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Evaluation of Platelet Rich Fibrin Content Among Individuals With Different Blood Groups

Farklı Kan Grubuna Sahip Bireylerde Trombositten Zengin Fibrin İçeriğinin Değerlendirilmesi

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ABSTRACT

Objectives: Platelet Rich Fibrin (PRF), obtained by centrifuging the peripheral blood sample of the person is an autogenous material and can be affected by systemic and genetic characteristics of the belonging person. This study was undertaken for evaluating the effect of blood group types and the diverse preparation protocols on growth factors and cytokines contained in the PRF.
Methods: In total, 192 blood samples were taken from 64 donors, including 16 individuals from each blood group of 4, and from each individual 3 samples were taken for obtaining PRF, titanium platelet-rich fibrin (T-PRF), and concentrated growth factors (CGF). The platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), angiogenin (Ang), osteocalcin, and osteonectin contents of the PRF were measured with ELISA set.
Results: When the relationship between blood groups was examined, the results indicated that there were no statistically significant differences (*P*>.05). On the other hand, growth factor content was evaluated to be higher in T-PRF than PRF and CGF (*P*<.05).
Conclusion: These data clearly demonstrate that PRF, T-PRF and CGF preparations contain significant amounts of growth factors capable of stimulating wound healing. However, this content is independent of blood group distribution and depends on fibrin acquisition protocols.
Keywords; Blood group antigens; Enzyme-linked immunosorbent assay; Fibroblast growth factors; Osteocalcin; platelet-rich fibrin; Vascular endothelial growth factor

ÖZ

Amaç: Kişinin periferik kan örneğinin santrifüj edilmesiyle elde edilen Plateletten Zengin Fibrin (PRF), otojen bir materyal olup, kişinin sistemik ve genetik özelliklerinden etkilenebilmektedir. Bu çalışma, kan grubu tiplerinin ve çeşitli hazırlama protokollerinin PRF'nin içerdiği büyüme faktörleri ve sitokinler üzerindeki etkisini değerlendirmek amacıyla yapıldı.
Yöntem : Her 4 kan grubundan 16'şar kişi olmak üzere 64 donörden toplam 192 kan örneği alındı ve her kişiden PRF, titanyum trombositten zengin fibrin (T-PRF) ve konsantre büyüme faktörleri (CGF) elde etmek için 3'er örnek alındı. PRF'nin trombosit kaynaklı büyüme faktörü (PDGF), fibroblast büyüme faktörü (FGF), vasküler endotelyal büyüme faktörü (VEGF), anjiyogenin (Ang), osteokalsin ve osteonektin içerikleri ELISA seti ile ölçüldü.
Bulgular: Kan grupları arasındaki ilişki incelendiğinde istatistiksel olarak anlamlı bir fark olmadığı görüldü (*P*>.05). Büyüme faktörü içeriğinin ise T-PRF'de PRF ve CGF'ye göre daha yüksek olduğu değerlendirildi (*P*<.05).
Sonuç: Bu veriler PRF, T-PRF ve CGF preparatlarının yara iyileşmesini uyarabilen önemli miktarda büyüme faktörü içerdiğini açıkça göstermektedir. Ancak bu içerik kan grubu dağılımından bağımsızdır ve fibrin edinim protokollerine bağlıdır.
Anahtar Kelimeler; Kan grubu antijenleri; Enzim bağlı immünosorbent deneyi; Fibroblast büyüme faktörleri; Osteokalsin; trombosit açısından zengin fibrin; Vasküler endotelyal büyüme faktörü

INTRODUCTION

Intercellular interaction, local and systemic growth factors and various mediators are important stimuli in the development and regeneration of a tissue. It is necessary to understand the cellular and molecular events and mechanisms required to determine the regenerative treatment procedure in dentistry [1]. The oral cavity consists of hard and soft tissues originating from various tissue layers (ectodermal and mesodermal) [2]. Various materials of human, animal, and synthetic origin are used to support the regeneration of these tissues. Three-dimensional thrombocyte concentrates developed by Witman et al.[3] are one of these materials. Concentrated growth factor (CGF) is an autologous platelet concentrate that contains of platelets, leukocytes, stem cells and cytokines with in a complex three - dimensional fibrin network. The high tensile

strength and viscosity of CGF protects from proteolysis and prolongs release time of growth factors. Thus, it is suggested that CGF is a strong biomaterial with an integrated growth factor reservoir [4]. Autogenous platelet-rich fibrin (PRF) is obtained by centrifugation of peripheral blood samples in glass, titanium or special tubes at once without anti-coagulant or any biochemical process [5]. This fibrin layer is rich in platelets and leukocytes, as well as various growth factors and cytokines such as transforming growth factor-beta1 (TGF-β1), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), interleukin (IL)-1β, IL-4, and IL-6 [6]. In addition, when fibrin formed in the last stage of coagulation reactions combines with cytokines secreted by platelets, it acts as a matrix for the PRF and a reservoir for growth factors[7].

It has been known for a long time that blood has a vital importance for human beings. Shattock (1899) and Karl Landsteiner (1900) found that human blood differs from individual to individual in terms of some physiological properties. These different blood groups discovered are A, B and AB [8]. In 1902, Landsteiner's students Decastello, Sturli and Hectoen discovered the O blood group. The naming of these discovered blood groups was made in 1910 by Dungern and Hirszfeld [9].

Studies have shown that blood groups are associated with various diseases. Individuals with A blood group have gallstones, colitis and salivary gland tumors have been reported to be more prone [10]. It has been shown that O blood group is associated with duodenal ulcer disease, gastric ulcer and gastric carcinoma, especially with A, B and AB blood groups. Cardiovascular disease in subjects without blood group A and O found to be more prone [11]. It is thought that ABO blood subgroups and Rh factor may constitute a risk factor on the development of periodontal disease and the susceptibility to periodontitis increases in individuals with O blood group [12].

Like all autogenous materials, PRF [7] can be affected by systemic and genetic characteristics of the person from whom it is obtained. AB0 blood group phenotypes have an effect on platelet functions, platelet membrane lipids (Von Willebrand Factor (VWF), selectin, and Intercellular Adhesion Molecule (ICAM), and platelet glycoproteins (glycoprotein 1b/IX, glycoprotein 2b/3a) without affecting the platelet count [13]. There are also studies showing that the blood group phenotype affects the serum levels of endothelial adhesion molecules, including soluble P-selectin, E-selectin, ICAM-1, and intracellular, which affects endothelial-leukocyte interactions and the transition of leukocytes to the inflammation site [14].

It was seen clearly from the literature reviews that AB0 blood group phenotypes had an effect on leukocyte and platelet functions. The objective of this study was to evaluate the effect of blood group types on growth factors and cytokines contained in the PRF. In addition, the effect of the type of tube used while obtaining the fibrin sample on the fibrin content was determined.

METHODS

In terms of the methodology and the materials, this study was approved by the Ethics Committee of Atatürk University Faculty of Dentistry (Session Date: 11.01.2018, Decision No: 5) and supported by the Atatürk University Scientific Research Fund (Project ID: 6972, Project Code: TSA-2019-6972) as part of the Basic Research Project.

The study was carried out with volunteers between June to December in 2019; among the undergraduate students, clinical assistants and research assistants aged 20 to 35, from Atatürk University, Faculty of Dentistry. The sample size was obtained based on the Mohanty et al.[15] whose study examining the relationship between AB0 blood groups and plasma VWF level. In their findings, the effect width was found to be 1.111. The power analysis for the study indicated that 20 patients with 4 groups and a power range of 0.95 were sufficient in obtaining meaningful results. However, the number of patients in our study was taken to be 64, considering the adversities and differences that may occur during the study. Individuals included were over 18 years old and willing to provide in-formed consent. In addition, they did not have any systemic diseases and were not using any chronic anti-inflammatory drugs including anticoagulants.

Information on socio-demographic characteristics was obtained with the informed consent of volunteer donors. Volunteers were first divided into four groups based upon their blood group types, 16 participants each in 'AA, BB, AB, 0'. Three samples of blood were collected each of 64 volunteer donors (192 total samples).

- ***Platelet-rich fibrin preparation protocol***

To prepare fibrin samples 30 ml whole blood was taken from the venous vein. It was evenly transferred into glass, titanium and CGF tubes without having chemicals. To prepare the PRF, blood sample was centrifuged at 2700 rpm for 12 min[16] whereas titanium platelet-rich fibrin (T-PRF) was centrifuged at 3000 rpm for 10 min[17] in the PC-02 centrifuge (Hettich® EBA 20 centrifuge). Also, blood samples placed in CGF tubes were centrifuged for 13 minutes at varying speeds and angles between 2400 and 2700 rpm using The Silfradent Medifuge MF200 device (Silfradent S. R. L., Santa Sofia, Italy)[18]. At the end of the centrifugation, three parts were obtained in the tube; red blood cells at the bottom, platelet-poor plasma at the top and fibrin layers also called "buffy coat" in the middle part[5]. The obtained fibrin tissue was put into the eppendorf tubes and placed in a cabinet at -80 degrees until it was taken for biochemical analysis.

Before the biochemical analysis, the samples were taken into a +4 degrees. The concentrations of PDGF, Fibroblast Growth Factor (FGF), VEGF, Angiogenin (Ang), Osteocalcin and Osteonectin in PRF, T-PRF, and CGF samples were determined using human Enzyme-Linked Immunosorbent Assay kits (ELISA- SunLong Biotech Co., LTD, Hangzhou, Zhejiang, China).

- ***Statistical analysis***

The statistical analysis was performed using a commercially available software program (SPSS 22.0 SPSS Inc., Chicago, IL). The data were reported as the mean value ± standard deviation (SD). Tukey's multiple comparison test was used to determine the difference between groups as a result of one-way analysis of variance (ANOVA). For statistical significance, p values <0.05 were accepted.

RESULTS

A total of 64 individuals, 38 females and 26 males, with a mean age of 24.9 ± 3.15 were included in the study. The participants do not have any systemic discomfort or any systemic medication used.

The result of this study indicated that the fibrin content does not differ according to the blood type. There were no statistically significant differences in the PDGF, FGF, VEGF, Ang, osteocalcin and osteonectin of the PRF, T-PRF or CGF obtained from the blood samples of different blood groups at p > 0.05 (Table 1-2).

In a first set of experiments, based upon gender distribution, although it was observed that the averages of the PDGF, FGF, and VEGF were higher in females compared to males, the differences between the means were not statistically significant (*P*> .05) (Table 3). Similarly, there was no statistically significant difference between the smokers and non-smokers in terms of measured values (*P*> .05) (Table 4).

When the relationship between WBC levels and PDGF, FGF and VEGF markers of the participants was examined, it was determined that there was a negative relationship (*P*<.05 for PDGF, p<0.01 for FGF-1 and VEGF) (Table 5).

The concentrations of growth factors in PRF, T-PRF, and CGF preparations are shown in Figure 1,2, and 3. Significantly, all growth factors investigated demonstrated a significantly higher from T-PRF when compared to PRF and CGF (*P*<.05). However, there were no significant differences between the growth factor contents of the PRF and CGF samples (*P*>.05). When the fibrin samples were examined, although a difference in terms of growth factor contents was obtained, there was no statistically significant difference between the other parameters (ang, osteonectin, and osteocalcin) at *P*> .05.

Table 1. The ANOVA results for the PDGF, FGF, VEGF, angiogenin, osteocalcin, and osteonectin ratios of blood groups and the PRFs.

		Sum of Squares	df	Mean Square	F	Sig.
OT marker	Between Groups	791484.411	3	263828.137	0.934	0.430
	Within Groups	16949875.241	60	282497.921		
	Total	17741359.653	63			
ANG marker	Between Groups	418848517.820	3	139616172.607	0.463	0.709
	Within Groups	18096391243.376	60	301606520.723		
	Total	18515239761.196	63			
ON marker	Between Groups	1562.082	3	520.694	0.626	0.601
	Within Groups	49924.449	60	832.074		
	Total	51486.530	63			
PDGF marker	Between Groups	10343375.037	3	3447791.679	0.341	0.796
	Within Groups	606791567.830	60	10113192.797		
	Total	617134942.868	63			
FGF-1 marker	Between Groups	29471.671	3	9823.890	0.269	0.847
	Within Groups	2187650.073	60	36460.835		
	Total	2217121.744	63			
VEGF marker	Between Groups	262367.889	3	87455.963	0.309	0.819
	Within Groups	16975684.181	60	282928.070		
	Total	17238052.069	63			

OT: Osteocalcin
ANG: Angiogenin
ON: Osteonectin
PDGF: Platelet-derived growth factor
FGF: Fibroblast growth factor
VEGF: Vascular endothelial growth factor
PRF: Platelet-rich fibrin

Table 2. Levels of growth factors according to blood groups

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean Lower Bound	Upper Bound	Minimum	Maximum
PDGF marker	A	16	3269,0881	3127,86130	781,96532	1602,3685	4935,8078	388,40	13013,28
	B	16	4137,5675	3943,79508	985,94877	2036,0674	6239,0676	367,37	14630,10
	AB	16	3792,3356	3198,25265	799,56316	2088,1071	5496,5642	344,79	11803,90
	0	16	3139,6438	2210,63685	552,65921	1961,6785	4317,6090	406,78	6734,95
	Total	64	3584,6588	3129,82312	391,22789	2802,8522	4366,4653	344,79	14630,10
FGF-1 marker	A	16	222,1075	139,47160	34,86790	147,7883	296,4267	27,41	443,38
	B	16	276,8125	244,19533	61,04883	146,6900	406,9350	23,76	772,27
	AB	16	240,2581	184,28278	46,07070	142,0608	338,4555	28,04	549,34
	0	16	226,7556	181,10635	45,27659	130,2509	323,2604	30,13	619,42
	Total	64	241,4834	187,59640	23,44955	194,6233	288,3436	23,76	772,27
VEGF marker	A	16	437,2881	321,12939	80,28235	266,1703	608,4059	39,40	981,48
	B	16	526,9425	451,09584	112,77396	286,5705	767,3145	29,85	1226,92
	AB	16	512,6300	490,48615	122,62154	251,2684	773,9916	31,53	1620,98
	0	16	617,4975	764,54174	191,13543	210,1020	1024,8930	49,25	3153,86

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
PDGF value	Between Groups	10343375,037	3	3447791,679	,341	,796
	Within Groups	606791567,830	60	10113192,797		
	Total	617134942,868	63			
FGF-1 value	Between Groups	29471,671	3	9823,890	,269	,847
	Within Groups	2187650,073	60	36460,835		
	Total	2217121,744	63			
VEGF value	Between Groups	262367,889	3	87455,963	,309	,819
	Within Groups	16975684,181	60	282928,070		
	Total	17238052,069	63			

PDGF: Platelet-derived growth factor
FGF: Fibroblast growth factor
VEGF: Vascular endothelial growth factor

Table 3. Effect of gender on PDGF, FGF and VEGF markers

Group Statistics

	Gender	N	Mean	Std. Deviation	Std. Error Mean
PDGF marker	Female	38	4190,0276	3485,78492	565,46898
	Male	26	2699,8888	2308,93909	452,82021
FGF-1 marker	Female	38	265,9742	181,82041	29,49517
	Male	26	205,6892	193,68501	37,98476
VEGF marker	Female	38	609,2737	588,11412	95,40471
	Male	26	398,3588	387,49553	75,99413

	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference
PDGF marker	3,018	,087	1,910	62	,061	1490,13879	780,36219
			2,057	61,960	,044	1490,13879	724,43172
FGF-1 marker	,108	,743	1,269	62	,209	60,28498	47,51654
			1,254	51,569	,216	60,28498	48,09165
VEGF marker	1,415	,239	1,604	62	,114	210,91484	131,50186
			1,729	61,942	,089	210,91484	121,97199

PDGF: Platelet-derived growth factor
FGF: Fibroblast growth factor
VEGF: Vascular endothelial growth factor

Table 4. The effect of smoking status on PDGF, FGF and VEGF markers

Group Statistics

	Smoking status	N	Mean	Std. Deviation	Std. Error Mean
PDGF marker	No	43	3829,9160	3352,40966	511,23768
	Yes	21	3082,4652	2619,43656	571,60792
FGF-1 marker	No	43	242,2914	162,81545	24,82912
	Yes	21	239,8290	234,91101	51,26178
VEGF marker	No	43	506,6477	391,03828	59,63278
	Yes	21	558,2800	734,10417	160,19466

	F	Sig.	t	df	Sig. (2 -tailed)	Mean Difference	Std. Error Difference
PDGF marker	,155	,695	,896	62	,374	747,45081	834,54325
			,975	49,662	,334	747,45081	766,87651
FGF-1 marker	4,137	,046	,049	62	,961	2,46235	50,34272
			,043	29,706	,966	2,46235	56,95837
VEGF marker	3,970	,051	-,368	62	,714	-51,63233	140,22325
			-,302	25,692	,765	-51,63233	170,93390

PDGF: Platelet-derived growth factor
FGF: Fibroblast growth factor
VEGF: Vascular endothelial growth factor

Table 5. Correlation relationship between WBC value and PDGF, FGF and VEGF markers

Correlations

		WBC value	PDGF marker
WBC value	Pearson Correlation	1	-,304*
	Sig. (2-tailed)		,028
	N	52	52
PDGF marker	Pearson Correlation	-,304*	1
	Sig. (2-tailed)	,028	
	N	52	64

*. Correlation is significant at the 0.05 level (2-tailed).

Correlations

		WBC value	FGF-1 marker
WBC value	Pearson Correlation	1	-,380**
	Sig. (2-tailed)		,005
	N	52	52
FGF-1 marker	Pearson Correlation	-,380**	1
	Sig. (2-tailed)	,005	
	N	52	64

**. Correlation is significant at the 0.01 level (2-tailed).

Correlations

		WBC value	VEGF marker
WBC value	Pearson Correlation	1	-,366**
	Sig. (2-tailed)		,008
	N	52	52
VEGF marker	Pearson Correlation	-,366**	1
	Sig. (2-tailed)	,008	
	N	52	64

**. Correlation is significant at the 0.01 level (2-tailed).

WBC: White Blood Cell
PDGF: Platelet-derived growth factor
FGF: Fibroblast growth factor
VEGF: Vascular endothelial growth factor

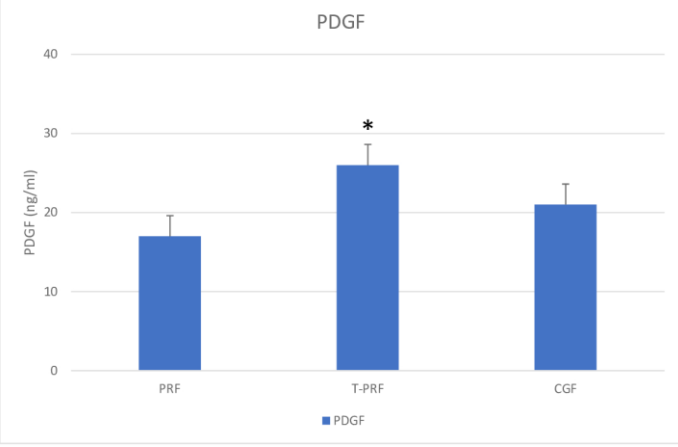

Figure 1. PDGF contents according to the method of obtaining fibrin tissue
*p < 0.05 significantly higher than all other groups.
PDGF: The platelet-derived growth factor
PRF: Platelet rich fibrin
T-PRF: Titanium platelet-rich fibrin
CGF: Concentrated growth factors

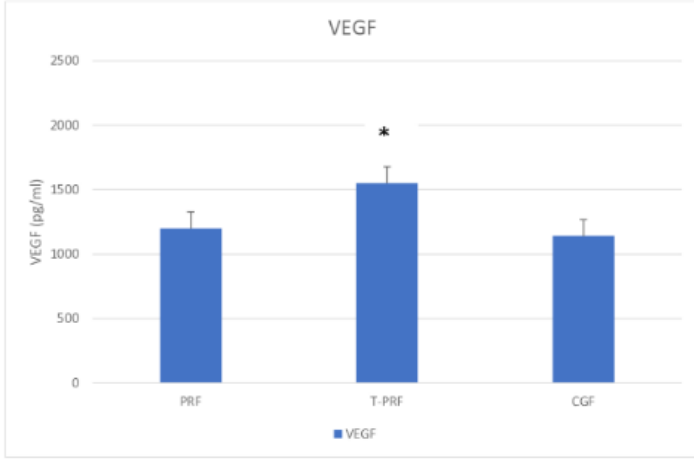

Figure 2. VEGF contents according to the method of obtaining fibrin tissue
*p < 0.05 significantly higher than all other groups.
VEGF: Vascular endothelial growth factor
PRF: Platelet rich fibrin
T-PRF: Titanium platelet-rich fibrin
CGF: Concentrated growth factors

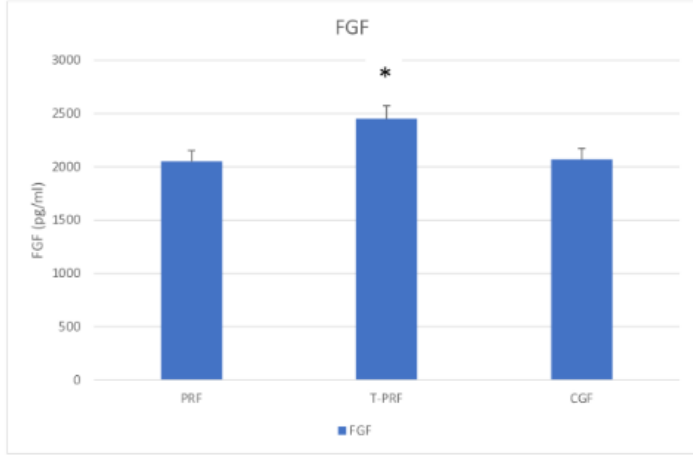

Figure3. FGF contents according to the method of obtaining fibrin tissue
*p < 0.05 significantly higher than all other groups.
FGF: Fibroblast growth factor
PRF: Platelet rich fibrin
T-PRF: Titanium platelet-rich fibrin
CGF: Concentrated growth factors

DISCUSSION

The tooth is a whole with the hard and soft tissues around it. Many materials are used to protect the health of these tissues, to prevent disease formation or to treat the existing disease. PRF, which is a biomaterial, is frequently preferred for protective and regenerative processes. Many studies on the PRF have been examined in the literature, but no study has been found that examines the effects of blood group on the PRF. This clinical research is a pilot study evaluating the effect of blood groups on the content of the PRF.

PRF is a fibrin clot that can be used as a membrane that slowly releases various growth factors and cytokines factor into its environment during wound healing[19,20]. It has been shown by several independent studies that PRF contains PDGF, FGF and VEGF[21-24] that are effective on wound healing[25]. PRF is also involved in bone regeneration with osteonectin and osteocalcin in its content[26]. For this reason, these growth factors and mediators were included in our research.

Gil'miiarova et al.[27] investigated the relationships between AB0 blood groups and humoral immune parameters. In individuals with chronic generalized periodontitis, the highest Immunoglobulin A (IgA) (against transglutaminase) content was found in patients with A blood group, while the lowest content was found in AB blood group patients. In our study, growth factors and cytokine contents of the PRF obtained from individuals from different blood groups were examined, but no statistically significant difference was found.

Arabacı and Albayrak[28] evaluated the release of growth factor, osteoprotegerin (OPG) and receptor activator nuclear kappa B (RANKL) in gingival fluid and examined wound healing by applying T-PRF together with flap surgery in patients with chronic periodontitis. In the T-PRF used study group, the growth factor level was reported to be high until the 6th week after the surgical procedure, and the RANKL/OPG ratio was reported to be low, and recovery was better. Similarly, in this study, considering the fibrin diversity, it was determined that T-PRF is richer in terms of growth factors.

In a study evaluating the effect of the number of cycles per minute of the centrifuge device (rpm) on the growth factors in the PRF, three protocols were determined by keeping the centrifuge time constant; I: 710 g; 2400 rpm; 8 minutes, II: 177 g; 1200 rpm; 8 minutes III: 44 g; 600 rpm; 8 minutes. Blood samples were taken from six healthy volunteers (3 males and 3 females) for each of these protocols evaluated. The first protocol-I (710 g) centrifuged at the highest speed showed the lowest leukocyte count among the three experimental protocols. The protocol-III (44 g) was found to be statistically significantly higher in leukocyte count, the TGF-and VEGF concentration compared to protocol-I. As a result of automatic cell counting, the total platelet count tended to increase with the decrease in the number of cycles[29]. Similarly, Choukroun et al.[30] showed that it was possible to enrich the amount of leukocytes, platelets and growth factors in the PRF matrix structure by making a single change in the centrifugation settings within the clinical routine. In our study, the growth factor content of T-PRF was found to be more intense when PRF (2700 rpm/ 12 min.) and T-PRF (3000 rpm/10 min.) obtained in the same centrifuge device with different cycles and time were compared.

Kim et al. evaluated the effect of platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and concentrated growth factor (CGF) on bone healing. It was determined that fibrin samples had significant contributions in wound healing, but this did not make a significant difference with the control group[18]. In another study in which the effect of T-PRF and PRF on the healing of intrabony defects was evaluated with clinical parameters, no significant difference was found between fibrin samples[17]. In another study in which concentrations of growth factors (TGF-β1, PDGF-BB, VEGF) and pro-inflammatory cytokines (IL-1β, IL-6) were evaluated, the order of growth factor levels (TGF-β1, PDGF-BB, VEGF) were advanced PRF (A -PRF) ≥ CGF> PRP (P<.05). IL-1β and IL-6 were determined at similar levels (P>.05)[21]. In our study, T-PRF content was found higher than PRF and CGF in terms of growth factors. There was no significant difference in terms of other parameters.

Study Limitations

The study has a limited number of patients. Also, analyzing additional growth hormones and cytokines could be useful in examining the relationship between blood type and fibrin tissue.

CONCLUSION

In this pilot study on evaluating the effect of blood groups on growth factors and cytokines in the PRF content, no significant differences in the measured parameters between the blood group types were obtained (p> 0.05). It is suggested to use of T-PRF for periodontal regeneration for getting more positive results since it contains more intense growth factor as compared to the other fibrin samples. However, long-term studies are needed to make a more comprehensive assessment of the effects of ABO group on growth factors and cytokines in the PRF content.

Etik Komite Onayı: Bu çalışma, yöntem ve materyal açısından Atatürk Üniversitesi Diş Hekimliği Fakültesi Etik Kurulu tarafından onaylanmış (Oturum Tarihi: 11.01.2018, Karar No: 5)
Hasta Onamı: Sosyo-demografik özelliklere ilişkin bilgiler gönüllü bağışçıların bilgilendirilmiş onamları ile elde edildi.
Hakem Değerlendirmesi: Dış bağımsız.
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Informed Consent: Information on socio-demographic characteristics was obtained with the informed consent of volunteer donors.
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