Is montelukast effective in regression of endometrial implants in an experimentally induced endometriosis model in rats?

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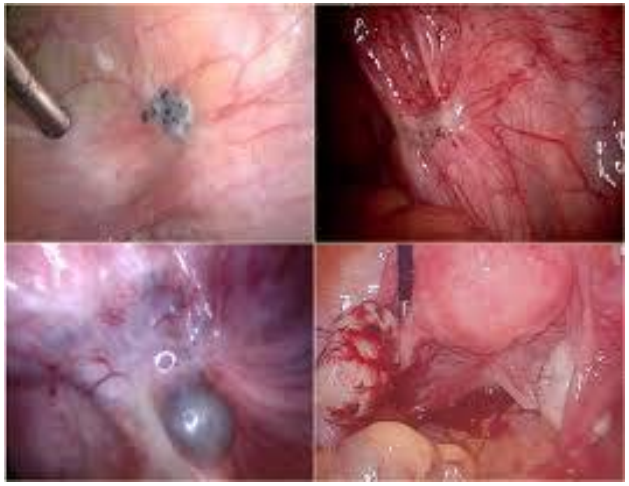
Introduction (I)

- Endometriosis is a chronic recurrent disease, defined as the presence of endometrium-like viable tissue outside the uterine cavity.

- It is one of the most problematic diseases affecting women of reproductive age.

Introduction (II)



The critical steps include

(1) Attachment of endometrial cells to the peritoneal surface

(2) Invasion of the cells into the mesothelium.

Consequently, the process has to be mediated by many complex interactions of immunologic, hormonal, genetic and environmental factors, including abnormal matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinases (TIMPs) expression, and aberrant local aromatase activity.

Montelukast

- A selective antagonist of Type 1 cysteinyl leukotriene receptor ($CysLT_1Rs$).

- Montelukast antagonizes the proinflammatory and proasthmatic activities of $CysLT_1Rs$. Even though it is approved for use in asthma and/or allergic rhinitis, there is an ongoing research on its use in other disorders.

Mini-Review
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Anti-Inflammatory Activities of Montelukast	Disorders
Primary	
Inhibition of CysLTRs.	Allergic rhinitis Atopic asthma Aspirin-induced bronchospasm
Secondary	
Inhibition of 5-lipoxygenase	COPD, cystic fibrosis, viral bronchiolitis, idiopathic pulmonary fibrosis
Inhibition of PDEs	Paranasal sinus disease, allergic fungal sinusitis, nasal polyposis, otitis media, allergic conjunctivitis
Suppression of HAT activity	Chronic urticaria, atopic dermatitis, systemic mastocytosis
Interference with P2Y receptor signaling	Atherosclerosis
Inhibition of eosinophil adhesion to vascular endothelium	Irritable bowel syndrome, pancreatitis, vulvovaginal candidiasis, interstitial cystitis
	Sepsis
	Immune reconstitution syndrome (IRIS)
	Hepatic ischemia-reperfusion injury

Objective: Our objective was to investigate whether montelukast could have an effect on endometriotic implant growth and morphology and on the histological characteristics of immunoreactivity of MMP-2 and VEGF in a rat model.

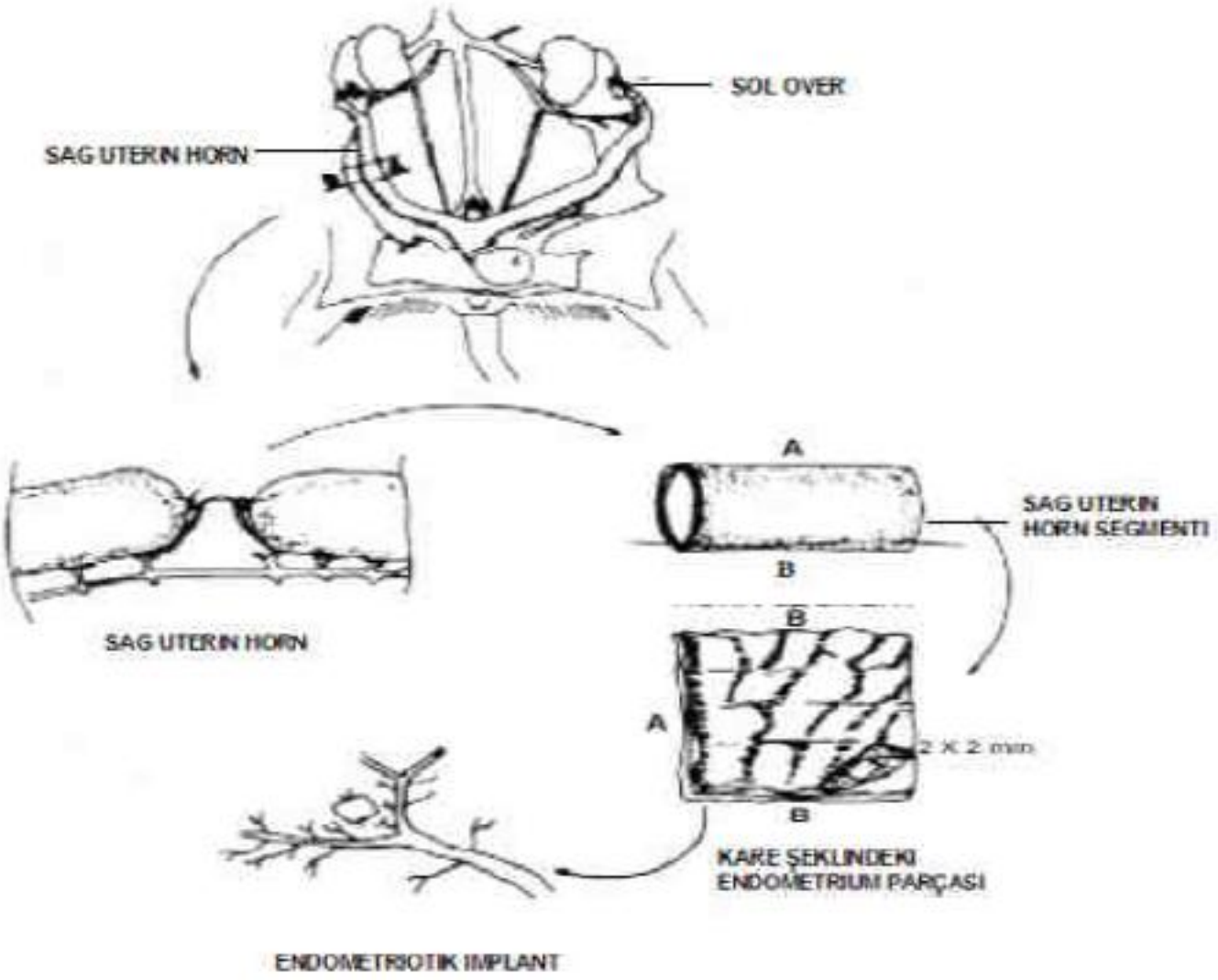
Materials and Methods (I)

Animals

- Thirty-three sexually mature, cycling, female Wistar-Albino rats weighing 200 to 230 g, were used. The rats were checked for three consecutive regular estrous cycles for homogeneity.

- Endometriosis was surgically induced using the method described by Vernon and Wilson.

Vernon & Wilson, Fertil Steril 1985;44:684-94.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A
2 X 2 mm
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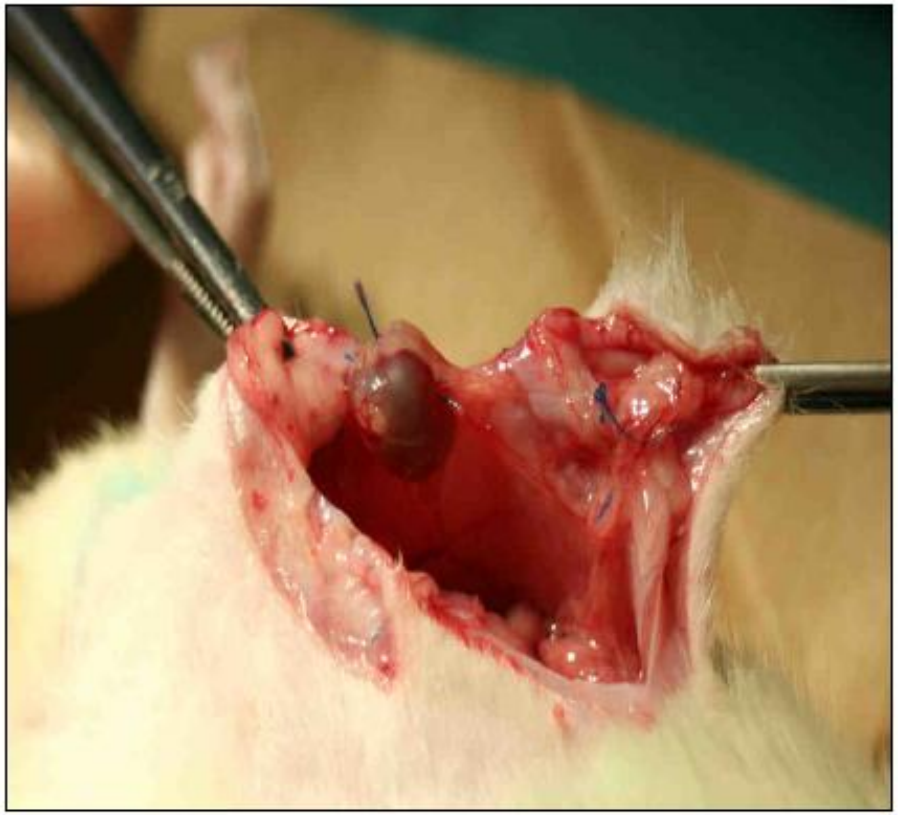
KARE ŞEKLINDEKI
ENDOMETRIUM PARÇASI
ENDOMETRIOTIK IMPLANT

Materials and Methods (II)

- Three weeks after the initial surgery, the remaining rats underwent a second exploratory laparotomy to visualize the endometriotic implants. The surface areas of the implants (length x width) were calculated to the nearest 0.1 millimeter using a caliper and recorded. Presence of endometriotic implants was confirmed in all rats.



Materials and Methods (III)

The rats were randomly divided into three groups.

- Group I [Montelukast (M), 10 rats)] was given 1.6 mg/kg/day of oral montelukast sodium.
- Group II [Leuprolide acetate (L), 11 rats] was given 1 mg/kg single dose of s.c. leuprolide acetate.
- Group III [Control (C), 11 rats] received saline solution through an orogastric tube and served as controls.

Materials and Methods (IV)

After a 3-weeks medication, the rats were sacrificed to investigate the endometriotic implants for size and morphological and histological characteristics, including immunoreactivity of MMP-2 and VEGF.

Results (I)

- Endometriotic implants formed in all the rats while one rat died after first laparotomy.

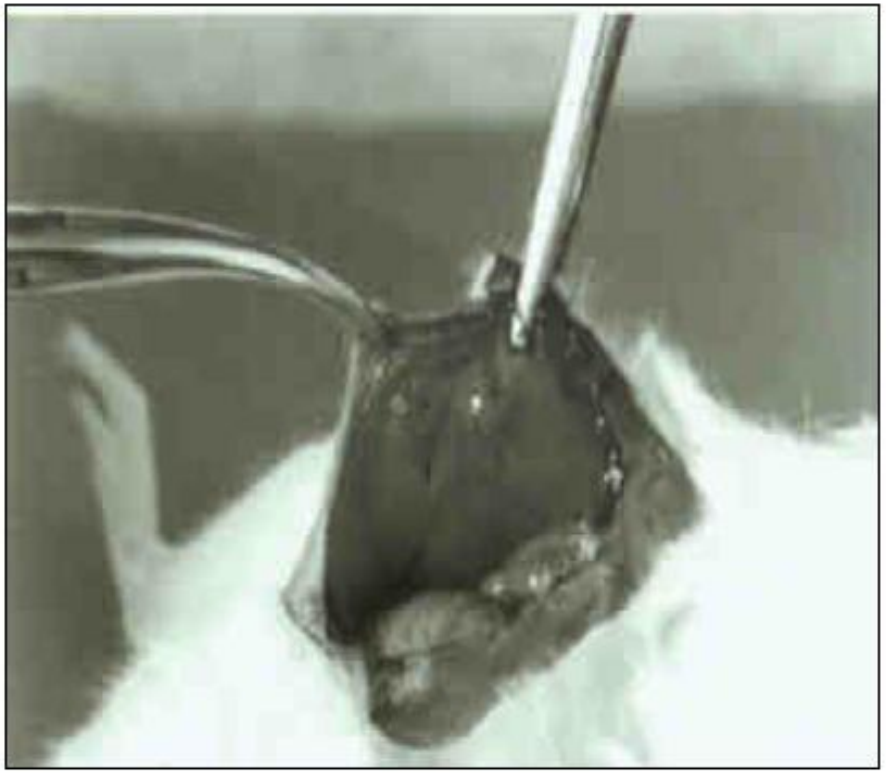
- Overall 32 rats from 3 groups were evaluated for three parameters; pre and post-treatment alterations of the surface area of the endometriotic implants, the histopathological scores of the implants and the immunohistochemical scoring of MMP-2 and VEGF in endometrial implants.

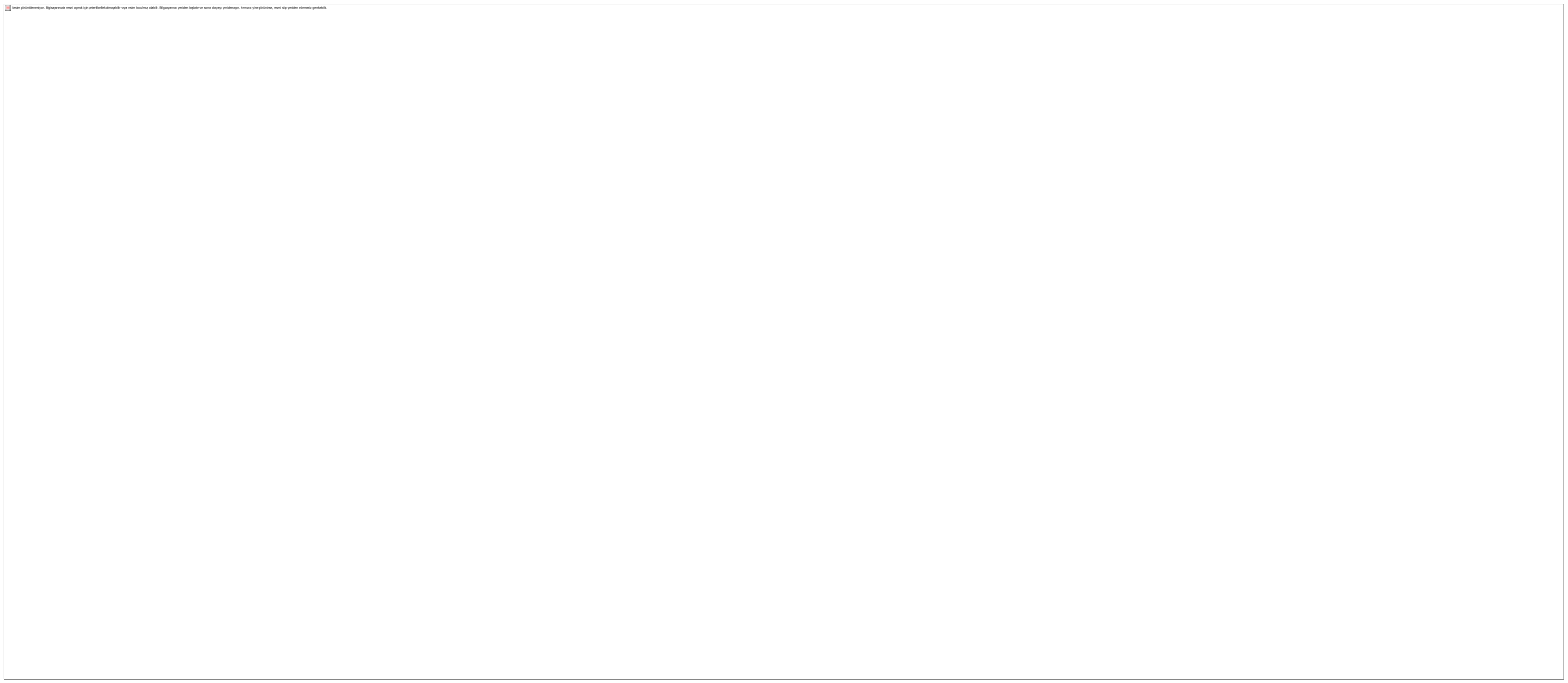
Results & Table 1. Changes in area of implants before and after treatment

	Area of implants (mm^2)		
	Before treatment	After treatment	p[a]
Group I	46 (20-90)	24.5 (9-56)	**0.008**
(M)	[48.2 ± 24.7]	[29.3 ± 15.8]	
Group II	48 (28-143)	36 (15-70)	**0.003**
(L)	[62 ±32.1]	[39.9 ± 18.1]	
Group III	35 (12-99)	56 (18-132)	**0.025**
(C)	[41.1 ± 31.1]	[60.4 ± 37.1]	
p[b]	0.164	**0.015**	

[a] Wilcoxon signed rank test

[b] Kruskal-Wallis test





Results & Table 2. Histopathological and immunohistochemical scoring of MMP-2 and VEGF in endometrial implants

	Group I (M) (n: 10)	Group II (L) (n:11)	Group III (C) (n:11)	P value
Histopathologic score of implants**	0 (0-1)[b] [0.4 ± 0.16]	1 (0-3)[a] [1.1 ± 0.35]	2 (0-3)[a] [1.7 ± 0.3]	**0.008**
MMP-2 (epithelia)*	5 (0-210)	0 (0-240)	170 (0-400)	0.158
MMP-2 (stroma)*	60 (0-320)	125 (0-360)	160 (0-400)	0.794
VEGF (epithelia)*	0 (0-100)[c]	0 (0-150)[c]	140 (0-360)[d]	**0.006**
VEGF (stroma)*	5 (0-140)	100 (0-160)	100 (0-210)	0.115

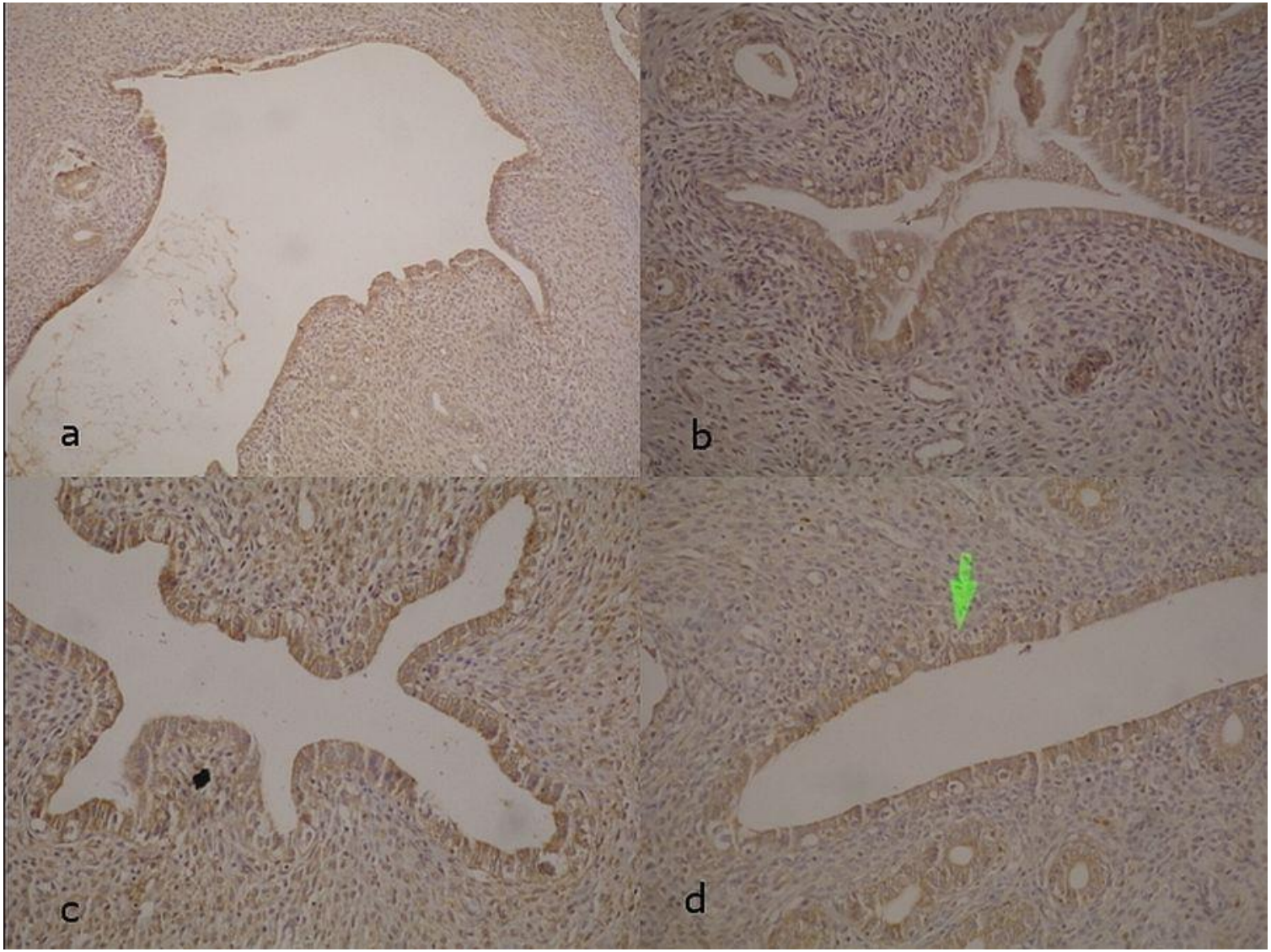
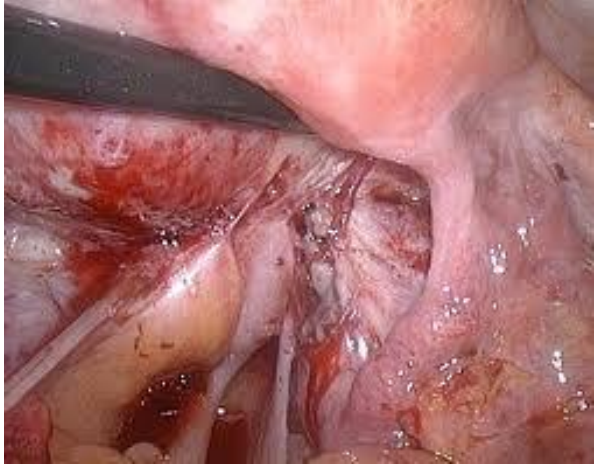


Figure 1. (a) high intensity of MMP-2, (b) low intensity of MMP-2, (c) high intensity of VEGF, (d) low intensity of VEGF (arrow shows stained epithelial area)

Discussion (I)



The present study was designed with the aim of assessing the effect of a potent and highly selective LTD_4 receptor antagonist, montelukast, on the regression of endometriotic implant growth and its probable use for the treatment of endometriosis.

Discussion

- Previous studies have revealed that human uterine tissue has the capacity to synthesize and metabolize LTs and the endometrium and uterine smooth muscle are known to possess leukotriene receptors.

  Levinson SL.1984, Rees MC, et al. 1987

- Antileukotriene therapy in dysmenorrhea and in prevention of ischemia-reperfusion injury has also been demonstrated.

  Harel et al 2004, Fujiwara et al. 2010, Akdemir A et al. 2014

- The probable acting mechanism in dysmenorrhea was thought to be related to the suppressive effect of montelukast on smooth muscle contraction and anti-inflammatory effect through suppression of vascular permeability and suppression of cytokines.

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Result(s): In the rats treated with leukotriene receptor antagonist, a significant decrease in stromal proliferation was observed when compared with nontreated rats. The treated rats showed not only the suppression of infiltration and activation of mast cells but also widespread apoptosis of proliferative fibroblasts in the lesions.

Conclusion(s): Our results reveal that a leukotriene receptor antagonist has significant therapeutic value for the treatment of rat endometriosis. It is likely that antileukotriene therapy would be efficacious in the treatment and prevention of human endometriosis. (Fertil Steril® 2004;81(Suppl 1):819–23. ©2004 by American Society for Reproductive Medicine.)

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Cysteinyl Leukotriene Receptor Antagonists Inhibit Tumor Metastasis by Inhibiting Capillary Permeability

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RESEARCH PAPER

Montelukast inhibits neutrophil pro-inflammatory activity by a cyclic AMP-dependent mechanism

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Conclusions and implications: Montelukast, primarily a cysteinyl leukotriene ($CysLT_1$) receptor antagonist, exhibited previously undocumented, secondary, neutrophil-directed anti-inflammatory properties, which appeared to be cAMP-dependent.

In the present study, we observed the effectiveness of montelukast treatment in **the reduction of the size of endometriotic implants**, and histopathological analysis showed statistically **significant lower scores** in this treatment group.

VEGF

In the present study, immunohistochemical analysis of endometriotic implants demonstrated **a significantly reduced epithelial VEGF immunoexpression** in montelukast-treated group. Although stromal VEGF immunostaining was not remarkably reduced, the scores were lower than that of GnRH analogue and control groups.

MMP

- Though development of endometriosis requires a process involving MMPs, contrary to expectations **we were not able to demonstrate any significant difference in MMP-2 immunohistochemical scores** in this study.
- This result may be explained by two assumptions; either **montelukast does not affect through MMP2** or **the effect of montelukast may act through other MMPs.**

Limitations

1. Experimental rat model, which may have limited applicability to human.

2. Only MMP-2 and VEGF expression on the endometriotic implants were examined.

CONCLUSION

Montelukast has a **significant effect** on the **reduction of endometrial implant growth** and suggests promising further research as a remarkable therapeutic option in endometriosis.