Government of Newfoundland and Labrador

Department of Health and Community Services
Provincial Blood Coordinating Program

PROTHROMBIN COMPLEX CONCENTRATES	NLBCP-061

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Overview

Prothrombin complex concentrates (PCCs) such as Octaplex® and Beriplex® are human plasma-derived blood products that contain the vitamin K dependent procoagulant factors II, VII, IX and X, as well as protein C and S. PCCs are used in the treatment of active bleeding and prophylaxis of bleeding prior to an invasive procedure to reverse the effects of vitamin K antagonists (e.g., warfarin).

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 International Normalized Ratio (INR) 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 should be completed in each individual case.

The National Advisory committee on Blood and Blood Products convened a working group in 2021 to revise and update its recommendations on the use of PCCs in Canada. They considered available literature, audit data and a consensus opinion of the working group to publish updated guidelines in 2022 found here.

Policy

1. NL Health Services (NLHS) facilities shall implement policies, processes and procedures for ordering, receipt, handling, storage, distribution, preparation (for administration), and administration of PCCs. The policy should state the maximum total dose.
2. Requests for PCCs shall be made through the Transfusion Medicine Laboratory (TML)
3. PCCs are indicated for:
   - 3.1. Rapid reversal of warfarin therapy or vitamin K deficiency in patients exhibiting major bleeding manifestations.
   - 3.2. 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. Refer to American College of Chest Physicians 2018 Antithrombotic Therapy for Atrial Fibrillation recommendations or Thrombosis Canada for management of bleeding.*
4. Thrombotic events post infusion shall be reported as an Adverse Transfusion Reaction.
5. An INR test shall be performed prior to administration of PCCs, when time permits.

   Note: INR is not used for DOAC reversal.

6. A Repeat INR shall be repeated 10-30 minutes post administration (every dose), except for DOAC reversal.
   Note: If correction to an INR < 1.7 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.

7. Different PCC products should not be mixed within the same infusion.
   Note: There is no evidence to suggest that infusing a second dose of the alternate product would be detrimental.

8. PCCs may be used 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., idarucizumab (Praxbind™) for dabigatran}.
   Note: 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.

9. NLHS facilities shall adopt a process to facilitate the rapid availability and delivery of PCCs for patients with major bleeding manifestations, such as expedited processes for subgroups of patients, expedited delivery of product to end user, or supply availability (limited) in emergency departments.

10. PCCs shall be stored, transported, prepared, and administered according to manufacturer instructions (consult product monographs).

11. 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.
    11.1. PCCs shall be administered intravenously by direct IV push, syringe pump or minibag.
    11.2. Distribution and use of PCCs shall be limited to only facilities capable of performing the necessary diagnostic evaluations (e.g., INR test).
    11.3. The completed blood product administration card shall be returned to the TML 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 PCCs) 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. PCC adult dosing guideline for warfarin patients see Appendix A.
   2.1. Single doses should not exceed 3000IU, but adjustments may be required in certain clinical situations where extremes of weight are present and ongoing bleeding is demonstrated requiring repeat doses.

2.2. Facilities should have a policy addressing maximum total dose and a dosing policy to monitor for efficacy.

2.2. If the INR is unknown, oral anticoagulant use is suspected, and major bleeding is present 2000IU of PCCs may be administered.

3. PCCs are not indicated for:
   3.1. Elective reversal of oral anticoagulant therapy prior to invasive procedure.
   3.2. Treatment of elevated INR ***without*** bleeding or need for surgical intervention.
   3.3. Coagulopathy associated with liver dysfunction.
   3.4. Patients with recent history of a thrombotic event (e.g., myocardial infarction, venous thromboembolism, ischemic stroke, systemic embolism) and disseminated intravascular coagulation (DIC).
4. Contraindications:
   4.1. Patients with a history of heparin induced thrombocytopenia.
   4.2. Patients who are hypersensitive to any of the components in the formulation, or components of the packaging.
   4.3. Patients with immunoglobulin A deficiency with known antibodies against IgA.
5. Special patient populations:

   There may be extenuating clinical circumstances necessitating use of PCCs in the clinical situations listed below and in other indications. They should be evaluated on a case-by-case basis with a physician experienced in the use of PCCs.
   Note: The NAC guidelines, published recommendations/literature and the product monograph on use and dosing, should be referenced for more information, if needed.

   5.1. Cardiac surgery: PCCs may be used in treatment of coagulation defects/bleeding in cardiac surgery. The lowest possible dose that achieves hemostasis should be utilized and to consider concomitant assessment of fibrinogen.

   5.2. Reversal of direct anti-Xa inhibitor anticoagulants: PCCs may be effective in the reversal of direct anti-Xa therapy, but no consensus has been reached on its efficacy for this purpose. Facility policies should be developed including relevant laboratory testing and hemostatic management.

   Note: Specific reversal agents should be used, if available.

   5.3. For management of coagulopathy in clinical scenarios where the risk/benefit profile of plasma transfusion is deemed to be unfavourable.

   5.4. Coagulopathy associated with liver dysfunction: PCCs may be used instead of plasma to prevent fluid overload, but evidence regarding efficacy and safety is limited to support this practice.

   5.5. For replacement of coagulation factors if plasma transfusion is refused for religious or other reasons and patients are accepting human plasma-derived protein products.

5.6. 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.

5.7. Pediatric patients: There is insufficient published evidence available to allow a recommendation for dosing and/or use of PCC in this patient population.

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

5.9. Reversal of non-dabigatran direct thrombin inhibitors (DTI)- there is insufficient published evidence to allow a recommendation for this use.

5.10. Use in bleeding/massive hemorrhage patients, when plasma is unavailable- PCCs and fibrinogen concentrates may be substitutes for plasma where plasma is not readily available.

Key Words

INR, PCC, prothrombin complex concentrate

Supplemental Materials

Appendix A: Dosing Guideline for Warfarin Patients-Adult

References

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Appendix A

Dosing Guideline 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)

Recommended maximum single dose is 3000 IU
Facilities should develop a dosing guideline. See NAC (2022) recommendations and product monographs for full dosing guidelines.