VIA MEDICA

REVIEW ARTICLE

Journal of Transfusion Medicine
2021, vol. 14, no. 4, 214–224
DOI: 10.5603/JTM.2021.0012

ISSN 1689-6017
eISSN 2080-1505

Fibrin glues — the current state of knowledge

Paulina Goczyńska, Joanna Lasocka, Elżbieta Lachert

Department of Transfusion Medicine, Institute of Hematology and Transfusion Medicine in Warsaw

Summary

Fibrin glue is a two-component biological material obtained as result of extemporaneous preparation of equal volumes of fibrinogen concentrate and thrombin solution. On a mass scale fibrin glue is acquired either commercially by way of plasma fractionation, or in laboratory setting by chemical precipitation or cryoprecipitate method. Fibrin glue mimics the blood clotting mechanism. Thrombin converts fibrinogen into fibrin clot, which — due to hemostatic properties-contributes to sealing the wound and supporting damaged tissue regeneration. The clot adheres to adjacent tissues, and the structure becomes a natural scaffold for precursor and effector cells as well as hematopoietic growth factors that actively promote wound healing. Fibrin glue has found application as wound sealant mostly for patients with coagulation factor deficiencies and problems with spontaneous wound repair. The material is commonly used i.a. in general surgery (wound sealing or vascular suture), regenerative surgery (bone implant fixation), plastic surgery (better cosmetic results, prevention of unaesthetic scarring), skin tissue regeneration for burn injury, neurosurgery (prevention of cerebrospinal fluid leak and nerve repair), cardiovascular surgery and stomatology. Fibrin glue embedded with drugs, antibiotics, cytostatic agents or stem cells, may increase the effectiveness of therapy and facilitate targeted delivery of active substances for localized drug release.

The aim of the article is to present the current state of knowledge on the methods of preparation and application of fibrin sealants as well as on other possible use in various fields of medicine.

Key words: fibrin glue, regeneration, wound healing

J. Transf. Med. 2021; 14: 214–224

Introduction

For years now, scientists and clinicians have conducted research to develop a cheap, easily applicable material to be used both for sealing and dressing wounds as well as supporting wound healing — a material that would induce no inflammatory responses. An alternative to classical surgical sutures or suture support are synthetic, semisynthetic or natural glues which adhere to adjacent tissues through adhesion mechanisms such as van der Waals forces, capillary forces, hydrogen bonding, static electric forces, and chemical bonds. The natural processes of tissue healing and regeneration are intensified by glues of natural origin which are rapidly adsorbed. Moreover, adhesive-embedded wound dressings create impermeable barriers against microorganisms and potential contaminants. Glues can be used together with surgical sutures or as separate dressings/patches, e.g.

Correspondence address: Paulina Goczyńska, MSc., Department of Transfusion Medicine, Institute of Hematology and Transfusion Medicine, Warsaw, 14 Indiry Gandhi St, phone 22 349 6386, e-mail: pgoczynska@ihit.waw.pl

Translation: mgr Krystyna Dudziak

when the tissue is too thin or too sensitive for classic suturation. The production of tissue adhesives is based on substances such as fibrinogen, gelatin, polyethylene glycol, polyacrylate (e.g. cyanoacrylate), chondroitin sulfate, collagen, dextran, albumin or chitosan. Literature reviews show that the most common synthetic preparations are cyanoacrylate-based adhesives while the most widely used natural adhesives are based on fibrinogen concentrate.

Cyanoacrylates are polymers derived from many molecules of ethyl cyanoacrylate. In the presence of water polymerization proceeds rapidly so cyanoacrylates are widely used not only in medicine and industry, but also in everyday life, as the so-called "super glues". They isolate the wound completely as they are waterproof and impermeable to body fluids. They are not however intended for internal use due to increased risk of causing inflammatory reactions. Applied externally, cyanoacrylates have no toxic properties, although in rare cases they may induce allergic reactions [1–3].

Unlike synthetic and semi-synthetic adhesives, natural sealants are fully biodegradable. Moreover, the immune system does not recognize this biological dressing as a foreign body so no pro-inflammatory reaction is initiated. An example of such material are two-component fibrin glues (FG) also called fibrin sealants (FS) obtained by mixing solutions of fibrinogen and thrombin in the presence of calcium chloride. FG also contains factor XIII and fibronectin. Both solutions, mixed in a 1:1 volume ratio, give fibrin glue which mimics the natural blood coagulation mechanism. When mixed with thrombin, soluble fibrinogen is transformed into insoluble fibrin. The complicated fibrin network forms a fibrin clot, which has sealing and hemostatic properties that promote wound healing (Fig. 1). When the dressing comes into contact with tissue of enhanced fibrinolytic activity, it is also advisable to use antifibrinolytic agents (aprotinin or aminocaproic acid) to delay clot adsorption [4, 5].

The role of fibrin in wound healing

There are three stages of wound healing; inflammatory phase (stage 1), proliferative phase (stage 2), remodeling phase which finally leads to wound closure and scar formation (stage 3).

Apart from its sealing (hemostatic) properties, the fibrin clot is also a natural matrix/scaffold for adhesion, proliferation and differentiation of precursor cells, e.g. fibroblasts. In the first stages of tissue regeneration, effector and precursor cells migrate to the fibrin network (the so-called scaffold); growth factors also penetrate into the fibrin network and initiate the healing process. Tissue-specific stem cells proliferate and mature into adult cell type. In the final stage of regeneration, the clot exfoliates and the wound contracts. The process of regeneration is additionally intensified by fibronectin (FN) — a glycoprotein that participates in cell growth, migration, differentiation and adhesion. In the process of healing, the clot is gradually dissolved by plasmin. The existing matrix (fibrin network with trapped red blood cells, platelets, etc) is thus rebuilt into healthy tissue [4, 6–8].

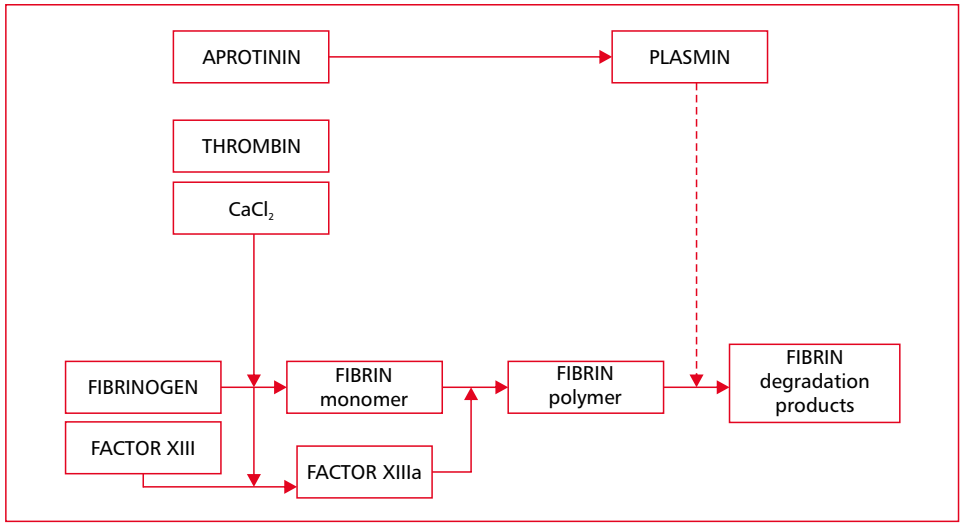

Figure 1. Mechanism of action of fibrin glue — simulation of the blood clotting mechanism. Author's own diagram

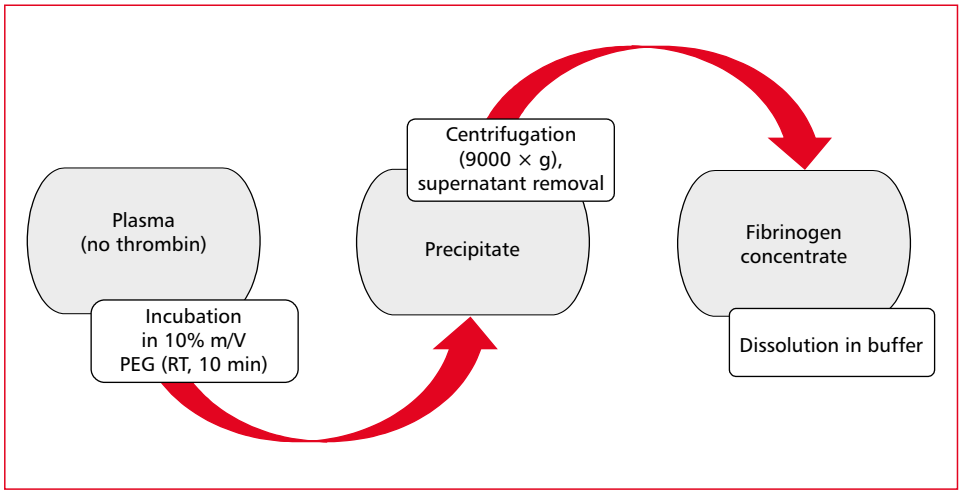

Figure 2. Chemical method of preparation of fibrinogen concentrate using polyethylene glycol (PEG). Author's own diagram. RT — room temperature; % m/V — mass-volume concentration; g — spin force

Historical outline

The first attempts at making use of plasma proteins, fibrinogen and fibrin reach back to the time of World War I when Gray and Harvey applied fibrin swabs to control bleeding from the abdominal parenchymal organs. In 1940, Young and Medawar used plasma as a natural binder to connect peripheral nerves, and in 1944 Cronkite mixed fibrinogen concentrate with bovine thrombin to obtain the first fibrin glue which was used for fixation of skin graft. Cronkite' s method of glue preparation has been subjected to constant modifications; fibrinogen concentration has been increased and various active substances have been added. In 1949 the production of first cyanoacrylate-based adhesives was launched but due to high frequency of allergic reactions attention was soon switched to natural adhesives e.g. fibrin glue. In 1970 the first commercial Tissucol fibrin glue was produced from pooled plasma (Immuno AG). In the 1980s, other fibrin glue preparations from pooled plasma were approved for the markets of Europe, Japan and Canada: Beriplast (ZLB Behring, Germany), Bolheal (Fujisawa, Japan), Hemassel (Haemacure Corporation, Canada), Tissel (Baxter, Austria), Tissucol (Baxter, Austria), Quixil (Omrix, Belgium). In the USA the first commercial glue was approved in 1998 (Tissel by Immuno AG, now Baxter). The Food and Drug Administration (FDA) explained the delay in giving its approval for commercial fibrin sealants by concern for higher risk of pathogen transmission; the solvent/detergent (SD) method for pathogen inactivation in pooled plasma was not yet in use at the time. The approval for clinical use of commercial tissue adhesives was given in the USA only after implementation of improved virus inactivation techniques such as nanofiltration and the SD method. As there was no FDA approval for commercial fibrin glues in the USA, the years 1970–1998 witnessed the development of numerous methods of fibrinogen concentrate preparation in laboratory setting [3, 4, 9–11].

Methods of obtaining fibrinogen concentrate — the basic component of fibrin glue

Chemical methods

The first laboratory methods of obtaining fibrinogen concentrate were based on chemical precipitation. Fibrinogen precipitates from plasma in the presence of chemical substances such as ammonium sulfate, ether, ethanol, polyethylene glycol (PEG) or glycine ("cold" precipitation). One of these substances is added to plasma in appropriate proportion, then the mixture is incubated in strictly programmed conditions. As result, fibrinogen precipitates and the supernatant is centrifuged to obtain fibrinogen concentrate which is then dissolved to a desired volume, e.g. in citrate buffer (Fig. 2). The preparation may be stored for up to 3 weeks at –20°C.

To increase fibrinogen concentration, the polyethylene glycol (PEG) concentration was increased (by 10–15%) or freezing-thawing of the precipitate was included. No doubt, chemical precipitation has the advantage of producing higher yields of fibrinogen concentrate but it must be kept in mind that the chemical substances cannot

be completely eliminated from the final material. Moreover, by increasing PEG concentration the amount of impurities in the final product grows and residual amounts of chemical compounds may affect the physical and chemical properties of fibrin glue. Residual ethanol for instance may accelerate clotting and activate factor XIII which renders the clot less resistant to stretching. When the procedure is performed in an open system, as is the case with chemical precipitation, even the use of sterile disposable equipment does not reduce the high risk of bacterial contamination. Due to the above-mentioned limitations of the chemical method (sterile reagents and sterile disposable equipment, preparation in an open system in class A clean rooms), more attention is now being paid to cryoprecipitation. The cryoprecipitate method allows to isolate fibrinogen concentrate in a closed system which markedly reduces the risk of pathogen transmission [10, 12, 13].

Cryoprecipitate method

The starting material for isolation of fibrinogen concentrate is autologous or allogeneic plasma obtained from whole blood either by manual or automated plasmapheresis. Allogeneic plasma must be subjected to quarantine or pathogen inactivation with one of the PRT inactivation systems (Theraflex MB Plasma, Mirasol PRT, Intercept). The plasma must also be AB0 and RhD compatible with the recipient's blood type. Cryoprecipitate method consists in slow thawing of one unit of fresh frozen plasma (FFP) at 2–6°C, followed by centrifugation to obtain 20 to 30 ml of cryoprecipitate rich in plasma proteins such as: fibrinogen, fibronectin, factor VIII, IX and von Willebrand factor (Fig. 3). The material can be stored for up to 12 months at –80°C or up to 4 hours at room temperature [2, 4, 5, 9].

The concentration of fibrinogen is lower than that obtained with chemical precipitation. However, the material has the advantage of being prepared within a closed system with sterile connection device (SCD) used for cutting tube segments which markedly reduces the risk of pathogen transmission. Fibrinogen concentration can be increased by applying additional isolation. In contrast to commercial products, where the amount of active substance per vial is standardized (same amount for each batch), laboratory-prepared (in house) fibrinogen concentrates are not. Factors such as quality of raw plasma, donor characteristics as well as conditions of collection, preparation and storage may affect fibrinogen concentration.

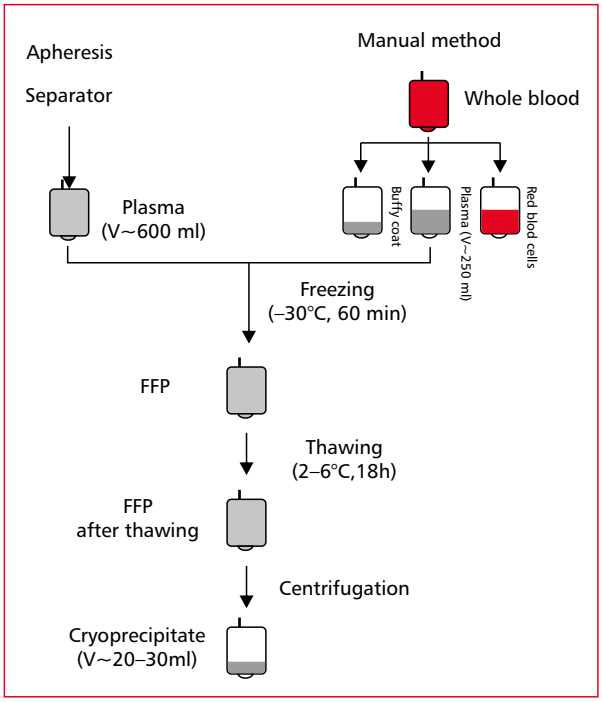

Figure 3. Fibrinogen concentrate prepared by cryoprecipitate method. WB — whole blood; RBCC — red blood cell concentrate; FFP — fresh frozen plasma; V — (average) volume. Author's own diagram

In laboratory conditions fibrinogen concentrate is prepared approximately within two days of blood/plasma collection. The fact should be taken into account while planning the procedure; it is of particular significance in the case of autologous preparation [10, 12, 13].

An automated CryoSeal system was developed (Thermogenesis, USA) which allowed to shorten preparation time and obtain 4 portions of fibrinogen concentrate and thrombin solution from one unit of plasma in a closed system. The CryoSeal system consists of a cryochamber, a Thrombin Processing Device (TPD) kit and a set of 4 pairs of 3 ml barcoded syringes. Fibrinogen concentrate is obtained by cryoprecipitate method, and thrombin is produced through activation of plasma prothrombin by negatively charged ceramic beads. When the process is terminated, the syringes are filled with equal volumes of thrombin solution and fibrinogen concentrate (Fig. 4). At application, the two solutions mix to give fibrin glue. The whole procedure lasts approximately 60 minutes. The Vivostat (Vivostat A/S, Denmark) is another available system though based on whole blood instead of plasma. Whole blood collected from the patient is subject to chemical precipitation. In this system, biotin-batroxobin mixture and

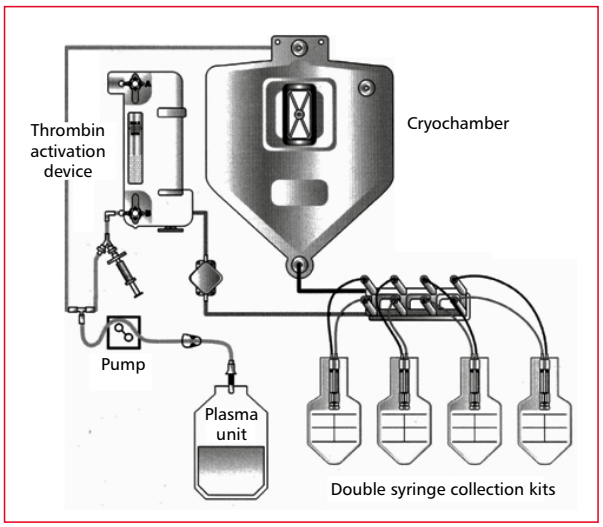

Figure 4. CryoSeal (Thermogenesis) system [10]

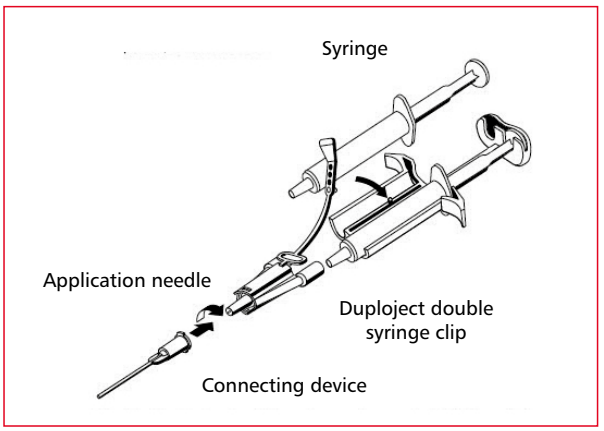

Figure 5. DUPLOJECT syringe for application of fibrin glue (source: Tissel product characteristics — http://chpl.com.pl/data_files/2012-12-03_v2_20121122_tisseal_frozen_spc.pdf) (access: 10.10.2021)

buffer with appropriately selected pH are used to obtain fibrinogen concentrate and thrombin. In the Vivostat system the entire procedure takes about 30 minutes [8, 10].

Fibrin glue — properties and application

The physical and chemical properties of fibrin glue primarily depend on the concentration of thrombin and fibrinogen. Higher thrombin concentration induces faster clot formation; at low thrombin concentration (400 IU/ml), the clot is formed within a minute, with higher thrombin concentration (2000 IU/ml) and 3:1 thrombin/fibrinogen ratio the clot is formed within seconds. Higher thrombin concentration is preferable for rapid wound sealing, while lower concentrations are better for procedures requiring time and precision (skin grafting). On the other hand, the higher fibrinogen concentration, the stronger tissue adhesion with positive impact on bleeding arrest. Sometimes thrombin is replaced by batroxobin — a thrombin-like serine protease from the venom of *Bothrops atrox moojeni*. Batroxobin binds fibrin with higher affinity than thrombin, and is not inhibited by antithrombin and antithrombin homologs [6, 9, 14–17].

To date, numerous modifications of fibrin glue have been developed. Dyes (such as indigo carmine) have been added to the otherwise colorless material to facilitate glue application and to mark the wound site. To upgrade the physical properties of fibrin glue, research is underway to develop mixtures of fibrin with other materials (hybrids), e.g. to obtain fibrin-chitosan or fibrin-alginate. This would largely expand the scope of application of fibrin glue. Apart from modifications in proportion or composition of fibrin glue, various active substances such as antibiotics or stem cells can also be added (section "Fibrin glue as carrier of active substances"). Tissue adhesives are quickly absorbed at application site (after 3 weeks on average) [7, 17].

Commercial fibrin glues (Tissel, Beriplast etc.) are available as frozen or in form of lyophilisate. The material is prepared immediately before use — it is dissolved in a special buffer or thawed at the temperature indicated by the manufacturer.

Laboratory-prepared fibrin glues are usually stored frozen and thawed at 37°C. Glue is applied by extemporal mixing of the two basic components i.e. fibrinogen concentrate and thrombin solution to form a fibrin clot at the bleeding site. The components of fibrin glue are mixed either simultaneously or sequentially. When both substances are applied simultaneously, a two-syringe set with a common cannula is used, which, if necessary, can be extended with a teflon tube (for hard-to-reach application site, endoscopic surgery) (Fig. 5) [2, 10].

The components of fibrin glue can also be mixed sequentially in a Petri dish to obtain a thin, film-like layer of glue to be transferred to the surgical field. Some procedures, like skin grafts require separate application of the component, eg thrombin solution on facial muscles, and fibrinogen solution on the transplanted tissue. For a large surgical surface or a minor-bleeding area spray application is recommended which allows to obtain extra thin layers of fibrin. The volume of the applied glue depends on numerous factors such as application method (syringe/spray), site (dry/wet tissue,

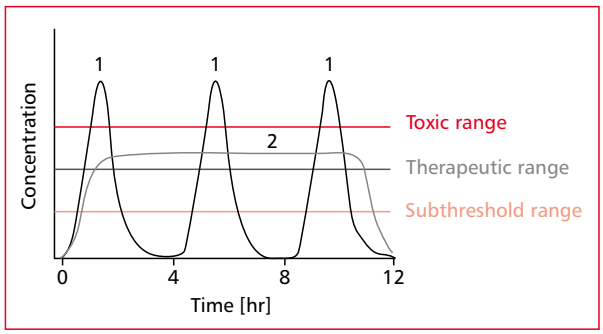

Figure 6. Drug release kinetics 1) common drug 2) drug with prolonged release. Author's own drawing

good/poor adhesion), size of the treated area and the presence/absence of bleeding. The volume of 1 cm^3 of fibrin glue has been demonstrated to cover the surface of 10 cm^2 with syringe and 25 cm^2 with spray application [2, 3].

Fibrin glue as carrier of active substances

The unique features of fibrin, such as network structure, biocompatibility, controlled biodegradability or potential for target delivery of active substances, render it a suitable carrier for antibiotics, cytostatic agents, growth factors and stem cells, bacteriophages or genetic vectors. Comparison of drug kinetics (curve 1, Fig. 6,) and kinetics of the cross-linked form — drugs immobilized in fibrin glue (curve 2) shows the latter to have prolonged and targeted action, so the concentration of active substances in blood does not fluctuate (therapeutic range is above the subthreshold and toxic ranges). This is brought about by constant, slow release of active substance from the drug-embedded fibrin glue. Therapy with cross-linked substances is therefore more effective [18].

Site-directed application of drug-embedded fibrin glue (e.g. with lidocaine, sisomycin, doxorubicin) may support postoperative pharmacotherapy. Physicians from Harbin Medical University have successfully used sustained-release lidocaine from fibrin glue to relief post-tonsillectomy pain and subpectoral breast augmentation. In the absence of metastases, the punctual effect of cytostatics delivered to tumor site via fibrin carrier, may be used as alternative to devastating chemotherapy. Mesenchymal stem cells (MSCs) suspended in the fibrin network were applied for esophageal reconstruction (stromal cell autografting), regeneration of damaged peripheral nerves and skin regeneration [19–22].

An open wound is the gateway for microorganisms and fibrin glue (like plasma) —an ideal medium for their growth and multiplication. Although fibrin has been demonstrated to delay colonization of microorganisms to the wound, antibiotics are sometimes added to either component of fibrin glue with the aim of inhibiting bacterial infection. Wound-healing is accelerated and antibiotic activity significantly extended which counteracts drug resistance. *Staphylococcus aureus* for instance, has been shown to activate prothrombin through its own coagulases and to form a fibrin "shield". On the other hand, the pathogen has been demonstrated as easily removed from the organism due to adhesion to fibrin. Scientists from the Department of Cardiac Surgery at the University of Tokyo evaluated the effectiveness of site-directed delivery of vancomycin-embedded fibrin sealant to *Staphylococcus aureus* (MRSA strain)-infected hospital rats. Following application of vancomycin-embedded fibrin glue, small amounts of vancomycin were detected in rat serum whereas no bacteria were detected in microbiological tests. Targeted administration of antibiotic-saturated fibrin glue was therefore found to resolve infection with no significant effect on the rest of the organism. The study also assessed sustained vancomycin release from fibrin and disc diffusion assays were performed to detect vancomycin-resistant *Staphylococcus aureus MRSA*. Vancomycin release from fibrin glue lasted 14 days and the antibacterial activity was strong throughout the period [24]. It must be noted however that antibiotics added to components of fibrin glue may alter the physical properties of fibrin, e.g. clotting time or adhesive strength. Greco et al. demonstrated that cefotaxime disturbs the process of clot formation. The effect of mesocillin on adhesive strength of fibrin glue was also observed. The study of Kram et al. demonstrated that gentamicin and neomycin extend clotting time. In conclusion, the properties of the clot as well as time of clot formation should always be checked in laboratory setting before using fibrin glue as a drug delivery system [7, 14, 23–25].

In some cases, eg. when a bacterial biofilm is formed or infections caused by drug-resistant bacteria occur, the application of bactericidal or bacteriostatic agents may prove insufficient. According to recent scientific reports, bacteria are becoming increasingly resistant to most common antibiotics, which only suggests that in the future antibiotics may prove completely useless. Phage-

based therapy seems to be the solution here. Scientists led by Evgenia Rubalski investigated the use of fibrin glue with embedded PA5 bacteriophages. Biocompatibility of bacteriophages embedded in the fibrin network was studied with scanning electron microscopy (SEM); the release was monitored and activity against *Pseudomonas aeruginosa* (responsible for most hospital-acquired infections) was measured. Numerous bacteriophages were shown to be evenly incorporated into the fibrin network, and the structure of bacteriophage-fibrin glue was identical with control glue. PA5 phage release was observed an hour after immobilization, and continued until fibrin breakdown (about 11 days). After the blood clot is resolved products of fibrin degradation remain in the blood stream with no influence on bactericidal effect of phages.

Other types of viruses, e.g. viral vectors with transgenes can also be site-delivered with fibrin glue. In 2010, study reports appeared on successful use of fibrin glue with an adenovirus vector and β-galactosidase transgene for transformation of eukaryotic cells. Cells transfected in a mixture of fibrin glue and vector contained more β-galactosidase transcripts than cells transfected with the virus alone. The supportive effect of fibrin glue may be important for upgrading the techniques of site-directed therapy for genetic diseases (absence of enzyme, topical treatment) or for development of more effective viral vector-based vaccines [27].

Clinical application

Fibrin glue has found wide application in many fields of medicine as sealant, adhesive, healing aid or for facilitating site-delivery of active substances. As emphasized earlier, changes in the concentrations of the two basic components of fibrin glue may significantly affect the nature of the clot [3, 9, 13].

Regenerative surgery

Regenerative medicine uses fibrin glue for bone reconstruction. Fibrin network serves as a scaffold and supportive material for bone debris or bone-forming cells (osteoblasts), incorporated into the broken, chipped or fractured sites. Bony reconstruction is usually based on bone grafts or synthetic bone implants (e.g. made of stainless steel). Homogeneous biografts are rare while synthetic bone substitutes are usually maladjusted, integrate poorly and are susceptible to fibrosis instead of being osteoinductive. A modern bone bio-substitute should consist of a scaffold (fibrin network), bone debris or osteoblasts, and substances which stimulate new-bone development and growth. For joint injuries or fine-grained fractures (with small bone fragments) traditional methods of graft immobilization (metal plates, wires and screws) do not work. Cavities of less than 1 cm in diameter can be "repaired" with bone debris with fibrin glue. Compared to traditional materials such as wires and screws, fibrin glue is absolutely natural, the components may be autologous and properties modified by altering the concentration of the basic components. For better wound healing, the preparation can be enriched with platelet-rich plasma or platelet concentrate which contains numerous growth factors to support tissue regeneration (platelet-derived growth factor, PDGF; transforming growth factor TGF etc.). Such implants have osteoinductive and osteoconductive properties and are fully biocompatible, the patient therefore does not have to be subjected to re-surgery for screw or wire removal. Moreover, during the clotting process, fibrin integrates the elements of tissues and graft which markedly facilitates surgeon's work. Fibrin glue also supports cartilage, tendon and ligaments repair. Scientists from São Paulo research center removed 5 mm fragments of rat thighbone (femur) and the defect was filled with a mixture of fibrin, calcium phosphate and stem cells. Following the period of convalescence, spontaneous differentiation of cells into osteoblasts was observed as well as gradual deposition of bone matrix on a fibrin scaffold (C.V. Cassaro, L.A. Justuli, 2019) [32]. A Chinese research group used an in vitro prepared chondrocyte-microtissues laden fibrin gel scaffold for reconstruction rabbit's ear (A. Noori, S.J. Ashrafi, 2017) [18]. Technological advancement opens opportunities for fibrin glue application still further. An example here is bioink for 3D printing of the desired tissue [9, 18, 28].

Fibrin glue is also used in reconstructive urology. In a study performed by a center in Texas, fibrin glue was successfully applied for reconstruction of the organs of gentitourinary tract in 17/18 men. No incidents of hematoma, seroma or pleural effusion were reported. Postoperative complications occurred in 1/18 patients and were rather related to the patient's preoperative condition as well as complexity of the procedure itself [29].

Aesthetic medicine

In aesthetic surgery, fibrin glue is primarily used for affixing/securing large skin surfaces or skin grafts (particularly in facial or hand burns). Numerous experiments demonstrate that the use

of fibrin sealant in aesthetic surgery increases the chances of skin graft tolerance; the graft adheres more firmly, has a longer life span, fewer hematomas are formed, and the wound requires no special drainage. Sutures are more flexible than surgical threads, and the final scars are more pleasing to the eye which is of crucial importance in aesthetic surgery. Fibrin glue can be applied in hard-to-reach sites or in places susceptible to bending or stretching. It has been proved beneficial for face lifting and wrinkle removal e.g. in neck modeling with fascial and temporal muscle suspension. Fibrin glue is also used in burnt wound cleansing, oral and maxillofacial surgery, in otorhinolaryngology, e.g. mandible reconstruction or filling in empty spaces after a surgical intervention (tissue excision). Treatment with fibrin has been shown to reduce the frequency of seroma, eg. during breast and arm-pit surgery.

Application of fibrin glue to 100 patients undergoing facial surgery, eliminated the need for drainage, dressings or use of compression underwear. No postoperative complications were observed and the patient's satisfaction and well-being were much improved. Additionally, proliferation of granulation tissue at wound-site was observed to increase significantly. Physicians from the South Alabama University searched hospital archives for medical histories of patients with burns on 10% of body surface. They compared the effects of two techniques of skin grafts fixation; with fibrin glue (study group) and staples (control group). In the study group, transplant rejections were much less frequent, and on average patients were discharged two days earlier than control patients. A Philadelphia center reported shorter surgery time by approx. 40 minutes and convalescence by approx. 3 days. There was no need for negative pressure wound therapy for patients with split-thickness skin grafting (STSG). In another study, neck contouring with fibrin sealant was performed and convalescence was shortened from 7–10 days to 2–3 days with reduced post-surgery swelling, petechiae and less frequent seroma. During a face lifting procedure, a research team from California center used fibrin glue only on half of the face surface. 24 hours after surgery, seous fluid was collected; 10 ml from the fibrin glue-treated part and 30 ml from the other half. Physicians from a center in Nottingham applied fibrin for removal of hair cyst from the sacrococcygeal region (pilonidal cyst). After two rounds of curettage, the method was found 97% effective [9, 26, 30–36].

Other applications of fibrin glue

Apart from wide application of fibrin glue in regenerative medicine and aesthetic surgery, the sealant is also used in dental surgery, general surgery, ophtalmic surgery, laryngology, neurological surgery, cardiovascular surgery, thoracic surgery, gynecology and urology.

Fibrin glue is administered to patients with coagulation disorders (haemophilia A, B, or von Willebrand's disease) when surgery or tooth extraction is indicated. Fibrin glue achieves hemostasis in patients with prolonged clotting time on anticoagulant medication.

The decision to apply fibrin glue does not necessarily mean discontinuation of anticoagulant therapy. Hemostatic properties of fibrin may affect the number of transfused blood components (FFP rich in coagulation factors) and contribute to rational blood management. Moreover, fibrin glue adheres to moist and slippery tissue surfaces and can therefore be applied in parenchymal-sparing surgery. Its application reduces the risk of bleeding from the testicles, liver, kidneys, spleen or pancreas and the flesh is more likely to be spared from partial or total resection. Fibrin glue has also been found effective in endoscopic surgery of gastric ulcers, ruptured esophageal varices or closure of perianal and rectovaginal fistulas. Physicians from a South Korean center applied fibrin glue for fixation of surgical mesh in 78/160 patients subjected to inguinal hernia repair. Patients who were administered fibrin glue required fewer painkillers than patients who were treated with traditional staples (H. Vossoughinia, M.A. Zarringhalam, 2020) [36].

The effectiveness of fibrin embedded with adipose tissue stem cells (ATSCs) was evaluated at Marmara University for the treatment of rats following delayed tooth replantation. Stem cell-embedded glue was used to bind teeth and was found to accelerate regeneration and reduce ankylosis (teeth stiffening so frequent after tooth replantation) by 61% as compared to control. Scientists from the Ahmedabad center tested the viability of human dental pulp stem cells (HDPS) in 2D and 3D fibrin scaffolds of various concentrations. They found that 25% fibrin glue prolongs HDPS viability which may be of great importance for regenerative endodontics [9, 36–40].

Fibrin glue is also in common use for eye surgery. Surgical suture of eye tissue often leads to red eye symptoms, irritation, infection, and sometimes even transplant/graft rejection. Natural tissue adhesives (e.g. fibrin) are a much safer and more convenient for tissue binding in ophthalmology. Fi-

brin glue is used for eye reconstruction and eyelid surgery, conjunctival closure following pterygium excision, strabismus surgery, closure of corneal perforation and corneal ulcers, cornea transplant or to prevent leakage following glaucoma surgery.

Fibrin glue is also used by otolaryngologists during tympanoplasty, tonsillectomy, and other head- and- neck involving procedures. Doctors from the Catholic University of Korea described the novel procedure of applying commercial Tissel glue for endoscopic nasopharyngeal angiofibroma removal. Endoscopic tumor surgery is burdened with heavy bleeding so the procedure is difficult often brings about complications. However, it also helps to limit disease recurrence. Fibrin glue seals blood vessels, arrests bleeding and helps to avoid embolization which is another source of further postoperative complications. Endoscopic injections of fibrin glue were used by physicians from several Iranian centers for pharyngocutaneous fistula (PCF) removal after complete laryngectomy. Fistula closure was reported after a month which suggests that fibrin glue can be effectively used for fistula repair in otolaryngology [9, 25, 39–42].

Fibrin glue is also used in neurological surgery. Cerebrospinal fluid consists mostly of water (approx. 99%) with small amounts of proteins (e.g. coagulation factors) so it has no hemostatc properties. Fibrin glues are used to stop the leakage of cerebrospinal fluid during such procedures as dura mater repair or intracranial meningeal hernia closure. Physicians from a center in Rome applied Hemopatch with fibrin glue as dural sealant in cranial and spinal surgery of 22 patients. No cerebrospinal fluid leaks were reported. Moreover, they confirmed the effectiveness of fibrin glue for microvascular decompression, rhizotomy, laminectomy (removal of spinous processes and vertebral arches) and tumor craniotomy. The outcome of studies on rat models demonstrated that neurotrophic factor-embedded fibrin glue can successfully be used for targeted therapy [9, 43].

In cardiovascular surgery, small amounts of glue are used for sealing complex sutures, for circulatory atomosis and immobilization of venous cannulation. Fibrin glue has been demonstrated as effective for heavy mediastinal bleeding, for stopping pericardial fluid discharge or for arterial suture sealing. One study suggested that connective tissue growth factor (CTGF) embedded adhesive can be effectively used for covering vascular prostheses. Z. Yan, J. Wei et al. used glue for embolization and sclerotherapy in arteriovenous malformation and found that in 20/25 patients the frequency of embolic episodes was reduced by 90%, by 75% in 3 and by 50% in 2. The results are clearly indicative that procedures supported by fibrin glues are absolutely safe and effective for treatment of small and medium congenital maxillary defects [9, 44].

Application of fibrin glue in thoracic surgery is more problematic due to the anatomical structure and physiological properties of the lungs (constant volume change, moist surface). Despite the obstacles, fibrin glue is successfully applied to stop postoperative air leakage (during segmentectomy or lobectomy), for closure of bronchopleural fistulas, or for suture reinforcement following thoracotomy. Already in 1993, there appeared reports on successful application of fibrin glue in pleurodesis of neonatal persistant pneumothorax. Scientists from the Tokyo center reported reduction in the incidence rate of postoperative complications following partial lung cancer surgery and the use of fibrin glue [9, 44–47].

Fibrin adhesives have also found application in gynecology, eg. in preterm prelabor rupture of membranes (PPROM) which result in higher perinatal morbidity and mortality. The adhesive was injected prior to cervical cerclage insertion and in the days that followed it was prophylactically applied into the genital tract to stop further leakage. Integration of the amniotic and allantoic fluids was reported. Intrauterine infections were infrequent. In urology, on the other hand, fibrin glue is used to repair bladder fistulas, in nephrectomy, renal tumor and cyst resection. As compared to traditional methods of stones removal, the use of fibrin glue results in fewer recurrences. Since 2005, there have appeared reports on the use of fibrin glue as sealant for 3-suture vasovasostomy. One of the advantages is shorter procedure time [48, 49].

Further advancement in traumatology may be the development of autologous fibrin bandages. A biological bandage obtained from autologous blood would not only arrest bleeding (like ordinary gauze dressings) but would also actively support wound repair [9].

Summary

Application of fibrin glues is a non-invasive method of supporting tissue regeneration and wound healing. The preparations are increasingly safe as they are based on fibrinogen concentrate obtained either from autologous plasma or from pathogen inactivated allogeneic plasma. Moreover, fibrin glues prepared in a closed system of labora-

tory setting significantly reduce the risk of bacteria transfer. Fibrin glues are routinely used in various fields of medicine but on top of that, adhesives are increasingly popular in targeted chemotherapy or modern genetic engineering. Despite extensive literature which illustrates the effectiveness of adhesives in various areas of surgery, in Poland fibrin glues are not so common. The aim of the paper was therefore to proximate the issues related to fibrin glue, with special focus on the increasingly wide scope of their application.

References

1. Ge L, Chen S, Ge L, et al. Recent advances in tissue adhesives for clinical medicine. Polymers (Basel). 2020; 12(4), doi: 10.3390/polym12040939, indexed in Pubmed: 32325657.
2. Panda A, Kumar S, Kumar A, et al. Fibrin glue in ophthalmology. Indian J Ophthalmol. 2009; 57(5): 371–379, doi: 10.4103/0301-4738.55079, indexed in Pubmed: 19700876.
3. Albala DM, Albala DM. Fibrin sealants in clinical practice. Cardiovasc Surg. 2003; 11 Suppl 1: 5–11, doi: 10.1016/S0967-2109(03)00065-6, indexed in Pubmed: 12869982.
4. Brennan M, Brennan M. Fibrin glue. Blood Reviews. 1991; 5(4): 240–244, doi: 10.1016/0268-960x(91)90015-5.
5. Cavichiolo J, Buschle M, Carvalho B, et al. Comparision of fibrin adhesives prepared by 3 different methods. Int Arch Otorhinolaryngol. 2013; 17(1): 62–65, doi: 10.7162/S1809-97772013000100011, indexed in Pubmed: 25991996.
6. Tavares K, Mayo J, Bogenberger K, et al. Fibrin versus cyanoacrylate glue for fixation in laparoscopic inguinal hernia repair: a network meta-analysis and indirect comparison. Hernia. 2020; 24(5): 927–935, doi: 10.1007/s10029-019-02072-x, indexed in Pubmed: 31773552.
7. Roberts IV, Bukhary D, Valdivieso CYL, et al. Fibrin Matrices as (injectable) biomaterials: formation, clinical use and molecular engineerin. Macromol Biosci. 2020; 20(1), doi: 10.1002/mabi.201900283, indexed in Pubmed: 31769933.
8. Pikuła M, Langa P, Kosikowska P, et al. Stem cells and growth factors in wound healing. Postepy Hig Med Dosw (Online). 2015; 69: 874–885, doi: 10.5604/17322693.1162989, indexed in Pubmed: 26270514.
9. Mintz PD, Mayers L, Avery N, et al. Fibrin sealant: clinical use and the development of the University of Virginia Tissue Adhesive Center. Ann Clin Lab Sci. 2001; 31(1): 108–118, indexed in Pubmed: 11314860.
10. Lachert E. Kleje fibrynowe i żele płytkowe w Korsak J, Łętowska M. Transfuzjologia kliniczna. A-medica Press. 2009; 17: 291–301.
11. Tamer AE, Dare E, Hincke M, et al. Fibrin: a versatile scaffold for tissue engineering applications. Tissue Eng Part B Rev. 2008; 14(2): 199–215, doi: 10.1089/ten.teb.2007.0435, indexed in Pubmed: 18544016.
12. Masri MA, Masri SA, Boyd ND. Isolation o human fibrinogen of high purity and in high yield using polyethylene glycol 1000. Thromb Haemost. 1983; 49(2): 116–119, indexed in Pubmed: 6868007.
13. Arnaud F, Simeoni U, Stechison MT. Rapid polymerizing fibrin glue from autologous or single-donor blood: preparation and indications. J Neurosurg. 1992; 76(4): 626–628, doi: 10.3171/jns.1992.76.4.0626, indexed in Pubmed: 1545256.
14. Thompson DF, Davis TW. The addition of antibiotics to fibrin glue. South Med J. 1997; 90(7): 681–684, doi: 10.1097/00007611-199707000-00005, indexed in Pubmed: 9225887.
15. Mosesson MW. Fibrinogen and fibrin structure and functions. J Thromb Haemost. 2005; 3(8): 1894–1904, doi: 10.1111/j.1538-7836.2005.01365.x, indexed in Pubmed: 16102057.
16. Biscola NP, Cartarozzi LP, Ulian-Benitez S, et al. Multiple uses of fibrin sealant for nervous system treatment following injury and disease. J Venom Anim Toxins Incl Trop Dis. 2017; 23(13), doi: 10.1186/s40409-017-0103-1, indexed in Pubmed: 28293254.
17. Tan ES, Wang H, Lua GW, et al. Fibrin glue spray as a simple and promising method to prevent bleeding after gastric endoscopic submucosal dissection. Dig Surg. 2016; 33(6): 455–461, doi: 10.1159/000446252, indexed in Pubmed: 27220883.
18. Noori A, Ashrafi SJ, Vaez-Ghaemi R, et al. A review of fibrin and fibrin composites for bone tissue engineering. Int J Nanomedicine. 2017; 12: 4937–4961, doi: 10.2147/IJN.S124671, indexed in Pubmed: 28761338.
19. Zhibo X, Miaobo Z. Effect of sustained-release lidocaine on reduction of pain after subpectoral breast augmentation. Aesthet Surg J. 2009; 29(1): 32–34, doi: 10.1016/j.asj.2008.10.008, indexed in Pubmed: 19233003.
20. Kitajiri S, Tabuchi K, Hiraumi H, et al. Relief of post-tonsillectomy pain by release of lidocaine from fibrin glue. Laryngoscope. 2001; 111(4 Pt 1): 642–644, doi: 10.1097/00005537-200104000-00015, indexed in Pubmed: 11359133.
21. Ao Q, Wang S, He Q, et al. Fibrin Glue/Fibronectin/Heparin-Based Delivery System of BMP2 Induces Osteogenesis in MC3T3-E1 cells and bone formation in rat calvarial critical-sized defects. ACS Appl Mater Interfaces. 2020; 12(11): 13400–13410, doi: 10.1021/acsami.0c01371, indexed in Pubmed: 32091872.
22. Deller RC, Richardson T, Richardson R, et al. Artificial cell membrane binding thrombin constructs drive in situ fibrin hydrogel formation. Nat Commun. 2019; 10(1): 1887, doi: 10.1038/s41467-019-09763-0, indexed in Pubmed: 31015421.
23. Ozaki S, Saito A, Nakaminami H, et al. Comprehensive evaluation of fibrin glue as a local drug-delivery system-efficacy and safety of sustained release of vancomycin by fibrin glue against local methicillin-resistant Staphylococcus aureus infection. J Artif Organs. 2014; 17(1): 42–49, doi: 10.1007/s10047-013-0746-9, indexed in Pubmed: 24292855.
24. Shin DW, Sohn MJ, Cho CR, et al. Evaluation of cumulative and conditional antibiotic release from vancomycin-embedded fibrin sealant and its antibacterial activity : an in vitro study. J Korean Neurosurg Soc. 2020; 63(1): 45–55, doi: 10.3340/jkns.2019.0161, indexed in Pubmed: 31916426.
25. Mohamad SH, Barnes M, Jones S, et al. A new technique using fibrin glue in the management of auricular hematoma. Clin J Sport Med. 2014; 24(6): e65–e67, doi: 10.1097/JSM.0000000000000095, indexed in Pubmed: 24699189.
26. Rubalskii E, Ruemke S, Salmoukas C, et al. Fibrin glue as a local drug-delivery system for bacteriophage PA5. Sci Rep. 2019; 9(1): 2091, doi: 10.1038/s41598-018-38318-4, indexed in Pubmed: 30765740.
27. Spicer PP, Mikos AG. Fibrin glue as a drug delivery system. J Control Release. 2010; 148(1): 49–55, doi: 10.1016/j.jconrel.2010.06.025, indexed in Pubmed: 20637815.
28. Cassaro CV, Justulin LA, de Lima PR, et al. Fibrin biopolymer as scaffold candidate to treat bone defects in rats. J Venom Anim Toxins Incl Trop Dis. 2019; 25: e20190027, doi: 10.1590/1678-9199-JVATITD-2019-0027, indexed in Pubmed: 31723344.
29. Evans LA, Morey AF. Current applications of fibrin sealant in urologic surgery. Int Braz J Urol. 2006; 32(2): 131–141, doi: 10.1590/s1677-55382006000200002, indexed in Pubmed: 16650289.

30. Mooney E, Loh C, Pu LLQ, et al. ASPS/PSEF technology assessment committee. The use of fibrin glue in plastic surgery. Plast Reconstr Surg. 2009; 124(3): 989–992, doi: 10.1097/PRS.0b013e3181b039a3, indexed in Pubmed: 19730324.
31. Currie LJ, Sharpe JR, Martin R. The use of fibrin glue in skin grafts and tissue-engineered skin replacements: a review. Plast Reconstr Surg. 2001; 108(6): 1713–1726, doi: 10.1097/00006534-200111000-00045, indexed in Pubmed: 11711954.
32. Grossman JA, Capraro PA, Burneikis V. Minimizing complications in the use of fibrin sealant in aesthetic facial procedures. Aesthet Surg J. 2001; 21(1): 32–39, doi: 10.1067/maj.2001.113197, indexed in Pubmed: 19331869.
33. Butts CC, Sahawneh J, Duffy A, et al. Cost-benefit analysis of outcomes from the use of fibrin sealant for fixation of skin grafts in small-size burns compared to staples as historical controls: a retrospective review. Ann Plast Surg. 2015; 74(2): 173–175, doi: 10.1097/SAP.0000000000000397, indexed in Pubmed: 25590248.
34. Mullens CL, Messa CA, Kozak GM, et al. To glue or not to glue? Analysis of fibrin glue for split-thickness skin graft fixation. Plast Reconstr Surg Glob Open. 2019; 7(5): e2187, doi: 10.1097/GOX.0000000000002187, indexed in Pubmed: 31333930.
35. Sian TS, Herrod PJJ, Blackwell JEM, et al. Fibrin glue is a quick and effective treatment for primary and recurrent pilonidal sinus disease. Tech Coloproctol. 2018; 22(10): 779–784, doi: 10.1007/s10151-018-1864-4, indexed in Pubmed: 30413996.
36. Kouketsu A, Shimizu Y, Nogami S, et al. Wound healing effect of autologous fibrin glue and polyglycolic acid sheets in a rat back skin defect model. Transfus Apher Sci. 2021; 60(4): 103144, doi: 10.1016/j.transci.2021.103144, indexed in Pubmed: 33893027.
37. Choi BJo, Jeong WJ, Lee SC. Fibrin glue versus staple mesh fixation in single-port laparoscopic totally extraperitoneal inguinal hernia repair: A propensity score-matched analysis. Int J Surg. 2018; 53: 32–37, doi: 10.1016/j.ijsu.2018.01.029, indexed in Pubmed: 29410137.
38. Ceylan S, Erdoğan C, Sozen T, et al. The Fibrin Glue Application enhances surgical success rate in endonasal endoscopic dacryocystorhinostomy with lacrimal sac preservation. Ear, Nose & Throat Journal. 2019; 100(5_suppl), doi: 10.1177/0145561319882123, indexed in Pubmed: 31625404.
39. Vossoughinia H, Zarringhalam MA, Hamidi Alamdari D, et al. Fibrin glue in postlaryngectomy fistula-a case report. Iran J Otorhinolaryngol. 2020; 32(109): 113–119, doi: 10.22038/ijorl.2019.38563.2366, indexed in Pubmed: 32219078.
40. Demirel S, Yalvac ME, Tapsin S, et al. Tooth replantation with adipose tissue stem cells and fibrin sealant: microscopic analysis of rat's teeth. Springerplus. 2016; 5(1): 656, doi: 10.1186/s40064-016-2263-9, indexed in Pubmed: 28443212.
41. Kim JiS, Kim DH, Jeon EJ, et al. A case of nasopharyngeal angiofibroma removed using a minimally invasive endoscopic endonasal technique. Wideochir Inne Tech Maloinwazyjne. 2018; 13(4): 551–555, doi: 10.5114/wiitm.2018.75862, indexed in Pubmed: 30524630.
42. Chan S, Gole GA, Lee GA. Amniotic membrane-covered conformer and fibrin glue for toxic epidermal necrolysis. Cornea. 2021; 40(4): 525–528, doi: 10.1097/ICO.0000000000002591, indexed in Pubmed: 33881813.
43. Montano N, Giordano M, Caccavella VM, et al. Hemopatch® with fibrin glue as a dural sealant in cranial and spinal surgery. A technical note with a review of the literature. J Clin Neurosci. 2020; 79: 144–147, doi: 10.1016/j.jocn.2020.07.011, indexed in Pubmed: 33070884.
44. Yan Z, Wei J, Wu W, et al. Embolization and sclerotherapy of maxillofacial arteriovenous malformations with the use of fibrin glue combined with pingyangmycin. Oral Surg Oral Med Oral Pathol Oral Radiol. 2020; 130(1): 25–31, doi: 10.1016/j.oooo.2020.02.003, indexed in Pubmed: 32493683.
45. Kawashima M, Kohno T, Fujimori S, et al. Feasibility of autologous fibrin glue in general thoracic surgery. J Thorac Dis. 2020; 12(3): 484–492, doi: 10.21037/jtd.2020.01.01, indexed in Pubmed: 32274115.
46. Berger J, Gilhooly J. Fibrin glue treatment of persistent pneumothorax in a premature infant. The Journal of Pediatrics. 1993; 122(6): 958–960, doi: 10.1016/s0022-3476(09)90028-2.
47. Drovandi L, Cianchi I, Pratesi S, et al. Fibrin glue pleurodesis for pneumothorax in extremely preterm infants: a case report and literature review. Ital J Pediatr. 2018; 44(1): 91, doi: 10.1186/s13052-018-0533-6, indexed in Pubmed: 30107847.
48. Jung YMi, Park CW, Park JS, et al. Application of tissue engineering and regenerative medicine in prelabor rupture of membranes: a review of the current evidence. Reprod Sci. 2021; 28(6): 1774–1784, doi: 10.1007/s43032-021-00525-2, indexed in Pubmed: 33847975.
49. Ho KL, Witte M, Bird E, et al. Fibrin glue assisted 3-suture vasovasostomy. J Urol. 2005; 174(4 Part 1): 1360–1363, doi: 10.1097/01.ju.0000173941.87775.35.