynes, i.e., IL-1, IL-2, IL-4, IL-5, IL-10, interferon-γ and TNF-α, produced by orbital macrophages and fibroblasts or by infiltrating activated lymphocytes, are potent stimulators of GAG synthesis and other immunomodulatory proteins, like intercellular adhesion molecules and heat shock protein-72)[33-36]. However, their practical use in chronic disease states is limited by the need to deliver these proteins parenterally. Additionally, studies are required to establish the safety, effectiveness, and the favorable cost-benefit ratio of these agents[33-36].

In this prospective and randomized trial, colchicine was used for the first time in the treatment of the inflammatory phase of GO and its effect compared with prednisone, the drug considered to be the first choice in the treatment of this disease. Patients were euthyroid throughout the period of observation, and an interval of 3 months between therapy and assessment of therapeutic outcome was observed, in order to make spontaneous improvement less likely.

The response to therapy in GO is difficult to assess; as a result, several parameters have been evaluated. Among them, it is reported that a higher T2 relaxation time indicates inflammation rather than fibrosis and that the cause of the elevated T2 relaxation time is due to the increased water content of the retroorbital tissues[17]. In this trial we used the combination of the clinical activity score (CAS)[18-19] and the signal intensity ratio on MRI (SIR)[20-21] and showed that the therapeutic outcome in patients after 3 months of colchicine was equally effective and better tolerated than prednisone, with 72% of orbits responding to colchicine. Considering an improvement of at least 2 points in CAS, 68% of orbits showed amelioration of activity of the disease. Furthermore, of considerable importance is the fact that all patients receiving colchicine did not present side effects; on the other hand, there were complaints related to steroids in six prednisone-treated patients, besides those two patients initially excluded from the trial. The evaluation of signal intensity ratio on MRI after treatment also revealed a significant reduction in both groups; in G1 the therapeutic outcome was effective, demonstrating that colchicine is a valuable agent in the reduction of soft tissue inflammation.

The sites where colchicine might act include chemotaxis, phagocytosis, adherence of polymorphonuclear cells, fibroblast proliferation and collagen synthesis rate, as well as inhibition of cytokines (e.g. IL-1, IL-6, TNF-α, TGF-β)[8-9,37-38]. Furthermore, colchicine also downregulates the surface expression of intercellular adhesion molecule-1[39]. The inhibition of leukocyte adhesion, fibroblast proliferation and cytokine release may cause a reduction of GAG secretion and an inhibition of the inflammatory cascade.

In this study, the smokers, as expected, had more severe ophthalmopathy than the nonsmokers. Smoking can decrease immunosuppression, allowing greater expression of the autoimmune process[40-41]. Our results, comparing smokers and nonsmokers, independently of the used drug, indicate that there was a tendency for nonsmokers to present lower values

of initial CAS (p=0.08). In addition, 10 of 15 smokers (66%) were considered responders, compared with 18 of 19 (94%) nonsmokers; although there was not a significant statistical difference, the nonsmokers showed a higher percentage of cure of inflammation. Since the value of p=0.06 is very close to the critical rate, this can suggest a tendency of a higher probability of cure among nonsmokers, as it has been the experience of others[2].

In conclusion, colchicine had a beneficial effect on the inflammatory phase of Graves' ophthalmopathy, providing symptomatic relieve, reduction of clinical activity score and signal intensity ratio; in addition, in this study it was equally effective when compared to the classic treatment with corticosteroids, but safer and better tolerated and did not present side effects when used in the proposed dose. Therefore, it is a new option for patients with GO and can be used for a prolonged time, avoiding recurrence of the disease.

RESUMO

Objetivo: Investigar se a colchicina é eficaz no tratamento da oftalmopatia de Graves, nós comparamos o seu efeito com a prednisona em 22 pacientes tratados na fase inflamatória da doença. **Métodos:** Todos os pacientes, similares quanto à idade, sexo e hábitos de tabagismo, estavam em eutiroidismo por pelo menos três meses e foram randomizados em dois grupos. O grupo 1 (G1) recebeu colchicina (1,5 mg/dia) e o grupo 2 (G2) foi tratado com prednisona (0,75 mg/kg/dia). Os pacientes foram acompanhados com avaliação oftalmológica (escore de atividade clínica - CAS) e de imagem por meio da ressonância magnética, usando a relação da intensidade de sinal (SIR) dos músculos reto em comparação com a substância alba cerebral. **Resultados:** Diminuição no CAS de 68% foi notada em ambos os grupos. A SIR também apresentou redução significante após o tratamento: A mediana inicial do G1 de 1,14 e 1,27 do G2 diminui após o tratamento para 1,07 no G1 e 0,69 no G2. A variação entre os grupos após o tratamento não foi significante (p=0,22). Nenhum paciente tratado com colchicina apresentou efeito colateral; ao passo que os efeitos colaterais no G2 foram ganho de peso, edema, queixas gástricas, fraqueza, depressão e alteração na pressão arterial. **Conclusão:** A colchicina apresenta efeitos benéficos na fase inflamatória da oftalmopatia de Graves sem os efeitos colaterais da prednisona.

Descritores: Oftalmopatia de Graves/quimioterapia; Colchicina/uso terapêutico; Prednisona/efeitos adversos; Tabagismo; Estudos prospectivos

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