DRUG TREATMENT COMPARISON FOR TOTAL KNEE REPLACEMENT SURGERY

A Thesis
Submitted to the Graduate Faculty
of the
North Dakota State University
of Agriculture and Applied Science

By

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In Partial Fulfillment of the Requirements
for the Degree of
MASTER OF SCIENCE

Major Department:
Statistics

May 2015

Fargo, North Dakota

North Dakota State University
Graduate School

Title

Drug Treatment Comparison for Total Knee Replacement Surgery

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The Supervisory Committee certifies that this ***disquisition*** complies with North Dakota State University's regulations and meets the accepted standards for the degree of

MASTER OF SCIENCE

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ABSTRACT

In this study, we aim to better understand how spinal block, anticoagulant, and antifibrinolytic drug treatments are associated with hospital costs, lengths of stay, prevalence of early readmissions, and prevalence of blood transfusions for total knee replacement patients. Analysis of variance, multiple comparison testing, ordinary least squares regression, and logistic regression were used to identify which combinations of these drug treatments were associated with higher or lower health outcomes. The combination of Lidocaine and Ropivacaine was the spinal block treatment associated with the highest mean hospital cost, length of stay, highest proportion of early readmissions, and required blood transfusions. The combination of Warfarin and Enoxaparin was the anticoagulant treatment associated with the highest mean hospital cost, length of stay, and highest proportion of early readmissions. Patients who received Tranexamic Acid had a significantly shorter length of stay, smaller likelihood of a blood transfusion, and no significant difference in hospital cost.

ACKNOWLEDGEMENTS

I would like to thank Dr. Rhonda Magel for advising me throughout the process of this thesis, and also for encouraging and supporting the pursuit of this topic and data set which deeply interests me. She has played an important role in my graduate education at NDSU.

I also want to thank the rest of my committee members, Dr. Megan Orr, and Dr. Craig Schnell for the time and input they contributed towards this thesis.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Figure Page

1. INTRODUCTION

More than 4.5 million Americans are currently living with at least one total knee replacement. This group contains almost 5% of the population of all Americans over the age of 50 (Fawzi 2012). Knee replacements, or knee arthroplasties, have been on the rise in recent history. From 1997 to 2009, the number of knee arthroplasties increased by 84% (Fawzi 2012). What exactly is a knee replacement and why are they gaining popularity? A knee replacement is a surgical procedure that replaces the surface of the bones that bear the weight of an individual. Resurfacing is done by implanting metal and plastic components that take over the function of the typical healthy knee joint. A replacement is considered when the bone and cartilage mechanism begin to fail due to wear and tear, acute injuries, or disease. Knee pain, stiffness, swelling, and limited mobility are common side effects of these events (Foran 2011).

Since 1968, when the first knee arthroplasty was completed, drastic improvements in surgical materials and techniques have made knee replacements among the most common and successful surgeries today. “There are few procedures that return as much quality of life as joint replacement,” stated Steven M. Kurtz, PHD, director of a Philadelphia engineering and scientific consulting firm. Kurtz led a team that recently projected that the number of procedures for firsttime total knee-replacement will rise by 673% - to 3.48 million – in 2030 (Kurtz, Ong, Lau, Mowat, Halpern 2007). Their team cited several reasons for the expected jump. Among them are an increased acceptance of the procedures, an aging population with arthritis, a physically active baby-boomer generation, and an increased prevalence in obesity (Kurtz et al. 2007). The current supply of orthopedic surgeons will not be able to meet the future demand of knee replacements (Kurtz et al. 2007). If the number of orthopedic surgeons does not rise to the demand, there will be much longer wait times for these procedures (Kurtz et al. 2007). This creates a strong incentive for health care providers to complete them as efficiently and effectively as possible, from both a financial and patient-care perspective.

In this study we aim to better understand how different drug treatments for total knee replacement surgeries are associated with health outcomes such as hospital cost, length of stay, prevalence of early readmissions, and prevalence of blood transfusions. Drug categories under consideration in this study are spinal blocks, anti-coagulants, and antifibrinolytics. A spinal block is an anesthesia that is injected into the spinal fluid of the lower back to reduce sensation from the point of injection down to the feet. The effects typically last a few hours and are commonly used in lower body surgeries such as knee replacements (Liou 2013). The spinal block drugs under consideration in this study are bupivacaine, lidocaine, and ropivacaine, and combinations of these drugs. Anticoagulants are drugs used prevent blood from coagulating. One major concern after a knee replacement surgery is the immediate and/or prolonged risk of a blood clot, or deep vein thrombosis. (Foran 2011). Blood clots can be life-threatening if they travel to the lungs, therefore, they are routinely avoided. In many cases, anticoagulant medications are administered to prevent this scenario (Warwick 2012). The anticoagulant drugs under consideration in this study are warfarin, enoxaparin, and rivaroxaban, and combinations of these drugs. Antifibrinolytics are drugs used as inhibitors of fibrinolysis, which is the process that prevents blood clots from occurring/expanding (Sepah, Umer, Ahmad, Nasim, Chaudry, Umar 2011). The antifibrinolytic considered in this study is tranexamic acid. Tranexamic acid is used in surgeries to prevent or treat blood loss. It is commonly administered for knee replacement surgeries because of the risk of excessive blood loss. This drug is typically given to prevent the use of blood transfusions. Although blood transfusions are widely accepted – almost

3 million were performed in the United States in 2011 – they invite extra health risks and increased financial costs. For this reason, they are avoided in surgical procedures, if possible (Sepah et al. 2011). Hence, the use of tranexamic acid.

We will analyze an existing data set of total knee replacement patients given a variety of different spinal block combinations, anticoagulant combinations, and with some patients given tranexamic acid, while others were not. Statistical tests will be conducted to determine differences in hospital costs, length of stay, and early readmissions for patients given the various spinal blocks. Similar tests will be conducted to compare patients receiving various anticoagulant combinations, and then comparing patients receiving and not receiving tranexamic acid.

2. LITERATURE REVIEW

For knee replacement arthroplasty, there have been many studies to compare effectiveness of drug treatments. However, current research is mainly centered on effectiveness from a medical standpoint. A randomized, double-blind study for the efficacy of spinal blocks on pain relief of arthroscopic knee surgeries concluded that ropivacaine and bupivacaine were both excellent analgesia at 0 and 4 hours post operation (Huey-Ping, Nordstrom, Axelsson, et. al 2006). The other spinal blocking drug considered in this thesis, lidocaine, can be used in a combination with other longer lasting anesthesia, such as ropivacaine or bupivacaine. A 2009 study found benefits to this combination for lower limb surgeries. In that study, subjects that received lidocaine in combination with either ropivacaine or bupivacaine reported significantly shorter onset times of pain relief than those who received only ropivacaine or bupivacaine. Another finding was that adding lidocaine to the anesthesia list did not significantly increase the chance of an adverse event (Cuvillon, Nouvellon, Ripart, et al. 2009). To summarize the two studies, it appears lidocaine, bupivacaine, and ropivacaine all have documented success as an anesthesia for lower limb surgeries, while combinations of lidocaine and either bupivacaine or ropivacaine have the added benefit of more rapid pain relief.

Anticoagulants are administered in knee replacement surgeries for the primary goal of preventing venous thrombosis which is development of a blood clot within a vein. The balance is that these medications can also create extra bleeding complications. A study with over 3,000 subjects from 156 locations compared the rates of venous thrombosis between anticoagulant treatments of warfarin and enoxaparin in hip replacement patients. The major findings of the study were that both warfarin and enoxaparin treatments were associated with very low venous thrombosis and bleeding complication rates. However, patients who received enoxaparin were found to have a significantly lower rate of venous thrombosis than patients who received warfarin during the time of hospitalization (Colwell, Collis, Paulson 1999). A more recent study compared venous thrombosis rates between rivaroxaban and enoxaparin treatments for knee and hip replacement patients. The study found rivaroxaban was associated with significantly lower rates of venous thrombosis, but at the cost of significantly higher risk of bleeding complications in comparison to enoxaparin (Gomez-Outes Terleira-Fernandez, Suarez-Geau, et al. 2012). To summarize these two studies, warfarin, rivaroxaban, and enoxaparin are all well accepted anticoagulant drug treatments for lower limb surgeries. Enoxaparin may be associated with lower rates of venous thrombosis than warfarin, while rivaraoxaban may have the lowest rates of the three. However, this is at the expense of an increase of bleeding complications.

Tranexamic acid, an antifibrinolytic, is used in knee replacement surgeries with the primary objective of preventing blood transfusions. A study (Sepah et al. 2011) compared blood transfusion rates and bleeding levels between patients who received a tranexamic acid drug treatment and patients who did not. The study concluded that tranexamic acid is effective in reducing post-operative drainage and requirement of blood transfusions after knee replacement (Sepah et al. 2011).

Much has been concluded about the medical benefits of the antifibrinolytic, spinal blocks, and anticoagulants under consideration. This study builds on the current research by determining the association between well accepted drug treatments and health outcomes that are of more importance to the health care provider from a financial and resource perspective using statistical techniques that are well documented in similar circumstances.

3. DATA DESCRIPTION

The data set used in this study was provided by a hospital system with five locations in the Midwestern United States. It included over 2,000 observations with no indication of the range of time. Variables used for analysis in this study include demographic information, health outcomes, and indicator variables for drug treatments. The variable “Age” is the age of each patient, given in years. The variable “Age_Group” is coded as “0” for patients under 65 years old, and “1” for patients older than or equal to 65 years of age. The variable “Gender” refers to the gender provided and is coded as “1” for males, and “0” for females. The variable “Early_Readmit” refers to the event of a patient being readmitted to the hospital within thirty days of their initial stay for the total knee replacement surgery. “Early_Readmit” is coded as “1” for a readmission within thirty days of the original hospital stay and “0” otherwise. The variable “Blood_Transfusion” refers to the event of a patient requiring at least one blood transfusion as a result of their knee replacement surgery. “Blood_Transfusion” is coded as “1” for a required blood transfusion and “0” otherwise. The variable “Hospital_Cost” is the overall cost, given as the dollar amount of the hospital stay for each patient during the initial stay of the total knee replacement surgery. The variable “Length_Stay” is the number of days the patient stayed in the hospital, calculated as the date of exit minus the date of entry. Indicator variables were created to represent the possible drug combinations that each patient received for spinal blocks, anticoagulants, and the antifibrinolytic. Tables 1, 2, and 3, describe the indicator variables and how they were coded.

Table 1. Indicator Variables for Spinal Block Treatments

Variable	Value	Spinal Blocks Administered if Value = 1
S_0	0 or 1	None
S_1	0 or 1	Bupivacaine
S_2	0 or 1	Lidocaine
S_3	0 or 1	Ropivacaine
S_1S_2	0 or 1	Bupivacaine, Lidocaine
S_1S_3	0 or 1	Bupivacaine, Ropivacaine
S_2S_3	0 or 1	Lidocaine, Ropivacaine
$S_1S_2S_3$	0 or 1	Bupivacaine, Lidocaine, Ropivacaine

Table 2. Indicator Variables for Anticoagulant Treatments

Variable	Value	Anticoagulants Administered if Value = 1
A_0	0 or 1	None
A_1	0 or 1	Warfarin
A_2	0 or 1	Enoxaparin
A_3	0 or 1	Rivaroxaban
A_1A_2	0 or 1	Warfarin, Enoxaparin
A_1A_3	0 or 1	Warfarin, Rivaroxaban
A_2A_3	0 or 1	Enoxaparin, Rivaroxaban
$A_1A_2A_3$	0 or 1	Warfarin, Enoxaparin, Rivaroxaban

Table 3. Indicator Variable for Antifibrinolytic Treatments

Variable	Value	Antifibrinolytic Administered if Value = 1
TA	0 or 1	Tranexamic Acid

4. METHODS

4.1. Hospital Cost

First, the mean hospital cost will be compared among patients receiving different spinal block treatments using an ANOVA test controlling for "Age_Group" and "Gender". Residual analysis will be conducted to identify potential outliers. If influential outliers are present, the observations may be deleted, and the ANOVA test recalculated. If age group and/or gender are not significant blocking factors, they will be removed from the model. An example of blocking in an experiment (or controlling for sources of variation) is given in Fleiss (1986), pages 126128, with respect to a data set measuring blood clotting times of patients. Residual analysis will also be conducted to check model assumptions. If a transformation is necessary as indicated by a violation of assumptions in the residual analysis, a transformation will be performed and a new model will be developed. A conclusion will be made about whether or not different spinal block treatments were associated with significantly different hospital costs. An example of an ANOVA test to determine differences in average weights of patients engaged in three different dieting regimens is given in Blair and Taylor (2008), page 266 and in comparing quality of care ratings of emergency care in four metropolitan hospitals in Blair and Taylor (2008), page 271.

If there is a difference in mean total cost associated with the different spinal block treatments, multiple comparison testing (MCT) will be done to determine which spinal block treatments have significantly smaller/ larger mean total costs associated with them. The TukeyKramer adjustment will be used as the method of multiple comparison testing. The TukeyKramer adjustment is chosen because it is effective for MCT when all simultaneous pair-wise comparison are being considered with unequal group sample size, which is the case in this study (Montgomery 2013). Estimates for the differences will also be calculated and conclusions will be drawn about which spinal block drug treatments significantly differ from each other in terms of the response variable, hospital cost. The same tests will be used for the anticoagulant drug treatments. Because there are only two groups being compared among antifibrinolytic treatments, we will use a two sample t-test to compare the group means for hospital cost.

4.2. Length of Stay

The mean length of stay will be compared among patients receiving different spinal block treatments using a ANOVA test controlling for "Age_Group" and "Gender". Residual analysis will be conducted to check model assumptions and indications of necessary transformations, as in Section 4.1. If there is a significant difference in mean length of stay associated with the different spinal block treatments, MCT will be conducted to determine which spinal block treatments have significantly smaller/larger mean lengths of stay associated with them. Refer to Section 4.1 for the Tukey-Kramer method. The same tests will be used for the anticoagulant and antifibrinolytic drug treatments.

4.3. Early Readmissions

A Pearson's Chi-Square Test will be conducted to determine if one or more of the spinal block treatments had a significantly higher proportion of early readmissions. Age and gender will not be considered in this analysis due to the small sample size of early readmissions. The main assumption of this test is that the observations are independent. We will make this assumption considering it is not possible to check how response variables of each observation changed over time. The Pearson's Chi-square Test calculates expected values for cells in a contingency table that are crosses of nominal or ordinal variables. If the expected values calculated are less than five, we will remove that drug treatment from the analysis and repeat the test, because, in this scenario, the interpretation of the test statistic can be misleading. A use of a chi-square test comparing proportions may be found in Pagano and Gaureau (2000) comparing the proportion of head injuries between those individuals wearing a helmet versus those not wearing a helmet when a sample of 793 bicycle accidents is considered, pages 342- 347.

If one or more spinal block treatments had a significantly higher proportion of early readmissions, a logistic regression will be constructed with the dependent variable "Early_Readmit" and independent variables as the indicator variables for different spinal block treatments as well as age group and gender. The baseline drug treatment will be left out of the model so that it can be interpreted as the intercept when all other indicator variables are "0". Multicollinearity will be assessed and if present, correlated variables may be dropped to raise the accuracy of parameter estimates. Model fit adequacy will be determined by calculating a Hosmer-Lemeshow Goodness-of-Fit test statistic (Hosmer, Lemeshow 2000). The parameter estimates will be used to determine how spinal block treatments affect the likelihood of an early readmission. A similar logistic regression procedure will be followed as in the low birth weight study, the prostate cancer study, and the ICU study given in Hosmer and Lemeshow (2000). The same tests and procedures will be used for the anticoagulant and antifibrinolytic drug treatments.

4.4. Blood Transfusions

A Pearson's Chi-Square Test will be conducted to determine if one of the spinal block treatment groups had a significantly higher proportion of blood transfusions. Refer to Section 4.3 for Pearson's Chi-Square test assumptions and procedures. If the treatments had significantly different proportions of blood transfusions, a logistic regression will be constructed with the dependent variable "Blood_Transfusion" and independent variables as the indicator variables for different spinal block treatments as well as age group and gender. Refer to Section 4.3 for the logistic regression assumptions and procedure.

4.5. Hospital Cost Overall Model

An ordinary least squares (OLS) regression will be constructed with the dependent variable "Hospital_Cost" and independent variables including: indicators for spinal blocks, anticoagulants, and antifibrinolytics, "Age_Group", and "Gender". Treatments A_0 and S_0 will be left out of the model as a baseline for interpretation. There are four main assumptions of the OLS model. The first assumption is that the relationship between dependent and independent variables is linear and additive. This can be checked by observing plots of observed versus fitted values or residuals versus predicted values. If a non-linear trend is apparent, we will consider a non-linear transformation on the dependent variable and/or the independent variables. The second assumption is that the error terms are independent of each other, in particular, uncorrelated over time. We have already made this assumption in the first steps of analysis due to lack of time component in the data set. The third assumption is that of homoscedasticity, or constant variance, of error terms. This can be determined by checking plots of residuals vs predicted valued. The final assumption is that of normality of error terms, this can be determined from checking a histogram of the residual distribution. Stepwise and backward regression techniques may be performed along with a residual analysis to help determine which of the variables significantly affect hospital cost. An example using the stepwise and backward ordinary least squares regression techniques is given in Kleinbaum, Kupper, Muller, & Nizam (1998) to predict weight among children based on various other variables including race, gender, age, and height, among others, pages 403-422.

4.6. Length of Stay Overall Model

An OLS model will be constructed, as in Section 4.5, with the dependent variable "Length_Stay". As before, A_0 and S_0 will be left out of the model so that our parameter estimate of the intercept can be interpreted as a patient not receiving any of the anticoagulants or spinal blocks under consideration in this study.

4.7. Early Readmissions Overall Model

A logistic regression model will be constructed just as in Section 4.3 with the dependent variable "Early_Readmit". In this model, drug indicator variables will be considered simultaneously along with age group and gender, while leaving out A_0 and S_0 as our baseline to compare with.

4.8. Blood Transfusions Overall Model

A logistic regression model will be constructed just as in Section 4.7, except with the dependent variable "Blood_Transfusion". As before, A_0 and S_0 will be left out of the model as our baseline to compare with.

4.9. Locations

The five locations provided in the data set will be assessed for their association with the combinations of spinal block anticoagulant and antifibrinolytic drug treatments. If it is found that these treatments have significant associations with location, the location with the most variation will be selected. Analysis in Sections 4.1, 4.2, 4.3, and 4.4 will be conducted with only the observations from the selected location.

5. RESULTS

5.1. Spinal Blocks

5.1.1. Hospital Cost

Before performing the one-way ANOVA as described in the previous section, an investigation for potential outliers found two observations that were extreme and influential. These two observations were not included in the analysis as they were both greater than ten standard deviations above the population mean hospital cost. The group of patients that received the spinal block treatment "S_2" were not considered in the analysis due to inadequate sample size (n=23). A one-way ANOVA was performed and assumptions were checked. Age group and gender were not significant so they were dropped from the model. The distribution of the residuals was right skewed and did not represent a normal distribution. A natural log transformation was performed on the dependent variable "Hospital_Cost" which helped meet the assumptions. The histogram of the distribution of residuals using the transformed dependent variable, shown in Figure 1, appears approximately normal and reasonably meets the normality assumption of the one-way ANOVA.

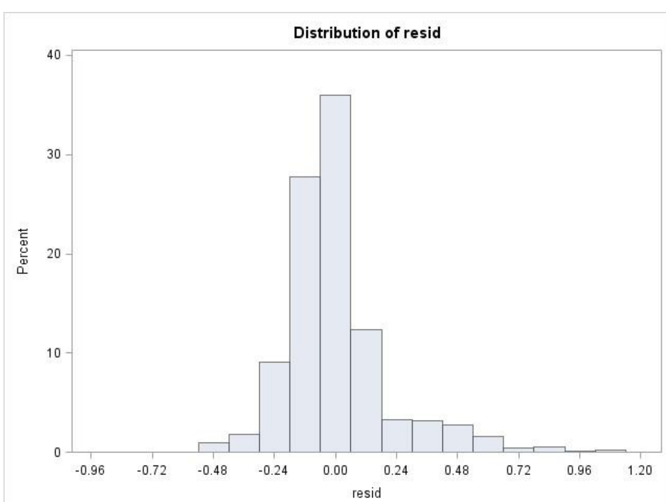

Figure 1. Histogram of Residuals

A plot of the residuals vs. fitted values was created to aid in gauging equality of variances across groups, as well as descriptive statistics of the spinal block treatment groups, shown in Table 4.

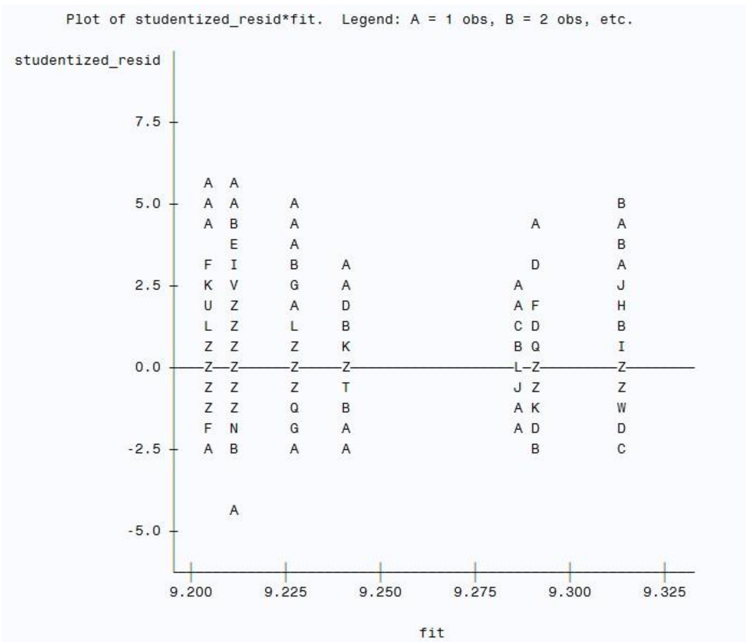

Figure 2. Plot of Studentized Residuals vs. Fitted Values

Table 4. Descriptive Statistics of Spinal Block Treatments for LN(Hospital Cost)

Level of Treatment	N	LN(Hospital Cost)	
		Mean	Std Dev
S_0	31	9.2858	0.1636
S_1	70	9.2398	0.1807
S_1S_2	460	9.2273	0.1547
$S_1S_2S_3$	783	9.2112	0.2125
S_1S_3	420	9.2055	0.2092
S_2S_3	149	9.3132	0.2865
S_3	121	9.2898	0.2248

As seen in Table 4, the largest group sample standard deviation is not more than twice the smallest group sample standard deviation. In practice, this is used as a rule of thumb to meet the assumption of equal variances between groups (Moore, McCabe 2003). By this rule, we will assume the groups have approximately equal population variances.

Table 5. Descriptive Statistics of Spinal Block Treatments for Hospital Cost

Level of Treatment	N	Hospital Cost	
		Mean	Std Dev
S_0	31	$10,929.95	$1,905.29
S_1	70	$10,475.36	$2,066.71
S_1S_2	460	$10,307.93	$1,934.94
$S_1S_2S_3$	783	$10,264.11	$2,626.52
S_1S_3	420	$10,202.94	$2,675.37
S_2S_3	149	$11,613.53	$4,158.61
S_3	121	$11,128.20	$2,928.29

Although analysis was conducted using the transformed dependent variable, descriptive statistics are provided for the untransformed dependent variable in Table 5 for better understanding of the hospital costs associated with different spinal block treatments. After meeting assumptions, the one-way ANOVA rejected the null hypothesis of the test, that the group means were equal. This is indicated by the F-statistic of 8.22 and corresponding p-value less than .0001.

Table 6. One-Way ANOVA for Dependent Variable LN(Hospital Cost)

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	6	2.0892	0.3482	8.22	<.0001
Error	2027	85.9027	0.0424		
Total	2033	87.9919			

Now that we have found there is a difference in mean total cost associated with the different spinal block treatments, MCT was conducted to compare specific groups. From the Tukey-Kramer method, differences between group means are shown in Figure 3.

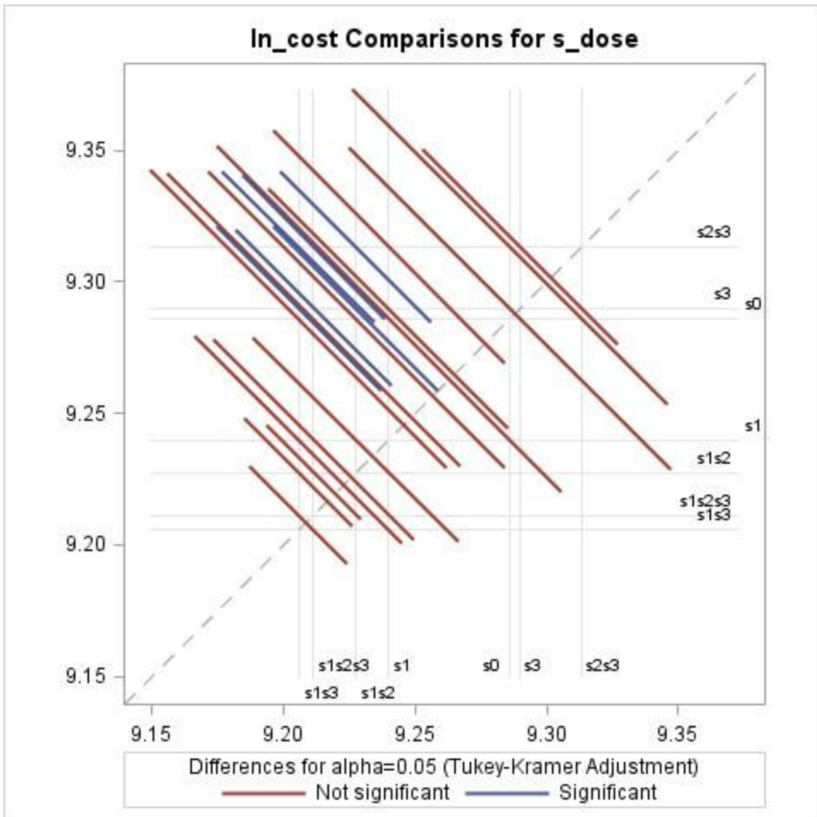

Figure 3. Tukey's Comparisons for LN(Hospital Cost)

The pairwise comparisons that are significant at the alpha=.05 level are displayed in Table 6 with estimates and corresponding confidence intervals. The values represent the percent difference in hospital cost from the first treatment to the second in the comparison. For example, the first row in Table 6 shows that the patients who received the spinal block treatment S_2S_3 (lidocaine and ropivacaine) are estimated to have a hospital cost 8.96% greater than patients who received the spinal block treatment S_1S_2 (lidocaine and bupivacaine).

Table 7. Tukey's Comparisons for LN(Hospital Cost) Significant at alpha = .05

Treatment Comparison	Percent Difference	Simultaneous 95% Confidence Limits	
$S_2S_3 - S_1S_2$	8.96%	2.90%	15.39%
$S_2S_3 - S_1S_2S_3$	10.73%	4.88%	16.91%
$S_2S_3 - S_1S_3$	11.37%	5.10%	18.01%
$S_3 - S_1S_2$	6.45%	0.04%	13.26%
$S_3 - S_1S_2S_3$	8.17%	1.94%	14.79%
$S_3 - S_1S_3$	8.79%	2.18%	15.83%

In Table 7 above, Percent Difference is calculated as: $1 - \exp[\ln(mi) - \ln(mj)]$. Where mi and mj refer to the two group sample means in each pairwise comparison. The confidence intervals of the natural log transformed variable hospital cost can only be interpreted as a ratio, instead of a difference of dollar amounts. After performing the same method on the untransformed data, very similar results were found. Table 8 provides confidence intervals for the mean difference of dollar amounts between treatments, using the untransformed data, for ease of interpretation.

Table 8. Tukey's Comparisons for Hospital Cost Significant at alpha =.05

Treatment Comparison	Difference Estimate	Simultaneous 95% Confidence Limits	
$S_2S_3 - S_1S_2$	$ 1,305.60	$ 571.80	$ 2,039.40
$S_2S_3 - S_1S_2S_3$	$ 1,349.40	$ 653.60	$ 2,045.20
$S_2S_3 - S_1S_3$	$ 1,410.60	$ 668.30	$ 2,152.90
$S_3 - S_1S_2$	$ 820.30	$ 24.90	$ 1,615.70
$S_3 - S_1S_2S_3$	$ 864.10	$ 103.60	$ 1,624.50
$S_3 - S_1S_3$	$ 925.30	$ 122.00	$ 1,728.50

Spinal block treatment S_2S_3 had the significantly highest hospital costs, while treatment S_1S_3 had the significantly lowest, with a mean difference of $1,410.40.

5.1.2. Length of Stay

Before performing the one-way ANOVA, an investigation for potential outliers found one observation that was extreme and influential (Length of Stay = 54 days). This observation was not included in the analysis. The group of patients that received the spinal block treatment "S_2" were not considered in the analysis due to inadequate sample size (n=23). An ANOVA was performed and assumptions were checked. Age group and gender both had significant blocking effects so they were left in the model. The distribution of residuals for the model using LOS were approximately normal. Our variances can be assumed equal by the 2x standard deviation rule of thumb. Descriptive statistics for LOS of different spinal block treatments are given in Table 9.

Table 9. Descriptive Statistics of Spinal Block Treatments

Level of Treatment	N	Length of Stay	
		Mean	Std Dev
S_0	31	2.9677	0.6575
S_1	70	3.0427	0.7696
S_1S_2	460	2.4978	0.9015
$S_1S_2S_3$	783	2.9623	0.9046
S_1S_3	420	3.0667	0.9723
S_2S_3	149	3.3893	1.2009
S_3	121	3.116	0.9590

The one-way ANOVA rejected the null hypothesis of the test, that the group means were equal. This is indicated by the F-statistic of 26.45 and corresponding p-value less than .0001.

Table 10. One-Way ANOVA for Dependent Variable Length of Stay

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	8	181.4223	22.6778	26.45	<.0001
Error	2025	1736.3044	0.8574		
Total	2033	1917.7266			

Now that we have found there is a difference in mean length of stay associated with the different spinal block treatments, MCT was conducted to compare specific groups. From the Tukey-Kramer method, differences between group means are shown in Figure 4.

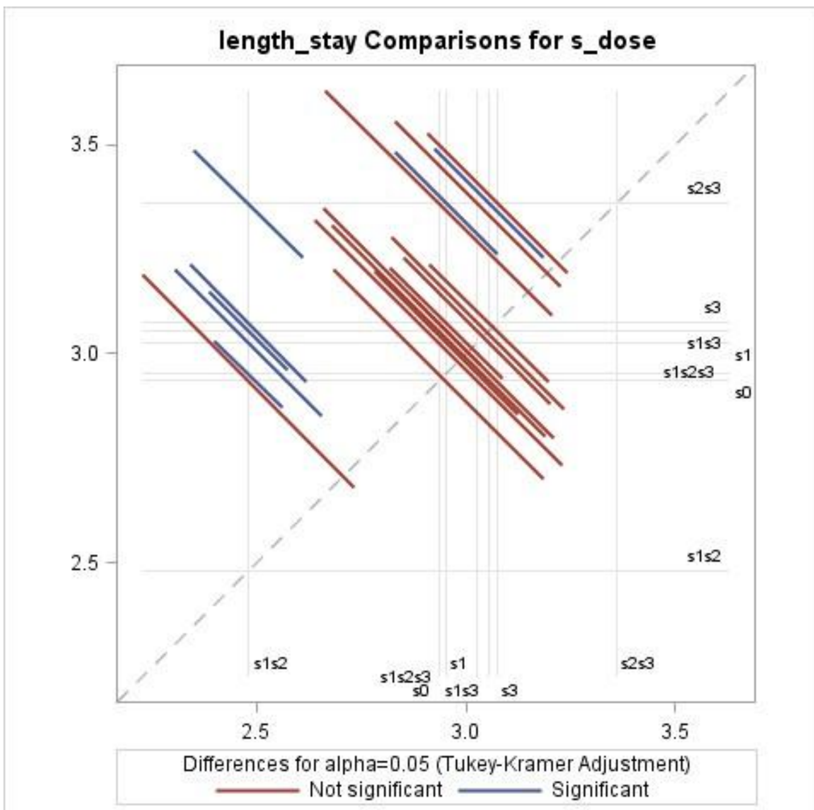

Figure 4. Tukey's Comparisons for Length of Stay.

Diagonal lines in Figure 4 represent the width of the 95% confidence interval for the difference between the two spinal block treatment groups being compared. If this interval intersects with the dotted reference line, then the intersection treatment groups were not significantly different. If the intervals are completely above the reference line, the difference was significant.

The pairwise comparisons that are significant at the alpha=.05 level are displayed in Table 11 with estimates and corresponding confidence intervals for the mean difference in LOS between treatments being compared.

Table 11. Tukey's Comparisons for Length of Stay Significant at alpha = .05

Treatment Comparison	Difference Estimate	Simultaneous 95% Confidence Limits	
$S_2S_3 – S_1S_3$	0.32	0.06	0.58
$S_2S_3 – S_1S_2S_3$	0.43	0.18	0.67
$S_2S_3 – S_1S_2$	0.89	0.63	1.15
S_3 - S_1S_2	0.62	0.34	0.90
S_1S_3 - S_1S_2	0.57	0.38	0.75
S_1 - S_1S_2	0.55	0.19	0.90
$S_1S_2S_3$ - S_1S_2	0.47	0.30	0.63

Spinal block treatment S_2S_3 had the significantly longest LOS, while treatment S_1S_2 had the significantly shortest, with a mean difference of 0.89 days.

5.1.3. Early Readmissions

A Pearson's Chi-Square Test was conducted to determine if one or more of the spinal block treatments had a significantly higher proportion of early readmissions. Patients that received drug treatment S_0 (n=31) and S_2 (n=23) were not included in this analysis, because the expected value of early readmissions, assuming independence of treatment and status of early readmission, from these groups was less than 1, which can make Pearson's test invalid. After removing those groups, Pearson's Chi-square was calculated to 9.1067 with a corresponding pvalue of .1049. This indicates mild significance that at least one spinal block treatment may be associated with a higher proportion of early readmissions. Viewing the contingency table given in Table 12, it appears S_2S_3 may have a higher proportion of early readmissions than other treatments.

Table 12. Contingency Table of Spinal Block Treatments by Early Readmit

	Early Readmit	S_1	S_1S_2	$S_1S_2S_3$	S_1S_3	S_2S_3	S_3	Total
Frequency % Row % Col %	0	70 3.49 3.59 100	449 22.42 23.05 97.61	760 37.94 39.01 97.06	410 20.47 21.05 97.62	140 6.99 7.19 93.96	119 5.94 6.11 98.35	1948 97.25
Frequency % Row % Col %	1	0 0 0 0	11 0.55 20 2.39	23 1.15 41.82 2.94	10 0.5 18.18 2.38	9 0.45 16.36 6.04	2 0.1 3.64 1.65	55 2.75
	Total	70 3.49	460 22.97	783 39.09	420 20.97	149 7.44	121 6.04	2003 100

A logistic regression model was built with the dependent variable "Early_Readmit" (event=1) and age group, gender, and spinal block treatment indicators as independent variables - leaving out S_2, S_0, and S_1 due to small sample size and/or no early readmissions. After a stepwise selection process, the only two significant variables found to be significantly associated with early readmission were gender and S_2S_3. The criteria used for the stepwise selection was the p-value of the chi-square statistic for each variable candidate. There were no signs of multicollinearity and the Hosmer-Lemeshow Goodness of Fit test provided an insignificant pvalue (0.82), indicating the model fit was adequate.

Table 13. Parameter Estimates and Odds Ratios

Variable	Estimate	Standard Error	Odds Ratio Estimate	P-Value
S_2S_3	0.9359	0.3753	2.55	.0126
Gender F vs M	-0.4513	0.135	0.41	.0008

As seen in Table 13, the odds-ratio estimate for S_2S_3 was 2.55, meaning on average, the odds of an early readmission for patients who received the spinal block treatment S_2S_3 were 2.55 times (95% CI: 1.22, 5.32) higher than the odds for patients who received any other spinal block treatment. The odds of an early readmission for males were 2.44 times higher than the odds for females.

5.2. Anticoagulants

5.2.1. Hospital Cost

As previously mentioned, two observations were not included in the analysis as they were both greater than ten standard deviations above the population mean hospital cost. The group of patients that received the anticoagulant treatments $A_1A_2A_3$ (n=3), A_1A_3 (n=8), or A_2A_3 (n=23) were not considered in the analysis due to inadequate sample size. An ANOVA was performed and assumptions were checked. The residuals appeared approximately normal. Age group and gender were not significant so they were dropped from the model. A natural log transformation was performed on the dependent variable "Hospital_Cost" which enabled the data to meet model assumptions.

Table 14. Descriptive Statistics of Anticoagulant Treatments

Level of Treatment	N	LN(Hospital Cost)	
		Mean	Std Dev
A_0	326	9.2275	0.1555
A_1	770	9.2417	0.1798
A_1A_2	123	9.3225	0.2968
A_2	495	9.2086	0.2441
A_3	309	9.1786	0.1992

As seen in Table 14, the largest group sample standard deviation is not more than twice the smallest group sample standard deviation. By this rule, we will assume the groups have equal population variances. After meeting assumptions, the ANOVA rejected the null hypothesis of the test that the group means were equal. This is indicated by the F-statistic of 12.9 and corresponding p-value less than .0001.

Table 15. One-Way ANOVA for Dependent Variable LN(Hospital Cost)

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	4	2.1772	0.5443	12.9	<.0001
Error	2018	85.1278	0.0422		
Total	2022	87.3050			

Because it was found there is at least one significant difference in mean total cost associated with the different anticoagulant treatments, MCT was conducted to compare specific groups. From the Tukey-Kramer method, differences between group means are shown in Figure 5.

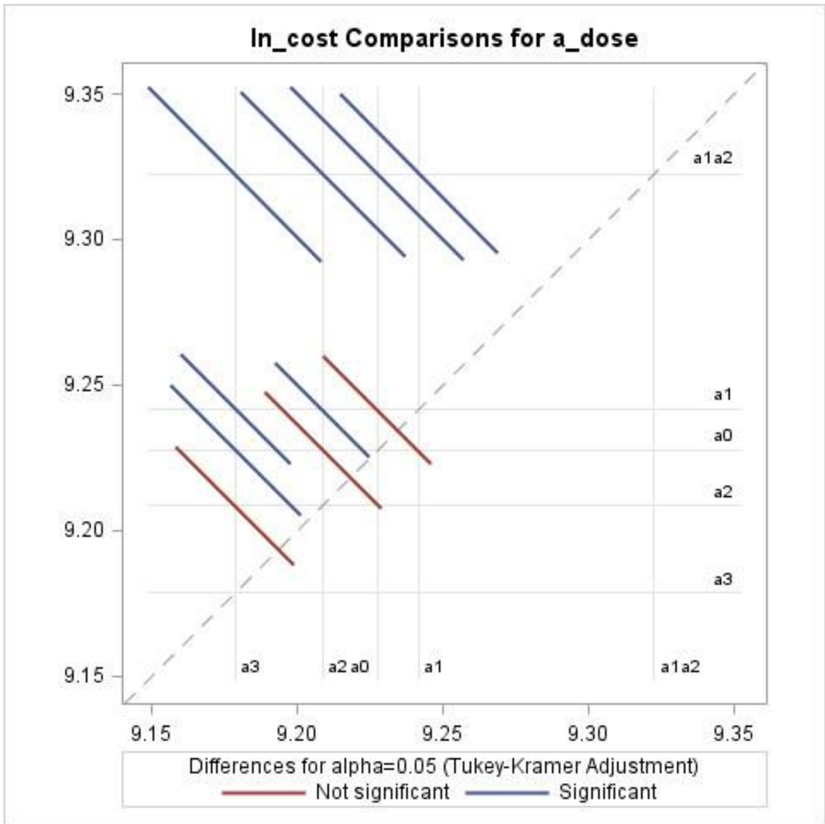

Figure 5. Tukey's Comparisons for LN(Hospital Cost)

The pairwise comparisons that are significant at the alpha=.05 level are displayed in Table 16 with estimates and corresponding confidence intervals. The values represent the percent difference in hospital cost from the first treatment to the second in the comparison.

Table 16. Tukey's Comparisons for LN(Hospital Cost) Significant at alpha = .05

Treatment Comparison	Percent Difference	Simultaneous 95% Confidence Limits	
A_1A_2-A_1	8.42%	2.67%	14.48%
A_1A_2-A_0	9.96%	3.63%	16.69%
A_1A_2-A_2	12.06%	5.91%	18.58%
A_1A_2-A_3	15.47%	8.77%	22.58%
A_1- A_2	3.36%	0.08%	6.76%
A_1- A_3	6.51%	2.56%	10.60%
A_0- A_3	5.01%	0.43%	9.79%

After performing the same method on the untransformed data, similar results were found, although two less comparisons were deemed significant. The conclusions drawn from the analysis on the transformed data should be more reliable. Dollar amount differences for the most significant pairwise comparisons of the untransformed data are provided in Table 17 for ease of interpretation.

Table 17. Tukey's Comparisons for Hospital Cost Significant at alpha =.05

Treatment Comparison	Difference Estimate	Simultaneous 95% Confidence Limits	
A_1A_2-A_1	$1,284.00	$590.40	$1,977.70
A_1A_2-A_0	$1,471.00	$715.00	$2,226.90
A_1A_2-A_2	$1,460.40	$740.80	$2,180.10
A_1A_2-A_3	$1,868.50	$1,107.00	$2,630.10
A_1- A_3	$584.50	$103.50	$1,065.60

Anticoagulant treatment A_1A_2 had the significantly highest hospital costs, while treatment A_3 had the significantly lowest, with a mean difference of $1,868.50.

5.2.2. Length of Stay

As previously mentioned, an investigation for potential outliers found one observation that was extreme and influential (Length of Stay = 54 days). This observation was not included in the analysis. The group of patients that received the anticoagulant treatments $A_1A_2A_3$ (n=3), A_1A_3 (n=8), or A_2A_3 (n=23) were not considered in the analysis due to inadequate sample size. A one-way ANOVA was ran and assumptions were checked. The residuals appeared approximately normal. Age group and gender both had significant blocking effects so they were left in the model. The natural log transformation was applied to LOS to better meet model assumptions.

Table 18. Descriptive Statistics of Anticoagulant Treatments

Level of Treatment	N	LN(LOS)	
		Mean	Std Dev
A_0	326	0.8665	0.2641
A_1	770	0.9860	0.2745
A_1A_2	123	1.2122	0.3743
A_2	495	1.1134	0.2551
A_3	309	1.0662	0.2534

As seen in Table 18, the largest group sample standard deviation is not more than twice the smallest group sample standard deviation. By this rule, we will assume the groups have equal population variances. The one-way ANOVA rejected the null hypothesis of the test, that the group means were equal. This is indicated by the F-statistic of 55.63 and corresponding pvalue less than .0001.

Table 19. One-Way ANOVA for Dependent Variable LN(LOS)

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	6	23.8204	3.9701	55.63	<.0001
Error	2016	143.8633	0.0714		
Total	2022	167.6837			

Evaluation of the analysis indicates that there is a difference in mean length of stay associated with the different spinal block treatments, MCT was conducted to compare specific groups. From the Tukey-Kramer method, differences between group means are shown in Figure 6.

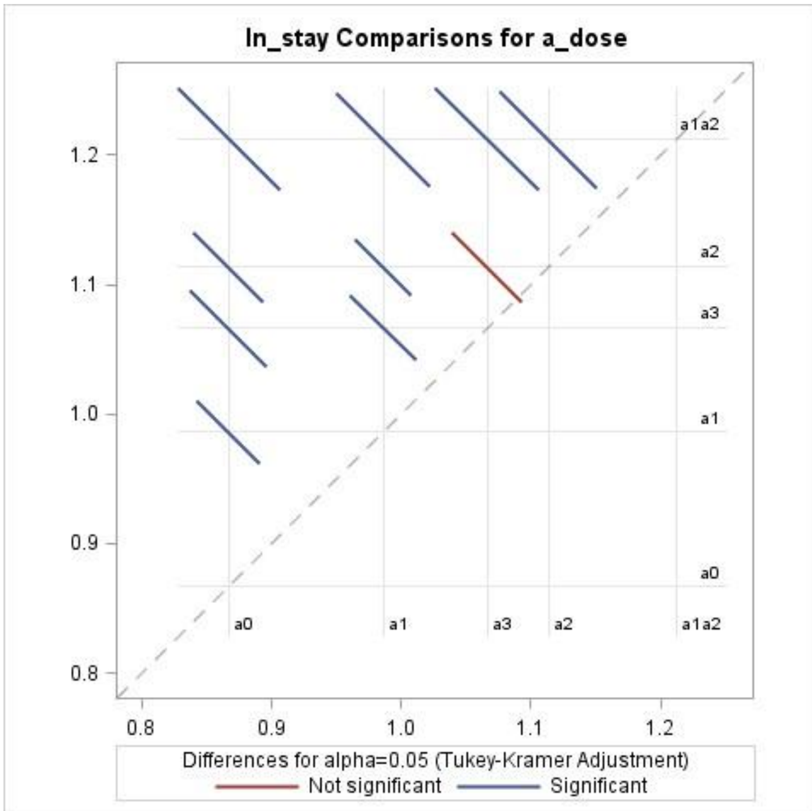

Figure 6. Tukey’s Comparisons for LN(LOS)

The pairwise comparisons that are significant at the alpha=.05 level are displayed in Table 20 with estimates and corresponding confidence intervals for the percentage difference in LOS between treatments being compared.

Table 20. Tukey's Comparisons for LN(LOS) Significant at alpha = .05

Treatment Comparison	Percent Difference	Simultaneous 95% Confidence Limits	
A_1A_2-A_2	10.38%	2.56%	18.80%
A_1A_2-A_3	15.73%	7.07%	25.08%
A_1A_2-A_1	25.39%	16.81%	34.59%
A_1A_2-A_0	41.29%	30.80%	52.63%
A_2-A_1	13.59%	8.92%	18.47%
A_2-A_0	28.00%	21.51%	34.84%
A_3-A_1	8.35%	3.16%	13.80%
A_3-A_0	22.09%	15.22%	29.37%
A_1-A_0	12.68%	7.38%	18.36%

After performing the same method on the untransformed data, similar results were found. The conclusions drawn from the analysis on the transformed data should be more reliable. LOS mean differences for the most significant pairwise comparisons of the untransformed data are provided in Table 21 for ease of interpretation.

Table 21. Tukey's Comparisons for LOS Significant at alpha = .05

Treatment Comparison	Difference Estimate	Simultaneous 95% Confidence Limits	
A_1A_2-A_2	0.4867	0.2408	0.7325
A_1A_2-A_3	0.6374	0.3772	0.8976
A_1A_2-A_1	0.8458	0.6089	1.0828
A_1A_2-A_0	1.1648	0.9066	1.4231
A_2-A_1	0.3592	0.2186	0.4998
A_2-A_0	0.6782	0.5041	0.8522
A_3-A_1	0.2085	0.0441	0.3728
A_3-A_0	0.5274	0.3337	0.7212
A1-A_0	0.3190	0.1557	0.4802

Anticoagulant treatment A_1A_2 had the significantly longest LOS, while treatment A_0 had the significantly lowest, with a mean difference of 1.16 days.

5.2.3. Early Readmissions

A Pearson's Chi-Square Test was conducted to determine if one or more of the anticoagulant treatments had a significantly higher proportion of early readmissions. Patients that received the anticoagulant treatments $A_1A_2A_3$ (n=3), A_1A_3 (n=8), or A_2A_3 (n=23) were not considered in the analysis due to inadequate sample size to calculate the test statistic. After removing those groups, Pearson's Chi-square was calculated as 20.3685 with a corresponding pvalue of .0004. This indicates strong significance that at least one anticoagulant treatment may be associated with a higher proportion of early readmissions. Viewing the contingency table given in Table 22, it appears A_1A_2 may have a significantly higher proportion of early readmissions than other treatments.

Table 22. Contingency Table of Spinal Block Treatments by Early Readmit

	Early Readmit	A_0	A_1	A_1A_2	A_2	A_3	Total
Frequency % Row % Col %	0	317 15.67 16.12 97.24	747 36.93 38 97.01	112 5.54 5.7 91.06	486 24.02 24.72 98.18	304 15.03 15.46 98.38	1966 97.18
Frequency % Row % Col %	1	9 0.44 15.79 2.76	23 1.14 40.35 2.99	11 0.54 19.3 8.94	9 0.44 15.79 1.82	5 0.25 8.77 1.62	57 2.82
	Total	326 16.11	770 6.08	123 6.08	495 24.47	309 15.27	2023 100

A logistic regression model was built with the dependent variable "Early_Readmit" (event=1) and age group, gender, and anticoagulant treatment indicators as independent variables

– leaving out $A_1A_2A_3$, A_1A_3, and A_2A_3 due to small sample size and/or no early readmissions. After a stepwise selection process, the only two variables that were significantly associated with early readmission were gender and A_1A_2. There were no signs of multicollinearity and the Hosmer-Lemeshow GOF Test provided an insignificant p-value (0.63), indicating the model fit was adequate.

Table 23. Parameter Estimates and Odds Ratios for Early Readmissions

Variable	Estimate	Standard Error	Odds Ratio Estimate	P-value
A_1A_2	1.3661	0.1486	3.92	<.0001
Gender F vs M	-0.4428	0.1351	0.41	.0010

As seen in Table 23, the odds-ratio estimate for A_1A_2 was 3.92, meaning on average, the odds of an early readmission for patients who received the anticoagulant treatment A_1A_2 were 4 times (95% CI: 1.97, 7.80) higher than the odds for patients who received any other anticoagulant treatment. We get the same result for gender as seen in Table 12.

5.3. Antifibrinolytics

5.3.1. Hospital Cost

As previously mentioned, two observations were not included in the analysis as they were both greater than ten standard deviations above the population mean hospital cost. Only two groups were considered in this part of the analysis, those who received the tranexamic drug treatment and those who didn't. Since age and gender were not significant and only two groups are being compared, a two sample t-test will be conducted to compare mean hospital costs. The assumption of groups being approximately normal is reasonably met after checking plots of the dependent variable by group. The assumption of approximately equal population variances is reasonably met. A 95% confidence interval is calculated and provided with descriptive statistics in Tables 24 and 25. Level of treatment = “0” refers to the group that did not receive a tranexamic drug treatment, while level of treatment = “1” refers to the group that did receive a tranexamic drug treatment.

Table 24. Descriptive Statistics of Variable “TA”

Level of Treatment	N	Hospital Cost	
		Mean	Std Dev
0	1039	$10,342.90	$2,961.80
1	1018	$10,523.90	$2,378.70

Table 25. 95% Confidence Interval for Difference

TA Comparison	Difference Estimate	95% Confidence Limits	
		Lower	Upper
Dif (1 – 0)	$181.00	-$51.56	$2,961.80

As seen in Table 25, patients who received the tranexamic drug treatment had hospital costs on average $181.00 more expensive than patients who did not receive the drug, however, the two-sample t-test deems this difference insignificant.

5.3.2. Length of Stay

As previously mentioned, an investigation for potential outliers found one observations that was extreme and influential (LOS = 54 days). This observation was not included in the analysis. Only two groups were considered in this part of the analysis, those who received the tranexamic drug treatment and those who didn’t. An ANOVA was performed and assumptions were checked. The residuals appeared approximately normal. Age group and gender both had significant blocking effects so they were left in the model. Descriptive statistics for LOS of the two treatment groups are given in Table 26.

Table 26. Descriptive Statistics of Anticoagulant Treatments

Level of Treatment	N	Length of Stay	
		Mean	Std Dev
0	1039	3.18	1.03
1	1018	2.66	0.84

As seen in Table 26, the largest group sample standard deviation is not more than twice the smallest group sample standard deviation. By this rule, we will assume the groups have equal population variances. The ANOVA rejected the null hypothesis of the test, that the group means were equal. This is indicated by the F-statistic of 72.16 and corresponding p-value less than .0001.

Table 27. One-Way ANOVA for Dependent Variable Length of Stay

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	186.7814	62.2605	72.16	<.0001
Error	2053	1771.3878	0.8628		
Total	2056	1958.1692			

Now that we have found there is a difference in mean length of stay associated with the different treatment groups, the groups were compared using the Tukey-Kramer method. A 95% confidence interval for the difference (0 - 1) was calculated to be (0.43, 0.59) with a mean difference of 0.51 days. This means on average, patients who received the tranexamic drug treatment had a significantly shorter length of stay, and the 95% confidence interval for that difference is centered on half a day.

5.3.3. Early Readmissions

A Pearson’s Chi-Square Test was conducted to determine if the tranexamic drug treatment had a significantly different proportion of early readmissions than the group with no treatment. Pearson's Chi-square was calculated as 1.574 with a corresponding p-value of .2101. This p-value indicates there is not sufficient evidence to conclude that the proportions of early readmissions were different for the two groups.

Table 28. Contingency Table of Tranexamic Treatment by Early Readmit

	Early Readmit	Tranexamic Acid		
		0	1	Total
Frequency % Row % Col %	0	1005 48.86 50.28 96.73	994 48.32 49.72 97.64	1999 97.18
Frequency % Row % Col %	1	34 1.65 58.62 3.27	24 1.17 41.38 2.36	58 2.82
	Total	1039 50.51	1018 49.49	2057 100

5.3.4. Blood Transfusions

A Pearson's Chi-Square Test was conducted to determine if the tranexamic acid drug treatment group had a significantly different proportion of blood transfusions than the group with no treatment. Since the main purpose of this drug treatment in knee replacement arthroplasty is to prevent blood transfusions, we would expect to see the group of patients who received tranexamic acid had a significantly smaller proportion of blood transfusions. Pearson's Chisquare was calculated to 75.73 with a corresponding p-value <.001. This p-value indicates there is strong evidence to conclude that the proportions of blood transfusions were significantly different for the two groups, as expected.

Table 29. Contingency Table of Tranexamic Treatment by Blood Transfusion

	Blood Transfusion	Tranexamic Acid		
		0	1	Total
Frequency % Row % Col %	0	926 45.02 48.03 89.12	1002 48.71 51.97 98.43	1928 93.73
Frequency % Row % Col %	1	113 5.49 87.60 10.88	16 0.78 12.40 1.57	129 6.27
	Total	1039 50.51	1018 49.49	2057 100.00

A logistic regression model was built with the dependent variable "Blood_Transfusion"(event=1) and age group, gender, the tranexamic acid indicator, and interactions as independent variables. After a stepwise selection process, the only variables that were significantly associated with early readmission were age group, gender, and the tranexamic drug indicator. There were no signs of multicollinearity and the Hosmer-Lemeshow GOF Test provided an insignificant p-value (0.89), indicating the model fit was adequate.

Table 30. Parameter Estimates and Odds Ratios

Variable	Estimate	Standard Error	Odds Ratio Estimate	P-value
TA	-2.0455	0.2725	0.13	<.0001
Gender F vs M	0.3874	0.1081	2.17	.0003
Age Group 0 vs 1	-0.5014	0.1054	0.37	<.0001

The odds of requiring a blood transfusion were 7.69 (95% CI: 4.55, 12.50) times higher for patients who did not receive tranexamic acid compared to patients who did receive tranexamic acid. The odds of requiring a blood transfusion were 2.17 (95% CI: 1.42, 3.32) times higher for females compared to males. The odds of requiring a blood transfusion were 2.70

times (95% CI: 1.81, 4.12) higher for the older group (at least 65) compared to the younger group.

5.5. Hospital Cost Overall Model

An ordinary least squares (OLS) regression was constructed as described in section 4.5. The natural log transformation was applied to the dependent variable, hospital cost, to better meet model assumptions. Independent variables considered were drug indicators for spinal block, anticoagulant, and antifibrinolytic treatments, age group, and gender, leaving out A_0 and S_0 as baseline treatments. The full model was developed with all the aforementioned independent variables. Fit diagnostics are assessed below for assumptions of the OLS model.

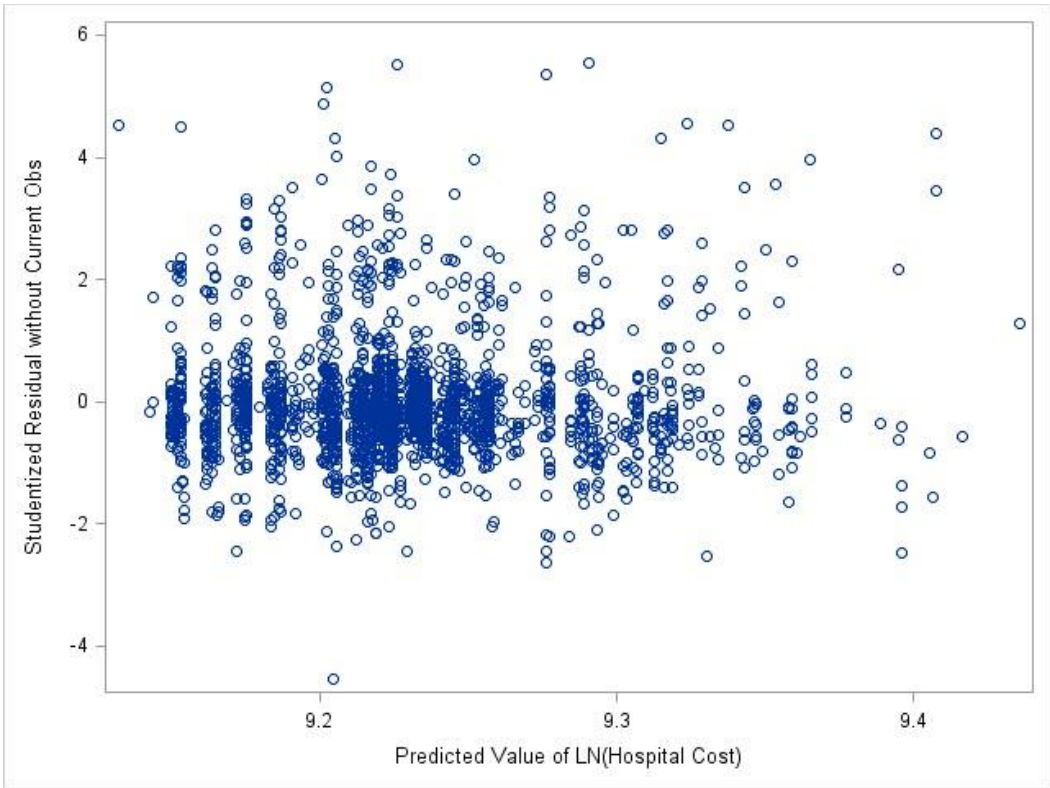

Figure 7. Plot of Studentized Residuals vs Predicted Values.

Figure 7 shows a random scatter of studentized residuals with no visible trend. This satisfies the assumption of constant variance. The assumption of a linear relationship between the dependent variable and the independent variables is automatically satisfied, because the only significant variables in our model are indicator variables. Independence of errors is assumed to be true due to the lack of time element. The assumption of normally distributed error terms is assessed in Figure 8.

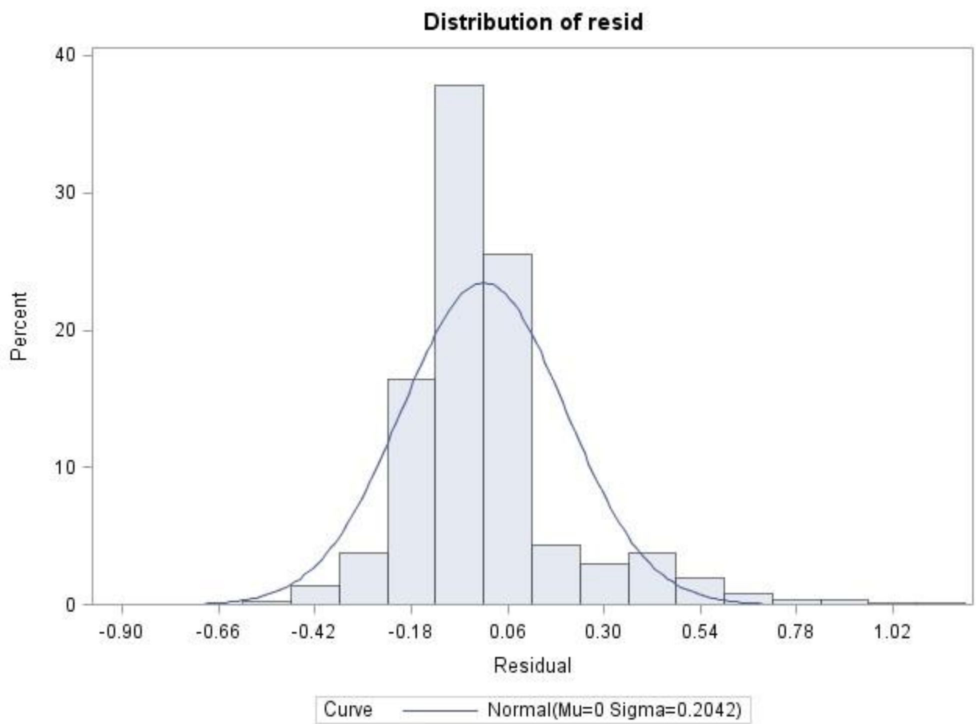

Figure 8. Distribution of Residuals.

It appears, from Figure 8, the residuals are approximately normal and centered on zero. Variance inflation factors (VIF) were calculated to assess potential multicollinearity. No VIF's were greater than ten, indicating multicollinearity is not apparent within the independent variables. This satisfies the last assumption of the OLS model. The parameter estimates are provided in Table 31.

Table 31. Parameter Estimates for LN(Hospital Cost)

Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|	VIF
Intercept	1	9.2562	0.0312	296.30	<.0001	0
Gender	1	-0.0010	0.0093	-0.10	0.9188	1.0067
$S_1S_2S_3$	1	-0.0433	0.0291	-1.49	0.1375	9.7940
S_1S_2*	1	-0.0643	0.0306	-2.10	0.0359	7.9860
S_2S_3*	1	0.0586	0.0327	1.79	0.0735	3.5263
S_1S_3	1	-0.0459	0.0302	-1.52	0.1285	7.2413
S_1	1	-0.0270	0.0374	-0.72	0.4702	2.2485
S_3	1	0.0285	0.0336	0.85	0.3973	3.0663
A_1A_2*	1	0.0927	0.0221	4.20	<.0001	1.3417
A_1*	1	0.0041	0.0137	0.30	0.7665	2.1691
A_2*	1	-0.0259	0.0158	-1.65	0.0999	2.2211
A_3*	1	-0.0482	0.0175	-2.75	0.0059	1.9206
TA*	1	0.0398	0.0104	3.82	0.0001	1.3339
Age_Group	1	-0.0116	0.0091	-1.28	0.2020	1.0139

The purpose of building the overall model is to see if any type of drug treatments are significant when controlling for the other drug types. If the parameter estimates are positive, the variables can be interpreted as having a greater hospital cost than our base line, conversely if the parameter estimates are negative, the variables can be interpreted as having a mean hospital cost less than our baseline. The p-values indicate if the difference is significant. Variables with corresponding p-values <.10 have an asterisk. This model selects the same significant variables that we discovered when only looking at one drug type at a time, and also would rank them the same. This indicates that the treatments that are significant are not associated with the administration of other treatments.

5.6. Length of Stay Overall Model

Independent variables considered were drug indicators for spinal block, anticoagulant, and antifibrinolytic treatments, age group, and gender, leaving out A_0 and S_0 as baseline treatments. The full model was developed with all the aforementioned independent variables. Model assumptions were checked just as in Section 5.5 and reasonably met by the same criteria.

Table 32. Parameter Estimates for Length of Stay

Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|	VIF
Intercept	1	1.0099	0.0397	25.41	<.0001	0
Gender*	1	-0.0557	0.0119	-4.70	<.0001	1.0067
S_1S_2S3	1	0.0099	0.0370	0.27	0.7884	9.7940
S_1S_2*	1	-0.0832	0.0390	-2.14	0.0329	7.9860
S_2S_3*	1	0.1178	0.0416	2.83	0.0047	3.5263
S_1S_3	1	0.0239	0.0384	0.62	0.5333	7.2413
S_1	1	0.0411	0.0475	0.86	0.3872	2.2485
S_3	1	0.0412	0.0428	0.96	0.3350	3.0663
S_1S_2*	1	0.2028	0.0280	7.23	<.0001	1.3417
A_1	1	0.0081	0.0175	0.46	0.6446	2.1691
A_2*	1	0.1057	0.0200	5.28	<.0001	2.2211
A_3*	1	0.0373	0.0223	1.67	0.0941	1.9206
TA*	1	-0.1116	0.0133	-8.41	<.0001	1.3339
Age_Group*	1	0.0898	0.0116	7.75	<.0001	1.0139

If the parameter estimates are positive, the variables can be interpreted as having a greater mean length of stay than our base line, conversely, if the parameter estimates are negative, the variables can be interpreted as having a mean length of stay less than our baseline. Significant variables with corresponding p-values <.10 have an asterisk. This model selects the same significant variables that we discovered when only looking at one drug type at a time, and also would rank them the same. This indicates that the treatments that are significant are not associated with the administration of other treatments.

5.7. Early Readmissions Overall Model

A logistic regression model was constructed with the dependent variable "Early_Readmit" (Event=1) and drug treatment indicators, age group, and gender as independent variables, leaving out A_0 and S_0 as baseline treatments. The full model was developed with all the aforementioned independent variables. VIF's calculated in the previous two sections gave no significant concern of multicollinearity between the independent variables chosen in this model. The Hosmer-Lemeshow Goodness of Fit test yielded an insignificant p-value (.32) indicating the model fit is adequate.

Table 33. Parameter Estimates for Early Readmissions

Variable	DF	Parameter Estimate	Standard Error	P-value
Intercept	1	-3.4801	0.7019	<.0001
$S_1S_2S_3$	1	0.2684	0.6308	0.6705
S_1S_2	1	-0.0617	0.7043	0.9302
S_2S_3*	1	1.0214	0.6882	0.1378
S_1S_3	1	0.0660	0.6801	0.9227
S_3	1	-0.5284	0.9282	0.5692
A_1A_2*	1	1.0370	0.4804	0.0309
A_1	1	-0.0576	0.4038	0.8866
A_2	1	-0.6520	0.4967	0.1893
A_3	1	-0.8522	0.5873	0.1468
TA	1	-0.2448	0.3224	0.4475
Age_Group (0 vs 1)	1	-0.1509	0.1387	0.2765
Gender (F vs M)*	1	-0.4408	0.1372	0.0013

Table 34. Odds Ratio Estimates for Early Readmissions

Variable	Point Estimate	95% Wald Confidence Limits	
$S_1S_2S_3$	1.308	0.380	4.503
S_1S_2	0.940	0.236	3.739
S_2S_3*	2.777	0.721	10.699
S_1S_3	1.068	0.282	4.051
S_3	0.590	0.096	3.636
A_1A_2*	2.821	1.100	7.232
A_1	0.944	0.428	2.083
A_2	0.521	0.197	1.379
A_3	0.426	0.135	1.349
TA	0.783	0.416	1.473
Age_Group (0 vs 1)	0.739	0.429	1.274
Gender (F vs M)*	0.414	0.242	0.709

The variables selected that had a significant association with adverse effects, or early readmissions, were the same variables selected in the reduced models earlier in this study. We now know that the effect on early readmissions obvserved before is not related to these drug treatments being administered together. The odds ratio estimates are very similar to the previous analysis and can be interpreted the same.

5.8. Blood Transfusions Overall Model

A logistic regression model was constructed with the dependent variable "Blood_Transfusion" (Event=1) and drug treatment indicators, age group, and gender as independent variables, leaving out A_0 and S_0 as baseline treatments. The full model was developed and the Hosmer-Lemeshow Goodness-of-Fit test yielded an insignificant p-value (.38) indicating that the model fit was adequate.

Table 35. Parameter Estimates for Blood Transfusions

Variable	DF	Parameter Estimate	Standard Error	P-value
Intercept	1	-2.7118	0.5513	<.0001
$S_1S_2S_3$	1	0.3475	0.4603	0.4503
S_1S_2	1	-0.0152	0.5914	0.9796
S_2S_3*	1	1.2128	0.4974	0.0147
S_1S_3	1	0.3904	0.4796	0.4157
S_3	1	0.4074	0.5640	0.4700
A_1A_2*	1	0.7298	0.4164	0.0796
A_1*	1	-0.6755	0.3787	0.0744
A_2	1	0.2730	0.3613	0.4499
A_3	1	-0.3990	0.4035	0.3228
TA*	1	-1.8792	0.3030	<.0001
Age_Group (0 vs 1)*	1	-0.5214	0.1075	<.0001
Gender (F vs M)*	1	0.3901	0.1100	0.0004

Table 36. Odds Ratio Estimates for Blood Transfusions

Variable	Point Estimate	95% Wald Confidence Limits	
$S_1S_2S_3$	1.416	0.574	3.489
S_1S_2	0.985	0.309	3.139
S_2S_3*	3.363	1.269	8.914
S_1S_3	1.478	0.577	3.782
S_3	1.503	0.498	4.539
A_1A_2*	2.075	0.917	4.692
A_1*	0.509	0.242	1.069
A_2	1.314	0.647	2.668
A_3	0.671	0.304	1.480
TA*	0.153	0.084	0.277
Age_Group (0 vs 1)*	0.352	0.231	0.537
Gender (F vs M)*	2.182	1.418	3.358

It was found earlier that Females, and the older group were more likely to require blood transfusions. We also discovered earlier that patients who received tranexamic acid were much less likely to require a blood transfusion, as we would expect, based on the literature review. Those findings are reiterated in this model's results. A new finding is that the treatments S_2S_3, A_1A_2, and A_1 are associated with blood transfusions. In comparison to the baseline of not receiving any of the considered spinal block combinations, patients who received S_2S_3 were more likely to require a blood transfusion. In comparison to the baseline of not receiving any of the considered anticoagulant combinations, patients who received A_1A_2 were more likely to require a blood transfusion, while patients who received A_1 were less likely to require a blood transfusion.

5.9. Locations

First we need to assess if there are significant associations between the five locations provided in the data set and the drug treatments that were given to the knee replacement patients. Three separate Pearson's Chi-Square tests were conducted to measure these associations. Table 37 provides the results of these three tests.

Table 37. Pearson's Chi Square Test Results

Association Between	Chi-Square	P-value
Location and Spinal Blocks	1321.29	<.0001
Location and Anticoagulants	1485.09	<.0001
Location and Antifibrinolytic	852.21	<.0001

The tests indicate that the location of the performing hospital is highly associated with the combinations of drug treatments selected in each of the three drug categories. It is important to note that this finding must be used when considering the interpretation of the previous sections. For example, spinal block treatment S_1S_2 was found to be associated with the significantly shortest length of stay. However, location is also found to be associated with the administration of S_1S_2. It is possible that the location that administers S_1S_2 with the highest frequency, is also releasing patients out of their hospital quicker for other reasons. Therefore, when interpreting the differences between drug treatments for the outcomes of hospital cost, length of stay, adverse effects, and blood transfusions, one must also consider the location as a confounding variable.

We decided to isolate the location that was the most varied across drug treatments and had adequate sample size. One location stood out in this respect, and will be referred to as "Location A" for the rest of this thesis (N=1,035). Tables 38-40 show sample sizes of drug treatments at Location A.

Table 38. Spinal Block Treatments Administered at Location A

Treatment	N
S_0	8
S_1	40
S_1S_2	7
$S_1S_2S_3$	516
S_1S_3	363
S_2	1
S_2S_3	71
S_3	45

It is important to note that when analysis was conducted to compare spinal block treatments for the overall data set, we did not include treatment S_2 due to small sample size. Now that we are comparing spinal block treatments just for "Location A", we must leave out S_0, S_1S_2, and S_2 due to inadequate sample size. One should consider this when comparing the significant treatments found from the overall analysis and the "Location A" analysis.

Table 39. Anticoagulant Treatments Administered at Location A

Treatment	N
A_0	48
A_1	201
A_1A_2	64
$A_1A_2A_3$	3
A_1A_3	8
A_2	442
A_2A_3	20
A_3	265

When analysis was conducted to compare anticoagulant treatments for the overall data set, we did not include treatment $A_1A_2A_3$, A_1A_3, or A_2A_3 due to small sample size. Now that we are comparing spinal block treatments just for "Location A", we will leave out the same treatments due to inadequate sample size. This is ideal for comparison of the significant treatments found from the overall analysis and the "Location A" analysis.

Table 40. Tranexamic Acid Administered at Location A

TA	N
0	744
1	307

When comparing the results between the overall data set and the "Location A" data set, the same drug combinations were found to be significantly associated with the highest outcomes of hospital cost and length of stay. This indicates that the mean differences found were mostly due to the drug treatments and not significantly affected by location. Tables 41 and 42 summarize these results in a side-by-side comparison. Treatments that share a same group letter are not significantly different from each other.

Table 41. Hospital Cost Side-by-Side Comparison (Location A and Overall)

	Location A			Overall	
Group	Mean HC	Treatment	Group	Mean HC	Treatment
A	$11,164.70	S_2S_3	A	$11,613.53	S_2S_3
B	$10,078.19	S_1S_3	A	$11,128.20	S_3
B	$10,075.69	S_3	A,B	$10,929.95	S_0
B	$9,992.63	S_1	A,B	$10,475.36	S_1
B	$9,948.46	$S_1S_2S_3$	B	$10,307.93	S_1S_2
			B	$10,264.11	$S_1S_2S_3$
			B	$10,202.94	S_1S_3
Group	Mean HC	Treatment	Group	Mean HC	Treatment
A	$11,281.40	A_1A_2	A	$11,781.13	A_1A_2
A,B	$10,390.73	A_2	B	$10,497.09	A_1
B,C	$9,565.22	A_0	B,C	$10,310.15	A_0
C	$9,692.24	A_1	C,D	$10,320.68	A_2
C	$9,608.43	A_3	D	$9,912.58	A_3
Group	Mean HC	TA	Group	Mean HC	TA
A	$10,523.90	1	A	$10,523.90	1
B	$9,910.10	0	A	$10,342.90	0

In Table 41, the spinal block treatment S_2S_3 had the significantly highest hospital cost for both the overall data set and the "Location A" data set. This indicates that the difference can be attributed to the actual drug treatment and is not being affected by the location. Spinal block treatment $S_1S_2S_3$ is associated with lower hospital costs for both analyses. Anticoagulant treatment A_1A_2 had the highest hospital cost for both analyses, while A_3 had the lowest for both analyses. One contradiction found is that patients who received tranexamic acid at "Location A" had a significantly higher hospital cost than those who did not receive it, while this difference was not significant for the overall group of patients.

Table 42. Length of Stay Side-by-Side Comparison (Location A and Overall)

	Location A			Overall	
Group	Mean LOS	Treatment	Group	Mean LOS	Treatment
A	3.54	S_2S_3	A	3.39	S_2S_3
B	3.15	$S_1S_2S_3$	A,B	3.12	S_3
B	3.10	S_1S_3	A,B	3.04	S_1
B	3.04	S_3	A,B	2.97	S_0
B	3.00	S_1	B	3.07	S_1S_3
			B	2.96	$S_1S_2S_3$
			C	2.50	S_1S_2
Group	Mean LOS	Treatment	Group	Mean LOS	Treatment
A	3.95	A_1A_2	A	3.63	A_1A_2
B	3.13	A_2	B	3.15	A_2
B	3.09	A_1	B	3.00	A_3
B	3.03	A_3	C	2.79	A_1
B	2.81	A_0	D	2.47	A_0
Group	Mean LOS	TA	Group	Mean LOS	TA
A	3.20	0	A	3.18	1
B	3.03	1	B	2.66	0

In Table 42, the spinal block treatment S_2S_3 had the significantly highest length of stay for both the overall data set and the “Location A” data set. The rest of the spinal block treatments seem to vary in ranking between the two analyses. Anticoagulant treatment A_1A_2 had the highest length of stay for both analyses, while A_0 had the lowest for both analyses. Patients who received Tranexamic Acid at “Location A” had a significantly lower length of stay for both analyses, when compared to patients who did not receive the drug.

When comparing the results between the overall data set and the “Location A” data set, most of the same drug combinations were found to be significantly associated with the highest proportions of early readmissions and blood transfusions. Tables 43 and 44 summarize the comparisons.

Table 43. Early Readmissions Side-by-Side Comparison (Overall and Location A)

Early Readmit	Overall	Location A
Most Likely	A_1A_2	A_1A_2
	S_2S_3	S_2S_3

Table 44. Blood Transfusions Side-by-Side Comparison (Overall and Location A)

Blood Transfusions	Overall	Location A
Most Likely	S_2S_3	S_1S_2
	A_1A_2	S_2S_3

Analysis on both data sets found A_1A_2 to be the treatment group most likely to have an early readmission, while S_2S_3 was the second most likely group. S_2S_3 was the only treatment group that made the top two of most likely to require a blood transfusion for both data set analyses.

6. CONCLUSIONS

There are several conclusions that can be drawn from this study. Three different drug categories with multiple treatments within each category were compared across four outcomes of hospital cost, length of stay, early readmissions, and blood transfusions.

The first conclusion is that S_2S_3 (Lidocaine, Ropivacaine) appears to be the least favorable spinal block treatment. Among all spinal block treatments, this group is associated with the highest hospital cost, the highest length of stay, the most likely to have an early readmission, and the most likely to require a blood transfusion. There is not a clear most favorable spinal block treatment. $S_1S_2S_3$ (Bupivacaine, Lidocaine, Ropivacaine) appears to be consistently one of the lowest in terms of hospital cost of and length of stay, with no association between higher proportions of early readmissions or blood transfusions, however, this treatment is not significantly different from other spinal block treatments that perform similarly.

A_1A_2 (Warfarin, Enoxaparin) appears to be the least favorable anticoagulant treatment. Among all anticoagulant treatments, this group is associated with the highest hospital cost, the highest length of stay, and most likely to have an early readmission. There is not a clear most favorable anticoagulant treatment. In general, it appears treatments with just one anticoagulant perform better than combinations of anticoagulants. A_1 (Warfarin), A_2 (Enoxaparin), and A_3(Rivaroxaban) are among the lowest anticoagulant treatment groups in terms of hospital cost and length of stay, and are also significantly less likely to require blood transfusions than other anticoagulant treatment groups.

Tranexamic acid drug treatment is associated with a significantly lower length of stay without significantly increasing hospital costs. It also greatly reduces the chances of requiring a blood transfusion. It appears to be a much better option than no antifibrinolytic treatment.

Age and gender played a significant role in the health outcomes of this study. It was found from our data set that males had slightly shorter length of stay and higher odds of an early readmission compared to females. It was also found that females had higher odds of requiring a blood transfusion than males and a significantly shorter length of stay. Finally, the older age group (at least 65 years old) had higher odds of an early readmission and requiring a blood transfusion compared to the under 65 group.

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