A Study on Islanders to Determine the Effects of Morphine Consumption on Pain Threshold

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I. Abstract

The goal of medicine is to ease pain and relieve suffering. Oftentimes, however, pain is either lasting or severe enough to warrant therapeutic approaches. Doctors will then prescribe analgesics to help their patients. Unfortunately, the most commonly prescribed analgesic, opioids, have festered even greater pain in countries across the globe, spawning a public health emergency in the wake of hundreds of thousands of overdose deaths and shattered communities, and even inviting harder drugs into the hands of desperate and addled users. To better understand pain management, we chose to study morphine and its effect on perceived pain. Our study employed pressure algometry over the biceps in order to measure each subject's pain threshold. We surveyed 192 islanders and set up an experiment with a two-way randomized block design, which was analyzed using a two-way ANOVA with blocking. We blocked the islanders along age and gender and assigned three different treatments of various morphine doses (20 mg, 40 mg, and 60 mg) along with a 3 ml saline solution as the control. From the two-way ANOVA and boxplots, there was no statistically significant pain reduction elicited by any dosage of morphine compared to the saline control: all of the p-values were well above the significance level of 0.05, with the p-value of dosage injected at 0.2232 followed by gender and age with a p-value of 0.6664 and 0.3073 respectively.

II. Introduction

Morphine is the archetypal analgesic: the drug to which all other analgesics are compared. The term analgesic comes from the Greek word for "absence of pain." Unlike anesthesia, morphine does not induce a loss of sensation, much less consciousness; although its inventor did christened the drug with a name invoking the Greek god of dreams, Morpheus. Despite the cheerful, sunny repose the name suggested, morphine has morphed into a fevered nightmare: its chimeras oxycodone, heroine, and fentanyl suffocating the life out of many. What began as doctors' well-intentioned conviction to do no harm has become a pernicious evil on society. If the goal of prescribing an analgesic is to reduce pain, then it stands to reason that a patient's perception of pain following the injection of a drug must be studied in order for a physician to best weigh the trade-offs. By studying the gold-standard of pain management morphine, the aim is to better educate physicians on morphine's efficacy and how it compares to future, less-addictive therapies. Without properly studying morphine's effectiveness, physicians risk fomenting the next crisis without properly understanding the current one.

In October 2017, the US Government declared the opioid epidemic a public health emergency. The year before, 64,000 died from overdose; of which 42,000 were opioid deaths. For two-and-a-half decades, the opioid epidemic has strained hospitals, emergency rooms, and government facilities; all while claiming more lives unabated. The crisis' boundaries do not end on the United States' shores; it is a global epidemic afflicting Australia, Canada, the United Kingdom, and Europe. In the United States, the opioid epidemic has come in three waves: the first wave Oxycontin from 1999 to 2013, the second wave heroin from the 2010s, and the third

wave fentanyl from 2013 onward. The first two substances are derived from morphine, but the last one, fentanyl though similar to morphine, is synthetically made. Before international drug cartels captured the market for opioids, pharma companies namely Purdue Pharmaceuticals peddled Oxycontin, promising it would be less addictive by muting euphoric effects with its slow-release mechanism. Before long, through Purdue's aggressive marketing and corporate-funded research, opioid analgesics became the most prescribed class of therapeutics in the United States (during the first wave of the crisis, the volume of dispensed prescription opioids quadrupled) .

Prescription opioids have single-handedly caused the current opioid crisis, serving as a gateway drug, only to snowball into harder drugs like heroin and fentanyl. From Oxycontin's inception, many users have abused the drug: in fact, the original safety warning inadvertently told users how to abuse it: *OxyContin Tablets are to be swallowed whole, and are not to be broken, chewed, or crushed. Taking broken, chewed, or crushed OxyContin Tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone.* Afterwards when Oxycontin prices rose, the Sinaloa Cartel in Mexico saw an opportunity and converted their marijuana fields into poppy fields. This lowered the price of heroin by almost 75% leading to the second wave of the opioid crisis. The third wave of the opioid crisis was caused by fentanyl's sheer potency: some estimates say fentanyl is almost 30 to 100 times more potent than morphine.

Morphine's history dates back 200 years while its precursor opium is nearly a millennium old. Morphine was invented in the early-19th century shortly before the needle and the syringe. During the Civil War, morphine was widely used to treat soldiers, but it caused widespread addiction; in order to find a less addictive painkiller, heroine was invented though it was found to be more addictive. Finally, by the turn of the 20th century, governments began to regulate morphine. However, morphine remains the gold standard for treating chronic and acute pain; it is often used as a reference point to gauge other painkillers.

In light of the opioid crisis, and the massive loss and trauma it has wrought on families and the world at large, new drug therapies must be sought that can better manage pain without leading to withdrawal and debilitating addiction. In the United States alone, 25 million adults suffer from chronic pain, and many are rightfully wary of opioids. In order to better research new therapies, morphine and its effects must be taken into account, so that researchers can compare novel therapies with the current gold-standard–a gold-standard whose efficacy they must understand no less.

III. Methods

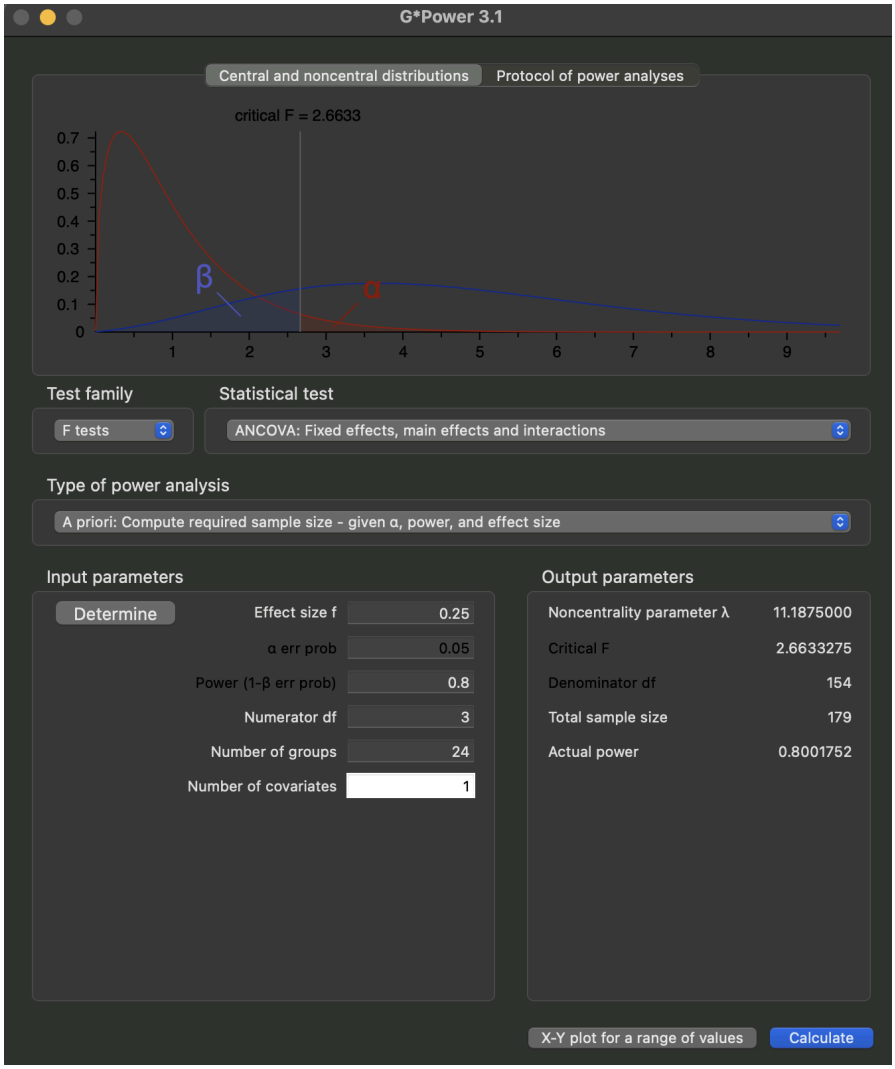
A. Participants

Our participants in this study will be the islanders from the website *Islands* who willingly participate in our study. We will balance the gender into half male and half female and divide the

ages into three groups, 18-25, 26-50, and 50+ years old. We will give each islander a unique ID and then use the sample function in R to select each islander into different dosages of the treatment randomly among different age groups. We also set a seed in the randomization step to ensure the data is consistent.

B. Sample Size Determination

We used G-Power to determine the sample size of this study. The effect size is 0.25 for a medium size, the power of 0.8 and the alpha is 0.05 as often used. Our highest degree of freedom is taken from the treatment with four levels and the number of groups is calculated as multiply four levels from the treatment, two levels from the gender, and three levels from the age. As a result, we need 179 participants as the sample size to establish 0.80 power. We rounded the sample size to 192 for it to be divisible by 24 combinations.

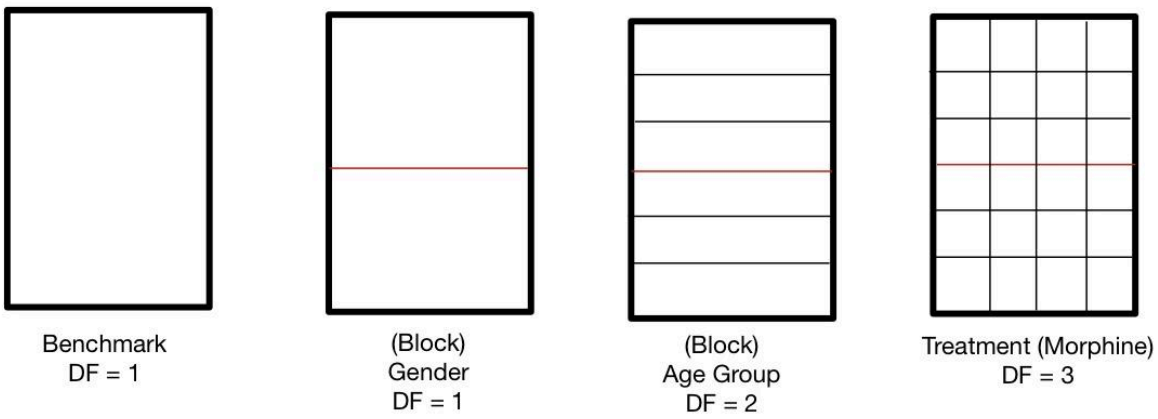


C. Design

This study will be set up as a Randomized Block Design with four different dosages of morphine as treatment, gender with two levels and age with three levels as blockings, and pressure pain threshold biceps as our response variable. Since we believe that gender and age group play a significant role in determining pain perception, we will block these variables to reduce the variability in our study. For the control group, Saline is used as a placebo since this injection has been chosen to be a "control placebo" in various drug effect studies.

Response Variables	Pressure Pain Threshold			
Treatment (Morphine)	Control (Saline 3ml)	20mg (Low)	40mg (Medium)	60mg (High)
Blocking (Gender)	Female		Male	
Blocking (Age)	18-25 (years old)		26-50 (years old)	50+ (years old)

The factors diagram is as follows:



D. Procedure

Step 1: Determine the sample size using G-Power with 0.80 power, 0.25 effect size, and alpha of 0.05.

Step 2: Find islanders who give us consent and make sure the gender is balanced between male and female.

Step 3: Measure each participant's pre-treatment pressure pain threshold biceps and record it in a spreadsheet.

Step 4: Randomize the dataset by using the sample() function to randomly assign each participant to one of the four treatment groups: Control, Low Dose, Medium Dose, or High Dose. We additionally set a seed to ensure the randomization is reproducible. To define the number of participants per block, we created a n_per_block variable to be used across the entire dataset with replace=TRUE. After each participant received a treatment assignment independently, the dataset was saved to a CSV file.

Step 5: Give each islander their assigned treatments (Saline 3mL, Morphine 20, 40, or 60mg) given in step 3 and measure/record their pressure pain threshold biceps again.

E. Instruments

To collect data for this study, we use the website *Island* (https://islands.smp.uq.edu.au/index.php) which has virtual islanders who can give us consent to participate in the study. Then using the available tasks, we measure our response variable through the Pressure Pain Threshold Biceps and our treatments through injections with Morphine 20mg and Saline 3mL tasks. We recorded our data which consists of PatientID, Age, Gender, PreTreament, Dosage, and PostTreatment for each participant in a spreadsheet. For analysis, we used R to perform the Diagnostic Plots, Tukey HSD, Box Plots, and ANOVA Table.

IV. Data Analysis

For the analysis, we loaded our data into R and computed the change in pain perception by calculating the difference between pre-treatment and post-treatment pain thresholds. We converted Dosage, Gender, and Age (AgeGroup) into factors to represent the treatment groups and blocking factors for the ANOVA model. We then used aov() to perform a two-way ANOVA without interaction, focusing on the main effects of Dosage, Gender, and Age on change in pain. To check model validity, we assessed the residuals diagnostic plots by using plot() to check for normality and constant variance. After we checked our assumptions, we interpreted the degrees of freedom, sum of squares, mean sum of squares, F-values, and p-values for each factor. In the visualization of these results, we created box plots using the boxplot() function to show the

distribution of pain changes across Dosage, Gender, and Age groups. These box plots allowed us to see how the response variable from Pre-Treatment to Post-Treatment (pain change) varied within each treatment group. We did not include interaction effects in this model because we used a randomized complete block design, which focuses on the main effects of each factor while managing the variability within the blocks.

V. Results & Discussion

A. Diagnostic Plots

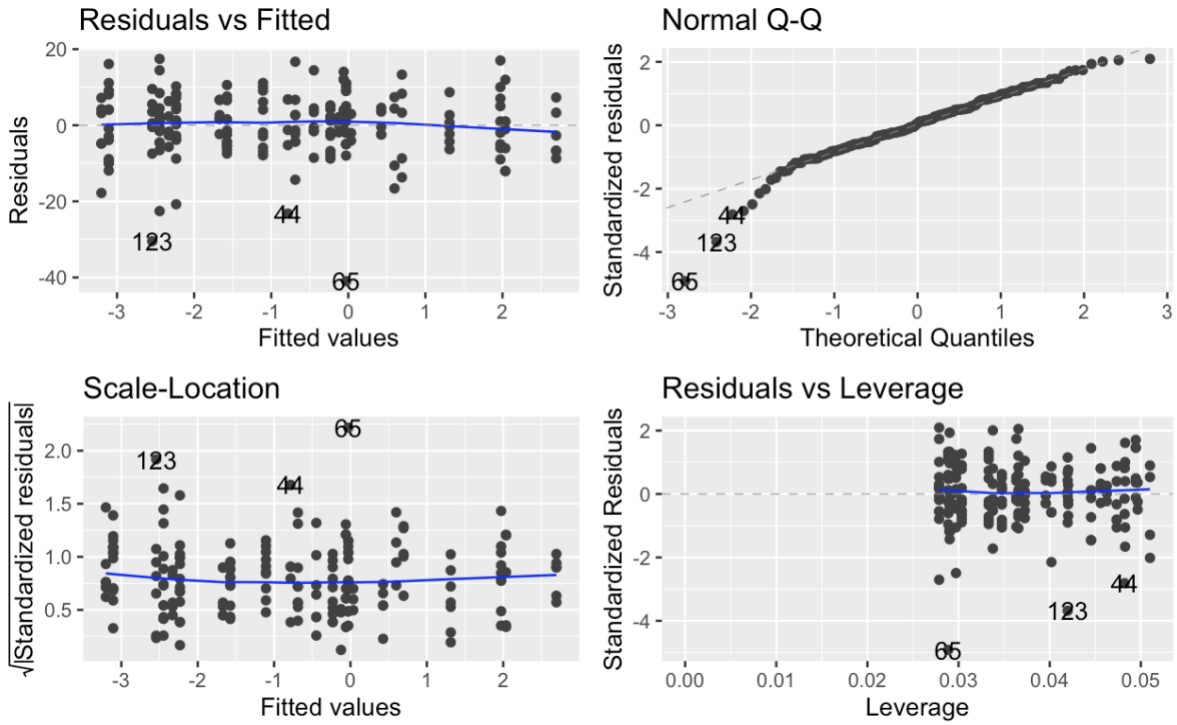


Figure 1: Diagnostic Plots for ANOVA Assumptions. The residuals vs. fitted plot reveals a lack of randomness, indicating potential non-linearity and unequal variance in the model. The normal Q-Q plot shows some deviations from normality, especially in the tails, suggesting non-normality of residuals. The scale-location plot highlights heteroscedasticity, with some uneven spread across fitted values. The residuals vs. leverage plot identifies a few influential points (e.g., observations 123, 44, 65) but none appear to be overly influential. These diagnostics suggest potential issues with the assumptions of normality and equal variance in the ANOVA model.

B. Tukey HSD

```
  Tukey multiple comparisons of means
    95% family-wise confidence level

Fit: aov(formula = PainChange ~ Dosage + Gender + AgeGroup, data = patients)

$Dosage
                            diff       lwr      upr     p adj
High.Dose-Control      0.7984694 -4.184184 5.781123 0.9757706
Low.Dose-Control      -1.7111460 -6.075823 2.653532 0.7400349
Medium.Dose-Control   -2.5506685 -6.804409 1.703072 0.4072323
Low.Dose-High.Dose    -2.5096154 -7.435159 2.415928 0.5507656
Medium.Dose-High.Dose -3.3491379 -8.176651 1.478375 0.2772706
Medium.Dose-Low.Dose  -0.8395225 -5.026223 3.347178 0.9542304
```

Table 1: Tukey's Post-Hoc Test for Pairwise Comparisons of Morphine Dosage. The table shows the differences in pain change between dosage groups along with their confidence intervals and adjusted p-values. None of the comparisons between dosage groups are statistically significant, as all p-values are greater than 0.05. The lack of significant differences between any dosage groups, including Control vs. High Dose, supports the conclusion that morphine dosage did not have a substantial effect on pain perception. These results align with the non-significant findings in the ANOVA.

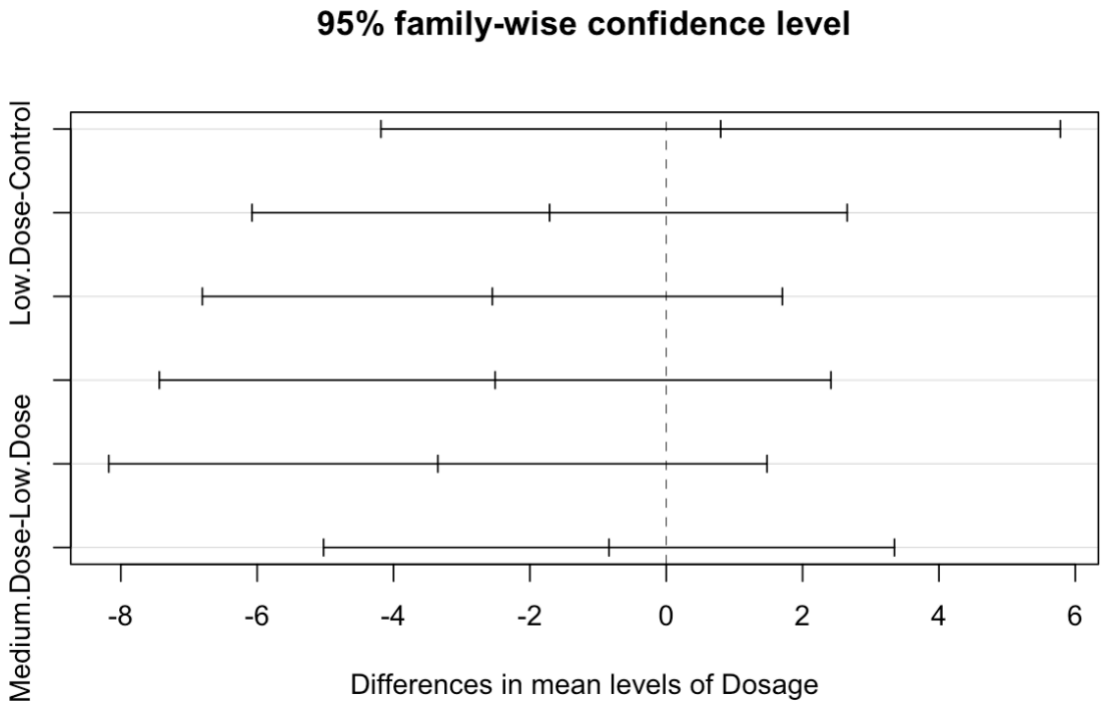


Figure 2: Tukey's Post-Hoc Comparison Plot for Morphine Dosage Levels. The plot illustrates the differences in pain change between dosage levels, with horizontal lines representing the 95% confidence intervals. None of the confidence intervals exclude zero, confirming that there are no significant differences between dosage groups, consistent with the non-significant ANOVA results. This visually reinforces that morphine dosage had no substantial effect on pain perception in this study.

C. Box Plots

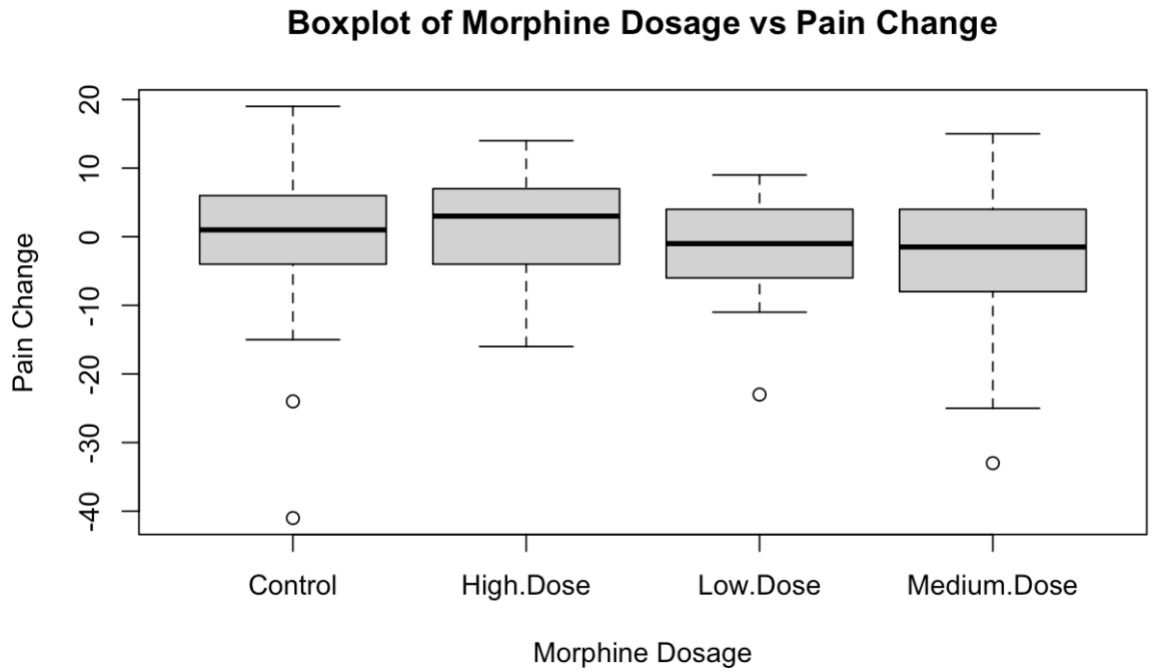


Figure 3: Box Plot Comparing Pain Change Across the Four Levels of Morphine Dosage. The black bar represents the median change in pain perception, while the box indicates the interquartile range (IQR). The whiskers extend to the most extreme data points within 1.5 times the IQR, with the potential outliers plotted as individual points. The outliers in the Low and Medium Dose groups suggest some variability in pain change. However, there is minimal difference in the median pain change between the dosage groups, indicating that morphine dosage had little to no effect on pain perception. This visually supports the non-significant results found in the ANOVA for morphine dosage.

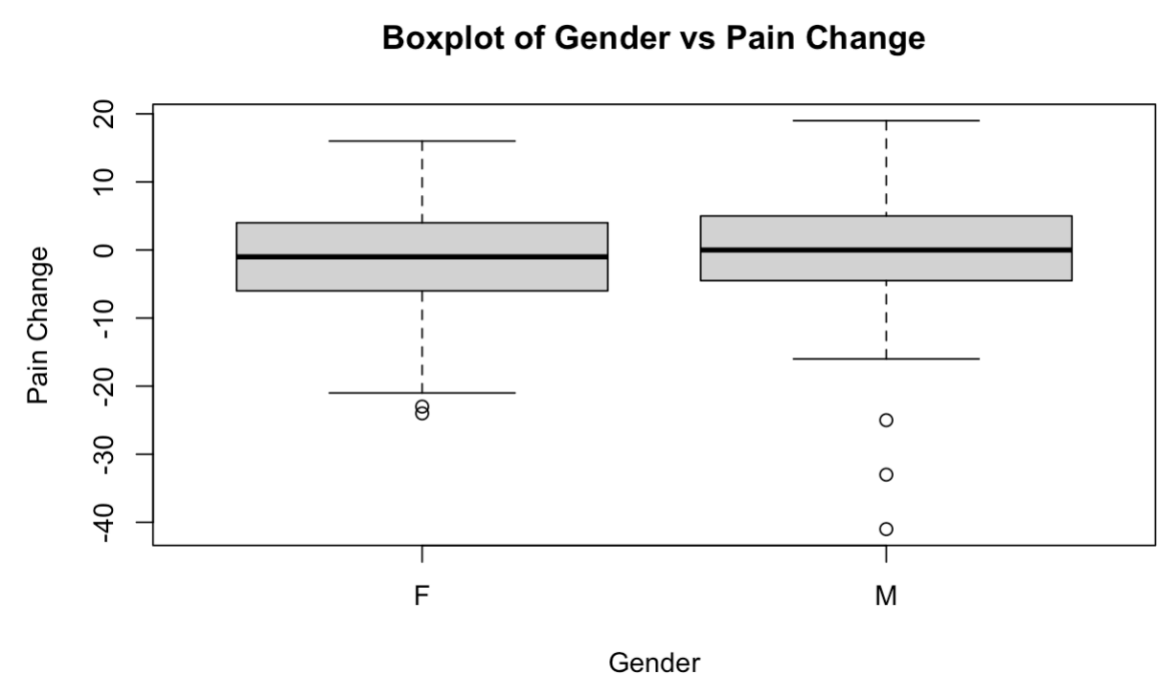


Figure 4: Box Plot Comparing the Distribution of Pain Change in Males and Females. The medians for both genders are both similar, and the interquartile ranges show comparable variation. There are a few outliers in the male group, indicating that some male participants experienced more extreme change in pain perception. However, overall, gender does not appear to have a significant effect on pain change, which aligns with the non-significant ANOVA results for gender.

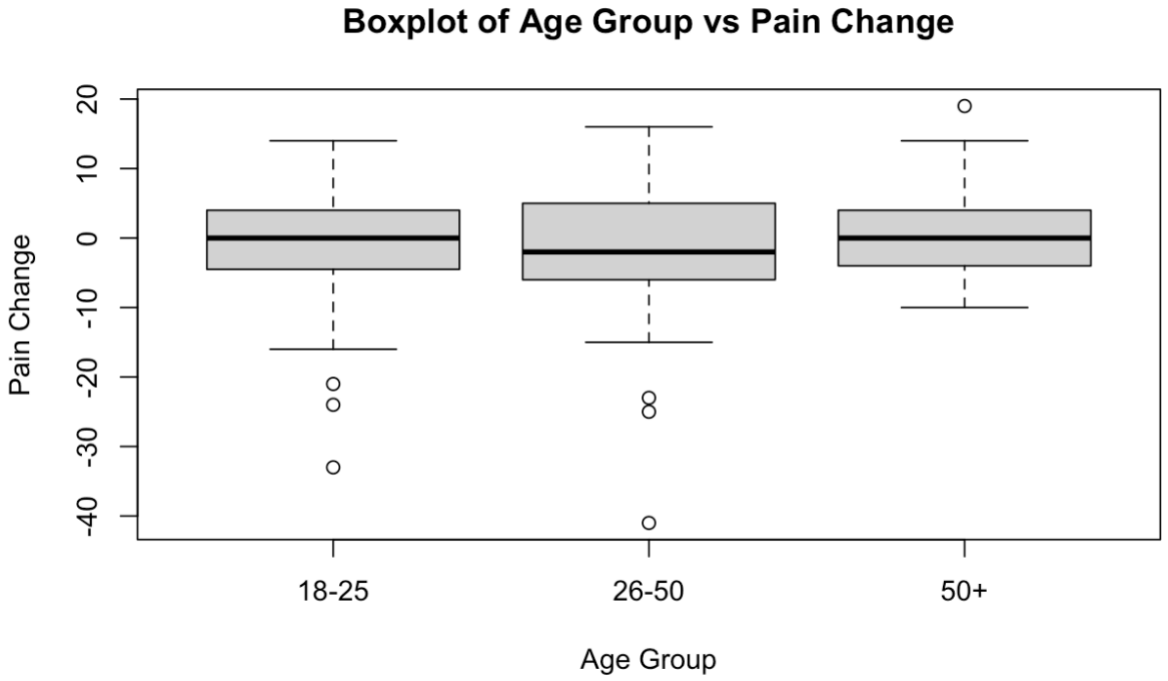


Figure 5: Box Plot Comparing the Pain Change Across Three Age Groups: 18-25, 26-50, 50+. The black bar in each box represents the median, and the box captures the interquartile range for each group. While the median pain change is similar across the age groups, the 18-25 group shows more variability with potential outliers at the lower end. The 50+ group exhibits the least variability. This suggests that age does not have a significant effect on pain change, despite the greater variability seen in the 18-25 age group further supporting the non-significant findings from the ANOVA.

D. ANOVA Table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Dosage	3	316.1	105.365	1.4737	0.2232
Gender	1	13.3	13.330	0.1864	0.6664
AgeGroup	2	169.8	84.912	1.1876	0.3073
Residuals	184	13155.5	71.497		

Table 2 : Two-way ANOVA Table with Blocking Factors. The ANOVA results show that Dosage (p=0.2232), Gender (p=0.6664), and AgeGroup (p=0.3073) did not significantly affect pain perception at the 0.05 significance level. This suggests that different morphine dosages (Control, Low Dose, Medium Dose, High Dose) did not result in notable changes in pain tolerance, and neither did Gender or AgeGroup. The large residuals in the sum of squares indicates unexplained variability, suggesting that other factors may be influencing the results.

VI. Conclusion

The purpose of our study was to evaluate the effect of morphine dosage in respect to pain perception attempting to visualize a correlation between our factors age, gender, and dosage on the human body. The data and analysis brought forward sought to prove or reject the belief that the shift in dosage for morphine, difference in age groups, or gender individually affect the perception of pain.

Following the desired goal of a 0.8 power, we decided to conduct our experiment on 192 individuals. Performing these treatments on the Islanders, we decided to use an ANOVA to produce accurate results in terms of significance for our factors. Through the results, none of the factors produced a proper level of significance towards pain tolerance. Our dosage factor which was divided into 4 treatments beginning from the control treatment to the high dose of morphine had no apparent change in its median. Depicted by the boxplots for the study, the medians had no evident shift in value. The goal was to easily distinguish between the 3 factors using these boxplots but each of our factors produced nearly the same result. Correlating the ANOVA results with this graphical data, we can conclude that these factors indeed had no apparent influence of pain tolerance.

The two initial factors being age and gender were blocked in our study in order to reduce variability in the results. Our initial ideology of these factors during the pretreatment was that age and gender would definitely have an impact on pain perception because of human nature. As one grows older, pain tolerance tends to decrease accompanied by gender which statistically demonstrates a difference in the ability to perceive pain. Our dosage factor was not taken into consideration as a blocking factor due to the belief that morphine tends to shift levels of pain

within the human body. By performing a pressure pain threshold test on biceps, we were able to transfer statistical data relating to the kPa value of these individuals into our study. Taking into account pain perception before and after these factors were utilized allowed for a proper distinction in determining effect.

The diagnostic plots also support our results produced in the anova table. As visualized in the normal Q-Q plot, there is a lack of linearity within the plotted points. There appears to be a skewed distribution within the plot as well as outliers demonstrating this lack of normality in distribution. Points in the initial residuals plot are set in a pattern format instead of a scattered distribution which is an additional point in proving an unideal model for our study. The plots show an evident fault in correctness allowing us to use these graphical outputs and continue to add credibility in the produced work.

As covered in the TukeyHSD model, the differences in means for the factors appears to be minimal. The p-adjusted values for every group is higher than the 0.05 significant value proving the means between the groups are not statistically different. None of the presented confidence intervals include 0 within their bounds which portrays the lack of significance in between the factor groups. As a whole, the multiple graphical outputs as well as statistical functions resulted in properly refuting the claim initially made in terms of pain perception being affected by any of the factors studied. There was no specific goal in proving either a positive or negative relationship but instead observing whether the factors were inefficient or efficient towards the desired response variable of pain tolerance. Taking this into consideration, the possibility of pain tolerance being affected can still take place through the use of other factors which when tested can produce evident change.

VII. References

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