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Frozen Plasma: Addressing the Epidemic of Inappropriate Use

By: Alan Tinmouth and Doris Neurath. Hematology and Transfusion Medicine, The Ottawa Hospital

Over 220 000 units of Frozen Plasma (either FFP or FP-24) are transfused annually in Canada with an estimated cost in excess of $30 million dollars. Among standard blood components, Frozen Plasma has the highest rate of inappropriate utilization. We know that there is wide variation in use among different hospitals with inappropriate utilization rates of 45%[1,2]. Improving Frozen Plasma utilization is important in order to reduce unnecessary adverse transfusion reactions. Additionally, reducing inappropriate use will increase the amount of Canadian plasma available for fractionated plasma products including IVIG. Monitoring of blood component utilization by retrospective or prospective review is the best way to understand utilization and appropriateness[3]. Prospective reviews are ideally set up to evaluate appropriateness of the request and have the advantage of allowing interventions prior to transfusion but they are extremely resource intensive and have a potential to cause delays in patient treatment. Retrospective (chart) reviews are possibly less resource intensive and can provide aggregate utilization data but determining appropriateness can be challenging and will not resolve inappropriate utilization in a timely fashion. Continuous audits of all blood components may be too resource intensive but the goals of understanding Frozen Plasma use can be achieved by performing rotating or selective audits, which could target known problem areas. Audits which only report the number of units and/or patients transfused, or number of units per patient transfused provides little meaningful data to assess appropriateness especially given temporal changes. Using the ratio of RBC to Frozen Plasma transfused has also been suggested as a measure of appropriateness of Frozen Plasma utilization. However, this is a crude measure that has greater meaning on a macroscopic level such as national data[4]. On a local level, the ratio may vary significantly month to month and comparisons between hospitals will be difficult due to differences in patient population. Simple correlation of Frozen Plasma transfusions with pre-transfusion coagulation data (e.g. number of Frozen Plasma transfusions given to patients with an INR< 1.5) will provide greater insights into appropriateness of use and is easily retrievable through the lab information system though this data will lack important clinical details such as bleeding. While monitoring Frozen Plasma use involves additional work there are some simple methods available that could result in significant reductions in the nearly 50% of all Frozen Plasma transfusions given inappropriately.

[1] Luk C, Eckert KM, Barr RM, Chin-Yee IH. Prospective audit of the use of fresh-frozen plasma, based on Canadian Medical Association transfusion guidelines. CMAJ 2002; 166(12):1539-40.
[2] Lauzier F, Cook D, Griffith L, Upton J, Crowther M. Fresh frozen plasma transfusion in critically ill patients. Crit Care Med 2007; 35(7):1655-1659.
[3] Tinmouth AT. Approaches to blood utilization auditing. Monitoring blood product utilization. In AABB Technical Manual (16th Edition). AABB Press. Bethesda, Maryland. In press 2008.
[4] Wallis JP, Dzik S. Is fresh frozen plasma overtransfused in the United States? Transfusion 2004; 44(11):1674-1675.

In This ISSUE

What's New at ORBCoN

Welcome to the third edition of our newsletter! Spring was a busy time for our offices highlighted by the three major educational events:

- March 31, 2008 - Transfusion Committee Forum
- April 9, 2008 - North East CBS/ORBCoN Videoconference Symposium
- April 18-19, 2008 - Provincial CBS/ORBCoN Symposium

The theme for this newsletter is the appropriate use of plasma. Stay tuned for more information on the provincial plasma audit scheduled to take place in the fall of 2008.

In addition to the work currently underway related to the IVIg Utilization project and the Red Cell Redistribution project described in our previous newsletter, there are several new and exciting initiatives to look forward to in 2008/09 as listed below:

Project	Pilot	Provincial Roll Out
Web based Technologist competency program	June 08	Sept 08
e-Learning program for Nurses	N/A	July 08
Web based Provincial plasma audit	May 08	Sept 08
Patient information pamphlet	N/A	Aug 08

For more information related to these events and other transfusion topics, please visit our website at www.transfusionontario.org.

Contact Us

Central ORBCoN Office
416.480.6100 ext. 89433

Northern and Eastern ORBCoN Office
613.798.5555 ext. 19741

Southwest ORBCoN Office
905.525.9140 ext. 22915

www.transfusionontario.org

Plasma Transfusion Therapy: Treating What Matters

By: Donald M. Arnold, Assistant Professor, Department of Medicine, McMaster University.

The ultimate goal of plasma transfusion is to treat or prevent bleeding. It is generally reserved for patients whose coagulation factor proteins are deficient, often detected by a high international normalized ratio (INR), such as what might occur with an overdose of warfarin. There is no question that plasma transfusions are indicated for the *treatment* of active bleeding in those patients, but what is less certain is its role in bleeding *prevention*.

Not as simple as I-N-R

Many patients every year are given plasma transfusions because they have a high INR. But is this a good enough reason? An accurate assessment of an individual patient's risk of bleeding requires detailed knowledge of their medical history, medication use, recent surgeries and multiple other factors. In lieu of that, the INR is often used as a substitute, or *surrogate* for the risk of bleeding – the higher the INR, the higher the risk. While the relationship between a high INR and bleeding is supported by several clinical studies[1-3], what is not known is whether or not giving plasma transfusion to correct the INR actually translates into a reduction in bleeding events.

Back to basics

One way of studying the relationship between bleeding prevention and plasma transfusions is by simulating high risk bleeding situations in mice. Scientist Dr. William Sheffield, and physician Dr. Donald Arnold, both with Canadian Blood Services and McMaster University are doing just that. Feeding the mice small amounts of warfarin resulted in a predictable increase in the INR and bleeding time following a standardized injury. By giving the mice plasma transfusions, the investigators were able to improve the INR in a dose dependent fashion – the more plasma that was transfused, the more the INR

Plasma Transfusion Therapy: Treating What Matters *continued*

improved. Bleeding time also improved, but beyond a certain dose of plasma there was no incremental benefit.

Looking ahead

For plasma transfusions, as for all transfusions, less is more. It is time to revisit the notion that correcting the INR number improves bleeding outcomes, using well-designed basic science experiments and clinical studies. Treating the INR with plasma transfusions might make doctors feel better; but treating patients with important risks of bleeding is treating what really matters.

1. Reynolds MW, Fahrbach K, Hauch O, Wygant G, Estok R, Cella C, Nalysnyk L. Warfarin anticoagulation and outcomes in patients with atrial fibrillation: a systematic review and metaanalysis. Chest. 2004 Dec;126(6):1938-45.

2. Kucher N, Connolly S, Beckman JA, Cheng LH, Tsilimingras KV, Fanikos J, Goldhaber SZ. International normalized ratio increase before warfarin-associated hemorrhage: brief and subtle. Arch Intern Med. 2004 Oct 25;164(19):2176-9.

3. Fang MC, Chang Y, Hylek EM, Rosand J, Greenberg SM, Go AS, Singer DE. Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. Ann Intern Med. 2004 Nov 16;141(10):745-52.

There is life after fresh frozen plasma: reversing warfarin with a pathogen-inactivated human-derived blood product

Jeannie L Callum, Associate Professor, University of Toronto

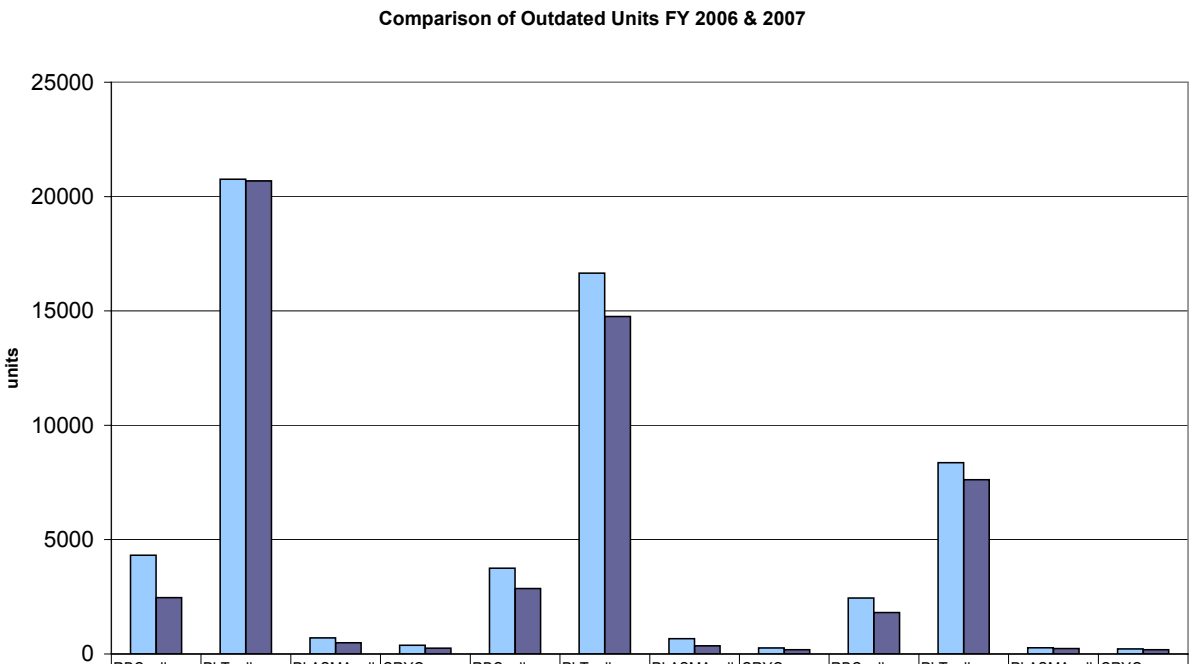
Warfarin increases your risk of a major hemorrhage 7.7-fold when compared to placebo in clinical trials.[i] The annual risk of an intracranial bleed on warfarin is 0.1 to 0.9%, with a mortality risk approaching 50%.[ii] The most commonly employed strategy in Ontario to reverse warfarin anticoagulation in the setting of a major life-threatening hemorrhage is intravenous vitamin K and frozen plasma at a dose of 15 mL/kg. The vitamin K must be given promptly, intravenously[iii], and at a sufficient dose (5-10 mg). In retrospective series of patients with warfarin-related hemorrhage, only 55% of patients received vitamin K as recommended by the American College of Chest Physician's guidelines.[iv] Vitamin K requires approximately 6 hours for its onset of action and therefore frozen plasma is employed as a temporizing strategy. There are several drawbacks of frozen plasma: 1) The product must be thawed; 2) AB plasma must be employed when waiting for the blood group could be detrimental to the patient; 3) The total volume required is difficult to administer in elderly patients; 4) Plasma is high risk for adverse transfusion events, particularly transfusion-related acute lung injury. In addition, all these strategies must be deployed quickly, as the time to warfarin-reversal may be important for survival after a warfarin-related intracranial hemorrhage.[v] The American College of Chest Physician's guidelines currently do not recommend the use of frozen plasma for the reversal of warfarin in a life-threatening hemorrhage, instead they recommend prothrombin complex concentrates (PCC) or rVIIa. PCCs are human-derived, virally inactivated, concentrates of factors II, VII, IX, and X. There are multiple commercially available concentrates, but one has just been approved for use in Canada, Octaplex (Octapharma AG, Switzerland). This product is only of value in the reversal of the coagulopathy from warfarin or vitamin K deficiency. It has no role in the reversal of the coagulopathy associated with hepatic failure or DIC. There has been extensive experience with PCCs in other jurisdictions, with minimal concerns regarding thrombosis.[vi] The dose employed in these reports is generally between 25 to 50 IU/kg, recognizing that the dose is

There is life after fresh frozen plasma: reversing warfarin with a pathogen-inactivated human-derived blood product *continued*

dependent on the brand utilized. The approximate volume per dose is 80 to 100 mL, requires no pre-transfusion testing, and therefore can be administered without delay. Superior benefit in terms of mortality or morbidity over frozen plasma has not been demonstrated. The effect is immediate and allows the patient to be taken to the operating room for emergency neurosurgery without awaiting repeat of the INR. Vitamin K must be administered concurrently or rebound rise in the INR will be seen at six hours after administration.

[i] Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis. JAMA. 1999;282:2058-67.
[ii] Hylek EM. Complications of oral anticoagulant therapy: bleeding and nonbleeding, rates and risk factors. Semin Vasc Med. 2003 Aug;3(3):271-8.
[iii] Lubetsky A, Yonath H, Olchovsky D, et al. Comparison of oral vs intravenous phytonadione (vitamin K1) in patients with excessive anticoagulation: a prospective randomized controlled study. Arch Intern Med. 2003;163:2469-73.
[iv] Atreja A, El-Sameed YA, Jneid H, et al. Elevated international normalized ratio in the ED: clinical course and physician adherence to the published recommendations. Am J Emerg Med. 2005;23:40-4.
[v] Yasaka M, Minematsu K, Naritomi H, et al. Predisposing factors for enlargement of intracerebral hemorrhage in patients treated with warfarin. Thromb Haemost. 2003;89:278-83.
[vi] Aguilar MI, Hart RG, Kase CS, et al. Treatment of warfarin-associated intracerebral hemorrhage: literature review and expert opinion. Mayo Clin Proc 2007; 82: 82-92.

Blood Product Outdates in Ontario



	Central				North/East				South/West			
	RBC_all	PLT_all	PLASMA_all	CRYO	RBC_all	PLT_all	PLASMA_all	CRYO	RBC_all	PLT_all	PLASMA_all	CRYO
2006	4314	20762	706	380	3748	16654	670	265	2447	8362	275	224
2007	2463	20683	489	255	2863	14759	353	189	1812	7617	237	189

[RBC_all=RBC+RBCWASHED+RBCDEGLY+WB]
[PLT_all=PLT+PLTBUFFY+PLTAPHER]
[PLASMA_all=FP+FFP+FFPDIVIDED+FFPAPHER250+FFPAPHER500+CRYOSUP]
[CRYO=Cryoprecipitate]

The graph illustrates a Provincial comparison of the number of outdates for blood products from FY 2006 to FY 2007.

Overall for the province of Ontario, the number of red cell outdates has decreased by 3371 units or 32%.

One of the mandates of the Ontario Regional Blood Coordinating Network is to monitor blood product utilization and to assist hospitals to improve utilization.

The end goal is to ultimately decrease the wastage of blood products within the province.

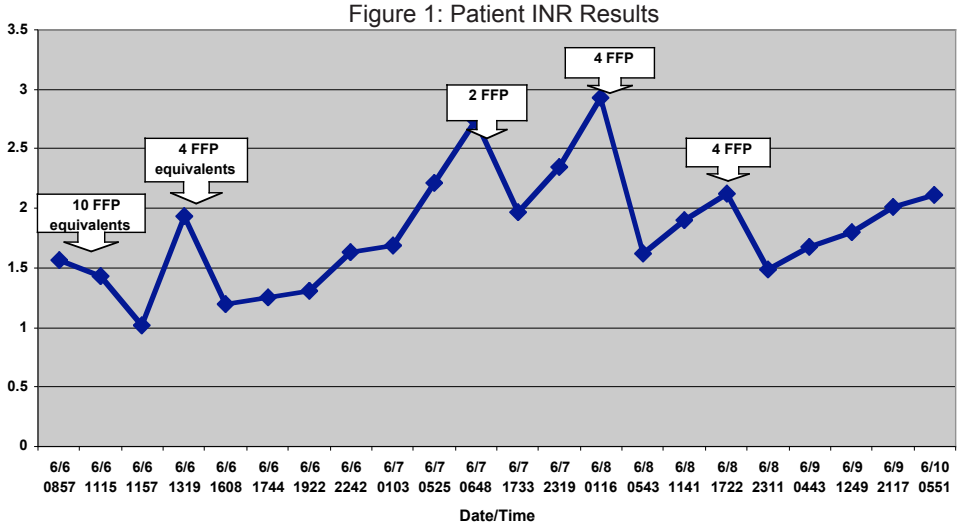
ORBCoN would like to congratulate all the hospitals in Ontario for their hard work in decreasing the outdate rates of this precious resource.

Case Study - Appropriate Use of Frozen Plasma During Massive Transfusion

Jeannie L Callum, Sunnybrook Health Sciences Centre and Troy Thompson, ORBCoN

An 18 year old female was admitted to the trauma room after a serious motor vehicle accident on Hwy 400. She was not wearing her seatbelt and was ejected from the vehicle. She sustained massive injuries including a lacerated liver, ruptured spleen, and a fracture of her right femur. No obvious head injury on admission. Baseline blood work was as follows: haemoglobin 114 g/L, platelet count 189, INR 1.4, aPTT 77 sec, and fibrinogen 1.37. Upon arrival she receives 10 O negative RBC's for hypovolemic shock and massive intra-abdominal bleeding in the trauma room and then is promptly taken to the operating room. Intra-operatively and immediately post-operatively she receives a total of 19 units of electronically crossmatched blood. Over the same time period, she is transfused 24 units of frozen plasma in attempts to maintain her INR<1.5 and PTT<45 sec (See Figure 1). In addition, she was also administered: 4 pools of platelets and 8 cryoprecipitate. In the first 24 hours after injury, she had 10 INR/PTT, 7 fibrinogen, and 15 CBC measurements. All frozen plasma transfusions were appropriate as at all points of administration., she was actively bleeding and had an INR/PTT at least 1.5 times the normal range. She survived her injuries and was discharged from the intensive care unit after 8 days.

Figure 1: Patient INR Results



Upcoming Education Events Calendar

Event	Where	When
AATB 32nd Annual Meeting	Chicago, Illinois	September 6-9, 2008
SABM 2008 Annual Meeting	Baltimore, Maryland	September 12-14, 2008
AABB Annual Meeting	Montreal, Quebec	October 4-7, 2008
OSMT 2008 Conference	Ottawa, Ontario	October 30 - November 1, 2008
LLSG/ORBCoN/CBS Symposium	London, Ontario	November 8, 2008

For a complete list of upcoming events please visit www.transfusionontario.org.

Quote

A wise man will make more opportunities than he finds.

~ Sir Francis Bacon (1561-1626)