

Uses of Prothrombin Complex

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Background

- Introduction of Octaplex, a 4-factor Prothrombin Complex Concentrate in Ireland
- Development of guidelines and summary card for use in reversal of warfarin
- Sharing of information with other hospitals
- Audit of its use and efficacy Warfarin reversal
- Use in selected cases of liver disease
- Only experience of Octaplex
- No other PCC currently available in Ireland

Prothrombin complex concentrates

- Highly concentrated product
- Plasma-derived
- Contains factors II, VII, IX and X
- Similar amounts of II, IX and X
- Lower amount of VII
- May contain Protein C, Protein S
- Usually contain small amount of heparin

Octaplex

One vial contains:	
Factor II	220-760 IU
Factor VII	180-480 IU
Factor IX	500 IU
Factor X	360-600 IU
Protein C	140-620 IU
Protein S	140-640 IU

Octaplex

- 500u per vial
- Dose 25-50u/kg
- Round up to nearest vial (in adults)
- Concentrated product – small volume – 500ml reconstituted in 20ml
- Infuse 1ml/min initially then up to 3ml/min (license)
- However faster infusion ok
 - US license application – 8-10 ml/min
 - Bolus infusion for ICH (France)

Indications for PCC (SPC)

- Treatment of bleeding or perioperative prophylaxis of bleeding in acquired deficiency of the prothrombin complex factors
 - Eg caused by treatment with vitamin K antagonists / overdose
 - When rapid reversal is required

Indications for PCC (SPC)

- Treatment of bleeding and perioperative prophylaxis in congenital deficiency of the the vitamin K dependent coagulation factors II and X when purified specific coagulation factor product is not available
 - Factor IX – purified concentrate eg recombinant is generally available
 - Factor VII – recombinant factor VIIa or purified VII concentrate

Indications for PCC

- Warfarin reversal – main indication
- Liver disease – SPC warns of caution re risk of thrombosis
- Vitamin K deficiency – rarely requires blood product treatment
- Others – used in some locations – I've no experience
 - Dilutional coagulopathy
 - Sepsis / DIC

Advantages of PCC versus Plasma

- Concentrated product - fluid volume much smaller than 15ml/kg of plasma (max dose we use is 50 U/Kg = 2ml/kg
 - Reduced risk of fluid overload
- Rapid infusion
- Rapid and complete reversal of warfarin compared to plasma
- Shelf life
- Rapid reconstitution versus thawing
- Viral inactivation
- Not ABO group specific

Disadvantages

- Potentially thrombogenic
 - Data mostly from older products with much higher levels of activated factors
 - Caution in liver disease
 - Why is the patient on anticoagulants?
 - Low risk
 - Atrial fibrillation without valvular disease
 - Distant DVT/PE
 - High risk
 - Recent thrombosis
 - Mitral valve disease etc
 - Consider use of Inferior Vena Cava filter (removable)

Disadvantages

- Rate of infusion in SPC not fast enough – 1ml/min initially, followed by 3ml/min
 - We do give it faster in certain emergencies
- Not available in all countries
- Heparin content
 - Allergy
 - HITT
- Shorter duration than warfarin effect – factor VII 6 hours
 - Applies to all blood products/components
 - Don't forget to give vitamin K 5-10mg as well and recheck INR after 6 hours and next day as well as immediate
- Some PCC are only 3 factor – need to give factor VII also

Warfarin

- Vitamin K antagonist
- Inhibits γ -carboxylation of clotting factors II, VII, IX, X
- Prolongs Prothrombin time (PT)
- $INR = (PT/Mean\ normal\ PT)^{ISI}$
- In excessive doses, also prolongs Activated Partial Thromboplastin Time (APTT)

Warfarin as an anticoagulant

- Narrow therapeutic window
- Unpredictable dose requirement
- Slow onset – makes induction difficult
- Slow offset – possibly seen as disadvantage – but:
- Can be reversed

The non-bleeding patient

- In non-urgent situations, blood or blood products should not be used to reverse warfarin
- Options
 - Omit/reduce warfarin
 - Typically 4-5 days before surgery
 - Delayed reversal – risk factors:
 - Advanced age
 - Low warfarin dose requirement
 - Extreme elevation in INR
 - Decompensated CCF
 - Active cancer
 - +/- vitamin K

– Hylek *et al*, Ann Int Med 2001;135:393-400

Risk of bleeding awaiting reversal

- In 2 studies of 352 patients only 2 patients bled (0.6%)

– Glover *et al*, Chest 1995;108:987-990

– Lousberg *et al*, Arch Intern Med 1998;158:528-534

- Larger, more recent study of simple withdrawal of warfarin

– INR > 5 – bleeding 1.3%

– INR >9 – bleeding 9.6%

– Garcia *et al*, J Am Coll Cardiol 2006;47:804-808

Vitamin K

- Accelerates the fall in INR to normal
- Useful where INR very high (eg > 8.0), delayed recovery anticipated, or risk of bleeding increased
- Very useful if surgery needed, but not immediately eg omission of warfarin has failed to bring INR down sufficiently

If patient to stay on warfarin...

- If patient to go back on warfarin immediately, give **small dose (0.5mg-2.5mg) vitamin K**
- 0.5mg effective in returning INR to therapeutic range
 - Shetty *et al* Thromb Haemost 1992;67:13-15)
- RCT vs placebo– no effect on bleeding (over 90 days)
 - Crowther *et al*, Ann Intern Med 2009;150:293-300
- Oral vitamin K effective
- Paediatric Konakion 2mg injection can be given orally
- Randomised trial in Mechanical heart valves
 - INR 6.0-12.0 but asymptomatic
 - Vitamin K 1mg more commonly restored INR to near therapeutic range within 1 day than just omitting warfarin
 - No difference between groups in no. of patients with INR < 1.8
 - Ageno, J Am Coll Cardiol 2005;16:732-733

If patient finished warfarin...

- Vitamin 5-10mg iv or po

In all cases:

- Delay in vitamin K effect 8-12 hours
- Recheck INR (usually next day) to verify response

The bleeding patient

Or the patient who requires **immediate (<6 hours)** surgery/invasive procedure/neuroaxial anaesthesia

- Will require a blood product or component to replace factors II, VII, IX and X
- **AND** vitamin K 5-10mg

General principles of blood component/product therapy

- Because of risks of transfusion, both known and unknown –
- Avoid transfusion unless necessary and benefits outweigh risks
- Give the most efficacious and safe – usually the most specific - product available

Dose of Octaplex

INR	Dose of Octaplex based on FIX content
2.0-3.9	25 u/kg
4.0-6.0	35 u/kg
> 6.0	50 u/kg

Efficacy of PCC *versus* plasma

- Plasma
 - Relatively ineffective
 - Large volume needed – 15ml/kg
 - Difficult to give rapidly
 - Still the norm in North America
- Makris compared PCC with FFP
 - Complete correction of INR occurred within 15 minutes in:
 - 28/29 patients treated with PCC
 - NONE of 12 patients treated with FFP
 - Makris et al, Semin Vasc Med 2003;3:279-284
- Several studies have shown rapid correction of bleeding with PCC
 - Preston et al, Br J Haematol 2002;116:619-624

Local experience

HSE
 Heilthúseamannacht na Seirbhíse Sláinte
 Health Service Executive

Clinical Audit on the use of Prothrombin Complex Concentrate in the Midland Regional Hospitals, Ireland.

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INTRODUCTION
 Prothrombin Complex Concentrate (PCC) is being used for bleeding complications and preoperative reversal of coagulopathy arising from vitamin K antagonists and liver disease. In September 2005 guidelines were formulated for appropriate use of PCC in the Midland Regional Hospitals, Ireland.

AIMS
 The aim of the audit is
 1. To evaluate the compliance with the guidelines for the use of PCC in the Midland regional Hospitals during September 2005 to September 2006.
 2. To evaluate the efficacy of PCC.

METHODS
 Data was collected retrospectively from the charts of the patients who received PCC from September 2005 to September 2006 in the Midland Regional hospitals of Ireland and audited against the standard guidelines for the use of PCC.

RESULTS
 36 Patients (26 Tullamore, 6 Mullingar and 4 Portlaoise) had received PCC. Among the 36 patients who received PCC 21 were females and 15 were males. The mean age distribution of the patients was 71 years (Standard deviation = 13.0, Median - 72) - Table 1.

Parameter	Value
Number of patients	36
Hospital Distribution	Tullamore - 26 Mullingar - 6 Portlaoise - 4
Gender	Female - 21 Male - 15
Age mean (SD)	71yrs (13.0)

24 patients received PCC for emergency warfarin reversal out of which 12 patients received PCC for major bleeding and 12 patients for emergency preoperative warfarin reversal. 10 patients received PCC for coagulopathy secondary to liver disease out of which 3 patients had major bleeding and 7 patients had PCC for correction of preoperative coagulopathy. Two patients received PCC for coagulopathy of unknown cause (figure 1).

The mean Pre PCC INR value of the patients was 2.8 (standard deviation 1.7, median 2). The mean first post PCC INR was 1.3 (standard deviation 0.3, median 1.2). The first post PCC INR was

checked within 1hr in 44% of patients. The average time for the first post PCC INR to be checked was 3 hours 38 minutes (N = 31). Post PCC INR was not done in 5 patients (1 patient transferred to another hospital). 10 patients who had PCC for warfarin reversal had INR checked within 1 hour. All the 10 patients had successful correction of INR following PCC infusion (mean pre INR = 3.3, mean post INR < 1hr = 1.4) - figure 2. The mean second post PCC INR was 1.2 (standard deviation 0.2, median 1.3). The second post PCC INR was checked within 4-8hrs in 16% of patients (3 patients died, 1 patient was given a second dose, 1 patient was transferred to another hospital).

Figure 2:
 INR reduction in patients who had PCC for Warfarin reversal

22 patients had second post PCC INR checked within 24hrs, the mean time being 12 hours 51 minutes. 5 patients had second post PCC INR checked between 4 - 8 hrs. 9 patients did not have the second post PCC INR checked (3 patients died, 1 patient transferred). Among the patients who received PCC for liver coagulopathy reversal only 3 patients had INR checked within 1 hour (figure 3). 87.5% of patients who received PCC for warfarin reversal had Vitamin K. 75% of patients had haematology team's advice prior to PCC infusion. The overall mortality of the patients who received PCC was 34% (1 patient transferred to another hospital).

Figure 3:
 INR reduction in patients who received PCC for liver coagulopathy

CONCLUSIONS
 PCC has been appropriately used for proper indications but the post PCC infusion INR has not been checked according to the protocol in most of the patients. According to the guidelines of the Midland Regional Hospitals, post PCC infusion INR should be checked within 1 hour and 6 hours after the completion of PCC infusion but very few patients had their INR checked as per the protocol. Vitamin K should be given to all patients who receive PCC for warfarin reversal. Haematology team should be consulted prior to PCC infusion in all patients. PCC is effective in warfarin reversal.

References
 1. Guideline - The use of Factor Concentrates (2005). HSE Midland Area BT 007.

Figure 1: Indication for PCC

- Clinical audit on the use of PCC (n=36) in Midland Regional Hospitals

– INR post PCC= 1.4

– Senthil Kumar R *et al*,
 Haematology Association of
 Ireland (poster) 2006

- 10 patients with coagulopathy of liver disease

– INR post PCC 1.0-1.2

– No thrombosis observed

All blood products

- Repeat INR after use to check effect
 - Maximum dose of PCC
- Give vitamin K simultaneously as half life of coagulation factors is far less than that of warfarin effect
- Recheck INR 6 hours later

Use of rVIIa to reverse warfarin

- Rapidly reverses INR prolongation in volunteers on acenocoumarol and in patients with excessive anticoagulation but:
 - Limited data
 - Unlicensed
 - ?dose (?15-90µg/kg)
 - ?monitoring – produces *shortened* PT
 - Risks of thrombosis Routine use should be avoided
 - O'Connell KA *et al*, JAMA 2006;295:293-298
- ASH Evidence-based Review 2008: What Is the Evidence for the Off-label Use of Recombinant Factor VIIa (rFVIIa) in the Acute Reversal of Warfarin? Rachel P Rosovsky & Mark A Crowther
 - We recommend against routine use of rVIIa in acute warfarin reversal (Grade 2C)
- If used, give vitamin K as well, and monitor closely as half-life is less than 60 minutes

Jehovah's witnesses

- Accept all modern medical treatment apart from transfusion of blood components
- Will not accept autologous transfusion but will usually accept cell salvage or haemodilution if not detached from body
- Fractions such as **PCC**, immunoglobulins, albumin etc up to individual conscience
- Recombinant products accepted
- Vitamin K accepted

Haemovigilance and PCC

- Real-time:
 - Transfusion laboratory staff
 - Consultant haematologist/registrar approval (training)
 - NCHD and consultant knowledge and attitude
 - “INR”
- Induction / training / handbook etc

Conclusions

- PCC – highly effective rapid reversal of deficiency of vitamin K dependent factors
- Main use – reversal of warfarin but other uses possible
- Faster infusion than license possible and advised in urgent cases
- Risk of thrombosis – largely dependent on underlying condition of patient