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Research article

Comparison of indicators of autologous serum obtained by different methods and used for the treatment of macular hole

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BACKGROUND: In recent years, autologous serum has been increasingly used in the treatment of macular hole. The study carried out a biological analysis of autologous serum obtained by various methods.

AIM: The aim of the investigation is to compare the cellular and biochemical composition of autologous serum obtained using different methods for use in the macular hole treatment.

MATERIALS AND METHODS: The study of the number of platelets, leukocytes and fibrinogen level in the blood serum of 24 patients obtained by centrifugation in original systems for harvesting autologous serum and laboratory test tubes was performed.

RESULTS: : The indices of P-PRP obtained in the Arthrex ACP system and in a laboratory test tube do not statistically differ in quantitative indices of fibrinogen and platelets ($p < 0.05$), and differ in the content of leukocytes ($p > 0.05$) in the direction of increasing the number of leukocytes in the substrate obtained in a laboratory test tube. The indicators of L-PRP obtained in the Ycellbio-Kit system and in a laboratory test tube do not statistically differ in the amount of fibrinogen ($p < 0.05$) and differ in the content of platelets and leukocytes ($p > 0.05$) in the direction of decreasing the concentration of leukocytes and platelets in the autologous serum obtained in a laboratory test tube.

CONCLUSIONS: Currently, autologous serum obtained in the Arthrex ACP system is of great interest for macular hole surgery due to the minimal content of leukocytes, the closed character of the system, and the best coagulation properties of the substrate obtained. Laboratory test tubes may be considered a more affordable alternative for the production of autologous serum (P-PRP) for the treatment of macular hole. The autologous serum (L-PRP) obtained in the Ycellbio-Kit system and in a laboratory test tube is less suitable for macular hole surgery according to its composition.

Keywords: autologous serum; macular hole; P-PRP; L-PRP; autologous conditioned serum; ACS.

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Научная статья

Сравнение показателей получаемой разными способами аутоплазмы, используемой для лечения пациентов с макулярным разрывом

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Актуальность. В последние годы в лечении пациентов с макулярным разрывом всё чаще применяют аутологичную плазму крови. В исследовании проведён биологический анализ аутоплазмы, получаемой различными способами.

Цель исследования — сравнить клеточный и биохимический состав аутоплазмы, получаемой с помощью разных способов для использования в лечении пациентов с макулярным разрывом.

Материалы и методы. Выполнено исследование количества тромбоцитов, лейкоцитов и фибриногена в плазме крови 24 пациентов, полученной центрифугированием в оригинальных системах для заготовки аутоплазмы и в лабораторных пробирках.

Результаты. Показатели P-PRP, полученной в системе Arthrex ACP и в лабораторной пробирке, статистически не отличаются по количественным показателям фибриногена и тромбоцитов ($p < 0,05$) и отличаются по содержанию лейкоцитов ($p > 0,05$) в сторону увеличения количества лейкоцитов в субстрате, полученном в лабораторной пробирке. Показатели L-PRP, полученной в системе Ycellbio-Kit и в лабораторной пробирке, статистически не отличаются по количеству фибриногена ($p < 0,05$) и отличаются по содержанию тромбоцитов и лейкоцитов ($p > 0,05$) в сторону понижения их концентрации в аутоплазме, получаемой в лабораторной пробирке.

Заключение. Большой интерес для хирургии макулярного разрыва в настоящее время представляет аутоплазма, получаемая в системе Arthrex ACP по причине минимального содержания лейкоцитов, закрытости системы, лучших коагуляционных свойств получаемого субстрата. Лабораторные пробирки можно рассматривать как более доступную альтернативу для получения аутоплазмы (P-PRP) в целях лечения макулярного разрыва. Аутоплазма (L-PRP), получаемая в системе Ycellbio-Kit и лабораторной пробирке по своему составу в меньшей мере подходит для хирургии макулярного разрыва.

Ключевые слова: аутоплазма; макулярный разрыв; P-PRP; L-PRP; аутологичная кондиционированная плазма; ACP.

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ЭКО•ВЕКТОР

BACKGROUND

In recent years, treatment methods using autologous serum with increased platelet concentration gain ground in medicine, in particular in ophthalmology [1–3]. The therapy with such serum is a safe treatment method, and indications for its use are steadily on the rise [4]. Thus, these technologies may be used in macular hole surgery, rhegmatogenous retinal detachment surgery, in corneal diseases [5–8].

At the ophthalmology chair name after Professor V.V. Volkov of the Military Medical Academy named after S.M. Kirov, studies are carried out on the reparative ability of autologous serum with increased platelet concentration in macular hole surgery [9].

In modern Russian literature, there are multiple publications on the use of autologous serum with increased platelet concentration in clinical ophthalmology, but there are no common terminology and no common understanding concerning the features of obtained serum preparations depending on their cellular composition and on the fibrinogen activated state [10–12].

Following the classification proposed by M. Dohan Ehrenfest, et al. [13], four main groups of serum preparations with increased platelet concentration according to their cell composition and fibrinogen activation.

1. P-PRP – pure platelet-rich plasma, or leucocyte-poor plasma. Products of this group have low viscosity, are practically devoid of leucocytes and contain an increased concentration of platelets (platelet concentration increases 2–3-fold from the initial content in blood), fibrinogen in them is not activated. P-PRP products are widely used in clinical medicine (traumatology, sports medicine, cosmetology, dermatology), including the use in ophthalmologic practice. A commercial P-PRP product is ACP (autologous conditioned plasma), obtained using an original system Arthrex ACP double syringe system (Arthrex, Germany).

2. L-PRP (leucocyte-platelet-rich plasma) is a group of serum preparations, enriched in platelets, which the same as P-PRP, have low viscosity, fibrinogen in them is not activated, but they have higher concentration of platelets 3, 4 times higher than the initial concentration), and higher leucocyte content. L-PRP is also widely used in different areas of clinical medicine including ophthalmology. It is for procuring of this family of serum preparations, maximal number of systems exists, which allow to minimize the processing of blood samples and maximally standardize the obtained substrate. The original system for plasma harvesting Ycellbio-Kit (Ycellbio Medical, Korean Republic) is a part of the group.

3. P-PRF (pure platelet-rich fibrin) – fibrin preparations with increased platelet content, practically do not contain leucocytes and have activated fibrinogen with high density fibrin net.

4. L-PRF (leucocyte-platelet-rich fibrin) – fibrin preparations with increased platelet and leucocyte content, having activated fibrinogen with high density fibrin net.

P-PRF and L-PRF possess high viscosity, exist only as a gel form. They are used in the reconstructive osteoplastic surgery, abdominal surgery, urology, combustiology. In ophthalmology, they come into use as fibrin glues in the reconstructive surgery of the ocular surface.

Currently, in clinical ophthalmology, two original systems for procurement of autologous serum with increased platelet content – Arthrex ACP and Ycellbio-Kit – gained more wide use. These systems may be not always available for use due to several reasons. This gave us an idea to look for more affordable methods to procure autologous plasma with increased platelet content to be used in vitreoretinal surgery of a macular hole.

The aim of the study – to compare the cellular and the biochemical composition of the autologous serum obtained by different methods – to be used in treatment of patients with a macular hole.

MATERIALS AND METHODS

24 volunteers (12 men, and 12 women) were included into the study from among patients and the team members of the Military Medical Academy ophthalmology department, without systemic diseases at the destabilization stage, anemia of any origin, and not taking any anticoagulants and antiplatelet therapy (according to clinical blood testing and coagulogram results, in the studied group, there were no deviation from normal values). The mean age of study participants was 41 ± 17 years.

Each individual was subject to blood sampling in the conditions of a blood collection room at a room temperature of 20–22 °C, from a peripheral vein, a continuous blood sampling of 54 ml was performed into a 60 ml syringe prefilled with 6 ml anticoagulant (sodium citrate – 2,2%, glucose – 2,45%, citric acid – 0,8%). ACD-A is one out of anticoagulants for autologous serum sampling recommended for clinical ophthalmology, and the blood to the anticoagulant ratio 9 : 1 corresponds to recommendations of manufacturers of autologous plasma sampling systems Arthrex ACP and Ycellbio-Kit and to those on laboratory diagnosis (laboratory serum testing without anticoagulant is difficult because of the coagulation development within a short time and the bias of the study results) [14–16]. After sampling, the blood was mixed with the anticoagulant by the rotational syringe motion during 30 sec and moved to systems for autologous plasma sampling and to laboratory tubes.

After centrifugation, in the obtained substrate, the number of platelets, leucocytes and fibrinogen was analyzed. The results were processed using standard instruments of descriptive statistics Microsoft Office Excel 2016. Parameters are presented as $M \pm SD$, where M is a mean

value, and *SD* – standard deviation. To determine the confidence paired Student *t*-test for dependent samples was used. For control, investigated parameters were also determined in the venous blood with anticoagulant. Quantitative parameters of the cellular composition were investigated using a hematologic analyzer BC Mindray 5800 (Shenzhen Mindray, China), parameters of the blood coagulation system – using an automatic coagulometer ACL TOP 500 (Instrumentation Laboratory, USA).

Investigation of the autologous plasma rich in platelets and poor in leucocytes (P-PRP)

P-PRP for the investigation was obtained by two methods: using the Arthrex ACP system and a laboratory test-tube.

P-PRP acquisition using the Arthrex ACP system. Into the Arthrex ACP system, 15 ml of blood with anticoagulant were introduced, and further acted according to the system producer's recommendations. The investigation was carried out using the centrifuge Rotofix 32A (Hettich, Germany) at a speed 1500 rpm during 5 min. After centrifugation, the serum was collected in the system's vertical position by means of pulling the internal syringe plunger, not reaching 1.5 mm from the red blood cell level. With this method, on average 5.1 ± 1.2 ml of serum were collected (Fig. 1).

P-PRP acquisition using a laboratory test-tube. Into the test-tube of 12 ml capacity, 10 ml of blood with anticoagulant were introduced and centrifuged in the Multi Centrifuge CM 6M (Elmi, Latvia) at 1500 rpm speed during 5 min. After centrifugation, the serum was withdrawn into a 5 ml syringe through an injection needle 22 Ga 40 mm, not reaching 1.5 mm to red blood cell level. I such a way, in average 3.9 ± 0.8 ml of serum were got (Fig. 2).

Investigation of the autologous plasma rich in platelets and in leucocytes (L-PRP)

L-PRP for investigation was got by two methods: using Ycellbio-Kit system and using laboratory tube.

L-PRP acquisition using the Ycellbio-Kit system. Into the Ycellbio-Kit system, 14 ml of blood with an anticoagulant were brought without regard to sex, and further, proceeded according to the manufacturer's recommendations [15]. For the investigation, a centrifuge Armed 80–2S ("Armed", Russia) was used with the speed 3500 rpm during 5 min. After centrifugation, the platelet-leucocyte layer concentrates in the narrow part of the system, between the red blood cell layer and that of the serum. The platelet-leucocyte cellular poll together with the serum was withdrawn into the 5 ml syringe through an injection needle 22 Ga 40 mm in 1.5 ml volume. For maximal aspiration of cell elements, the layer of platelets and leucocytes was gently shaken up by rotational movements of the injection needle (Fig. 3).

L-PRP acquisition using the laboratory tube. In to a 12 ml tube, 10 ml of blood with an anticoagulant were brought, and then centrifugated in the Centrifuge CM 6M at a 1500 rpm speed during 5 min. After centrifugation, the serum was withdrawn into a 5 ml syringe through an injection needle 22 Ga 40 mm, not reaching 1.5 mm to red blood cell level, and further brought into a 12 ml tube, and centrifugation using the same centrifuge was performed at 2800 rpm during 2 min. At increased speed and/or duration of the centrifugation, the activation of platelets occurs with insoluble clot formation (Fig. 4). At decreased speed and/or duration of the centrifugation, in the obtained substrate, the number of platelets decreases.

After centrifugation, cellular elements shift towards the bottom of the tube, and are seen as greyish-red deposit.

The upper 2/3 of the poor in platelets and leucocytes serum were aspirated, in the tube, there was only 1/3 of serum rich in platelets and leucocytes. Sedimented cellular elements were transduced into the solution by accurate oscillating motions of the tube. In average, 1.3 ± 0.3 ml of plasma were obtained with such method.

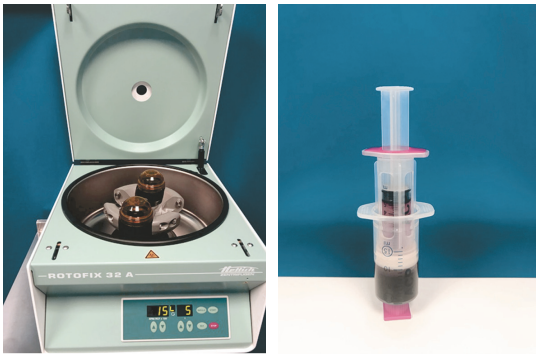

Fig. 1. The Rotofix 32A centrifuge and the Arthrex ACP system for producing autologous conditioned serum
Рис. 1. Центрифуга Rotofix 32A и система Arthrex ACP для получения аутологичной кондиционированной плазмы

Fig. 2. Multi Centrifuge CM 6M centrifuge and laboratory test tube for producing platelet-rich autologous serum
Рис. 2. Центрифуга Multi Centrifuge CM 6M и лабораторная пробирка для получения богатой тромбоцитами аутоплазмы


Fig. 3. The Armed 80-2S centrifuge and the Ycellbio-Kit system for producing platelet-rich autologous serum
Рис. 3. Центрифуга Armed 80-2S и система Ycellbio-Kit для получения богатой тромбоцитами аутоплазмы

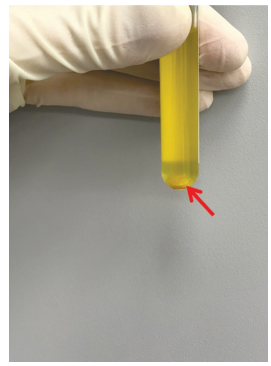


Fig. 4. Precipitated blood cell elements (indicated by arrow), and obtained L-PRP
Рис. 4. Клеточные элементы крови (указаны стрелкой), выпавшие в осадок и полученная L-PRP

STUDY RESULTS

Quantitative indices of fibrinogen, platelets and leucocytes of the autologous serum, obtained by different methods, are shown in the table.

The studied indices of P-PRP, obtained in the Arthrex ACP system and in a laboratory tube do not have statistically significant differences concerning quantitative indices of fibrinogen and platelets ($p < 0.05$) and have significant differences in leucocyte content ($p > 0.05$) in the direction if their increase in number in the substrate obtained in a laboratory tube. The compared L-PRP indices of plasma obtained both in the Ycellbio-Kit system and a laboratory tube do not show statistically significant differences concerning the amount of fibrinogen ($p < 0.05$) and differ in number of platelets and leucocytes ($p > 0.05$) towards their concentration decrease in the autologous serum obtained in a laboratory tube.

DISCUSSION

According to several authors, the most important autologous plasma indices that determine the ability to form a platelet-fibrin "plug" in the macular hole diastasis and platelet-fibrin film on the macular retina surface, are the fibrinogen and platelets [17, 18], which, being physiological factors of the hemostasis and of vascular wall recovery, assure more delicate in comparison to mechanical techniques closure of the macular hole. Growth factors of the platelet α-granules assure the damaged tissue recovery, at that the intensity of the reparatory activity depends on the platelet concentration. It is believed that the maximal reparatory effect of the autologous serum is reached at platelet concentration in it starting from 1 million cells in 1 mcl [19]. To the contrary, inflammation mediators of leucocytes could adversely affect the macular hole area causing retinal alteration, edema, and ischemia, at the same time, the expression of inflammatory manifestations is in direct proportion to the leucocyte concentration in the autologous serum [20].

Obtained in a laboratory tube P-PRP has more leucocytes, and this may increase the inflammatory reaction risk in vitreal surgery, and taking into account that in autologous plasma acquisition using a laboratory tube, there is a contact of the blood with the outside environment, the possibility of the substrate microbial contamination increases, making higher the probability of postop infectious inflammatory complications.

L-PRP, obtained in a laboratory tube, along with the decrease of leucocyte concentration, contains less

Table. The average amount of fibrinogen, platelets and leukocytes in venous blood with anticoagulant and autologous serum obtained by various methods

Таблица. Среднее количество фибриногена, тромбоцитов и лейкоцитов в венозной крови с антикоагулянтом и аутоплазме крови, полученной различными способами

Method	Fibrinogen, g/l	Platelets, $\times 10^9$/l	Leucocytes, $\times 10^9$/l
Control indices of venous blood with anticoagulant	3.51 ± 0.68	203.83 ± 42.05	5.39 ± 1.24
Indices of P-PRP obtained in the Arthrex ACP system	3.57 ± 0.56	451.17 ± 114.32	0.48 ± 0.74
Indices of P-PRP obtained in laboratory tube	3.56 ± 0.59	454.33 ± 104.90	0.85 ± 0.56
Indices of L-PRP obtained in the Ycellbio-Kit system	3.30 ± 0.64	740.08 ± 209.26	3.57 ± 1.87
Indices of L-PRP obtained in laboratory tube	3.42 ± 0.64	643.67 ± 163.51	1.45 ± 0.79

platelets, and this from one side, may diminish the inflammatory response to the injection into tissues, and from the other side, decreases the autologous serum reparative activity.

A not unimportant aspect of the autologous serum coagulative activity is a presence or absence of anticoagulant. Thus, the protocol of the autologous plasma acquirement in the Arthrex ACP system allows obtaining a substrate without anticoagulant's use, and at the same time fibrinogen concentration and that of cellular elements increase, and the coagulation capacity increases. Same properties are characteristic for the autologous serum (P-PRP), obtained without anticoagulant in a laboratory tube. The protocol of the autologous plasma acquisition using the Ycellbio-Kit system without anticoagulant in the laboratory tube is not fore see, that is why serum obtained in the Ycellbio-Kit system would have admittedly inferior procoagulation capacities.

CONCLUSION

Data obtained as a result of the study testify that nowadays the maximal interest for macular hole surgery represents autologous serum, received in the Arthrex ACP system, due to the fact that it has minimal leucocyte content, maximal protection of the system from external influences, possibility to obtain autologous serum without anticoagulant. Laboratory tubes may be considered as a more affordable alternative for P-PRP acquirement aim to treat patients with macular hole but with undoubted higher risk of inflammatory complications development. The autologous serum received in Ycellbio-Kit system to a lesser extent is suitable for macular hole surgery, for higher leucocyte content, necessity to use anticoagulant at acquirement, difficulty of technological process of acquirement. L-PRP, obtained in a laboratory tube, has similar shortcomings with autologous serum, obtained in the Ycellbio-Kit system, and as well hardly suitable for macular hole surgery.

Thus, in spite multiple carried out studies in the field of autologous serum acquirement with the aim of macular hole surgery, the search continues for autologous plasma preparation with optimal characteristics, combining low viscosity before use, ability to form a platelet-fibrin "plug" in the macular hole diastasis and to stimulate maximal reparatory effect.

ADDITIONAL INFORMATION

Input of authors. All authors confirm the conformity of their authorship to the international ICMJE criteria (all authors significantly contributed to the concept development, study implementation, and article preparation, read and confirmed the final version before publishing).

Conflict of interests. Authors declare the absence of obvious and potential conflict of interests related to publishing of the present article.

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