Effect of Four Treatments on QTcM

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Abstract: This analysis paper considers the effect of a four treatments on QTcM. QTcM is a heartbeat interval typically measured during an electrocardiogram. And we consider the multiple linear models and comparing the change of QTcM across the four treatment groups. The results could be show that with 95% confidence, none of the treatment groups experienced a significant change in QTCM over the course of the two-week trial.

1. Aim of the project:

In this project will discuss the effects of different for four treatments on QTcM. interval in patients. The QT interval is a measure in milliseconds of a certain portion of one's heartbeat. A QT interval that is longer than normal is very dangerous and may lead to cardiac arrest. We are concerned with QTcM, which is an individualized correction of the QT interval that takes heart-rate into account.

2. Description of the data set:

We have the clinical trial was designed to assess the treatment effects on ECG. variables for 72 patients who are completely randomized. There are 70 males and 2 females and the age is between 19 and 59. The patients divided to four groups (0, 1, 2, and 3) of treatment which was randomly selected. The treatments level are placebo, active control, low dose, high does, respectively. QTcM interval was selected for 3 days, one day before the treatment (day -1), one day after (day 1) and in day fourteenth (day 14), by the times. On day before the treatment, QTcM was measured twenty times. One day after began the treatment and on day fourteen, QTcM was measured nine times. The number of observations is 1439 for the QTcM, and the number of observation per the patient is 38, no missing data.

3. Methodology:

We have multiple observations per patients, and then we will use the linear mixed models. Regard to the three different days in data (day -1, day 1, and day 14). The first model will be describing data from day -1 and day 1, and the second mode will be describing data from day -1 and day 14. We will be done on the baseline data from day before began the treatment (day -1), but this will only be used to help us build the other two models. We want to construct our linear mixed models; we want to select which effects are necessary in the models. Then, we will run a general linear model with all class-by-covariate interactions and eliminate the interactions that are insignificant (at alpha=.05). After that, we want to test various covariance structures. When we have the repeated measures for patient, then we will run our model with all appropriate covariance structures and use the lowest AIC criterion will be considered "best". The different covariance structures could change the significance level of certain effects, and then we will treat our selection process as a repeated process. From the model effects and covariance structures, we decided for both models, we will test the model assumptions. The first assumption is the residuals are independent of each other and are normally distributed with constant variance. The second assumption is the regression relationship between the dependent variable and the predictors is linear. Then, we want to test the two assumptions. The first assumption tests by running standard diagnostics on the residuals, plotting the residuals against the ordered patient numbers, and examining a Q-Q plot and histogram of the residuals. The second assumption tests by plotting the residuals against the dependent variable, each of the predictors and checking for noticeable trends. If the assumptions are not satisfied, the variable transformations will be considered in order to correct the problem. Otherwise, if the assumptions are satisfied, we want to compute least-square mean estimates and run paired t-tests to decide which treatments had a significant effect on QTcM. We will be using SAS program to figure out the effect of treatments on QTcM at a significance level of .05 when making decisions based on these t-tests. We will default to the "between-within" method of estimating degrees of freedom.

4. Result:

First, we run general linear models on two datasets one day before and after the treatment (day -1 and day 1), and one before and day fourteen (day -1 and day 14). After that, we included the effects: PTSEX (patient sex), DAY (excluded in the baseline model), HOUR, GROUP (treatment group), and PTAGE (patient age), as class-by-covariate interactions. Which we found that for all three datasets, the significant effects were HOUR, GROUP, PTAGE, and GROUP*PTAGE. We have just two females in the study; we decided to drop off the gender (PTSEX) effect, regardless if it was significant. The partial F-tests for each model as presented in (TABLE 1). We calculated the mean QTcM for each group in the baseline data; we found that each group seemed to differ significantly (TABLE 2). If a significant difference existed between the treatment groups at the beginning of the study, then we can not do to directly compare the treatment groups at the end of the study. We dealing with this problem, when we subtracted the baseline mean QTcM of each treatment group from each observation within that group. We were centering the data at 0. After the data centered and with the preliminary model effects chosen, we check the covariance structures. We had run linear mixed models, we accounted for all logical covariance structures based on our data. We compared each model's AIC (TABLE 3). Then, we had at different covariance structures for each dataset. For the one before and after the treatment (day -1 and day 1 data), we compound symmetry. Each patient as the block, we had the lowest AIC. The covariance structure gave that a random error term. The error term this correlated the observations within each patient (TABLE 4). For one day before and day fourteen began the treatment (the day -1 and day 14) data, we had heterogeneous compound symmetry, with patient*day (PTNO*DAY) as the block, and

we had the lowest AIC. The covariance structure gave that a random error term. The twenty error terms, this correlated all observations at each hour across both days (TABLE 5). We had chosen the covariance structures; the model effects that we had chosen earlier remained highly significant in both models. The means of QTcM that we needed to see the effect before and after the treatment, we had the estimates of QTcM for each group in both models. We used to estimates with an "LSMEANS" statement in SAS program. We wanted to include the group*day interaction in both models. Even though this is insignificant in both models, then we wanted to reduce AIC for both models. The process, we created and examined various diagnostic plots for each model, then we looked at histograms and Q-Q plots of the residuals. And the plots of the residuals against the time-ordered observations. We found that, the histograms appeared unimodal, symmetric, and look normal. For the Q-Q plots appeared to mimic the straight line x=y, for the time-ordered residuals exhibited no noticeable trends (TABLE 6). After that the residuals are independent and normally distributed with constant variance. Form these plot, we decided that a linear model was appropriate and that our second assumption was satisfied (TABLE 7). We proceeded with pairwise t-tests to look for significant differences across treatment groups, which was significant interaction with Age*Group (PTAGE*GROUP). We took estimates at various ages to fully interpret the treatment effect. For the one day before and after (day -1 and 1) model, the all information we want contrasts for model (TABLE 8). The age which is between 19 and 59 and the median of 37, we decided to probe at ages 25, 37, and 50 to get an idea of the treatment effect for those ages.

1. At age 25, we found that the significant was at the treatment "the high dose" increased QTcM significantly more than the treatment "low dose".
2. At age 37, we found that no treatments significantly with the others.
3. At age 50, we found that the treatment "low dose" increased QTcM significantly more than the treatment "high dose".

The second model, the one day before and day fourteen (day -1 and day 14) data gave that good of the treatment effects.

1. At age 25, we found that the placebo increased QTcM significantly more than the treatment "low dose", and the treatment "high dose" significantly increased QTcM more than all of the other treatments.
2. At age 37, we found that there are no significant differences.
3. At age 50, we found that the active control increased QTcM significantly more than the treatment "high dose". The treatment "low dose" increased QTcM significantly more than the treatment "high dose" and the placebo.

5. Conclusion

we consider that the fact that increasing the QT interval is associated with (possibly fatal) heart problems, we can note that the high dose of the drug increased QTcM for the younger patients the most (near age 25), and the active control and the treatment "low dose" increased QTcM for older patients the most (near age 50). All of this occurred while nothing significant happened to the QTcM of the patients near the median age of 37. If we are conducting this trial to test for adverse reactions (i.e. a limited increase of QTcM), there is a chance that the drug may satisfy the FDA's requirements.