Does the dosage of pre-operative steroids impact hospital length of stay after pituitary adenoma resection?

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The Question

Does the dosage of pre-operative steroids impact hospital length of stay after pituitary adenoma resection?

Disclaimer: This project analyzes simulated data. The questions and hypotheses are real, but the results and conclusions are not.

Sub-Field of Biology:

Endocrinology (Physiology)

Rationale and Background:

Pituitary adenomas are tumors that arise from the pituitary gland, a small gland located at the base of the brain that is responsible for producing and regulating hormones that control various bodily functions. The hormonal imbalances arising from the tumor can lead to several dire symptoms including growth disturbances, metabolic abnormalities, reproductive dysfunction, headaches, as well as hypopituitarism. Clinically evident pituitary adenomas occur in approximately 1 in 1100 people and can be further complicated by syndromes of hormone excess as well as visual field defects and hypopituitarism from mass effect in large tumors. These visual disturbances are caused by the compression of surrounding structures by pituitary adenomas which can even be as harmful as blindness. Additionally, patients suffering from hypopituitarism caused by pituitary adenomas have an approximate twofold increase in all-cause mortality in comparison to the general population. If we can ensure proper management of pituitary adenomas and make timely interventions we can thus ensure that any such problems are diagnosed faster and appropriately dealt with in order to prevent such dire consequences like morbidity and mortality. If these pituitary adenomas spread to other regions of the body, it can also lead to poor prognosis. Management of the tumors, however, can prevent the harmful effects from escalating and tumor from metastasizing. Transsphenoidal pituitary surgery (TSS) is first-line therapy for all pituitary adenomas requiring treatment except for prolactinomas, which are generally treated medically. Patients with Cushing disease or acromegaly require surgery. Less commonly, a craniotomy is necessary to resect a large, invasive, and/or aggressive tumor. Radiation therapy may be used after surgery and medical therapy for patients with somatotropinomas, prolactinomas, or thyrotropinomas.

Examples of relevant literature

Review article title:

Diagnosis and Management of Pituitary Adenomas A Review

URL:

https://doi.org/10.1001/jama.2023.5444 (https://doi.org/10.1001/jama.2023.5444) (https://doi.org/10.1001/jama.2023.5444 (https://doi.org/10.1001/jama.2023.5444))

Abstract:

Importance Pituitary adenoma is the second most common primary brain tumor. Perioperative hydrocortisone has been used for decades to avoid postoperative adrenal insufficiency. Recent studies suggest that withholding perioperative hydrocortisone may be safe for patients with an intact hypothalamus-pituitaryadrenal (HPA) axis. Objective To assess the safety of withholding hydrocortisone during the perioperative period of pituitary adenoma surgery for patients with an intact HPA axis. Design, Setting, and Participants A parallel-group, triple-masked, noninferiority randomized clinical trial was conducted at Peking Union Medical College Hospital from November 1, 2020, to January 31, 2022, among 436 patients aged 18 to 70 years with an intact HPA axis undergoing surgery for pituitary adenomas. Interventions Hydrocortisone supplementation protocol (intravenous and subsequent oral hydrocortisone, using a taper program) or no-hydrocortisone protocol. Main Outcomes and Measures The primary outcome was the incidence of new-onset adrenal insufficiency (morning cortisol level, <5 μg/dL with adrenal insufficiency–related symptoms) during the perioperative period (on the day of operation and the following 2 days). The secondary outcome was the incidence of adrenal insufficiency in postoperative month 3. Analysis was on an intention-to-treat basis. Results Of the 436 eligible patients, 218 were randomly assigned to the hydrocortisone group (136 women [62.4%]; mean [SD] age, 45.4 [13.0] years) and 218 to the no-hydrocortisone group (128 women [58.7%]; mean [SD] age, 44.5 [13.8] years). All patients completed 3-month postoperative follow-up. The incidence of new-onset adrenal insufficiency during the perioperative period was 11.0% (24 of 218; 95% CI, 6.9%-15.2%) in the no-hydrocortisone group and 6.4% (14 of 218; 95% CI, 3.2%-9.7%) in the hydrocortisone group, with a difference of 4.6% (95% CI, –0.7% to 9.9%), meeting the prespecified noninferiority margin of 10 percentage points. The incidence of adrenal insufficiency at the 3-month follow-up was 3.7% (8 of 218) in the nohydrocortisone group and 3.2% (7 of 218) in the hydrocortisone group (difference, 0.5%; 95% CI, –3.0% to 3.9%). Incidences of new-onset diabetes mellitus (1 of 218 [0.5%] vs 9 of 218 [4.1%]), hypernatremia (9 of 218 [4.1%] vs 21 of 218 [9.6%]), hypokalemia (23 of 218 [10.6%] vs 34 of 218 [15.6%]), and hypocalcemia (6 of 218 [2.8%] vs 19 of 218 [8.7%]) were lower in the no-hydrocortisone group than in the hydrocortisone group. Lower preoperative morning cortisol levels were associated with higher risks of the primary event (<9.3 μg/dL; odds ratio, 3.0; 95% CI, 1.5-5.9) and the secondary event (<8.8 μg/dL; odds ratio, 7.8; 95% CI, 2.6-23.4) events. Conclusions and Relevance This study found that withholding hydrocortisone was safe and demonstrated noninferiority to the conventional hydrocortisone supplementation regimen regarding the incidence of newonset adrenal insufficiency among patients with an intact HPA axis undergoing pituitary adenomectomy.

Relevant original research article title:

Safety of Withholding Perioperative Hydrocortisone for Patients With Pituitary Adenomas With an Intact Hypothalamus-Pituitary-Adrenal Axis A Randomized Clinical Tria

URL:

https://doi.org/10.1001/jamanetworkopen.2022.42221 (https://doi.org/10.1001/jamanetworkopen.2022.42221) (https://doi.org/10.1001/jamanetworkopen.2022.42221 (https://doi.org/10.1001/jamanetworkopen.2022.42221))

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Hypotheses

The Biological Hypothesis:

Steroids have a dose dependent impact on the immune system and as such can either reduce or suppress the body's response to stress, such as during surgery, which in turn can modify a patient's length of stay in the hospital.

The Biological Prediction:

Steroids will reduce post-operative inflammation and therefore allow earlier recovery and reduce length.

A Statistical Alternative Hypothesis:

There is a correlation between dosage of pre-operative steroids and hospital length of stay after pituitary adenoma resection.

A Statistical Null Hypothesis:

There is no correlation between dosage of pre-operative steroids and hospital length of stay after pituitary adenoma resection.

Experimental Design

The study investigates the impact of pre-operative steroids on hospital length of stay after pituitary adenoma resection is of an observational design. It aims to observe and analyze the relationship between the dosage of pre-operative steroids and the length of hospital stay in patients who have undergone pituitary adenoma resection. Since it is an observational study, methods such as randomization and blocking are not applicable in this context. We will simply collect data retrospectively from patients' medical records instead of actively dividing patients into control and experimental groups. We will focus on observing adult patients undergoing pituitary adenoma resection for any cause. The dosage of preoperative steroids by patients are dependent on external factors such as a person's specific medical condition or upon their physician's discretion. Controls in this study can be implemented to minimize confounding variables and strengthen the validity of the findings. Although our study does not have specific positive controls, the negative controls of this study would be those patients who did not receive preoperative steroids. This groups can be used as a reference to compare the outcomes with those patients who did receive the preoperative steroids. Including these controls helps to isolate the specific effect of preoperative steroids on hospital length of stay and identify any confounding factors. Blinding may not be applicable in this observational study as the assignment of patients to receive preoperative steroids or not is determined by their medical condition and the discretion of the treating physicians, not us (the researchers). However, blinding can be implemented during the phase of data collection and analysis to minimize bias. Those of us collecting data from the patients' medical records should be blinded to the patients' treatment status as well as medical conditions to ensure that the data is collected objectively. Also, whilst we are analyzing the data, we must be blinded to the patients' treatment status in order to reduce any potential bias in the interpretation of results. In conclusion, the experimental design for this study is an observational design that aims to observe and analyze the relationship between the dosage of pre-operative steroids and hospital length of stay after pituitary adenoma resection. Controls can be implemented to minimize confounding variables. While randomization, blocking, and stratification are not applicable in this context, we will implement blinding during data collection and analysis to reduce any potential bias.

Sampling Design:

Since, we are conducting an observational study, and the data is collected from medical records, we will utilize a convenience sampling approach. Patients undergoing pituitary edenoma resection will be consecutively selected, and information regarding the dosage given to them will be taken from their medical records. The sample size is 500 patients. Although, convenience sample can introduce potential biases and limitations to the study, the feasibility of random sampling is difficult to estimate the given the criteria that each of the patients must meet in order to be considered for the study, that is, to be undergoing pituitary edenoma resection and have variying dosages to other patients in the study.

Explanatory and Response Variables:

Due to the limitations of the provided data set, explanatory and response variables are difficult to explore in this simulated study. However, in a real life study, the variables we would consider are age, gender, and race since these are all variables that can impact the length of a patient's recovery.

Sample size:

500 patients

Alpha:

The alpha chosen for this study is 0.05, which means a 5% level of significance. This is a threshold value often used in statistical analysis and hypothesis testing. ———————————————————————————

Data Analysis Plan

[Input your answer and delete these brackets]

The primary statistical analysis of this study is a correlation analysis. Correlation analysis is suitable for this study because we want to examine the relationship between preoperative steroids (independent variable) and length of hospital stay (dependent variable). Correlation analysis makes it possible to assess the strength and direction of the relationship between these two variables. By calculating the correlation coefficient, we can quantify the degree of association between our chosen variables. Although, regression analysis is also a viable choice for statistical analysis in such a case, correlation is more suitable for this study due to the nature of our independent variable. In our study, the dosage of preoperative steroids is a continuous variable.

Assumptions and Exploratory Data Analysis (EDA)

There are several assumptions needed in order to perform a correlation analysis. The relationship between the variables must be linear, each of the observations must be independent, and homoscedasticity: the variability of the dependent variable is consistent. Another necessary assumption is that the dependent variable, in our case, the hospital length of stay must be normally distributed, and that there are no outliers, since outliers can heavily influence the correlation coefficient. Such assumptions can be ensured through eyeball tests on scatter plots, normality tests and residual plots. If any of our tests do not meet these conditions, we can use transformations, or other methods to ensure that these conditions are met. We can use the R ‘plot()’ function to generate plots, the ‘ks.test()’ for normality, and ‘boxplot()’ to check for outliers. Several other methods can be used for transformation such as the ‘log()’, ‘sqrt()’, etc.

```
data <- read.csv("refaisal.csv")
head(data)
```

```
##   X pre.operative.steroids
## 1 1                27.20189
## 2 2                15.80531
## 3 3                26.56135
## 4 4                30.83722
## 5 5                26.91488
## 6 6                19.27898
##   Hospital.length.of.stay.after.pituitary.adenoma.resection
## 1                                                   2.720715
## 2                                                   3.433553
## 3                                                   3.114186
## 4                                                   2.521327
## 5                                                   3.104684
## 6                                                   2.828390
```

```
dosage <- data$pre.operative.steroids
length_of_stay <- data$Hospital.length.of.stay.after.pituitary.adenoma.resection

variable <- data$pre.operative.steroids
ks_result <- ks.test(variable, "pnorm", mean(variable), sd(variable))
```

Interpretation of EDA:

Since the data is already in a tidy format, there was not much manipulation needed in the data set itself. It is important to note that one of the assumptions needed for a correlation analysis is nomrality in our data. In order to test for this, we used the Kolmogorov-Smirnov test. We recieved a p-value of 0.9117 from this test, which leads us to accept the null-hypothesis indicating that our data is normal. Since, our data is already normal, we did not have to implement any data transformations. Additionally, our data does contain outliers. Since this is a simulated study, we have no information regarding errors in data collection, so, for now, all data points in the study are valid and we cannot eliminate any data point even if it deviates from the norm.

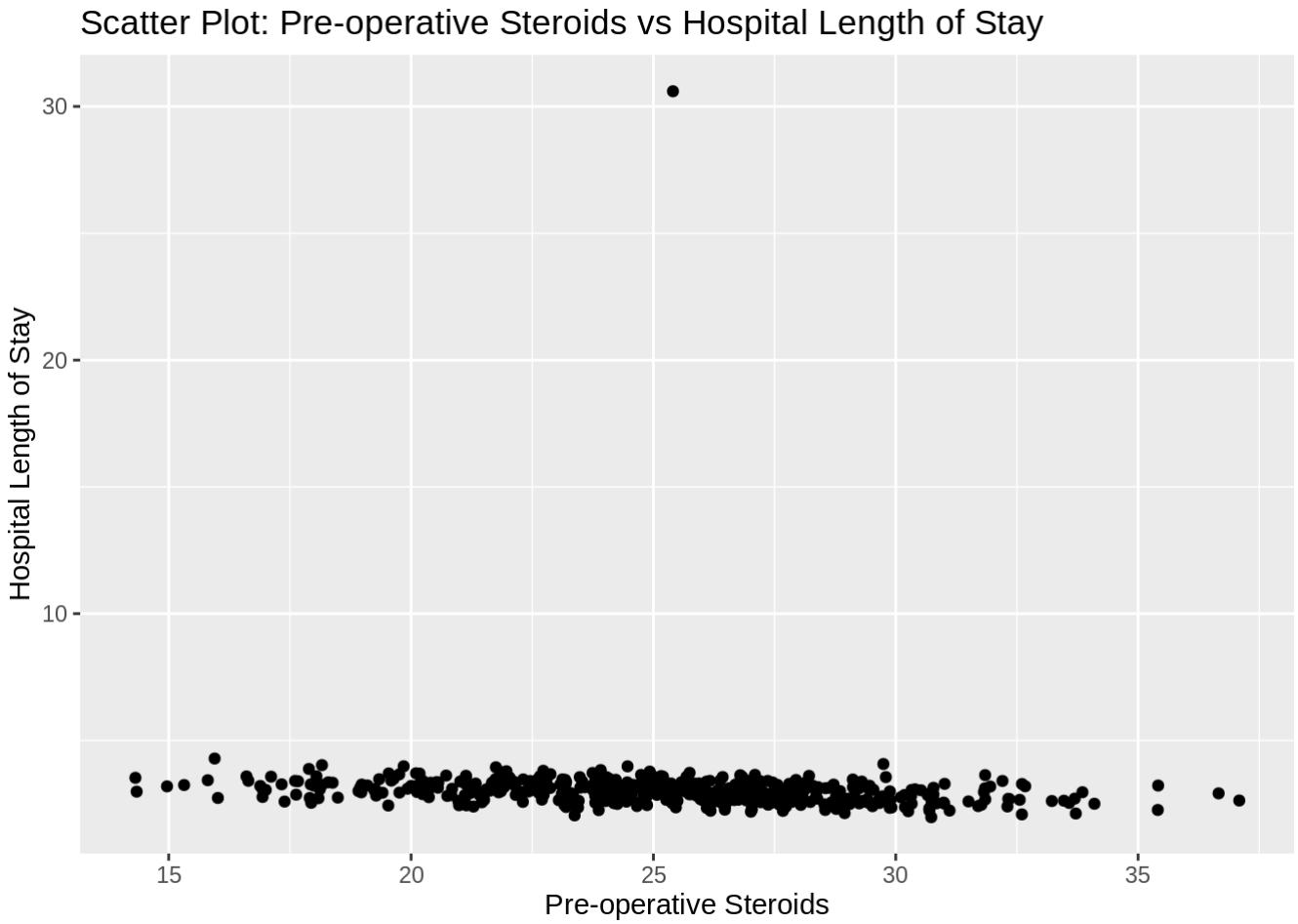
Primary Statistical Analysis

```
correlation <- cor(dosage, length_of_stay)

print(correlation)
```

```
## [1] -0.1060236
```

Data Visualization

```
library(ggplot2)

# Create the scatter plot
ggplot(data, aes(x = pre.operative.steroids, y = Hospital.length.of.stay.after.pituit
ary.adenoma.resection)) +
  geom_point() +
  labs(x = "Pre-operative Steroids", y = "Hospital Length of Stay") +
  ggtitle("Scatter Plot: Pre-operative Steroids vs Hospital Length of Stay")
```



Conclusions

Based on our analysis, the available data provides limited evidence for an association between preoperative steroid dosing and length of hospital stay after pituitary adenoma resection. The correlation analysis conducted showed a weak inverse correlation between the variables, with a correlation coefficient close to zero. This indicates that there is no strong association between preoperative steroid dose and length of hospital stay.

The scatter plot further supports this conclusion as there are no clear patterns or trends. The data points appear to be clustered around the same area with one outlier value, with a hosipital stay of just above 30 days. However, since this is only one occurence out of the five hundered sample patients, the occurence is disregarded. The weak trend with a correlation coefficient of -0.1060236 suggests that the dosage preoperative steroid dose may not have a significant effect on thelength of hospital stay for pituitary adenoma resection. However, it is still important to consider the limitations and uncertainties associated with these findings. Since this is a simulated stidy, the lack of contextual information and lack of control variables also make it difficult to determine causality between variables. Other factors, such as the explanatory and response variables mentioned above as well as perhaps the severity of the adenoma or individual patient characteristics, may also influence the duration of hospitalization, but these were not taken into account in the analysis.

Therefore, we interpret the results with caution.The results of this limited data set do not provide conclusive evidence on the effect of preoperative steroid dosing on length of hospital stay. A larger and more diverse data set and a well-designed study that controls for confounding variables, such as age, sex, and socio economic status are needed to obtain stronger and more reliable results.

Future Directions

The current analysis did not consider several confounding variables that could influence the association between preoperative steroid dosing and length of hospital stay. These include age, tumor characteristics, surgical complications, and postoperative care. In the future, the study design and data collection process could be improved to address these variables as well.

A prospective controlled study with a larger sample size would allowbetter control of confounding. Randomization of patients to different treatment groups, including different doses of steroids, would ensure comparability between groups. In addition, performing multivariate analysis with specific factors and conditions of each group in mind could help us eliminate external variables and analyze the tru independent effect of steroids on length of hospital stay in specific subgroups.

Collecting additional patient data such as their medical history and emographicscould also help improve the validity of the study. These improvements would provide a more comprehensive understanding of the relationship between preoperative steroid dosing and length of hospital stay in patients undergoing pituitary adenoma resection and perhaps even provide findings very different to the ones we presently did.

Citations

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