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THE ROLE OF FIBRINOGEN IN COAGULATION STATUS, METHODS OF ITS CORRECTION. LITERATURE REVIEW AND CLINICAL CASE

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Abstract

Fibrinogen is an important protein of hemostasis. In blood plasma, its concentration is the highest of all coagulation proteins - clotting factors. When coagulation cascade activated, thrombin splits fibrinogen and triggers fibrin polymerization to the form required for efficient clot formation. In acute blood loss, dilutional coagulopathy may develop, causing decreasing fibrinogen levels, which is critical for clot formation. Recently, there has been emerged and rapidly increased the interest in fibrinogen replacement during acute bleeding as a point of the bleeding treatment and prevention, especially in the perioperative patients. This study reviews current data on relevant plasma fibrinogen levels and dosing in various clinical settings, as well as clinical experience with the use of fibrinogen concentrate in patients with dilutional coagulopathy and disseminated Intravascular coagulation syndrome is described.

Фибриногеннің коагуляция статусындағы рөлі, оны түзету әдістері. Әдебиет шолуы және клиникалық жағдай

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Түйін сөздер:
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Аңдатпа

Фибриногенгемостаз үшін маңызды ақуыз болып табылады. Қан плазмасында оның концентрациясы барлық коагуляциялық ақуыздардың ең жоғарысы - ұю факторлары. Коагуляция каскады белсендірілгеннен кейін тромбинфибриногенді ыдыратады және ұйығыштың тиімді түзілуіне қажетті фибрин желісін құру үшін фибриннің полимерленуін іске қосады. Жедел қан жоғалту кезінде сұйылтылған коагулопатия дамуы мүмкін, бұл фибриноген деңгейінің төмен деңгейге дейін төмендеуіне әкеледі, бұл қан ұйығыштарының пайда болуы үшін өте маңызды. Соңғы кездері қан кетуді емдеу және алдын алу мақсаты ретінде, әсіресе операциядан кейінгі кезеңде, жедел қан кету кезінде фибриногенді ауыстыруға қызығушылық артуда. Ол әртүрлі клиникалық жағдайларда плазмадағы сәйкес шекті деңгейлермен дозалау туралы ағымдағы деректерді, сондай-ақ сұйылту коагулопатиясы және тамырішілік шашыранды қан ұю синдромы бар науқастарда фибриноген концентратын қолданудың клиникалық тәжірибесін қарастырады.

Роль фибриногена в коагуляционном статусе, методы его коррекции. Обзор литературы и клинический случай

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Аннотация

Фибриноген является важным белком для гемостаза. В плазме крови его концентрация самая высокая из всех коагуляционных белков – факторов свертывания. После активации коагуляционного каскада тромбин расщепляет фибриноген и запускает полимеризацию фибрина с образованием фибриновой сети, необходимой для эффективного образования сгустка. При острой кровопотере может развиться дилюционная коагулопатия, вызывающая снижение уровня фибриногена до низкого уровня что является критическим для образования сгустков. В последнее время растет интерес к восполнению фибриногена во время острого кровотечения как к мишени для лечения и профилактики кровотечения, особенно в периоперационных условиях. Здесь рассмотрены актуальные данные о соответствующих пороговых уровнях в плазме и дозировании в различных клинических условиях, а также приведен клинический опыт применения концентрата фибриногена у пациентов с дилюционной коагулопатией и ДВС-синдромом.

Introduction

Fibrinogen is an important protein for hemostasis. In blood plasma, its concentration is the highest of all coagulation proteins – coagulation factors [1]. After activation of the coagulation cascade, thrombin cleaves fibrinogen and triggers the fibrin polymerization to a fibrin mesh which is necessary for effective clot formation. With acute blood loss, dilution coagulopathy may develop, causing a fibrinogen level decreasing to a very low level, which is critical for the formation of clots [2]. Recently, there has been a growing interest in replenishing fibrinogen during acute bleeding as a target treatment and prevention of bleeding, especially in perioperative period. The current data on the corresponding threshold levels in plasma and dosage in various clinical conditions are considered here, as well as the clinical experience of using fibrinogen concentrate in patients with dilution coagulopathy and disseminated intravascular coagulation (DIC) syndrome is presented.

Fibrinogen is of fundamental importance for effective clot formation, playing a crucial role in achieving and maintaining hemostasis, and is the first blood clotting factor whose level decreases to a critically low level during major bleeding [2, 3]. Correction of fibrinogen deficiency is critically important for improving patient survival [4, 5], which is confirmed by several studies in which fibrinogen was administered to patients with injuries. A positive correlation with a decrease in mortality has been shown [6].

Fibrinogen is a plasma glycoprotein with a molecular weight of 340 kDa synthesized in the liver [7] and is a physiological substrate of three enzymes: thrombin, factor (F) XIIIa and plasmin [8]. The average half–life of fibrinogen is 3.74 days (range 3.00-4.08 days) [9]. During coagulation, thrombin breaks down the fibrinogen molecule, forming a soluble fibrin monomer. These monomers can form a loose mesh into which red blood cells enter and a clot begins to form. The cross-linking of fibrin polymers induced by FXIIIa is of fundamental importance for the coagulation process, increasing the elasticity of the clot and its resistance to fibrinolysis. Fibrinogen also acts as a ligand for glycoprotein IIb/IIIa receptors found on the platelet surface, which are responsible for aggregation. Platelets become entangled in fibrin filaments, stabilizing the growing clot. There are several reasons that can contribute to a decrease in the concentration and function of fibrinogen during major bleeding. For example, increased consumption of fibrinogen exceeding its synthesis in massive bleeding [10]. In addition, hemodilution after blood loss and subsequent volume replenishment leads to a decrease in the level of fibrinogen [11], a violation of fibrin polymerization (when using synthetic colloids to replace volume) and a decrease in the stability of the clot [12].

Thus, restoration of plasma fibrinogen is the key to normalizing the function of blood coagulation [13-15].

Hypofibrinogenemia is the term used to describe fibrinogen deficiency and usually refers to a level below the normal range (2.0–4.5 g/L in a healthy individual) [16]. Low plasma fibrinogen is shown to be a risk factor for perioperative bleeding in several studies including cardiovascular surgery, trauma [6] and obstetrics [17] patients. However, the threshold limit which initiates the treatment of hypofibrinogenemia is quite subjective and varies from study to study.

Historically threshold level of 1.0 g/L has been established as a trigger for fibrinogen replacement in patients with congenital fibrinogen deficiency. This level was considered sufficient to prevent excessive bleeding and ensure hemostasis in these patients [18] because they usually did not have any other clotting factor deficiency or hemostasis disorders. Achieving a fibrinogen level above 1.0 g/l does not bring any obvious benefit to a patient with congenital fibrinogen deficiency unless there are other abnormalities. It is important to note that, due to limitations associated with this approach, fibrinogen concentrations of less than 1.0 g/l also cause prolongation of other coagulation tests (such as prothrombin time or activated partial thromboplastin time) [19] which should not be interpreted as additional coagulopathy congenital fibrinogen deficiency.

For patients without congenital fibrinogen deficiency, but who develop a fibrinogen deficiency due to severe bleeding in trauma or surgery, there are insufficient data to establish a definitive trigger threshold. The 2007 European trauma Guidelines [20] recommend a threshold of 1.0 g/L. The American Society of Anesthesiologists recommendations 2006 [21] set a threshold of 0.8 to 1.0 g/L. However, current expert opinion suggests that this may be too restrained, and some patients may require a higher target level to ensure effective clot formation [22] and improve clinical outcomes during cardiac surgery [23]. Some scientists have shown in studies that the strength of the clot increases linearly with the concentration of fibrinogen [19, 24]. Thus, these results suggest that fibrinogen supplementation increases clot strength regardless of plasma fibrinogen levels. The revised European trauma recommendations published in 2013 [25] recommend fibrinogen correction in patients with plasma fibrinogen levels below 1.5–2.0 g/L.

Document	Application area	Trigger level
American Society of Anesthesiologists ASA	Perioperative transfusion	<0.8-1.0 g/l
British Standards Committee in Hematology	Massive blood loss	<1.0 g/l
UK Blood Service	Transfusion therapy	≤1.0 g/l

Table 1.
Objective levels of fibrinogen in plasma in various references

Scandinavian recommendations	Massive blood loss	≤1.0 g/l
German Medical Association	Transfusion therapy	≤1.0 g/l
Austrian Society of Anesthesiologists, and Intensivists	Bleeding from trauma	≤1.5-2.0 g/l
Association of Anesthesiologists of Great Britain and Ireland	Massive bleeding	≤1.0 g/l
Italian Society of Transfusion Medicine	Massive bleeding	The target level is not specified, 3 g of fibrinogen concentrate is recommended to increase plasma fibrinogen levels by 1 g/l
Task Force on Advanced Management of Trauma Bleeding	Bleeding from trauma	≤1.5-2.0 g/l
European Society of Anesthesiologists	Massive perioperative bleeding	≤1.5-2.0 g/l

To replenish the concentration of fibrinogen in plasma, world practice uses several methods: plasma transfusion, cryoprecipitate transfusion, and the introduction of fibrinogen concentrate.

Plasma contains 1-3 g/l of fibrinogen. When using FFP at a dose of 12.2 ml/kg, an increase in plasma fibrinogen concentration of only 0.4 g/l was observed; 33.5 ml/kg was required to achieve an increase of 1.0 g/L. In addition, the preparation of plasma for administration requires a long time. First, it is necessary to determine the patient's blood type, as well as compatibility with the recipient. An appropriate number of units must be thawed and delivered to the patient. In general, 60 to 90 minutes may elapse, before plasma is available for transfusion [26–28], which can be an unacceptable delay in emergency situations.

Cryoprecipitate has a fibrinogen content than plasma, usually around 15 g/l [6], which allows more efficient replenishment of plasma fibrinogen levels. Cryoprecipitate is currently used in combination with fibrinogen in cases of increased perioperative bleeding. Cryoprecipitate is a blood product without viral treatment, due to antiviral and other factors of its use in Europe for safety reasons. As with plasma, cryoprecipitate must be checked for blood group compatibility and thawed before transfusion.

Fibrinogen concentrate is made from human plasma and sold as a pasteurized lyophilized powder. During the plasma production process, resulting in a fibrinogen concentrate, a series of virus inactivation and removal processes are released that inactivate all currently present types of viruses, including enveloped and non-enveloped viruses [29]. Thus, fibrinogen concentrate can be considered safer in terms of pathogen transmission than standard (non-inactivated) cryoprecipitate and FFP. Virus inactivation and removal processes also remove antibodies and antigens from the fibrinogen concentrate and significantly reduce the risk of immunological and allergic reactions [29]. Fibrinogen concentrate does not require blood group testing and can be stored at ambient temperature (2-25°C). Thus, the fibrinogen concentrate is practically available for immediate use, and relatively large doses can be administered over several minutes.

Six forms of fibrinogen concentrate are currently available worldwide: Haemocomplettan (CSL Behring), RiaSTAP (CSL Behring), Clottagen/Clottafact (LFB Biomedicaments), Fibrinogen HT (Benesis), FibroRAAS (Shanghai RAAS), and Fibryga (Octapharma).

A number of studies have shown that the dose of fibrinogen required to increase plasma fibrinogen levels by a certain amount depends on the underlying clinical condition of the patient. A dose of 70 mg/kg increased the level of fibrinogen by an average of 1.0 g/l in congenital afibrinogenemia.

In patients with diffuse bleeding after cardiopulmonary bypass surgery, the mean plasma fibrinogen level increased by 0.28-0.3 g/l after administration of 1 g of fibrinogen concentrate 106, 107. In the setting of obstetric bleeding, the mean increase in plasma fibrinogen concentration is 0 .36-1.01 g/l per 1 g of injected fibrinogen [30, 31].

In that work, we want to present our experience with the use of fibrinogen concentrate in the form of clinical observations.

Cases report

Clinical case 1. Patient A., a 46-year-old man with a body weight of 69 kg. He was admitted for transplantation of a liver fragment from a living related donor. Patient has virus B with Delta agent hepatitis, liver cirrhosis, class A by CTP, MELD 6. Thrombosis of the portal vein. Portal hypertension, splenomegaly. Esophageal varices 3rd degrees, with history of variceal bleeding. State after ligation of esophageal varices. Hepatocellular carcinoma Sg VI, VII. T1NxM0, stage B. During the examination in the preoperative period, the patient revealed a decreased level of fibrinogen - 1.96 g/l.

During surgery, in the hepatic period, the patient has decompensation of the hemostasis system, which manifested itself as diffuse bleeding. The coagulation

parameters were as result: prothrombin time (PT) - does not fold (normal 11-21 seconds), prothrombin index (PI) - 0% (normal 80-110%), international normalized ratio (INR) - does not fold (normal 0, 85-1.4), thrombin time (TT) - does not clot (normal 14-21 seconds), activated partial thrombosed time (APTT) - does not clot (normal 24-35 seconds), fibrinogen - 0.77 g / l (normal 2-4 g/l). The thromboelastogram parameters were as result: reaction time (R) - 9.7 minutes (normal 2-8 minutes), clot formation time (K) - 5.9 minutes (normal 1-3 minutes), clot formation kinetics (angle alpha) - 19.6 degrees (normal 55-78 degrees), maximum amplitude (MA) - 34 mm (normal 51-69 mm), coagulation index (CI) - -10.7 (normal -3.0 - 3.0).

Analyzing these indicators, we can conclude that there is a deep deficiency of coagulation factors and fibrinogen, which developed because of the lack of synthetic liver function, blood loss and hemodilution.

To correct the hemostasis system, the patient underwent fresh frozen plasma (FFP) transfusion 20 ml/kg of body weight, and a fibrinogen concentrate at a dose of 6 grams.

As a result, it was possible to achieve consistent hemostasis and stop intraoperative bleeding. The control coagulation tests appeared as: PT - 23 sec, PI - 34.5%, INR 2.1, PT – n/a, APTT - 143.9 sec, fibrinogen 1.75 g/l; thromboelastogram parameters appeared as: R - 11.9 min., K - 5.9 min., alpha angle - 35.3 degrees, MA - 36.7 mm, CI - -10.6.

Clinical case 2. Patient T., a 38-year-old man with a body weight of 67 kg. with a diagnosis virus B with a delta agent hepatitis. Liver cirrhosis, MELD 16. Class C by CTP. Esophageal varices of 2 degrees. Progressive hepatic encephalopathy, type C. Hypersplenism. He was admitted for transplantation of a liver fragment from a living related donor. Examination in the preoperative period revealed TT - 23.5 sec, PI - 33.6%, INR 2.15, TT - 21.4 sec, APTT - 48 sec, fibrinogen - 0.94 g/l.

Intraoperatively, at the stage of liver mobilization, the patient had diffuse bleeding and rather massive blood loss, while the coagulogram and thromboelastogram parameters at the peak of blood loss were as: TT - 22.7 sec, PI - 35%, INR 2.07, TI - 49.8 sec ., APTT - 66.5 sec, fibrinogen 0.93 g/l; R - 7.2 min., K - 6.2 min., alpha angle - 39.9 degrees, MA - 32.8 mm, CI - -7.8.

Considering the bleeding from tissues in the surgical wound and the presence of coagulopathy, it was decided to use fibrinogen concentrate at a dose of 4 grams.

As a result, it was possible to achieve good hemostasis and stop the diffuse bleeding from the tissues in the surgical wound. The coagulation tests after using fibrinogen concentrate in this case were as: TV - 19.1 seconds, PI - 43.3%, INR 1.72, TV - 46.1 seconds, APTT - 62.6 seconds, fibrinogen 1.14 g / l; thromboelastogram parameters were as: R - 8.2 min., K - 4.9 min., alpha angle - 43 degrees, MA - 36.4 mm, CI - -7.4.

Clinical case 3. Patient N., a 62-year-old woman weighing 58 kg. Admitted on an emergency basis with a diagnosis of Invasive intraductal muco-papillary carcinoma of the pancreas (IPMC) pT3 pN0 R0 G2 LV0 PL0 StIIA. State after radical total duodenopancreatectomy with resection of 2/3 of the stomach and splenectomy. Arterial hypertension 3 degree, risk 4. Diabetes mellitus type 2, insulin-depended state. Diabetic nephropathy, chronic kidney disease stage 2. Diabetic polyneuropathy stage 2. Exocrine pancreatic insufficiency. Malabsorption syndrome. Syndrome of protein-energy insufficiency. Syndrome of water and electrolyte disorders. Acute fatty liver. Hepatocellular insufficiency. Ascites 3 degree. Secondary coagulopathy. Disseminated intra-vascular clotting syndrome (DIC). Bilateral hydrot-horax. Acute renal failure prerenal form, stage R by RIFLE. Residual encephalopathy of complex origin. Multiple organ failure.

The patient had DIC syndrome against the background of multiple organ failure, which was accompanied by hemorrhagic syndrome. While the parameters of the coagulogram and thromboelastogram at the peak of blood loss were as: TT - 25.7 sec, PI - 30.1%, INR 2.36, TI - 29.8 sec., APTT - 66.3 sec., fibrinogen 0, 51 g/l; R - 6.5 min., K - 3.4 min., alpha angle - 31.5 degrees, MA - 48.1 mm, CI - -4.9.

We decided to use fibrinogen concentrate at a dose of 4 grams.

As a result of fibrinogen correction, it was possible to achieve success in hemostasis and eliminate ongoing diffuse bleeding from the level of tissues in good condition. At the same time, the control parameters of the coagulogram were as: PT - 37.9 seconds, PI - 18.9%, INR 3.58, PT - 23.8 seconds, APTT - 87.3 seconds, fibrinogen 1.0 g / l; thromboelastogram parameters were as: R - 8.2 min., K - 2.7 min., alpha angle - 59.4 grade, MA - 44.5 mm, CI - 4.2.

Conclusion

Fibrinogen concentrate may reduce the number of transfusions of allogeneic blood products and improve outcomes, with no evidence of an increased risk of side effects.

Fibrinogen concentrate has several advantages over alternative therapies: it is available for immediate administration, it can be administered in very small volumes, it has a very good safety profile, and it is virus-inactivated as standard. Unlike plasma and cryoprecipitate, which contain varying amounts of fibrinogen, fibrinogen concentrate can be used to deliver a standard dose.

In addition, standard laboratory tests or, increasingly, viscoelasticity tests allow for individual dosing based on pre-treatment fibrinogen levels and current hemostatic capacity. Fibrinogen concentrate is often considered more expensive than plasma or cryoprecipitate.

However, a prospective comparison of the direct and indirect costs of allogeneic blood products and fibrinogen concentrate is necessary before drawing any conclusions about cost-effectiveness. Fibrinogen concentrate is an important treatment option for coagulopathic bleeding by reducing or even avoiding the transfusion of allogeneic blood products.

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