Use of Coagulation Algorithm at the Bedside During Extra Corporeal Membrane Oxygenation in Neonatal and Pediatric Patients

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Abstract

It can be difficult to achieve the perfect balance of coagulation of the blood for patients on extra corporeal membrane oxygenation (ECMO) therapy. The anticoagulation of the blood must be adequate to allow the ECMO pump to run smoothly, but prevent patient bleeding. This study focused on the introduction of a coagulation algorithm used by the ECMO specialist. The study compared the number of complications prior to and after the algorithm was implemented. The use of the ECMO Coagulation Algorithm was found to be associated with an increase in pump clotting complications and an increase in Atryn® boluses, though patient acuity was also higher in the group using the algorithm. Although the algorithm was not useful in decreasing the rate of complications from ECMO, it does appear to be a useful, educational tool for assisting the novice ECMO specialist with an understanding of the complicated partial coagulation pathway used with ECMO patients.

Use of Coagulation Algorithm at the Bedside During Extra Corporeal Membrane Oxygenation in Neonatal and Pediatric Patients

Extracorporeal membrane oxygenation is used in intensive care medicine. It is a bypass machine that supports the heart and lungs when all other treatments have failed. One major component to a successful ECMO (extracorporeal membrane oxygenation) case is balanced coagulation. The pump and patient must be adequately anticoagulated for the pump and oxygenator system to run efficiently. However, too much anticoagulation will lead to the patient having uncontrolled bleeding. The problem is achieving coagulation within specific limits for each patient. A registered nurse (RN) that is specially trained as an ECMO specialist is responsible for management of the ECMO pump and patient. That nurse is the first line of communication with the ECMO team of physicians and must spend his or her entire shift observing the patient and pump. The ECMO specialist monitors and manages coagulation on the patients within written parameters. Yet there is some acceptable variability in managing the coagulation status of the ECMO patient by the ECMO specialist.

Significance of the Problem

ELSO is the Extracorporeal Life Support Organization. It is an international consortium of healthcare professionals whose primary mission is to maintain a registry of the use of extracorporeal membrane oxygenation in active ELSO centers. ELSO data is broken down into categories by age. Neonatal is newborn to 30 days of life, pediatric is greater than 30 days and less than 18 years of life, and adult is greater than18 years of life. This database was started in 1986. The number of neonatal and pediatric patients on ECMO support since 1986 is 48,416. According to this registry, 82% of all patients on ECMO are pediatric or neonatal. ECMO therapy is used to treat three main diagnoses: respiratory failure, heart failure, and sepsis. When

discussing ECMO treatment, many times the word ECMO "run" is used. This term describes the amount of time the patient was on ECMO. The same patient may be on ECMO at different times in their life for different diagnoses. For example, a congenital heart disease patient may go on ECMO for the first time for postoperative cariogenic shock. A year later the same patient may go on ECMO for respiratory support with the flu. These are described as two separate ECMO runs. When broken down in the ELSO data base NICU patients are put on ECMO for a diagnosis of congenital diaphragmatic hernias (CDH), meconium aspiration syndrome (MAS), persistent pulmonary hypertension (PPHN), respiratory distress syndrome (RDS), sepsis, pneumonia, air leak syndrome, congenital heart defect, cardiac arrest, cardiogenic shock, cardiomyopathy, myocarditis, or other similar causes. Pediatric patients are put on ECMO for diagnoses that include the following: viral pneumonia, bacterial pneumonia, pneumocystis pneumonia, aspiration pneumonia, ARDS (acute respiratory distress syndrome)-postop/trauma, ARDS-not postop trauma, acute respiratory failure non ARDS, congenital defect, cardiac arrest, cardiogenic shock, cardiomyopathy, myocarditis, and other similar cases (Extracorporeal Life Support Organization, January 2014). ECMO is typically used as an escalation of therapy with ECMO being the most invasive intervention that is wrought with complications due to coagulation issues. ECMO therapy does not directly heal any patient disease but can take over the heart and lung system function to give the patient time to heal and/or give treatment therapies time to work. It is often considered a bridge while other medical therapies are being used. ECMO is only used for severe acute and potentially reversible disease processes (Froehlich, 2010).

For the majority of patients, complications that arise during ECMO therapy involve anticoagulation and bleeding problems such as hemorrhages and clots throughout the circuit.

These bleeding problems and clots make up the majority of complications for an ECMO therapy session.

The cost of an ECMO therapy is extensive. It involves daily intensive care unit costs, consults with specialty physicians, frequent lab draws, two specialty trained RN's at the bedside at all times, many radiologic studies, and parental nutrition.

Anticoagulation is achieved in ECMO therapy by a combination of heparin and antithrombin titration and maintenance. During this time the ECMO specialist is continually evaluating the ECMO circuit and the patient for signs of clotting and bleeding. Coagulation problems occur when the blood is pumped outside the patient's body and comes into contact with artificially made tubing. The ECMO specialist is the first person to process the patient and pump information and in most institutions the specialist has an order set to titrate heparin drip therapy based on the physical assessment and laboratory results. Research is needed on the best management methods for coagulation of the patient on ECMO. The ECMO specialists have parameters to assist them in managing coagulation, but if there is a need to go outside the parameters, then they consult the entire ECMO team which includes the intensivist, ECMO physician, a perfusionist, or the cardiovascular/general surgeons.

Problem Statement

The coagulation pathway is complex and the decision pathway is complicated when a patient is artificially anticoagulated. ECMO specialists require guidance for prevention of over coagulation (clots) and/or excessive bleeding. This balance between anticoagulation and bleeding must be constantly evaluated and maintained. For this research project, we evaluated the coagulation management and coagulation status of patients after the introduction of a specific coagulation algorithm (appendix A) for use by the ECMO specialist. The goal of this study was

to have improved coagulation management of patients by the ECMO specialist using the coagulation algorithm.

Hypotheses/Research question

Does the initiation of a coagulation algorithm by the ECMO specialist in the neonatal/pediatric population decrease coagulation complications while on ECMO?

Conceptual Framework

Rosswurm and Larrabee's model for evidence-based practice change was used to show the steps taken to understand the framework of this study (see Appendix B). This model was derived from theoretical and research literature and has been successfully applied by nurses implementing change (Rosswurm & Larrabee, 1999).

A conceptual model was developed to explain the concepts of the study (see Appendix C). This model shows the patient, intervention, and work flow processes. When balanced coagulation is not achieved on a patient on ECMO; it leads to bleeding and clotting complications. This study focused on the bleeding complications of: gastrointestinal bleeding, cannulation site bleeding, hemolysis, disseminated intravascular coagulation (DIC), tamponade, pulmonary hemorrhage, and central nervous system hemorrhage. This study focused on the clotting complications of: mechanical clots, thrombosis, limb ischemia, and central nervous system infarction.

Literature Review

The literature on ECMO is extensive. The literature review began with a history of ECMO and how it evolved, moved into coagulation management on ECMO, and finished with a review of ECMO complications.

History of ECMO

ECMO is basically a long-term heart lung bypass machine. John Gibbon invented the first heart lung bypass machine. The first time ECMO therapy was used with a patient was in 1954. At this time, it allowed surgeries to be done on the heart but only for an hour at a time due to the damage the machine caused to the blood, which in turn caused multiple organ failure. A complication arose when the blood was exposed directly to oxygen. In the 1960's the first gas exchange device was created. This put a silicone barrier between the blood and oxygen. The gas exchange device allowed long-term heart and lung bypass. ECMO became the acronym because of the artificial lung was a unique part of the device. Dr. Robert H. Bartlett, a thoracic surgeon, began his work on extracorporeal circulation in 1965 with a goal to improve the efficiency of the membrane oxygenators. His primary motivating factor was that 50% of the pediatric patients with congenital heart defects died during post-cardiac surgical repair due to low cardiac output, oliguria, acidosis, and respiratory failure (Bartlett, 2005).

Dr. Bartlett, in combination with Dr. Robert Gross, Dr. Francis Moore, and the MIT engineer Phil Dinker, worked on building and testing membrane oxygenators in the lab. They improved the efficacy of the oxygenators. Dr. Bartlett continued to do in depth studies on physiology using sheep with extracorporeal support. This important research was and still is supported by the National Institutes of Health (Bartlett, 2005).

In 1971, the first ECMO case was reported on an adult patient in respiratory failure and was successful. By 1974, the use of ECMO in the adult population was improving but the survival rates were low; for example, only 10-15% survived after being placed on ECMO. By 1975, most institutions had stopped using ECMO therapy to treat patients due to its low survival rate (Wolfson, 2003).

It is interesting that ECMO therapy was introduced to the pediatric and neonatal population due to the low success in the adult population. The first ECMO center for pediatric patients was at the Orange County Medical Center. The first successful case was a two yearold child following a Mustard operation who then developed cardiopulmonary failure. In 1975, the neonatal world was introduced to the idea of ECMO with a newborn infant who was diagnosed with meconium aspiration syndrome followed by persistent pulmonary hypertension (Bartlett, 2005). This case was successful and ECMO became a tool for newborn respiratory failure when other less invasive measures were unsuccessful. Of note, Dr. John White and Dr. Bill Dorson attempted to use the umbilical vessels for ECMO support and were unsuccessful due to bleeding problems and device failure (Bartlett, 2005). Dr. Bartlett noted that he used the jugular and carotid for vascular access and used anticoagulation at low levels. The results of the first year of ECMO were as follows: 13 infants went on ECMO, nine were neonates with respiratory failure, and three patients survived (Bartlett, 2005). The next year the numbers improved and were as follows: 16 infants in neonatal respiratory failure were placed on ECMO and nine improved on ECMO and six survived to discharge (Bartlett, 2005). These results were published and discussed at conferences. The pediatric and neonatal world responded with skepticism and criticism while the cardiothoracic field considered these results with cautious optimism. Pediatric and cardiothoracic surgeons began to visit and learn about the techniques being used. Soon other centers began using ECMO across the United States. By 1982, 45 cases of neonatal ECMO due to respiratory failure were reported with a 55% survival rate (Bartlett, 2005).

Neonatologists started to take notice of the success rate of ECMO because of their frustration with current treatment failures. A few key neonatologists established their own ECMO programs and the pioneers were accused of “academic suicide” at the time. The

technology and survival numbers continued to rise. In 1984, ECMO survival rate for neonatal respiratory failure was up to 90% and 70% for CDH (Bartlett, 2005).

ECMO worked better on infants with lung problems due to the reversible nature of the infant's respiratory failure. The neonatal lung may be inherently more capable of repair. Another reason the success with ECMO occurred is that the neonates were started on ECMO earlier in the disease process before permanent damage to the lung occurred (Wolfson, 2003).

With the high success rate of ECMO treatment in neonates, a randomized control study would be the next logical step. However, this proved to be quite difficult because of the immense success with neonatal ECMO. The researchers felt that if they did not place their patients on ECMO with the high success rate, the patients would die. In essence, the control group's death was inevitable and ethically it was harming the patient when ECMO therapy was not introduced. After searching to find an ethical solution to this problem, and in an attempt to minimize the ethical dilemma, they used a method that had not been previously used in a clinical trial. It was identified as a randomized "play the winner" technique. With this technique, patients were randomly assigned, but if one treatment proved to be superior, the chance of assignment to the superior group increased. In this trial, the superior group was ECMO with high success rates. When the study was published it was met with harsh criticism (Bartlett, 2005).

In 1989, another chance for a randomized control trial developed at Boston Children's Hospital. In the pediatric intensive care unit (PICU) the doctors were using ECMO to treat their CDH patients. In the NICU the doctors were not using it as a treatment therapy. Again, to be ethically fair to the patients the same model of randomization was used. In this study ECMO

proved superior with 97% survival rate of ECMO patients and 60% survival rate in the conventional medical therapy group (Wolfson, 2003). Again, the study was harshly criticized.

In 1996, a truly randomized trial in the United Kingdom occurred. Patients at the five ECMO centers would be treated with ECMO and patients at non-ECMO centers would receive conventional medical therapy. Again, ECMO patients prevailed with 70% survival rate of the ECMO infants and 41% with conventional therapy (Wolfson, 2003).

ECMO therapy can still be considered controversial but for most mainstream pediatric and neonatal hospitals in the United States, ECMO is therapy used when conventional medical therapies fail. Therefore, with its increase in use, the ECMO community must continually evaluate how to improve the outcomes of ECMO and prevent morbidity and mortality. The most common causes of morbidity and mortality in ECMO patients are complications from bleeding or clotting. Improving the coagulation management will improve the outcomes of ECMO.

Coagulation Management on ECMO

Patients on ECMO only require partial coagulation because there is no large venous reservoir in the ECMO circuit like there is in the traditional heart-lung bypass machine. This is important when managing coagulation. The balance of anticoagulation and bleeding during ECMO is critical to patient survival through ECMO treatment. Failure to adequately anticoagulate the patient results in coagulation factor and platelet consumption that will likely increase bleeding tendencies (Niebler et al., 2011).

The gold standard for monitoring anticoagulation during an ECMO run has been the activated clotting time (ACT) or an activated partial thromboplastin times (aPTT). The most common anticoagulant used during ECMO therapy is unfractionated heparin (UFH). The most common causes of morbidity and mortality on ECMO are bleeding and thrombosis. There is no

specific test to verify how the UFH is working. It is up to the staff/clinicians to evaluate the assortment of tests and patient status changes to achieve a balanced pump and patient anticoagulation.

The ACT and aPTT use the intrinsic and common coagulation pathways and as these levels increase, they show the heparin's effect. Gruenwald, DeSouza, Chan, & Andrew, 2000, and Chan, Leaker, & Burrows, 1997, have done studies that indicate ACTs have poor correlation to heparin levels in the pediatric population. The poor correlation may be due to increased hemodilution and underdeveloped coagulation systems. The common goal of most ECMO centers is to titrate heparin drips to reach ACT levels of 180-220 while a patient is on ECMO while continually evaluating the patient for bleeding or clots and evaluating the circuit for clots.

There are other anticoagulation tests that are used such as factor Xa (iXa) and heparin assay. Antithrombin (AT) levels can also be used. If the AT levels are low, heparin will not have its desired effect. Many centers have started to replace AT with antithrombin III (AT III) recombinant when the levels are low. The thromboelastography (TEG) has been used also to monitor coagulation factors (Sievert, Uber, Laws, & Cochran, 2010).

It is important to understand that the ECMO team is evaluating this information for the patient. The ECMO team is a highly specialized and trained team for each ECMO center. There is an ECMO specialist that is either a NICU/PICU RN, respiratory therapist, or certified, clinical perfusionist trained in long-term bypass techniques. There is always an ECMO specialist in the room when a patient is on ECMO. They have been specially trained to watch for ECMO complications and to treat/manage ECMO pump complications. They are the first person to evaluate ACTs and other coagulation labs. On the ECMO team is an ECMO physician and many specialists such as cardiothoracic or pediatric surgeons, neonatologists or pediatric

intensivists, pediatric surgeons, cardiologists, and radiologists. Surgical support usually comes from the team that places the ECMO cannulas in the patient. Perfusionists are usually active members and provide on-call coverage for priming the circuit when the patient goes on ECMO (Rais-Bahrami & Short, 2000). All of these team members are crucial when evaluating coagulation and treatment management. According to this literature search, there is presently no research on how the ECMO specialists evaluate coagulation management and synthesize this vast amount of complicated information.

Complications on ECMO

Complications for patients on ECMO therapy are numerous. The following data is from the Extra Corporeal Life Support Organization, January 2014. Mechanical clots (clots in the ECMO circuit) have been reported in 11,961 of neonatal patients and 2,270 of pediatric patients. Hemorrhagic complications such as GI bleeds, cannulation site bleeding, surgical site bleeding, hemolysis, (hemoglobin >50mg/dl), and disseminated intravascular coagulation were reported in 7,893 neonatal ECMO runs and 3,139 of pediatric ECMO runs. Other less common anticoagulation complications are tamponade from blood or serous, pulmonary hemorrhage, CNS infarction, CNS hemorrhage, or limb ischemia. These complications occurred in 5,392 of neonates and 1,292 in the pediatric patients (Extracorporeal Life Support Organization, January 2014).

In summary, the history of ECMO has been complicated, but the management has not changed much since ECMO was developed. Due to the complicated coagulation system and the importance of maintaining that anticoagulation balance, a coagulation algorithm may assist new and experienced ECMO specialists to evaluate the information for these pediatric patients. The

purpose of this study was to evaluate coagulation status in patients prior to the institution of the coagulation algorithm and after the institution of the algorithm.

Methods

Design

A retrospective chart review was done to evaluate the use of the coagulation algorithm. The algorithm was introduced to the entire ECMO specialist team in March 2012. A thorough education of its usefulness to evaluate patient coagulation status on ECMO patients was given to the members of the team. The algorithm has been used since 2012 by the specialist when making coagulation decisions while the patient is on ECMO. It is especially important for new ECMO specialist to follow the algorithm as they learn and gain experience in ECMO anticoagulation.

Sample and Setting

The target population was neonatal and pediatric patients utilizing ECMO therapy. Data was collected from two targeted groups. The first group was 20 patients before the ECMO algorithm was implemented and the second group was the first 20 patients that were placed on ECMO after the algorithm was implemented. The sample was a convenience sample of the forty patients that received ECMO before and after the algorithm was initiated to evaluate coagulation status.

The setting for this study was a large, children's hospital in Midwest United States. This study focused on a pediatric patient population from birth to 19 years old that receive ECMO therapy during their hospitalization. The inclusion criteria were all patients that received ECMO therapy during the time frame of the study.

Instruments/Tools/Measures

The coagulation algorithm in this study was developed to decrease the variation in treatment plans for the ECMO patients. The ECMO specialists were feeling frustrated with the differing opinions of the ECMO team on coagulation status and interventions. The author developed the algorithm with Dr. Jeff DeMare, the ECMO director. The basic concept came from a combination of patient assessment, ECMO circuit assessment, and the present titration of anticoagulants based upon the combination of those two assessments. There were no inter-rater reliability studies done on this algorithm.

Data Collection Procedure

This study was approved by the Institutional Review Board (IRB) prior to implementation of data collection. IRB approval number 329-14-EX. All data points were collected anonymously. Data was collected from a chart review on these patients. Data collected were the following: gender, age of patient at cannulation, gestational age if under one year of age, diagnosis for patient being placed on ECMO, concurrent diagnosis, pump complication, description of pump complication , hour pump complication occurred, patient bleeding complication, description of bleeding complication, hour bleeding complication occurred, patient clotting complication, description of patient clotting complication, hour patient clotting complication occurred, total hours on ECMO, algorithm use, number of heparin bolus, number of atryn bolus, number of calcium bolus, number of atryn drip changes, number of heparin drip changes, and type of ECMO (see Appendix D).

Results

Data Analysis

One patient was eliminated due to short ECMO run time in the post-algorithm implementation group. Using the Fisher's Exact test, there was no association between gender

and algorithm use. There was no detectable association between having at least one pump complication and algorithm use. Although, based on this sample, the odds of having at least one pump complication, given the algorithm was followed, are 2.5 times (95% confidance interval[0.60, 10.34]) greater than if the algorithm was not used, (see table Appendix E). There was no detectable association between having bleeding complication and algorithm use (see Appendix F). There was not a statistically significant difference between the means of hours on ECMO between the two groups, the algorithm group did have more hours on ECMO than the non algorithm group (see Appendix G). Of the remaining comparisons, only the number of atryn boluses was significantly different between the algorithm vs no algorithm groups. The median number of boluses for algorithm patients was higher than the non-algorithm patients (see Appendix H & I).

Discussion

One of the statistically significant data findings found in this study was an increase in the atryn boluses in the post algorithm group. This is likely due to the ECMO specialist following the algorithm. There was not an increase in bleeding complications in the post algorithm group, so it is reasonable to deduct that the increase in boluses did not adversely effect the patient by causing bleeding complications.

Data Collection Information

Of the data collected in the pre algorithm group, run 13 was missing 24 hours of data from the records. In the post algorithm group Run 30,31, and 32 were the same patient with 3 different runs. During all three ECMO runs, the patient had a stable grade 1 intraventricular hemorrhage prior to and after the initiation of ECMO.

Limitations of the Study

Limitations of this study were: 1) it was a convenience sample, 2) every patient was managed slightly differently when it comes to coagulation, and 3) medical management also differs between patients of the medical diagnosis.

Future Implications

This study should continue with a larger population of patients. A larger group of patients could be expanded to find statistically significant data. A tool to evaluate severity of illness should be considered. Also inter-rater reliability studies should be done on the algorithm.

Other factors to consider are that during the time of the study, the coagulation factor antithrobin III replacement was switched from the brand name of thrombate to atryn. The difference between these medications could have lead to different patient coagulation status.

The goal of this study was to decipher if education and implementation of a coagulation algorithm for bedside ECMO specialist would decrease negative patient complications for patients receiving ECMO therapy that involve bleeding or clotting. This goal was not met according to the data gathered. However, this tool is intended to help inexperienced ECMO specialist critically think through the coagulation pathway and how it affects the ECMO pump and patient. This tool is essential to assisting ECMO specialist move from novice to expert. Overall, with the use of the tool, the number of pump complications, clotting and bleeding complications are decreased in this institution when compared to ELSO data. This tool will continue to be used as an educational tool.

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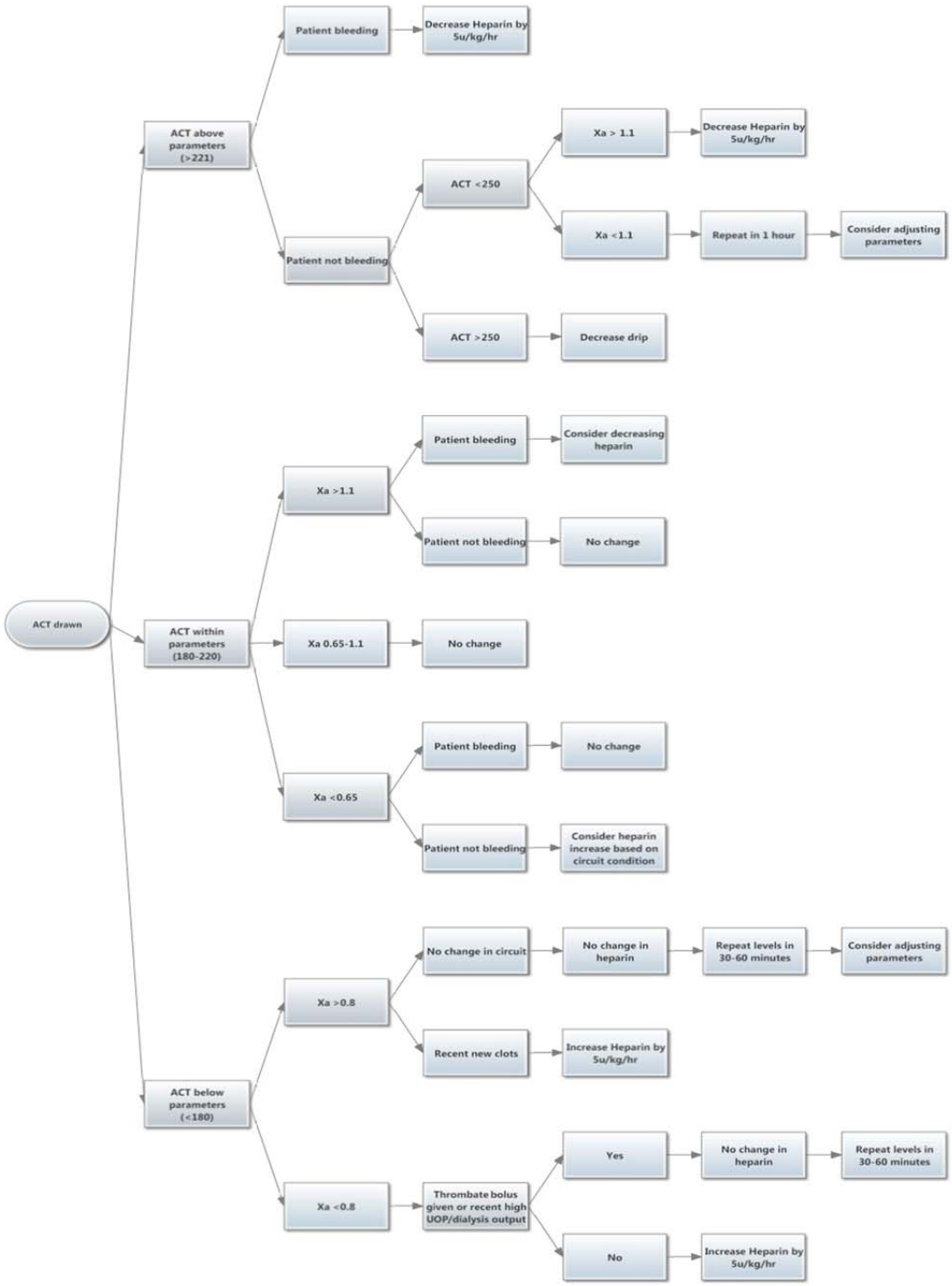
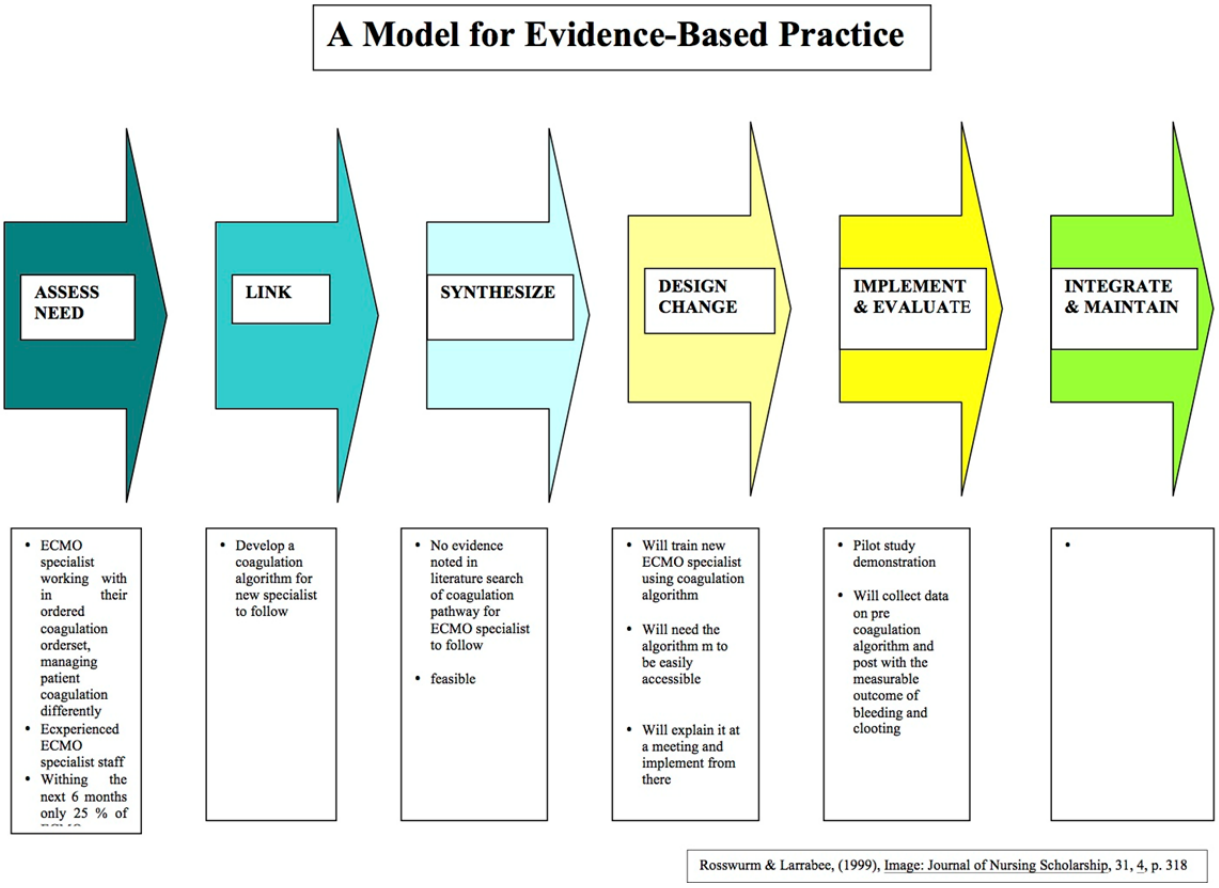
Appendix A

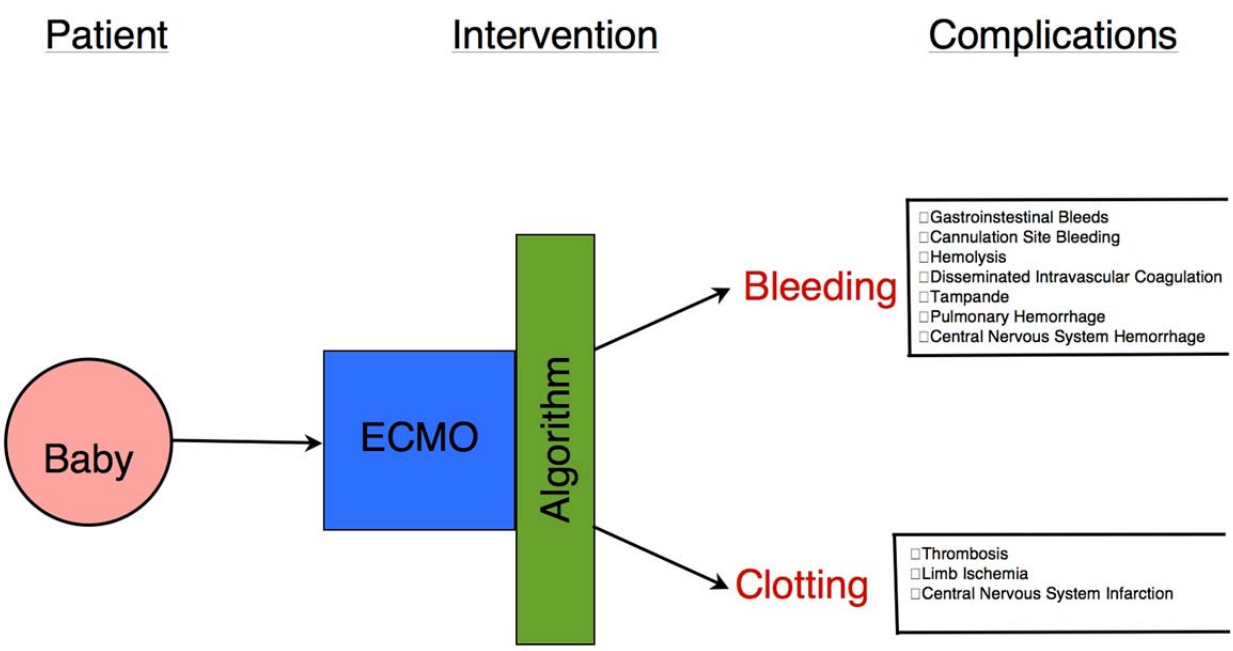

ACT drawn
ACT above parameters (>221)
Patient bleeding
Decrease Heparin by 5u/kg/hr
Patient not bleeding
ACT <250
Xa > 1.1
Decrease Heparin by 5u/kg/hr
Xa <1.1
Repeat in 1 hour
Consider adjusting parameters
ACT >250
Decrease drip
ACT within parameters (180-220)
Xa >1.1
Patient bleeding
Consider decreasing heparin
Patient not bleeding
No change
Xa 0.65-1.1
No change
Xa <0.65
Patient bleeding
No change
Patient not bleeding
Consider heparin increase based on circuit condition
ACT below parameters (<180)
Xa >0.8
No change in circuit
No change in heparin
Repeat levels in 30-60 minutes
Consider adjusting parameters
Recent new clots
Increase Heparin by 5u/kg/hr
Xa <0.8
Thrombate bolus given or recent high UOP/dialysis output
Yes
No change in heparin
Repeat levels in 30-60 minutes
No
Increase Heparin by 5u/kg/hr

Appendix B



Rosswurm & Larrabee, (1999), Image: Journal of Nursing Scholarship, 31, 4, p. 318

Appendix C


Patient
Intervention
Complications
Baby
ECMO
Algorithm
Bleeding
Clotting
Gastroinstestinal Bleeds
Cannulation Site Bleeding
Hemolysis
Disseminated Intravascular Coagulation
Tampande
Pulmonary Hemorrhage
Central Nervous System Hemorrhage
Thrombosis
Limb Ischemia
Central Nervous System Infarction

Appendix D

Data Collection Tool

	Gender	Age	GA birth	REASON (Diagnosis)	Concurrent Diagnoses	Pump Complications	Bleeding Clots	Hours on ECMO	Algorithm Used YES/NO
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									
14									
15									
16									
17									
18									
19									
20									

Appendix E

Table of pump by algorithm_use			
pump	**algorithm_use**		
Frequency	**n**	**y**	**Total**
0	15	12	27
1	4	8	12
Total	19	20	39

Fisher's Exact Test	
Two-sided Pr <= P	0.3008

Estimates of the Relative Risk (Row1/Row2)			
Type of Study	**Value**	**95% Confidence Limits**	
Case-Control (Odds Ratio)	2.5000	0.6042	10.3441
Cohort (Col1 Risk)	1.6667	0.6994	3.9717
Cohort (Col2 Risk)	0.6667	0.3728	1.1922

Sample Size = 39

Appendix F

Table of pump by algorithm_use			
pump	**algorithm_use**		
Frequency	**n**	**y**	**Total**
0	15	12	27
1	4	8	12
Total	19	20	39

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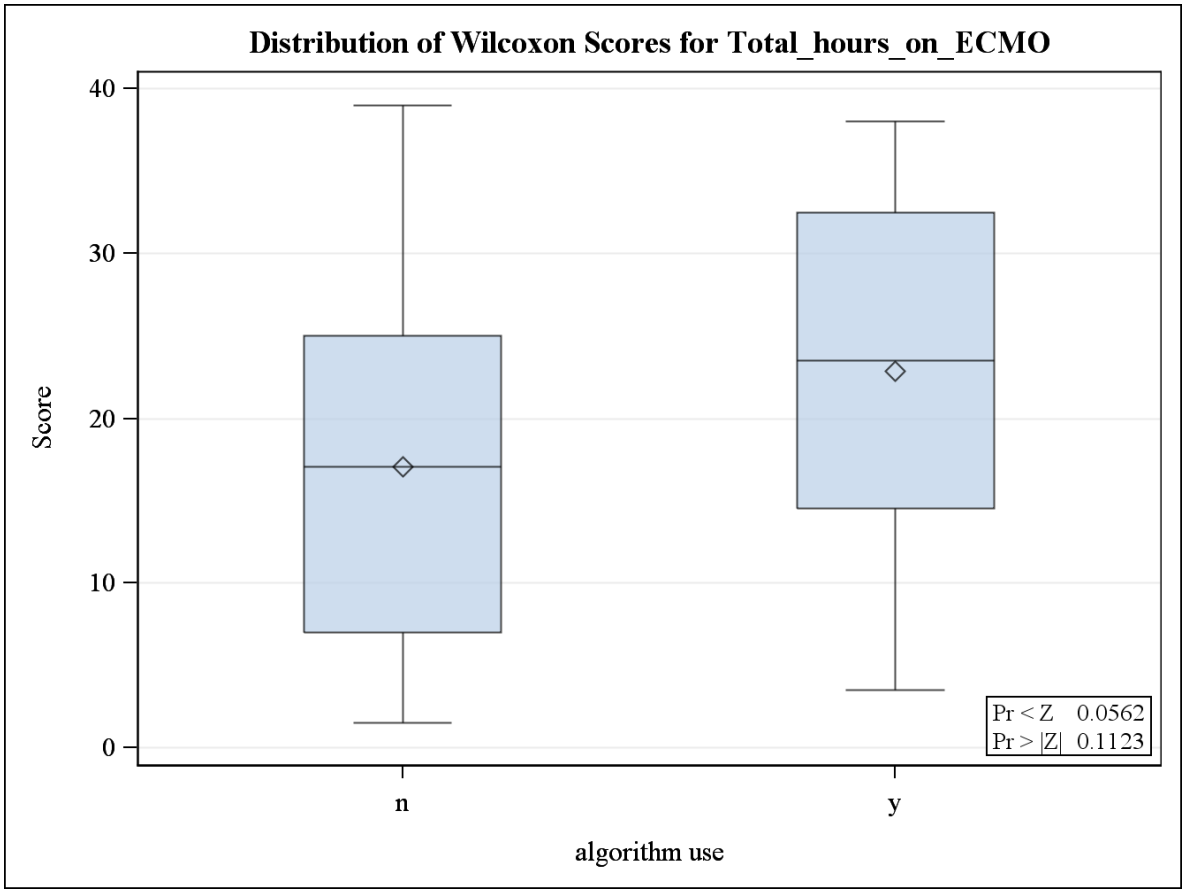
Cohort (Col1 Risk)	1.6667	0.6994	3.9717
Cohort (Col2 Risk)	0.6667	0.3728	1.1922

Sample Size = 39

Appendix G

Wilcoxon Scores (Rank Sums) for Variable Total_hours_on_ECMO Classified by Variable algorithm_use					
algorithm_use	**N**	**Sum of Scores**	**Expected Under H0**	**Std Dev Under H0**	**Mean Score**
n	19	323.0	380.0	35.583056	17.000
y	20	457.0	400.0	35.583056	22.850
Average scores were used for ties.					

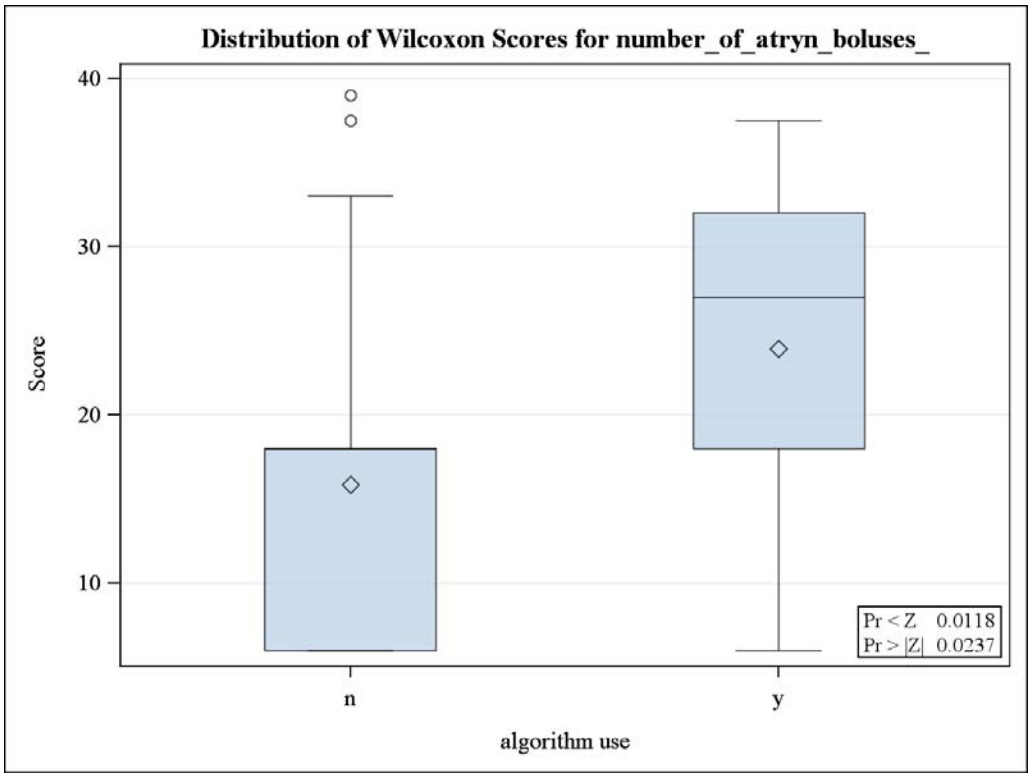
Wilcoxon Two-Sample Test	
One-Sided Pr < Z	0.0603
Two-Sided Pr > |Z|	0.1206



Appendix H

Wilcoxon Scores (Rank Sums) for Variable number_of_atryn_boluses_ Classified by Variable algorithm_use					
algorithm_use	**N**	**Sum of Scores**	**Expected Under H0**	**Std Dev Under H0**	**Mean Score**
n	19	301.50	380.0	34.474071	15.868421
y	20	478.50	400.0	34.474071	23.925000
Average scores were used for ties.					

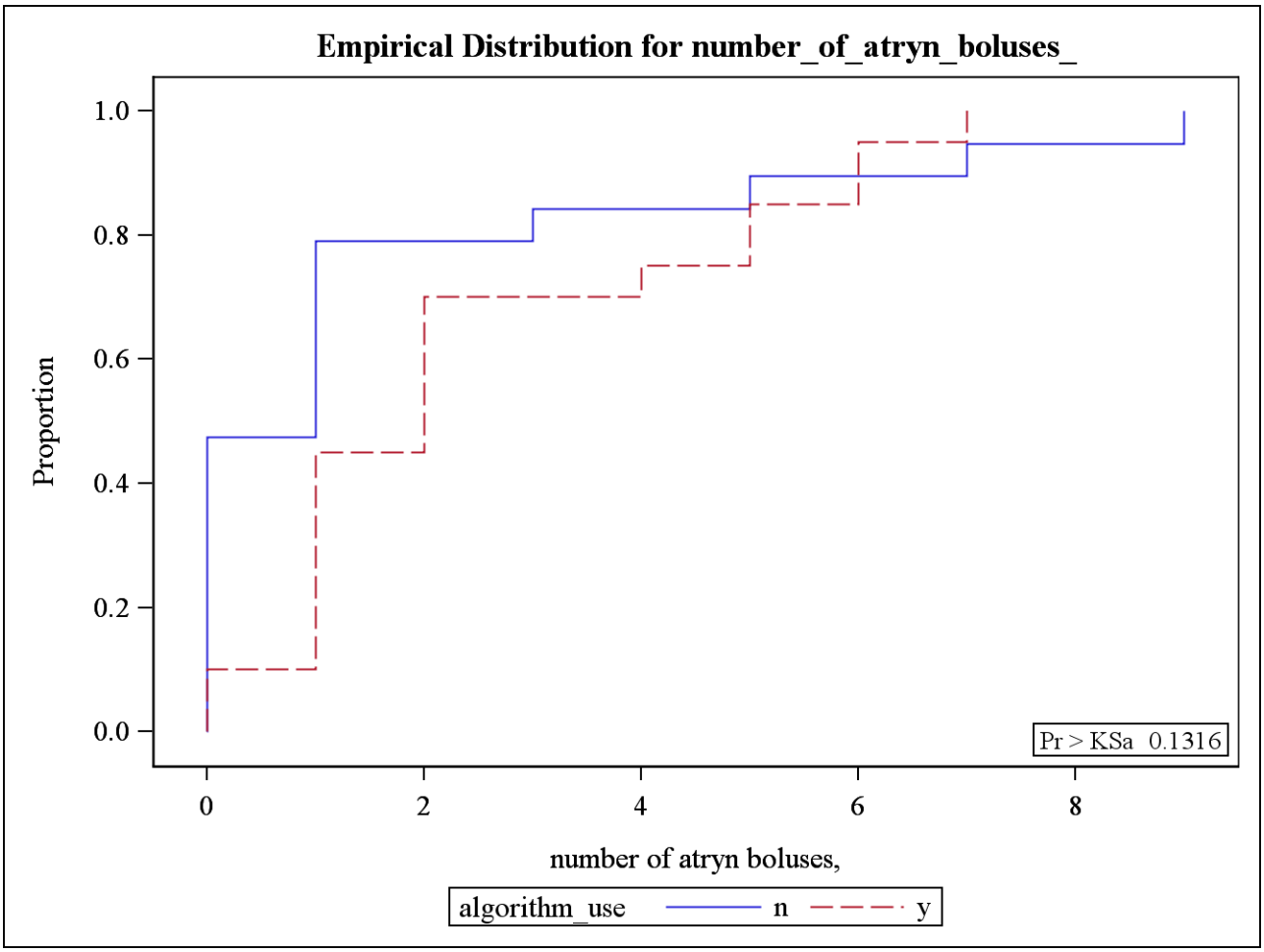
Wilcoxon Two-Sample Test	
One-Sided Pr < Z	0.0147
Two-Sided Pr > |Z|	0.0295



Appendix I

Kolmogorov-Smirnov Test for Variable number_of_atryn_boluses_ Classified by Variable algorithm_use			
algorithm_use	**N**	**EDF at Maximum**	**Deviation from Mean at Maximum**
n	19	0.473684	0.835309
y	20	0.100000	-0.814158
Total	39	0.282051	
Maximum Deviation Occurred at Observation 28			
Value of number_of_atryn_boluses_ at Maximum = 0.0			

Kolmogorov-Smirnov Two-Sample Test (Asymptotic)			
KS	0.186781	**D**	0.373684
KSa	1.166445	**Pr > KSa**	0.1316


Empirical Distribution for number_of_atryn_boluses_
Proportion
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
number of atryn boluses,
Pr > KSa 0.1316
algorithm_use
n
y