Statistical Analysis of Study Conducted to Evaluate Administration of Oxytocin Through Intravenous Infusion and Intermuscular Injection and Its Effects on Blood Loss During Pregnancy

A new study was recently published investigating if the effect of the route of prophylactic administration of oxytocin through intravenous (IV) infusion or intermuscular (IM) injection on preventing postpartum hemorrhaging (PPH). Current guidelines can be confusing because some only specify IM administration while others suggest both IM injections and IV infusions are equally effective. In the study, a group of 480 women in active labor at a hospital in Argentina consented to be in the study and didn't have a c-section. It was double-blind, randomized clinical trial to investigate the effect of the route of prophylactic administration of oxytocin (IV infusion or IM injection) on PPH outcomes. An outcome of this study was blood loss (in millimeters; mL) at 60 minuets postpartum.

The population of interest is women in labor. This analysis will be answering the following two research questions:

1. Is shock index 15 minuets after birth (*SI15*) a predictor of blood loss (in mL) at 60 minuets postpartum (*BloodLoss60*), after adjusting for study group (*StudyGroup*)?
2. What is the best model for predicting blood loss (in mL) at 60 minuets postpartum?

Secondary Study Outcomes

The summary statistics for the research project can be explored to compare outcomes between the groups in the clinical trial. Table 2 below compares the groups.

Table 2: Study Outcomes by Study Group

	IM group	**IV group**	**Relative Risk[a] or Estimate[b] (95% CI)**	***p*-value**
Sample size (n)	241	239		
Postpartum hemoglobin (Hb) (in g/dL), mean (SD)	10.4 (1.6)	10.36 (1.4)	-0.22, 0.31	0.74
Blood Loss 30 minutes after birth (in mL), mean (SD)	328.89 (309.86)	293.77 (280.12)	-17.97, 88.23	0.19
Blood loss $\geq$ 750 mL, n (%)	12.97%	8.82%	0.34, 1.21	0.19
Blood loss $\geq$ 1000 mL, n (%)	7.53%	5.88%	0.34, 1.68	0.58

[a]Risk for IM group compared to risk in IV group.
[b]Difference in means comparing IM group to IV group.

None of the study outcomes appear to be statistically significant. All the of confidence intervals include 0 or 1, and none of the p-values are less than 0.05.

Model 1

Shock index can be used associated with blood loss in each group to test if it is a predictor. Shock index is the ratio of pulse to systolic blood pressure. The variable *SI15* was created and added to the initial dataset by calculating the ratio of pulse rate 15 minutes after birth and systolic blood pressure 15 minutes after birth. The relationship is explored in Figure 1 below.

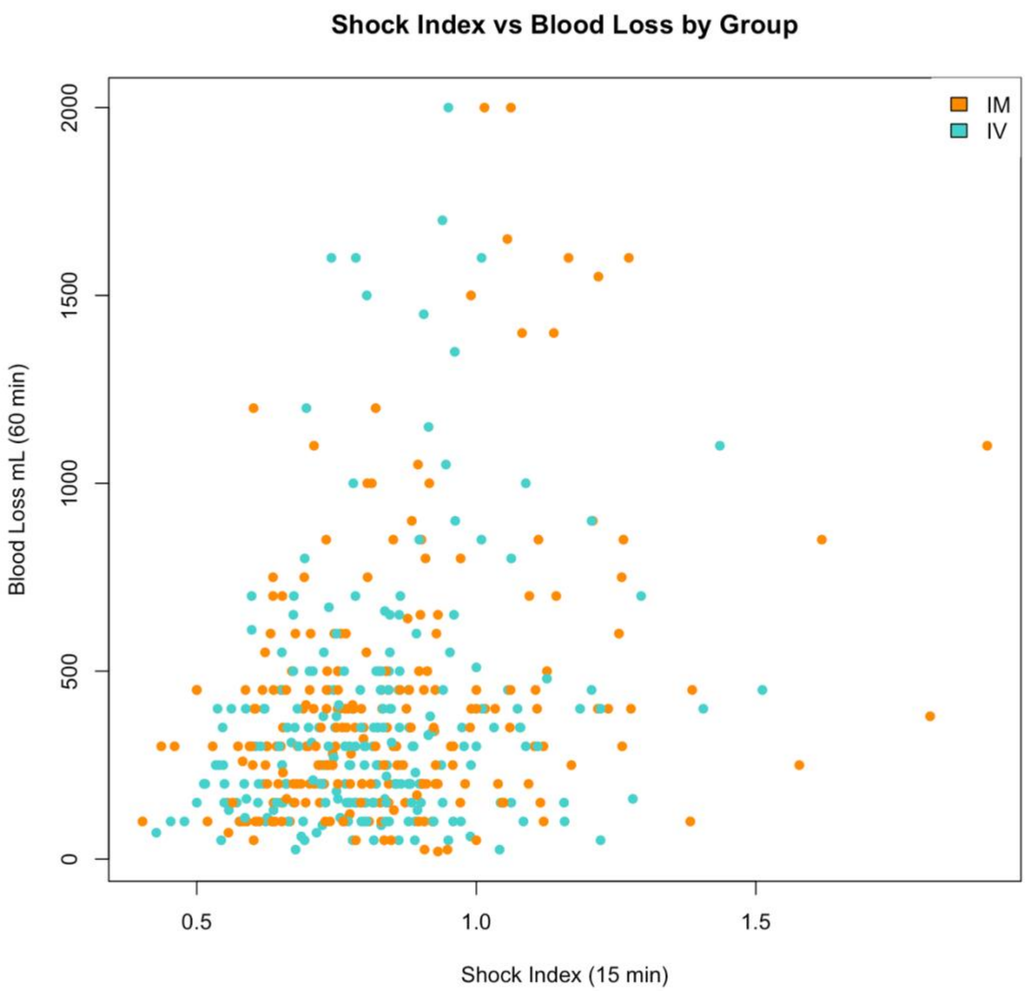

Figure 1: Scatter plot of shock index vs blood loss by group. IM group is represented by the orange dots and IV by the blue dots.

Figure 1 depicts the IM group and IV group relationship with blood loss mL at 60 minuets postpartum and the shock index. A shock index less than 0.90 is normal while greater than 0.90 is abnormal. Most of the data is clustered below 0.90 but there are a few outliers that are greater than 1.5. Also, those data points are below 500 mL of blood loss after 60 minuets. To further explore this, a model can be created to predict blood loss at 60. Minuets postpartum from the shock index 15 minutes after birth when adjusting for study group.

The equation for the fitted regression model is BloodLoss60 = 22.13 + (456.82 * SI15) + (-33.64 * StudyGroup). The intercept of 22.13 means that when the shock index is 0, the predicted blood loss at 60 minuets is 22.13 mL. This would not be a typical patient outcome, but it represents where the regression line crosses the y-axis. Next, the *SI15* estimate is 456.82 which is the slope of the relationship. When there is an increase of 1.0 in the shock index, then the predicted blood loss value increases by 456.82 mL. Then, the group estimate is -33.64 which is the difference between the groups. The IV group is predicted to have 33.64 mL less blood loss than the IM group. Assumptions can be checked next to see if they are met or not.

Graphs can be created to check the assumptions. Figure 2 below holds those graphs.

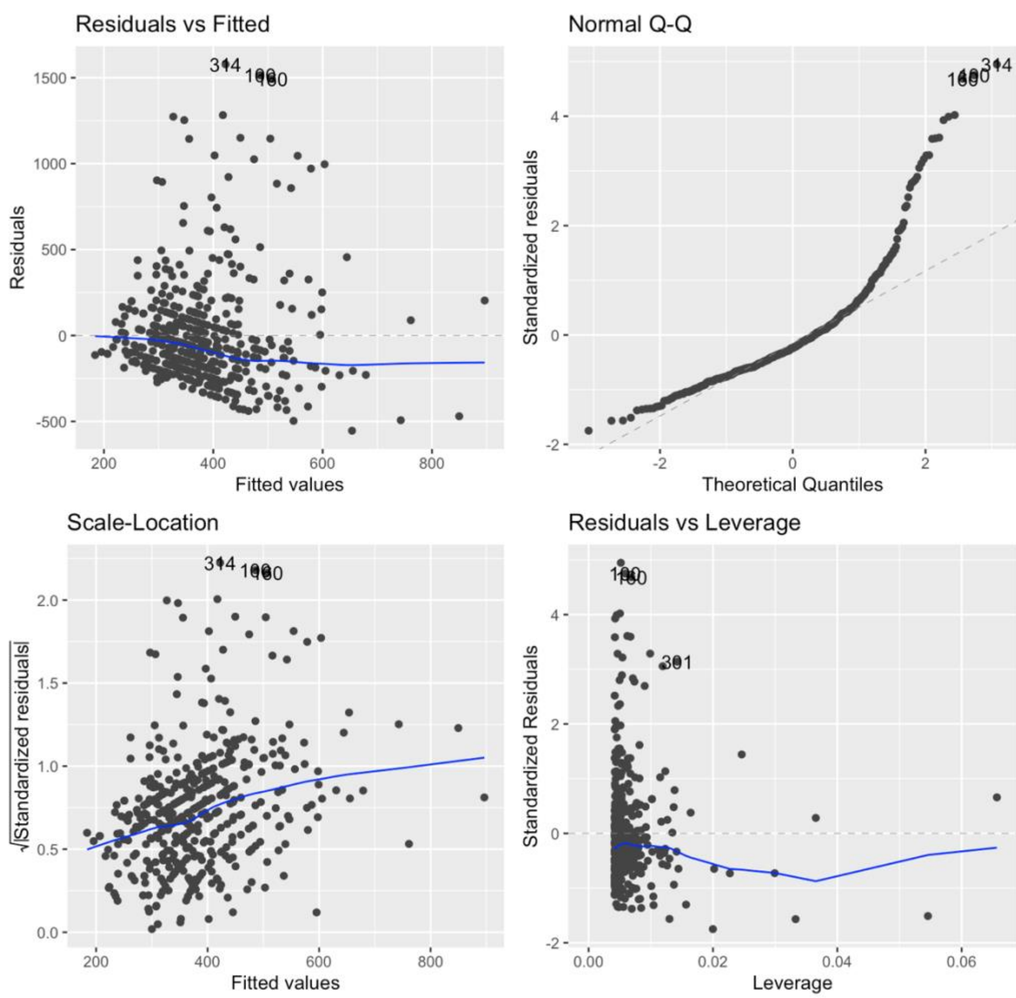

Figure 2: Assumption Models for Residuals vs Fitted, Normal Q-Q, Scale-Location, and Residuals vs Leverage.

The four graphs in Figure 2 show different assumptions for the model. The Residuals vs Fitted graph checks if there is a linear relationship, variance, and any outliers. There are three noted outliers in that graph, but the blue regression line dips a little below zero. The curve is significant enough to say that there is no linear relationship, so assumption is not met. The Normal Q-Q plot finds if the points are normally distributed on a reference line. The reference line is indicated by the dashed line. The points initially follow the line but then skews upwards as there are some outliers showing how assumption is not fully met. The Scale-Location graph finds how spread the values are and the blue regression line should be flat. The line trends upward as the fitted values increase and assumptions are not met. Then, the Residuals vs Leverage graph finds if there are any outliers that could be pulling the regression line. There are a few outliers present that could be pulling the line, but they aren't completely altering the regression line. Assumption is not met in this graph either.

The R^2 value can be determined to find the best fit of the model from the data and how well it matches the model's predictions. A value of 1 means that the variability of the dependent variables is explained by the independent variable. If the value is 0, then the independent variable does not explain variability. The R^2 value for this model is 0.08 which means only 8% of the model is explained by variation. More models can be created to find if they fit the prediction better.

Finding the "Best" Model

Three more models were created to find a "best" fit model to predict blood loss (mL) at 60 minuets postpartum. Predictors were added in each new model.

Table 3: "Best" Model for Predicting Excess Blood Loss

Model	Appropriate R^2
BloodLoss60, SI15, Age, StudyGroup	0.07
BloodLoss60, SI15, Age, BloodLoss30, StudyGroup	0.88
BloodLoss60, SI15, Age, BloodLoss30, HbBaseline, StudyGroup	0.88

Table 3 highlights the three models used their R^2 values. Each model builds off each other to further increase the R^2 value. Adding multiple variables allows more predictors for variance in the dependent variable. The second and third models in Table 3 had value of $R^2 = 0.88$. This value indicates a strong fit for both models. *BloodLoss30* had a significant t-value of $t = 55.68$ which contributed to the R^2 value.

Conclusion

Shock index 15 minutes after birth is a strong predictor of blood loss (in mL) at 60 minuets postpartum. The two models in Table 3 that had a value of $R^2 = 0.88$ are why. Those predictors contributed meaningful correlation to the *BloodLoss60* and *SI15* variables. The variable *BloodLoss30* had a great impact on the models. One concern with the models was that the predictors I added had low t-values that would have not greatly affected the R^2 value.

Appendix

```
> #Load data

> pph <- read.csv('/Users/davidkeefer/Documents/PUBH 6450/Project 2/PPH-Oxytocin-RCT.csv', header = TRUE)

>

> View(pph)

>

> table(pph$StudyGroup)


 IM  IV

241 239

>

> #Create new variable

>

> pph$SI15<- pph$HR15 / pph$SBP15

>

> #Summary Statistics

>

> describeBy(pph$HbPost, pph$StudyGroup)


 Descriptive statistics by group

group: IM

   vars   n mean  sd median trimmed  mad min  max range

X1    1 240 10.4 1.6   10.5   10.45 1.19 5.5 15.4   9.9

    skew kurtosis  se

X1 -0.27     0.99 0.1

---------------------------------------------
```

```
group: IV
   vars   n  mean  sd median trimmed  mad min  max range
X1    1 236 10.36 1.4    10.5   10.38 1.19 5.9 14.7   8.8
    skew kurtosis   se
X1 -0.15     1.04 0.09
> t.test(pph$HbPost ~ pph$StudyGroup, data = pph)

	Welch Two Sample t-test

data:  pph$HbPost by pph$StudyGroup
t = 0.32649, df = 467.66, p-value = 0.7442
alternative hypothesis: true difference in means between group IM and group IV is not equal to 0
95 percent confidence interval:
 -0.2250290  0.3147041
sample estimates:
mean in group IM mean in group IV 
        10.40458         10.35975 

>
> describeBy(pph$BloodLoss30, pph$StudyGroup)

 Descriptive statistics by group 
group: IM
   vars   n   mean     sd median trimmed    mad min  max
X1    1 239 328.89 309.86    250  271.53 222.39   0 1650
   range skew kurtosis    se
X1  1650 2.09     5.01 20.04
```

```
--------------------------------------------
group: IV
   vars   n   mean     sd median trimmed    mad min  max
X1    1 239 293.77 280.12    200  241.79 148.26  20 1700
   range skew kurtosis    se
X1  1680 2.44     7.38 18.12
> t.test( pph$BloodLoss30 ~ pph$StudyGroup, data = pph)

        Welch Two Sample t-test

data:  pph$BloodLoss30 by pph$StudyGroup
t = 1.3, df = 471.23, p-value = 0.1942
alternative hypothesis: true difference in means between group IM and group IV is not equal to 0
95 percent confidence interval:
 -17.96793  88.21897
sample estimates:
mean in group IM mean in group IV
        328.8912         293.7657

>
> describeBy(pph$BL750, pph$StudyGroup)

 Descriptive statistics by group
group: IM
   vars   n mean   sd median trimmed mad min max range skew
X1    1 239 0.13 0.34      0    0.04   0   0   1     1 2.19
   kurtosis   se
```

```
X1     2.81 0.02
--------------------------------------------
group: IV
   vars   n mean   sd median trimmed mad min max range skew
X1    1 238 0.09 0.28      0       0   0   0   1     1 2.89
   kurtosis   se
X1     6.35 0.02
> BL750Table <- table(pph$StudyGroup, pph$BL750)
> prop.table(BL750Table, margin = 1)

             0          1
  IM 0.87029289 0.12970711
  IV 0.91176471 0.08823529
> fisher.test(BL750Table)

	Fisher's Exact Test for Count Data

data:  BL750Table
p-value = 0.1857
alternative hypothesis: true odds ratio is not equal to 1
95 percent confidence interval:
 0.3430196 1.2103854
sample estimates:
odds ratio
 0.6499139

>
```

```
> describeBy(pph$BL1000, pph$StudyGroup)

 Descriptive statistics by group
group: IM
   vars   n mean   sd median trimmed mad min max range skew
X1    1 239 0.08 0.26      0       0   0   0   1     1  3.2
   kurtosis   se
X1     8.26 0.02
--------------------------------------------
group: IV
   vars   n mean   sd median trimmed mad min max range skew
X1    1 238 0.06 0.24      0       0   0   0   1     1 3.73
   kurtosis   se
X1    11.94 0.02
> BL1000Table <- table(pph$StudyGroup, pph$BL1000)
> prop.table(BL1000Table, margin = 1)

             0          1
  IM 0.92468619 0.07531381
  IV 0.94117647 0.05882353
> fisher.test(BL1000Table)

	Fisher's Exact Test for Count Data

data:  BL1000Table
p-value = 0.5836
alternative hypothesis: true odds ratio is not equal to 1
```

```
95 percent confidence interval:
 0.3441949 1.6794141
sample estimates:
odds ratio
 0.7677885


>
> #Model 1
>
> plot(pph$SI15, pph$BloodLoss60,
+      col = c("darkorange", "mediumturquoise")[factor(pph$StudyGroup)],
+      pch = 16,
+      xlab = "Shock Index (15 min)", ylab = "Blood Loss mL (60 min)",
+      main = "Shock Index vs Blood Loss by Group")
> legend("topright", legend = levels(factor(pph$StudyGroup)),
+        fill = c("darkorange", "mediumturquoise"),
+        box.lty = 0)
>
> pph_model <- lm(pph$BloodLoss60 ~ pph$SI15 + factor(pph$StudyGroup))
> summary(pph_model)

Call:
lm(formula = pph$BloodLoss60 ~ pph$SI15 + factor(pph$StudyGroup))

Residuals:
    Min      1Q  Median      3Q     Max
-553.78 -191.58  -75.82   93.78 1577.54
```

```
Coefficients:
                          Estimate Std. Error t value
(Intercept)                  22.13      64.95   0.341
pph$SI15                    456.82      73.59   6.208
factor(pph$StudyGroup)IV    -33.64      29.35  -1.146
                          Pr(>|t|)
(Intercept)                  0.733
pph$SI15                  1.18e-09 ***
factor(pph$StudyGroup)IV     0.252
---
Signif. codes:
0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 319.7 on 473 degrees of freedom
  (4 observations deleted due to missingness)
Multiple R-squared:  0.07929,	Adjusted R-squared:  0.0754
F-statistic: 20.37 on 2 and 473 DF,  p-value: 3.275e-09

>
> library(ggfortify)
> autoplot(pph_model)
>
> #Find best model
> pph_model2<- lm(pph$BloodLoss60 ~ pph$SI15 + pph$Age + factor(pph$StudyGroup))
> summary(pph_model2)
```

```
Call:
lm(formula = pph$BloodLoss60 ~ pph$SI15 + pph$Age + factor(pph$StudyGroup))

Residuals:
    Min      1Q  Median      3Q     Max 
-529.76 -193.53  -75.95   88.26 1597.37 

Coefficients:
                         Estimate Std. Error t value
(Intercept)                81.602    102.352   0.797
pph$SI15                  445.789     75.072   5.938
pph$Age                    -2.068      2.750  -0.752
factor(pph$StudyGroup)IV  -34.234     29.372  -1.166
                         Pr(>|t|)    
(Intercept)                 0.426    
pph$SI15                  5.6e-09 ***
pph$Age                     0.452    
factor(pph$StudyGroup)IV    0.244    
---
Signif. codes:  
0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 319.8 on 472 degrees of freedom
  (4 observations deleted due to missingness)
Multiple R-squared:  0.08039,	Adjusted R-squared:  0.07455 
F-statistic: 13.75 on 3 and 472 DF,  p-value: 1.296e-08
```

```
>

> pph_model3 <-lm(pph$BloodLoss60 ~ pph$SI15 + pph$Age + pph$BloodLoss30 +
factor(pph$StudyGroup))

> summary(pph_model3)


Call:

lm(formula = pph$BloodLoss60 ~ pph$SI15 + pph$Age + pph$BloodLoss30 +

    factor(pph$StudyGroup))


Residuals:

    Min      1Q  Median      3Q     Max

-152.84  -68.36  -36.32   31.21 1122.15


Coefficients:

                          Estimate Std. Error t value

(Intercept)               -0.64303   37.23664  -0.017

pph$SI15                  32.55755   28.28150   1.151

pph$Age                    1.35400    1.00146   1.352

pph$BloodLoss30            1.04842    0.01883  55.684

factor(pph$StudyGroup)IV  -4.32634   10.69089  -0.405

                          Pr(>|t|)

(Intercept)                  0.986

pph$SI15                     0.250

pph$Age                      0.177

pph$BloodLoss30             <2e-16 ***

factor(pph$StudyGroup)IV     0.686

---
```

```
Signif. codes:
0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 116.3 on 471 degrees of freedom
  (4 observations deleted due to missingness)
Multiple R-squared:  0.8787,  Adjusted R-squared:  0.8777
F-statistic: 853.2 on 4 and 471 DF,  p-value: < 2.2e-16

>
> pph_model4 <-lm(pph$BloodLoss60 ~ pph$SI15 + pph$Age + pph$BloodLoss30 +
pph$HbBaseline + factor(pph$StudyGroup))
> summary(pph_model4)

Call:
lm(formula = pph$BloodLoss60 ~ pph$SI15 + pph$Age + pph$BloodLoss30 +
    pph$HbBaseline + factor(pph$StudyGroup))

Residuals:
    Min      1Q  Median      3Q     Max
-152.79  -68.42  -35.80   31.03 1122.18

Coefficients:
                         Estimate Std. Error t value
(Intercept)              -3.62813   57.81456  -0.063
pph$SI15                 31.70516   28.44442   1.115
pph$Age                   1.36853    1.00430   1.363
pph$BloodLoss30           1.04840    0.01887  55.566
```

```
pph$HbBaseline           0.28589    3.58345   0.080
factor(pph$StudyGroup)IV -4.13206   10.72231  -0.385
                         Pr(>|t|)
(Intercept)              0.950
pph$SI15                 0.266
pph$Age                  0.174
pph$BloodLoss30          <2e-16 ***
pph$HbBaseline           0.936
factor(pph$StudyGroup)IV 0.700
---
Signif. codes:
0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 116.5 on 469 degrees of freedom
  (5 observations deleted due to missingness)
Multiple R-squared:  0.8786,  Adjusted R-squared:  0.8773
F-statistic: 678.9 on 5 and 469 DF,  p-value: < 2.2e-16
```