Surgical Considerations for Kcentra (prothrombin complex concentrate) a Factor Replacement for Acute Surgical Procedures

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Abstract

There is a growing number of individuals receiving warfarin anticoagulation therapy in the United States, which increases the chances that anesthesia providers will provide care to this population. Receiving anticoagulation therapy places individuals at a high risk for bleeding complications when undergoing emergency surgery. Traditional treatment to lower supratherapeutic International Normalized Ratio (INR) has been Fresh Frozen Plasma (FFP) and vitamin K. However, receiving large volumes of FFP makes this population prone to several severe complications, which ultimately increase cost and decrease patient safety. Kcentra prothrombin complex concentrate (PCC) was approved in 2013 by the FDA and is able to fully reverse warfarin while avoiding the serious and costly side effects of FFP administration. The average volume of Kcentra needed to fully reverse warfarin was found to be only 11% of the total volume of FFP needed for full reversal. Kcentra was ultimately found to decrease surgical bleeding, which consequently decreased transfusion of blood products, overall cost of hospitalization, and adverse transfusion effects. The aim of this quantitative scholarly project was to develop an educational PowerPoint presentation with the purpose of increasing the knowledge base of 22 Advent Health University Student Registered Nurse Anesthetists. The student registered nurse anesthetist baseline knowledge was assessed by the completion of a 10-multiple choice question pre-test prior to the presentation. Following the presentation, a posttest (identical to pre-test) was given to assess a change in knowledge base. Statistical analysis was performed using a (paired t-test) on the mean pre- and posttest scores to determine the effectiveness of the educational PowerPoint presentation on increasing the knowledge base of the participants. The pretest standard deviation was 19.73855, while the posttest was 10.45502. The obtained T value was (-9.167) and is associated with $p<.001$ which is statistically significant.

Table of contents

Introduction

Cardiovascular disease and embolic events are on the rise in the United States, which means there is an increasing number of individuals receiving warfarin. Warfarin is used to treat individuals who are at increased risk of thrombotic and embolic events by preventing blood coagulation. Warfarin provides anticoagulation by antagonizing vitamin K, which is needed to synthesize clotting factors (II, VII, IX, X) and proteins C and S that are necessary for coagulation (Lip & Douketis, 2018). The patient population requiring warfarin anticoagulation therapy mainly consists of older individuals who have an increased probability of other comorbidities.

This increases their need for scheduled or urgent surgery. Chronic anticoagulation with warfarin places these individuals at an increased risk for several surgical complications. Full reversal of anticoagulants prior to surgery is imperative in order to minimize large amounts of blood loss.

Recommended discontinuation of warfarin therapy prior to scheduled surgery is five days (Douketis et al., 2012). However, emergency surgery may be needed in these individuals who are anticoagulated with warfarin. Lip & Douketis (2018) recommend that individuals receiving warfarin should have their international normalized ratio (INR) below 1.4 prior to any surgical procedure. Standard treatment to reverse the effects of warfarin include a balanced regimen of fresh frozen plasma (FFP) and vitamin K. The standard dose of FFP needed to reverse warfarin is 10-15ml/kg (Butterworth, Mackey, Wasnick, 2013), while the vitamin K dose varies depending on the severity of the elevation of the INR and ranges from 1-2mg orally for INR 4.5-10 and 5-10mg IV for INR>10 (Lip & Douketis, 2018).

In 2013 the FDA approved Kcentra, a prothrombin complex concentrate (PCC), which is able to reverse warfarin and replace key coagulation factors for patients experiencing major

bleeding or needing emergency surgery. This medication is able to effectively treat supratherapeutic INR levels while avoiding unwanted side effects of FFP administration. These conflicts raise several questions. Is FFP the best practice for reversing warfarin in the acute cardiovascular surgical setting? Is Kcentra a safer and more cost-effective treatment option available to reverse warfarin anticoagulation? Due to these conflicts, it is imperative that AHU SRNAs are able to identify the best practices for reversing warfarin in the acute surgical setting. The goal of this Scholarly Project was to increase the knowledge base of AHU SRNAs as it pertains to pharmacokinetics, pharmacodynamics, and to the clinical applications of Kcentra.

Project Questions

Our literature review and intervention was guided by the following PICO questions.

In patients undergoing surgical procedures (P), how does Kcentra, a prothrombin complex concentrate(I), compared to fresh frozen plasma (C), affect warfarin reversal (factor replacement) (O) within the acute surgery setting?

In Advent University student registered nurse anesthetists (P), does a 30-minute educational PowerPoint (I & T) presentation regarding the use of Kcentra in the acute surgical setting result in an increased knowledge base (O)?

Literature Review and Synthesis (overall themes)

The Centers for Disease Control and Prevention (CDC) (2018) states that as many as 900,000 Americans suffer from an embolic event each year and that 2.7-6.1 million Americans suffer from atrial fibrillation. These are two of the main reasons patients are placed on chronic anticoagulation therapy. Patients that require anticoagulant therapy often have other comorbidities such as cardiovascular and chronic kidney disease, which further complicate anesthetic management when encountering acute surgery and could potentially lead to poorer

patient outcomes. Patients who receive chronic anticoagulation therapy are at a significant risk for complications when faced with acute surgery. These complications include but are not limited to surgical delay, increased cost of care, longer hospitalizations, hemorrhage, and volume overload related to FFP administration in an attempt to reverse anticoagulant effects (Rafaai et al., 2015).

FFP is gathered from human donor blood and contains all soluble coagulation factors, plasma proteins and immunoglobulins (Stanworth et al., 2004). FFP has long been a popular choice for providers when replacing coagulation factors, replacing volume due to hemorrhage, and reversing warfarin anticoagulation. The recommended FFP dosage (10-15ml/kg) needed to reverse the effects of warfarin on an average 70kg patient would be 700-1,050ml. The patient population receiving warfarin therapy may be more susceptible to other disease processes such as cardiovascular and renal disease due to their age, decreasing their ability to tolerate such large volumes of FFP. With such large volumes of FFP administered to reverse warfarin, a direct correlation between the number of FFP units administered and the incidence of fluid overload when treating supratherapeutic INR was identified (Rafaai et al., 2015). Large blood product transfusions also place the patient at risk for complications such as transfusion-related acute lung injury, anaphylactic reactions, febrile reactions, and viral infections (Butterworth, Mackey, Wasnick, 2013). All of these side effects require further treatment and ultimately increase hospital/patient cost, length of hospital stay, and poor outcomes.

FFP is stored frozen and is thawed over an average time of 45 minutes once needed. In acute settings where anticoagulation reversal is needed immediately, the transfusion of FFP can be delayed due to the time it takes to thaw, cross match and transfuse the unit (Berntson et al., 2015). The researchers also discovered that FFP rarely fully reverses elevated INR related

vitamin K antagonists leaving the patients susceptible to increased surgical bleeding (Berntson et al., 2015).

FFP is relatively inexpensive. On average only costing only $60.71. However, therapy needed to treat the side effects of large FFP infusions could be costly. This suggests that the risks of complications outweigh the potential reward of adequately reversing these patients with FFP.

Kcentra a prothrombin complex concentrate (PCC) is a relatively new anticoagulant reversal agent that has the potential to transform the way chronically anticoagulated patients are surgically cared for. Prothrombin complex concentrate contains all vitamin K dependent factors (II, VII, IX, X) as well as protein C and S making it clinically effective in reversing vitamin K antagonist. Due to the prevalence of this problem, it is important to review the available literature to extrapolate best practices and present the information in a manner that would impact SRNAs and other anesthesia providers in the care they give to this specific patient population.

A significant characteristic of prothrombin complex concentrate or Kcentra is the dosing amount required to reverse the effects of Warfarin prior to surgery. The median dose of Kcentra was found to be 25 IU/kg administered in an average volume of 90-100ml, while the other test group was administered a volume of 800ml of fresh frozen plasma (Milling et. al, 2016; Tanaka, et. al, 2014). As a pre-operative measure to counter the increased INR caused by Warfarin, Kcentra averages a dosage volume of 90ml with a range of 48 to 230ml to bring the INR to the target of $\leq$1.3 (Milling et. Al). Another area of focus found in the literature was the use of PCC postoperatively rather than preoperatively in cases of persistent life-threatening bleeding that occurred even after conventional treatment. A mean of 2,154 units ranging from 1,000 to 4,000 units per case was administered prior to chest closure during open-heart surgery. The greatest

benefit of this significant difference in volume between Kcentra and plasma is the reduction of cases where there is build-up of fluid in the lungs and body, and consequently peri- and post-operative complications when Kcentra is used.

In cases where Kcentra was used as opposed to plasma either preoperatively or peri-operatively, there were indications of fewer blood products needed overall confirmed by several studies. According to Song et al, patients who were given a prothrombin complex concentrate prior to completion of surgery, then received a mean fresh frozen plasma transfusion of 0.68 (range, 0-7; SD, 1.5; P =.0001) units compared to 4.76 (range, 2-10; SD, 2.5) units needed prior to the administration of the PCC. The mean platelet transfusion also showed a drastic contrast at 2.76 (range, 1-5; SD, 1.0) units needed for transfusion before Kcentra was administered and 0.52 (range, 0-5; SD, 1.1; P < .0001) following the inhibitor bypassing activity. Twenty-five patients were identified that needed and received the rescue treatment; of those twenty five, seventeen patients in the postoperative period presented no further need for plasma or platelet transfusion, only two patients needed cryoprecipitate and sixteen of the twenty-five did not receive red blood cell transfusion (Song, et al). Additionally, in cases where Kcentra is used in place of FFP, the need for additional elements such as albumin, antithrombin, fibrinogen, and immunoglobulins is obsolescent (Tanaka, et al). The literature reveals a resounding reduction in bleeding and consequently a lower risk of RBC transfusions and decreased amount of RBC units when PCC was selected as a post-operative treatment for coagulopathy (Cappabianca et. al., 2016; Fries, 2013).

Another aspect of Kcentra to consider is the amount of time it takes to administer this prothrombin complex concentrate comparative to that of fresh frozen plasma. Research studies have reported that it took 90 minutes to administer the full dose of plasma and only 17 minutes to

administer the Kcentra (Milling et. al, 2016; Tanaka et. al, 2014). In acute cardiac cases, especially those that are emergent, this time difference can make a significant impact on the timeframe that a patient can undergo surgery and ultimately affect the outcome of the procedure.

Not only are there benefits in the amount of time it takes to administer Kcentra compared to that of plasma, one study also discovered a significant difference in the speed of onset between the two. Tanaka et al. discovered that plasma vitamin K factor levels were rapidly recovered within 30 minutes after administration of Kcentra whereas procoagulant levels took at least 3 hours to return to ≥50% in patients receiving plasma.

The benefits involved with using Kcentra as an alternative to plasma seem to far outweigh the inherent risks that the concentrate poses. One such benefit is the reduction of post-operative complications encountered as a result of excess bleeding and/or fluid build-up. One study reported "excellent" outcomes when PCC was used as a perioperative measure (Song et. al, 2014). In this study, complex patients who were on Warfarin prior to cardiac surgery were unable to discontinue the Warfarin due to the emergent nature of the procedures done which included aortic procedures, left ventricular assist device implants, or heart transplants with or without an LVAD explant. At the conclusion of the procedures in which the patients were given Kcentra as a rescue treatment, no patients required chest packing and none of the patients needed re-exploration for bleeding. Furthermore, no operation related deaths occurred and patients remained in the ICU for a mean of 7 days with a total length of stay mean of 12.8 days (Song et. al, 2014).

A subsequent study found that the overall safety profile of a four-factor prothrombin complex concentrate was very comparable to that of plasma, but there was a significant difference in the number of fluid overload events. In this study of 388 patients by Milling et. al,

(2016) there were 13 reported deaths for patients in both the PCC and plasma groups. Fourteen patients in both the PCC group as well as the plasma group experienced a thromboembolic event, 54 patients in the PCC group had a serious adverse event compared with 49 in the plasma group, and 124 patients underwent an adverse event in the plasma group conversely to 115 in the PCC group. Patients suffering from fluid overload events numbered 25 in the plasma group but only 9 in the PCC group, a difference of nearly 3 to 1. Moreover, 14 of the fluid overload or similar cardiac events in the plasma group were determined to be related to the treatment whereas no events in the PCC group were found to be related creating a difference between the groups of -7.1%. In a listing of deaths reported in this same study, only 1 of the deaths in each study group of plasma or PCC was determined to be possibly related to complications from bleeding. The patient in the PCC group had a history of iliofemoral DVT which increases the risk of a thromboembolic event and the actual cause of death is unknown while the patient in the plasma group went into a ventricular tachycardia rhythm on day 7 and died on day 8. It was determined that the thromboembolic events and death were possibly related to plasma administration (Milling et al).

No patients in this study in the PCC group discontinued treatment due to an adverse event, whereas 3 patients in the plasma group had to discontinue treatment. However, it is stated in the article that this may be due to the length of time required for plasma as opposed to PCC (Milling et. al, 2016).

Another noteworthy advantage of using Kcentra for the reversal of the effects of Warfarin is that it can be used effectively for any blood type and can be produced in large quantities as needed. Since Kcentra is pasteurized, it is not dependent on blood type. Adversely, plasma's effectiveness and risk factors are dependent on both blood type and availability.

Tanaka et al investigates the drawbacks of using plasma that is not uniquely specific to a patient's needs, especially a patient in need of emergent cardiac care. Since multiparous females are often sensitized to HLA antigens, male plasma is preferential for administration. However, roughly 40% of plasma available in an emergency situation is still derived from female donors. For a patient who may already have multiple risk factors, this poses yet another risk by introducing foreign antigens. Additionally, Tanaka et al examined a cohort study of 568 trauma patients and found that there were increased risks of acute respiratory distress syndrome and sepsis in patients treated with ABO compatible plasma compared to those treated with ABO-identical plasma. They concluded that "the risks of transfusion related acute lung injury (TRALI) and other complications are theoretically increased after the exposure to multiple plasma units and donor antibodies." Conversely, the manufacturing process of Kcentra includes steps to prevent lipid-enveloped viruses (Tanaka et. al, 2014). The risks of viral transmission in plasma patients is further investigated by Milling et. al, (2016) in which no viral transmission was confirmed in patients treated with Kcentra whereas 2 patients in the plasma group had indications of a viral transmission.

While Kcentra does pose significantly fewer risks of transfusion related acute lung injury, sepsis, fluid overload, and anaphylactic reactions, it does have a higher risk of kidney complications and thrombosis in some trauma and surgical patients (Tanaka et. al, 2014). Cappabianca et al notes that patients who received PCC showed an increased risk of post-operative acute kidney disease at 31.3% opposed to 23.4% in plasma administered patients and a 3.1% chance of renal replacement therapy for those receiving PCC in comparison to 1.2% of plasma patients. They further highlight animal models in which PCC use showed increased risk of thromboembolic complications and disseminated intravascular coagulation. However, most of

the human studies indicate little inherent difference in these risks between those administered plasma versus prothrombin complex concentrate or Kcentra.

Contribution and Dissemination/Justification

Traditional education of blood components and products were discussed concisely over the past year in the Advent University Nurse Anesthesia program; however, a better understanding of these anesthetic implications can be achieved by increasing the knowledge base of all SRNA students at AHU about prothrombin complex concentrates as an alternative in the management of patients on blood thinners. Kcentra is one of these products now being considered for acute surgeries. In order to contribute to the awareness of Kcentra and its implications in acute surgery, this current project will laconically summarize the use of prothrombin complex concentrate along with distinct perioperative and postoperative events.

The target population for this scholarly project was the SRNA class of 2019 at AHU. As Critical Nurses in the Anesthesia program, there is a familiarity with blood products and components already; however, an educational PowerPoint presentation appeared necessary with emphasis on anesthetic implications as it pertains to the use of Kcentra. The primary goal was to increase the knowledge base of the participants about a newer option for management of patients taking coumadin and requiring emergent surgery. The timeframe of this project presentation is the fall semester of 2018.

Project Aims

The aim of this scholarly project is to increase the knowledge base of the student registered nurse anesthetist's in the 2019 cohort (n = 22) regarding the acute surgical management of patients on chronic warfarin therapy, specifically the reversal of an anticoagulated state, undergoing acute surgical procedures. This information was presented via

an educational PowerPoint presentation in the fall of 2018. The effectiveness of the presentation was determined by an increase in mean posttest scores as compared to mean pre-test scores. During this presentation, the students were equipped with clinically relevant information regarding this topic which will allow them to safely manage this specific patient population. The independent variable in this research project is the educational PowerPoint presentation and the dependent variable is the difference between mean pre-test and post-test scores.

Project Methods

This scholarly project is quantitative in design. A convenient and homogenous sample of 22 student registered nurse anesthetists currently enrolled in the Advent University Masters of Nurse Anesthesia Program 2019 cohort was included in the scholarly project. After IRB/SRC approval or exemption, the study began. Inclusion criteria included current enrollment in the Advent University Masters of Nurse Anesthesia Program, present the day of the presentation, and a signed informed consent. Exclusion criteria are individual refusal to participate in the study and physical absence the day of the presentation. Participants who arrived late to the presentation and missed the pre-test were invited to stay for the presentation but were excluded from the study.

Prior to the pre-test administration, each participant voluntarily signed an informed consent or were excluded from the study. A 10-multiple choice question pre-test was administered to evaluate the students' baseline knowledge regarding the topic. A 30-minute educational PowerPoint presentation regarding the acute surgical management of patients receiving warfarin therapy was presented to the sample group. A posttest (same 10-multiple choice questions as the pre-test) was then be administered to evaluate an increase in knowledge base regarding the topic. Both the pre and post-tests were collected via numbered envelopes

without the participants name to assure anonymity and allow easy organization when reviewing the results. The tests results were then placed into a Microsoft Excel Spreadsheet; the results were then analyzed using a paired t-test.

The data that was collected was stored on the investigator's laptops as well as Google Drive, both of which are password protected. Once the final project has been completed, submitted and approved, the data that was collected will be deleted from the investigator's laptops and Google Drive.

Timeline

The work of this project is spread over the course of three trimesters. Beginning in the summer semester of 2018, the topic will be approved by the faculty, a project chair and mentor will be selected, and a detailed literature review completed. The project topic will be submitted to the IRB/SRC and exemption or approval was determined. The information gathered was compiled into a 30-minute presentation and presented to the 2019 cohort of student nurse anesthetists during the fall trimester of 2018. A pre-test was administered prior to the presentation with a post-test immediately following. Data collection began by comparing the results of the pre and post-test to assess for an improvement of the knowledge base regarding the topic. During the 2019 spring trimester, the findings of the research will be shared during the scholarly poster presentation.

Data Collection Plan

Data from this Scholarly Project is comprised SRNA students at AHU in the 2019 cohort. After the consent forms were signed and returned, the investigators handed out a pre-test with randomized numbers to avoid accidental identification of any one particular participant. There

was an envelope clearly marked for each participant for both the pre and post-tests, and all questions were identical for all students.

To ensure that students' identities were kept confidential, only the numbers encountered on the envelopes during data collection were used. Questions will be all multiple choice so that handwritten answers were avoided. Students were given specific instructions to complete the pre-test first and place it in the appropriate envelope and turn them in prior to the PowerPoint presentation.

After the PowerPoint presentation, all students took the posttest which was the same questions as in the pre-test. The post-tests were then placed in the appropriate envelope and turned in. Researchers collected the posttests and arranged them together with the pre-tests according to the number assigned. Instructions were given to students not to write their names on the envelopes or tests. The tests would then be graded and all scores were transcribed and placed into an Excel spreadsheet for examination and final report.

Evaluation Plan

After all tests were compiled and graded, the results from the pre-test and posttest were separately transcribed into a Microsoft Excel spreadsheet. Investigators then enlisted the help of Advent University statistician, Dr. Roy Lukman. Pre- and posttest data were analyzed to identify if an increase in knowledge had occurred. The data was then analyzed through a SPSS computer program using a paired t-test to determine if there was a difference between the pre-test and posttest scores and if the presentation was effective in increasing the knowledge base.

Feedback from Dr. Lukman was further analyzed and the investigators determined if SRNA's from the 2019 cohort who received the educational PowerPoint presentation about Kcentra had an increased knowledge base on the topic, as evidenced by higher posttest scores.

Researchers will then present this information and research by poster presentation in the spring 2019 semester.

Results

The registered nurse anesthesia students at Advent University baseline knowledge was assessed by the completion of a 10- multiple choice question pre-test prior to the presentation. Following the presentation, a posttest (identical to pre-test) was given to assess a change in knowledge base. Statistical analysis was performed using a (paired t-test) on the mean pre- and posttest scores to determine the effectiveness of the educational PowerPoint presentation on increasing the knowledge base of the participants. The pretest mean was 40.9091 and the posttest mean was 90.4545. The pretest standard deviation was 19.73855, while the posttest was 10.45502. The obtained T value was (-9.167) and is associated with $p<.001$ which is statistically significant.

Limitations

Limitations of this study include a small convenient homogenous sample size at one clinical site and one university. The sample size will be 22 senior AHU SRNA from the 2019 cohort. Another limitation of the study was a limited timeframe to present the scholarly project. The post test was given immediately following an educational PowerPoint presentation limiting the ability to fully assess knowledge retention and learning of the material presented.

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Appendix A

ADVENT UNIVERSITY NAP CAPSTONE PROJECT – INFORMED CONSENT

This is a Capstone Project on *Kcentra in Acute Surgical Procedures*. The chair for this project is a Nurse Anesthesia program faculty member. We would like to invite you to participate in this project. The main purpose of this consent form is to provide information about the project so you can make a decision to participate.

What Is This Project About?
This project is intended to assess the Student Nurse Anesthetist's level of understanding and educate the SRNA cohort of 2019 on the importance of Kcentra in Acute Surgical procedures.

What Does Participation In This Project Involve?
If you decide to participate in this project, you will be asked to complete an anonymous pre-assessment quiz, attend a classroom presentation of approximately 45 minutes, and then complete an anonymous post-assessment quiz. The post-assessment will measure the increase of knowledge of the SRNA student as compared to the pretest.

Why Are You Being Asked To Participate?
You have been invited to participate as part of the sample of students enrolled in the Adventist University of Health Sciences Nurse Anesthesia Program and your participation is voluntary. If you wish to withdraw from participation you may do so at any time.

What Are The Risks Involved In This Project?
No Project is completely risk-free however, we don't anticipate that you will be harmed or distressed by participating in this project.

Are There Any Benefits To Participation?
We do not expect that any direct benefits will be gained from participation from this project. The possible indirect benefits of participation in this project will be the opportunity to gain additional knowledge about the anesthetic implication of using Kcentra in Acute Surgical procedures.

How Will The Investigators Protect Participants' Confidentiality?
Results of this project will be published, but your name or identity will remain confidential. To maintain confidentiality of assessment quizzes, the investigators will conduct this project using numbers without participants identification. There will be no identifying information on the pre- or posttests. All tests will be stored in the project chair's office and remained locked. After the data has been collected and the results have been analyzed the tests will be shredded.

Will It Cost Anything Or Will I Get Paid To Participate In The Project?
Participation in this project will not require monetary cost on your part. You will not get paid to be a participant. Your participation will cost approximately 45 minutes of your time.
Voluntary Consent

Your participation in this study is voluntary. You may choose to not to participate. The decision to participate or not participate in this research study is completely up to you. If you choose not to participate your refusal to participate in this research study will involve no penalty or loss of benefits to you. If you choose to participate, you can change your mind later and withdraw your consent and discontinue participation from this study at any time. If you chose to withdraw informed the PI of your wishes. You do not have to participate in this research study and choosing not to participate in this study will not involve any penalty or loss of benefit to you. The decision to participate or not participate in this research study is completely up to you. If you choose to participate, you can change your mind later and withdraw your consent and discontinue participation from this study at any time. If you chose to withdraw from the study informed the PI of your wishes.

By signing this form, you are stating that you have read this form and you understand the risks and benefits of this project. The investigators will be happy to answer and questions you have about the project. If you have any concerns about the project or investigators, please contact the Nurse Anesthesia Program and Adventist University of Health Sciences at (407) 303-9331.

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Participant Signature

Appendix B

Pre and Post Questionnaire

1. How does Kcentra differ from FFP?
   a. Has a increased risk of anaphylactic reactions
   b. Has a increased risk of viral transmission
   c. Has a decreased risk of fluid overload
   d. Kcentra requires more volume administered than FFP

2. Kcentra has been shown to have a slightly higher risk of _____ post op VS FFP
   a. Kidney complications
   b. blood borne diseases
   c. Cardiovascular complications
   d. Neurovascular complications

3. What is Kcentra used for?
   a. All patients undergoing surgery with bleeding problems
   b. Only patients undergoing cardiovascular surgery
   c. Urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonists
   d. None of the above

4. What is the recommended dosage of Kcentra?
   a. 10-15ml/kg
   b. 15-20 ml/kg
   c. 50 IU/kg
   d. 25 IU/kg

5. Kcentra contains which vitamin K dependent factors?
   a. II, VII, X
   b. Protein C and Protein S
   c. II, VII, IX, X (Protein C and Protein S)
   d. II, VII, IX, X

6. Kcentra is contraindicated for which patients?
   a. Patients with supratherapeutic INR
   b. Patients with DIC
   c. Patients with low Hgb/Hct
   d. Patients with elevated PTT

7. Kcentra significantly reduces what conditions?
   a. **Decreased INR levels**
   b. Transfusion related acute lung injuries
   c. hypovolemia
   d. hypernatremia

8. Kcentra increases which of the following?
   a. hospital stays
   b. transfusion requirements
   c. transfusion related side effects
   d. **cost per unit**

9. How fast can kcentra decrease INR to less than 1.3?
   a. **In 30 minutes after infusion**
   b. In 60 minutes after infusion
   c. In 90 minutes after infusion
   d. None of the above

10. How long does Kcentra effectively maintain hemostasis?
    a. 12 hours
    b. 12-18 hours
    c. **up to 24 hours**
    d. greater than 24 hours

Appendix C

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-Test	40.9091	22	19.73855	4.20827
	Post-Test	90.4545	22	10.45502	2.22902

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Pre-Test - Post-Test	-49.54545	25.35036	5.40471	-60.78517	-38.30574	-9.167	21	0

Kcentra

Anesthetic Implications for Patients on Blood Thinners Requiring Urgent/Emergent Surgery

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Objective

The aim of this project is to increase the knowledge base of the student registered nurse anesthetist's in the 2019 cohort regarding the acute surgical management of patients on chronic warfarin therapy, specifically the reversal of an anticoagulated state, undergoing acute surgical procedures

PICOT Questions

- In patients undergoing surgical procedures (P), how does Kcentra, a prothrombin complex concentrate(I), compared to fresh frozen plasma (C), affect warfarin reversal (factor replacement) (O) within the acute surgery setting?
- In Adventist University student registered nurse anesthetists (P), does a 30-minute educational PowerPoint (I & T) presentation regarding the use of Kcentra in the acute surgical setting result in an increased knowledge base (O)?

Problem

- Growing incidence of cardiovascular disease and embolic events in the US
- This increases the incidence of individuals receiving warfarin anticoagulation therapy
- Increased occurrence of surgical procedures
- Increases the chance that an anesthesia provider will be faced with managing one of these patients emergently in the operating room
- Full reversal of warfarin prior to surgery is imperative to minimize large mounts of blood loss and other negative consequences

Incidence of anti-coagulation therapy

- 900,000 Americans suffer from an embolic event each year (CDC, 2018)
- 2.7-6.1 million Americans suffer from atrial fibrillation

Case Study

- 75 yr Male
- **Hx.** CAD, HTN, Afib, CVA (2016), MI (2014), EF 35% (2016), DM type 2
- **Medications.** Coumadin 2mg daily, metoprolol 25mg BID, lisinipril 2.5mg daily, pravastatin 40mg daily, metformin 500mg daily, Lasix 20mg daily
- **Pertinent labs.** BNP 584, Glucose 112, Hgb 10, Hct 31, Plt 244, INR 2.8, K 3.4
- Patient presents with deep abdominal pain radiating to the back, abdominal CT reveals an acute abdominal aortic aneurysm measuring >5.5cm. Vascular surgeon notified and emergent open surgical repair indicated.

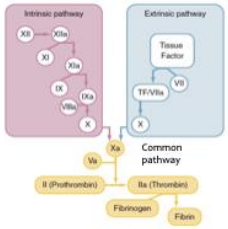
Anesthetic plan

- Rapid Sequence Induction- NPO status?
- iStat/Hemochron for labs
- Blood products in the room
- Adequate access (large bore Ivs/CVL)
- **Management of anticoagulation?**
- Vasodilators/Vasopressors for cross clamping
- Inotropes

Warfarin

- **Indications**-used to treat individuals who are increased risk for thrombotic and embolic events
- **MOA**-depletes functional vitamin K reserves thereby reducing hepatic synthesis of clotting factors II, VII, IX, X, protein C and S.

Clotting Cascade



Warfarin perioperative management

- Discontinued 5 days prior to elective surgery
  - Half life 36-42hours
- INR < 1.4 prior to surgery

Surgical Complications While On Warfarin

- Surgical delay
- Hemorrhage
- Volume overload
- Longer hospitalizations
- Increased cost of care
- Decreased patient outcomes

Traditional Warfarin Reversal

- Fresh Frozen Plasma (FFP) 10-15ml/kg
- Vitamin K 1-2mg PO (INR4-10) and 5-10mg IV (INR>10)

Fresh Frozen plasma

- Derived from human donor blood
  - 1 unit of whole blood=200-250ml of FFP
- Contains all soluble coagulation factors
- **Indications**
  - Replacing coagulation factors
  - Reversing warfarin anticoagulation
  - Elevated INR
  - Plasma exchange

Fresh Frozen plasma

- **Storage**
  - Frozen at -18 to -30 C within 8 hours of collection
  - If properly stored, usable 1 year after collection
- **Preparation**
  - Thawed over 45 minutes
  - Does not need to be cross matched but should be ABO compatible
- Average cost to administer - $60.71

FFP Adverse Side Effects

- **Risk for fluid overload**
- Transfusion-related acute lung injury
- Anaphylactic reactions
- Febrile reactions
- Viral infections
- Risk for HIV, hepatitis, and other blood borne infections
- Rarely fully reverses warfarin

Kcentra

- 4-Factor prothrombin complex concentrate (F4 PCC) made from human plasma
- **Contains all Vitamin K Factors (II, VII, IX, X) and Protein C and Protein S**
- **Indications:** urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist, non-warfarin related life threatening bleed
- **Onset:** significant INR decline within **10 minutes**

Kcentra Dosing

- **INR: 2 to <4:** Administer 25 units/kg; maximum dose: 2,500 units
- **INR: 4 to 6:** Administer 35 units/kg; maximum dose: 3,500 units
- **INR: >6:** Administer 50 units/kg; maximum dose: 5,000 units

Preparation and Administration

- Reconstitute 500unit vial with 20ml and 1000unit vial with 40ml
- Do not mix Kcentra with other IV medications, run through a separate IV line
- IV infusion at a rate of 0.12 mL/kg/min (~3 units/kg/min), up to a **maximum rate of 8.4 mL/min (~210 units/min)**
  - 25units/kg average dosage 70kg patient=1,750 units/210 units=8.3 minutes
- Must be used within 4 hours after reconstitution

FFP vs. Kcentra

	Fresh Frozen Plasma	Kcentra
Average infusion volume (70kg)	700-1,050ml (10-15ml/kg)	25units/kg (1000units/40ml)= 70ml
Risk of transmission of viral blood diseases	Yes	No
Need ABO compatibility	Yes	No
Preparation time	45 mins thaw time + ABO matching	No
Recommended administration time	(1-2ml/kg/hr) =1.7 hours	8-12 mins
Onset	Dependent on infusion time	10 mins

Kcentra Contraindications

- Known anaphylactic or severe reactions to Kcentra or any components including factors II, VII, IX, X
- Known Heparin Induced Thrombocytopenia, Antithrombin III, Human Albumin (contains heparin)
- Disseminated Intravascular Coagulation

Adverse Reactions to Kcentra

- Most common - headache, nausea and vomiting
- Most serious – thromboembolic events including stroke, pulmonary embolism, and deep vein thrombosis

Adverse reactions	No. (%) of subjects	
	Kcentra (N=101)	Plasma (N=197)
Nervous system disorders		
Headache	14 (7.3%)	7 (3.6%)
Respiratory, thoracic, and mediastinal disorders		
Pleural effusion	8 (4.2%)	3 (1.5%)
* Respiratory distress/dyspnea/hypoxia	7 (3.7%)	10 (5.1%)
Pulmonary edema	3 (1.6%)	10 (5.1%)
Gastrointestinal disorders		
Nausea/vomiting	12 (6.3%)	8 (4.1%)
Diarrhea	4 (2.1%)	7 (3.6%)
Cardiac disorders		
* Tachycardia	9 (4.7%)	2 (1.0%)
Atrial fibrillation	8 (4.2%)	6 (3.0%)
Metabolism and nutrition disorders		
* Fluid overload*	5 (2.6%)	16 (8.1%)
Hypokalemia	9 (4.7%)	14 (7.1%)
Psychiatric disorders		
Insomnia	9 (4.7%)	6 (3.0%)
Vascular disorders		
* Hypotension†	14 (7.3%)	10 (5.1%)
Injury, poisoning, and procedural complications		
Skin laceration/contusion/subcutaneous hematoma	8 (4.2%)	5 (2.5%)
Blood and lymphatic disorders		
Anemia‡	11 (5.8%)	16 (8.1%)

*Includes fluid overload and cardiac failure congestive.
†Includes orthostatic hypotension, hypotension, and hemorrhagic shock.
‡Includes anemia, hemoglobin decreased, and hematocrit decreased.

Kcentra *does not increase the risk of* thromboembolic (TE) events vs plasma

Serious events occurring in both RCTs		
Serious adverse reactions	No. (%) of subjects	
	Kcentra (N=101)	Plasma (N=197)
TE events*	13 (6.8%)	14 (7.1%)
Fluid overload events†	9 (4.7%)	25 (12.7%)
Deaths	13 (6.8%)	13 (6.6%)

Case Study done by Milling et. al.

- Kcentra dose of 25 iu/kg
- One test group received average dose of 90 ml Kcentra
- The other test group received 800 ml of FFP
- Primary endpoint achieved INR < 1.3 at 30 mins (P=.0001)

Case study done by Tanka et. al.

- Kcentra dose 25 iu/kg
- Average 99.4ml kcentra verses 813.5ml of FFP to obtain INR <1.4 P=(.0001)
- Study showed less albumin, fibrinogen, antithrombin was needed post op (effects lasted up to 24hrs)
- Increased risk of kidney disease of 31.3% compared to 23.4% with the FFP group

Song et. al.

- Study of 25 patients
- 17 pts required no further treatment
- 2 pt required treatment with cryoprecipitate
- 16 of the 25 did not require RBC's at all
- Showed 32% decrease in peri op bleeding with significant decrease in RBC usage as opposed to the FFP group

Cappabianca et. al.

- Showed need for fewer blood products when Kcentra was used
- Significant decrease in 24 hr post-op blood loss 636ml verse 935ml (P= < .0001)
- FFP group transfusion of 4.76 units RBC's (range of 4-12 units) needed when Kcentra was not used. When Kcentra was used 1.76 units (range of 1-2)

Reduced Post-Op Complications in Emergent Surgery

- No chest packing
- No re-exploration for bleeding
- No operative-related deaths
- 7 days in ICU versus mean of 12.8

Fluid Overload Events FFP vs. Kcentra

- Study of 388 patients
- 13 deaths in both groups
- 14 thromboembolic events in both
- Serious adverse event: 54 in PCC, 49 in FFP
- Adverse event: 115 in PCC, 124 in FFP
- Fluid overload: 9 in PCC, 25 in FFP

Why is Blood Type Important?

- 40% of plasma available in an emergency situation is still derived from female donors although male plasma is preferred
- Increased risks of acute respiratory distress syndrome and sepsis in patients treated with ABO compatible plasma compared to those treated with ABO-identical plasma

USAP PCC Protocol

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