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FREEZE-DRIED PLASMA FOR EMERGENCY TRANSFUSION CARE IN EXTREME CONDITIONS

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Introduction. In the context of limited availability of fresh frozen plasma, the use of freeze-dried plasma offers significant logistical advantages in extreme conditions. The effectiveness of freeze-dried plasma depends on the preservation of coagulation potential in the manufacturing process.
Objective. Review of research achievements both in Russia and aboard in the field of freeze-dried plasma technologies, including manufacturing, quality control, and blood component application.
Discussion. Commercial products such as FLyP, LyoPlas N-w, Bioplasma FDP, OctaplasLG Lyo, as well as freeze-dried plasma (Belarus or China), which have proven their effectiveness and safety, are available in glass vials. The production of freeze-dried plasma in polymer containers using membrane technology is a promising direction offering the advantage of using blood components in extreme conditions. The freeze-dried plasma products developed by Terumo BCT Biotechnologies and Teleflex Inc. are currently undergoing clinical trials and are used in military operations to a limited extent. In the Russian Federation, the Lyokon polymer container has been registered. During the lyophilization process, the pH increases to alkaline pH values of 8, which is associated with the removal of carbon dioxide. When assessing the coagulation potential, the most significant decrease is observed in the activity of factor VIII — up to 50%, factor V — up to 37%, protein S — up to 34%, and von Willebrand Factor — up to 25%. The prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT) is noted. In the Russian Federation, freeze-dried plasma belongs to the group of blood components; therefore, the introduction of foreign production experience (the introduction of cryo- and lyoprotectors, pH adjustment, etc.) is restrained by legislation. This emphasizes the importance of developing domestic technologies.
Conclusions. The production of freeze-dried plasma in polymer containers contributes to uninterrupted transfusion support in the provision of medical care, thus increasing the survival rate of the injured with acute blood loss in emergency situations. In this regard, creation of domestic plasma lyophilization technologies and enhancement of their effectiveness are relevant tasks.

Keywords: freeze-dried plasma; production technology; lyophilization; coagulation potential; transfusion therapy

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ЛИОФИЛИЗИРОВАННАЯ ПЛАЗМА ДЛЯ ОКАЗАНИЯ ЭКСТРЕННОЙ ТРАНСФУЗИОЛОГИЧЕСКОЙ ПОМОЩИ В ЭКСТРЕМАЛЬНЫХ УСЛОВИЯХ

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Введение. В условиях ограниченных возможностей применения свежезамороженной плазмы в экстремальных условиях важны логистические преимущества, которые дает использование лиофилизированной плазмы. Эффективность ее применения зависит от сохранности коагуляционного потенциала в процессе производства.
Цель. Анализ перспективных направлений совершенствования технологий получения лиофилизированной плазмы с использованием международного и отечественного опыта производства, оценки контроля качества и применения гемокомпонента.
Обсуждение. Применяющиеся и доказавшие свою эффективность и безопасность коммерческие препараты FLyP, LyoPlas N-w и Bioplasma FDP, OctaplasLG Lyo, а также лиофилизированная плазма Республики Беларусь и КНР выпускаются в стеклянных флаконах. Перспективным направлением считается получение лиофилизированной плазмы в полимерных контейнерах с применением мембранной технологии, что обеспечивает преимущества использования гемокомпонента в экстремальных условиях. Известны разработки компаний Terumo BCT Biotechnologies и Teleflex Inc., полученные ими продукты лиофилизированной плазмы находятся на стадии клинических исследований и ограниченно применяются в военных операциях. В Российской Федерации зарегистрирован полимерный контейнер «Лиокон». В процессе лиофилизации наблюдается увеличение pH до щелочных значений порядка 8, что связано с удалением углекислого газа. При оценке коагуляционного потенциала наиболее значимо снижение активности фактора VIII до 50%, фактора V — до 37%, протеина S — до 34%, фактора Виллебранда — до 25%. Отмечена пролонгация протромбинового

времени (ПВ) и активированного частичного тромбопластинового времени (АЧТВ). В Российской Федерации лиофилизированная плазма относится к гемокомпонентам, поэтому внедрение зарубежного опыта производства (внесение крио- и лиопротекторов, корректировка pH и др.) ограничено законодательно, что подчеркивает важность разработки отечественных технологий.
Выводы. Производство лиофилизированной плазмы в полимерных контейнерах является одним из путей бесперебойного трансфузионного обеспечения при оказании медицинской помощи, что будет способствовать повышению выживаемости раненых с острой кровопотерей в чрезвычайных ситуациях. В связи с этим актуально создание отечественных технологий лиофилизации плазмы и разработка подходов к повышению ее эффективности.

Ключевые слова: лиофилизированная плазма; технология получения; лиофилизация; коагуляционный потенциал; трансфузионная терапия

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INTRODUCTION

The availability of blood component therapy is extremely important for patients with massive blood loss already at the stage of their medical evacuation [1, 2]. In treatment of post-traumatic coagulopathy, the use of donor plasma as a source of physiological procoagulants and anticoagulants, activators and inhibitors of fibrinolysis is justified [3, 4, 5]. The use of fresh frozen plasma (FFP) in extreme conditions, including remote and hard-to-reach areas, at sea, and during air transportation, is complicated by logistical factors and the impossibility of providing a cold chain. The limited use of FFP is also associated with the fragility of containers with frozen blood components and the high risk of damage during transfer with plasma transportation and thawing. Up to 40% of containers are written off as expenditure due to defects [6]. Prior to transfusion, the blood component must be thawed and warmed, which requires time and specialized equipment. Similar problems in the provision of transfusion care arise in cases of mass destruction due to natural or man-made disasters accompanied by damage to infrastructures [4–8].

Due to logistical challenges of using FFP in extreme conditions, dry plasma offers significant advantages, including the ease of transportation and preparation for transfusion, as well as its long shelf life. This increases the availability and efficiency of transfusion care in life-threatening conditions [4–8].

Lyophilization is an effective method of dry plasma production [9]. Liquid plasma is subjected to shock freezing following its freeze-drying under low vacuum conditions (less than 35 Pa). The solvent is removed from the product by its transfer from the frozen state to the gaseous state during gradual heating in the temperature range from –45 °C to +35 °C, which reduces the loss of functional activity of the target proteins during dehydration.

Freeze-dried plasma (FDP) is included in the list of blood components approved by Enactment of the Government of the Russian Federation No. 797 (dated 22.06.2019)[1].

Another method for biomaterial dehydration is spray drying, when plasma is dispersed in a stream of hot air at a temperature of 60–150 °C [5, 7, 10, 11]. In comparison with freeze-drying technology, spray drying requires no sophisticated equipment but ensures high productivity. However, the as-dehydrated plasma is not available in European countries; in the USA, such technologies are currently under development and clinical trials [10, 11]. In Russia, spray-dried plasma is not included in the list of blood components[2].

The effectiveness of FDP largely depends on the preservation of blood coagulation factors, natural anticoagulants, and other proteins that enable plasma hemostasis [3–5]. In Russia, FDP can be obtained from quarantined or pathogen-reduced plasma[3]. The technological process includes shock freezing, thawing and refreezing, exposure to light and chemical agents to inactivate pathogens, as well as direct freeze-drying. These stages have a significant impact on the structure and functional activity of plasma proteins, especially thermolabile ones, which include blood clotting factors [4, 5, 7, 12]. In this regard, the technological parameters of FDP production should be selected such that to ensure its maximum preserved coagulation potential and safety parameters in full compliance with regulatory requirements.

In this article, we review promising directions in the field of freeze-dried plasma production technologies,

[1] Enactment of the Government of the Russian Federation No. 797 (dated 22.06.2019) “On approval of the Rules for Procurement, Storage, Transportation and Clinical Use of Donated Blood and Its components and on the Invalidation of Certain Acts of the Government of the Russian Federation.” Moscow: RF Government; 2019.
[2] ibid.
[3] ibid.

both in Russia and abroad, evaluating approaches to quality control and use of the blood component.

MATERIALS AND METHODS

The literature search was conducted across electronic bibliographic databases in the Russian (eLibrary, CyberLeninka) and English (PubMed, Web of Science, Scopus) languages, as well as patent sources (Google Patent Search, FIPS). The search queries included the following keywords: lyophilized plasma, freeze-dried plasma, production technology, lyophilization, coagulation potential, transfusion therapy (lyophilized plasma, technology of acquiring, lyophilization, coagulation potential, transfusion therapy). The search depth was 10 years. The publications containing information on freeze-dried plasma production technologies and promising developments in this field were included in the review.

RESULTS AND DISCUSSION

First experiments on the production and application of freeze-dried plasma

The FDP production technology was developed in the 1930s [3, 5, 7, 8, 13, 14]. In 1939, specialists of the Leningrad Institute of Blood Transfusion (since 2011, Russian Research Institute of Hematology and Transfusiology) under the supervision of Prof. L.G. Bogomolova developed one of the world's first chamber-type sublimation devices, which marked an important stage in the development of lyophilization in Russia [14]. Research efforts in the field of blood plasma lyophilization and the development of respective equipment were undertaken in the UK, USA, Canada, and other countries [3, 5, 7, 8, 13].

Large-scale FDP production began during World War II. Millions of dry plasma units were supplied from the USA and Great Britain to the allied forces [5–8]. In the USSR, even during the blockade, FDP production was carried out in Leningrad (1941–1944), primarily for the needs of the Baltic Fleet. Blood components were produced mainly from blood plasma of the AB (IV) blood group, packaged in glass bottles or ampoules [14, 15].

In the USSR, FDP had been produced on an industrial scale since the 1960s. Plasma was manufactured according to the following standard regulations. Prefreezing was carried out in glass vials in alcohol baths. To distribute the plasma over the surface of the vial, the containers were rotated at an angle of 3–5° around the horizontal axis. This process yielded the thinnest possible layer of frozen product and allowed the evaporation surface to be extended. This approach, as well as the selected lyophilization regime, made it possible to dehydrate the plasma to a residual humidity of less than 1% within 20–26 h or 28–32 h, depending on the lyophilization device used. All technological operations were carried out in compliance with aseptic technique and sterility control. For better preservation of plasma proteins, a glucose-based protective medium was used. During lyophilization, a sterile solution of this monosaccharide (5 or 40%) was added to plasma in a 1:9 ratio [9, 16].

The finished products were monitored according to the following quality parameters: solubility — no more than 10 min, authenticity — formation of a dense clot in the presence of a 5% calcium chloride solution (qualitative reaction to the presence of fibrinogen), residual moisture — less than 1%, sterility — sterile, total protein — not less than 55 g/L. The shelf life of such a medicinal product was 5 years at a storage temperature of 5–25 °C. According to the results of studying the product stability after 8 years of storage, the dissolution time increased 2.5 times without exceeding the norm (4–10 min); the remaining parameters did not change significantly. The pH of the FDP was close to neutral, comprising 7.5 ± 0.2 [9]. However, it should be noted that in the 1960s, it was not possible to assess the hemostasis system parameters, their level in production batches was not normalized, and the shelf life was set without taking into account the dynamics of the activity of thermolabile proteins during storage.

FDP was used mainly in cases where it was not possible to transfuse donated blood; its use proved its effectiveness in the wounded with acute blood loss and traumatic shock. The large-scale production of FDP was discontinued in the 1980s due to the detection of cases of hemotransmissive viral infections (HTVI). Attempts made to reduce the infection risk of recipients by removing viruses and reducing the plasma pool size were ineffective [3, 5–8].

Development of freeze-dried plasma production technologies

Freeze-dried plasma technologies have received a new impetus for development since the emergence of reliable standardized methods for ensuring virus security. In 1991, to meet the need for blood transfusions and its components during military operations in the Persian Gulf, FDP production was resumed in France [5–8]. Safety was ensured by the formation of small plasma pools (less than 11 donors) with strict control over the absence of HTVI markers, plasma quarantine and repeated examination of donors. An additional measure to increase the product safety was the introduction of blood plasma screening from females for the presence of antibodies to the human leukocyte antigen.

The French Military Blood Institute produces FDP under the trade name of FlyP. It is a pooled, pathogen-reduced by amotosalene and ultraviolet radiation, AB0-universal FDP. In order to ensure the required level of factor VIII in the dry blood component, taking into account the effect of pathogen reduction, FFP with an activity of at least 0.96 IU/mL is preferred [17]. After thawing, the

selected plasma doses are pooled, aseptically poured into glass vials, and freeze-dried. The lyophilization process lasts for 4–6 days [17–20].

In the early 1990s, the Blood Service of the German Red Cross began producing pulled FDP (up to 1000 donors) treated with a solvent-detergent method. Due to the concerns that the technology used was not capable of inactivating the prions that cause Creutzfeldt-Jakob disease, since 2007, the pooled plasma has been replaced with a single donor FDP. Currently, LyoPlas N-w is a single-donor quarantined FDP. The plasma is stored frozen for at least four months until the donor is examined again, then it is thawed and connected to a patented sterile filling system consisting of a glass vial and a rubber stopper inside a plastic bag [5–8, 20]. Plasma (200 mL) is poured into the vial through a filter with a nominal pore size of 0.2 μ; the vial is closed with a stopper and removed from the system. The plasma is then frozen to –30 °C. Drying occurs with a stepwise increase in temperature from –45 °C to +15 °C for six days; the residual humidity of the plasma is no more than 1% [5, 20].

The commercial Bioplasma FDP product has been manufactured by the National Bioproducts Institute of South Africa since 1996. It is pulled, treated with a solvent-detergent method, AB0-universal FDP [6–8, 20].

Since 2016, the Republican Scientific and Practical Center for Transfusiology and Medical Biotechnology of the Republic of Belarus has been actively developing pooled (at least 10 units of plasma), pathogen-reduced (photochemical treatment using riboflavin or amotosalene), fibrinogen-standardized FDP. To reduce the loss of blood clotting factors during lyophilic drying, auxiliary substances are added to the intermediate product, the composition of which is not disclosed [21, 22].

The Swiss company Octapharma AG has received approval from European regulatory authorities for the production of OctaplasLG Lyo FDP [23]. It is obtained from a pool consisting of 630–1520 units of single-group donor plasma, which is filtered to remove aggregates and cell fragments. A solvent-detergent treatment method is used to ensure virus safety. The fundamental difference between this technology and the previously described ones is the stage of chromatographic purification using affinity ligands for prion proteins. The plasma is subjected to sterilizing filtration and bottled in non-pyrogenic glass vials of 200–210 mL followed by lyophilization. It should be noted that the production stages of OctaplasLG Lyo are accompanied by pH adjustment using citric acid or phosphoric acid to compensate for the increase in this indicator during the lyophilization process. Glycine in a final concentration of 5 g/L is used as a stabilizer. Prior to application, the FDP is rehydrated in 190 mL of water for injection [20, 24].

Plasma lyophilization technologies, including platelet-rich plasma, have been patented in China (Institute of Pharmacology and Toxicology of AMMS, First Medical Center of PLA General Hospital, Qilu Cell Therapy Technology Co ltd Yinfeng Biological Group Ltd). The blood component is dried for 4–6 days. The material is cooled to –45 °C, then gradually heated to +20 °C at a vacuum value of 0.1 mbar. At the secondary drying stage, the pressure is reduced to 0.001 mbar, and the temperature is raised to +25 °C [25–27].

The above FDP products are produced in glass vials. The disadvantages of this package are fragility, bulkiness, and significant weight. Care is required during transportation, which is quite difficult to ensure in extreme conditions. In addition, for the filling stage and lyophilization itself, it is necessary to create aseptic conditions to prevent contamination of the product [28–29].

Innovative technologies for producing freeze-dried plasma in polymer containers

The inconveniences of transporting and using FDP in glass vials drive the need to develop technologies for producing freeze-dried plasma in polymer containers. The lightness, compactness, strength, and tightness of such consumable systems increases the availability and efficiency of early transfusion therapy in extreme situations outside of inpatient conditions. To date, the most promising direction has been the membrane lyophilization technology, when one of the container surfaces is made of a gas-permeable polymer. This material is highly hydrophobic and non-toxic, capable of preventing the penetration of microorganisms and at the same time being permeable to water vapors. All this allows the FDP manufacture in a closed system while maintaining the sterility contour, thus offering the advantages of using dry blood components in extreme conditions [8, 28, 29].

Abroad, the United States is the leader in the development of FDP production technologies in polymer containers. In 2007–2008, the U.S. Army Medical Materiel Development Activity (USAMMDA) and the U.S. Army Special Operations Command (USASOC) launched programs for the production of FDP in polymer containers. In 2008–2013, HemCon Medical Technologies, Inc. was a partner of the U.S. Department of Defense. Although plasma pooling ensured its standardization in terms of the level of blood clotting factors, preference was given to FDP obtained from a single donor. In 2011, this product successfully passed the first phase of clinical trials. Afterwards, however, the collaboration with HemCon Medical Technologies, Inc. was terminated. In 2014, together with a new partner Vascular Solutions, Inc., the FDP under the commercial name of RePlas was developed and passed the first phase of clinical trials [5, 7, 20, 30]. This company also produces ESPLAS, an FDP from a single donor [8].

In 2016, Terumo BCT Biotechnologies, LLC, a biotech company, received funding to develop a decentralized FDP production in polymer containers from plasma pools (up to 10 donors) for use in blood centers and extreme situations. Currently, the technology

and consumables developed by this company for FDP production are used not only in the USA, but also in Canada [31–33].

The gas permeable membrane of lyophilization polymer containers developed in the USA is made on the basis of foamed polytetrafluoroethylene (e-PTFE). The choice of this material is due to its porous and flexible structure, chemical stability, and biocompatibility [34]. The presence of negative charges on the polymer surface blocks the coagulation of blood proteins and limits platelet activation. The pore size of the lyophilization container membrane ranges within 0.2–0.3 μ, ensuring protection of the product from microbial contamination. The porosity of 50–95% allows efficient removal of liquid vapors. The developed containers are presented in a two-piece design. One of the parts is equipped with a gas-permeable membrane, while the other is made of a non-breathable polymer material such as polyvinyl chloride or polypropylene. To increase the sublimation efficiency during the process, the plasma does not come into contact with the membrane surface [35–37].

The design of Terumo BCT Biotechnologies, LLC containers may include a temporary seal in the form of a reinforcing insert separating a part of the plasma container and an unfilled section with a breathable membrane. In this case, an occlusion area is required to create an air space in order to accelerate the outflow of solvent vapors during the sublimation process [35, 36]. In the design of Teleflex Inc. containers, a device can be provided in the form of a frame made of inert medical plastic supporting the membrane above the plasma layer [37].

The duration of plasma drying in such polymer containers is comparable to that of lyophilization in vials, being about 4–7 days. After lyophilization, the dry product is stored in the non-breathable part of the container (or poured thereon, if necessary), which is separated from the membrane section by a sealed seam. The container in which the FDP is stored is equipped with the ports for solvent injection and transfusion of rehydrated plasma [35–37].

A number of developments in the field of plasma lyophilization in polymer containers are also known in the Russian Federation. In 2021, Haemogenics patented a system consisting of a container comprising two sections hermetically connected by a peel-open heat-sealed seam, which makes it possible to freeze, store and use the blood component while maintaining the sterile contour [38]. A non-woven polymer Tyvek is used as an air-permeable material, which performs the function of a membrane. Plasma drying is carried out in the gas-permeable part of the container. The second section, into which the lyophilizate is poured at the end of the process, is made of polyvinyl chloride and is used for storage, transportation, and transfusion of the blood component. A similar principle was implemented by NPO Biotech-M when developing a method for plasma lyophilization in a two-section container, characterized by the design features of the intersectional seam, a different composition of the breathable material, and the configuration of ports and tubing lines [39]. Later, the authors noted that the main disadvantage of binary containers is their large area, which requires a significant increase in the working surface of the freeze chamber. The membrane materials are hygroscopic; therefore, the transfer of FDP from one section to another can lead to a significant increase in the moisture content of the blood component [40].

Single-section containers are easy to manufacture and are free from the above disadvantages. Currently, such containers are registered as a Liokon medical device (NPO Biotech-M, Russia) and are used for plasma drying according to a protocol integrated into the software of the Liomed lyophilization unit (the same producer). The containers are made in the form of a flattened container with an area of about 420 cm^2 (linear size 15.5 cm×27.3 cm). One of its surfaces is made of water-, gas-, and vapor-proof material, the other is a membrane with a pore size in the range of 0.1–0.45 μ and a porosity of 20–80%. Lyophilic drying of plasma in these containers is carried out at temperatures from –40 to +37 °C for 4–7 days. After completion of lyophilization, immediate sealing of the membrane surface is necessary. For additional protection against ingress of moisture from the environment and damage during storage and transportation, the container is placed in an external bag and evacuated [41].

Research is underway in the institutions of the Federal Medical and Biological Agency (FMBA of Russia) to develop production technologies of FDP in polymer containers [42]. Since 2024, the Kirov Scientific Research Institute of Hematology and Blood Transfusion has been working on the production of dry plasma with increased coagulation potential using membrane technology as part of a versatile package to provide emergency transfusion care to the wounded and injured with massive blood loss in extreme situations.

Use of pathogen reduction technologies to ensure the infectious safety of freeze-dried plasma

Pathogen reduction technologies make it possible to increase the infectious safety of blood components. Such technologies are aimed at removing a wide range of viruses, and not just four HTVI, the detection of which is mandatory during a medical examination of donors [5, 43]. There exists evidence that modern technologies prevent hemotransmissive bacterial sepsis. The introduction of the pathogen reduction stage eliminates a long period of quarantine, avoids the rejection of the product due to the failure of donor re-examination, and reduces the time to obtain a suitable blood component for clinical use [43].

From the point of view of ensuring viral safety, the single-donor FDP production is preferable. However, the wide variability of the plasma physiological

parameters makes it difficult to ensure the quality of the finished product. Combining plasma units into a pool makes it possible to standardize the product in terms of total protein, blood clotting factors, fibrinogen, and natural anticoagulants. In this case, the introduction of the pathogen reduction stage is of particular importance [7, 28].

The solvent-detergent method, introduced in 1991 as an alternative to quarantine, is used to process plasma pools (up to hundreds and thousands of units). The disadvantage of this method consists in a decrease in the activity of natural anticoagulants: protein S up to 44% and α_2-antiplasmin up to 79% [44].

Methods based on photoinactivation of pathogens are used to process individual plasma units and pools of up to 2–3 units. Such technologies involve visible light and methylene blue treatment (THERAFLEX system, Macopharma, France) for plasma doses of 235–315 mL, ultraviolet irradiation with riboflavin (Mirasol system, Terumo BCT, USA) for plasma doses of 170–360 mL, ultraviolet in combination with amotosalene (INTERCEPT system, Cerus Corporation, USA) for apheresis doses of plasma with a volume of no more than 650 mL or pooled plasma with a volume of 385–650 mL obtained from whole blood [43].

The conducted comparison of photochemical technologies for pathogen reduction [43] found their effect on the plasma coagulation potential. In 2014, Jose Coene et al. noted a decrease in fibrinogen concentration (16.8–33.2%), activity of factors II (2.2–22.6%), V (7.8–38.2%), VIII (22.3–44.7%), IX (9.2–33.9%), and XI (14.8–47.4%). The greatest change in the plasma hemostatic properties was observed when irradiating plasma with ultraviolet light and treating with riboflavin [45]. The same trend was observed when studying the coagulation potential of pathogen-reduced FDP produced in Belarus using the Mirasol and INTERCEPT systems. The decrease in the activity of factor VIII was 39.3% and 19%, and the decrease in fibrinogen content was 33.6% and 25.3%, respectively [21]. The [46] of plasma drying technologies in 10 mL glass vials involving three pathogen reduction methods found no significant effect of the viral activation method of the biomaterial on the preservation of its hemostatic properties. The work observed a decrease in the activity of factors V and VIII by 18–20% and 15–19%, respectively, as well as an increase in PT and aPTT compared with the same parameters in the FDP. The remaining parameters ranged within the physiological norm [46].

The introduction of pathogen reduction technologies requires specialized equipment and expensive consumables. At the same time, the expenditures are justified by increasing safety, reducing the duration of the FDP production, and making more rational use of the donor resource [43, 46].

Production of group AB(IV) freeze-dried plasma

FDP can be effectively applied only provided the comparability of the AB0 system between donor and recipient. The use of group AB(IV) plasma in extreme conditions provides a time advantage and reduces the risk of transfusion of a blood component incompatible with the blood group. Therefore, due to the possibility of immediate transfusion, products based on the group AB(IV) blood component are in high demand [6, 28, 29].

According to literature data, the AB(IV) blood group prevalence among the population is only 8–9%. To increase the availability of plasma transfusions in extreme situations, it is allowed to use plasma with a low titer of anti-A antibodies as a “universal” plasma or to combine plasma of groups A, B, and AB in certain proportions. For example, there is a known method for forming a pool for FDP production with a relative content of individual plasma units of group A(II): 40–45%, group B(III): 40–45%, group AB(IV): 10–20% [6, 17, 19, 28, 29].

In accordance with Enactment of the Government of the Russian Federation No. 797[4] (dated 22.06.2019), in the absence of same-group plasma, only AB(IV) plasma transfusion is allowed. In this regard, the formation of a reserve of AB(IV) donor plasma is of strategic importance for Russian healthcare.

Studying the properties of freeze-dried plasma

During plasma lyophilization, it is important to maximize its coagulation potential, i.e., the activity of blood clotting factors and natural anticoagulants, and the concentration of fibrinogen. At the same time, these values should be considered in conjunction with the data of global coagulological tests, such as thromboelastography. Humidity is controlled in the finished product. Under its of less than 2%, it is believed that FDP stability is ensured during long-term storage. The amount of total protein is determined, and a sterility test is performed. In addition to the main quality parameters, the physicochemical properties and FDP composition are verified by the dissolution time, pH, osmolarity, and residual concentrations of excipients.

When studying the properties of FLyP, the following values of coagulation potential were obtained: fibrinogen level — 2.4 ± 0.3 g/L; factor V activity — 0.51 ± 0.16 IU/mL; factor VIII — 0.62 ± 0.10 IU/mL; factor IX — 0.79 ± 0.11 IU/mL; factor XIII — 1.03 ± 0.12 IU/mL; protein C — 96 ± 9%; protein S — 77 ± 16%; antithrombin III — 1.01 ± 0.05%; α_2-antiplasmin — 95 ± 30%. At the same time, out of the nine studied parameters, only two showed a significant decrease during lyophilization. The activity of factors V and VIII decreased by 25 ± 12 and 20 ± 7%, respectively. The remaining parameters were stable, varying within 7%.

[4] Enactment of the Government of the Russian Federation No. 797 (dated 22.06.2019) «On approval of the Rules for Procurement, Storage, Transportation and clinical use of donated blood and its components and on the invalidation of certain acts of the Government of the Russian Federation ». Moscow: RF Government; 2019

A prolongation of aPTT by 11% and PT by 8% was also observed, which was associated with a decrease in the activity of V and VIII factors [17, 18, 20].

The thromboelastography data for FFP and FLyP were found to be similar, which indicates the preservation of the hemostatic properties of the blood component after lyophilization [18]. FDP humidity did not exceed 2%. The lyophilizate is dissolved in 200 mL of water for injection in less than 6 min. The pH value of the rehydrated hemocomponent is alkaline-shifted equaling about 8. The shelf life is limited to 2 years at room temperature [4, 17, 18]. Regarding the stability of FLyP, this product was found to be most susceptible to changes in the activity of VIII and V factors, as well as the concentration of fibrinogen, at an elevated ambient temperature of 38–53 °C [14].

In the process of obtaining FDP LyoPlas N-w, a 21.6% decrease in the activity of VIII factor was observed (to a level of 0.79 ± 0.12 IU/mL). In comparison with the study results of French FDP, no changes in the factor V activity during lyophilization was noted, with the value of 1.07 ± 0.08 IU/mL being obtained. At the same time, a 25% decrease in the activity of the von Willebrand factor was shown, which was not evaluated in the FLyP study. The glycoprotein structure remained intact before and after lyophilization, which indicates the preservation of the function of the primary link of hemostasis. The remaining parameters varied in the range of 5.1–11.1% and corresponded to the physiological norm. A decrease in the factor VIII activity led to a prolongation of aPTT by 12.8%. Data on changes in PT was not provided. When LyoPlas N-w was rehydrated in 200 mL of water for injection, the dissolution time did not exceed 10 min [20, 47, 48]. The pH value of the rehydrated blood component was 7–7.2 [10]. After recovery, the product is recommended for use within 6 h. The shelf life of LyoPlas N-w is 15 months at a storage temperature 2–25 °C [5, 20, 48]. The results of a study of the safety limits of LyoPlas N-w under extreme conditions showed the stability of the blood component under a short-term temperature increase to 50 °C [48].

Highly limited information is available on the effect of lyophilization on the hemostatic properties of Bioplasma FDP. This product is known to have an efficiency profile similar to that of FFP. Bioplasma FDP is available in doses of 50 mL and 200 mL and is reconstituted with water for injection. The dissolution time does not exceed 10 min. The shelf life is 2 years at a temperature not exceeding 25 °C [6–8, 20].

The study of OctaplasLG Lyo showed a 30% decrease in the activity of factor VIII compared to FFP, as well as significantly lower protein S safety than for FLyP and LYOPLASN-w (a 34% decrease in activity). The remaining parameters of coagulation potential, including the activity of factor V and von Willebrand factor, varied within 7–19%. The most stable parameters were fibrinogen, factors X, XII, XIII, and protein C. The hemostasis system parameters were within the reference ranges established for blood plasma. No significant changes in PT and aPTT during lyophilization were recorded. The parameters of OctaplasLG Lyo thromboelastometry are comparable to the parameters of FFP. Other quality parameters met the requirements of the specification, including osmolarity — 333–350 mOsmol/kg; pH — 7.4–7.6; protein content — 55 mg/mL; humidity — no more than 1%; dissolution time — no more than 15 min. Since the production of OctaplasLG Lyo involves the introduction of excipients of citric and phosphoric acids, concentrations of citrate and phosphate ions of 20 mmol/L and 5.3 mmol/L, respectively, were additionally determined. These concentrations were higher than the similar values for FFP (16 mmol/L and 3.3 mmol/L, respectively). The identified deviations were recognized as acceptable, provided that the compliance of the quality and safety parameters with the established requirements was confirmed. The glycine content was determined at a level of 5 mg/mL. In general, the conclusion was made about the comparability of OctaplasLG Lyo and FFP quality profiles. The shelf life of the blood component is 2 years at room temperature storage [20, 24].

According to the results of quality control studies of pilot-scale FDP series developed in Belarus, compliance with the requirements of the internal specification was established. Coagulation potential was studied (II, V, VII, VIII, IX, X, XI, and XII factors, protein C, antithrombin III and α_2-antiplasmin, PT, aPTT). The activity of factor VIII was found to be 0.82 IU/mL, the other coagulation factors were 0.66–0.83 IU/mL, natural acticoagulants — 83–99%, and fibrinogen content –2.51 ± 0.25 g/L. Data on changes in the parameters during lyophilization are not provided [21].

In an *in vitro* experiment, when adding FDP to the blood of patients with acquired coagulopathy, normalization of thromboelastometry parameters was shown. This indicated the potential clinical effectiveness of the blood component [22]. The conducted assessment of the FDP physicochemical properties found its humidity ranging 0.58 ± 0.3%, osmolarity — 284.1 ± 29.2 mOsmol/kg, and the total protein content — 53 ± 2 g/L. It was shown that the content of citrate ions, calcium, sodium, and potassium did not exceed the reference ranges [21]. According to the results of pyrogenicity and abnormal toxicity tests, FDP was recognized as safe [22].

When studying the FDP properties obtained without the addition of protective agents (Institute of Pharmacology and Toxicology of AMMS, China), a decrease in the activity of factor V by 19.3%, factor VIII by 21.4%, and von Willebrand factor by 26.5% was noted; despite this, the values of the parameters corresponded to the physiological norm. The activity of factors II, VII, IX, X, XI, XII, plasminogen, antithrombin III, α_2-antiplasmin, protein C, and protein S decreased by no more than 5% during lyophilization [25]. To increase the coagulation potential, mannitol was introduced into the plasma at a

concentration of 25 g/L and the pH of the solvent (water) was adjusted to 7.3–7.4 with a phosphate-buffer saline (First Medical Center of PLA General Hospital, China). This made it possible to increase the safety of factors V and VIII by 12% and 18%, respectively, and to achieve their activity in FDP of more than 0.8 IU/mL. The residual moisture content of the dry blood component did not exceed 2%, and the recovery time with water for injection was 13 min [26].

Studies of a new generation FDP product developed by Teleflex Inc. (USA) using polymer containers with a membrane demonstrated a slight decrease in fibrinogen content within 7%, factor V activity within 15%, factors VIII and von Willebrand within 10%, as well as protein C and protein S within 9% and 7%, respectively. The decrease in the activity of other blood coagulation factors did not exceed 16%. Prolongation of PT to 12.9 s (by 7%) was noted. All parameters of the coagulation potential of FDP were in the range of reference values. The revealed differences did not exceed the threshold of bioequivalence of FDP with FFP — 20%. The experimental samples were characterized by humidity of the order of 1%, protein content of at least 50 g/L, osmolarity of 298.1 ± 7.2 mOsmol/kg, pH of 6.9 ± 0.2, and recovery time with water for injection of 1 min. According to the results of stability assessment, it is recommended to store FDP for no more than 3 years at a temperature 2–8 °C and for several months at room temperature [20, 30].

In the process of obtaining a similar product manufactured in the USA and Canada using the Terumo BCT Biotechnologies technology, factor VIII turned out to be the most susceptible to inactivation with its activity during lyophilization decreasing by 12.8–14.8%. A decrease in the concentration of α_2-antiplasmin by 14.3% and protein S by 12.1% was observed. Changes in other coagulation parameters (fibrinogen, protein C) were absent or ranged 2.2–8.7%. The aPTT and PT levels increased by 4.9% (to 29.4 ± 2.5 s) and 4.1% (to 11.3 ± 0.7 s), respectively. In general, the changes in coagulation potential observed during lyophilization did not exceed 20%; therefore, the FDP hemostatic properties were considered comparable to those of FFP. In addition, no deterioration in the parameters of thromboelastometry was established when comparing FDP with native plasma. The quality parameters of the dry blood component were within the normal range: humidity — less than 2%, total protein — more than 50 g/L. The dissolution time ranges within 5 min in water for injection. The values of osmolarity of 280.8 ± 12.8 mOsmol/kg and pH of 7.8 ± 0.1 were measured for the rehydrated blood component. Based on the results of the stability analysis, a shelf life of 2 years at room temperature was determined [20, 31–33].

In the Russian Federation, the following requirements for FDP safety parameters are set: humidity — less than 2%, total protein — more than 50 g/L, factor VIII activity — at least 0.5 IU/mL, sterility. The shelf life is 5 years at a temperature 2–20 °C[5]. The FDP produced using the Lyokon lyophilization technology exhibits the total protein content of 61.9 ± 3.6 g/L, the factor VIII activity of 0.56 ± 0.03 IU/mL, the fibrinogen concentration of 2.5 ± 0.2 g/L, aPTT of 79 ± 3 s, and PT of 23 ± 1 s. When comparing the plasma coagulation profile before and after lyophilization, a significant inactivation of factor VIII by 50% and prolongation of aPTT by 2.3 times were determined. Practically no changes in PT were observed [49]. When FDP was dissolved in 250 mL of 0.9% saline solution, moderate hyperosmolarity of the blood component at a level of 640 ± 22 mOsmol/L was noted [50]. A stability study after 3 months of storage in a hot climate with an increase in ambient temperature to 40 °C showed inactivation of factor VIII to 0.01 IU/mL and a significant decrease in fibrinogen content. During the same period at room temperature 20–25 °C, the activity of factor VIII fell below normal (0.46 ± 0.02 IU/mL). When stored in a refrigerator at 5 °C, it was at the lower limit of the regulated range and amounted to 0.49 ± 0.03 IU/mL [51]. Long-term stability tests are currently underway [50].

The presented results of studying the properties of FDP indicate the relevance of developing approaches to improving its coagulation potential. To increase the stability of FDP, it is possible to introduce lyoprotectors, such as glutamine, glycine, sucrose, trehalose, sorbitol, mannitol, or pH regulators [40, 52, 53]. To compensate for the pH value, it is possible to add bicarbonate buffer solution, citric or phosphoric acids to the native plasma, or saturate the dry blood component with purified CO_2 after the completion of the drying process [20, 24]. The possibility of using HEPES medium (4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid), which is a high-capacity zwitterionic organic buffer at neutral pH values (pH = 7.55), was demonstrated [54]. In the presence of HEPES, the activity of factor VIII in FDP was found to increase by 12–18% compared to that in FDP obtained without the addition of stabilizers [12, 40]. Correction of the hydrogen index can also be carried out by restoring FDP with water for injection, acidified to a pH value of 1.5 ascorbic acid or citric acid [5, 7, 20]. Some authors recommend avoiding the use of glucose and other reducing sugars as lyoprotectors, which may interact with free amino acid residues during lyophilization, affecting protein properties [52]. It should be noted that when introducing excipients into the plasma, their harmlessness must be carefully proven. In the Russian Federation, it is currently possible to use only solutions and media approved in transfusion practice[6].

[5] Enactment of the Government of the Russian Federation No. 797 (dated 22.06.2019) «On approval of the Rules for Procurement, Storage, Transportation and clinical use of donated blood and its components and on the invalidation of certain acts of the Government of the Russian Federation ». Moscow: RF Government; 2019.

[6] ibid.

Use of freeze-dried plasma in extreme conditions

FDP is used in the provision of medical care in many countries. The FDP effectiveness for early transfusion therapy has been repeatedly confirmed in practice.

FLyP was used to provide transfusion assistance in military operations in the Sahel region of Central Africa, Djibouti, Afghanistan, and Iraq. Its clinical effectiveness has been studied in patients in intensive care units in Afghanistan. This product is approved in France for civilian use in extreme conditions [4–8, 17]. The United States also used FLyP in special military operations in Afghanistan and Iraq; since July 2018, its emergency use has been allowed [6, 10].

LyoPlas N-w has been used in medical institutions in Germany, by helicopter ambulance crews in the UK, Sweden, Norway, Finland, and Australia and, since 2012, by foot patrols in the UK. The safety and effectiveness of its use at the prehospital stage in the treatment of traumatized children has been proven [4–8]. Since 2013, the Israel Defense Forces has approved the use of FDP LyoPlas Nw at the pre-hospital stage. Currently, Israeli air and ground ambulances are equipped with LyoPlas Nw [5, 8, 48]. Military specialists in extreme medicine (physicians and paramedics) have two sets of AB(IV) FDP in their tactical vests [8].

Since 1996, Bioplasma FDP has been used in South Africa along with joint ventures to provide transfusion care to patients with blood loss resulting from trauma or postpartum bleeding [6–8].

CONCLUSION

The most promising areas of FDP production include quarantined or pathogen-reduced plasma, or a single-donor pooled blood component.

Plasma quarantine makes it possible to protect the patient from transmission of hemotransmissive infections. However, this is a rather lengthy process that takes at least 120 days. Pathogen reduction makes it possible to increase the infectious safety of FDP products and shorten the duration of their production for clinical use; at the same time, it can negatively affect their hemostatic potential. From the point of view of infection safety, it is preferable to use a single-donor product. At the same time, pooling makes it possible to standardize the blood component.

In extreme situations, the use of group AB(IV) FDP is of particular relevance due to the absence of the need to select a donor–recipient pair. This increases the efficiency of early transfusion therapy, which plays a key role in providing emergency medical care outside of hospital settings.

The currently known commercial FDP products are available in glass vials. The advantages of using FDP in polymer containers for providing transfusion care at the prehospital stage are obvious. Developments in this area are actively underway in the USA, Canada, and the Russian Federation. The use of membrane technology allows for a full cycle of blood component production in a single closed system while maintaining sterility.

The mass production of new-generation medicines in durable compact polymer containers is one of the ways to ensure uninterrupted transfusion care at the pre-hospital stage. This may increase the survival rate of the wounded and those with acute blood loss as a result of severe injuries in emergency situations. Therefore, creation of domestic technologies and consumable systems for plasma lyophilization, as well as development of approaches to improve the FDP effectiveness, are highly important tasks for Russian transfusiology.

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