ORIGINAL ARTICLE

The effect of platelet-rich plasma on intra-abdominal adhesions in rabbit uterine horn model

El efecto del plasma rico en plaquetas en las adherencias intraabdominales en modelo de cuerno uterino de conejo

Begum Kurt[1], Caglar Yildiz[1], Tulay Koc[2], Nese Kurt-Ozkaya[3], and Serkan Celikgun[4]*

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Sivas Cumhuriyet University, Sivas; [2]Department of Medical Pathology, Faculty of Medicine, Sivas Cumhuriyet University, Sivas; [3]Department of Plastic, Reconstructive and Aesthetic Surgery, Sivas Medicana Hospital, Sivas; [4]Department of Public Health, Institute of Health Sciences, Dokuz Eylul University, Izmir. Turkey

Abstract

Objective: *This study was carried out to investigate the effect of autologous platelet-rich plasma (PRP) on intra-abdominal adhesion at the cesarean section incision line in the uterus.* **Material and methods:** *As experimental animals 16 white New Zealand rabbits, 5-months-old, unmated, were used. Animals were divided into two groups the control group and PRP application group. In each group, a transverse incision was made to the uterus to mimic the cesarean section and sutured. Relaparotomy was performed 21 days after the first operation.* **Results:** *When the groups were evaluated in terms of inflammation, there was a significant difference between the two groups. When the groups were evaluated in terms of Mason's Trichrome staining and fibrosis, There was a significant difference between groups. When the groups were evaluated in terms of vascular endothelial growth factor-1, there was also a significant difference between the groups. In an experimental rabbit uterine horn adhesion model, PRP is effective in preventing post-operative adhesion formation.* **Conclusions:** *This result may guide clinical studies using autologous PRP to prevent post-operative adhesion formation after gynecological operations.*

Keywords: *Gynecological surgery. Platelet-rich plasma. Post-operative complications- Repeat cesarean sections. Surgical adhesions.*

Resumen

Objetivo: *Este estudio se llevó a cabo para investigar el efecto del plasma rico en plaquetas (PRP) autólogo sobre la adhesión intraabdominal en la línea de incisión de la cesárea en el útero.* **Material y métodos:** *Como animales de experimentación se utilizaron 16 conejos blancos de Nueva Zelanda, de 5 meses de edad, sin aparear. Los animales se dividieron en dos grupos como grupo de control y grupo de aplicación de PRP. En cada grupo, se hizo una incisión transversal al útero para imitar la cesárea y se suturó. La relaparotomía se realizó 21 días después de la primera operación.* **Resultados:** *Cuando los grupos se evaluaron en términos de inflamación, hubo una diferencia significativa entre los dos grupos. Cuando los grupos se evaluaron en términos de tinción MT y fibrosis, hubo una diferencia significativa entre los grupos. Cuando los grupos se evaluaron en términos de VEGF-1, también hubo una diferencia significativa entre los grupos. En un modelo experimental de adherencia al cuerno uterino de conejo, el PRP es eficaz para prevenir la formación de adherencias posoperatorias.*

***Correspondence:**
Begum Kurt
E-mail: begumkurt@cumhuriyet.edu.tr

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Conclusiones: *Este resultado puede guiar los estudios clínicos que utilizan PRP autólogo para prevenir la formación de adherencias postoperatorias después de operaciones ginecológicas.*

Palabras clave: *Cirugía ginecológica. Plasma rico en plaquetas. Complicaciones postoperatorias. Repita las cesáreas. Adherencias quirúrgicas.*

Introduction

Every year, millions of laparotomies are performed worldwide due to trauma, malignancies, acute abdomen syndrome, infections, vascular pathologies, and gynecological and urogenital diseases. Unfortunately, peritoneal adhesions inevitably occur after these operations. Peritoneal adhesions are fibrous tissues formed between the peritoneum and intra-abdominal organs such as the small intestine, colon, and uterus and play an essential role in post-operative morbidity. Adhesions after pelvic surgery are the leading cause of complications such as chronic abdominopelvic discomfort, pain, and infertility. The remarkable increase in morbidity and mortality due to pelvic adhesions has revealed the necessity of developing more safe and effective anti-adhesion auxiliary models[1-3]. Numerous pharmaceutical studies have recently investigated the trial of drugs with anti-inflammatory effects on various animal models and their usability in clinical settings[4-7].

Peritoneal adhesions begin to form on the peritoneal and visceral surfaces concerning post-operative trauma. The vascular permeability of the tissue increases, followed by the exudation of inflammatory cells. The fibrin matrix is gradually organized and replaced by tissue fibroblasts, macrophages, and giant cells. In the next step, fibrin bands are modeled, and connections are formed between the injured tissue and the peritoneum. The fibrinolytic system destroys fibrin bands, and peritoneal healing is achieved. If this system is insufficient, fibrin bands become permanent[8]. Tissue response may be exaggerated after surgical interventions, and tissue regeneration and remodeling may result in adhesion formation[9].

Platelet-rich Plasma (PRP) obtained from the patient's blood contains growth factors and biomolecules necessary for wound healing. Using autologous PRP eliminates the risks of cross-contamination, disease transmission, or immune reactions. Another significant advantage is that it is simple and fast to prepare, and the preparation cost is low (approximately 30 minutes from blood collection to administration). PRP is prepared from the centrifugation of autologous whole blood and combined with thrombin and calcium chloride to produce a viscous coagulation gel[7]. PRP contains many growth factors and various proteins that can stimulate the healing process. Therefore, it has widespread clinical use. PRP accelerates neovascularization and increases blood flow and nutrient flow required for cell regeneration in damaged tissues. It also stimulates the proliferation and differentiation of cells involved in the healing process[10].

Transverse incision on the uterus is applied in many surgical interventions such as myomectomy and cesarean section in surgical practice. This study was designed to investigate the effect of PRP on the healing process and intra-abdominal adhesion at gynecologic surgery.

Material and methods

Preparation of PRP

Locally applied PRP was used in this study. Three milliliters of blood collected from the rabbits' ear veins were slowly injected into a tube containing 10:1 sodium citrate. 0.5 ml of blood was taken into a separate tube, and platelet count (489.000/μl) was measured with a complete blood count panel (Mindray BC-6800). The blood was centrifuged at 160 G for 10 min. The blood components were divided into two: the clear supernatant forming PRP and the other part containing erythrocytes and leukocytes. A portion of the clear supernatant is centrifuged again at 300 G for 10 min. With the complete blood count, it was determined that the platelet count reached approximately three times (1463.000/μl). Calcium chloride (10:1) was added for platelet activation before injection[7].

Animal experiments

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

In the research within this project's scope, 16 adults, an average of 20 weeks old, unmated, female, 2500-3000 g

white New Zealand rabbits were used as experimental animals. Rabbits were left to acclimate to laboratory conditions for 1 week after purchase. Rabbits are kept as single individuals in a cage. The animals were kept in the laboratory's standard animal housing conditions with 12 h of light-dark, 21°C temperature, 50-60% humidity, and optionally standard pellet rabbit food and water. All rabbits fasted for 12 h before surgery.

Animals were randomly divided into two groups, 8 for each, as the control group and the PRP application group. Animals were anesthetized by intramuscular injection of 10 mg/kg xylazine (Rompun; Bayer, Turkey) and 30-35 mg/kg ketamine (Ketalar; Parke Davis, Turkey, Istanbul) and allowed to breathe spontaneously. A rectal tube was inserted into the animals and placed on a heating pad to maintain their body temperature at 37°C. All surgical procedures were performed by the same surgeon. Rabbits were fixed in the supine position. The surgery was limited to 10 min per rabbit to control the effect of tissue drying in room air, with care being taken to avoid large amounts of bleeding from the tissues. The midline lower abdomen of each rabbit was shaved and disinfected with an iodine solution. The abdomen was entered with an approximately 5 cm long midline vertical incision. In each group, a transverse incision was made on the uterus for wound healing and adhesion evaluation. The abdominal wall was opened, and a typical lesion was created by making a 10 mm long transverse incision on the antimesenteric face of one of the uterine horns with a scalpel. The uterus was duly closed with 4-0 vicryl. After the bleeding control was achieved with cautery, the PRP prepared on the wound lips was applied equally to the PRP group with an insulin syringe. Since we injected PRP into the sutured uterine incision, local injection with saline was applied as a placebo fluid for the control group, considering the damage that the injection needle would cause to the uterine tissue. Then, the abdominal wall was closed with two layers of 4/0 vicryl. Antibiotic prophylaxis was administered during and after the surgery. Relaparotomy was performed in both groups 21 days after the first operation. The uterine incision site was excised and preserved for histopathological examination.

Macroscopic adhesion scoring

Adhesions formed after relaparotomy on the 21st day were evaluated macroscopically by two independent researchers unaware of the applications. The mean score of both researchers was used for that rabbit.

Table 1. Macroscopic Adhesion Scoring[11]

Score	Definition
Adhesion prevalence (0-4)	
0	0%
1	< 25%
2	25-50%
3	50-75%
4	> 75%
Adhesion severity (0-4)	
0	Absent
1	Self detached
2	Separated by withdrawal
3	Separated by blunt dissection
4	Separated by sharp dissection
Total adhesion score (range 0–8)	Total adhesion prevalence and severity score

Grading of adhesions was evaluated in terms of adhesion prevalence and severity, with scores from 0 to 4. The total adhesion score (0-8) was found for each rabbit by summing the adhesion prevalence and severity scores[11] (Table 1).

Histopathological evaluation

The uterine incision site was excised 21 days after the first operation. These tissues were fixed in 10 % neutral buffered formaldehyde solution at room temperature for 24 h. In the 15-h follow-up process with the tissue tracking device (Sacura), dehydration, transparency, and tissue hardening processes were completed by passing through alcohol, xylene, and paraffin stages. Then, the tissues were made into blocks by embedding paraffin in a tissue embedding device (Thermo Shandon). After the blocks were cooled in the refrigerator, 3-micron-thick sections were taken on the microtome device (Leica). Some of these sections were taken from standard slides for hematoxylin-eosin (HE) and Mason's Trichrome (MT) staining, and some of them were taken on a positively charged slide for anti-vascular endothelial growth factor-1 (VEGF-1) immunohistochemistry staining. Sectioned preparations for HE (Facepath) staining were stained in an automatic staining-off device (Sacura) and closed. MT staining (Facepath) was applied to the slides manually with the kit. VEGF-1 antibody (Abcam, Clone: Y103, 1/100 dilution, 32 min incubation time) immunohistochemical staining was performed on the preparations taken on positively loaded slides in an automatic Ventana Benchmark XT device.

Then, the slides were closed by dripping entellan. After staining procedures, the samples were assessed in a blinded manner by two pathologists to avoid bias with a light microscope (Leica DM 750). Inflammation and fibrosis were evaluated in HE-stained preparations[9,12,13] (Table 2).

Statistical review

Count data were given with numbers and percentages, and measurement data with mean, standard deviation, minimum and maximum values. Mann–Whitney U test, a non-parametric test, was used to compare both groups. $p < 0.005$ was considered statistically significant.

Results

A veterinarian checked the rabbits daily, and no problems were encountered throughout the study. The total adhesion score of the control group was 38, and the total adhesion score of the PRP group was 32 (Table 3). A statistically significant relationship was found between the two groups regarding total adhesion score ($p = 0.005$) (Table 4). The histopathological findings of both groups were compared, and the results were scored (Table 5).

When the control group and PRP group were evaluated in terms of inflammation (Fig. 1), there was a significant difference between the two groups ($p = 0.041$). When the control and PRP groups were evaluated in terms of MT staining and fibrosis, There was a significant difference between groups ($p = 0.041$) (Figs. 2 and 3). When the control and PRP groups were evaluated in terms of VE GF-1, there was also a statistically significant difference between the groups ($p = 0.020$) (Table 6) (Figs. 4 and 5).

Table 2. Histopathological evaluation[9,12,13]

The degree of inflammation	
0	
1	No inflammation
2	Rarely presence of giant cells, lymphocytes, and plasma cells
3	Presence of giant cells, plasma cells, eosinophils, and neutrophils Presence of many inflammatory cells and microabscesses
The degree of fibrosis	
0	No fibrosis
1	Mild
2	Moderate
3	Severe
Percentages of VEGF-1 immunoreactive cells	
0	Negative for staining
1	33% positive staining
2	33-66% positive staining
3	66% recorded as positive staining

VEGF: vascular endothelial growth factor.

Table 3. Macroscopic adhesion scoring in groups

Macroscopic adhesion	Control group	PRP group
Adhesion prevalence	3, 3, 2, 3, 3, 2, 3, 2	2, 2, 2, 2, 2, 2, 1, 1
Adhesion severity	3, 3, 3, 3, 2, 2, 3, 3	2, 3, 2, 2, 3, 2, 2, 2
Total adhesion score	6, 6, 5, 6, 5, 4, 6, 5	4, 5, 4, 4, 5, 4, 3, 3

PRP: platelet-rich plasma.

Discussion

Adhesion development after abdominopelvic surgery is a common complication (60-93%). This situation forms the basis of many problems, such as intestinal obstruction, chronic pain, and infertility[14].

First of all, in this study, when PRP produced from the rabbits own blood was applied to the uterine incision, it was observed that adhesion was reduced in all the examined parameters, both macroscopically and histopathologically.

PRP is 3-5 times more concentrated than the amount of autologous rabbit platelets in whole blood. It contains growth factors and biomolecules that accelerate wound healing[15-19]. Using autologous PRP eliminates the risks of cross-contamination, disease transmission, or immune reactions. By accelerating neovascularization, PRP helps the proliferation and differentiation of cells involved in the healing process[10].

Many studies have been conducted on using PRP as a gel on the wound to accelerate wound healing. The common conclusion in these studies is that PRP contributes to wound healing[20-22]. After the acute inflammatory phase, wound healing occurs with increased fibroblastic activity. It continues for several weeks to months to restore tissue strength and maturation. During this continuity, the healing response may occur more than necessary. These results in delayed adhesion formation are related to the time of surgery because post-operative adhesions in the peritoneum most commonly become permanent within the 1st week and after the 2nd week[23]. Unlike previous

Table 4. Statistical comparison of macroscopic adhesion scoring

Macroscopic adhesion	Control group	PRP group	p-value
Adhesion prevalence	2.62 ± 0.51 (min-2, max-3)	1.75 ± 0.46 (min-1, max-2)	**0.009**
Adhesion severity	2.75 ± 0.46 (min-2, max-3)	2.25 ± 0.46 (min-2, max-3)	0.051
Total adhesion score	5.37 ± 0.74 (min-4, max-6)	4.00 ± 0.75 (min-3, max-5)	**0.005**

Results were given as mean ± standard deviation (n = 8 for each group).
PRP: platelet-rich plasma.

Table 5. Scoring of histopathological findings

Histopathological findings	Control group	PRP group
Inflammation	2, 1, 1, 2, 1, 1, 2, 1	1, 1, 1, 1, 1, 0, 1, 0
Fibrosis	1, 2, 1, 1, 2, 1, 1, 2	1, 1, 1, 1, 1, 0, 1, 0
MT	1, 2, 1, 1, 2, 1, 1, 2	1, 1, 1, 1, 1, 0, 1, 0
VEGF-1	3, 2, 3, 3, 3, 3, 3, 3	3, 2, 2, 2, 3, 2, 2, 2

PRP: platelet-rich plasma; MT: Mason's Trichrome staining; VEGF: vascular endothelial growth factor.

Table 6. Statistical comparison of histopathological scoring

Histopathological findings	Control group	PRP group	p-value
Inflammation	1.38 ± 0.51 (min-1, max-2)	0.75 ± 0.46 (min-0, max-1)	0.041
Fibrosis	1.38 ± 0.51 (min-1, max-2)	0.75 ± 0.46 (min-0, max-1)	0.041
MT	1.38 ± 0.51 (min-1, max-2)	0.75 ± 0.46 (min-0, max-1)	0.041
VEGF-1	2.88 ± 0.35 (min-2, max-3)	2.25 ± 0.46 (min-2, max-3)	0.020

Results were given as mean ± standard deviation (n = 8 for each group).
PRP: platelet-rich plasma; MT: Masson's trichrome staining; VEGF: vascular endothelial growth factor.

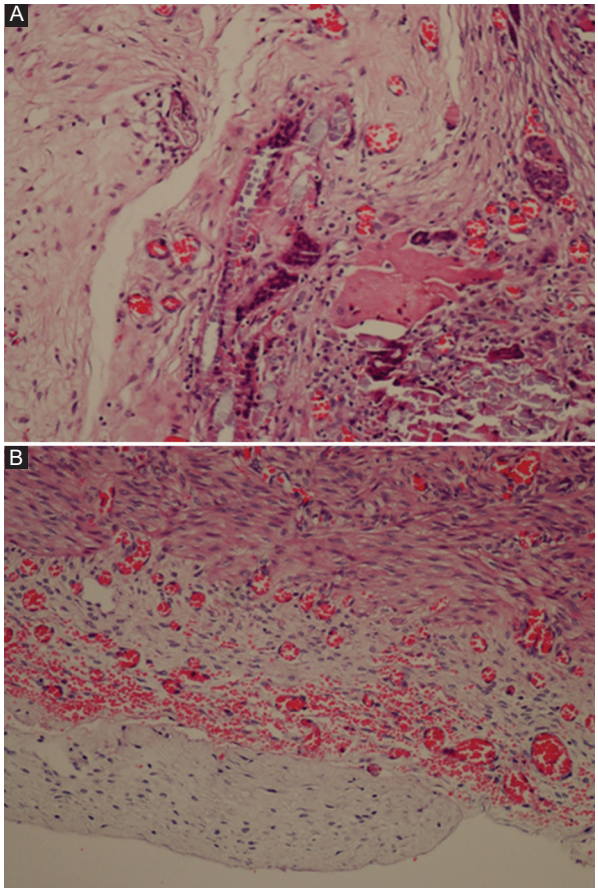

Figure 1. *Control group.* **A:** *moderate fibrosis, inflammation with giant cells and signs of increased vascularization (hematoxylin-eosin [HE] x 200).* **B:** *mild fibrosis (HE x 200).*

studies, in which the degree of adhesion was evaluated at day 7, 10, or 14 postoperatively[12,24,25], fibroblastic activity and degree of fibrosis were evaluated at day 21 in this study. When the adhesion scoring was performed macroscopically, it was determined that the extent of adhesion and the total adhesion score were significantly lower in the PRP group, and the adhesion severity was close to the significance level.

The first step in peritoneal adhesion formation is inflammation[26]. In our study, as expected, inflammation was detected significantly less in the PRP group compared to the control group.

Fibrosis score is another important parameter in the evaluation of peritoneal adhesions, and it is frequently used to evaluate the effectiveness of anti-adhesion studies[27]. A low fibrosis score is indicative of weak adhesions. Fibroblasts and many growth factors released from them increase during the healing process and contribute to wound healing. It has also been reported that PRP application increases fibroblast migration and proliferation[28,29]. This study detected a significantly reduced fibrosis score histopathologically in the PRP group compared to the control group.

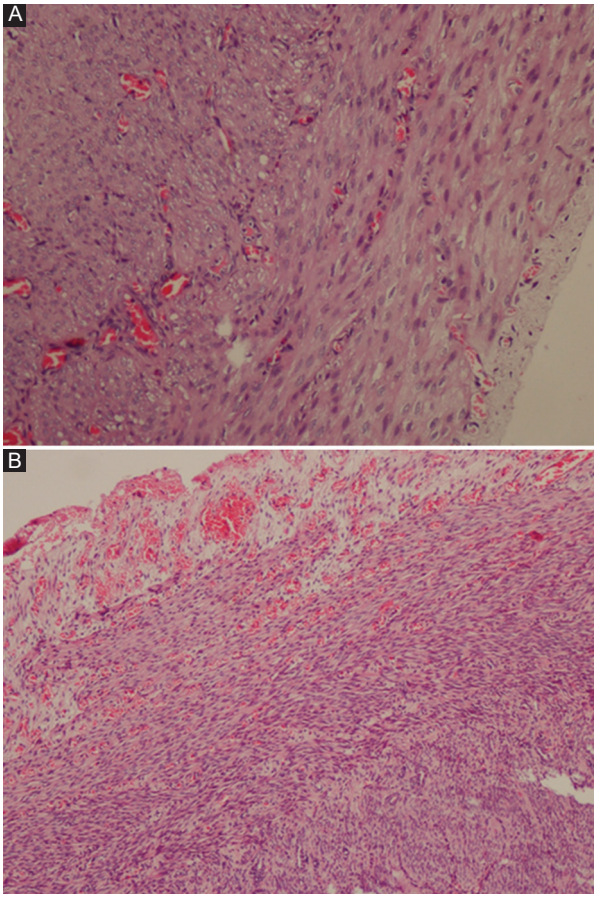

Figure 2. *Platelet-Rich Plasma group.* **A:** *no fibrosis (hematoxylin-eosin [HE] × 200).* **B:** *mild fibrosis, mild signs of inflammation (HE × 100).*

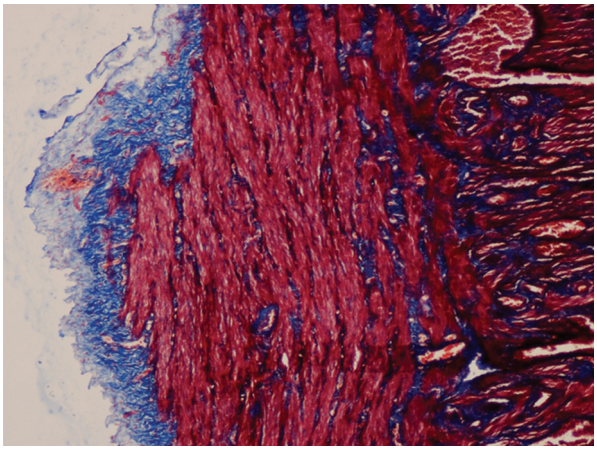

Figure 3. *Fibrosis with Mason's Trichrome staining (× 200).*

Another parameter examined immunohistochemically is VEGF-1. High expression levels of VEGF-1 are thought to stimulate angiogenesis and fibrosis. In addition, tissue expression of VEGF-1 will result in adhesion formation secondary to tissue damage. VEGF-1 is a major factor in wound healing and is responsible for adhesion formation[30,31]. In this study, as in all other parameters, tissue expression of VEGF-1 decreased significantly with PRP application. The strength of this study is the autologous preparation and use of PRP.

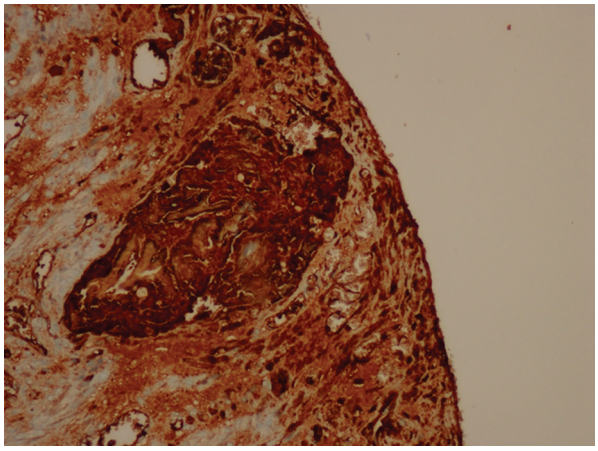

Figure 4. *Severe staining with vascular endothelial growth factor-1 in the control group (× 200).*

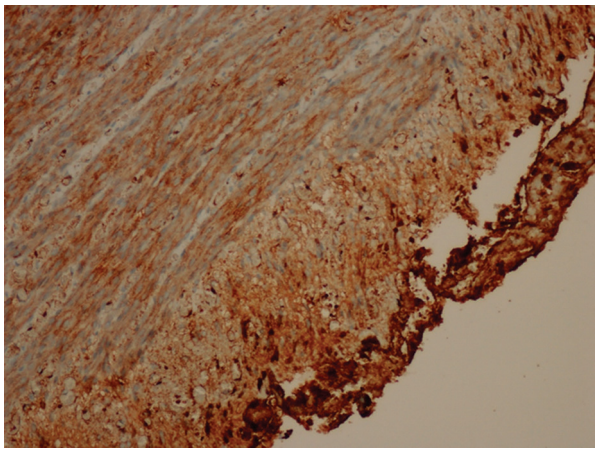

Figure 5. *Moderate staining with vascular endothelial growth factor-1 in the platelet-rich plasma group (× 200).*

Our study is the first to reveal the effect of autologous PRP on uterine wounds. In experimental rat models, the blood volume is too low to produce autologous PRP, so allogeneic preparations are preferred[9]. We chose rabbits in the study to use autologous PRP and test its effectiveness. Thus, risks such as cross-contamination, disease transmission, or immune reactions are eliminated. In the literature, there is no other intra-abdominal adhesion study using autologous PRP.

Conclusions

Our study concluded that using PRP in the experimental rabbit uterine horn adhesion model is effective in preventing post-operative adhesion formation and can guide clinical studies using autologous PRP to prevent post-operative adhesion formation after gynecological operations.

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Conflicts of interest

The authors declare no conflicts of interest for this article.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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