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Original Article

Transfusion Medicine Section

Clinical Utilisation of Cryoprecipitate at a Tertiary Care Centre in Telangana, India: A Quasi-experimental Study

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ABSTRACT

Introduction: Cryoprecipitate is a slushy product derived from Fresh Frozen Plasma (FFP) through centrifugation at specific temperatures and speeds. It is rich in factor VIII or antihaemorrhagic factor, fibrinogen, and minor amounts of other clotting factors. Cryoprecipitate is primarily used to correct hypofibrinogenaemia or replenish depleted fibrinogen levels.

Aim: To examine the appropriate clinical utilisation of cryoprecipitate (cryo) by various departments in the Institute and evaluate the improvement in patients through laboratory tests.

Materials and Methods: A single group quasi-experimental study was conducted in the Department of Immunohaematology and Transfusion Medicine (IHBT) at Nizam's Institute of Medical Sciences (NIMS), Hyderabad, Telangana, India. The duration of the study was over a period of six years, from May 2016 to April 2022.. A total of 486 cases where cryoprecipitate was requested were included in the present study. The results were analysed using Prothrombin Time (PT) and International Normalised Ratio (INR). Percentages and means were used to assess various parameters in this study. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 25.0.

Results: The mean age of the study participants was 52.7 years. A total of 486 cases were included over a period of six years, with 3375 cryoprecipitate transfusions performed. The youngest patient was a 9-year-old male, the oldest patient was an 83-year-old male. Most of the cryoprecipitate was appropriately utilised by the Medical Oncology Department (995 cases, 995 units, 20-25 mL per unit-29.48%), while the Cardiology Department had the lowest utilisation (12 cases, 12 units-0.35%). Utilisation by other departments ranged between 45 and 564 cases or units (1.33% to 16.71% per department). The majority of cryoprecipitate units were issued for multiple myeloma and acute leukaemias (new cases and relapse)-28.38% (958 units), while the least were issued for minor surgery and medical cases (29 cases or 29 units-0.85%).

Conclusion: Cryoprecipitate should be used appropriately to achieve desired results and avoid unnecessary transmission. Clinicians, residents, and surgeons should adhere to comprehensive regulatory guidelines for the appropriate usage of cryoprecipitate or any other blood products, as outlined by their hospital transfusion committee.

Keywords: Acute leukaemia, Fibrinogen, Mutiple myeloma, Prothrombin time

INTRODUCTION

Cryoprecipitate is a frozen blood product of the plasma that contains a significant amount of factor VIII, also known as antihaemophilic factor or Antihaemophilic Factor (AHF). According to the literature, Dr. Judith Graham Pool's discovery in 1965, that cryoprecipitate is rich in factor VIII and can be transfused, led to a major advancement in the treatment of haemophilia A. Cryoprecipitate is prepared from FFP stored at -30°C and -80°C for atleast two hours before thawing in a cryobath and undergoing centrifugation. After centrifugation, the cryoproteins are resuspended in a minimal volume of plasma, and the excess plasma after cryopreparation is called Cryoprecipitate-poor Plasma (CPP). Compared to plasma, cryoprecipitate has higher concentrations of factor VIII, factor XIII, fibrinogen, Von Willebrand factor (VWF), factor XIII, and fibronectin. Each unit (approximately 15 to 25 mL) typically provides fibrinogen levels of 150-250 mg/dL, factor VIII levels of 100-150 IU, VWF levels of 100-150 IU, factor XIII levels of 50-75 IU, and fibronectin. Normal fibrinogen levels in the Indian population range from 200 to 400 mg/dL or 2 to 4 g/L.

The normal range of Activated Partial Thromboplastin Time (aPTT) is 30-40 seconds, while the normal range of PT and INR is 11-14 seconds and 0.8 to 1.1 INR, respectively. Although the use of cryoprecipitate is limited, it plays a major role in hypofibrinogenaemia, (globally), life-threatening haemorrhage related to Tissue Plasminogen Activator (TPA), massive transfusion, uremic bleeding, Von Willebrand's disease, haemophilia A and factor VIII deficiency, and reversal of warfarin action [1,2]. In the new era, cryoprecipitate is used to replenish fibrinogen levels in patients with acquired coagulopathy, such as in clinical settings with haemorrhage including cardiac surgery, trauma, Liver Transplantation (LT), or obstetric haemorrhage. Prophylactically, cryoprecipitate is used in Coronary Artery Bypass Grafting (CABG), Transurethral Resection of the Prostate (TURP), febrile illnesses, and sepsis [1]. All cryoprecipitate units are screened, and viral status is checked before being issued to patients.

Cryoprecipitate is a pooled product that does not undergo pathogen inactivation, and its administration has been associated with a number of adverse events, particularly the transmission of blood-borne pathogens and transfusion-related acute lung injury. All cryoprecipitate units must contain a minimum of 80-100 International units of factor VIII and 150-250 mg of fibrinogen in order to benefit the patient [1]. Compatibility testing or group specificity is not required for cryoprecipitate issue and transfusion as cryoprecipitate contains negligible amounts of plasma. Cryoprecipitate can be transfused within two hours of thawing for issue using a standard blood filter and an 18 gauge cannula. The aim of the present study was to analyse the appropriate clinical usage of cryoprecipitate by various departments and evaluate the improvement in those patients through laboratory tests.

MATERIALS AND METHODS

This is a single-group quasi-experimental study was conducted in the Department of IHBT at Nizam's Institute of Medical Sciences

in Hyderabad, Telangana, India. The duration of the study was six years, from May 2016 to April 2022. A total of 486 cases where cryoprecipitate was requested were included in the present study. The study was done after taking approval from the Institutional Ethics Committee (IEC).

Inclusion criteria: All patients admitted to the Institute for the treatment of various inherited or acquired bleeding and clotting disorders and only requisitions with appropriate clinical indications were included, apart from inherited and acquired bleeding and clotting disorders. Patients of all age groups and disease conditions treated in the Institute were included, except obstetric cases. Laboratory investigations that showed appropriateness for cryoprecipitate transfusion were included in the study.

Exclusion criteria: Cryoprecipitate issued to outside hospitals and absolute inappropriate indications such as warfarin reversal, haepatic coagulopathy, and surgical haemostasis. Obstetric cases and no single PT with INR report before the first cryoprecipitate transfusion were excluded from the study.

Study Procedure

All requisitions received in the blood centre from various departments were thoroughly analysed, and the indications for cryoprecipitate were noted. The date of transfusion, patient's diagnosis, the number of cryoprecipitate units requested, the number of previous transfusions and products transfused during the hospital stay, and the number of episodes of cryoprecipitate transfusions were recorded. Corresponding laboratory investigation reports such as PT (aPTT), platelet count, fibrinogen levels, renal function test, liver function test, and serum electrolytes were also noted. The normal range of PT is 12 to 16 seconds, and the normal range of INR is 0.085 to 1.15 [1]. PT and INR were calculated twice (pre and post-transfusion of cryoprecipitate). After analysing the requisitions, appropriate requests were included in the study. All inappropriate requisitions were reviewed after discussing with the respective department clinicians and taking necessary actions.

STATISTICAL ANALYSIS

The results were presented as percentages, means, and Standard Deviations (SD). All statistical analyses were performed using SPSS version 25.0. A comparison of the means between the two groups was conducted using an independent samples t-test.

RESULTS

A total of 486 cases were included in the present study over a period of six years, and 3375 cryoprecipitate transfusions were performed in these patients. The youngest patient was 9-year-old male, and the oldest patient was an 83-year-old male [Table/Fig-1]. The mean age was 52.7 years. In the present study, males accounted for 211 (43.4%) cases, and females accounted for 275 (56.6%) cases. The Medical Oncology Department appropriately utilised the maximum number of cryoprecipitate units, while the Cardiology Department appropriately utilised the least number of cryoprecipitate units. The utilisation of cryoprecipitate by various departments in the Institute. Appropriateness was calculated based on the indication for cryoprecipitate units used [Table/Fig-2]. The majority of cryoprecipitate units were issued for cases of multiple myeloma and acute leukaemias (new cases), accounting for 958 (28.38%) units, while the least number of units were issued for minor surgeries and medical cases, accounting for 29 (0.85%) units, requiring 1 or 2 cryoprecipitate units [Table/Fig-3]. Six units of cryoprecipitate were given per episode. The total number of units used in cases of multiple myeloma and acute leukaemias was 958, but the number of episodes varied from patient to patient. Some units were discarded due to minor reactions or because the product was not usable due to various reasons like storage, etc.

Age group (in years)	n (%)	Number of cryoprecipitate units issued (n%)
06-15	58 (11.93)	426 (12.63)
16-25	44 (9.05)	388 (11.49)
26-30	79 (16.26)	427 (12.65)
31-45	88 (18.10)	659 (19.53)
46-55	98 (20.16)	767 (22.72)
56-65	54 (11.11)	433 (12.83)
66-75	39 (8.04)	186 (5.52)
76- 85	26 (5.35)	89 (2.63)
Total	486 (100)	3375 (100)

[Table/Fig-1]: Age-wise distribution of the cases and the number of cryoprecipitate issued.

Department	Number of issues (n)	Percentage (%)
Medical oncology	995	29.48
Cardiothoracic surgery	564	16.71
General medicine	407	12.05
Haematology	365	10.81
Surgical gastroenterology	295	08.74
Emergency medicine	244	07.22
Neurology	147	04.36
Orthopaedics	104	03.08
Plastic surgery	72	02.13
Rheumatology	64	01.89
Nephrology	61	01.80
Surgical oncology	45	01.33
Cardiology	12	00.35
Total	3375	100

[Table/Fig-2]: Department-wise utilisation of cryoprecipitate.

Clinical diagnosis	Number of units transfused (n)	Percentage (%)
Multiple myeloma and leukaemias	958	28.38
Liver failure	447	13.24
Polytrauma	414	12.26
Post Coronary Artery Bypass Grafting (CABG)	358	10.60
Leukaemias (relapse)	298	08.82
Aortic dissection repair	287	08.50
Liver transplant	144	04.26
Kidney transplant	132	03.91
Limb amputations	108	03.20
Mitral value replacement	97	02.87
Chronic kidney disease	59	01.75
Intracranial bleed and decompression craniectomy	44	01.30
Other minor surgeries such as burns excision and debridement, laproscopy surgeries. Arthroscopies, breast biopsy, carotid endarterectomy etc.,	29	0.85
Total	3375	100

[Table/Fig-3]: Indications of cryoprecipitate transfusion.

When analysing the number of episodes of cryoprecipitate transfusion, it was found that the majority of units and episodes occurred in cases of multiple myeloma and acute leukaemias (4 to 8 episodes), while the least number of episodes were performed in minor surgeries and medical cases (1 to 3 episodes) [Table/Fig-4].

In the present study, cryoprecipitate was most appropriately used for hypofibrinogenemia and least as fibrin glue or fibrin

Number of cases (n)	Diagnosis	Number of units	Number of episodes
134	Multiple myeloma and acute leukaemias (new and relapse cases)	958	4 to 8
86	Aortic dissection repair, liver and kidney transplant	837	4 to 7
98	Polytrauma, liver failure	629	3 to 6
62	Intracranial bleed and decompression craniectomy	218	2 to 6
43	Limb amputations	198	2 to 5
29	Post-CABG	263	2 to 4
15	Mitral valve replacement	144	1 to 4
19	Minor surgeries such as burns excision and debridement, laproscopy surgeries. arthroscopies, breast biopsy, carotid endarterectomy etc.,	128	1 to 3
Total 486		3375	

[Table/Fig-4]: Number of episodes of cryoprecipitate transfusion.
CABG: Coronary artery bypass grafting

sealant [Table/Fig-5]. When analysing PT and INR, it was found that after 1 to 7 episodes of cryoprecipitate transfusions, most cases had PT and INR levels brought to normal or near-normal levels (normal range of PT=12 to 16 seconds and INR=0.085 to 1.15) [Table/Fig-6]. Similarly, aPTT was reversed to normal after cryoprecipitate transfusion. The mean pretransfusion (global) aPTT was 23±5.8 seconds, the mean post-transfusion aPTT was 40.4±6.9 seconds, and the p-value was significant (p=0.0396). When considering the mean fibrinogen levels for the 486 cases, the pretransfusion fibrinogen levels were 1.09±0.43 g/L, the post-transfusion levels were 2.01±0.65 g/L, and the p-value was significant (p=0.048).

Indications	Number of patients	Number of units transfused
Hypofibrinogenemia	179	1347
Massive transfusion	111	598
Uremic bleeding	83	535
Tissue plasminogen activator-associated bleeding	68	645
Fibrin glue	45	250
Total	486	3375

[Table/Fig-5]: Indications of cryoprecipitate.

Diagnosis	Mean pretransfusion PT and INR	Mean post-transfusion PT and INR
Multiple myeloma and acute leukaemia	48 seconds and 1.89	19 seconds and 1.15
Aortic dissection	39 seconds and 1.82	18 seconds and 1.15
Leukaemias (relapse cases)	38 seconds and 1.81	18 seconds and 1.15
Liver transplants	36 seconds and 1.79	17 seconds and 1.14
Kidney transplants	34 seconds and 1.71	18 seconds and 1.16
Liver failure	32 seconds and 1.76	16 seconds and 1.13
Polytrauma	31 seconds and 1.74	17 seconds and 1.14
Intracranial bleed	30 seconds and 1.73	16 seconds and 1.12
Chronic kidney disease	29 seconds and 1.71	16 seconds and 1.13
Limb amputations	30 seconds and 1.70	15 seconds and 1.10
Post-CABG	29 seconds and 1.68	14 seconds and 1.08
Mitral valve replacement	28 seconds and 1.65	14 seconds and 1.07
Minor surgeries	26 seconds and 1.62	13 seconds and 1.05

[Table/Fig-6]: Prothrombin Time (PT) and International Normalised Ratio (INR) ratio pre and post-transfusion of cryoprecipitate.
CABG: Coronary artery bypass grafting

DISCUSSION

Cryoprecipitate is a slushy product derived from FFP by storing it at -80°C for at least two hours, followed by thawing in a cryobath at 4 to 6 degrees centigrade for 45 minutes to two hours. The thawed FFP is then centrifuged at 3200 RPM for 10 minutes at four degrees centigrade. The resulting insoluble precipitate, which is around 15-25 mL, is suspended in 10-15 mL plasma and can be stored for upto one year at -30°C (-30 degrees centigrade). Cryoprecipitate contains factor VIII, fibrinogen, VWF, factor XIII, fibronectin, platelet microparticles, albumin, and associated coagulation factors in minor concentrations. It is primarily used to treat congenital or acquired hypofibrinogenemia and dysfibrinogenemia [2-5].

Platelet aggregation and secondary haemostasis depend on fibrinogen levels, and its deficiency can be either congenital or acquired. Acquired hypofibrinogenemia is the more common form and is secondary to consumptive coagulopathies such as Disseminated Intravascular Coagulation (DIC), trauma, massive transfusion, or postpartum haemorrhage. Other causes include underlying disease states that limit fibrinogen synthesis (hepatic dysfunction, haematological malignancies), dilutional effects in massive blood transfusion, or increased fibrinolysis [5]. Fibrinogen levels below 100 mg/dL are generally considered deficient and impair haemostasis [6]. Cryoprecipitate has been successfully used to supplement fibrinogen in patients with acquired hypofibrinogenemia and dysfibrinogenemia [7].

Von Willebrand's Disease (VWD) is the most common inherited bleeding disorder [7]. The goal of therapy in VWD is to increase both VWF and factor VIII levels. However, severe cases may require alternative treatment options. Congenital factor XIII (FXIII) deficiency is a very rare form of haemophilia, with a prevalence of one in 5 million [8]. Acquired causes include DIC, liver disease, L-asparaginase therapy, or fibrinolytic therapy. Bleeding manifestations are characterised by umbilical stump bleeding in up to 80% of cases [8-10], as well as spontaneous abortion, mucosal bleeding, and a high rate of spontaneous intracranial haemorrhage [11].

Massive transfusion is defined as the replacement of a patient's total blood volume in less than 24 hours or the administration of four units of packed red blood cells within four hours, or rapid transfusion of blood at a rate exceeding 150 mL/minute or 70 mL/kg [12]. Patients who undergo massive transfusions may develop a dilutional coagulopathy or DIC, resulting in thrombocytopenia and hypofibrinogenemia [13]. Bleeding in these patients is often related to thrombocytopenia, but there is an evidence suggesting a potential benefit of using cryoprecipitate in such cases [13,14]. The American Society of Anaesthesiologists (ASA) Task Force guidelines for perioperative transfusion recommend the use of cryoprecipitate to correct excessive microvascular bleeding when fibrinogen levels cannot be measured promptly. Uremic bleeding syndrome is a well-recognised consequence of renal failure, wherein platelet dysfunction and abnormal platelet-endothelial interaction are the primary determinants of bleeding.

In the present study, the mean age was 52.7 years, which is slightly higher than the mean age reported in the study by Zaher GF and Adam SA (43.4%) [15]. The majority of cryoprecipitate units were issued to correct hypofibrinogenemia (39.9%), which is consistent with the findings of Pantanowitz L et al., where cryoprecipitate was used in 49.8% of cases for hypofibrinogenemia [16]. A total of 17.71% of cryoprecipitate units were issued for the purpose of massive transfusion, whereas in the studies conducted by Pantanowitz L et al., 17.59% were used for massive transfusion, and in the study by Zaher GF and Adam SS, only 9.5% of cryoprecipitate units were transfused [15,16].

In the present study, 15.85% of cryoprecipitate units were transfused to correct uremic bleeding. This finding is comparable to the study conducted by Zaher GF and Adam SS, where three

patients with chronic renal failure and acute bleeding episodes were transfused with six units of cryoprecipitate after failure of tranexamic acid and synthetic vasopressin. The first patient was a 64-year-old male with End-stage Renal Failure (ESRF) who had post-renal transplantation and presented with uncontrolled rectal bleeding due to a peptic ulcer. The bleeding was successfully controlled with the transfusion of six units of cryoprecipitate. The second patient was a 50-year-old female on continuous maintenance haemodialysis, who experienced intraoperative haemorrhage during Permcath removal. The bleeding was controlled by transfusion six units of cryoprecipitate. The third patient received six units of cryoprecipitate to control postmenopausal bleeding [15].

Cryoprecipitate was also used as a fibrin glue or fibrin sealant in 9.2% of the cases in the present study, which is consistent with the findings of Pantanowitz L et al., where cryoprecipitate was used as a fibrin sealant in 9.1% of cases [16]. When analysing PT, INR, and aPTT values, improvement was observed after cryoprecipitate transfusions ranging from one to seven episodes in different categories of patients. According to authors Soloway HB and Bereznak CE, as well as Levy JH et al., better replenishment of fibrinogen levels occurs with episodic cryoprecipitate transfusion, particularly in cases of massive haemorrhage, consumption, and dilution coagulopathies [17,18]. Rourke C et al., Stanworth SJ and Lee SH et al., also stated that pooling and episodic transfusions are more effective in improving PT, INR, aPTT, and overall coagulation, as the fibrinogen levels in donor units can vary based on their physical conditions [19-21]. However, the authors did not mention the sample size or provide specific details regarding the exact improvement of PT, INR, and aPTT values in episodic transfusions compared to random cryoprecipitate transfusions.

According to Raturi M et al., the appropriate use of cryoprecipitate was 92.5% [22]. In the study by Zhu C et al., a systematic review and meta-analysis (which included 17 studies on cryoprecipitate), the appropriate usage of cryoprecipitate was reported as 67.2% [4]. The present study shows a slightly higher rate of appropriate usage, exceeding 95%, which aligns closely with the findings of Raturi M et al., where 92.5% of cryoprecipitate transfusions were deemed appropriate (370 cases out of 400 cases-92.5%) [22]. However, the study conducted by Iliassa II et al., reported that a majority of cryoprecipitate prescriptions were found to be inappropriate, with a rate of 81.2%. This finding contradicts the results of the present study and the study by Iliassa II et al., [Table/Fig-7] [4,15,16,22-24].

Study	Year and place of study	Appropriate use of cryoprecipitate percentage	Maximum used for	Maximum cryoprecipitate used by department
Zaher GF and Adam SS [15]	2012 Jeddah, Saudi Arabia	51.9%	Hypofibrinogenemia	Gastroenterology
Pantanowitz L et al., [16]	2003 Boston, USA.	80.0%	Hypofibrinogenemia	Oncology
Raturi M et al., [22]	2018, Karnataka, India.	92.5%	Hypofibrinogenemia	Haematology and oncology
Zhu C et al., [4]	2015, Shanghai, China.	67.2%	Hypofibrinogenemia	Surgical departments
Iliassa II et al., [23]	2016, Malaysia	18.8%	Hypofibrinogenemia	Neurovascular surgery
Kouroki S et al., [24]	2022, Japan	100%	Hypofibrinogenemia	Obstetrics
Present study	India	>95%	Hypofibrinogenemia	Medical oncology and cardiothoracic surgery

[Table/Fig-7]: Comparison of various studies [4,15,16,22-24].

The mean pre-transfusion aPTT was 23±5.8 seconds, and the mean post-transfusion aPTT was 40.4±6.9 seconds, with a significant p-value (p=0.0396). This finding was compared to the study conducted by Raturi M et al., where the p-value was not significant [22]. When considering the mean fibrinogen levels for 486 cases, the pre-transfusion fibrinogen levels were 1.09±0.43 g/L, and the post-transfusion levels were 2.01±0.65 g/L, with a significant p-value (p=0.048). This finding was also compared to the study conducted by Raturi M et al., which reported a significant p-value [22].

Limitation(s)

Cryoprecipitate used for warfarin reversal, surgical haemostasis, etc., were not included in the present study as they fall under inappropriate indications. However, their inclusion could have potentially impacted the overall percentage of appropriate usage. Minor reactions and discontinuation of specific cryoprecipitate units were not considered, although only a few units caused these reactions. The study did not take into account the knowledge of first-year residents regarding the appropriate indications of cryoprecipitate. It is possible that some residents may have opted for liberal transfusions. The use of other products such as albumin, immunoglobulins, vitamin K, and recombinant products was not taken into account. The present study focused on mean fibrinogen levels, PT, INR, and aPTT for the correction of hypofibrinogenemia and assessing the coagulation profile. However, some expired cases did not receive full correction of fibrinogen levels, which could have influenced the post-transfusion mean fibrinogen levels, PT, INR, and aPTT levels. The study did not separately consider overcorrection and undercorrection levels.

Furthermore, further research is needed to address these limitations and provide a better assessment of improvement in cryoprecipitate usage.

CONCLUSION(S)

Blood components are products derived from the centrifugation of whole blood units and can be used in various patient categories where there is an appropriate indication. Cryoprecipitate is primarily used in cases of hypofibrinogenemia, as part of massive transfusion, and in cases of uremic bleeding. Clinicians, residents, and surgeons should adhere to thorough regulatory guidelines set by their hospital transfusion committee to ensure the appropriate usage of cryoprecipitate and other blood products. Consistent haemovigilance and compliance monitoring should be implemented to achieve 100% appropriate usage of blood and its products.

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