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Platelet-rich fibrin decreases adhesion to polypropylene prosthetic mesh material in ventral hernia repair

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Mesh adhesion is an important complication in prosthetic hernia repairs which may lead to intestinal obstruction, enterocutaneous fistula and viscus perforation. Therefore, direct contact between visceral organs and mesh should be avoided. The aim of this study was to investigate the efficacy of platelet rich fibrin (PRF) as an adhesion barrier. Thirty-six Wistar-Albino rats were used in the study. Four rats were used to obtain platelet-rich fibrin. Remaining rats were divided to four separate groups. In sham group, abdominal wall was repaired by suture without mesh following laparotomy. Abdominal walls of remaining rats were excised for about 2 cm in length with margins 2 cm wide. The defect was repaired with polypropylene mesh, Parietex composite mesh, or PRF coated polypropylene mesh in three separate groups. Rats were sacrificed on the 14th postoperative day. Macroscopic Zühlke and Greca adhesion scores, histopathological fibrosis grading and multinucleated giant cells were evaluated. There was statistically significant difference of adhesion scores of Zühlke ($p = 0.013$) and Greca ($p < 0.001$) between all groups. It was observed that the adhesion score in the platelet-rich fibrin group was lower than the polypropylene mesh group ($p = 0.003$), and there was no significant difference between the composite mesh group and the PRF group ($p = 0.13$). Fibroblast density and degree of fibrosis were higher in the platelet-rich fibrin group than in the polypropylene group ($p < 0.001$), but there was no significant difference with the composite mesh group. Giant cell formation, an indicator of inflammation, was significantly higher in the platelet-rich fibrin group than in the polypropylene mesh group ($p = 0.001$), and it was significantly less than in the composite mesh group ($p = 0.007$). Platelet-rich fibrin significantly reduces the incidence of adhesion to polypropylene meshes in the early postoperative period and enhances fibrosis at the mesh–abdominal wall interface. Acting as a biological barrier, platelet-rich fibrin shows potential as an alternative to composite meshes and antiadhesive barriers.

Keywords Hernia, Platelet rich fibrin, Mesh adhesion, Intraperitoneal mesh repair

The use of mesh in ventral hernia repairs reduces recurrence. While strong mesh integration is essential for successful hernia repair, excessive or abnormal adhesion to nearby organs may also lead to an increase in mesh-related complications. One of the most important mesh related complications is mesh adhesion which may cause intestinal obstructions and enterocutaneous fistulas[1]. Although there are various mesh materials, there is no consensus on an ideal mesh and almost all of them cause more or less adhesion[2].

Adhesion formation is a complex and time-dependent process which starts with the fibrin layer formed during the coagulation process with the suppression of fibrinolytic activity in conditions that cause local ischemia such as surgical trauma. This fibrin matrix is gradually replaced by vascular granulation tissue consisting of macrophages, fibroblasts and giant cells, and over time this granulation tissue turns into fibrous bands. Opposing of two damaged peritoneal surfaces triggers adhesion formation[3]. Intraperitoneal meshes are in direct contact with visceral organs as in minimal invasive hernia repairs, so mesh adhesion is a serious complication[4].

Platelet-rich fibrin (PRF) is a second generation concentrate obtained autologously; it is a relatively new technique in the field of regenerative medicine[5]. The basic principle in the preparation of platelet concentrates is that concentrated platelets and the cytokines and growth factors they contain can be combined and used locally in the surgical field. The fact that the dense fibrin network formed is also rich in leukocytes both triggers tissue

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healing and shows antibacterial effect. It undergoes slow resorption in the tissue and continues to spread the cytokines and growth factors it contains to the surrounding tissue for 7–10 days[6].

PRF may be useful in hernia mesh surgery for several aims, such as reduction of adhesions, enhanced tissue healing, anti-inflammatory effects, and improved mesh integration. Local application of platelet concentrates was shown to reduce biological mesh adhesion, intraperitoneal adhesions and intrauterine adhesions in rodent experimental studies[7–9]. There is no study in the literature showing the effect of PRF on adhesion to prosthetic meshes. The aim of this study was to investigate the efficacy of PRF membrane as an adhesion barrier to prosthetic meshes.

Materials and methods

10-week-old male Wistar-Albino rats weighing between 250 and 350 g and fed with standard laboratory feed were used. The rats were obtained from Kobay Experimental Animals Laboratory Inc. (Ankara, Turkey). The study was approved by the Hacettepe University Animal Ethics Committee (Approval number: 2022/01–10). Animal housing, care, and application of experimental procedures were all performed in accordance with institutional regulations. The experiments were carried out according to the Guide for the Care and Use of Laboratory Animals and reported in accordance with the ARRIVE guidelines. The animals were housed under a 12-hour light-12-hour dark cycle at a temperature of 22 ± 3 °C and 40–60% humidity and allowed free access to food and water.

Thirty-two male Wistar-Albino rats were divided into four subgroups, each containing eight rats. Four rats were used to obtain platelet-rich fibrin. General anesthesia was achieved in all groups by intraperitoneal administration of a mixture of 90 mg/kg ketamine HCl and 10 mg/kg Xylazine HCl. The abdomen was shaved and disinfected with povidone–iodine solution. Following 4 cm-long midline skin incision, 2 cm-long laparotomy was done and repaired by running suture without mesh in sham group. Abdominal wall and peritoneum were excised for about 2 cm in length with margins 2 cm wide in other groups. (one cm from midline to each side).

Group 1 (SH): Midline laparotomy was closed by running suture without mesh.

Group 2 (PR): The midline defect of rats in the polypropylene group was repaired intraperitoneally with 2.5 × 2.5 cm sized polypropylene mesh.

Group 3 (COM): The midline defect of the rats in the composite group was repaired intraperitoneally with 2.5 × 2.5 cm sized Parietex® composite mesh coated collagen film inside.

Group 4 (PRF): The midline defect of rats in the PRF group was repaired intraperitoneally with 2.5 × 2.5 cm sized PRF coated polypropylene meshes which was fixed platelet rich fibrin membrane on the inner side facing the intra-abdominal cavity.

Twelve ml of blood obtained by cardiac puncture from four rats was divided equally into eight separate anticoagulant-free tubes. The tubes were centrifuged at 2700 rpm for 12 min. Red blood cells and platelet-poor plasma were separated from the sample obtained after centrifugation and platelet-rich fibrin was isolated and taken into a separate container. Platelet-rich fibrin layer was attached to the polypropylene meshes cut in 2.5 × 2.5 cm in dimensions with 4 – 0 polypropylene sutures from both ends (Fig. 1).

Evaluation of adhesion formation

The animals were sacrificed on postoperative day 14 with intraperitoneal high dose ketamine HCl. Anterior abdominal wall was opened through a U-shaped incision and macroscopic adhesion assessment was performed at this stage. For macroscopic adhesion evaluation Greca adhesion scoring (Supplementary Table 1), which evaluates adhesion grade and surface area, Zühlke adhesion scoring (Supplementary Table 2), which evaluates adhesion tenacity were used[10,11].

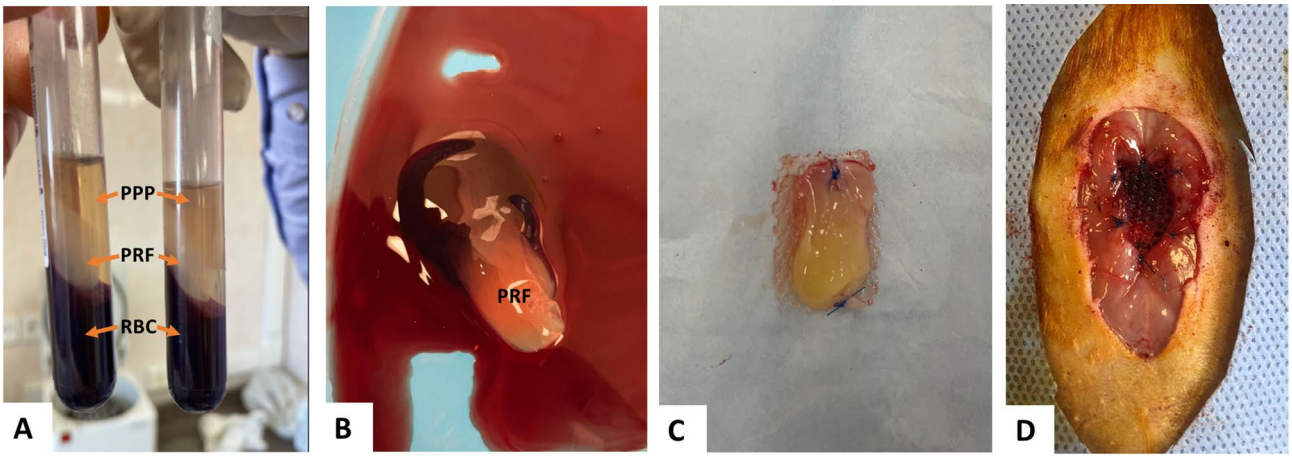

Fig. 1. Preparation of PRF-coated meshes. (**A**) Centrifugate of whole blood sample shows supernatant platelet poor plasm (PPP), platelet-rich fibrin (PRF) clot, and red blood cell corpuscle pellet. (**B**) Isolation of platelet rich fibrin. (**C**) Suturing the PRF membrane to polypropylene mesh. (**D**) Intraperitoneal mesh repair of ventral hernia in which the PRF membrane opposing to visceral cavity.

Histopathological examination

Tissue sample was taken from the edge where the abdominal wall and the mesh meet, including the mesh, and embedded in paraffin. Subsequently, sections of 5 µm thickness were obtained by staining with hematoxylin-eosin and Masson-Trichrome stain. The sections were evaluated by a pathologist blinded to the groups. Fibrosis scoring was performed according to the parameters described in the literature[12]. They were graded on a scale of 0 (none) to 4 (severe). The extent of fibrosis was graded as 1 if the area involved less than 10% of the slide; 2 if it was between 10% and 40%; 3 if it was between 40% and 70%; 4 if it was more than 70%. The grade of fibrosis and inflammation were evaluated using light microscopy in a high-power field (X40). One high-power field is approximately 0.16 mm^2. As an indicator of inflammatory response, foreign body-type giant cells were counted in the area where they were most numerous in a one high-power field (hot-spot).

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences version 25 (SPSS, IBM, USA). Since the data was not normally distributed, Kruskal-Wallis test was used to compare groups. Mann-Whitney U-test with Bonferroni correction was used for post-hoc analyses. p value less than 0.05 (two-sided) was appreciated as significant.

Results

There was no mortality in all groups. Surgical site infection, fistula, intestinal obstruction, and hernia recurrence were not observed in any animal. All rats were sacrificed and evaluated on postoperative day 14. In the sham group, no adhesion formation was observed only in one of the rats (12.5%), while omental adhesions involving the suture line were present in 7 rats (87.5%). In the polypropylene mesh group, visceral adhesions to the mesh surface were identified in 2 rats (25%), omental adhesions were observed in 6 of them (75%). In the composite mesh group, visceral adhesions to the mesh surface were detected in only in one of the rats (12.5%) and omental adhesions were present in 7 rats (87.5%). In the PRF group, no visceral adhesions were observed, while omental adhesions were present in all rats. Adhesion types are illustrated in detail in Fig. 2.

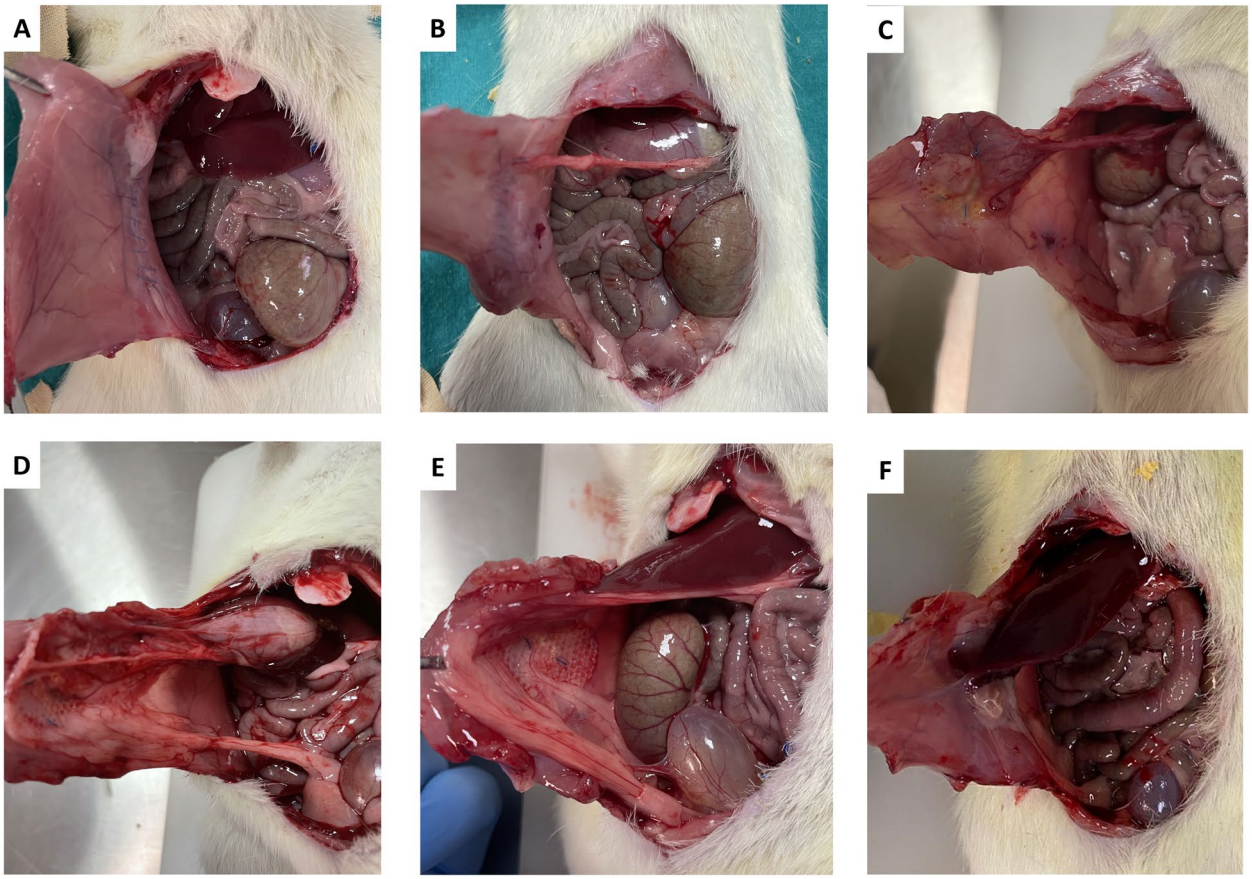

Fig. 2. Peritoneal adhesion types. (**A**) No adhesion. (**B**) Omental adhesion on suture line. (**C**) Omental adhesion on less than 50% of mesh surface. (**D**) Omental adhesion on more than 50% of mesh surface. (**E**, **F**) Visceral adhesion on mesh surface.

Groups (*n*)	Greca adhesion score	Zühlke adhesion score	Fibrosis score	Giant cell formation
Sham group (8)	2 (1–2)*	2 (0–3)***	1 (1–2)	6 (0–12)
Polypropylene group (8)	4 (3–6)	3 (2–4)	2 (1–3)	1 (1–3)
Composite group (8)	3 (2–6)	2 (1–4)	3 (3–3)	11 (6–20)
Platelet rich fibrin group (8)	3 (2–4)**	2 (2–3)	3 (3–3)$	3.5 (2–16) $$

Table 1. Grade of adhesions, fibrosis and giant cell formation on postoperative day 14 in the groups (median (range)). *$p < 0.001$ compared to polypropylene and $p = 0.001$ compared to composite group. **$p = 0.003$ compared to polypropylene group. ***$p = 0.004$ compared to polypropylene group. $$p < 0.001$ compared to sham group and $p = 0.001$ compared to polypropylene group. $$$p = 0.001$ compared to polypropylene group and $p = 0.007$ compared to composite group.

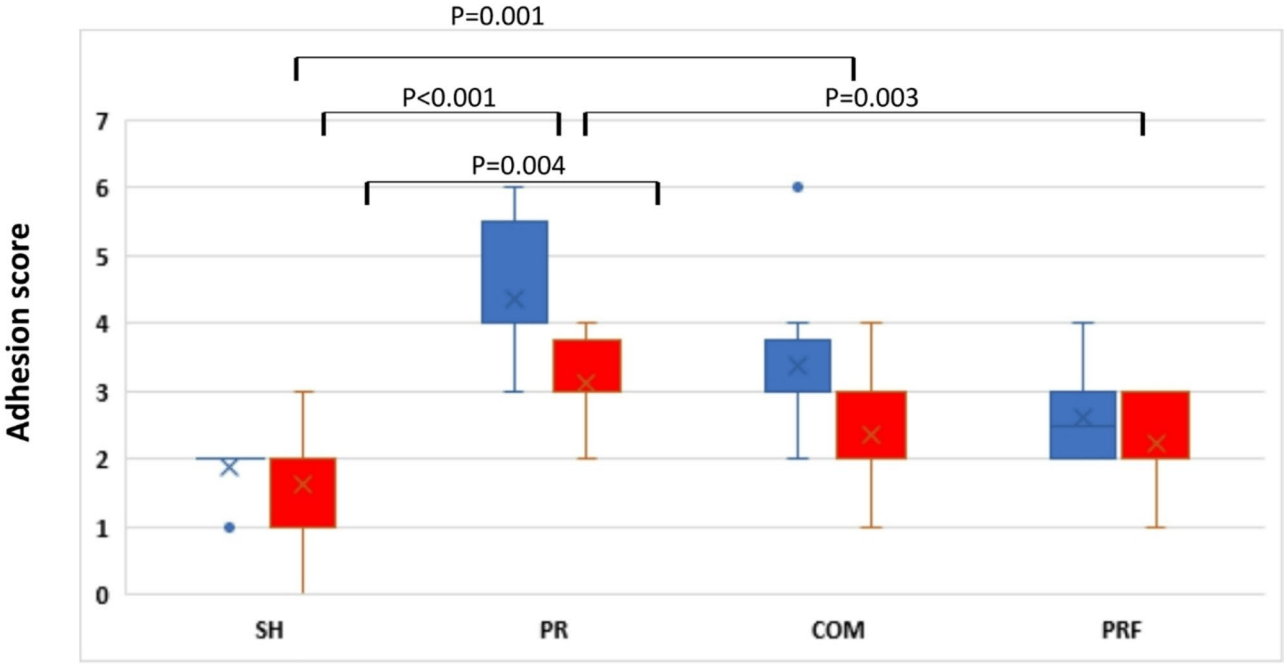

Table 2. Comparison of adhesion scores. The highest, lowest, and the IQR values are shown on the box plot. Blue box indicates Greca adhesion score and red box indicates Zühlke adhesion score.

Evaluation of adhesion formation

Each rat in four groups was evaluated according to Greca and Zühlke adhesion score as mentioned above. There was statistically significant difference between four groups ($p = 0.001$ Greca adhesion score, $p = 0.013$ Zühlke adhesion score, Kruskal-Wallis test). Pairwise comparison analysis showed that sham group had a significantly lower adhesion score than polypropylene and composite mesh groups. Platelet rich fibrin group had a significantly lower adhesion score than polypropylene group ($p = 0.003$, Mann-Whitney U test with Bonferroni correction). There wasn't significant difference between composite mesh group and PRF-coated mesh group ($p = 0.13$, Mann-Whitney U test Bonferroni correction) (Tables 1 and 2).

Histopathological evaluation

After macroscopic adhesion scoring in all groups, the anterior abdominal wall was excised and a sample was taken from the edge where the mesh and fascia meet, including the mesh. The specimens were stained with hematoxylin-eosin and Masson trichrome stain as shown in Figs. 3 and 4, then grade of fibrosis and inflammation were evaluated.

There was a statistically significant difference between four groups in fibrosis score ($p < 0.001$, Kruskal-Wallis test). Pairwise comparison showed that platelet rich fibrin group had a significantly higher fibrosis score than polypropylene mesh and sham groups ($p = 0.001$ and $p < 0.001$, Mann-Whitney U test with Bonferroni correction). There was a statistically significant difference between the groups in terms of giant cell formation as an indicator of inflammation ($p < 0.001$, Kruskal-Wallis test). Pairwise comparison showed that platelet rich fibrin group had significantly higher inflammation than polypropylene group but lower than composite mesh group (Table 1).

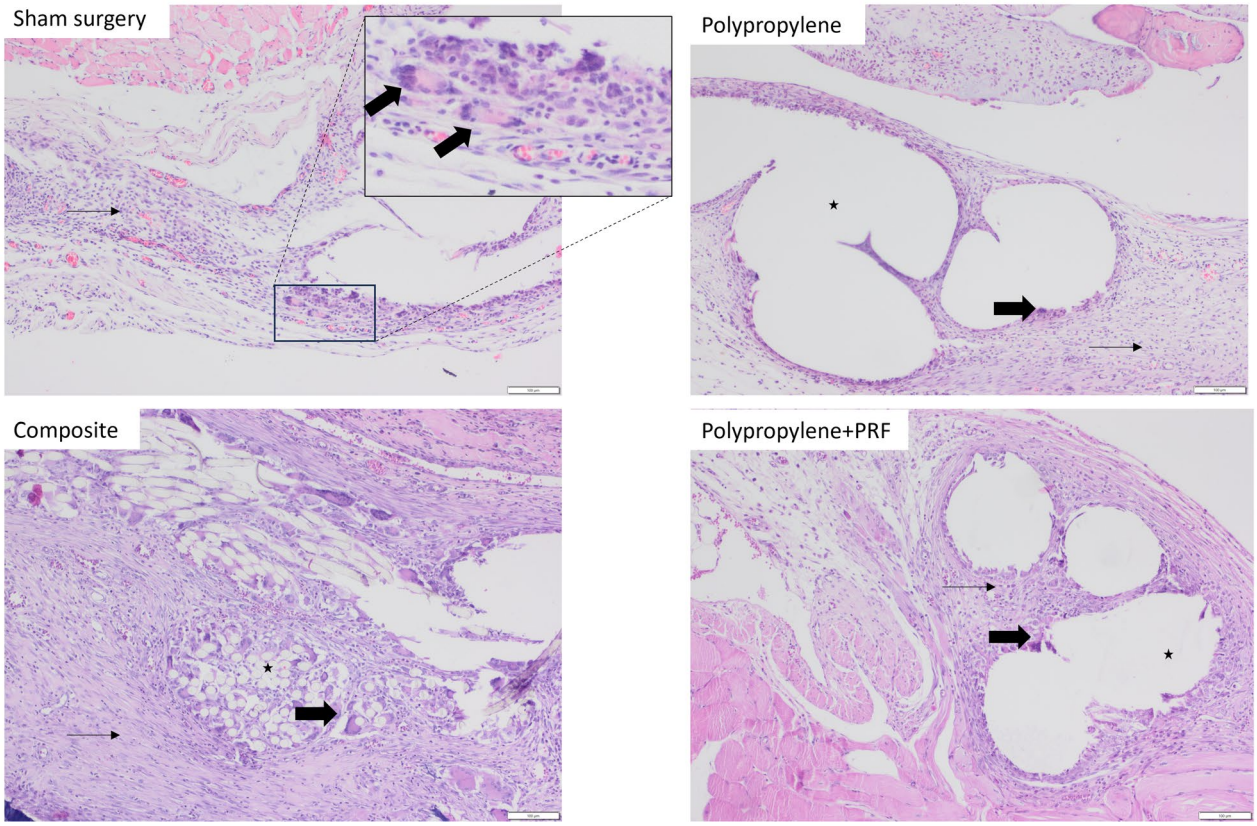

Fig. 3. Histopathological evaluation of groups by H&E staining. Thick arrows show multinucleated giant cells, thin arrows show fibroblasts/fibrosis, and asterisks show mesh. Scale bar: 100 µm.

Discussion

Adhesion of visceral organs to the mesh material causes significant complications. Intestinal obstruction and enterocutaneous fistula formation are the leading complications. In cases where the defect is too large to be closed with primary suture and in laparoscopic hernia repairs, the mesh surface and visceral organs are in direct contact. Although there are various mesh materials produced to prevent direct contact, there is no consensus on an ideal mesh material[13,14]. Platelet-rich fibrin is a second generation concentrate obtained autologously; it is a relatively new technique in the field of regenerative medicine. In our study, we investigated the effect of platelet-rich fibrin on the adhesion of visceral organs to polypropylene mesh material placed intraperitoneally in a ventral hernia model in rats. There are few studies in the literature on the adhesion of first- and second-generation platelet concentrates to intraperitoneal organs and mesh material.

In our study, two scoring systems were used to compare the groups in terms of mesh adhesion. Zühlke scoring system provides a semiquantitative scoring based on the tenacity of adhesion and ease of dissection. The Greca scoring system is a semiquantitative system defined by the severity and structure of the adhesion[10,11]. When evaluated with both systems, there was a significant difference between the groups in terms of adhesion scoring. Pairwise analysis between the groups showed that adhesion to the abdominal wall was less in the sham group without mesh compared to the other three groups. This was thought to be due to the primary approximation of the peritoneal surfaces and minimal contact of the damaged peritoneal surface with visceral structures.

In the pairwise analysis between the experimental groups, it was shown that adhesion to the mesh was higher in the group using polypropylene mesh than in the group using both composite mesh and PRF in both scoring systems. In many clinical studies in the literature, composite meshes have been shown to be superior to polypropylene meshes in terms of adhesion and are routinely used[15–17]. However, there is no study on PRF-coated meshes in the literature. Our study revealed that PRF-coated polypropylene meshes are as effective as composite meshes in preventing adhesion.

The basic principle of hernia repair with mesh is the increased tissue integrity due to fibrosis and fibroblast proliferation by mesh material. One of the indicators of this in the literature is the histopathologic demonstration of the intensity of fibroblast proliferation and fibrosis at the junction of the fascia and mesh and scoring based on this[12]. The subjectivity in histopathologic examination was reduced by the fact that the pathologist was blinded to the control and experimental groups and the area where the mesh and fascia meet and where fibrosis is most intense was evaluated. Fibrosis and fibroblast density were significantly higher in the PRF and composite mesh group than in the sham surgery group and the polypropylene group. This may be explained by the fact that cytokines and growth factors released from platelet and leukocyte-rich fibrin increase mesenchymal cell

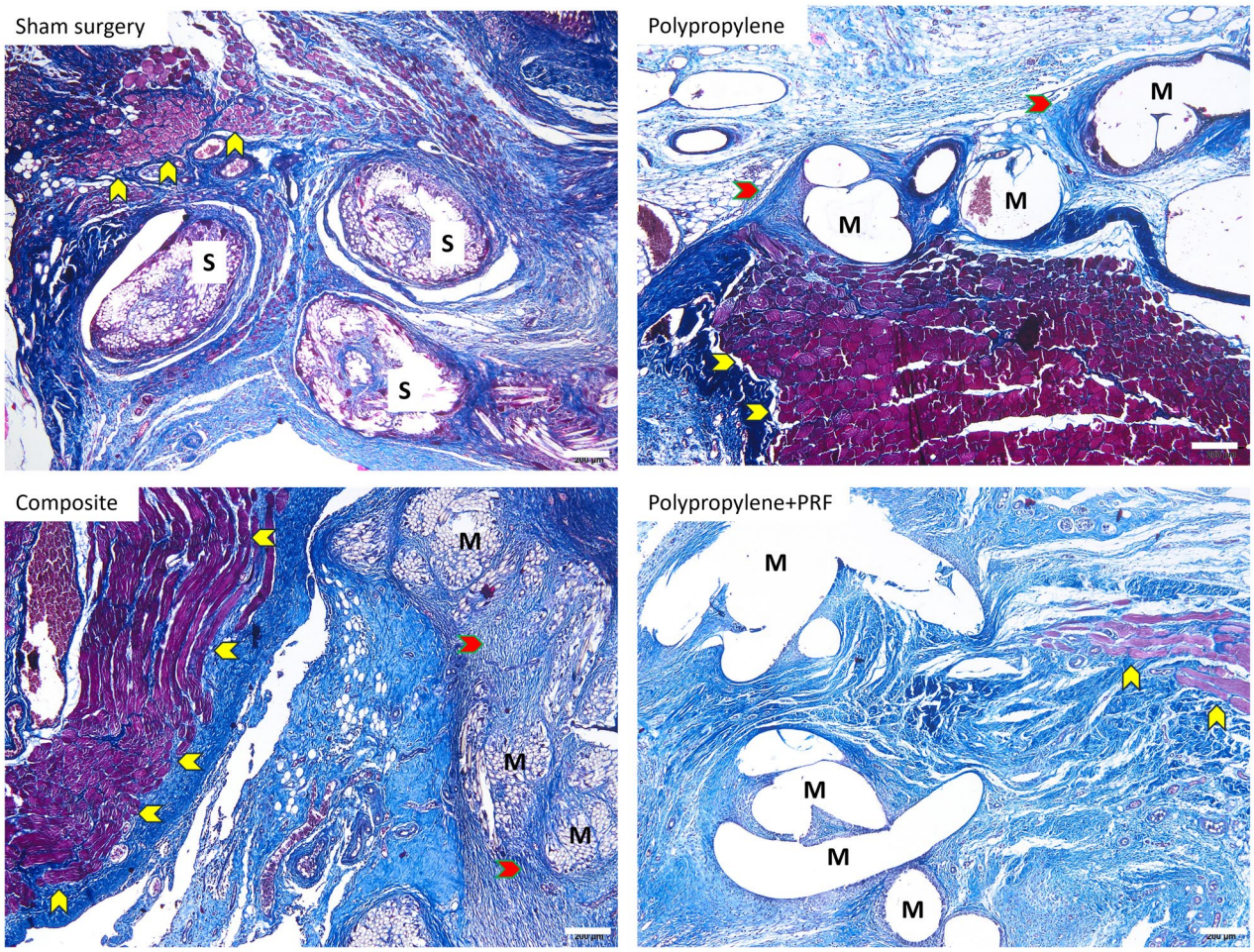

Fig. 4. Evaluation of fibrosis by Masson trichrome staining. M stands for mesh material, S stands for suture material, yellow arrowheads show muscle fibrils, and red arrowheads show fibrosis. Broad fibrosis around mesh material is noted in polypropylene + PRF group. Scale bar: 200 μm.

migration to the area, which provides tissue regeneration. No significant difference was found between PRF-coated mesh and composite mesh.

This study has two primary limitations. First, PRF was not applied autologously. Due to the relatively large volume of blood required for PRF preparation, it was not feasible to obtain sufficient quantities from the tail vein of a single rat. Consequently, PRF was prepared using blood collected via cardiac puncture from four donor rats that were sacrificed for this purpose. Since the rats used were inbred, they were considered genetically identical and therefore no immune reaction was observed in any animal in the experimental group. Second limitation is that the effect of platelet-rich fibrin on adhesion in the late period was not evaluated due to the small number of subjects and the fact that the subjects were sacrificed and examined on the 14th postoperative day.

Conclusion

Platelet-rich fibrin significantly reduces the incidence of adhesion to polypropylene meshes in the early postoperative period and enhances fibrosis at the mesh–abdominal wall interface. Acting as a biological barrier, platelet-rich fibrin shows potential as an alternative to composite meshes and antiadhesive barriers.

Data availability

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

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Author contributions

Dr. Dogu and Dr. Yorganci performed the operations and analyzed the adhesion score.Dr. Akyol and Dr. Sokmensuer conducted the pathologic investigations and analyses. Dr. Dogu and Dr.Akyol wrote the main manuscript text and prepared figures/tables.All authors reviewed the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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