Government of Newfoundland and Labrador

Department of Health and Community Services
Provincial Blood Coordinating Program

PROTHROMBIN COMPLEX CONCENTRATES	NLBCP-061

Office of Administrative Responsibility	Issuing Authority
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Overview

Prothrombin complex concentrates (PCC) are human plasma-derived blood clotting factors II, VII, IX and X, as well as protein C and S. PCC are used in the treatment of active bleeding and prophylaxis of bleeding prior to invasive procedure to reverse the effects of vitamin K antagonists.

Another potential use for PCCs has been in the reversal of **severe/life-threatening bleeding** for those on Direct Oral Anticoagulants (DOACs). If there is an antidote for the DOAC then that would be the recommended first course of treatment. Thrombosis Canada has guidelines available for management of bleeding in patients on DOACs found here.

PCCS are **not indicated** in situations in which there is ample time to allow the prothrombin time to return to normal by discontinuing the anticoagulant or through administration of vitamin K. PCCs are not without risk so prior to use a risk versus benefit evaluation shall be completed in each individual case.

Policy

1. Regional Health Authorities (RHAs) shall implement policies, processes and procedures for ordering, receipt, handling, storage, distribution, preparation (for administration), and administration of prothrombin complex concentrates (PCCs) that comply with the Newfoundland and Labrador Blood Coordinating Program (NLBCP) policies and guidelines.
2. PCCs are indicated for:
   2.1. Rapid reversal of warfarin therapy or vitamin K deficiency in patients exhibiting major bleeding manifestations.
   2.2. Rapid reversal of warfarin therapy or vitamin K deficiency in patients requiring urgent (within less than six hours) surgical procedures.

   ***Note**: M*anagement of vitamin K antagonist treatment with elevated INR depends on both the presence of bleeding and the severity of bleeding, Please refer to American College of Chest Physicians 2018 Antithrombotic Therapy for Atrial Fibrillation recommendations or Thrombosis Canada for management of bleeding.*
3. Thrombotic events 24 hours to 30 days post infusion shall be reported as an Adverse Transfusion Reaction.
4. There is some published evidence to support PCC use in the reversal of **severe life-threatening** bleeding for those on DOACs. However, if a reversal agent/antidote is available that is the recommended first course of treatment (e.g. Praxbind®/idarucizumab for dabigatran). Each case should be looked at individually for risk versus benefit evaluation due to the prothrombotic effect of PCCs. Each facility should have a protocol for bleeding management of patients on DOACs.

5. RHAs shall adopt a process to facilitate the rapid availability and delivery of PCC for patients with major bleeding manifestations, such as expedited approval processes for subgroups of patients, expedited delivery of product to end user, or supply availability (limited) in emergency departments.
6. PCCs shall be stored, transported, prepared and administered according to manufacturer instructions (consult product monographs).
7. PCCs shall be administered under the supervision of physicians who have access to adequate diagnostic and treatment facilities to ensure appropriateness of dosing, evaluation of treatment effect, and management of potential complications.
   7.1. PCCs shall be administered intravenously by direct IV push, syringe pump or mini-bag.
   7.2. Distribution and use of PCCs shall be limited to only facilities capable of performing the necessary diagnostic evaluations (i.e. PT/INR tests).
   7.3. The completed blood product administration card shall be returned to the transfusion medicine laboratory following administration of PCCs as per facility policy.

Guidelines

1. Vitamin K (10 mg IV) co-administration is strongly recommended if reversal is required for longer than 6 hours (the half-life of prothrombin complex concentrates) for patients on Warfarin. The onset of action of Vitamin K is 4-6 hours when administered intravenously.

   *Note: *Vitamin K is not recommended for patients on DOACs.*
2. PCCs are not indicated for:
   2.1. Elective reversal of oral anticoagulant therapy prior to invasive procedure.
   2.2. Treatment of elevated INR ***without*** bleeding or need for surgical intervention.
   2.3. Coagulopathy associated with liver dysfunction.
   2.4. Patients with recent history of thrombosis, myocardial infarction, or disseminated intravascular coagulation (DIC).
3. Contraindications:
   3.1. Patients with a history of heparin induced thrombocytopenia.
   3.2. Patients who are hypersensitive to any of the components in the formulation, or components of the packaging.
   3.3. Patients with immunoglobulin A deficiency with known antibodies against IgA.
4. Special patient populations:
   4.1. Pregnant and lactating women: There is insufficient evidence available to allow a recommendation for use of PCC in this patient population.

Caution should be exercised if used in pregnancy, particularly in the peripartum/early postpartum period because of heightened tendency of thrombosis.

4.2. Pediatric patients: There is insufficient evidence available to allow a recommendation for use of PCC in this patient population.

4.3. Congenital factor II or X deficient patients: Use of PCC should be at the discretion of the local Hemophilia clinic.

4.4. Reversal of direct thrombin inhibitors (DTI) – there is insufficient published evidence to allow a recommendation for this use. Idarucizumab (Praxbind®) is the antidote for dabigatran.

4.5. Reversal of direct anti-Xa inhibitors– there is some published evidence to suggest that PCCs may be effective in the reversal of direct anti-Xa therapy but no consensus has been reached on it's efficacy for this purpose.

*Note: *There may be extenuating clinical circumstances necessitating use of PCCs in these clinical situations. Use should be evaluated on a case-by-case basis by a physician experienced in the use of the product. If the decision is to use the product off-label in liver dysfunction or DIC, please consult the product monograph for further recommendations (e.g. the need for antithrombin levels or replacement).*

Procedure

1. Pre-printed order forms for PCC shall be available in acute care areas where PCC may be ordered and/or administered.
2. All requests for PCCs shall be made through the transfusion medicine laboratory.
3. A PT/INR test shall be performed prior to administration of PCCs, with the exception of DOAC reversal.
4. Follow (adult) PCC dosing guidelines Appendix A.
5. Administer as per manufacturer instructions.
   5.1. PCCs shall be administered intravenously by direct IV push, syringe pump or mini-bag.
   5.2. The manufacturer's recommended maximal rates of infusion are:
   - octaplex® = 3mL/min.
   - Beriplex® P/N = 8 mL/min.
6. Repeat PT/INR test 10-30 minutes post administration (every dose), with the exception of DOAC reversal.

*Note: *Do not mix two different PCC products within the same infusion (There is no evidence to suggest that infusing a second dose of the alternate product would be detrimental). If correction to an INR < 1.5 has not been achieved and there is insufficient*

time to wait for Vitamin K to take effect, a subsequent dose of PCC may be required if the patient continues to demonstrate clinical bleeding.

Key Words

INR, PCC, prothrombin complex concentrate

Supplemental Materials

Appendix A: Dosing Guidelines

Appendix B: Order Form

References

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Appendix A

Dosing Guidelines for Warfarin patients - Adult

	INR > 1.7 ≤ 3.0	INR > 3.0 ≤ 5.0	INR > 5.0 or Intracranial Hemorrhage
Dose of Prothrombin Complex Concentrate	1000 IU (40 mL)	**Up to** 2000 IU (80 mL)	**Up to** 3000 IU (120 mL)

***Maximum dose is 3000 IU in 24 hours**

**See NAC (2014) recommendations for full dosing guidelines.

Dosing Guidelines for DOAC patients found here.

Appendix B

Pre-Printed Order (Adult)
Prothrombin Complex Concentrates

Weight: _____kg

Name:

DOB: DD/MONTH/YYYY

HCN:

Allergies □ Nil known

Is informed consent confirmed? □ Yes □ No INR _____ **(Must be >1.7 for Warfarin patients)**

Indication:

□ Warfarin therapy **or** vitamin K deficiency **with** active bleed.

□ Warfarin therapy **or** vitamin K deficiency with **imminent emergency** operative or invasive procedure **within** six (6) hours.

□ Reversal for **severe/life threatening bleeding** for those on Direct Oral Anticoagulants (DOACs). If there is an antidote for the DOAC that is the recommended treatment. DOAC presently on: _____

Contraindications:

□ Yes □ No Recent thromboembolic event (within 30 days), e.g. AMI, thrombotic stoke, PE, DVT.

□ Yes □ No History of heparin-induced thrombocytopenia (HIT) or allergy to heparin.

Physician Orders:

□ Vitamin K 10 mg IV.

□ PCC _____ International Units (IU). (Administer as per product monograph/ facility policy.) RHA may specify PCC/dose/ infusion rate here.

REPEAT INR 10-30 minutes post **every** dose for Warfarin patients.

	INR > 1.7 ≤ 3.0	**INR > 3.0 ≤5.0**	**INR > 5.0 or Intracranial Hemorrhage**
Dose of Prothrombin Complex Concentrate	1000 IU (40 mL)	**Up to** 2000 IU (up to 80 mL)	**Up to** 3000 IU (up to 120 mL)

***Maximum dose is 3000 IU in 24 hours**

_____ _____ _____

Physician Signature: Print Name: Date: DD/MONTH/YYYY

Incomplete order forms may result in delays in treatment and may require consult with Laboratory Hematologist/Hematopathologist

Monitoring:

Vital signs every 5 min during infusion; 15 min post infusion (**every** dose).

Thrombotic events 24 hours to 30 days post infusion.

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Indications Confirmed □ Yes □ No

1. Initial Dose: _____
2. Additional Dose: _____ INR: _____
3. Additional Dose: _____ INR: _____

Human Coagulation Factor (per vial)	**octaplex® 500 Dose**	**octaplex® 1000 Dose**	**Beriplex® P/N 500 Dose**	**Beriplex® P/N 1000 Dose**
Factor II	280-760 IU	560-1520 IU	380-800 IU	760-1600 IU
Factor VII	180-480 IU	360-960 IU	200-500 IU	400-1000 IU
Factor IX	500 IU	1000 IU	500 IU	1000 IU
Factor X	360-600 IU	720-1200 IU	500-1020 IU	1000-2040 IU
Protein C	260-620 IU	520-1240 IU	420-820 IU	840-1640 IU
Protein S	240-640 IU	480-1280 IU	240-680 IU	480-1360 IU
Heparin	80-310 IU	160-620 IU	8-40 IU	16-80 IU
Antithrombin	none	none	4-30 IU	8-60 IU

*Note: Beriplex P/N contains 343 Mg of Sodium per 100mL. Consider effect on renal impaired or sodium restricted patients.