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Evaluation of Clinical Appropriateness of Cryoprecipitate Transfusion

Ocena prawidłowości wykonywania przetoczeń krioprecypitatu

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Summary

Background. *Cryoprecipitate (CRYO) is mainly used for management of hypofibrinogenemia during hemorrhage. The historical 1.0 g L^{-1} threshold of fibrinogen is considered quite inadequate, especially in massive bleeds. Furthermore, the appropriate dose and its impact on plasma fibrinogen levels are unclear. Our aim was to evaluate the appropriateness of CRYO transfusion at our hospital.*

Material and methods. *Retrospective review of indicators namely indications, dosage, pre-transfusion coagulation parameters and the magnitude of mean plasma fibrinogen increase (Fib_{inc}) to CRYO transfusion were undertaken at a multi-specialty hospital. Appropriateness was defined based on compliance to both national and international guidelines.*

Results. *A total of 400 transfusions were given in 253 patients. Commonest primary indication was hemorrhage (86%) against prophylaxis (14%). Conventionally commonest clinical scenarios were disseminated intravascular coagulation in hemato-oncology [110 episodes (28%)] followed by factor VIII deficiency [92 episodes (23%)] and cardiac surgery [52 episodes (13%)] respectively. Based on indications the overall appropriateness was 92.5%. Pre-transfusion fibrinogen levels were available in 66% (264/400) episodes including 204 events having fibrinogen < 1.0 g L^{-1}. In patients who did not receive plasma components 6 h prior to CRYO, a mean dose of 6.2 units caused a Fib_{inc} of 0.54 (± 0.36) g L^{-1}.*

Conclusion: *The overall Fib_{inc} per unit of CRYO transfused was 0.09 g L^{-1}. We have noted high level of appropriateness towards CRYO transfusion (92.5%) in the present study.*

Key words: *Cryoprecipitate, Transfusion, Appropriateness, Fibrinogen, Guidelines*

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Streszczenie

Wstęp. *Krioprecypitat (CRYO, cryoprecipitate) jest stosowany głównie w przypadku krwawienia u osób z nabytą hipofibrynogenemią. Historyczna wartość progowa stężenia fibrynogenu wynosząca 1,0 g/l jest uważana za niewłaściwą, zwłaszcza w przypadku masywnych krwawień. Ponadto odpowiednia dawka CRYO i jej wpływ na stężenie fibrynogenu w osoczu nie zostały określone. Badanie przeprowadzono w celu oceny prawidłowości stosowania CRYO w szpitalu autorów.*

Materiał i metody. *W szpitalu wielospecjalistycznym przeprowadzono retrospektywny przegląd wskaźników związanych z przetoczeniami CRYO, tj. wskazań, dawek, parametrów krzepnięcia oznaczonych przed przetoczeniem oraz średniego zwiększenia stężenia fibrynogenu w osoczu (Fib_{inc}, fibrinogen increase). Prawidłowość stosowania CRYO definiowano na podstawie zgodności z wytycznymi krajowymi i międzynarodowymi.*

Wyniki. *Wykonano łącznie 400 przetoczeń u 253 chorych. Najczęstszym podstawowym wskazaniem było krwawienie (86%); rzadziej przetaczano CRYO w ramach profilaktyki (14%). Tradycyjnie najczęstszym scenariuszem klinicznym było rozsiane wykrzepianie wewnątrznaczyniowe o podłożu hematoonkologicznym [110 epizodów (28%)], niedobór czynnika VIII [92 epizody (23%)] oraz zabiegi kardiochirurgiczne [52 epizody (13%)]. Odsetek prawidłowo przeprowadzonych przetoczeń w odniesieniu do wskazań wynosił 92,5%. Dane dotyczące stężenia fibrynogenu przed transfuzją były dostępne w przypadku 66% [264/400] epizodów, w tym 204 epizody ze stężeniem fibrynogenu < 1,0 g/l. W grupie chorych, którzy nie otrzymali składników osocza 6 h przed CRYO, średnia dawka wynosząca 6,2 jednostki powodowała Fib_{inc} wynoszące 0,54 (± 0,36) g/l.*

Wnioski. *Ogólna wartość Fib_{inc} na jednostkę przetoczonego CRYO wynosiła 0,09 g/l. W przedstawionym badaniu stwierdzono wysoki odsetek prawidłowych przetoczeń CRYO (92,5%).*

Słowa kluczowe: *krioprecypitat, transfuzja, prawidłowość stosowanie, fibrynogen, wytyczne*

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Introduction

Cryoprecipitate (CRYO) is produced from the cold insoluble fraction of fresh-frozen plasma (FFP), obtained by thawing a unit of FFP at 1 to 6°C. It is a source of high-molecular weight plasma proteins including fibrinogen, Factor (F) VIII, von Willebrand factor (VWF), FXIII and fibronectin [1]. As per current recommendations of published guidelines, CRYO administration is suggested when fibrinogen levels are less than 1.0 g L^{-1} with clinically relevant bleeding, or as second-line therapy for von Willebrand disease (vWD), FVIII deficiency, FXIII deficiency and uremic bleeding [2–4]. The guidelines clearly state that the use of CRYO must be narrowed down to instances such as the unavailability of specific pathogen-inactivated recombinant factors and/or fibrinogen concentrates and the potential to bleed being severe enough to warrant the risks associated with its administration. Our institution's recommended dose is one unit of CRYO per 7 to 10 kg of body weight which corresponds to approximately 1.5 mL kg^{-1} to 3.5 mL kg^{-1} in the recipients. Published literature suggests that the indications and dose of CRYO lack any evidence base in the patient population till date. Several observational studies have shown that 24% to 62% of CRYO transfusions are inappropriate and there is limited information on patterns of its use [5, 6]. Therefore, being a 2032-bed multi-specialty academic hospital, we aimed to retrospectively review the indications and appropriateness of CRYO, primarily with a focus to optimize the pattern of its use at our center.

Materials and Methods

The study was conducted at the department of Immunohematology and Blood Transfusion. Written informed consent was taken from the recipients before the receipt of any transfusion in accordance with the hospital transfusion policy. We

retrospectively reviewed the medical records of all recipients receiving CRYO (with or without other blood components) at our hospital from December 2012 through December 2015. Study protocol was approved by the institutional ethics committee prior to its commencement. Data captured included recipient age, gender, bodyweight, location, clinical diagnosis, cited indication for CRYO use and laboratory coagulation parameters such as prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT) and fibrinogen levels before and after transfusion. Patients enrolled in the study were diagnosed with multiple disorders. Broadly they were classified into two cohorts, namely "Hemorrhage Cohort" and "Prophylaxis Cohort". Pre-transfusion coagulation parameters within 6 hours preceding the request and post-transfusion parameters up to 12 hours were considered optimal for the assessment of change in laboratory coagulation test values after transfusion. However, this analysis could be carried out only in that group of patients who had both pre and post-transfusion laboratory parameters available. Fibrinogen levels, when ordered, were assessed by the conventional Clauss assay. Magnitude of mean fibrinogen increment (Fib_{inc}) per unit of CRYO was determined. The numbers of episodes, bags and the overall dose of CRYO were noted, along with or without other blood components transfused (Red blood cells [RBCs], FFP, Platelets [PLTs]). All CRYO transfusions were assessed for appropriateness towards indications and dose based on both national (Directorate General of Health Services [DGHS]) and international (British Committee for Standards in Hematology [BCSH]) standards [2, 4]. Data was analyzed using SPSS software version 20 [IBM Inc., Armonk, NY, USA]. Simple descriptive statistics were expressed as mean ± standard deviation and quantitative data was expressed as percentage. The two-tailed t-test was used to compare paired data such as pre and post-transfusion laboratory coagulation test values, whereby, p values of less than 0.05 were considered significant.

Results

During the three year study period, total 2502 units of CRYO were administered in 400 episodes to 253 patients at an average 6.2 bags per episode. Overall, the mean age ± SD (range) in years was 35 ± 19.2 (newborn to 84) and majority were adults 86% (n = 217/253). Mean body weight ± SD (range) in kilogram was 45.6 ± 13.7 (3.15 to 78). Sixty-three percent (n = 159/253) were males (Tab. 1). Location wise 63% (n = 252) requisitions came from intensive care units (ICUs) against 30% (n = 120) from trauma triage. Blood group wise majority were O group (38.1%) followed by B group (26.7%). Commonest primary indication was hemorrhage (n = 217/253 [86%]) against prophylaxis (n = 36/253 [14%]). Conventionally, most common clinical scenario were disseminated intravascular coagulation (DIC) in hemato-oncology [110 episodes (28%)] followed by factor VIII deficiency [92 episodes (23%)] and cardiac surgery [42 episodes (11%)]. Of these 92 episodes of CRYO transfusion, beneficiaries were twenty-five hemophilia A, nine VWD and four factor XIII deficiency patients (Tab. 2). The ratio of (number of CRYO units to other blood components (RBCs + PLTs + FFP) together) was 3.3 (2282/697) versus 1.9 (220/114) in hemorrhage and prophylaxis cohorts respectively.

Of all the requisitions raised, only 66% (n = = 264/400) events had documented pre-transfusion fibrinogen values. Of the 264 events, around 194 and 10 events had fibrinogen values < 1.0 g L^{-1} in hemorrhage and prophylactic cohorts respectively (Fig. 1). Amongst the Prophylaxis Cohort, one patient was diagnosed with necrotizing fasciitis with a pre-transfusion fibrinogen level of 2.41 g L^{-1} and two patients undergoing TURP with a pre-transfusion fibrinogen level of 2.1 g L^{-1} and 2.21 g L^{-1}. Furthermore, in the same Prophylaxis Cohort, around 44% (n = 16/36) were in post–cardiac surgery status and had a fibrinogen level greater than 1.0 g L^{-1}. In addition, 17% (n = 6/36) patients were transfused CRYO at fibrinogen less than 1.0 g L^{-1}. Fourteen of the thirty-six patients who underwent CABG had no fibrinogen level measured at all. Among the Hemorrhage Cohort, 56% (n = 122/217) patients were transfused CRYO at fibrinogen less than 1.0 g L^{-1}, and 10% (n = 22/217) had a fibrinogen level greater than 1.0 g L^{-1}. Around 34% (n = 73/217) patients excluding the factor deficiency cases, had no pre-transfusion fibrinogen level available (Fig. 1).

In Prophylaxis Cohort, mean pre- and post-transfusion fibrinogen levels were 1.35 ± 0.36 (0.08 to 2.0 g L^{-1}), and 1.71 ± 0.46 (1.0 to 2.7 g L^{-1}), respectively. On comparing fibrinogen levels before and after transfusion, the overall mean Fib_{inc} was 0.36 ± 0.3 (0.084 to 1.2 g L^{-1}). Additionally among Hemorrhage Cohort, the mean pre- and post-transfusion fibrinogen levels were

Table 1. Patients' baseline characteristics and transfusion data among two cohorts

S. No.	Variables (Mean ± S.D.)	Total Patients = 253 (Episodes = 400)	Hemorrhage Cohort Patients = 199 (Episodes = 344)	Prophylaxis Cohort Patients = 54 (Episodes = 56)	P
1	Age (years)	35 ± 19.1 (Newborn to 84)	31 ± 19.2 (Newborn to 84)	56 ± 19.4 (12 to 83)	0.0001
2	Weight [kg]	45.6 ± 13.7 (3.15 to 78)	44.4 ± 13.7 (3.15 to 78)	53.0 ± 13.9 (21 to 78)	0.0001
3	Gender [M:F] ratio	1.69:1	1.68:1	3.5:1	0.0513
4	Baseline Hematocrit	25.2 ± 4.5 (13.5 to 38.7)	24.2 ± 4.51 (13.5 to 32.2)	31.2 ± 4.5 (21.1 to 38.7)	0.0001
5	Dose [mL kg^{-1}]	3.09 ± 2.62 (0.37 to 25.4)	3.35 ± 2.62 (0.37 to 25.4)	2.6 ± 1.4 (0.4 to 4.8)	0.037
6	Pre-transfusion fibrinogen [g L^{-1}]	0.88 ± 0.35 (0.01 to 2.40)	0.81 ± 0.35 (0.01 to 2.40)	1.34 ± 0.35 (0.76 to 2.08)	0.0001
7	Change in fibrinogen [g L^{-1}]	0.53 ± 0.37 (0.025 to 1.79)	0.56 ± 0.37 (0.025 to 1.79)	0.36 ± 0.32 (0.084 to 1.19)	0.0002
8	Change in PTT [seconds]	16.7 ± 26.6 (–7 to 120)	16.6 ± 26.4 (–7 to 120)	17.9 ± 26.8 (–5.0 to 120)	0.7331
9	Pre-transfusion platelet count [× 10^9 L^{-1}]	88.5 ± 42.9 (2 to 303)	81.0 ± 54.2 (2 to 263)	131.6 ± 53.9 (15 to 303)	0.0001
10	In-vivo recovery of fibrinogen (%)	80.2 ± 79.7 (9.7–303)	83.0 ± 69.7 (9.7–139)	75.8 ± 65.4 (13.5–303)	0.4702
11	RBC before CRYO	2.10 ± 1.09 (1–4)	2.1 ± 1.10 (1–4)	2.0 ± 1.09 (1–4)	0.5280
12	FFP before CRYO	2.75 ± 1.19 (1–8)	2.7 ± 1.20 (1–8)	2.9 ± 1.19 (2–4)	0.2476
13	Platelets before CRYO	3.24 ± 1.30 (1–10)	3.3 ± 1.30 (1–10)	3.0 ± 1.20 (2–4)	0.1064
14	Total Hospital Stay [Number of days]	9.05 ± 7.78 (1 to 48)	8.95 ± 7.78 (1 to 48)	9.88 ± 7.88 (3 to 21)	0.4081

0.81 ± 0.36 (0.01 to 2.4 g L^{-1}) and 1.37 ± 0.46 (0.56 to 2.9 g L^{-1}), respectively. On comparing fibrinogen levels before and after transfusion, the mean Fib_{inc} was 0.56 ± 0.36 (0.068 to 1.79 g L^{-1}). Mean Fib_{inc} was 0.20 g L^{-1} higher in Hemorrhage Cohort against Prophylaxis Cohort (p = 0.0001; Tab. 3). Overall, the mean Fib_{inc} was 0.54 ± 0.36 (0.068 to 1.79 g L^{-1}) per 6.2 units of CRYO or 0.09 g L^{-1} per bag. Pre-transfusion PT/INR/APTT values within 6 h preceding CRYO transfusions were available in 69.5% (n = 278) episodes. The average values (32.8/2.66/52.7) varied widely. Post-transfusion average values (23.2/1.84/38.9) were available in only 56% (n = 225/400) episodes. Paired-t test was applied to compare means of both pre and post coagulation parameters which showed extreme statistical significance (p < 0.001; Tab. 3).

Additionally the mean dose (± SD) in mL kg^{-1} administered was 3.09 ± 2.62, ranging from 0.37 to 25.4 per episode. In Hemorrhage Cohort, mean dose of CRYO was 3.3 ± 2.6 (0.37 to 25.4) against Prophylaxis Cohort 2.6 ± 1.4 (0.4 to 4.8). This difference was statistically significant (p = 0.037). Total 55% (n = 221/400) episodes were given an appropriate dose in mL kg^{-1} ranging from 1.5 to 3.5 against 32% (n = 127) and 13% (n = 52) episodes of higher (> 3.5) and lower (< 1.5) threshold for dose, respectively. On the day of CRYO transfusion, RBCs, PLTs and FFP were transfused in 29% (73/253), 27% (68/253) and 20% (50/253) of patients.

Discussion

Guidelines such as those of the American Society of Anesthesiologists (ASA), BCSH and

Table 2. Indications for CRYO and appropriateness to DGHS and BCSH guidelines*

Clinical Indications	Total number of patients	Total number of events	Appropriateness of events
Hemorrhage Cohort			
1. Hemophilia A	25 (10%)	59	Yes
2. vWD	09 (3.6%)	22	Yes
3. Factor XIII deficiency	04 (1.6 %)	11	Yes
4. Fibrinogen [Fib < 1.0 g L^{-1}]			
• Congenital	02 (1.0%)	02	Yes
• Acquired	122 (48.2%)	192	Yes
5. Massive bleeds			
• With DIC	20 (7.9%)	35	Yes
• Obstetric bleeds	10 (4.0%)	16	Yes
• Trauma conditions	07 (2.8%)	07	Yes
Total	N = 199 (79%)	N = 344 (86%)	
Prophylaxis Cohort			
1. CABG			
• During procedure [Fib 1.0–1.5 g L^{-1}]	15 (6.0%)	16	Yes
• During procedure [Fib < 1.0 g L^{-1}]	10 (4.0%)	10	Yes
• Pre-procedure transfusion	16 (6.0%)	16	No
2. TURP	02 (1.0%)	02	No
3. Febrile illness	06 (2.0%)	06	No
4. Sepsis	05 (2.0%)	06	No
Total	N = 54 (21%)	N = 56 (14%)	Appropriateness
	Total Patients = 253	Total Events = 400	= 92.5%

*National guidelines — Directorate General of Health Services [Ministry of Health & Family Welfare, Government of India]; BCSH — British Committee for Standards in Hematology; CABG — Coronary Artery Bypass Surgery; TURP — Transurethral resection of the prostate; VWD — Von Willebrand disease; DIC — Disseminated intravascular coagulation

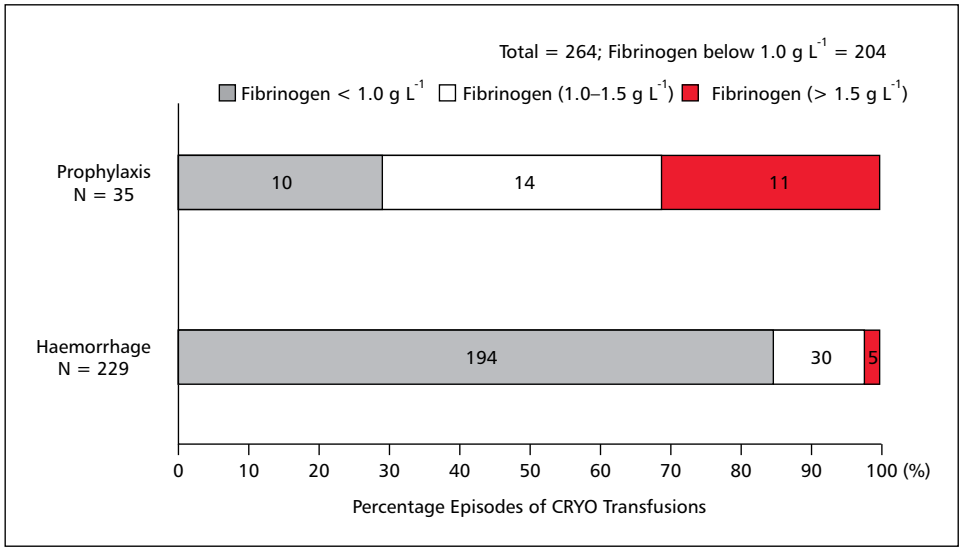

Figure 1. Primary indications for patients and pre-transfusion fibrinogen level

DGHS are among the few published benchmarks for the optimal use of blood components including CRYO. Recent concerns about the safety of CRYO have been raised in several observational studies revealing its inappropriate use ranging anywhere from 24 to 62% [5, 6]. In our study, most common

Table 3. Changes in laboratory coagulation test results after CRYO administration

Indication Cohorts	Coagulation parameters (n)	Pre-transfusion values	Post-transfusion values	▲ Difference in (pre-post) values	P value
1. Prophylaxis	PT (45) in seconds	32.8	26.1	6.7	0.001
	PTT (41) in seconds	52.7	37.0	15.7	0.000
	INR (45)	2.66	2.12	0.54	0.000
	Fibrinogen (35) g L^{-1}	1.34	1.70	–0.36	0.000
2. Hemorrhage	PT (178) in seconds	31.7	22.4	9.3	0.000
	PTT (180) in seconds	54.3	39.3	15.0	0.001
	INR (178)	2.41	1.77	0.64	0.000
	Fibrinogen (229) g L^{-1}	0.81	1.37	–0.56	0.000

PT — Prothrombin time (seconds); PTT — Partial thromboplastin time (seconds); INR — International Normalized Ratio

clinical scenarios for receiving CRYO transfusions included disseminated intravascular coagulation (DIC) in hemato-oncology, followed by factor VIII deficiency and cardiac surgery respectively. Our findings slightly differ from the study by Nascimento et al., wherein trauma had replaced cardiac surgery as the commonest clinical scenario including a sizeable proportion of transfusions with no reported indications towards bleeding [7].

Even though our hospital guidelines provided a clearly defined threshold for CRYO in bleeding (< 1.0 g L^{-1}) and this happens to be meticulously followed by the clinicians when ordering the component; instances such as massive bleeds defied this threshold, propelling us to issue CRYO at pre-transfusion fibrinogen levels as high as 1.5 g L^{-1}. Ranucci et al. have shown that at multivariable analysis, post-cardiac surgery fibrinogen levels lower than 2.2 g L^{-1} remained independently associated with risk of severe bleeding (odds ratio: 2.25; 95% confidence interval: 1.54 to 3.28) [8]. Similarly in our study we saw multiple events where patients undergoing cardiac surgeries with pre-transfusion fibrinogen levels up to 2.0 g L^{-1} were transfused with CRYO. Such clinical decisions of healthcare providers were considered justified despite deviation from the known recommendations. In addition, the mean CRYO dose administered was 3.09 mL kg^{-1}, which was in accordance with our existing hospital policy towards standard dose of CRYO transfusion.

Nascimento et al. suggested that a single dose of CRYO caused a 0.06 g L^{-1} mean increase in fibrinogen. Similarly, Rossaint et al. suggested that one unit of CRYO per 7–10 kg body weight increased fibrinogen level by 0.05 to 0.1 g L^{-1} [7, 9]. Both studies substantiated the observations during our study as well. Alport et al. in Canada used fibrinogen levels done within 6 h both before and after transfusions to categorize appropriateness. They concluded that only 24% in a sample of 453 patients were appropriate transfusions [10]. Considering the use according to various indications stated by clinicians, the appropriateness rate for cryoprecipitate use at our hospital was comparatively higher (92.5%) with regard to studies by Pantanowitz (76%) and Schofield (51%) et al., respectively. Schofield et al. went on to define CRYO transfusions as inappropriate based on pre-transfusion fibrinogen level only [6]. On the contrary, in our study we looked at the overall clinical situation and not just pre-transfusion fibrinogen levels while defining appropriateness.

Despite guidelines impressing upon the role of recombinant fibrinogen concentrate to manage coagulopathy as a safer alternative, the use of CRYO is justified in settings where massive bleeds and DIC are present along with dysfibrinogenemia and recombinant fibrinogen concentrates are not available [4].

Total 23 episodes of CRYO transfusions were given for twenty-five hemophilia-A patients, majority of whom had moderate deficiency of factor VIII (ranging from 2.1 to 4.2%). Of these twenty-five patients, two patients presented to the trauma triage with knee hemarthrosis and severe deficiency of VIII levels (factor activity level < 1%). Initially, these two patients were given factor VIII concentrates; however, later due to the exhaustion of the stock and subsequent unavailability of any further recombinant vials, clinicians ordered CRYO transfusion on an emergency basis in order to arrest bleeding. This instance was considered justified in that particular situation. Furthermore, there were five independent events where CRYO was given inappropriately for indications such as

febrile illnesses and sepsis without any bleeding or underlying coagulopathy. In each of these instances the pre-transfusion levels of fibrinogen were 1.35 and 1.65 g L^{-1} respectively, prompting us to classify them under the scenario of out-of-specifications (OOS).

We believe there are various local hospital--related as well as other contributing factors associated with high rates of appropriateness towards CRYO use at our hospital. Some of the reasons are high compliance rates among expert clinicians such as surgeons and anesthesiologists handling bleeding disorders and massive transfusion protocols at the hospital. Additionally, we also have a highly efficient clinical hematology laboratory team who expedite the delivery of coagulation screening test results usually within 60 minutes of the sample arrival. Furthermore the residents routinely checked for fibrinogen levels at blood bank before the release of CRYO units and prompted the clinicians whenever they were unavailable. All these factors together with a good inventory management of blood components have driven higher percentage of appropriateness (92.5%) of CRYO use in our study. However, there were many limitations, such as its retrospective design because of which we could not account for the change in laboratory parameters, especially fibrinogen, during the use of other blood components and/ /or the dilution effect of crystalloids during critical situations like massive trauma resuscitations. Commonest indications observed for its OOS use were febrile illness with sepsis and prophylactic use without any evidence of bleeding.

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