Bratislava Medical Journal
https://doi.org/10.1007/s44411-025-00241-2

RESEARCH

Investigation of the Effect of Autologous Cytokine Rich Serum (ACRS) and Platelet Rich Plasma (PRP) Treatment on Experimental Uterine Horn Peritoneal Adhesion Model in Rats

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Received: 8 May 2025 / Revised: 4 June 2025 / Accepted: 15 June 2025
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Abstract

Background Adhesion formation is a complex biological process defined as adhesion of intra-abdominal organs to one another or to the abdominal wall with fibrous bands. In recent years, various methods and drugs have been used for preventing the abdominal adhesion. Autologous cytokine rich serum (ACRS) is a blood-derived product obtained by incubating and centrifuging whole blood. It contains various cytokines and factors. Platelet rich plasma (PRP) is a blood product and rich in growth factors.

Objective The aim of this study is to compare and investigate the effects of PRP and ACRS on uterine horn peritoneal adhesion.

Methods The animal material of the study was consisted 42 healthy, 4 months old, non-pregnant female Wistar-Albino rats with 150–200 g, body weight. While 6 of these 42 animals included in the study were used as donors to PRP and ACRS, 36 animals were divided into six groups with 6 rats in each group.

Result Adhesion, inflammatory cell infiltration, TNF-α, IL-6, Col-I, α-SMA scores were compared between groups and ACRS group's scores were significantly lower than other groups.

Conclusion As result of this study, ACRS treatment has shown to provide more effective manipulation of the inflammatory response. Especially, ACRS treatment has more effective anti-inflammatory effect on peritoneal adhesion was seen with the histopathologic findings of this study. Our current findings suggest that ACRS has an anti-adhesion role by reducing the inflammatory response in adhesion tissues.

Keywords Adhesion · ACRS · PRP · Uterine-horn

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Published online: 23 June 2025

1 Introduction

Adhesion formation is a complex biological process defined as adhesion of intra-abdominal organs to one another or to the abdominal wall with fibrous bands. The cellular, biochemical and immunological factors take role in adhesion formation [1]. Different reasons such as pathologic conditions, peritonitis, malignancy, endometriosis, pelvic inflammatory diseases and long term peritoneal dialysis can cause adhesion [2]. Additionally, surgical trauma, ischemia, suture materials, electrocautery, the presence of foreign bodies, and infections have also been identified as adhesion reasons [3].

Peritoneal adhesion is known to occur in up to 90% of women in postoperative period after gynecological operation with intestinal obstruction, chronic abdominal pain, infertility, dyspareunia and dysmenorrhea [4, 5]. In recent years, various methods and drugs including barrier materials, non-steroid anti-inflammatory drugs, calcium channel blockers, corticosteroids, vitamin E, antihistamines, metformin, melatonin, progesterone, estrogen, gonadotrophin-releasing hormone (GnRH)-agonists and antagonists, anticoagulants, fibrinolytic agents, streptokinase, and antibiotics have been used for preventing the abdominal adhesion [1, 3, 6]. Despite these methods and drugs, the adhesion formation and prevention have not been achieved fully yet [1].

Autologous cytokine rich serum (ACRS) is a blood-derived product obtained by incubating and centrifuging whole blood [7]. This serum contains high concentrations of IGF-1, hepatocyte growth factor (HGF), and fibroblast growth factor (FGF), and there are IL-1 receptor antagonists (IL-1ra) and anti-inflammatory cytokines such as IL-4, IL-10, and IL-13 in this serum. In recent years, ACRS has been used for the treatment of various inflammatory and degenerative diseases [8–10].

Platelet rich plasma (PRP) is a blood product and rich in growth factors such as transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and insulin-like growth factor (IGF) [5].There are numerous studies on the treatment of different diseases with PRP [11, 12].The main therapeutic effect of PRP is to stimulate cellular proliferation, regeneration and differentiation by enhancing the release of growth factors and cytokines from platelets, and to activate the collagen, hyaluronic acid productions, epidermal cell growth, and angiogenesis [1].

Adhesions after gynecologic surgeries significantly affect the quality of life and are still important today. The aim of the study is to reduce postoperative intra-abdominal gynecologic adhesions by applying PRP and ACRS. While several studies have investigated the effects of PRP on peritoneal adhesions, there is a lack of research on the effects of ACRS in this context. To the best of our knowledge, this study is the first to compare the effects of PRP and ACRS on uterine horn peritoneal adhesion.

2 Materials and Methods

The present study was conducted at the Erciyes University Experimental Research Application and Research Center (DEKAM) with the approval of the Erciyes University Animal Experiments Local Ethics Committee (HADYEK, Decision no: 24/025). The animal material of the study was consisted 42 healthy, 4 months old, non-pregnant female Wistar-Albino rats with 150–200 g, body weight. While 6 of these 42 animals included in the study were used as donors to PRP and ACRS, 36 animals were divided into six groups with 6 rats in each group (G). Each of the rat was kept in a separate cage in the Erciyes University, Experimental Research, Application, and Research Center until the study began. Ad libitum feeding was allowed. The average room temperature and lighting were set at 21 ± 1 °C and 12 h light and 12 h dark. The randomly generated groups are listed below;

- GI: No operation (control group)
- GII: No operation (PRP control group)
- GIII: No operation (ACRS control group)
- GIV: Operation
- GV: Operation + PRP
- GVI: Operation + ACRS
- GVII: Donor

2.1 PRP and ACRS Preparation Protocols

GVII animals were anesthetized with a combination of 10 mg/kg xylazine HCl and 60 mg/kg ketamine HCl. 10 mL blood sample was collected from the heart of each animal into tubes containing 0.3% heparin sodium as an anticoagulant. For PRP preparation, the plasma was first separated by centrifugation at 300 × g for 10 min. The platelets in the plasma were then isolated through a second centrifugation at 300 × g for 10 min [5]. From each 10 mL blood sample, approximately 6 mL of PRP was obtained. For ACRS preparation, the blood samples were collected into special kit tubes and incubated for 3 h at 37 °C. Following incubation, the samples were centrifuged at 4000 × g for 5 min, and the serum was transferred to standard tubes [20]. From each 10 mL blood sample, approximately 6 mL of ACRS was obtained.

In operation groups (GIV, V, VII), general anesthesia was induced using a combination of 10 mg/kg xylazine

HCL and 60 mg/kg ketamine HCL, mixed in the same syringe and injected intraperitoneally. The abdominal region was shaved and the skin sterilized with 70% alcohol and 10% povidone-iodine. A 3 cm midline skin incision was made in the caudal abdomen and then entered abdominal cavity. After visualization of uterine horns, anti-mesenteric peritoneal surface of uterine horn and peritoneal surface were brushed for surgical trauma [13]. Subsequently, physiological serum (0.5 mL) in GIV, PRP (0.5 mL) in GV, ACRS (0.5 mL) in GVI were applied on traumatic surface of uterine horn, then operation area was closed routinely in all groups. Postoperative analgesia was provided to all operated animals using a single subcutaneous dose of ketoprofen (0.04 cc), and single dose of antibiotic (cefazolin sodium, 50 mg/kg) were performed. No application was made in GI. During post-operative period same amount of physiological serum, PRP and ACRS were injected intraperitoneally to operation groups on days 7, 14, 21. No specific nutritional program or dietary regimen was applied, and the animals were observed for 30 days postoperatively for complications such as infection, suture opening and die. In groups II and III 0.5 mL PRP and ACRS were injected intraperitoneally on days 7, 14, 21. At the end of the observation period (at 31th day) control and operation group animals were euthanized via decapitation under general anesthesia.

2.2 Histopathological Examination

The obtained samples from animals (fibrous band, peritonea and uterine horn) were fixed in 10% neutral formaldehyde solution for 48 h, then underwent routine tissue follow-up procedures. Afterwards the obtained paraffin blocks and sections were stained with Hematoxylin–Eosin (H-E) and Masson's Trichrome (MT). The stained sections were examined under the light microscope and evaluated according to Zühlke adhesion scoring system [14]. According to this system;

- Score 1: Loose connective tissue rich in cells, old and new fibrin, thin reticulin fibers,
- Score 2: Connective tissue with few collagen fibers, cells and capillaries,
- Score 3: Dense connective tissue with fewer cells, more vessels, few elastic and smooth muscle fibers,
- Score 4: Dense old granulation tissue with poorly cell serosal layers, have been defined.

Additionally, inflammatory cell infiltration between groups was evaluated and scored as 0 (none), 1 (mild), 2 (moderate), 3 (severe), 4 (very severe) [15, 16]. All evaluations were performed semi-quantitatively at × 20 magnification by a blinded pathologist.

2.3 Immunohistochemical Examination

Tissue sections taken from paraffin blocks were deparaffinized, and immunohistochemical staining was performed using a commercial kit according to the manufacturer's recommendations as previously reported [17]. Primarily α-SMA (alpha-smooth muscle actin, AF1032, USA, 1/200 dilution), IL-6 (Interleukin-6, Affinity biosciences, DF6087, 1/400 dilution), TNF-α (Tumor necrosis factor, Santa Cruz Biotechnology, sc-133192, 1/400 dilution), Col-I (Collagen-I, Affinity biosciences, AF7001, 1/400 dilution) antibodies were used as primers. 3,3'diaminobenzidine (DAB) was used as the chromogen and Mayers hematoxylin was applied for counterstaining. Immunohistochemical scoring was performed semi-quantitatively at × 20 magnification by a blinded pathologist (0; none, 1; mild staining, 2; moderate staining, 3; severe staining, 4; very severe staining) [16, 17].

2.4 Statistical Analysis

Statistical analysis was done using IBM SPSS Statistics for Windows, version 21.0 (USA). The animal number of each group was determined with one-way analysis of variance (6 groups) with 80% power, 5% type 1 error, large influence width ($f = 0.75$). Descriptive statistics were presented as numbers and percentages for categorical variables and as mean, standard error, minimum, and maximum for numerical variables. The Kruskal–Wallis test was used to compare non-normally distributed variables, and the Mann–Whitney U test was applied for pairwise comparisons between groups. A p-value of ($p < 0.001$) was considered statistically significant.

3 Results

All animals of operation groups have been controlled on days 7, 14, 21 in terms of post-operative complications such as infection, the suture opening and necrotic area in operation line of animals, and no complication was seen. Macroscopic appearance of traumatized area of groups after euthanasia at 31th day, the dense of adhesion was most pronounced in GIV compared to GV and GVI (Fig. 1A, B, C). The microscopic comparison of adhesion scores between groups is presented in Table 1. The peritoneal histology of the control groups (GI, GII, GIII) appeared normal (Fig. 2A). In the adhesion evaluation, a statistical difference was found between the three groups (GIV, GV, and GVI) ($p < 0.05$). The highest adhesion score was found in GIV and the lowest scores were found in GVI. The inflammatory cell infiltration in GV and GVI were significantly lower than GIV (Fig. 2B-E) ($p < 0.001$). In MT staining the collagen accumulation

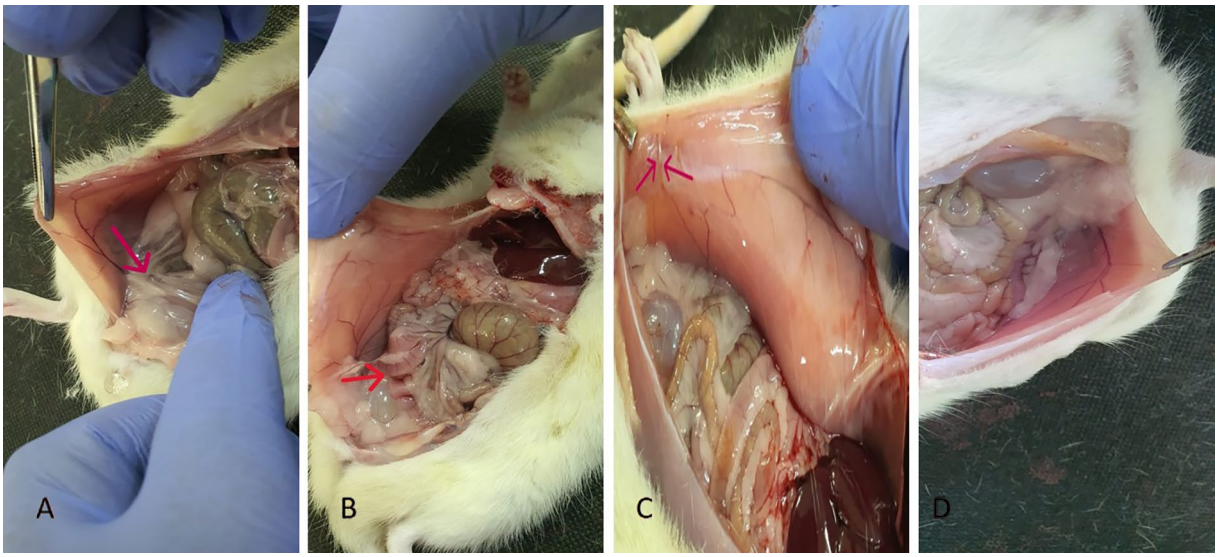

Fig. 1 **A** Adhesion band (GIV, red arrow), **B**: Adesion band (GV, red arrow), **C**: Adhesion band (GVI, red arrows), **D**: Control groups

Table 1 Histopathological scores between treatment groups (GIV, V, VI) (Mean ± SE)

Criterion	GIV	GV	GVI
Zuhlke adhesion score	3.33 ± 0.21^{a}	2.50 ± 0.22^{b}	1.83 ± 0.17^{c}
Inflammatory cell infiltration	3.17 ± 0.17^{a}	2.33 ± 0.33^{b}	1.67 ± 0.21^{b}

[a–c]Letters in the same row indicate statistical significance ($p < 0.001$)

G group

was denser in GIV than GV and GVI (Fig. 3B-D). In addition, frequent hemorrhage and edema were observed in GIV.

The immunohistochemical scoring results between groups are summarized in Table 2. Immunoreactivity in the control groups was either absent or very mild. In contrast, the scores of IL-6, TNF-α, Col-I and α-SMA were higher in GIV than others. Moreover, the compare of IL-6, TNF-α, Col-I and α-SMA between GV and GVI, GVI's score were statistically lower than GV ($p < 0.001$) (Fig. 4).

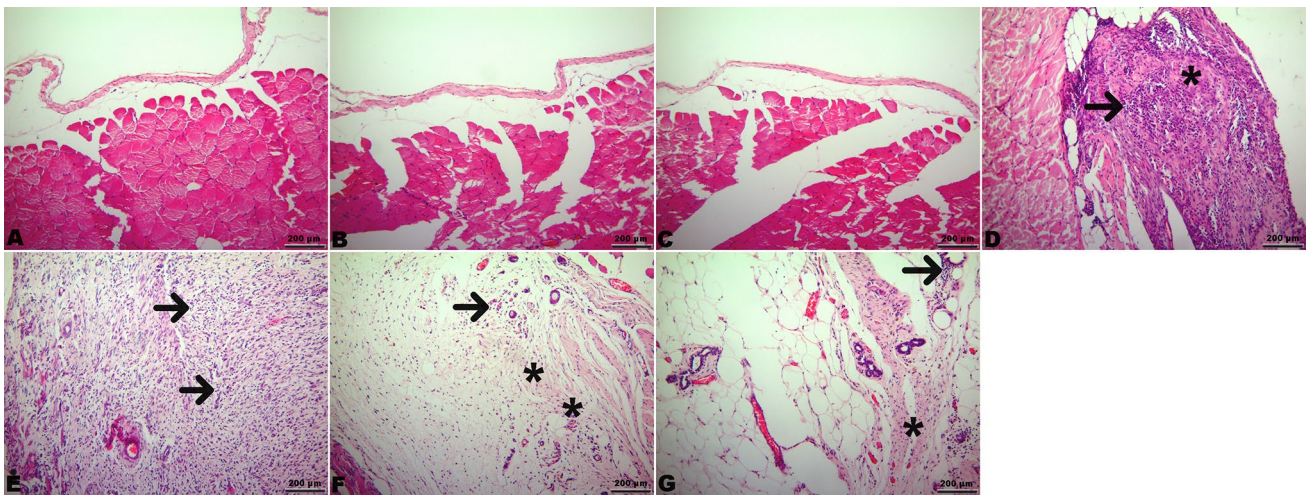

Fig. 2 Microscopic representation of the study groups with H-E staining method, **A-B-C**. Normal histological appearance of mesothelial cells in the control group (GI, GII, GIII respectively). **D-E**. Appearance of the adhesion zone (asterik) and inflammatory cell infiltrates (arrows) in GIV, Zühlke adhesion score 4. **F**. Appearance of the adhesion zone (asteriks) and inflammatory cell infiltrates (arrow) in GV, Zühlke adhesion score 3. **G**. Appearance of the adhesion zone (asterik) and inflammatory cell infiltrates (arrow) in the GVI, Zühlke adhesion score 2

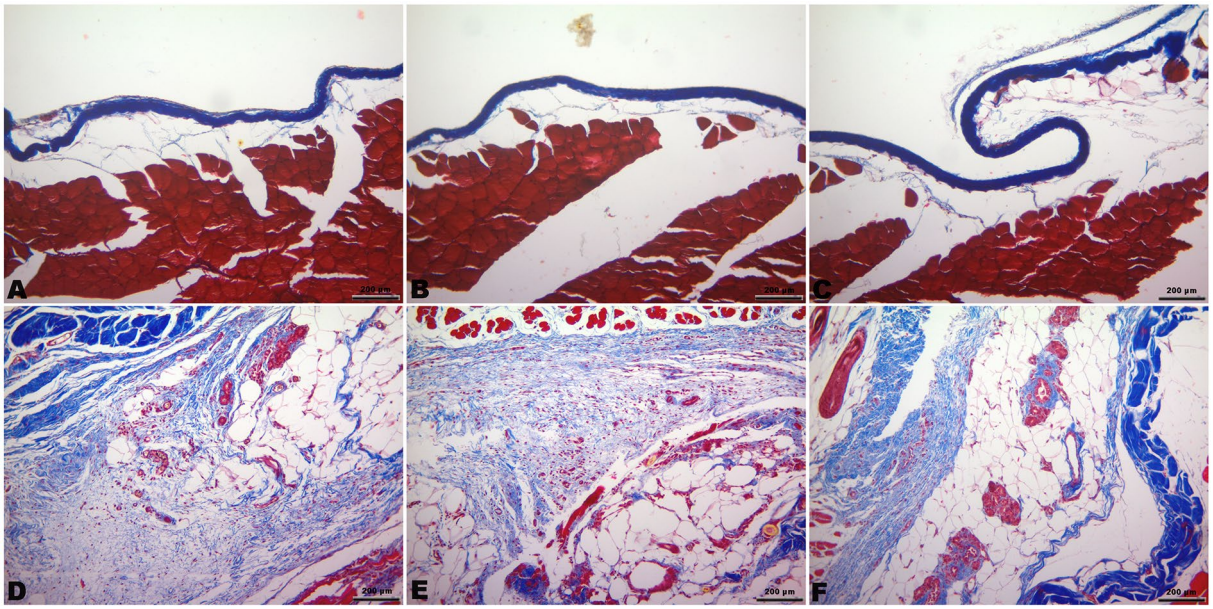

Fig. 3 Microscopic representation of the study groups using Masson's Trichrome method. **A-B-C**. Normal histological appearance of mesothelial cells in the control group (GI, GII, GIII respectively). **D**; GIV, **E**; GV and **F**; GVI groups

Table 2 The statistical immunohistochemical scores between groups (Mean ± SE)

Primary	GI	GII	GIII	GIV	GV	GVI
Col-I	0.17 ± 0.17^{d}	0.33 ± 0.21^{d}	0.33 ± 0.21^{d}	3.20 ± 0.20^{a}	2.14 ± 0.26^{b}	1.33 ± 0.21^{c}
α-SMA	0.33 ± 0.21^{c}	0.50 ± 0.22^{c}	0.67 ± 0.21^{c}	3.40 ± 0.24^{a}	2.28 ± 0.28^{b}	1.67 ± 0.21^{b}
TNF-α	0.17 ± 0.17^{d}	0.33 ± 0.21^{d}	0.50 ± 0.22^{d}	2.80 ± 0.20^{a}	2.00 ± 0.21^{b}	1.17 ± 0.17^{c}
IL-6	0.33 ± 0.21^{d}	0.33 ± 0.21^{d}	0.67 ± 0.21^{d}	3.40 ± 0.24^{a}	2.57 ± 0.36^{b}	1.67 ± 0.33^{c}

$^{a-d}$Letters in the same row indicate statistical significance ($p < 0.001$)

G group

4 Discussion

The peritoneal adhesion is still an important problem in abdominal surgery, and it will continue to be a major clinical problem in future. There are three major stages include in adhesion creating; acute inflammatory response, fibrinolytic response and extra cellular matrix remodeling [18]. Various agents including streptokinase, nonsteroidal anti-inflammatory drugs, antibiotics, histamine and calcium channel blockers have been investigated in recent years for their potential in preventing post-operative abdominal adhesion [1, 2, 19, 20]. In the present study, we evaluated and compared of the effects of ACRS and PRP on uterine horn peritoneal adhesion.

Lymphocytes and macrophages play important roles in repairing mesothelial damage and synthesis inflammatory cytokines such as of IL-6 and TNF-α. These mediators have been found active by triggering cellular defense mechanism in early response of peritoneal damage [21]. TNF-α, a proinflammatory cytokine is secreted by macrophage, and has an important role in adhesion formation during repair phase of mesothelium [22]. In our study adhesion and inflammatory cell infiltration scores were significantly lower in GV and GVII. This result supported to the anti-inflammatory effects of PRP and ACRS. Moreover, the levels of TNF-α and IL-6 were significantly lower in GVI compared to GV, indicating that ACRS may have a stronger anti-inflammatory effect than PRP, and it showed that ACRS is more effective than PRP in preventing adhesion formation in our study.

PRP contains cytokines such as IL-8, IL-1, which reduces the cytokines release with this way and shows the anti-inflammatory effect [23]. Marini et al. [24] reported a reduction in IL-1 and IL-8 release from endometrial tissue treated with PRP in their study, and they supported the anti-inflammatory effect of PRP. Conversely, Wang et al. [25] emphasized that the amount of platelet, cytokines and factors in PRP may depend on the preparation of PRP,

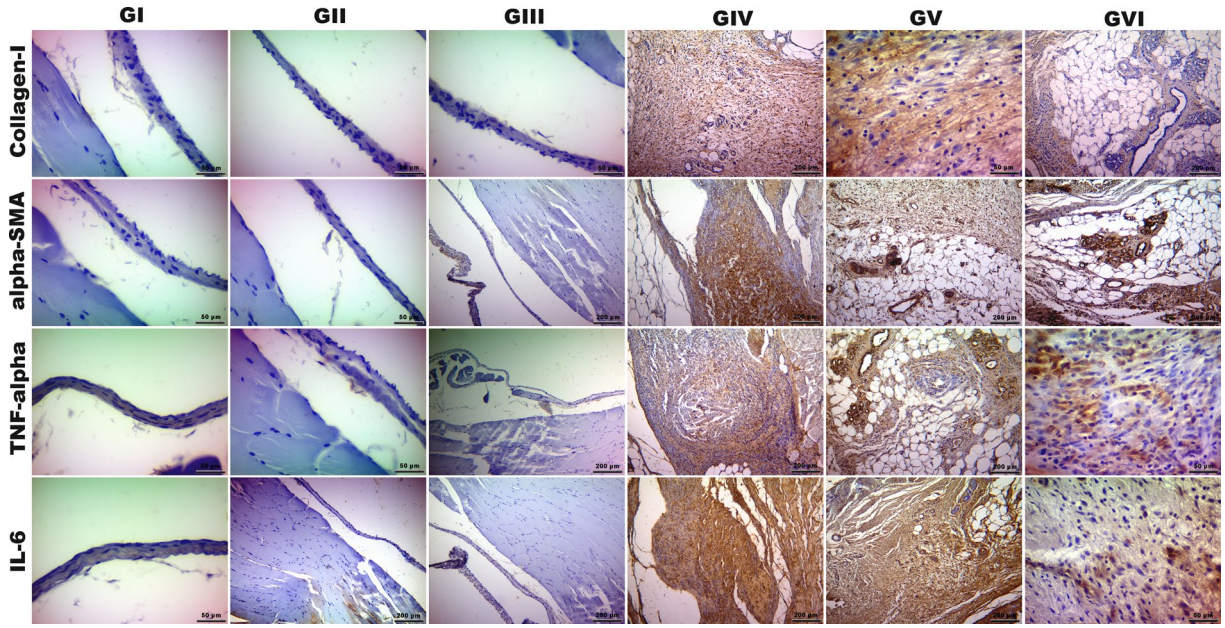

Fig. 4 Microscopic representation of the study groups by immunohistochemistry method (3, 3'diaminobenzidine (DAB) was used as chromogen). The immunohistochemical scoring results between groups are summarized in Table 2. IL-6, TNF-α, Col-I and α-SMA immunoreactivity were higher in the GIV group compared to the other groups

and these can be changeable. For this reason, the anti-inflammatory effect of PRP may be variable.

Oz et al. [5] compared the effects of PRP and hyaluronic acid on prevention of peritoneal uterine horn adhesion in rats. They found that the mean adhesion score was significantly lower in PRP group than others. They explained it with the less level of the transforming growth factor of Beta-I (TGF-βI) in PRP group. Because TGF-βI plays an important role in cell differentiation, angiogenesis and is a fibroblast activator in inflammatory response [3]. In the present study adhesion and inflammatory cell infiltration scores in GV were significantly lower than GIV. This condition supported Oz et al. [5] in parallel the effect of PRP on TGF-βI in adhesion formation. At the same time the lower scores of IL-6 and TNF-α of GV than GIV showed the anti-inflammatory effect of PRP in adhesion formation.

ACRS and PRP have higher concentration of cytokine and growth factor densities compared to whole blood and their inclusion rates are different. ACRS comprises IL-1Ra and anti-inflammatory cytokines (IL-4, IL-10, IL-13), whereas PRP contains VEGF, IGF-1, IGF-2, FGF, and HGF [26, 27]. Genç et al. [28] have been used ACRS and PRP in rat Achilles tendon injury and found that PRP group's recovery was better than ACRS group. They explained it with the effect of VEGF, which increases the angiogenesis and defined as main factor of PRP. ACRS is a new treatment method for inflammatory diseases. In this method anti-inflammatory substances are extracted from the patient blood and administered to the desired area. In this way, the natural and biological ability of the body are used for regeneration itself, and primarily affects IL-1 [29]. In this study both treatments were effective in reducing adhesion formation. The differences in efficacy between ACRS and PRP have been connected to the cytokine and growth factor densities of them. Moreover, the preparation techniques of ACRS and PRP may be affected the amount of cytokine and growth factor densities could be effective on adhesion formation was thought.

Collagen band formation typically begins 3–5 days after trauma and stabilizes around day 14. Therefore, the histopathologic evaluation should be done after this period [3, 30]. In our study the histopathologic evaluation was done after 30 days. Collagen-I (Col-I), an extracellular matrix protein and increases under hypoxic condition, which commonly occurs after tissue injury. Hypoxia after tissue injury plays an important role in wound healing and therefore it may be a critical factor in the development of postoperative adhesions. Col-I has been reported to have many functions such as fibroblastosis activity and re-epithelialization during the healing process. It is also reported to be chemotactic against fibroblasts that control the restoration of new tissue formed during healing [31]. In our study statistical significant differences of Col-I values were recorded between operation groups. The highest Col-I score in GIV showed that fibroblastosis activity is more pronounce in adhesion formation. However, suppression of fibroblast activation in inflammatory response, the inflammatory mediators and TGF-βI by ACRS and PRP

decrease Col-I level were thought. Our findings supported this condition.

α-SMA myofibroblasts constitute the majority of connective tissue in adhesive peritoneal lesions. It has also been reported that α-SMA increases the contractile activity of fibroblasts and plays important roles in adhesion maturation [32]. The compare of fibroblast obtained from normal peritoneum and adhesive tissue α-SMA positive myofibroblasts have more adhesion markers (fibronectin, Col-I, VEGF, TGFβ-I), tissue plasminogen activator inhibitor and tissue inhibitor of matrix metalloproteinase [33]. The fibroblasts up-regulate extracellular matrix proteins such as Col-I and are highly expression of α-SMA. These factors take important key role in the connective tissue remodeling and fibrosis formation during wound healing. Therefore, it is of significance to promote the growth of fibroblasts through up-regulation of Col-I and α-SMA proteins for wound healing [34, 35]. Li [36] investigated the effect of ACRS on wound healing in diabetic mice. He found that ACRS promotes wound healing in diabetic mice with enhancing fibroblasts via inactivate STING signaling pathway. In the present study, parallel to the findings of previous studies, α-SMA expressions were found higher than adhesion control group. PRP and ACRS treatments were found to significantly reduce α-SMA compared to the adhesion control group. In addition, PRP and ACRS treatments significantly reduced Col-I protein expressions and ACRS group showed the lowest statistical scores.

5 Conclusion

As a result of this study, ACRS and PRP treatments reduce post-operative uterine horn peritoneal adhesion formation. ACRS treatment has shown to provide more effective manipulation of the inflammatory response. Especially, ACRS treatment has more effective anti-inflammatory effect on peritoneal adhesion was seen with the histopathologic parameters findings such as inflammatory cell infiltration, Col-I, α-SMA, IL-6 and TNF-α of this study. Our current findings suggest that ACRS has an anti-adhesion role by reducing the inflammatory response in adhesion tissues. At the same time this study is the first study about the comparing of the effect of PRP and ACRS on peritoneal adhesion. However, we suggest that more study is needed on this subject.

Author Contributions HE planned the experimental design and in vivo experiments. EK, GA and OK entered the raw data and carried out statistical analyses using SPSS. HE, ME and NEA shared in the writing, checked the tables, and constructed the figures. HE and EK conducted the literature review, drafted and revised the literature, and HE wrote the final manuscript. All authors read and approved the article.

Funding Open access funding provided by the Scientific and Technological Research Council of Türkiye (TÜBİTAK). No funding was received for conducting this study.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict to interest The Authors declares that there is no conflict of interest. The authors have no relevant financial or non-financial interests to disclose.

Ethical Approval The present study was conducted at the Erciyes University Experimental Research Application and Research Center (DEKAM) with the approval of the Erciyes University Animal Experiments Local Ethics Committee (HADYEK, Decision no: 24/025).

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