Preemptive intraoperative administration of PCC4 in cardiac surgery patients at high risk of bleeding, a pilot study

Joseph Elder[1], Jennifer McComb[1], Seth Lirette[1], Bruce Herndon[1], Gerald Yancey[1], Asim Mohammed[1], and Hannah Copeland[1]

[1]Lutheran Hospital

September 26, 2022

Abstract

Background: Four factor prothrombin complex (PCC4), a concentrate of factors II, VII, IX, X and protein C and S, has been used selectively for reversal of oral anticoagulation prior to surgery. There is data to support PCC4 as opposed to supplemental fresh frozen plasma (FFP) to manage postoperative bleeding following cardiac surgery. The preemptive, intraoperative use of PCC4 in cardiothoracic surgery has not been studied though it may prevent postoperative bleeding, the need for blood transfusion and the risk of transfusion related acute lung injury, volume overload, and right ventricular (RV) heart failure. The purpose of this study is to evaluate the intraoperative administration of PCC4 to decrease bleeding and lower the rate of blood transfusion. Methods: A single institution retrospective chart review conducted from May 2020 to November 2021 of patients who received PCC4 intraoperatively during cardiothoracic surgery of high risk variety. Patients were evaluated for type of surgery, demographics, baseline anticoagulation, PCC4 dose, type and quantity of blood transfusion within 72 hours postoperatively, chest tube output, incidence of right ventricular failure, hypersensitivity reactions, acute kidney injury, thrombosis, acute lung injury, and mortality within 45 days of the operative dose of PCC4. Results: Thirty five patients received PCC4 at a mean dose of 2920 units. Sixty five percent of cases were LVAD or heart transplant. The protocol is to use PCC4 30 units/kilogram immediately after completion of protamine administration. Inclusion criteria are: cardiothoracic surgery with increased risk of postoperative right heart failure commonly secondary to blood product transfusion, or cardiothoracic surgery associated with increased risk of bleeding, including: heart transplant, LVAD implant, aortic dissection, and redo sternotomy (e.g. coronary artery bypass). Total chest tube output was recorded as a mean of 757 mL for 24 hours after surgery (32 ml/hr). Overall median event rates of fresh frozen plasma (FFP) and red blood cell (RBC) transfusion were 0 (interquartile range 0 - 3 units) and 4 (interquartile range 2-5 units). Overall, forty-three percent and eighty-nine percent of cases received FFP and RBC, respectively. There was one occurrence of right ventricular failure, one occurrence of acute kidney injury requiring renal replacement therapy, one occurrence of venoarterial extracorporeal membrane oxygenation, one occurrence of venous thromboembolism related to a central venous access line, and one death unrelated to surgery or PCC4 that was attributed to advanced heart failure not amenable to advanced therapies. Conclusion: Overall patients received a low rate of blood transfusion, had minimal chest tube output, and there was a small incidence of right heart failure. Patients did not have an increased risk of adverse effects such as acute kidney injury or venous thromboembolism. A randomized controlled clinical trial comparing the observed dose and timing of PCC4 versus routine postoperative bleeding management with blood product transfusion is recommended.

Preemptive intraoperative administration of PCC4 in cardiac surgery patients at high risk of bleeding, a pilot study

Joseph Elder PharmD BCPS, Jennifer McComb PharmD, Seth Lirette Ph.D., Bruce Herndon PharmD, Gerald Yancey MD, Asim Mohammed MD, Hannah Copeland MD FACS FACC

Corresponding Author(s): Joseph Elder PharmD BCPS

7950 West Jefferson Boulevard, Fort Wayne, Indiana 46804

Contact: joseph.elder@lhn.net M: 260-466-4979

IRB Review / Approval: 09/16/20

Data availability: not applicable to this retrospective review

Funding : no outside dedicated funding for this retrospective review

Patient consent statement : not applicable due to retrospective review

Clinical trial registration : not applicable for this retrospective review

Relevant conflict(s) of interest disclosure for authors otherwise nothing to disclose : Dr. Hannah Copeland is a speaker for Abbott Laboratories, Inc.

Lutheran Hospital of Indiana IRB # 00004318

Project approval 9/16/20

Word Count: ___2678____

Glossary

U = units; RV = Right Ventricular; FFP = fresh frozen plasma; PRBC = packed red blood cells;

PLT = platelets; CRYO = cryoprecipitate; CVP = central venous pressure; PAS = Pulmonary

Artery Pressure Systolic; PAD = Pulmonary Artery Pressure Diastolic; 24h = 24 hours; 96h = 96

hours; OAC = oral anticoagulation; AKI = acute kidney injury; RRT = renal replacement

therapy; ECMO = extracorporeal membrane oxygenation; NOTE 5 CRYO Units = 1 Unit Bag

(CRYO 10 units = 2 CRYO unit bags); PCC4 = prothrombin complex concentrate 4; IQR = interquartile range; iNO = inhaled nitric oxide; COVID-19 = coronavirus disease 2019; PEEP = positive end expiratory pressure; PaO2 = partial pressure of oxygen; FiO2 = fraction of inspired oxygen; TRALI = transfusion related acute lung injury; LOS = length of stay; ICU = intensive care unit; g/dL = grams per deciliter; mg/dL = milligrams per deciliter

Preemptive intraoperative administration of PCC4 in cardiac surgery patients at high risk of bleeding, a pilot study

Abstract

Background: Four factor prothrombin complex (PCC4), a concentrate of factors II, VII, IX, X and protein C and S, has been used selectively for reversal of oral anticoagulation prior to surgery. There is data to support PCC4 as opposed to supplemental fresh frozen plasma (FFP) to manage postoperative bleeding following cardiac surgery. The preemptive, intraoperative use of PCC4 in cardiothoracic surgery has not been studied though it may prevent postoperative bleeding, the need for blood transfusion and the risk of transfusion related acute lung injury, volume overload, and right ventricular (RV) heart failure. The purpose of this study is to evaluate the intraoperative administration of PCC4 to decrease bleeding and lower the rate of blood transfusion.

Methods: A single institution retrospective chart review conducted from May 2020 to November 2021 of patients who received PCC4 intraoperatively during cardiothoracic surgery of high risk variety. Patients were evaluated for type of surgery, demographics, baseline anticoagulation, PCC4 dose, type and quantity of blood transfusion within 72 hours postoperatively, chest tube output, incidence of right ventricular failure, hypersensitivity reactions, acute kidney injury, thrombosis, acute lung injury, and mortality within 45 days of the operative dose of PCC4.

Results: Thirty five patients received PCC4 at a mean dose of 2920 units. Sixty five percent of cases were LVAD or heart transplant. The protocol is to use PCC4 30 units/kilogram immediately after completion of protamine administration. Inclusion criteria are: cardiothoracic surgery with increased risk of postoperative right heart failure commonly secondary to blood product transfusion, or cardiothoracic surgery associated with increased risk of bleeding, including: heart transplant, LVAD implant, aortic dissection, and redo sternotomy (e.g. coronary artery bypass). Total chest tube output was recorded as a mean of 757 mL for 24 hours after surgery (32 ml/hr). Overall median event rates of fresh frozen plasma (FFP) and red blood cell (RBC) transfusion were 0 (interquartile range 0 - 3 units) and 4 (interquartile range 2-5 units). Overall, forty-three percent and eighty-nine percent of cases received FFP and RBC, respectively. There was one occurrence of right ventricular failure, one occurrence of acute kidney injury requiring renal replacement therapy, one occurrence of venoarterial extracorporeal membrane oxygenation, one occurrence of venous thromboembolism related to a central venous access line, and one death unrelated to surgery or PCC4 that was attributed to advanced heart failure not amenable to advanced therapies.

Conclusion: Overall patients received a low rate of blood transfusion, had minimal chest tube output, and there was a small incidence of right heart failure. Patients did not have an increased risk of adverse effects such as acute kidney injury or venous thromboembolism. A randomized controlled clinical trial comparing the observed dose and timing of PCC4 versus routine postoperative bleeding management with blood product transfusion is recommended.

Background

Perioperative bleeding is costly, as the result is use of blood products, pharmaceutical hemostatics, or repeat surgery. In complex cardiac surgery, the cost of care for patients who are transfused (receiving at least one unit of red blood cells, fresh frozen plasma, platelets, or cryoprecipitate) is 133.2 % greater compared with those not transfused.[1]

Two studies have found that PCC4 for warfarin reversal prior to heart transplant displayed a reduced utilization of blood products. Further in one of the retrospective studies, unrelated to anticoagulation at baseline, there was a nonsignificant trend towards lower utilization of blood transfusion when administering PCC4 at doses greater than 20 units/kilogram compared to 10-19.9 units/kilogram.[2]Every cardiothoracic surgery includes varying risk for blood loss and consequences of blood product administration and even further, a two to six times greater risk of mortality when performing a repeat sternotomy.[1] Increased bleeding risk translates to a higher rate of blood transfusion and transfusion associated morbidity: including pulmonary edema, right ventricular strain, increased ventilator time, and increased length of stay (LOS) in the ICU. Additionally, transfusion-related acute lung injury (TRALI) has an estimated 2-4% incidence in cardiac surgery that carries significant morbidity. TRALI typically has a twofold insult with an initial hyper inflammatory immune mediated response followed by diffuse pulmonary edema; it is the leading cause of transfusion-related morbidity and mortality.[2] Patients who receive more blood products after surgery have greater risk adjusted pulmonary complications, including TRALI, respiratory failure, acute respiratory distress syndrome (ARDS), clinically described by the *Berlin Criteria*where the ratio of the partial pressure of oxygen (PaO2) to the fraction of inspired oxygen (FiO2) is consistently less than 200-300 mmHg while the positive end expiratory pressure (PEEP) is greater than or equal to 5 centimeters of water which leads to increased time on the ventilator. Furthermore TRALI patients with and without RV overload, have higher rates of reintubation.[3,4] RV overload is an expensive complication to treat, with resource intensive therapeutic options that include inhaled nitric oxide (iNO) or pulmonary vasodilators such as epoprostenol, both of which increase acuity and contribute to higher cost of care. Limiting blood transfusion is important to the health system stewardship efforts, firstly due to the critical shortage of blood products in the United States that has been ongoing since the COVID-19 pandemic began, and secondarily due to the overall cost to the health system incurred from transfusion of blood products not solely ascribed to product acquisition cost, but also to subsequent higher acuity of care cost for patients after blood transfusion. Avoidance of post-operative bleeding prevents volume overload, transfusion related acute lung injury, and right ventricular heart failure.[1,3,7] This single center review sought to assess the benefit of preemptive, intraoperative dosing

administration of PCC4 in cardiothoracic surgery patients with increased risk of bleeding; the majority of cases (65%) being left ventricular assist device (LVAD) and heart transplant.

Methods

A single institution retrospective chart review of all consecutive patients from May 2020 to November 2021 who received PCC4 during cardiothoracic surgery were included. IRB approval to conduct the study was obtained. The institutional protocol is to use PCC4, a total dose of 30 units/kilogram immediately after completion of protamine administration for cases deemed an increased risk for bleeding and/or right heart failure including: heart transplantation, LVAD implantation, and/or aortic surgery (e.g. ascending aortic dissection repair), and for redo sternotomy cases (e.g. coronary artery bypass). Patients were monitored with standard bleeding assessment protocol to guide blood product resuscitation both intraoperatively and postoperatively with point of care laboratory monitoring, including point of care thromboelastogram and activated clotting time, as well as conventional laboratory monitoring including complete blood counts, and systemic coagulation panels (e.g. protime/international normalized ratio & partial thromboplastin time). For the purposes of establishing the blood transfusion threshold, products were administered based on the evidence of bleeding affirmed with laboratory results. Blood product selection was based on thromboelastogram in conjunction with clinical laboratory assessment (e.g. hemoglobin, platelets, and fibrinogen). As a general rule, packed red blood cells were considered for symptomatic need once hemoglobin was less than 7 grams per deciliter. The same criteria were used for fresh frozen plasma, an additional criteria being developed enzymatic hypocoagulability or clotting factor deficiency. Platelets were transfused for active bleeding with platelet count less than 50,000 per microliter and/or platelet dysfunction identified by thromboelastogram. Cryoprecipitate was transfused for active bleeding with evidence of fibrinolysis identified by thromboelastogram, as well as fibrinogen level less than 200 milligrams per deciliter.

Patients were validated for inclusion criteria. Data collection included: surgery type, PCC4 timing and dose, type and quantity of blood transfusion within 72 hours postoperatively, patient demographics, baseline anticoagulation, postoperative chest tube output, incidence of right ventricular (RV) failure, hypersensitivity reactions, acute kidney injury, thromboembolic events, and mortality within 45 days of intraoperative PCC4. Primary assessment included surgery type, hourly chest tube output, and type and quantity of blood product administration. Secondary assessment included documentation of adverse events such as incidence of hypersensitivity reactions, right ventricular failure, multi-organ failure requiring renal replacement therapy or ECMO, thromboembolic events, and mortality.

Results

Thirty five patients were identified and *Table 1.1* represents baseline characteristics. The mean patient age was 60 years (SD 48 - 73) and the majority of the cases were LVAD implants (35%) followed by heart transplants (31%). *Table 1.2* demonstrates outcome observations for PCC4. Summarizing the outcomes: the mean dose of PCC4 was 2920 units (31.4 units/kilogram). *Table 1.3* represents overall blood product usage of each of the four products, and *Table 1.4* represents the same review focusing solely on LVAD and heart transplant (n = 23). Overall median event rates of fresh frozen plasma (FFP) and red blood cell (RBC) transfusion were 0 (IQR 0 - 3 units) and 4 (IQR 2-5 units). Overall, 43% and 89% of cases received at least one unit of FFP and/or RBC, respectively. Additionally, 60% of all patients received a platelet transfusion (median 1, IQR 0-2 units) and 37% of all patients received cryoprecipitate (median 0, IQR 0-2 units). When focus was applied to the patients that actually received any blood product (excluding those who did not), transfusion rates were: median FFP 3 units (IQR 1-6) and RBC 4 units (IQR 2-5). For LVAD and heart transplant patients (n = 23) 39% received any FFP, with a median of 0 (IQR 0-3 units) and 91% received RBC with a median of 4 (IQR 2-5 units). Secondary results (*Table 1.2*) included: a mean chest tube output of 757 mL for 24 hours after surgery (32 milliliters/hour). There was one occurrence of right ventricular failure, acute kidney injury requiring renal replacement therapy (RRT), and veno-arterial ECMO all of which occurred in the same patient. Reviewing this case, there was high risk for complications - a redo coronary artery bypass with obesity, advanced coronary disease, and acutely decompensated heart failure. Acute kidney injury was attributed to vasopressor use and intravenous contrast media administration given while

evaluating the causes of right ventricular strain. Additionally, the case was attributed with the one occurrence of lower extremity venous occlusion that was secondary to suboptimal placement of a femoral central venous access line. One patient regressed ultimately to terminal wean, unrelated to surgery or PCC4; the patient expired as a result of prolonged, advanced heart failure that was not amenable to advanced therapies beyond pharmacological inotropes.

Discussion

Limitations including: single-center, unblinded study design, and retrospective chart review make it prohibitive to perform robust data analysis. It is difficult to discern true benefit compared to available meta-analysis data, which predominantly compares PCC4 to blood product administration *after* this surgical population is *already bleeding postoperatively* .[6]

Transfusion rates and amount of individual blood products compare favorably to available literature, including compared to the meta-analysis' data trending toward less products used ((overall FFP rate of 0 (IQR 0-3 units) compared to available literature 3-14 units)).[5,6,7] Further, chest tube output was lower than generally expected as described in the literature for this surgical population (overall output of 757 ml compared to 935ml +/- 583).[7] Comparable incidence of volume overload driven right ventricular failure and acute kidney injury were low when reviewing the current literature, where AKI has been described as potentially more likely post PCC4 dosing in this surgical population.[6,8,9] Our findings did not support the notion of this kidney injury risk, albeit a smaller sample size. To concretize the intervention and its potential benefit, this analysis at minimum establishes an intermediate weight based PCC4 dose, operative timing, and consideration for PCC4 where it is believed the data presented is favorable for the use in select patients undergoing high risk cardiac surgery, and perhaps more specifically, those patients undergoing aortic dissection, LVAD placement, or heart transplant.

From a cost to provide intervention perspective, PCC4 costs approximately $1.81 per unit. Therefore, a dose of approximately 3,000 units costs $5450 per dose. Comparatively, the acquisition cost at our institution to provide a single unit of fresh frozen plasma is $ 200, packed red blood cells $ 196, platelets $ 634, and cryoprecipitate $ 475 for one pooled bag of five units. The cost of intensive care management for a transfusion-dependent postoperative patient is substantial, and for the purposes of this review, is too challenging to quantitatively describe; although, the cost avoidance of such complications would seem significant. From this data it is reasonable to suggest that providing a single dose of PCC4 intraoperatively after protamine at minimum may positively impact critical blood product supply, and even more so offset the cost of blood product administration and its deleterious clinical consequences. Compared to available individual trial and meta-analysis data, the patients in our sample had less blood transfusion, decreased postoperative chest tube site bleeding, no increase in acute kidney injury or occlusive disease, and a low incidence of right ventricular dysfunction. Specifically, the cost-benefit to the patient by principally avoiding transfusion related acute lung injury, volume associated right ventricular dysfunction, additional intensive care unit time and ultimately, the associated increase in intensive care complications - may be where the patient most benefits. The use of intraoperative PCC4 timed to be given immediately after protamine may decrease bleeding complications, right heart failure, and the unfavorable collateral damage associated with blood product transfusion. Further large randomized controlled trials are recommended.

Conclusion

The review concludes that the institution's operatively timed weight based PCC4 dosing protocol is medically feasible, safe, and may further reduce post-operative bleeding and the associated complications of significant blood product transfusion. Intraoperative PCC4 was well tolerated. There was a trend towards an overall therapeutic benefit with a slowed rate of postoperative chest tube output (approximately 32ml/hr). We observed no increase in adverse events. An adequately powered randomized controlled trial comparing the observed intraoperative dose and timing of PCC4 versus traditional interventional bleeding management with blood product transfusion following high risk cardiothoracic surgery is recommended.

TABLE 1.1 Baseline Characteristics

N = 35	**N = 35**
Baseline Characteristics	**Mean (SD) or Numbe**
Age (Years)	60 (48 - 73)
Body Weight (kilogram)	90.3 (72.8 - 107.7)
Male / Female (%)	28 / 7 (80 / 20%)*
OAC at baseline (warfarin, DOACs)	2 (5%)*
Surgery Type: LVAD placement, heart transplant, aortic dissection, redo sternotomy for CABG	12 (35%), 11 (31%), 7 (20

*Denotes absolute number and percentage

OAC oral anticoagulant, DOAC direct oral anticoagulant

TABLE 1.2 Results

Outcome Measure(s)	**Mean (Standard Deviation)**
PCC4 Dose Unit(s)	2920 (2081 - 3683)
PCC4 Dose by weight units per kilogram	31.4 (21.6 - 41.4)
Post-operative Chest Tube Output mL (24 hours)	757 (195 - 1350)
Post-operative Hourly Chest Tube Output mL	32 (8 - 53)
PCC4 Intraoperatively after Protamine	35 (100%)
PCC4 Hypersensitivity Reaction(s)	0 (0%)
Evidence of RV Failure Post-operatively (24h)	1 (5%)
Sustained CVP above 20 mmHg	
Sustained PAS above 35 mmHg	
Sustained PAD above 18 mmHg	
Acute Kidney Injury Requiring RRT	1 (5%)
Multi-Organ Failure Requiring VA/VV ECMO	1 (5%)
Venous Thromboembolism Events (45 days)	1 (venous occlusion) (5%)
Mortality (45 days)	1 (unrelated to PCC4) (5%)

*Denotes absolute number and percentage

U = units; RV = Right Ventricular; FFP = fresh frozen plasma; PRBC = packed red blood cells; PLT = platelets; CRYO = cryoprecipitate; CVP = central venous pressure; PAS = Pulmonary Artery Pressure Systolic; PAD = Pulmonary Artery Pressure Diastolic; 24h = 24 hours; 96h = 96 hours; OAC = oral anticoagulation; AKI = acute kidney injury; RRT = renal replacement therapy; ECMO = extracorporeal membrane oxygenation; NOTE 5 CRYO Units = 1 Unit Bag (i.e. 10 units = 2 CRYO unit bags); CVP = central venous pressure; PAS = pulmonary artery systolic pressure; PAD = pulmonary artery diastolic pressure

Confirmed subgroup means only the patients that received the designated therapy.

TABLE 1.3 Overall blood product usage (N=35 cases)

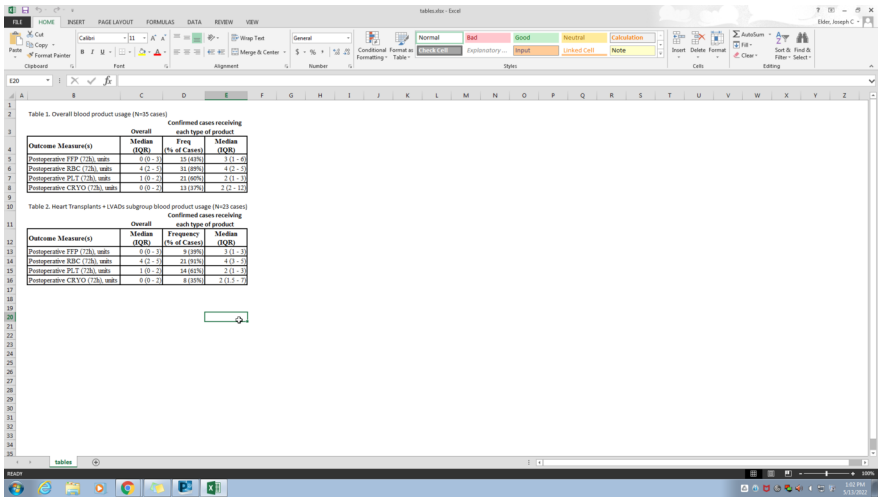
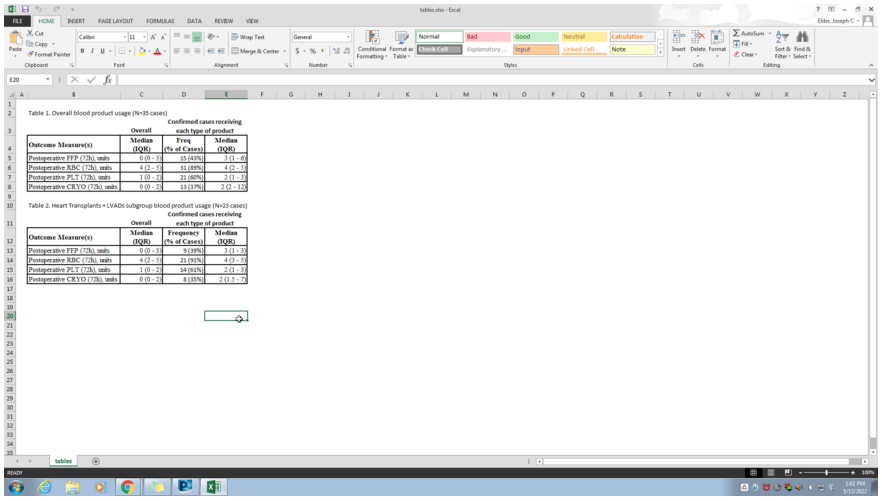


TABLE 1.4 Heart Transplants & LVADs subgroup blood product usage (N=23 cases)



U = units; RV = Right Ventricular; FFP = fresh frozen plasma; PRBC = packed red blood cells; PLT = platelets; CRYO = cryoprecipitate; CVP = central venous pressure; PAS = Pulmonary Artery Pressure Systolic; PAD = Pulmonary Artery Pressure Diastolic; 24h = 24 hours; 96h = 96 hours; OAC = oral anticoagulation; AKI = acute kidney injury; RRT = renal replacement therapy; ECMO = extracorporeal membrane oxygenation; NOTE 5 CRYO Units = 1 Unit Bag (i.e. 10 units = 2 CRYO unit bags) Confirmed subgroup means only the patients that received the designated therapy; 72h = seventy two hours; IQR = interquartile range

References

1. Massive bleeding in cardiac surgery. Definitions, predictors and challenges A Petrou*1*, P Tzimas*1*, S Siminelakis*2*. HIPPOKRATIA 2016, 20, 3: 179-186.
2. Prothrombin Complex Concentrates for Bleeding in the Perioperative Setting Kamrouz Ghadimi, MD, Jerrold H. Levy, MD, FAHA, FCCM, and Ian J. Welsby, BSc, MBBS, FRCA
3. Transfusion and Pulmonary Morbidity After Cardiac Surgery. Colleen Koch, MD, MS, Liang Li, PhD, Priscilla Figueroa, MD, Tomislav Mihaljevic, MD, Lars Svensson, MD, PhD, and Eugene H. Blackstone,

MD. Departments of Cardiothoracic Anesthesia, Quantitative Health Sciences, Laboratory Medicine and Clinical Pathology, and Thoracic and Cardiovascular Surgery, Cleveland Clinic, Cleveland, Ohio. Ann Thorac Surg 2009;88:1410 – 8.

4. The incidence, risk factors, and outcome of transfusion-related acute lung injury in a cohort of cardiac surgery patients: a prospective nested case-control study. Vlaar, et al. BLOOD, 21 APRIL 2011 VOLUME 117, NUMBER 16. Prepublished online as Blood First Edition paper, February 16, 2011; DOI 10.1182/blood-2010-10- 313973.
5. Comparison of 4-Factor Prothrombin Complex Concentrate With Frozen Plasma for Management of Hemorrhage During and After Cardiac Surgery A Randomized Pilot Trial.*Keyvan Karkouti, MD[1,2];Justyna Bartoszko, MD[1,2];Deep Grewal, MD[1]; et al Cielo Bingley, RN[1] ;Chantal Armali, BSc[3];Jo Carroll, BHA[1];Hans-Peter Hucke, PhD[4];Amie Kron, MSc[3];Stuart A. McCluskey, MD[1,2];Vivek Rao, MD[2,5];Jeannie Callum, MD[3,6,] JAMA Network Open.*2021;4(4):e213936. doi:10.1001/jamanetworkopen.2021.3936
6. Prothrombin Complex Concentrate in Cardiac Surgery: A Systematic Review and Meta-Analysis

Marius Roman 1, Fausto Biancari 2, Aamer B Ahmed 3, Seema Agarwal 4, Leon Hadjinikolaou 5, Ali Al-Sarraf 5, Geoff Tsang 6, Aung Y Oo 7, Mark Field 8, Francesco Santini 9, Giovanni Mariscalco 10jathoracsur.2018.10.01

Safety and efficacy of prothrombin complex concentrate as first-line treatment in bleeding after cardiac surgery.

Giangiuseppe Cappabianca1+ , Giovanni Mariscalco2*+ , Fausto Biancari3 , Daniele Maselli4 , Francesca Papesso1 , Marzia Cottini1 Sandro Crosta5 , Simona Banescu5 , Aamer B. Ahmed6 and Cesare Beghi. Cappabianca et al. Critical Care (2016) 20:5. DOI 10.1186/s13054-015-1172-6

Comparison of 4-Factor Prothrombin Complex Concentrate With Frozen Plasma for Management of Hemorrhage During and After Cardiac Surgery A Randomized Pilot Trial. Keyvan Karkouti, MD; Justyna Bartoszko, MD; Deep Grewal, MD; Cielo Bingley, RN; Chantal Armali, BSc; Jo Carroll, BHA; Hans-Peter Hucke, PhD; Amie Kron, MSc; Stuart A. McCluskey, MD; Vivek Rao, MD; Jeannie Callum, MD. JAMA Network Open. 2021;4(4):e213936. doi:10.1001/jamanetworkopen.2021.3936.

An Exploratory Cohort Study Comparing Prothrombin Complex Concentrate and Fresh Frozen Plasma for the Treatment of Coagulopathy After Complex Cardiac Surgery. Ortmann, Erik MD, DESA*; Besser, Martin W. MRCP, FRCPath+; Sharples, Linda D. PhD++; Gerrard, Caroline*; Berman, Marius MD, FRCS (CTh)§; Jenkins, David P. BSc, MBBS, FRCS(Eng), MS(Lond), FRCS(CTh)§; Klein, Andrew A. MBBS, FRCA* . Anesthesia & Analgesia: July 2015 - Volume 121 - Issue 1 - p 26-33

doi: 10.1213/ANE.0000000000000689