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Research Article

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Effect of Vaginal Miodesin™ in Pentravan™ on the Response to Progestin Therapy in Patients with Deep Endometriosis and Adenomyosis

Hugo Maia[1]*, Wilson Saback[2], Clarice Haddad[3] and Paulo R Sitya[4]

[1]*Medical Coordinator, Instituto da Mulher, Itaigara Memorial Day Hospital Salvador, Bahia, Brazil*

[2]*Department of Life Sciences, State University of Bahia (UNEB) Salvador, Bahia, Brazil*

[3]*Instituto da Mulher, Itaigara Memorial Day Hospital Salvador, Bahia, Brazil*

[4]*Gynecology and Obstetrics, Universidade Luterana do Brasil Canoas, Rio Grande do Sul, Brazil*

***Corresponding author**

Hugo Maia, Insituto da Mulher, Itaigara Memorial Hospital Dia, Centro Medico Linus Pauling, Rua Altino Seberto de Barros, 119 CEP: 41825-010; Tel: 3247 9155; E-mail: hmaiaf@terra.com.br

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Abstract

Introduction: *The effects of Myodesin™ (Fagron, Brazil) on pain scores were investigated in a group of 18 patients with endometriosis who failed to respond to oral dienogest or Mirena.*

Patient and Methods: *Eighteen patients with endometriosis were enrolled for this study and divided into 2 groups according to the treatment scheme. Group A (n=10) comprised of patients who were using 2 mg of dienogest and continuing to have pain and breakthrough bleeding when treatment with vaginal Miodesin™ (500 mg/dose daily) (Fagron Brazil) was initiated. In Group B (n=8) patients were treated with Miodesin™ after they had been using a Mirena ™ unsuccessfully to treat endometriosis pain for at least 3 months. Myodesin™ was always dispensed through the vaginal mucosa dissolved in Pentravan™ (Fagron, Netherland) at bedtime. Hysteroscopy with endometrial biopsies were performed in 4 patients in the Mirena™ group to evaluate the cause of uterine bleeding and to assess the presence of aromatase and VEGF expression in the endometrium by immunohistochemistry.*

Results: *In this group of deep endometriosis patients treatment with Dienogest or Mirena ™ caused a modest albeit significant reduction in total pain scores (VAS). However after vaginal Myodesin™ treatment was initiated there was a significant further reduction in pain scores in both groups albeit the post treatment scores were significantly smaller in Group B than in Group A. In Mirena™ users with bleeding and pain aromatase and VEGF expressions were detected in ¾(75%) of endometria but they became negative after Myodesin™ treatment in all cases. A great reduction in endometrial vascularization was also observed.*

Conclusion: *Miodesin treatment increased the efficacy of Dienogest and Mirena™ to reduce pelvic pain in patients with deep endometriosis and adenomyosis that were not responding adequately to these treatments. At least in Mirena™ users this was accompanied by a reduction in endometrial vascularization and in both VEG|F aromatase expression in the endometrium.*

Keywords: Pentravan, Miodesin, Endometriosis, Pelvic Pain, Dienogest Mirena

Introduction

Endometriosis is an estrogen depend pathology whose growth and clinical course depends on the presence of an inflammatory milieu which triggers the appearance of epigenetic changes in both eutopic endometrium and endometriosis lesions [1-3]. Currently the first option in endometriosis treatment is the use of a progestin alone such as dienogest whose therapeutic action depends on the binding to the progesterone receptor type B (PRB) in both eutopic and ectopic endometrium [3]. Tumor Necrosis Factor alpha (TNF α) an inflammatory cytokine constitutively expressed in endometriosis, induces in the endometrial stroma an increase in glucocorticoid receptor while at the same time decreases progesterone receptor ,thus explaining why some endometriosis patients shows an impaired response to progestin such as dienogest [1,4]. Inflammation would therefore be the major culprit for progesterone resistance in endometriosis. It is noteworthy mentioning that inflammation also affects endometrial cycle physiologically since it plays a pivotal role in important processes related to fecundity and menstruation and only when present excessively it may induce in some susceptible patients

the epigenetic changes in the endometrial cells that will render them more prone to implant in the pelvis and develop into endometriosis lesions [2,4,5]. The steady state of chronic inflammation present in the eutopic endometrium induces the aberrant expression of aromatase p450 and this will boost not only the local estrogen production but it will also further stimulate inflammation. As consequence of these endometrial changes progesterone resistance develops which leads not only to impaired decasualization, decreased fertility but they also contribute to the survival and implantation these cells outside the uterine cavity [3,4]. This hyper inflammatory state will therefore blunt the response of both endometrium and endometriosis lesions to progestin thus rendering them resistant to treatment and affecting negatively the clinical response [4]. Since inflammatory cytokines are known to cause progesterone resistance in endometriosis one possibility to circumvent this problem would be the concomitant use of naturally occurring anti-inflammatory agents in order to improve the response to progestin thus rendering these endometriosis patients less refractory to treatment [4]. In the present paper the effect a NF-KappaB inhibitor, Miodesin™ (Fagron, Brazil) was investigated in endometriosis patients that are poor responders to either oral dienogest or to a levonorgestrel intrauterine system (Mirena™, Bayer). Since in these patients pain and bleeding persist despite progestin therapy they could be the appropriate group to investigate whether the reduction in inflammation by Miodesin™ would decrease progesterone resistance thus allowing them to respond more effectively to progestin treatment. Miodesin™ (Fagron Brazil) is a plant extract from Uncaria tomentosa and Endopleura uchi that had been previously used by our group to improve the clinical response to vaginal gastronome in deep endometriosis patients [6]. The Uncaria tomentosa extract has been shown to suppress the production of TNF a pro-inflammatory cytokine that plays a pivotal role in the development of progesterone resistance in endometriosis [7]. This plant extracts acts through a NF-KappaB dependent mechanism to inhibit TNF alpha production decreasing therefore the inflammatory cascade [7, 8].

Patient and Methods

Eighteen patients were enrolled for the present study carried out at the Instituto da Mulher, Itaigara Memorial Day Hospital between August 2017 and September 2018. The inclusion criteria used in this study were patients with the diagnosis of deep or ovarian endometriosis, pain scores greater than 6 (VAS) after treatment with dienogest or Mirena™ for at least 3 months, presence of persistent breakthrough bleeding and being in the reproductive age (18-45 year old). The concomitant presence of adenomyosis was not an exclusion criterion since it was present in 8 patients in the dienogest group and in 7 patients using Mirena™. The diagnosis of endometriosis was suspected by clinical history and confirmed by image methods or videolaparoscpy in five cases. The presence of deep endometriosis or ovarian endometriosis was usually diagnosed by magnetic resonance (MRI) when it could not be detected initialed by routine vaginal ultrasonography. The patients were always interviewed by the same investigator (HM) and pain scores were assessed using a visual analogic scale (VAS) at the time of the first consultation and after the initiation of Miodesin™ treatment. The patients were asked to grade their pain in a visual scale of zero to ten 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 in this group of patients using dienogest or Mirena™ for at least 3 months and repeated again after 2 months of Miodesin. All clinical evaluations and hysteroscopy were done by the same investigator (HM).

The patients were divided in two groups. Group A (n=10) comprised of patients who were using dienogest for at least 3 months when they started to be treated with vaginal Miodesin™. In group B (n=8) the patients had been using a Mirena™ for at least the same period of time when vaginal Miodesin™ was administered .In both groups pain scores were above 6 and breakthrough was present. Miodesin™ is the trade name of plant derived extract prepared by Fagron (Brazil) from the leaves of Uncaria tomentosa and Endopleura uchi. The Uncaria tomentosa extract contains 2, 7% of oxindolic alkaloids which are potent inhibitors of NF-KappaB activity. The study was open in that both the patients and their attending physician were aware of the medications they were using. In both groups A and B the patients were treated with a daily dose of 500 mg of Miodesin™ dissolved in 3 ml of Pentravan that was administered in the vagina. The patients were instructed to use the medication daily at bedtime. Vaginal Miodesin™ was always prepared in the same compound pharmacy by the same pharmacist (WSJ).

An ambulatory hysteroscopy was carried out in 4 patients using Mirena™ before and two months after the use of vaginal Miodesin™ was initiated. An endometrial biopsy was taken during the exam and the tissue fragments were fixed in formalin 4% and sent to pathology for routine Hematoxylin–Eosin stain and determination of aromatase and VEGF expression by immunohistochemistry as previously described [9]. Pictures were taken in the areas adjacent to the Mirena and the number of visible enlarged blood vessels mostly engorged veins was counted.

Statistical analysis was performed using Student's t-test to evaluate differences in mean pain scores and endometrial blood vessels count before and after miodesin treatment in the two groups. Significance was established at p-values <0.05. For differences in percentages a Chi-square test was used.

The study was conducted at the Instituto da Mulher, Itaigara Memorial Day Hospital and was approved by the institute's internal review board. The patients gave informed consent after being explained of the vaginal use of Miodesin™.

Results

Miodesin Effects on Pain Scores

Pain scores before treatment with dienogest or Mirena™ had a mean value of 9 (VAS) and they were the same in the two groups. Both Mirena™ and dienogest treatment caused a small but statistically significant decrease in total pain scores (VAS) when used for at least 3 months in this group of deep endometriosis patients. However they were still reporting pain that required the use of analgesics for its control and 90% of them were not in amenorrhea. In 80% of the times the exacerbation of pain was associated with the occurrence of breakthrough bleeding.

In groups A and B a significant reduction in pain scores was observed two months after the introduction of vaginal Miodesin™. Although the mean post treatment pain scores were significantly lower in both groups when compared to pretreatment values this decrease was significantly greater in group B than in group A. These

results are shown in (Figures 1 & 2). The final mean pain scores were 2 and 0.2 in groups A and B respectively and this difference was statistically significant (p=0.001). There were also a smaller percentage of patients reporting no pain after Miodesin™ treatment in the Mirena™ group than in the diogenest group. The percentages of pain free patients were 87% and 40% n groups A nd B respectively. In all patients uterine bleeding subsided after the second month of vaginal Miodesin™ treatment.

Figure 1-Effect of vaginal Miodesin in Pentravan on pain scores in poor responders to dienogest alone .Note the reduction in the scores after the use of vaginal Miodesin

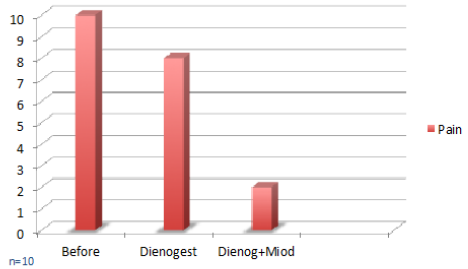
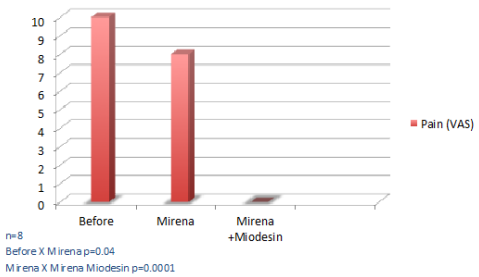


Figure 2-Effect of vaginal Miodesin in deep endometriosis patients that responded poorly to Mirena alone. Note the great reduction in pain scores following the use of vaginal Miodesin



The Effects Miodesin™ on VEGF and Aromatase Expression in the Endometrium

In the four endometriosis patients using Mirena™ submitted to hysteroscopy and who were still reporting pain and breakthrough at the time of the exam, endometrial biopsies taken during hysteroscopy showed that both aromatase and VEGF expression was still detected in the endometrium in ¾ (70%) of the cases. The staining reaction was always detected in the stroma while the endometrial glands were negative. After the second month of treatment with vaginal Miodesin™ all endometria became negative for both VEGF and aromatase expression and the patients became not only pain free but they went into amenorrhea (Figure 3 & 4).

Figure 3-Aromatase expression in the endometrial stroma of an endometriosis patient using Mirena and experiencing bleeding and pain . Note that VEGF positivity wanes off after the use of vaginal Miodesin

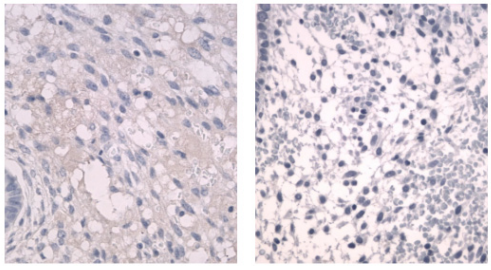
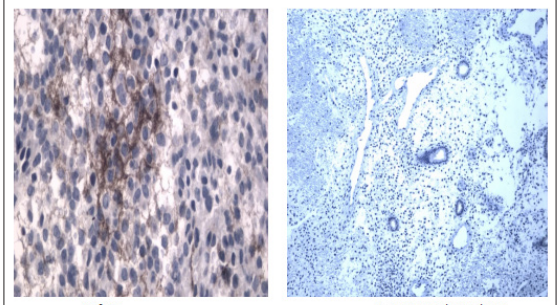


Figure 4-Effect of vaginal miodesin in Pentravan on VEGF expression in the endometrial stroma of an endometriosis patient experiencing pain and breakthrough during Mirena use .Note that VEGF expression became negative after vaginal Miodesin use



Hysteroscopy examination revealed that before Miodesin™ treatment there were more enlarged and friable blood vessels adjacent to the Mirena™ than after 2 months of treatment. The number of visible enlarged vessels decreased from a mean of 14 to 3 and this was statistically significant (p<0.01) these results are shown in (Figures 5 & 6).

Figure 5- Decrease in endometrial vascularization in a deep endometriosis patient using Mirena after the introduction of vaginal Miodesin in Pentravan.

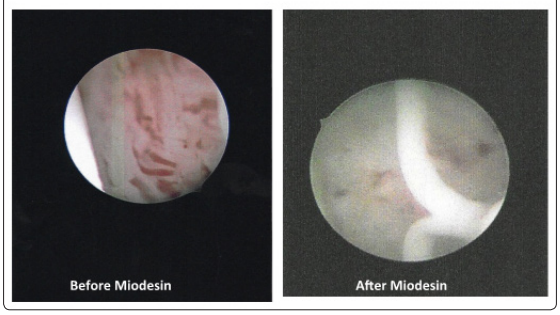
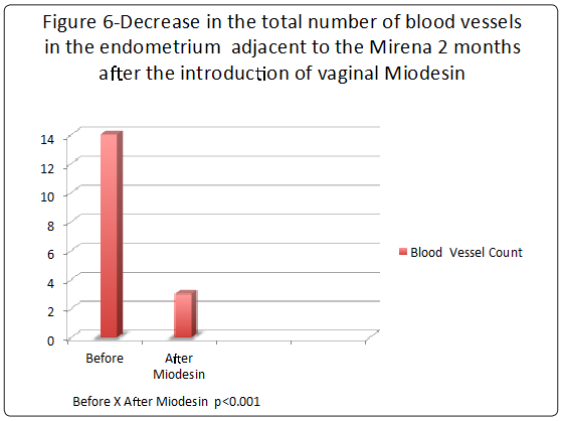


Figure 6-Decrease in the total number of blood vessels in the endometrium adjacent to the Mirena 2 months after the introduction of vaginal Miodesin



Discussion

The present study showed that vaginal Miodesin™ in Pentravan™ increased the efficacy of Mirena™ and dienogest in the treatment of endometriosis and adenomyosis pain. However the decrease in pain scores was more pronounced in the Mirena™ group probably because of the frequent association of adenomyosis with deep endometriosis. Similar results were reported in a recent study comparing Mirena™ with danazol for the relief of pain in endometriosis patients submitted to laparoscopy surgery [10]. In this study it was found that the mirena mirena is repeated twice in decreasing endometriosis pain following surgery than danazol. These findings are in agreement with the

results reported here that Miodesin™ albeit effective in both groups was significantly better to decrease pain in the Mirena™ group. One possible explanation for these findings would the frequent presence of adenomyosis in these patients. In Mirena™ users it had been previously shown that the endometrial concentrations of the progestin are much higher than those achieved with the systemic administration [11]. Since the uterus itself may be an important source of pain in these deep endometriosis patients it is expected the effects of Miodesin™ were significantly better in the Mirena™ group. Previous studies have shown that the intensity of pelvic pain in patients with deep infiltrating endometriosis correlates positively with the presence of adenomyosis which points out again toward a uterine origin for the pain [12]. Miodesin™ by decreasing inflammation will improve the clinical response of these patients to either Mirena™ or dienogest, although this was greater in the former group due to the presence of adenomyosis. Because Miodesin™ can block NF-KappaB activation thus decreasing inflammation this will allow both eutopic endometrium and the lesions to respond better to progestin therapy [4]. Mirena™ delivers Levonorgestrel locally in the uterus which makes the clinical response to Miodesin™ better in this group since the high endometrial levels of this progestin will abate the adenomyosis related inflammation more efficiently [4, 11]. Since the intensity of endometrial inflammation correlates positively in both deep endometriosis and adenomyosis patients with progesterone resistance the blockade of NF-KappaB activation with the use of Miodesin will reduce inflammation thus allowing a better response to progestin therapy [4, 7, 8, 11, 12]. The observation that the intensity of pelvic pain in deep endometriosis patients correlates positively with the presence of adenomyosis supports these findings [12, 11]. The presence of high levels of endometrial inflammation in endometriosis patients due to the persistent activation of NF-KappaB will impair the response to progestin and keep aromatase expression unabated [4]. Miodesin™ by blocking the constitutive NF-KappaB activation will render endometriosis patients more responsive to progestin therapy thus avoiding the necessity of surgery [7, 8, 13].

Previous studies in our group had also shown that the use vaginal gestrinone in Pentravan ™ with Miodesin™ was very effective to treat pain in deep endometriosis patients with less side effects than its use alone [6].

Another important conclusion from the present study is that the combination of hormonal therapy with NF-kappaB inhibitors preferably of plant origin like Miodesin™ will decrease inflammation and make hormonal treatments for endometriosis more efficiently. Since NF-KappaB is constitutively more activated in the eutopic endometrium of endometriosis patients compared to healthy individuals this will increase progesterone resistance and make progestin therapy more prone to failure [14-16]. Since the high inflammation rates were not totally abated in these endometriosis patients by progestin therapy , both aromatase and VEGF expressions persisted in the endometrium through a NF-KappaB dependent mechanism that will ultimately activate cyclooxygenase type 2 (Cox-2) and PGE2 production [16]. PGE2 is a potent stimulus for the induction of aromatase expression in the endometrium of endometriosis patients [17]. Since aromatase expression was still detected in the endometrium of the Mirena patients with pain and uterine bleeding as reported here, it is evident that the response to the high levels of levonorgestrel was blunted by inflammation thus allowing aromatase expression to remain unabated in these cases. However when Miodesin™ was used the decrease in inflammation allowed the Mirena to act more efficiently thus suppressing both aromatase and VEGF expression in the endometrium. Previous studies from our group had shown that in adenomyosis the persistence of uterine bleeding and pain with the use of Mirena™ was associated with the presence of unabated aromatase expression in the endometrium [9]. In patients with history of menorrhagia and using oral contraceptives containing gestodene in a continuous regimen the occurrence of breakthrough bleeding and pain was also associated with a persistent NF-KappaB activation in the endometrium [18]. These results indicate that inflammation plays a pivotal role in progesterone resistance.

In conclusion the use of NF-KappaB inhibitors such as Miodesin™ to curb down inflammation will allow a better response to progestin therapy in endometriosis and should be tried when progesterone resistance is suspected. This will certainly decrease the number of unnecessary surgeries in the future to treat the failures of clinical treatment.

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