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Research Article

Etamsylate Causes Regression of Endometriosis Lesions in a Rat Model

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Abstract

Intraperitoneal injections of etamsylate in a suitable rat model of endometriosis produced regression of implanted endometrial tissues. Our results indicate that etamsylate is a promising candidate for endometriosis treatment.

Keywords: Endometriosis; Rat; Etamsylate; Fibroblast Growth Factor; Vascular Endothelial Growth Factor

Abbreviations

EM: Endometriosis; FGF: Fibroblast Growth Factor; VEGF: Vascular Endothelial Growth Factor; GnRH: Gonadotrophin Releasing Hormone

Introduction

Endometriosis (EM) is defined as endometrial tissues found outside the uterus and is characterized by the presence of chronic pelvic pain, dysmenorrhea and infertility [1,2]. EM is a common benign disease that affects 10% of women during their reproductive period [3]. EM also represents a significant financial burden on health systems. EM is an angiogenesis-dependent disease [4]. The pivotal role of angiogenesis in the pathophysiology of this disease has been confirmed in many studies, also confirming a key role for Fibroblast Growth Factor (FGF) and Vascular Endothelial Growth Factor (VEGF) in this disease [5-12]. Furthermore, anti-angiogenic therapy has been proposed as a novel strategy in treating EM [13]. Currently available therapies for EM include surgical excision and various medical treatments such as the use of Gonadotropin-Releasing Hormone (GnRH) analogues, aromatase inhibitors and progestins. Unfortunately, these approaches often have only modest success and are associated with significant risks of complications and side effects. Consequently, the search continues for new, safe and effective long-term treatment. In this work we assessed the effect of etamsylate, a synthetic inhibitor of angiogenesis promoted by FGF and VEGF signalling, in a rat model of EM [14-15].

Material and Methods

Animals

Studies were performed in accordance with the Declaration of Helsinki and with the EU guidelines for the handling and care of laboratory animals.

Female Sprague-Dawley rats (6-8 weeks of age) were anesthetized with intraperitoneal administration of 50 mg/kg ketamine and 4 mg/kg diazepan.

Before surgery the abdominal skin was shaved, and antisepsis was obtained with 75% ethanol. A central incision was made, and then 1 mm of one uterine horn was excised and sutured to peritoneum using 10.0 nylon monofilament suture under a surgical microscope. After suturing the abdominal muscle and skin, 40,000 units/kg penicillin was injected into the muscle.

Treatment

Animals were randomly divided into two groups: Group A (n=8) received daily intraperitoneal injections of 0.9% NaCl during 2 weeks. Group B (n=8) received daily 200µl etamsylate (Sanofi-Aventis, France) intraperitoneal injections during the same period of time.

Histology

Implanted uterine horns were extracted and fixed in 4% paraformaldehyde and then embedded in paraffin and cut into serial 5µm sections. The deparaffined sections were stained with haematoxylin and eosin for microscopic studies.

Results

As Fig. 1 shows, the implanted uterine horn segment from an animal of the Group A appears with intense stromal vascularization. Fig. 2 shows histological findings from an animal of Group A (upper), showing a normal structure, and an animal of Group B (lower) with marked disorganization.

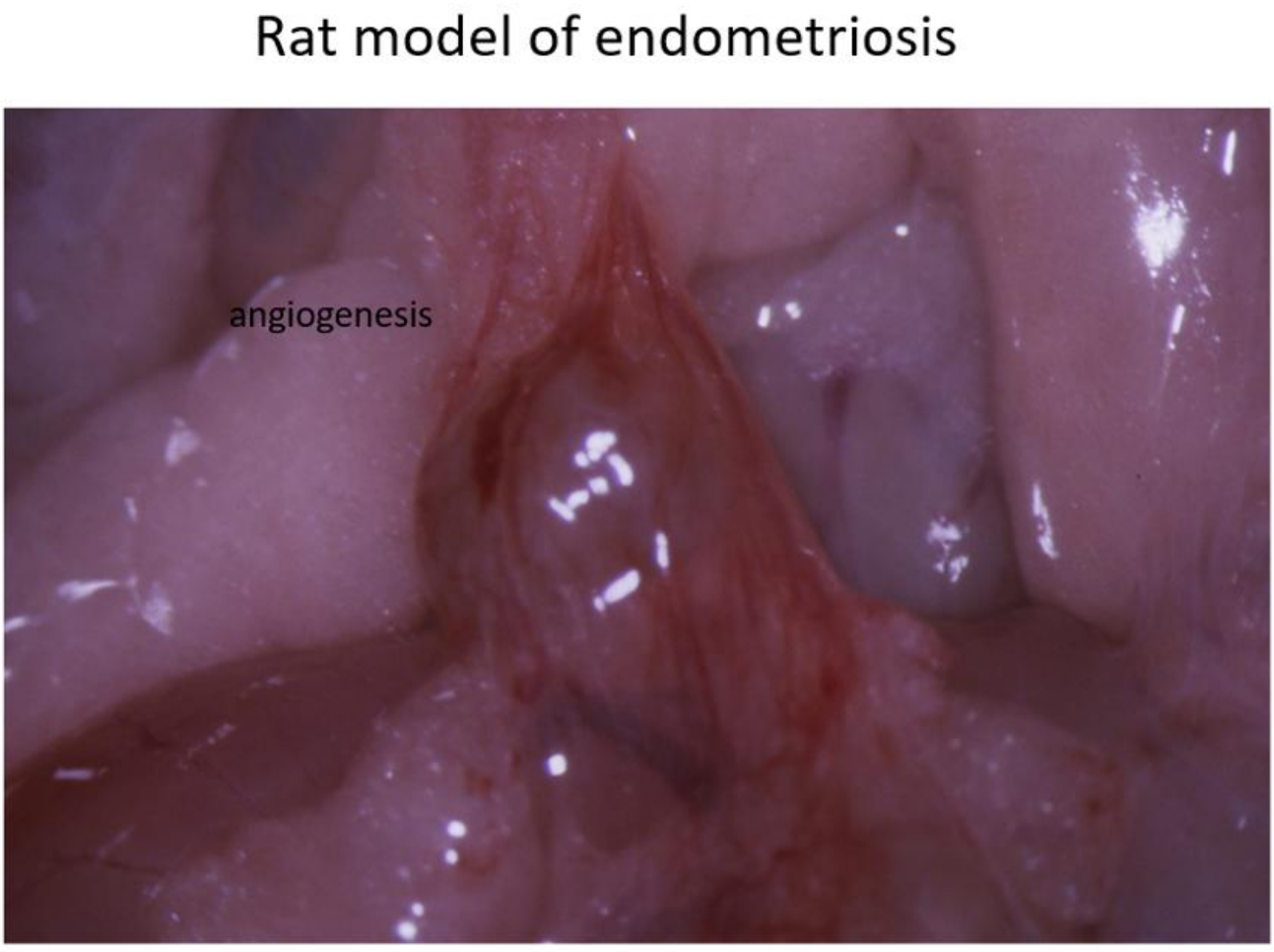

Figure 1: Uterine horn implanted in a rat model after two weeks showing notable neovascularization.

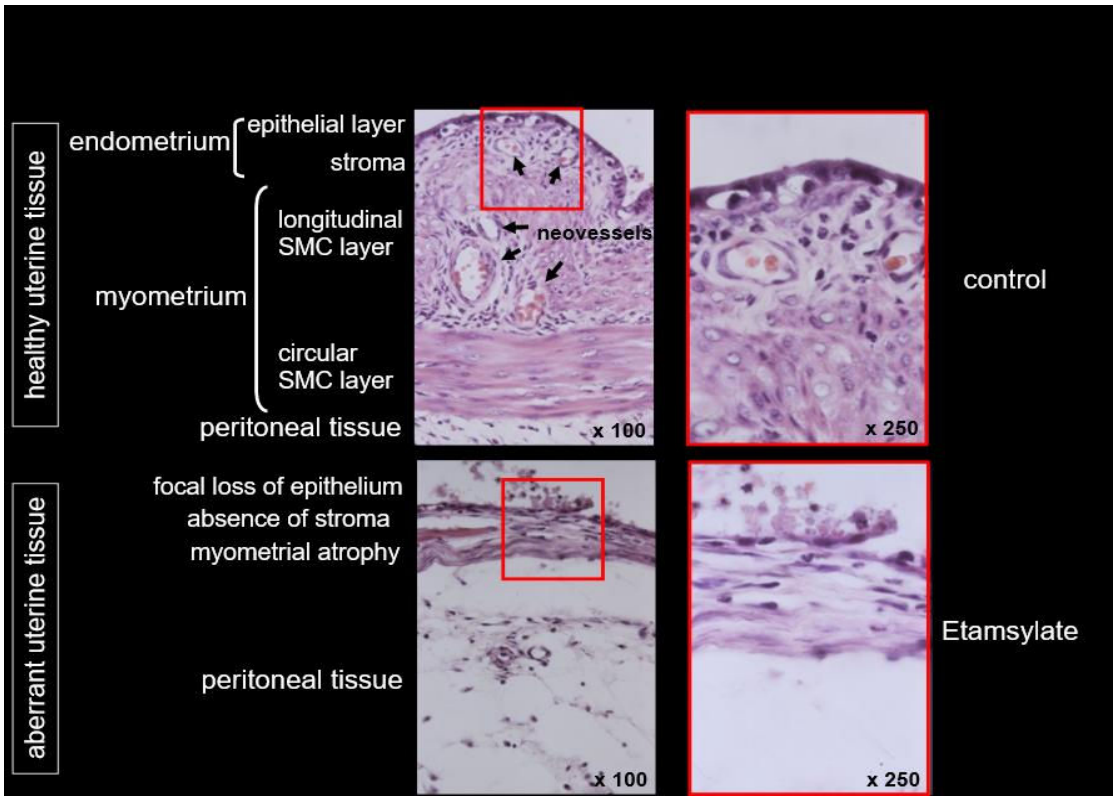

Figure 2: Histological sections of uterine implants from a control animal (upper panels) and an etamsylate treated animal (lower panels).

Discussion

In this report, we show that intraperitoneal administration of etamsylate promotes intense tissue disorganization in a rat model of EM. These results may be due to the anti-angiogenic activities of etamsylate, and are in accordance to previous studies showing the efficacy of etamsylate in several angiogenesis-dependent diseases [16-18]. Autophagy is known as a non-apoptotic form of programmed cell death that contributes to the pathogenesis of EM [19]. It has been reported that etamsylate restores autophagy by inhibition of VEGF signals [20]. Thus, drugs that promote autophagy may cover a new potential treatment for EM [21]. In conclusion, etamsylate is a promising value for EM management.

Conclusion

Etamsylate exerted a potent inhibitor effect on the development of endometriosis in the rat. The present study may lead to the development of novel treatment for endometriosis given the long history of etamsylate as a drug with a high safety profile.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Financial Disclosure

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Consent To Participate

The authors certify that they have obtained all appropriate patient consent.

Data Availability and Consent of Patient

Data is available for the journal. Informed consents were not necessary for this paper.

Author's Contribution

FC and PC performed the experiments. PC wrote the manuscript. BC performed histological preparations. JA prepared the iconography.

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