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Research Article

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Treatment of Endometriosis and Leiomyoma with the Association of Miodesin and Gestrinone in Pentravan Through the Vaginal Route

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Abstract

Introduction: *The effects of Myodesin™ (Fagron, Brazil) on uterine volume and pain scores were investigated in a group of patients with leiomyoma and endometriosis. Myodesin™ was used either alone or in combination with vaginal gastronone.*

Patient and Methods: *Forty two patients with uterine leiomyoma and endometriosis were enrolled for this study and divided into 3 groups according to the treatment scheme. In Group A (n=16) they were treated with a higher dose of vaginal Gastronome alone (5mg twice a week). In Group B (n=16) patients received a lower dose of Gestrinone (2.5 mg twice a week) together with vaginal Miodesin™ (500 mg/dose daily) (Fagron Brazil). In Group C (n=10) patients were treated only with Miodesin™. All medications were dispensed vaginally dissolved in Pentravan™ (Fagron, Netherland).*

Results: *The average uterine sizes before treatment were 200 cm3, 334 cm3, 242cm3 in group A, B and C respectively and they were not statistically different. After the second month a significant reduction in uterine volume was observed in all treated groups. However the reduction in uterine volume was greater in group than in group C. The proliferation rates in both stroma and endometrial gland measured by Ki-67 were low with a mean value of 2% with no significant differences between groups A and B. Treatment with Gestrinone decreased significantly total pain scores (VAS) when used either alone or in combination with Myodesin™. However this decrease was significantly greater in Group B than in Group A.Treatment with Miodesin alone (Group C) also decreased significantly pain scores.*

Conclusion: *Miodesin treatment increased the efficacy of Gestrinone to reduce pelvic pain and uterine volume in patients with endometriosis and leiomyoma.*

Keywords: Pentravan, Miodesin, Gestrinone, Endometriosis, Leiomyoma, Pelvic Pain

Introduction

Leiomyoma is a tumor whose growth is accelerated by inflammation and hormones such as progesterone and estradiol [1]. Gestrinone, neither a19 nor testosterone derivative is an effective treatment to reduce pain and uterine volume in patients with endometriosis and leiomyoma although the occurrence of androgenic side effects may hamper long term treatment in some patients [2]. One interesting approach to circumvent this problem would be to use lower doses of Gestrinone together with naturally occurring plant derived anti-inflammatory medications. One promising drug is the Uncaria tomentosa, an herbal medicine from Amazonas widely used to treat inflammatory conditions [3].

This medicinal plant has been shown to suppress the production of tumor necrosis factor (TN alpha) a pro-inflammatory cytokine. The Uncaria tomentosa extract acts through a NF-Kappa.Bdependent mechanism to inhibit TNF alpha production decreasing therefore the inflammatory cascade [4]. One current clinical application of this medication is the treatment of common inflammatorydisorders such as arthritis and gastritis [5]. This antagonist effect of Uncaria tomentosa extract on TNF alpha could also be used for the treatment of leiomyoma and endometriosis since the development of these pathologies is stimulated by inflammation. For instance, TNF alpha increased activinan mRNA production in myometrium and leiomyoma cells therefore increasing extra cellular matrix (EMC) production and stimulating their growth [5]. Furthermore the presence of a great number of inflammatory cells inside the leiomyoma suggests that inflammation plays a pivotal role in the

growth of these tumors [5]. In addition leiomyoma cells cultured in vitro also responded to Celecoxib by decreasing Cox-2 activity. This was achieved throughthe inhibition of a NF-Kappa.Bdependent pathway leading therefore to a decrease in the expression of genes related to both inflammation and growth factors synthesis [6]. One probable consequenceof diminishinginflammation would be the not only the reduction in leiomyoma growth but also the decrease in pain and abnormal uterine bleeding. Other pathologies of the female genital tract might also respond similarly to medications that suppress inflammation. In rats with experimental endometriosis the use of Uncaria tomentosa extract reduced the growth of endometrial auto transplants in the peritoneum [7].

Endometriosis is an inflammatory pathology and the coexistence of both leiomyoma and endometriosis occurs in a significant number of symptomatic patients [8]. The concomitances of these two pathologies might explain the high pain scores reported by some patients with leiomyoma. In this group of patients the development of medical therapies that could amelioratepelvic pain, abnormal bleeding and reduce uterine volume would be of utmost relevance [9]. In the present report, the effects of Myodesin™ (Fagron Brazil) on uterine size and painscores were investigated in a group of patients who had leiomyoma along withendometriosis. Myodesin™is the patent name of a plant extract of Uncaria tomentosa prepared by Fagron Brazil and it was used in the present study either alone or associated with vaginal Gestrinone.

This latteris neither a 19 nor testosterone derivative whose molecule has a potent androgenic activity together with stronganti estrogenic and anti-progesterone actions which may cause some undesirable androgenic side effects. One way to circumvent this problem would be to use lower doses of Gestrinone together with naturally occurring anti-inflammatory drugs such as Miodesin™. Previous study had shown that Gestrinone can be dissolved in Pentravan™ and administered through the vagina and this route of administration was found to be highly effective for treating endometriosis related pain since vaginal absorption may facilitate the concentration the medications in the pelvic organs [2].

Patient and Methods

Forty two patients were enrolled for the present study carried out at the Institutoda Mulher, Itaigara Memorial Day Hospital between January and August 2018. The inclusion criteria used in this study were patients with the diagnosis of associated endometriosis and leiomyoma, pain scores greater than 6 (VAS), presence of menorrhagia , being in the reproductive age (18-45 year old) and being sexually active since the medications were used in the vagina. The diagnosis of endometriosis was suspected by clinical history and confirmed by ultrasonography and magnetic resonance in some patients. Vaginal ultrasonography (USG) was used to measure uterine volume in all patients with leiomyoma before and after 2 months of treatment. The presence of deep endometriosis or ovarian endometriosis was confirmed by magnetic resonance (MRI) when it could not be detected by routine vaginal ultrasonography. The patients were initially interviewed by the same investigator (HM) and pain scores were assessed using a visual analogic scale (VAS) in which zero corresponded to the total absence of pain and ten to the worst pain imaginable.

A total pain score was calculated, which included dysmenorrhea, pelvic pain and dyschesia. When the patients gave different VAS scores for these different forms of pain, the one with the highest score was considered for the purpose of evaluation. Pain was assessed at the initial visit and again after the first and second month of treatment. Myodesin™ Fagron (Brazil) was administered in the vagina either alone or in combination with Gestrinone. Miodesin™ is a trade name of plant derived extract prepared by Fagron (Brazil) from the leaves of Uncaria tomentosa and Endopleura Uchi. This plant extract contains 2,7% of oxindolic alkaloids which are potent inhibitors of NF-Kappab activity [4]. Both Miodesin™ and Gestrinone were dispensed vaginally dissolved in Pentravan™. Since pain scores were not significantly different at baseline among the patients, their allocation of to the different treatment groups was not randomized. The study was open in that both the patients and their attending physician were aware of the medications they were using. The patients were divided into 3 groups according to their treatment scheme. In Group A (n=16) they were treated with a higher dose of vaginal Gestrinona alone(5mg/ml twice a week). In Group B (n=16) patients received a lower dose of Gestrinone (2.5 mg/ml twice a week) together with vaginal Miodesin™ (500 mg/dose daily). In Group C (n=10) patients were treated with Miodesin™ alone in the dose of 500 mg. In this group theyhad not received any hormonal treatment in the last 3 months.

Statistical analysis was performed using Student's t-test to evaluate differences in mean pain scores and uterine volume among the different treatment groups. The chi square test was used to calculate differences in percentages. In both tests p-values <0.05 were considered statistically significant.

The study was conducted at the Instituto da Mulher, Itaigara Memorial Day Hospital and was approved by the institute's internal review board.

A myomectomy by hysteroscopy was carried out in 10 patients after the second month of treatment to remove sub mucous leiomyoma and fragments of the endometrium. Six of these patients were using Gestrinone alone (n=6) and in the remaining four Gestrinone was used together with Miodesin™. The surgical procedure was carried out using the bipolar resect scope (Versapoint, Ethycon, USA) as previously described [10]. Leiomyoma and endometrial fragments were fixed in formalin 4% and sent to pathology for routine Hematoxylin–Eosin stain and immunohistochemical determination of Ki-67, a proliferation marker as previously described [11].

Results

Effect on uterine volume

The average uterine sizes were 200 cm3, 334 cm3, and 242cm 3 in group A, B and C respectively before treatment. There was no significant statistical difference between the groups. After the second month of treatment a significant reduction in uterine volume was observed in all treated groups witha mean reduction in uterine volume of 30%,34% and 24% in the three groups respectively. There were no significant differences between groups A and C but in group B the reduction was significantly greater than in group C ($p=0.03$).Although the mean values were greater in group B than in group and it did not reach statistical significance ($p=0.2$). These results are shown in (figure 1).

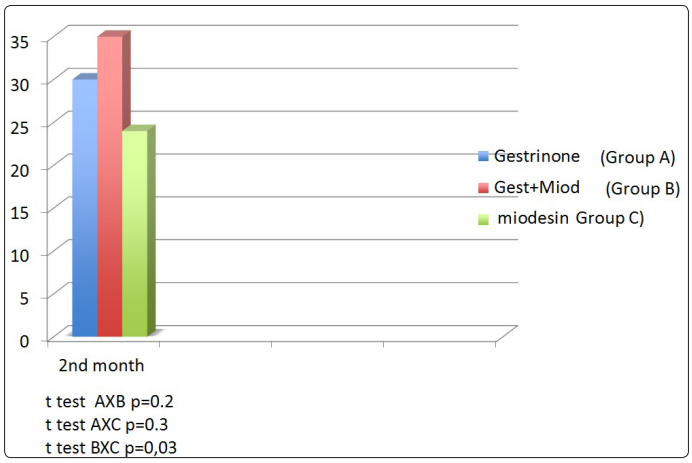

Figure 1: Reduction(%) of uterine volume in patients with leiomyoma and endometriosis using Gestrinone , Gestrinone with Miodesin or Miodesin alone

Effect on endometrial proliferation

In patients who were submitted to myomectomy after two months of treatment with gastronome either alone or associated with Miodesin™ there was a reduction in endometrial thickness and in the vascularization of both endometrium and myoma. The histological picture was of glandular atrophy with no decidual reaction in a fibrous stroma. Endometrial biopsies in group A and B showed very low mean Ki-67 values of 1 and 2% in both gland and stroma (Figure 2). In the leiomyoma cells the proliferation rates were also low similar to the atrophic endometrium (Figure 3).

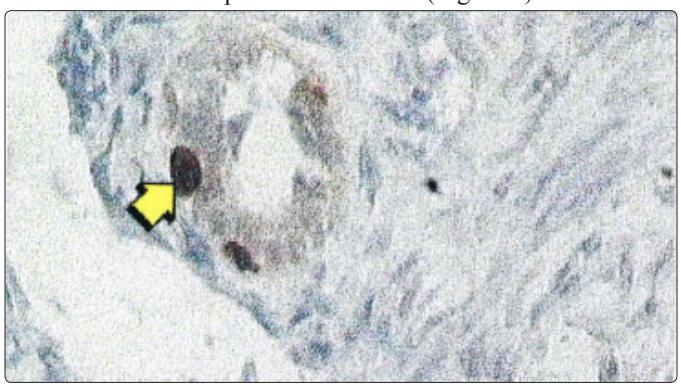

Figure 2: Basal endometrium in a patient using vaginal Gestrinone with Miodesin for 2 months . Note the low proliferation rates measured by Ki-67 in the glandular epithelium and stroma

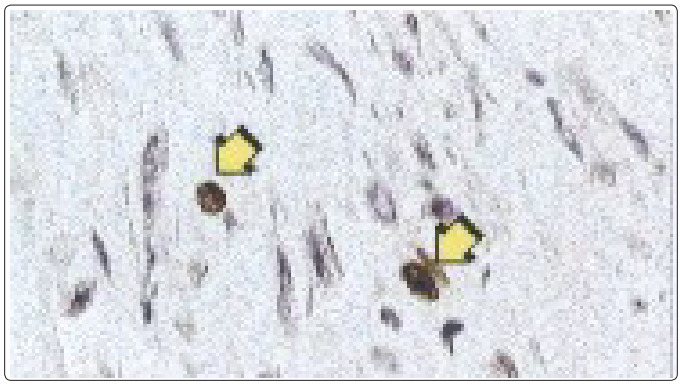

Figure 3: Low proliferation rates(Ki-67) in a leiomyoma of a patient using vaginal Miodesin

Effect on pain scores

Gestrinone significantly decreased total pain scores (VAS) when used alone or in combination with Miodesin™. In all three groups pain scores were the same before treatment was started with a mean value of 9 (VAS). In groups A and B total pain scores reduced significantly during treatment.This decrease was already significant after the first month of treatment and they further deceased with the continuation of therapy in both groups. However pain scores were always significantly less in patients using Miodesin™ with Gestrinone (Group B) than in those using Gestrinone alone (Group A) ($p<0.005$) both at the first and second month of treatment. In patients using Miodesin™ alone (Group C) pain scores decreased significantly during treatment. After the second month they were not different from Group B but significantly less than in group A($p<0.001$) (Figure 4). After two months of treatment the percentages of patients reporting no pain were the same in groups B and C and they were both significantly less than in group A ($p<0.001$). These percentages are shown in (Figure5).

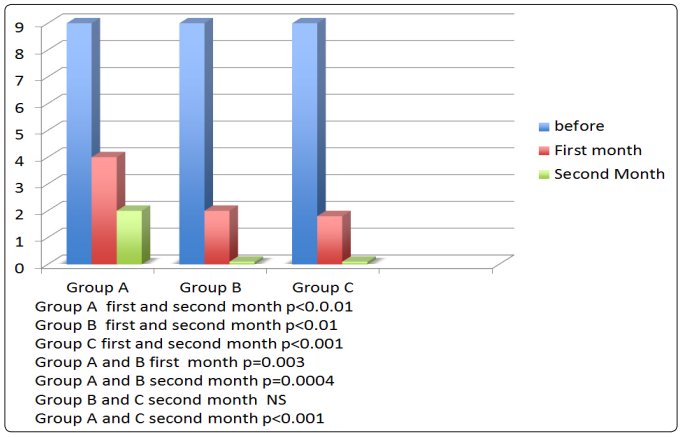

Figure 4: Reduction of pain scores in the three treatment groups

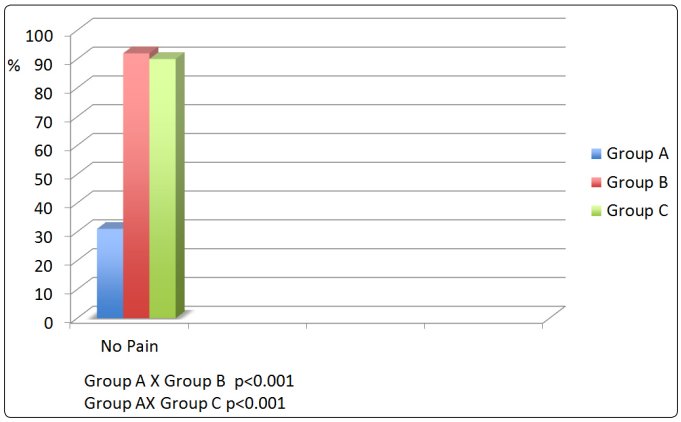

Figure 5: Percentage of patients reporting no pain after the second month of treatment in the three treatment groups

Side Effects

Side effects were mainly androgenic and they were observed in 20% and 10% of the patients in group A and B respectively and were mainly related to Gestrinone use. Miodesin™ on the hand, when used alone did not provoke any significant adverse reactions.

Conclusion

The present study shows that the use of lower doses of Gestrinone (2,5mg) together with Miodesin™ was more effective to reduce pain

and decrease uterine volume in patients with associated endometriosis and leiomyoma than the use of higher doses of Gestrinone alone. The greater efficacy of this combination was also associated with a lesser incidence of androgenic side effects because of the lower doses of Gestrinone used. Miodesin™ alone was also effective to reduce uterine volume in patients with leiomyoma and endometriosis albeit greater reductions were achieved when was used together with Gestrinone. However in terms of analgesic effects, Miodesin™, as consequence ofits NF-Kappa's blocking effect, proved to be a very efficient natural medication to reduce pain and inflammation therefore improvingthe analgesic effects of vaginal Gestrinone in patients with endometriosis and leiomyoma.The reduction of Gestrinone dose rendered the treatment more effective with less androgenic side effects. One can also speculate that the use of vaginal mucosa to administer both medications in Pentravan™ may lead to a better absorption and their increased concentration in the pelvic organs, thus explaining their great therapeutic efficacy. However due to the small sample of this study these results have to be considered preliminary and further trials using better methodology will be necessary to confirm these initial encouraging results. Despite these limitations Miodesin™ proved to be a very effective naturally occurring medication to treat leiomyoma and endometriosis when administered in Pentravan™either alone or in association with Gestrinone through the vagina.

The analgesic properties of Uncaria tomentosa extracts are mediated through the inhibition of NF-Kappa's pathway thus impeding the inflammatory cascade in these pathologies [4]. As the growth of both leiomyoma and endometriosis and its resulting induced fibrosis and symptoms depend on inflammation the use of anti-inflammatory medications associated with hormonal therapy may have a good biological plausibility [12,13]. Both Gestrinone and Miodesin proved to be an effective treatment to reduce uterine volume, and pelvic pain in patients with associated leiomyoma and endometriosiswhen used either alone or combined. However when Miodesin™ and Gestrinone were used together there was, not only a greater reduction in uterine volume but alsomorepain free patients than when they were used separately. These suggest a possible synergistic effect on these pathologies acting through different mechanisms. Recently a selective progesterone receptor modulator (SPRM) Ulipristal acetate (UPA) was introduced as a new therapeutic option for the treatment of symptomatic leiomyoma. UPA exerts both agonist and antagonist effects after binding to progesterone receptor and was found to be effective to reduce leiomyoma size and diminish uterine bleeding [14]. In this aspect their effects are similar to Gestrinone whose anti-progesteroneand anti-estrogeniceffects werefirst described more than 30 years ago [10]. The total suppression of endometrial proliferation in both stroma and glandular epithelium together with the absence of decidual reaction in patients using vaginal Gestrinone as reported here is strong evidence of the anti-progesteroneand anti-estrogeniceffects of Gestrinone. This feature of Gestrinone makes it superior to Ulipristal in terms of endometrial safety since the endometrium becomes atrophic instead undergoing unique histologic changes; albeit benign seem with the selective progesterone receptor modulators (SPRM) [15]. Miodesin™ was devoid of major side effects and increased the efficacy Gestrinone to treat leiomyomaand endometriosis due to its anti-inflammatory effects [16]. This association may be a novel approach to treat these pathologies using the vaginal mucosa to administer and concentrate these medications in the pelvic organs. These initial results with the Uncaria tomentosa extracts also confirm the role of inflammation in leiomyoma growth by stimulating the production of extra matrix in these tumors [5].

The effectiveness of Myodesin alone to treat endometriosis pain confirms the pivotal role of inflammation in the pathogenesis of endometriosis, supporting the role of naturally occurring anti-inflammatory medications in the treatment of this disease. The present encouraging results albeit preliminary suggest a novel and effective approach to treat leiomyoma and endometriosis by using the vagina as port of entry of naturally occurring anti-inflammatory medications together with Gestrinone to achieve a greater concentration in the pelvic organs and consequently better therapeutic results.

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