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The Role of Platelet Rich Plasma for Preventing Postoperative Peritoneal Adhesions in Adhesive Intestinal Obstruction in Rats

Ameliyat Sonrası İntestinal Obstrüksiyonu Olan Ratlarda Periton Yapışıklıklarının Önlenmesinde Trombositten Zengin Plazmanın Rolü

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ABSTRACT

Background: Various methods have been investigated to prevent postoperative peritoneal adhesions (PPA). It is thought that wound healing process would be better with the use of platelet rich plasma (PRP).

Materials and Methods: The aim of this study was to investigate the role of PRP in the formation of PPA and in preventing adhesion formation in rats. It was also planned to demonstrate the relationship between serum interleukin (IL)-6 and TNF-alpha levels and the severity of adhesions before creating the adhesion model and during sacrification. Rats were divided into 3 groups, each consisting of twelve rats. Groups were classified as; PRP, sham and control group. The rats were sacrified on the 14th day and relaparotomies were performed.

Results: The results were evaluated macroscopically and microscopically according to predetermined classifications. When the group treated with PRP was compared with the control groups according to the previously described macroscopic (Nair) and microscopic (Zuhlke) classifications, there was no significant difference in PPA formation both microscopically and macroscopically. It is thought that TNF-alpha and IL-6 should be used as markers in PPA formation process.

Conclusion: In the experimentally created adhesion model, the effect of PRP on preventing PPA formation could not be proved.

Keywords: Postoperative peritoneal adhesions, platelet rich plasma, adhesion in rats

ÖZ

Amaç: Ameliyat sonrası peritoneal adezyonları önlemek için çeşitli yöntemler araştırılmıştır. Trombositten zengin plazma (PRP) kullanımı ile yara iyileşme sürecinin daha iyi olacağı düşünülmektedir. Bu çalışmanın amacı, PRP'nin sıçanlarda ameliyat sonrası periton yapışıklıkları (PPA) oluşumunda ve adezyon oluşumunu önlemedeki rolünü araştırmaktır.

Gereç ve Yöntemler: Ratlarda adezyon modeli oluşturulmadan önce ve sakrifikasyon sırasında serum interlökin (IL)-6 ve TNF-alfa seviyeleri ile adezyonların şiddeti arasındaki ilişkinin gösterilmesi planlandı. Sıçanlar her biri on iki rattan oluşan 3 gruba ayrıldı. Gruplar şu şekilde sınıflandırıldı; PRP, sham ve kontrol grubu. Ratlar 14. günde sakrifiye edilerek relaparotomi yapıldı.

Bulgular: Sonuçlar önceden belirlenmiş sınıflandırmalara göre makroskopik ve mikroskobik olarak değerlendirildi. PRP ile tedavi edilen grup, daha önce açıklanan makroskopik (Nair) ve mikroskopik (Zuhlke) sınıflamalara göre kontrol grupları ile karşılaştırıldığında, hem mikroskobik hem de makroskopik olarak PPA oluşumunda anlamlı bir farklılık yoktu. PPA oluşum sürecinde belirteç olarak TNF-alfa ve IL-6'nın kullanılması gerektiği düşünülmektedir.

Sonuç: Deneysel olarak oluşturulan adezyon modelinde PRP'nin PPA oluşumunu önlemedeki etkisi kanıtlanamamıştır.

Anahtar Kelimeler: Postoperatif periton adezyonları, trombositten zengin serum, ratlarda adezyon

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Introduction

Postoperative peritoneal adhesions (PPA) are serious problems after abdominal surgery (1,2,3,4,5). The incidence of small bowel obstruction due to PPA is high in pediatric surgery (6). Among these problems, pain, intestinal obstruction, volvulus and infertility are the most common pathologies (3,7). In the formation of PPA, which is a kind of peritoneal damage; mechanical, ischemic, infective, inflammatory and chemical factors play a role.

Various methods have been searched for the prevention of adhesions and the use of different clinical techniques and medications has come forefront to prevent postoperative adhesion formation. There are two basic processes that can be interfered to minimize PPAs prevention of peritoneal trauma and prevention of adhesion of the damaged peritoneal surface to any surface. The first of these is the prevention of is a much simpler and effective method. By using careful and appropriate surgical technique, ensuring adequate hemostasis, leaving no foreign body or suture material in the abdomen, repairing peritoneal defects without causing tension if possible. The second is careful and appropriate surgical repair of, PPA formation can be prevented by leaving the defect open and fighting against infection by considering that bacteria are among the etiological factors (7). The second stage is a very complex process that begins after the trauma occurs. It is more difficult to tackle the second stage. The pathophysiology of these processes will be relatively low in applications without illumination. Moreover, regardless of the substance and method to be used after trauma; not only it should be non-toxic to peritoneal mesothelial cells, but also it will have to accelerate wound healing or prevent adhesion of mesothelial surfaces until the wound healing process is completed (8). A treatment method that includes all these preventive factors in a substance or method and moreover to optimize. Indeed, no such method has been found to date.

Platelet rich plasma (PRP) is getting popular on medical practice day by day. The platelets perform several essential functions in the body, including blood clot formation and the release of growth factors that help wound healing (9). These growth factors stimulate the stem cells to produce new host tissue as quickly as possible, which is why PRP is so effective in the post-treatment healing process. There have been various studies of PRP used in intra-abdominal procedures. For this purpose, it is planned to investigate the utilization of PRP and how it effects PPA formation.

The aim of this study was to investigate the role of PRP in the formation of PPA and in preventing adhesion formation in rats.

Material and Methods

Before starting the study, an application was made to the Ankara Hospital SAUM Animal Experiments Ethics Committee. Ethics committee approval was obtained at the meeting of the board dated 22.09.2017 by unanimous decision with the decision number 44.

In this study, rats were divided into 3 groups, each consisting of twelve rats. Groups were classified as PRP, sham and control group. In the PRP group, laparotomy was performed, adhesion was created and PRP was applied. In the sham group, laparotomy was performed adhesion was created without PRP. In the control group, laparotomy was performed without adhesion and PRP. The rats were sacrificed on the 14th day and relaparotomies were performed. The results were evaluated macroscopically and microscopically according to predetermined classifications.

Surgical procedures were performed in Ankara Hospital SAUM Experimental Animals Laboratory by providing aseptic conditions. Prophylactic antibiotics were not applied. Intraperitoneal ketamine (Ketalar®, Parke Davis and Co. Inc., 50 mg/kg) and xylazine (Rompun®, Bayer 5 mg/kg) were administered as an anesthetic agent. In order for the rats to be normothermic (37 °C) throughout the study, the temperature of the working environment was maintained with a heating lamp. Glove powder was tried to be removed by washing with sterile saline. After the abdominal skin was shaved and cleaned with 10% poviiodin, laparotomy was performed with a 3 cm midline incision with aseptic surgical technique followed by sterile covering. All subjects received 1 cc of blood from the tail vein before the procedure and were placed in biochemistry tubes. Then, to study the pre-op serum Tumor necrosis factor alpha (TNF-α) and interleukin (IL)-6 levels, the blood samples were centrifuged at 4000 rpm for 10 minutes and the serum was separated. Serum samples were placed in Eppendorf tubes (interlab A.C. TR) and stored at -80 °C until analysis day.

Adhesion model: After seeing that there was no adhesion in the abdomen, the cecum was exposed. Then, as a well-defined adhesion model in all rats; after the parietal area corresponding to the cecum was deserosalized, abrasion was formed on the antimezenteric surface of the cecum with a dry gauze. This process was continued until petechial bleeding foci were seen on serosal surfaces.

PRP: Four cc intracardiac blood was taken from each of the eight rats. The bloods were taken into tubes containing gel to separate the erythrocytes, ficoll to separate the white spheres and citrate-dextrose solution as an anticoagulant. The blood samples were delivered to the Ankara Hospital SAUM Biochemistry Laboratory. PRP prepared according to the procedure in the laboratory. After the adhesion model

was created, it was applied as 2 cc to the rats in the PRP group just before the abdomen was closed.

Sacrification and evaluation: In accordance with the Helsinki contract, after the rats were sacrificed with high-dose ether on the 14th day, a maximum view was achieved by making a U incision in the abdomen and retracting the abdominal walls downwards. Adhesions were then evaluated quantitatively with the classification defined by Nair et al. (9) an expression, evaluation was done by two different experts using double blind, in accordance with the criteria given in Table 1. Before sacrification from all subjects, intracardiac 1 cc blood was taken and the blood samples were centrifuged at 4000 rpm for 10 minutes to study the post-operative serum TNF-α and IL-6 levels. Serum samples were placed in Eppendorf tubes (interlab A.C. TR) and stored at -80 °C until analysis day.

In rats that developed adhesion after relaparotomy, the adhesive band was resected together with the affected organs and the parietal peritoneum in those who did not. The pathological specimens were then flicked in containers containing 10% buffered formol. The preparations, which were followed up with the classical laboratory method, were embedded in paraffin blocks. Sections five micrometers thick were taken on the slide. It was stained with hematoxylin-eosin dye and examined by light microscopy. Histopathological and microscopic examination of the samples taken was performed at the Ankara Hospital SAUM Lab of Pathology Department. The pathologist who made the examination did not know from which group the plays were taken. After histopathological evaluation, the preparations were subjected to microscopic grading as defined by Zühlke et al. (10) (Table 2).

Macroscopic Findings

The Nair classification evaluates the severity and extent of adhesion macroscopically. It is classified from 0 to 4 according to the severity and prevalence of adhesions (Table 3).

Tissue samples of approximately 3x2 cm intestinal wall of rats were embedded in paraffin after ethanol dehydration (50%, 75%, 96% and 100% respectively) and xylene translucency after fixation in 10% formaldehyde solution for 2 days. Four microns sections were taken with microtome and examined by staining with hematoxylin-eosin and Mason Trichrome. Histopathological examination was evaluated in OLYMPUS brand, BX51TF model x4, x10, x20, x40 lenses. Changes in the samples of the intestinal wall were evaluated according to the "Zühlke" microscopic adhesion classification with a semi-quantitative scoring system (Table 3).

TNF-α and IL-6 levels: Serum samples taken during the pre-operative period and during sacrification were stored at the SAUM Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital Biochemistry Laboratory until the day of analysis in Eppendorf tubes. Serum TNF-α level; SUNRED Rat was detected with TNF-α ELISA kit (unit value pg/mL) (Rat TNF- alpha ELISA Kit, catalog number: 201-11-0765, Shanghai). Serum IL-6 level; detected with SUNRED Rat IL-6 ELISA kit (unit value pg/mL) (Rat IL-6 ELISA Kit, catalog number: 201-11-0136, Shanghai). Serum samples from all groups were studied in the ELISA reader device (UQuant, Biotec instruments, Inc. Vermont, USA) in the Biochemistry Laboratory of the SAUM Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital using Rat TNF-α and Rat IL-6 kits. The results are shown in Table 4 and Table 5.

Table 1. "Nair" macroscopic adhesion classification

Grade 0	No adhesion	No adhesion
Grade 1	Adverse adhesion	One band between organs or between the organ and the abdominal wall
Grade 2	Pronounced adhesion	Two adhesive bands between organs and between the organ and the abdominal wall
Grade 3	Pronounced adhesion	Adhesion of intestinal loops between organs or between the organ and the abdominal wall, with no more than two adhesive band or adhesion to the abdominal wall
Grade 4	Severe adhesion	Viscera adheres directly to the abdominal wall

Table 2. "Zühlke" microscopic adhesion classification

Grade 0	Normal findings
Grade 1	Weak connective tissue, rich cell, old and new fibrin, thin reticulin fibrils
Grade 2	Connective tissue with cells and capillaries, rare collagen fibers
Grade 3	Thicker connective tissue, rare cells, more vessels, rare elastic and smooth muscle fibers
Grade 4	Old thick granulation tissue, poor removal from the cell, difficult separation of serosal layers

Statistical Analysis

While evaluating the findings statistically, IBM SPSS (Statistical Package for the Social Sciences, version 22.0; SPSS Inc., Chicago, IL) program was used in the study. In the analyzes, $p<0.05$ was considered statistically significant (Table 6).

When compared with the groups treated with PRP and the control groups were not significantly different in both microscopic and macroscopic PPA formation compared to the macroscopic (Nair) and microscopic (Zuhlke) previously defined.

Results

When the rats were evaluated according to the macroscopic adhesion classification (Nair's), while no adhesion formation was observed in 8 rats in the PRP group, 1st degree macroscopic adhesion was observed in 2 rats and 3rd degree macroscopic adhesion in 2 rats (Table 3). When the PRP and control groups were compared in terms of macroscopic adhesion, no statistically significant difference was found ($p>0.05$) (Table 6).

When the rats were evaluated according to the microscopic adhesion classification (Zühlke), no adhesion formation was observed in 6 rats, while 1st degree adhesion formation was observed in 2 rats, 2nd degree in 1 rat, 3rd degree in 2 rats and 4th degree in 1 rat (Table 3). When the PRP and control groups were compared in terms of microscopic adhesion, no statistically significant difference was found ($p>0.05$) (Table 6).

The three groups were examined in terms of TNF-α levels, it was found that the postoperative TNF-α levels of the control group were higher than the preoperative levels ($p<0.05$) (Table 4). On the contrary, there was no statistical difference between preoperative and postoperative TNF-α levels of Sham and PRP groups ($p>0.05$). In the statistical evaluation of independent groups in terms of preoperative and postoperative results, there was no difference between the groups' postoperative TNF-α levels, but there was a statistically significant difference between preoperative TNF-α levels ($p<0.05$). While there was no difference between the preoperative TNF-α levels of the control and PRP groups, the preoperative TNF-α levels of the sham

Table 3. Macroscopic and histopathological adhesion rating by groups

Rats	Macroscopic adhesion			Histopathological adhesion		
	PRP	Control	Sham	PRP	Control	Sham
1	0	1	0	0	2	2
2	0	4	4	1	4	4
3	1	0	0	2	1	2
4	3	0	0	3	0	1
5	0	0	0	0	0	1
6	0	1	0	0	1	1
7	0	2	0	0	1	1
8	0	1	0	1	0	1
9	0	1	1	0	1	3
10	0	1	0	0	2	2
11	1	1	1	3	1	4
12	3	1	0	4	1	1

PRP: Platelet rich plasma

Table 4. Pre-op and post-op TNF-α levels in all rat groups

	Control (C)		Sham (S)		PRP (P)		[b]p between groups	
	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
TNF-α	291±84 322 (60-374)	394±102 382 (258-645)	362±30 358 (294-402)	407±82 389 (307-569)	314±42 317 (220-369)	334±148 276 (179-622)	0.0030	0.0924
[a]p	0.0002		0.1506		0.4548			
					*Pre-op		<0.01, >0.05, <0.05	

group were higher than the preoperative TNF-α levels of the control and PRP groups (p<0.05).

The groups were analyzed in terms of IL-6 levels, it was found that the postoperative IL-6 levels of the control and sham groups were higher than the preop levels, unlike the PRP group (p<0.05) (Table 5). There was no statistical difference between the preoperative IL-6 levels of all three groups (p>0.05). Similarly, there was no statistical difference between the postoperative IL-6 levels of all three groups (p>0.05) (Table 5).

Discussion

PPAs is one of the major complications of abdominal surgery in children (1,2,3,4,5). The incidence of postoperative small bowel obstruction in children ranges from 2% to 30% and the incidence was 57% greater in neonates than in infants and children. Of all types of abdominal surgery, open colorectal surgery was found to result in the highest rate of adhesion-related readmissions (10,11). Unfortunately, there are not any devices able to totally prevent the intraperitoneal adhesion formation after abdominal surgery; only the use of correct surgical technique and the avoidance of traumatic intraperitoneal organ maneuvers may help to reduce postoperative adhesion incidence.

PPAs following abdominal surgery are among the most important causes of long-term morbidity. Therefore, studies on preventing PPAs are increasing day by day in the literature. PPAs can cause recurrent pain, intestinal obstructions, volvulus and infertility. For these reasons, patients need recurrent, outpatient or inpatient treatment, some patients even have to undergo surgery. In addition to the additional morbidity that this situation brings to patients, it is also reflected as a serious burden on health expenditures. A method that prevents the formation of PPA will eliminate repetitive surgeries and its morbidity and financial burden (12,13). In order to prevent PPA formation, it has been tried in many mechanical and physiological methods (14,15).

Platelet concentrates for topical and infiltrative use are used or tested as surgical adjuvants or regenerative medicine preparations in most of the medical fields, particularly in sports medicine and orthopedic surgery. These preparations are used on the surgical or wounded site in order to stimulate, improve and accelerate healing (12). Platelet-derived factors have been extensively used for clinical and surgical applications requiring tissue regeneration.

PRP has also been used in intra-abdominal operations. Since the positive effects of PRP on colon anastomosis has been shown in most of these studies and PRP has become a popular natural concentrate for wound healing

Table 5. Pre-op and post-op IL-6 levels in all rat groups

	Control (C)		Sham (S)		PRP (P)		[b]p between groups*	
	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
IL-6	29±8 29 (19-41)	58±34 42 (24-123)	34±7 36 (22-45)	52±22 45 (22-92)	31±3 32 (28-37)	42±22 32 (20-82)	0.2019	0.2053
[a]p	0.0012		0.0034		0.3110			

[a]Wilcoxon matched-paired test, [b]Kruskal-Wallis test (non-parametric ANOVA): The p-value is approximate (from chi-square distribution). * If p-value obtained by ANOVA is <0.05, p-values of between groups (respectively, C and S, C and P, and S and P) are compared with post-test and non-parametric data are given as mean, standard deviation and median (minimum-maximum). IL-6: Interleukin-6, PRP: Platelet rich plasma

Table 6. Comparison of control and PRP groups in terms of macroscopic and microscopic adhesion

		Control group n=12 (%)	PRP group n=12 (%)	p
Nair	Normal	9 (75)	8 (66.7)	0.383
	Oneband	2 (16.7)	2 (16.7)	
	Multiplebands	0	0	
	Organ adhesion	0	2 (16.7)	
	Dens ad	1 (8.3)	0	
Zuhlke	Normal	0	6 (50)	0.174
	Simple	6 (50)	2 (16.7)	
	Complex	3 (25)	1 (8.3)	
	Serious	1 (8.3)	2 (16.7)	
	Severe	2 (16.7)	1 (8.3)	

PRP: Platelet rich plasma

and anastomotic healing. Therefore, this study was planned to evaluate whether or not PRP prevents intra-abdominal adhesions.

PRP, is the name given to plasma in high platelet concentrations. There is no clear definition for this limit value, the average increase is considered to be "4-5 times" (14,16). PRP was first used by M. Ferrari (in 1987) as an autologous blood product transfusion component after open heart surgery. By using PRP, it is aimed to transfer biological molecules to the highest level of damaged tissue, which increases tissue regeneration in platelets. Due to its natural and reliable use, its popularity is increasing day by day. With recent studies, growth factors and cytokines in platelets include; it has been shown to be highly effective in inflammation, postoperative blood loss, infection and wound healing. In addition, platelets secrete bioactive proteins involved in macrophage and mesenchymal stem cell activation. Thus; not only they clean damaged and necrotic tissues, they also contribute to tissue regeneration and healing positively (17).

Alpha granules in platelets acts as a depot for growth factors in inactive state and cell growth, differentiation, cytokine release, angiogenesis; they show anti-apoptotic effect by stimulating collagen synthesis and chemotaxis. Complex interaction between growth factors and adhesion proteins such as fibronectin and vitronectin manage the regenerative process with chemotaxis, cell proliferation, tissue debris removal, angiogenesis and provides wound healing (18). In order to demonstrate the effect of PRP on PPA, PRP was applied to a group. As a result of the analysis, when the PRP group and the control group were compared, no statistical difference was observed.

Lymphocytes and macrophages; during mesothelial damage repair, they play an important role in the synthesis of growth factors that control fibroblast proliferation and collagen formation. Cytokines such as "platelet-derived growth factor", TGF-β, "fibroblast growth factor", IL-1, IL-6 and TNF-α can be counted among these. Peritoneal damage and microorganisms have been found to activate a large number of inflammatory mediators along with "early response cytokines" such as tumor TNF-α, IL-1, IL-6 by triggering cellular defense mechanisms of the host organism such as endotoxin. Future treatment strategies should aim to control cellular mediators in the peritoneal fluid at the beginning of the adhesion formation process (19). These mediators include IL-1α, TGF-α, EGF, TGF-β, IL-6 and TNF-α. In our study; in order to demonstrate the effect of PPA and cytokine levels, TNF-α and IL-6 results from samples taken before the procedure and before sacrification were examined. In subjects with high PPA formation; TNF-α and IL-6 levels were observed to be high. In the literature; there are studies supporting IL-10 to be adhesion preventive (20). TNF-α and IL-6 are thought to be used as markers in the PPA formation process.

Conclusion

In the experimentally generated adhesion model, the effect of PRP on preventing PPA formation could not be proved. TNF-α and IL-6 might be used as PPA formation markers.

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Ethics

Ethics Committee Approval: The study, an application was made to the Ankara Hospital SAUM Animal Experiments Ethics Committee. Ethics committee approval was obtained at the meeting of the board dated 22.09.2017 by unanimous decision with the decision number 44.

Informed Consent: Ethics committee approval was obtained as it was an animal experiment and it has been studied in accordance with the Helsinki Declaration.

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Authorship Contributions

Surgical and Medical Practices: G.D., H.T.T., Concept: G.D., Design: H.T.T., Data Collection or Processing: G.D., M.K., S.H., Analysis or Interpretation: G.D., P.C., Literature Search: G.D., H.T.T., Writing: G.D.

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