INTERCEPT Fibrinogen Complex:

A Modern Advancement in Cryoprecipitate Transfusions

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Through the years, cryoprecipitate antihemophilic factor has been crucial in the treatment of patients who suffer from bleeding disorders. INTERCEPT Fibrinogen Complex (IFC) can alleviate some of the weaknesses of traditional cryoprecipitate, such as its very short expiration time. IFC is an advancement in cryoprecipitate transfusions that can improve upon traditional cryoprecipitate and fibrinogen concentrates by being usable in more applications and with fewer of the drawbacks of classic cryoprecipitate.

Beginning in the 1940s, concentrated factor VIII was produced by Edwin J. Cohn (Kasper, 2012). Cohn fractionated plasma with ethanol to produce the first concentrated product of factor VIII. This product was used throughout the 1950s to treat bleeding disorders, and it was the first precursor of what we now know as cryoprecipitate. In 1964, Dr. Judith Graham Pool discovered the process of forming cryoprecipitate from frozen plasma. Dr. Pool recognized that factor VIII, along with many other coagulation factors, thawed slower than the rest of the frozen plasma. Dr. Pool slowly thawed frozen plasma to reveal a precipitated portion of the plasma containing many coagulation factors that could be separated and used for transfusions.

Cryoprecipitate provides patients with necessary coagulation factors that they may be deficient in. Each cryoprecipitate unit is prepared from fresh frozen plasma and contains fibrinogen, von Willebrand factor, factor VIII, and factor XIII (Nascimento et al., 2014). The fibrinogen level of cryoprecipitate is much more concentrated than the frozen plasma it is pooled from. This is helpful when a patient is receiving many units of blood, and the patient's fibrinogen levels are diluted to a low concentration. The AABB, the American Red Cross, and America's Blood Centers require that each unit of cryoprecipitate contain at least 150 milligrams of fibrinogen per unit, with a volume of 5-20 milliliters.

Cryoprecipitate transfusions will sometimes present with adverse effects. The most common reactions associated with cryoprecipitate transfusions are transfusion associated circulatory overload (TACO), transfusion related acute lung injury (TRALI), and transmission of infectious diseases (Nascimento et al., 2014). While the incidence of transfusion diseases related to cryoprecipitate is low, the commercial fibrinogen concentrates are safer. One factor in the safety of fibrinogen concentrates is their pathogen reduction process, consisting of pasteurization, adsorption, and precipitation. This process destroys most viruses, bacteria, and parasites which also allows for a safer transfusion and a larger donor pool.

Due to safety concerns surrounding cryoprecipitate transfusions, many countries in Europe have stopped using cryoprecipitates and have begun using fibrinogen concentrates (Nascimento et al., 2014). In the United Kingdom, a study was performed comparing the efficacy of cryoprecipitate to fibrinogen concentrates. The fibrinogen concentrate was able to raise the patient's blood fibrinogen levels 0.44 grams per liter on average, while the cryoprecipitate raised the patient's blood fibrinogen level 0.26 grams per liter on average. While both the cryoprecipitate and fibrinogen concentrate were able to treat the patients, the results suggest that the fibrinogen concentrate was more effective and safer to use than traditional cryoprecipitate in the application of raising fibrinogen levels. However, the downside of using fibrinogen concentrate is that they only contain fibrinogen and do not contain other necessary coagulation factors found in cryoprecipitate.

INTERCEPT Fibrinogen Complex is a new advancement in cryoprecipitate products. IFC seeks to improve patient treatment by building on the safety of fibrinogen concentrates while maintaining the other necessary coagulation factors found in cryoprecipitate (*Intercept fibrinogen complex,* 2024). IFC is pathogen reduced, boasts a five-day shelf life when thawed,

and contains the necessary clotting factors found in cryoprecipitate. INTERCEPT Fibrinogen Complex can be thawed and kept at room temperature for five days whereas traditional cryoprecipitate can only be kept for roughly four hours once it is thawed. IFC can also minimize waste in the lab because it has a much longer shelf life before expiration.

Traditional cryoprecipitate is not pathogen reduced, increasing the risk of complications after a transfusion. INTERCEPT Fibrinogen Complex is pathogen reduced. IFC is derived from plasma that has been treated with the INTERCEPT pathogen reduction system (*Intercept fibrinogen complex,* 2024). This pathogen reduction system uses amotosalen and UVA light to target and cross-link nucleic acids in potential pathogens, including viruses, bacteria, and parasites, inactivating them by halting their DNA replication. In addition to inactivating potential pathogens, the INTERCEPT system also inactivates leukocyte contaminants (Fachini et al., 2021). The removal of pathogens and leukocytes lowers the risk of both transfusion transmitted infections and transfusion-associated graft-versus-host disease.

Cryoprecipitate has a high risk of bacterial contamination, which is why it has such a short expiration time. In a study by the Cerus Corporation, bacterial contamination in cryoprecipitate was tested and compared to INTERCEPT Fibrinogen Complex (Lu et al., 2022). Bacterial growth was tested in both IFC and cryoprecipitated AHF by deliberate contamination of the product through different steps of their production. Both IFC and cryoprecipitated AHF were tested with nine different species of bacteria and varying quantities of bacteria. Each unit of plasma was given set amounts of bacteria prior to the freezing and thawing processes to create the cryoprecipitate, and bacterial concentrations were measured throughout the process and during storage afterward. The results showed that when plasma was spiked with bacteria, the traditional cryoprecipitate process would not eliminate the bacteria that it was exposed to. The

freezing process would eliminate some bacteria, but it was insufficient in clearing all contaminants. This also showed that bacteria could easily replicate in cryoprecipitate once thawed, contributing to its short expiration time. In contrast, the IFC that was tested showed that the INTERCEPT pathogen reduction method was able to effectively remove all bacteria contaminants from the unit of plasma. It was found that even when spiked with large amounts of bacteria, the production process of IFC was able to eliminate the bacteria to an undetectable level, and it maintained an undetectable level through its five-day expiration time.

In addition to being safer for the patient, once thawed, INTERCEPT Fibrinogen Complex can be used in more applications than traditional cryoprecipitate because of its much longer expiration time. One application is the use of IFC during surgery to treat hemorrhage (Cushing et al., 2024). Traditional cryoprecipitate can expire in as little as four hours once it is thawed. Because of this, each unit of cryoprecipitate is kept frozen until it is requested and then thawed on demand. The process of thawing the cryoprecipitate unit leads to a 45–60-minute delay between the order of the cryoprecipitate unit and the reception of the unit. This delay, combined with its short expiration time, makes it difficult for cryoprecipitate to be used during a surgery to treat intraoperative hemorrhage. In contrast, INTERCEPT Fibrinogen Complex can easily be used during surgical operations because IFC can be thawed and kept at room temperature for up to five days. Hospitals can always have a supply of thawed IFC on hand, allowing for quick access during surgery. Stanford Hospital saw a large decrease in waiting times in the operating room after beginning use of IFC (*INTERCEPT Fibrinogen Complex (IFC) at Stanford Hospital,* 2023). Before the hospital began using IFC, on average, it would take 45-60 minutes for the operating to receive a unit of cryoprecipitate. After beginning the use of IFC, Stanford Hospital was able to get units of cryoprecipitate to the operating room in only 15 minutes. Saving time is

crucial in the operating room to minimize blood loss, lower costs, and prevent unneeded transfusions.

Once a unit of cryoprecipitate has been thawed, due to its short expiration time, it cannot be frozen and put back into storage (*INTERCEPT Fibrinogen Complex (IFC) at Stanford Hospital,* 2023). This leads to many units of cryoprecipitate going to waste after being preemptively thawed for surgery and going unused. In 2022, Stanford Hospital began use of INTERCEPT Fibrinogen Complex as a source of cryoprecipitate. On average, Stanford Hospital would waste 10% of its cryoprecipitate units each year. Much of the wasted cryoprecipitate was in the operating room, where many of the requested units of cryoprecipitate would go unused. The operating room accounted for the majority of the wasted cryoprecipitate units, wasting roughly 17% of the units it ordered. After implementing IFC into the transfusion center at Stanford Hospital, the waste rate of cryoprecipitate units decreased substantially. The average waste rate for cryoprecipitate since the hospital began use of IFC is only 3.4%. Stanford Hospital always keeps four thawed units of IFC on standby in the lab. The five-day thawed shelf life allows them to supply the operating rooms with cryoprecipitate much faster, and with far less waste. One potential disadvantage to IFC is its cost (Fachini et al., 2021).

When compared to cryoprecipitate, IFC provides many benefits to improve patient treatment and mitigate transfusion risk. The INTERCEPT pathogen reduction system does a great job in removing viral, bacterial, and parasitic contaminants from plasma units used in the making of IFC, which greatly extends its shelf life. INTERCEPT Fibrinogen Complex can provide the safest and most effective supply of necessary coagulation factors in hospitals today.

References

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