The Impact of Various Factors on Total Postpartum Blood Loss: a 3 Factor ANOVA

STAT 6160 Final Project
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1. Problem Description

Maternal health care is still a vastly under researched topic, and one in which many more advancements can be made. In particular, bleeding after delivery, specifically postpartum hemorrhages (PPH), are one of the leading causes of maternal deaths. Oxytocin, commonly called the love hormone, has been shown to reduce rates of PPH when given during the third stage of delivery, or after the child is born.[1] Oxytocin falls under a category of drugs called uterotonics, which generally function to reduce bleeding after childbirth.[2] To investigate the effect of different delivery methods of oxytocin (specifically intravenous (IV) infusion vs intramuscular (IM) injection) on bleeding after delivery and rates of PPH, the Gynuity Health Project, in conjunction with the Hospital Materno Neonatal E.T. de Vidal in Corrientes, Argentina, conducted a double-blind, placebo-controlled randomized trial.[3] They randomly assigned intravenous or intramuscular oxytocin to study the impact on PPH and postpartum bleeding. The response was measured through a receptacle which was marked at intervals of 100cc of blood; the total blood loss for at least 1 hour, or until bleeding stopped, was recorded.

The Gynuity Health Project is a research organization that seeks to provide evidence that will make reproductive and maternal health care available globally. We accessed the data they collected for this clinical trial through the Harvard Dataverse. While this study has been analyzed previously, we will be using a different approach than the one published by the Gynuity Health Project, and thus are still conducting a novel analysis.

In our following analysis, using the data provided by this study, we analyze the effect of oxytocin administration route, use of additional uterotonics (besides oxytocin), and postpartum hemorrhage diagnosis on total blood loss in women after birth. We consider these factors independently, in addition to their interactions. Our analysis follows a 3-factorial design (which is really a 2^3 factorial design since all predictors are binary), but we ultimately did not include all possible interactions, so it is not a full factorial model.

2. Experimental Analysis

The data we received is from Harvard Dataverse. The data was collected from a double-blind randomized controlled trial which tested the impact of oxytocin admission route on postpartum blood loss and postpartum hemorrhage. The data was collected from patients who gave birth in a hospital in Argentina. In the original experiment, the independent variable is whether oxytocin was given to the patients via an intravenous infusion or intramuscular injection. In the data this variable is a categorical variable with a value of 0 for intravenous and a value of 1 for intramuscular. The response variable in the original study is the total amount of blood patients lost after active bleeding stopped, while giving birth. The response variable from the original data set is a categorical variable. The original data also includes many other variables for the patient's status before giving birth. In the original study, the only variable for which patients were randomly assigned was the original independent variable, the way that oxytocin was administered.

For the purposes of our experiment, we decided to treat the original response variable, total blood loss, as the response variable. The response variable, perdida_sangre_total, which we renamed total.bl, is a quantitative variable. This variable should be treated as a quantitative variable, because it is a more natural way to record the total amount of blood loss. In addition, it

would be unreliable to turn this into a qualitative variable because we would need to find a cut off for high amounts of blood loss and low amounts of blood loss. We will also treat the original randomized independent variable, the way oxytocin was administered, as one of our factors. This variable was originally categorical, and we will keep it categorical since it is a qualitative variable that cannot be made quantitative. Additionally, we decided to use two of the other factors in the data set for our experiment. In the original data, these factors were not and could not be assigned randomly, but we will treat them as random factors for the purpose of our experiment. The first of these factors is the use of additional uterotonics. This is a categorical variable that records whether or not a participant was given any uterotonics other than oxytocin as part of the study prior to giving birth. We decided to include this variable because it would have an obvious effect on postpartum blood loss since their administration is supposed to reduce the risk of bleeding during birth. This is an important variable to use in our study as a factor, since it should affect postpartum blood loss along with the original independent variable, oxytocin route. The third factor we chose to include is whether or not the participant was diagnosed with postpartum hemorrhaging. We chose this as a factor because although the experimenter did not randomly assign postpartum hemorrhage, nor could you realistically, we wanted to investigate the relationship between postpartum hemorrhage and blood loss after giving birth. We also knew that there should be a relationship between the two. This variable was coded as a binary, categorical variable since there are only two options, yes or no, to whether a patient had postpartum hemorrhaging. Logically, we would also not be able to block postpartum hemorrhage because we cannot control whether a woman has postpartum hemorrhaging or not. This was also the case for using the variable for additional uterotonics, because it would be unethical to randomly assign whether or not a woman received possibly necessary extra

medications. Thus, we decided to treat them both as factors to study these relationships, while acknowledging that our choice for the analysis is not a realistically randomized design.

Lastly, with regard to our experimental design, we decided to complete an ANOVA test. After looking at our design, we thought about either fitting a linear regression model or using an ANOVA model and test to see which variables are significant in predicting postpartum blood loss. Ultimately, we chose an ANOVA model because our factors are categorical variables and we were not sure about whether their relationship with postpartum blood loss would be linear or not. Additionally, we decided that an ANOVA approach would be a good way to test the factors on our response variable since our response variable is quantitative.

3. Statistical Analysis

Figure 1 shows the total blood loss vs oxytocin route in our study. There is not an obvious difference in the distribution of total blood loss by treatment group from looking at this plot alone. However, the original study was designed to explore the effect of the oxytocin administration routes, and we are still interested in the variable, so we chose to analyze it statistically in the model despite the minimal differences shown in EDA.

Figures 2 and 3 show how total blood loss in women varies by two other important factors, the use of additional uterotonics (besides oxytocin) and postpartum hemorrhage diagnosis. Because of the differences in total blood loss distribution shown in these two boxplots, we will continue with our plan of using these two variables in our model as well. They are both logically relevant to total blood loss, and appear to be significantly associated with it in these plots. Our model will therefore be a 3-factor factorial, with factors of oxytocin administration route, additional uterotonic use, and PPH diagnosis and a response variable of total blood loss.

We wanted to consider interactions between the three factors we selected, as a full-factorial model would. Our sample size was large enough to estimate the degrees of freedom even with all possible interactions. All three of our predictors were binary, categorical predictors, so we used plots of means to consider all possible two-way interactions.

In Figure 4, we see minimal evidence of an interaction between postpartum hemorrhage diagnosis and oxytocin route. The slopes of the lines are almost identical. In Figure 5, we see that postpartum hemorrhage diagnosis level affects the relationship between additional uterotonics and total blood loss. There is evidence of an interaction between additional uterotonics and postpartum hemorrhage diagnosis. Figure 6 shows a possible interaction between oxytocin route and use of additional uterotonics. The slopes do seem to differ between levels of the study group factor. Based on these EDA plots, we will not be including the interaction between postpartum hemorrhage and oxytocin route in our model, but we will include the other two two-way interactions. We will also not include the single possible three-way interaction based on this decision.

Figure 1

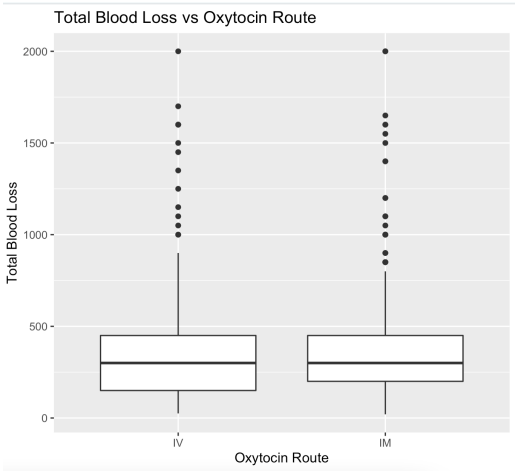


Figure 2

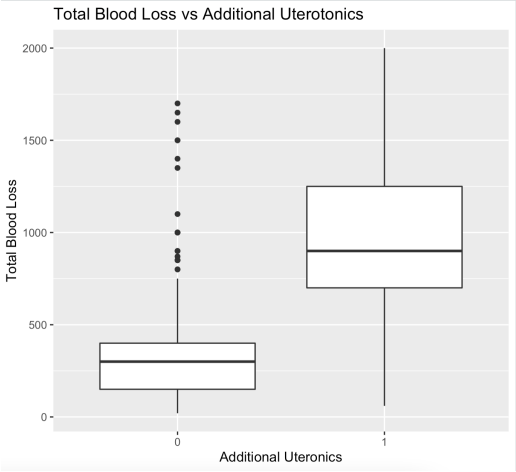


Figure 3

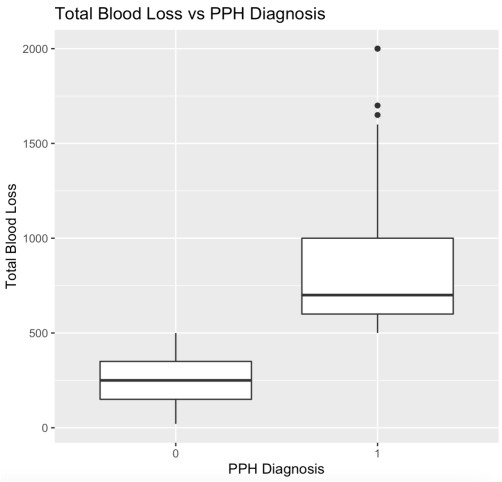


Figure 4

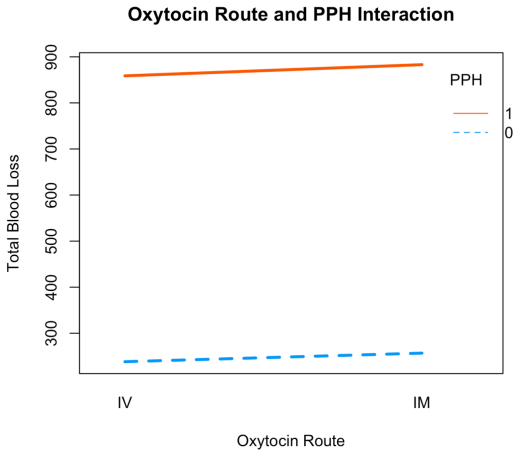


Figure 5

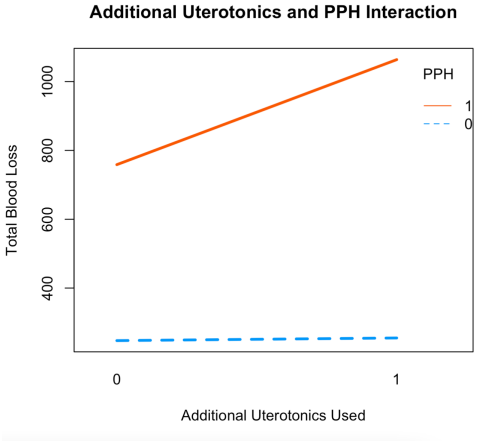
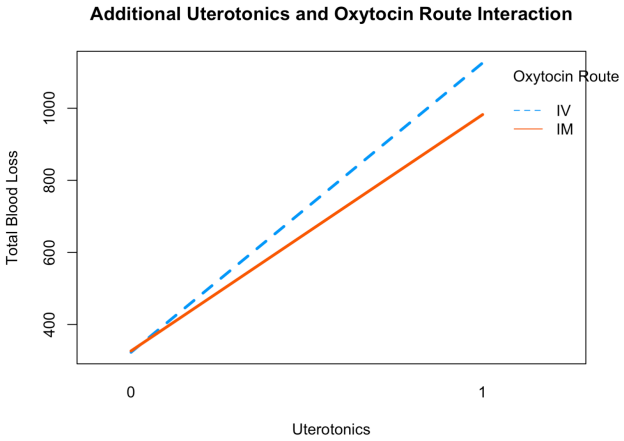


Figure 6



ANOVA Model (Original)

$$y_{ijkl} = \mu + \tau_i + \alpha_j + \beta_k + \tau\alpha_{ij} + \alpha\beta_{jk} + \epsilon_{ijkl}$$

```
                           Df   Sum Sq  Mean Sq F value  Pr(>F)
oxy.route                   1   218762   218762   5.580 0.01857 *
add.uterotonics             1 18132462 18132462 462.516 < 2e-16 ***
pph                         1 15720767 15720767 400.999 < 2e-16 ***
oxy.route:add.uterotonics   1   272561   272561   6.952 0.00865 **
add.uterotonics:pph         1   206791   206791   5.275 0.02208 *
Residuals                 471 18465073    39204
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```

After having fit the model, we needed to check the model assumptions. These included normality of residuals, constant variance across treatment groups, and independence (which we assumed, given that each observation was a separate patient).

The ANOVA assumption of normality of residuals is not met with our model, as seen in the QQ-plot in Figure 7. There seemed to be strong deviations at the high end. Before making any adjustments, we checked the constant variance assumption. As seen in Figure 8, a plot of the residuals vs the fitted values, there appears to be increasing variance. There is much more concentration on the low end of the graph, and more spread in the residuals as the fitted values increase. This indicates that the variance is likely not constant between treatments. Because of this, and given the results of the normal QQ-plot, chose to try a variance stabilizing transformation. Because the residuals fan out in Figure 8, and there were higher than the expected values on the right end of the QQ-plot, we chose a square-root transformation for our new model.

ANOVA Model (With Square-Root Transformation)

$$y^*_{ijkl} \text{ where } y^*_{ijkl} = \sqrt{y_{ijkl}}$$

```
                            Df Sum Sq Mean Sq F value Pr(>F)
oxy.route                    1    136     136   6.688 0.0100 *
add.uterotonics              1   7400    7400 364.055 <2e-16 ***
pph                          1   8482    8482 417.304 <2e-16 ***
oxy.route:add.uterotonics    1     59      59   2.900 0.0892 .
add.uterotonics:pph          1     69      69   3.380 0.0666 .
Residuals                  471   9574      20
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```

After transforming the response variable, the normal QQ-plot looks much better, as seen in Figure 9. The normality assumption is now reasonably met. The violations in constant variance appear to have been mostly resolved with our transformation, seen in Figure 10. The residuals are approximately centered around 0 and roughly fall within horizontal bands. While imperfect, we believe this assumption is now reasonably met under the square-root transformation and that the variances across different treatment levels are now roughly equal.

After obtaining a final model with our assumptions reasonably met, we wanted to confirm which oxytocin route was associated with higher total blood loss. We also wanted to get a sense of the clinical significance of different oxytocin routes, because while the result for this factor was statistically significant, there was not much visual evidence of a strong association in our EDA (see Figure 1). We formed a Tukey 95% confidence interval on the oxytocin route to examine it more closely.

```
$oxy.route
          diff       lwr      upr     p adj
IM-IV 1.067671 0.2564028 1.878939 0.0100071
```

95% Tukey CI for IM-IV on Square Root of Total Blood Loss = (0.2564, 1.8789)

Figure 7

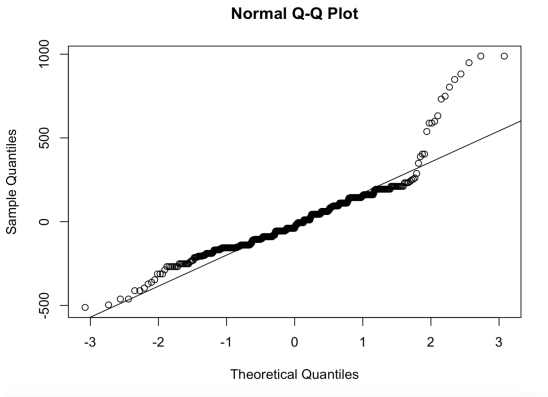


Figure 8

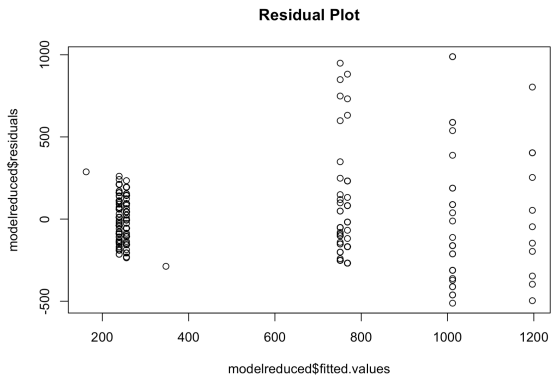


Figure 9

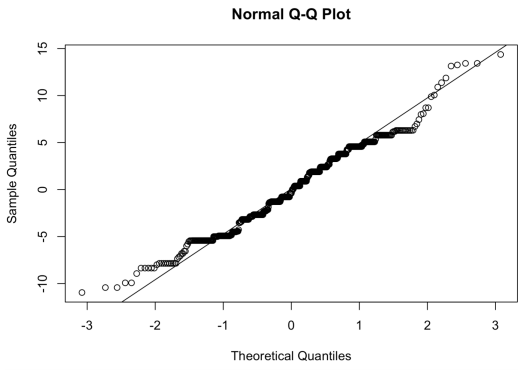
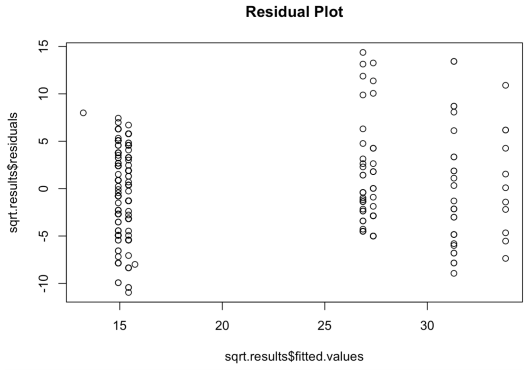


Figure 10



4. Conclusion

In conclusion, we found that all three factors were significant in predicting the square root of total blood loss after giving birth at a significance level of 0.05. The way oxytocin is administered to women in labor does appear to affect the (square root) of the total amount of blood loss after women have given birth. However, as seen in our confidence interval, intramuscular admission of oxytocin seems to have led to a rather small increase in total blood loss. Even if you were to square the interval to look at total blood loss rather than its square root, there is still a very small difference in excess blood loss with the intramuscular admission compared to intravenous admission. Our other two factors, whether pregnant women are given additional uterotonics and whether they have postpartum hemorrhaging, also appeared highly significant in their respective ANOVA F-tests, with p-values both below $2x10^{-16}$. However, these factors were not actually randomized in the original design, so we should not draw conclusions about their effect. It is likely that being able to randomize these factors may change the outcome due to possible confounding variables. This is an effect of the original experimental design set up, and to properly test their significance, we would also have to randomly assign these variables to participants. This, however, is unfortunately not feasible. Neither of our interaction terms included were significant at a level of 0.05. Although our analysis is not necessarily conclusive, our results do suggest that doctors should consider the use of additional uterotonics and the risk of postpartum hemorrhaging when preparing for and discussing with patients possible total blood loss. Most importantly, further research on the impact of oxytocin admission route on postpartum bleeding should be conducted. It appears that medical professionals might want to consider the way that they are administering oxytocin when trying to minimize a woman's amount of blood

loss in the birthing process, but the results from this analysis may only be statistically and perhaps not clinically significant.

5. Works Cited

1. World Health Organization. *WHO Recommendations Uterotonics for the Prevention of Postpartum Haemorrhage*. World Health Organization; 2018. Accessed May 8, 2022. https://apps.who.int/iris/handle/10665/277276
2. Gallos I, Williams H, Price M, et al. Background. In: *Uterotonic Drugs to Prevent Postpartum Haemorrhage: A Network Meta-Analysis.* NIHR Journals Library; 2019. Accessed May 8, 2022. https://www.ncbi.nlm.nih.gov/books/NBK537857/
3. Durocher J, Dzuba IG, Carroli G, et al. Does route matter? Impact of route of oxytocin administration on postpartum bleeding: A double-blind, randomized controlled trial. Rozenberg P, ed. *PLOS ONE*. 2019;14(10):e0222981. doi:10.1371/journal.pone.0222981

Data set accessed from:

https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/MDZRKU