Major Haemorrhage in the Remote and Retrieval Environment

Stuart Gillon
Royal Flying Doctor Service (Western Operations)
Aims

• Audit approach to major haemorrhage within RFDS (WO)

• Ascertain current major haemorrhage strategies within aeromedical retrieval organisations worldwide

• Evaluate potential solutions to shortfalls in care
A bloody revolution

- Greater understanding of pathophysiology of major haemorrhage and its associated coagulopathy (Brohi et al 2008)

- Development of the concept of damage control resuscitation - it's not just surgeons who stop bleeding (Beekley 2008)

- The earlier and more aggressive use of fresh frozen plasma (Hess et al 2008)

- Introduction of novel therapeutic agents (Berkhof & Eikenboom 2009), new roles for old agents (CRASH-2 2010) and changes to blood product preparations (Bruce & Nokes 2008; Rahe-Meyer et al 2009)

- Evolution of Major Haemorrhage Protocols (O’Keeffe et al 2008; Dente et al 2009)
The Western Australian Situation
Methods

• RFDS database search: financial year 2009-10

• ICD-9 codes manually searched for diagnoses deemed at risk of major blood loss

• Identified patients then searched for blood product administration

• Clinical notes of those at risk of bleeding who received blood products in flight pulled for further analysis

• Operational information, physiological parameters and blood product usage collected

• Follow up haemotological data collected from tertiary centre laboratory reporting system
Royal Flying Doctor Service (Western Ops)

- 7585 patients transported
- 1193 primary evacuations
ICD-9 diagnoses compatible with major haemorrhage

610 patients (8% of total patient population)

- Trauma 58% (n=354)
- Gastrointestinal 19% (n=117)
- Vascular 5% (n=31)
- Obstetric 16% (n=95)
Transfusion in Flight

- 9.5% (n=58) of patients with potential for major haemorrhage received blood products in flight.

Demographics

- Mean transport time 1 hour 55 min (range 0:34 -4:30)
- 71% (n=41) male
- Mean age 47.3
- 24 P1; 32 P2; 3 P3

- Gastrointestinal 52% (n=30)
- Trauma 29% (n=17)
- Obstetric 10% (n=6)
- Vascular 9% (n=5)
In flight physiology

- Lowest recorded systolic blood pressure: mean 94.1 mmHg; median 96 mmHg; SD 21.5
- Highest recorded heart rate: mean 108.7; median 107; SD 19
- Lowest recorded haemoglobin: mean 84.5 g/l; median 83 g/l; SD 18.9
- Lowest recorded temperature: mean 36.5 degrees
- 3 patients warfarinised; 2 post thrombolysis, 7 with documented liver dysfunction prior to haemorrhage
In flight physiology

• Lowest recorded systolic blood pressure: mean 94.1 mmHg; median 96 mmHg; SD 21.5

• Highest recorded heart rate: mean 108.7; median 107; SD 19

• Lowest recorded haemoglobin: mean 84.5 g/l; median 83 g/l; SD 18.9

• Lowest recorded temperature: mean 36.5 degrees

• 3 patients warfarinised; 2 post thrombolysis, 7 with documented liver dysfunction prior to haemorrhage
Physiology on arrival tertiary care

- Haemoglobin: mean 113g/l; median 110 g/l; SD 29

- Platelets: mean 151; median 135; SD 85

- International Normalised Ratio: mean 1.4; median 1.3; SD 0.4

- Activated Partial Thromboplastin Time: mean 36.8; median 34.0; SD 9.5

- Fibrinogen: mean 2.4; median 2.4; SD 0.9

- Bicarbonate: mean 20.0; median 20; SD 4.4

- Lactate - mean 3.0; median 1.5; SD 3.27
Management

• Packed Red Cells (mean number transfused)
  
  • Pre transfer - 2.6
  
  • During transfer - 1.5
  
  • Total - 4.1

• Fresh Frozen Plasma (mean number transfused)
  
  • Pre transfer - 1.2
  
  • During - 0.1
  
  • Total - 1.3
Management

- Platelets (mean number transfused)
  - Pre-transfer - 0.03
  - During transfer - 0.13
  - Total - 0.16

- Prothrombinex used 4 times (once in a non-warfarinised patient); calcium supplementation used once.

- In the trauma subgroup volume crystalloid and colloid infused: mean 4262ml; median 4925ml; IQR 2400.
Average blood product ratio of 4.1: 1.2: 0.2

Borgman *et al* (2007) describe mortality rates of 19, 34 and 65% with PRC:FFP ratios of 1.4:1, 2.5:1 and 8:1 respectively (*p*<0.001).
Regional hospital vs other

Comprehensive blood banks available in regional centres (Bunbury, Albany, Kalgoorlie, Geraldton, Carnarvon, Hedland, Karratha, Broome, Derby & Kununurra)

Regional hospital - 3.5:1
Non regional hospital - 13:1
The international approach to major haemorrhage in the pre-hospital and retrieval environment
International survey of the pre-hospital approach to major haemorrhage

- October 2010

- Pre-hospital and retrieval organisations identified via umbrella organisations

- Clinical contacts requested and invitations to participate issued

- 20 replies from 29 invitations (69%)
International survey of the pre-hospital approach to major haemorrhage

• Does your organisation carry blood products?

• Do you have immediate access to these blood products?

• Does your organisation regularly utilise pro-haemostatic agents in the context of major haemorrhage?

• Does your organisation operate a Massive Transfusion Protocol specific to your pre-hospital environment?
International survey of the pre-hospital approach to major haemorrhage

- Responses from Europe, North America, Asia, Australia, New Zealand, Africa
  - 3/20 urban, 8/20 remote, 9/20 mixture;
  - 7/20 primary, 13/20 secondary
  - 19/20 carried doctor for patients with major haemorrhage

Blood products

- None of urban organisations have access to blood
- 8/17 of those serving remote environments have immediate access to blood (<5min); all have arrangement for delayed access (45min)
- 1 organisation has immediate access to FFP (South Africa), 2 immediate access to platelets (SA & NZ)
International survey of the pre-hospital approach to major haemorrhage

- Major Haemorrhage Protocol
  - 10/20 organisations utilise a protocol
  - 5/10 are specific to the retrieval environment
- Prohaemostatic drugs and freeze dried agents
  - Tranexamic acid 1/20
  - Calcium preparations 3/20
  - Recombinant fVIIa 1/20
  - Prothrombin Complex Concentrate 1/20
Potential solutions?
Logistics

- Greater awareness of modern transfusion practices
- Early recognition of potential major haemorrhage
- Improved communication between hospitals, retrieval service and blood bank
- Major haemorrhage protocol
Tranexamic Acid

- Cochrane advocates use in elective surgery (OR Mortality 0.61 (CI 0.32-1.12))

- CRASH II (2010)
  - >20000 patients; 274 hospitals; 46 countries
  - No laboratory investigations
  - Improved mortality (if given within three hours)

- Ongoing trial in obstetric haemorrhage

- Does it apply to our environment?
  - PATCH (Prehospital treatment of Acute Traumatic Coagulopathy and Haemorrhage)
An easily stored, easily transported alternative to Fresh Frozen Plasma?
Fibrinogen concentrate

- Just introduced into Australia
- Licensed for congenital deficiency alone
- Potential alternative to cryoprecipitate/FFP (Nienaber et al 2011)
- Arguably even greater benefit in the retrieval environment
Prothrombin Complex Concentrate

- Available, freeze dried preparation of II, VII, IX, X.

- Accepted, licensed role in patients on vitamin K antagonists

- Expensive

- Limited experience in non-warfarinised patients

Prothrombin Complex Concentrate (Beriplex® P/N)

Lesley J. Scott
Adis, a Wolters Kluwer Business, Auckland, New Zealand

Contents

| Abstract |  |
| 1. Pharmacodynamic Profile | 1977 |
| 2. Pharmacokinetic Profile | 1979 |
| 3. Therapeutic Efficacy | 1980 |
| 4. Tolerability | 1981 |
| 5. Dosage and Administration | 1982 |

Abstract

Beriplex® P/N, a prothrombin complex concentrate derived from pooled human plasma, contains the vitamin K-dependent coagulation factors II, VII, IX and X, and the vitamin K-dependent coagulation inhibition proteins C and S.

Intravenous Beriplex® P/N provided rapid and sustained normalization of elevated international normalized ratios and controlled bleeding in adult patients participating in several prospective, noncomparative clinical studies (n = 5-43), with these data supported by clinical experience during its use over more than a decade.

Based on extensive clinical experience, Beriplex® P/N is also effective in the treatment of congenital deficiency of any of the vitamin K-dependent coagulation factors when purified specific coagulation factor products are not available.

Over a decade of clinical experience and more limited data from clinical studies have shown that intravenous infusions of Beriplex® P/N were generally well tolerated in adult patients with acquired or congenital deficiencies of the vitamin K-dependent coagulation factors. To date, there have been no proven cases of viral transmission reported in any published studies.

Features and properties of prothrombin complex concentrate (Beriplex® P/N)

| Indication |
| Treatment and perioperative prophylaxis of bleeding in acquired deficiencies of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, or in cases of overdose with vitamin K antagonists, when rapid correction of the deficiency is required, and in congenital deficiency of any of the vitamin K-dependent coagulation factors when purified specific coagulation factor products are not available |

| Mechanism of action |
| A prothrombin complex concentrate from pooled human plasma that inhibits bleeding through replacement of coagulation factors II, VII, IX and X, and of coagulation inhibition protein C and protein S |

| Dosage and administration |
| **Dose**: Depends on the severity of the disorder, on the location and extent of bleeding, and on the patient’s clinical condition |
| **Route of administration**: Intravenous |
| **Maximum infusion rate**: 3 IU/kg/min (maximum 210 IU/min) |

| Adverse events in prospective clinical studies |
| Thromboembolic events occurred at an incidence of ≤4.7% |
Summary

• Major Haemorrhage is a common problem in rural western Australia

• Retrieval services do not currently have the facility to deliver 21st century gold standard care in these patients

• New products hold promise for all practitioners managing the bleeding patient

• Retrieval practitioners perhaps stand the benefit the most and therefore should actively research


• Dente CJ, Shaz BH, Nicholas JM, Harris RS et al. (2009) Improvements in early mortality and coagulopathy are sustained better in patients with blunt trauma after institution of a massive transfusion protocol in a civilian level I trauma center. Journal of Trauma.66: 1616-1624.


