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The effect of rosiglitazone in the prevention of intra-abdominal adhesion formation in a rat uterine horn model

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BACKGROUND: Effects of rosiglitazone in the prevention of adhesion formation were evaluated. METHODS: Eighty Wistar albino rats were randomly grouped into eight equally sized groups. A 2-cm segment of the antimesenteric surface of the right uterine horn was traumatized to form a standardized lesion, using bipolar cautery. A dose–response study was performed with 0.1, 0.3, 1 and 3 mg/kg/day rosiglitazone. Fifteen days later, adhesions were evaluated clinically and histopathologically. A time–response study was performed with 1 mg/kg/day rosiglitazone (the minimum dose found to significantly affect adhesion formation). Rosiglitazone was given for 7 days post-operatively and results were compared with those of control and the 15-day group (time–response). In all these studies, rosiglitazone was orally administered 3 days before the operation and continued post-operatively. In two further experimental groups, rosiglitazone was only administered pre-operatively or post-operatively. RESULTS: Approximately 1 mg/kg/day rosiglitazone was found to reduce adhesion scores both clinically and histopathologically. Duration of treatment was also found to affect the extent of adhesion formation. However, giving rosiglitazone either just pre-operatively or post-operatively did not significantly reduce adhesion formation. CONCLUSION: Rosiglitazone with peroxisome proliferator-activated receptor (PPAR)-γ agonist activity reduced the formation of i.p. adhesion possibly by reducing the initial inflammatory response and the subsequent exudation in this study.

Key words: adhesion/PPAR-γ/rat model/rosiglitazone

Introduction

Despite recent advances in prevention and management, i.p. adhesion formation remains to be a major cause of morbidity in surgical clinics. Adhesion formation can occur following any surgical procedure with an incidence ranging from 67 to 93% after general surgical abdominal operations and up to 97% after open gynaecologic pelvic procedures (Weibel and Manjo, 1973; Menzies and Ellis, 1990; Operative Laparoscopy Study Group, 1991). It is associated with reduced quality of life as it causes pelvic pain, intestinal obstruction and impaired fertility. It also impacts negatively on clinical outcomes in patients undergoing surgery and increases health expenses (Diamond and Schwartz, 1998).

Adhesion formation is a complex process involving biochemical and biomechanical factors. At the molecular level, it involves migration and proliferation of infiltrating cells that release cytokines and constitutes a complex interaction of these cytokines, growth factors and components secreted by these cells. Modification of the inflammatory–coagulation cascade of events by some adjuvants has been shown to be effective in reducing adhesion formation to some extent (Steinleitner *et al*., 1990; Aytan *et al*., 2005). Macrophages seem to play an important role in the inflammatory process and are related to both the normal healing response and the response to peritoneal injury that leads to post-operative adhesion formation (Liakakos *et al*., 2001).

A new class of macrophage-modulating factors includes the peroxisome proliferator-activated receptors (PPARs). PPARs are ligand-dependent transcription factors of the nuclear hormone receptor superfamily. These receptors have been reported to regulate macrophage activation and inflammatory response (Ricote *et al*., 1999). Thiazolidinediones activate PPAR-γs and are among the compounds with the highest affinity and efficacy for PPAR-γ. We hypothesized that by blocking early monocyte infiltration by the thiazolidinedione, rosiglitazone, the subsequent activation of other cellular inflammatory mediators might be prevented and adhesion formation may be prevented to some extent.

The aim of this experimental study was to evaluate the effects of rosiglitazone, in the prevention of adhesion formation in a rat uterine horn model.

Materials and methods

A total of 80 female, non-pregnant, non-inbred Wistar albino rats weighing between 160 and 220 g were used as a model for post-operative adhesion formation. The rats were caged individually and were fed *ad libitum*. The guidelines for the care and use of the animals, approved by the local institution, were followed. All rats were observed for several days to ascertain the health before the operations. Vaginal smears were performed to determine the estrous cyclicity of the rats and only rats which were in estrus state were used, to ensure that all the rats were in the same cyclic period during the operation.

The study protocol is shown in Figure 1. A dose–response study was first performed with 50 rats, and before the operation, these 50 rats were randomly assigned into five groups each consisting of 10 rats. One group was assigned as the control group and the four groups were assigned as the study groups. A vehicle treatment (2 ml/day 5% dextrose) to the control group and rosiglitazone maleate (Avandia®, GlaxoSmithKline, Istanbul, Turkey) 0.1 mg/kg/day to Group 1, 0.3 mg/kg/day to Group 2, 1 mg/kg/day to Group 3 and 3 mg/kg/day to Group 4 were orally administered starting 3 days before the operation and continuing for 15 days post-operatively. Approximately 1 mg/kg/day was found to be the minimum dose with which a significant reduction in adhesion formation was observed, and with this dose, a time–response study and pre-operative and post-operative administration studies were performed. In the time–response study, 1 mg/kg/day rosiglitazone maleate was administered for 10 days (starting 3 days before the operation) (Group 5) and the results were compared with the results of the control and Group 3. For pre-operative arm (Group 6), 1 mg/kg/day rosiglitazone maleate was administered for 3 days before the operation and vehicle treatment was administered after the operation. In the post-operative arm (Group 7), 1 mg/kg/day rosiglitazone maleate was given starting the day of surgery for 15 days. Pre-operatively these rats got vehicle treatment for 3 days. Adhesion results in Groups 6 and 7 were compared with those in the control and Group 3.

The surgical technique was as follows. Each rat was anaesthetized with an i.m. injection of ketamine (75 mg/kg, Ketalar®; Eczacibasi, Istanbul, Turkey) and xylazine (5 mg/kg, Rompun®; Bayer, Istanbul, Turkey). Before surgery, the abdominal skin was shaved and antisepsis was obtained by 10% povidone iodine solution. Using sterile techniques, we made a 3-cm vertical midline incision and exposed both uterine horns, and then a 2-cm segment of the antimesenteric surface of the right uterine horn was traumatized in seven spots in the antimesenteric surface using bipolar cautery. Maximum attention was paid not to damage any other intra-abdominal organs, and handling of the other tissues was minimized. No pre-operative or post-operative antibiotics were administered.

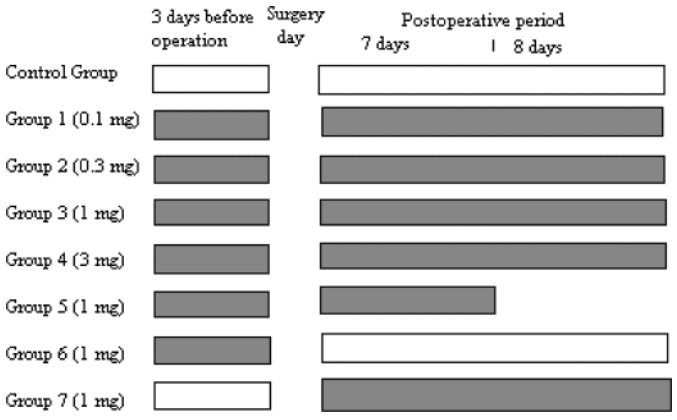

Figure 1. Drug administration protocol [grey scales indicate administration of rosiglitazone maleate (mg/kg/day) and white scales indicate placebo administration].

The abdominal incision was closed in two layers with the use of a simple interrupted 4-0 polyglactin 910 suture for the peritoneum–fascia and for the skin. The operation was limited to 10 min for each rat to control the effect of room air tissue drying. Also, tissues were irrigated with warm saline during surgery to maintain constant immersion in balanced fluid with appropriate pH and osmolarity to minimize variations in moisture and temperature.

For analgesia, 100 mg/kg aspirin was administered orally. All surgeries were performed by the second author, who was blinded to the treatment group. The rats were randomly assigned and not sequentially operated on in order to minimize bias. The surgeon was unblinded only after the lesions had been created.

The rats were individually caged after the operation and were left for a recovery period of 15 days (except Group 5 where rats were killed 7 days after the operation). During the treatment period, any adverse treatment effects were monitored and rats were weighed daily as rosiglitazone may cause fluid retention or swelling. Vaginal smears were performed on all rats after drug treatments to ensure that their reproductive cycles were not disrupted at the end of the study. Except for the 10 rats in Group 5, 15 days later all rats were killed and a second-look laparotomy was performed. I.p. adhesions were scored according to the clinical adhesion scoring system of Leach *et al*. (1998) by the first author, who had no prior knowledge of which group was being evaluated. Adhesions to the uterine horn defect were scored as follows: 0 = no uterine adhesion; 1 = 1–25% involvement; 2 = 26–50%; 3 = 51–75%; and 4 = 76–100%. Adhesions were further characterized on gross examination for severity as follows: 0 = no adhesions; 1 = filmy avascular; 2 = vascular or opaque; 3 = cohesive attachment of uterine horns to each other or other abdominal structure. The degree of adhesion formation was evaluated with the following adhesion scores: 0 = no adhesions; 1 = if the adhesion was separated from tissue with gentle traction; 2 = requiring moderate traction; and 3 = requiring sharp dissection. Therefore, a total score of 10 was possible.

The adhesions in the dose–response study groups were also examined histologically and graded for inflammation and fibrosis using previously published grading scales (Hooker *et al*., 1999). For that purpose, adhered tissues were photographed using a digital camera and then excised. Then tissue samples were fixed in 10% buffered formalin solution for 24 h. After fixation, routine tissue-processing procedure was performed, and then sampled tissues were embedded in paraffin. Paraffin wax blocks were cut into 4-μm thicknesses. Prepared sections were stained with haematoxylin–eosin. Inflammation was scored as follows: 0, no inflammation; 1, presence of giant cells, occasional lymphocytes and plasma cells; 2, presence of giant cells, plasma cells, eosinophils and neutrophils; and 3, presence of many inflammatory cells and microabscesses. The amount of fibrosis was scored as: 0 = no fibrosis; 1 = minimal, loose; 2 = moderate; and 3 = florid dense.

Statistical analysis was accomplished on a personal computer, using statistical program for social sciences version 12.0 (SPSS 12.0 demo, SPSS Inc., Chicago, IL, USA). Shapiro–Wilk test was used to test whether the variables used in the study were normally distributed. It was found that the variables were not normally distributed. The data

were expressed as the medians (minimum–maximum). Kruskal–Wallis test was used for comparisons of the groups. A *P*-value of <0.05 was assumed to be significant. When a significant result was found, Mann–Whitney *U*-test was used in order to determine which groups were differing. To allow for multiple comparison testing, we assumed a *P*-value of <0.005 ($\alpha = 0.05/10$) to be significant in dose–response study, <0.016 ($\alpha = 0.05/3$) in time–response study and <0.008 ($\alpha = 0.05/6$) in pre- and post-operative studies.

Results

The standardized surgical procedures and the administration of the protocols were well tolerated by the animals. All laparotomy sites were intact, and none of the animals had an incisional hernia. No adverse effects were noted, and there was no significant difference between groups with regard to weight change (data not shown).

Table I summarizes the extent, severity, degree and total adhesion scores as well as histopathological results in the control and Groups 1–4. The groups were found to be significantly different with respect to adhesion and histopathological scores; scores in Groups 3 and 4 were found to be significantly lower when compared with those in the control and Groups 1 and 2 (Table I, Figures 2 and 3). No significant difference was found when Groups 3 and 4 were compared. Histopathologically inflammation and fibrosis were more prominent in the control and Groups 1 and 2 compared with Groups 3 and 4 (Figure 4). Approximately 1 mg/kg/day was found to be the minimum effective dose that reduced the adhesion formation (Figure 2).

Duration of rosiglitazone maleate treatment was found to affect adhesion formation (Figure 5A). The median total adhesion score was significantly lower in Group 5 [median: 8 (3–9)] when compared with the control [median: 9.5 (6–10)] ($P = 0.005$); however, it was higher when compared with Group 3 ($P = 0.015$) (Figure 5A).

Administration of rosiglitazone maleate only pre-operatively or post-operatively was not found to affect adhesion formation significantly when compared with the control group (Figure 5B). However, adhesion score in Group 3 was found to be significantly lower when compared with Groups 6 and 7 (Figure 5B).

All the rats in the study had regular estrous cycles, and the histopathologic examination results of the endometria and ovaries in the control and rosiglitazone-treated groups were similar (data not shown).

Discussion

In this study, the effect of rosiglitazone on the formation of i.p. adhesion was assessed in a rat uterine horn model both clinically and histopathologically with the aid of adhesion scoring scales. First, a dose–response study was performed and administration of 1 mg/kg/day rosiglitazone starting 3 days before the operation and continuing for 15 days was found to reduce i.p. adhesion formation. Second, a time–response study was performed and it was found that the duration of administration affected adhesion formation. Finally, the effect of pre-operative and post-operative administrations alone was studied, and it was found that pre-operative or post-operative administrations alone did not reduce adhesion formation significantly.

Rosiglitazone is a thiazolidinedione with PPAR-γ agonist activity and insulin-lowering effect that has been used in the treatment of diabetes mellitus. PPAR-γs are expressed in adipocytes abundantly (Spiegelman, 1998) and in activated macrophages (Ricote *et al*., 1998), vascular smooth muscle cells (VSMCs) (Iijima *et al*., 1998), endothelial cells (Inoue *et al*., 1998) and several cancer cell lines (Iijima *et al*., 1998). PPAR-γ activation by PPAR-γ agonists in these cells modulates these cell functions such as the production of inflammatory cytokine by macrophages (Jiang *et al*., 1998), proliferation and migration of VSMCs, and growth or differentiation in cancer cells (Tontonoz *et al*., 1997).

Macrophages play an important role in inflammation and the subsequent adhesion formation (Liakakos *et al*., 2001). Following surgery, the macrophages increase in number and change function. These post-surgical macrophages are entirely different from the resident macrophages and secrete variable substances, including cyclooxygenase and lipoxygenase metabolites, plasminogen activator, plasminogen activator inhibitor (PAI), collagenase, elastase, interleukins (IL) 1 and 6, tumour necrosis factor (TNF), leucotriene B_4 and prostaglandin E_2 (Drollette and Badawy, 1992; di Zerega, 1992; Rodgers and di Zerega, 1993). Therefore, modulation of these cytokines might alter the course of the process, and it has been reported that PPAR-γ agonists inhibit the secretion of the inflammatory cytokines such as TNF-α, interleukin-1β (IL-1β), interleukin-6 (IL-6) and inducible nitric oxide synthase, gelatinase B, matrix metalloprotease (MMP)-9 or scavenger receptor A (Jiang *et al*., 1998; Marx *et al*., 1998). In the present study, the cytokine levels were not measured; however, inhibition of cytokine secretion with PPAR-γ agonists was clearly reported in the

Table I. Comparison of the clinical (according to adhesion scoring system by Leach *et al*.) and histological adhesion scores in all groups [data are presented as median (minimum–maximum)]

	Extent	Severity	Degree	Total	Inflammation	Fibrosis
Control group ($n = 10$)	4 (2–4)	3 (1–3)	3 (2–3)	9.5 (6–10)	3 (2–3)	3 (1–3)
Group 1 (0.1 mg/kg) ($n = 10$)	3 (3–4)	2 (2–3)	2 (2–3)	7 (7–10)	2 (2–3)	2 (1–3)
Group 2 (0.3 mg/kg) ($n = 10$)	3 (2–4)	3 (2–3)	3 (2–3)	8.5 (3–10)	3 (2–3)	2 (2–3)
Group 3 (1 mg/kg) ($n = 10$)	1 (0–2)	1 (0–2)	1 (0–2)	3 (0–6)	1 (0–3)	0.5 (0–2)
Group 4 (3 mg/kg) ($n = 10$)	1 (0–2)	1 (0–2)	2 (0–2)	4 (0–6)	2 (0–2)	1 (0–2)
P (Kruskal–Wallis test)	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*

*Mann–Whitney *U*-test yielded a *P*-value of <0.005 (α/10) for comparisons of control and Groups 1 and 2 with groups 3 and 4. Results in control, Groups 1 and 2 were not significantly different ($P > 0.005$). Meanwhile adhesion and histopathological score comparison of Groups 3 and 4 yielded no significant differences ($P > 0.005$).

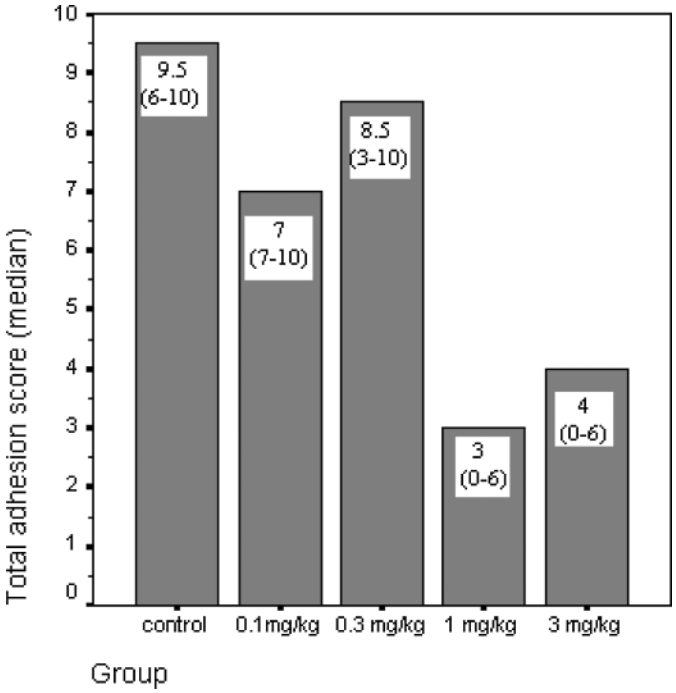

Figure 2. Dose–response study results. Total adhesion scores in medians (minimum–maximum) in control and first four groups are depicted.

literature, and it would not be imprudent to relate the reduction of adhesion formation in the present study to inhibition of cytokine secretion by rosiglitazone.

Adhesion formation is a dynamic process, so duration of administration of any drug that has a reducing effect on adhesion formation should affect the extent of adhesion. In the present study, administration of rosiglitazone starting 3 days before the operation and continuing for 7 days (Group 5) was found to decrease adhesion formation significantly when compared with the control. Continuing treatment for another 8 days (Group 3) resulted in even lower adhesion scores.

Pre- or post-operative administration of rosiglitazone alone did not reduce adhesion scores significantly, although the scores were lower than those in the control (Figure 5B). Only pre-operative treatment followed by post-operative drug administration was found to be effective. It may be concluded that in order for rosiglitazone to be effective on the adhesion formation process, it should be present in the serum during the active phases of adhesion formation.

It must be noted that rosiglitazone also reduces circulating insulin levels. In the present study, the reduction in adhesion formation has been attributed mainly to the PPAR-γ agonistic activity of rosiglitazone; however, there may be additional factors that might have played roles such as insulin. It has been reported that insulin elicits changes in the cytoskeleton, and insulin-regulated effects on the cytoskeleton may play important roles in cellular functions such as chemotaxis, vesicle secretion and endocytosis (Trifaro and Vitale, 1993; Downey, 1994; Vitale *et al*., 1995; Molitoris, 1997). By altering cellular functions, rosiglitazone's insulin-lowering effect might also have affected adhesion formation.

There are other subtypes of PPARs in clinical use today. PPAR-α agonists (such as the fibrates) have shown therapeutic utility as lipid-lowering agents. PPAR-α activation increases HDL cholesterol synthesis, stimulates 'reverse' cholesterol transport and reduces triglycerides (Vamecq and Latruffe, 1999; Tenenbaum *et al*., 2003; Desvergne *et al*., 2004; Berger *et al*., 2005). Recent studies revealed that ligand activation of PPAR-δ is associated with improved insulin sensitivity and elevated HDL levels, thus demonstrating promising potential for targeting PPAR-δ in the treatment of obesity, dyslipidaemias and type 2 diabetes (Burdick *et al*., 2006). Prostaglandin A_2 is an example of PPAR-δ agonist. Besides rosiglitazone, ciglitazone, troglitazone and piaglitazone are other PPAR-γ agonists. The effect of all these agents on adhesion formation is not known, as no study has been performed before.

There are some limitations in the present study that must be acknowledged. The semi-quantitative clinical evaluation of the

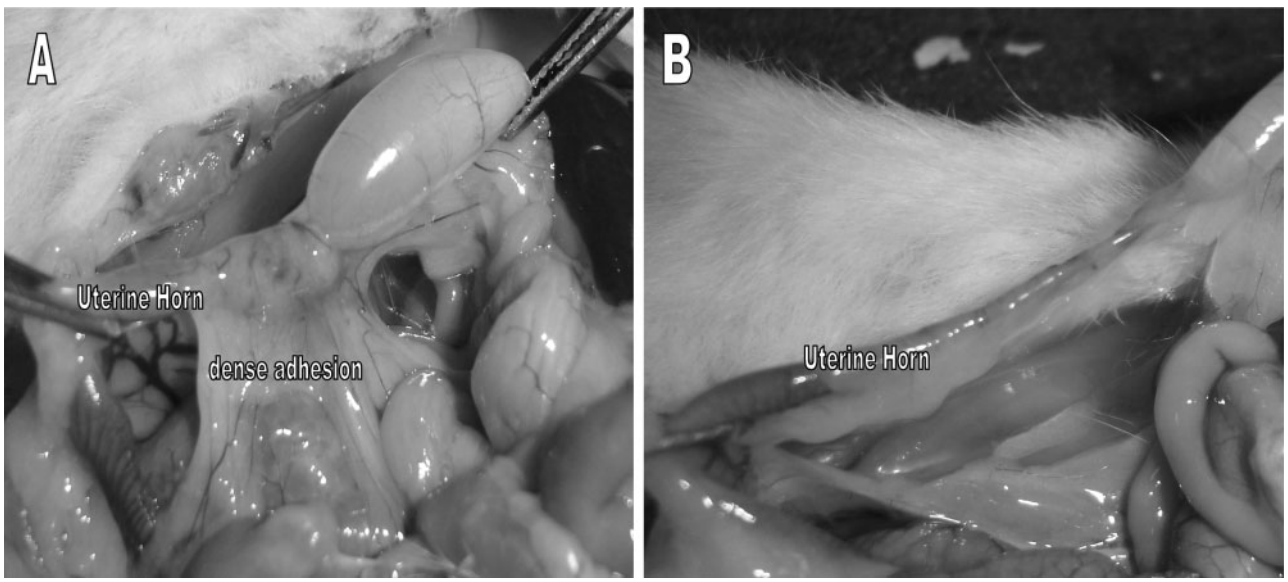

Figure 3. (**A**) Dense adhesion in the control group. (**B**) Almost no adhesion in the rosiglitazone-treated group (Group 3).

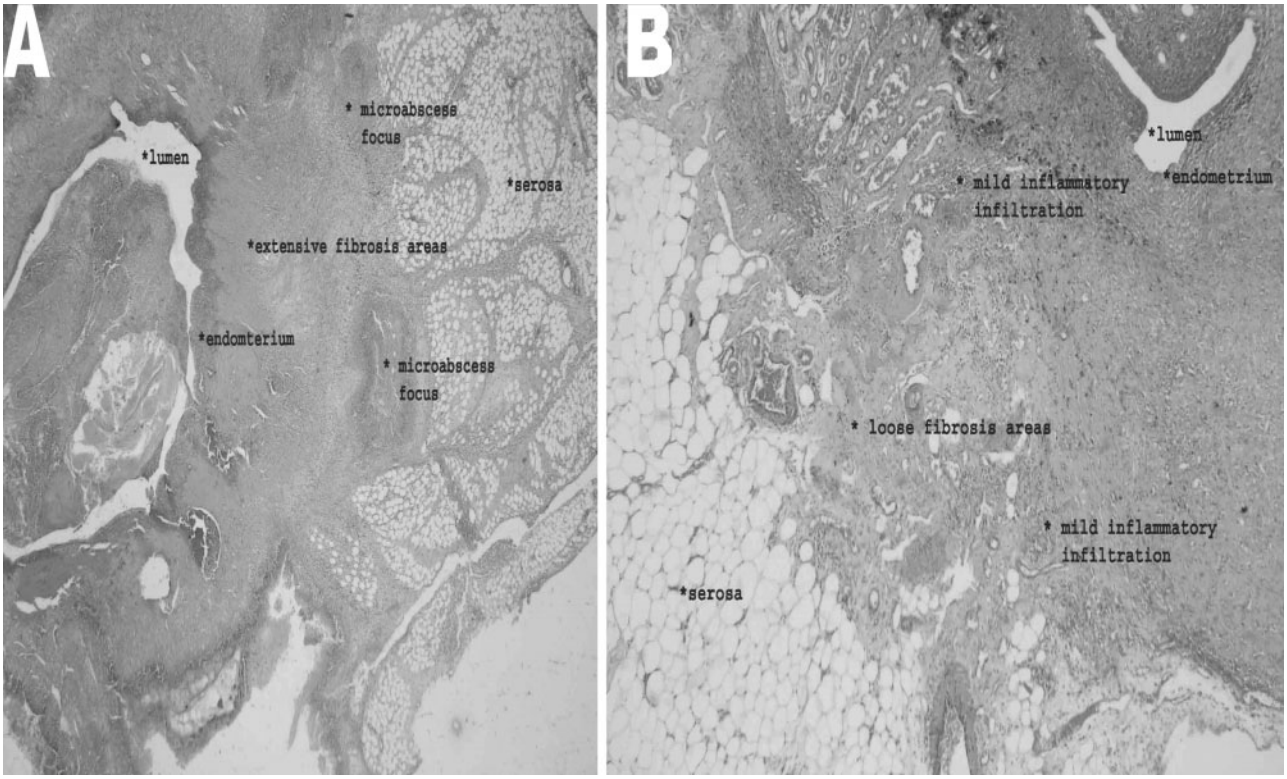

Figure 4. Histologic view of the adhesions. (**A**) Control group (note the extensive fibrosis and microabscess areas) (haematoxylin–eosin stain, ×5 magnification). (**B**) Rosiglitazone-treated group (Group 3) (note the loose fibrosis and mild inflammatory infiltration) (haematoxylin–eosin stain, ×10 magnification).

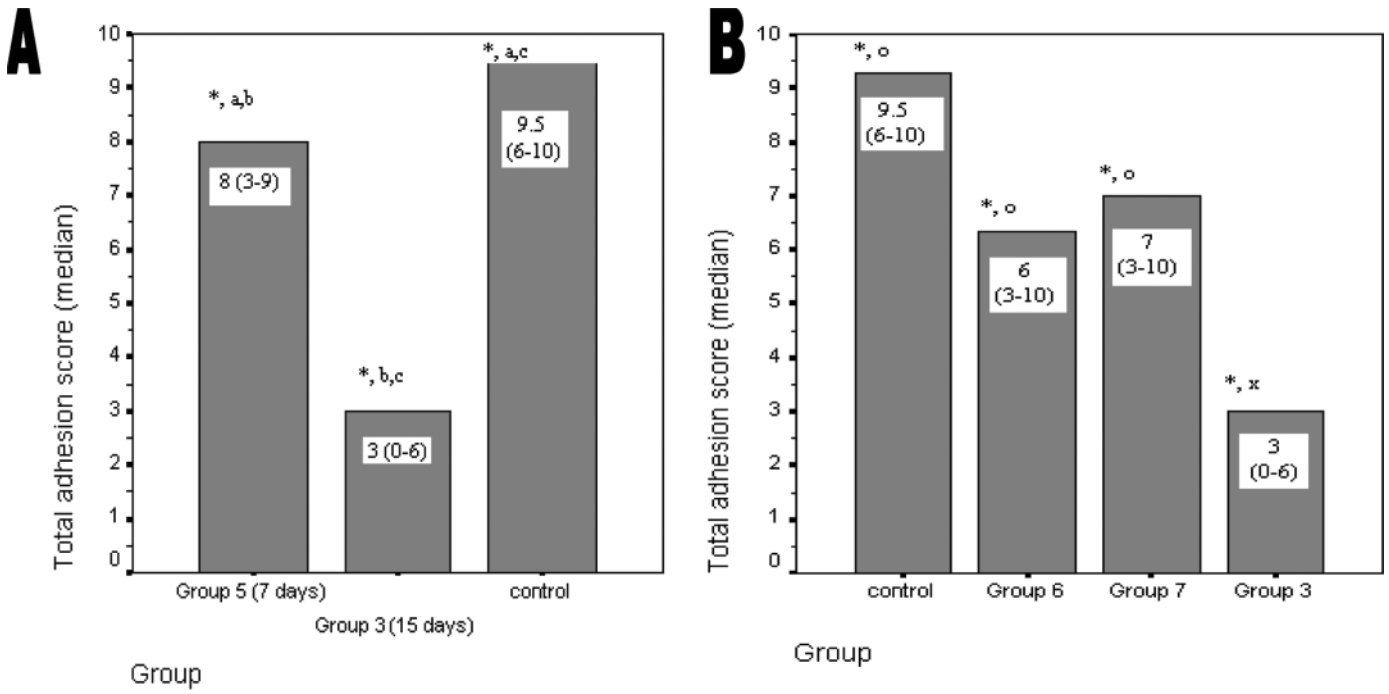

Figure 5. Comparisons of adhesion scores in time–response (**A**) and pre-operative and post-operative studies (**B**). '*' denotes comparison of three groups—Kruskal–Wallis test, $P < 0.05$; a, Group 5 versus control—Mann–Whitney *U*-test, $P < 0.016$; b, Group 5 versus Group 3—Mann–Whitney *U*-test, $P < 0.016$; c, Group 3 versus control—Mann–Whitney *U*-test, $P < 0.016$; o, comparisons of control and Groups 6 and 7 between themselves yielded no significant difference—Mann–Whitney *U*-test, $P > 0.008$; x, comparison of Group 3 and other three groups one by one yielded significant difference—Mann–Whitney *U*-test, $P < 0.008$.

extent of adhesion formation with a scoring system is subjective and there may be inter-observer variability. Various scoring systems have been developed in order to evaluate adhesions during clinical investigations (Linsky *et al*., 1987; Evans *et al*., 1993; Leach *et al*., 1998; Yoldemir *et al*., 2002); however, none of the current scoring systems in use have been validated. Thus, a study that demonstrates a significant change in adhesion score may not reflect a true clinical difference in the extent of adhesive disease. To overcome this problem, we also evaluated adhesions histopathologically in this study. For histopathological evaluation, we again used a previously published scale. Although there may also be interobserver variability, histopathologic evaluation when combined with clinical evaluation increased the accuracy of the results. Secondly, caution should be exercised when extrapolating data across species, as the immunological properties of species are quite different. Thirdly, the accuracy of the results would have been increased with the use of inbred animals that would overcome the possible inter-animal variability; however, this was not possible in the present study.

In conclusion, development of i.p. adhesions is a dynamic process including fibrinous exudates, cytokine production, cell migration, vascular oedema and suppression of fibrinolytic activity (di Zerega and Campeau, 2001). Adhesion formation may be reduced by several possible mechanisms, and inhibition of inflammatory response is one of them (Bakkum *et al*., 1996). Rosiglitazone with PPAR-γ agonist activity might have partly prevented the formation of i.p. adhesion by reducing the initial inflammatory response and the subsequent exudation in the present study.

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