

Reanalysis of 03-Zecca

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Reference

Zecca, E., Brunelli, C., Centurioni, F., Manzoni, A., Pigni, A., & Caraceni, A. (2017). Fentanyl Sublingual Tablets Versus Subcutaneous Morphine for the Management of Severe Cancer Pain Episodes in Patients Receiving Opioid Treatment: A Double-Blind, Randomized, Noninferiority Trial. *Journal of Clinical Oncology*, 35(7), 759–765. <https://doi.org/10.1200/JCO.2016.69.9504>

Notes from reading methods section

- Dependent variable: Pain intensity (PI) (average across follow-ups, AVP_30)
- Independent variable: treatment group
 - Fentanyl sublingual tablets FST (n=57, 1 from 58 was excluded)

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- Subcutaneous morphine SCM (n=56)
- Covariate: baseline PI
- Design: 1-way ANCOVA with group as IV and baseline PI as covariate

Reading data

Data is loaded, reshaped if necessary, and factors are specified.

```
PATH = file.path(path.expand("~"), "Data", "ancova") # ancova project folder
data = read_excel(file.path(PATH, "dataPrimaryStudies", "03-Zecca", "03-Zecca.xls"))
data = as.data.frame(data)
data$tratt = as.factor(data$tratt)
```

Descriptives

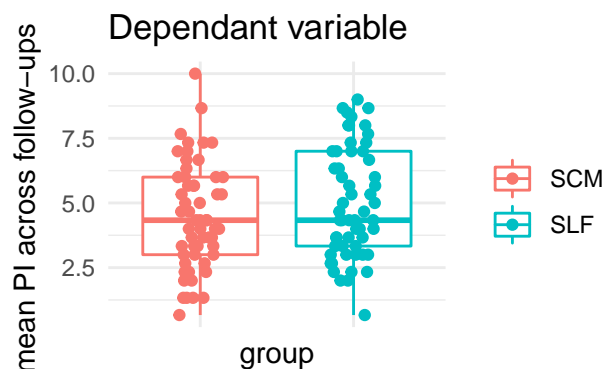
Dependant variable

Number of samples and mean (SD) in levels of the independent variables.

```
tab.dv = array(NA, dim=c(2,3))
tab.dv[,1] = levels(data$tratt)
tab.dv[,2] = summary(data$tratt)
tab.dv[,3] = tapply(data$pain_mea_30, data$tratt,
  function (x) sprintf("%.2f (%0.2f)", mean(x), sd(x)))
colnames(tab.dv) = c("group", "n", "mean (SD)")
print(tab.dv)
```

```
##      group n    mean (SD)
## [1,] "SCM" "56" "4.48 (2.03)"
## [2,] "SLF" "57" "4.97 (2.12)"
```

```
ggplot(data, aes(y=pain_mea_30, x=tratt, color=tratt)) +
  geom_boxplot() +
  geom_point(position = position_jitter(width = 0.15, height = 0)) +
  theme_minimal() +
  theme(axis.text.x = element_blank(), legend.title = element_blank()) +
  xlab("group") + ylab("mean PI across follow-ups ") + ggtitle("Dependant variable")
```

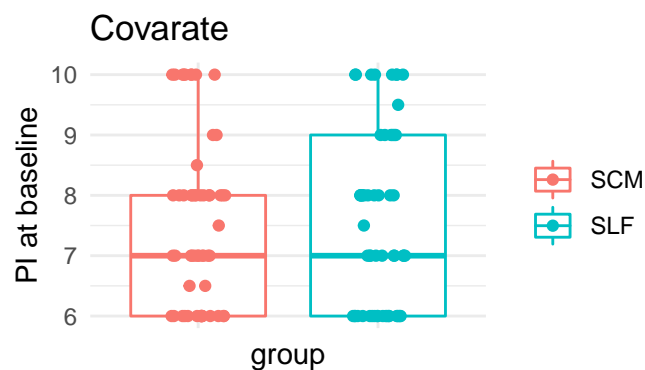


Covariate(s)

```
tab.cv = array(NA, dim=c(2,3))
tab.cv[,1] = levels(data$tratt)
tab.cv[,2] = summary(data$tratt)
tab.cv[,3] = tapply(data$pain_mea_bas, data$tratt,
                     function(x) sprintf("%.2f (%0.2f)", mean(x), sd(x)))
colnames(tab.cv) = c("group", "n", "mean (SD)")
print(tab.cv)
```

```
##      group n    mean (SD)
## [1,] "SCM" "56" "7.54 (1.39)"
## [2,] "SLF" "57" "7.53 (1.45)"
```

```
ggplot(data, aes(y=pain_mea_bas, x=tratt, color=tratt)) +
  geom_boxplot() +
  geom_point(position = position_jitter(width = 0.15, height = 0)) +
  theme_minimal() +
  theme(axis.text.x = element_blank(), legend.title = element_blank()) +
  xlab("group") + ylab("PI at baseline") + ggtitle("Covariate")
```



Main analysis ANCOVA

```
# Orthogonal contrasts
contrasts(data$tratt) = contr.helmert(2)

fit.ancova = aov(pain_mea_30 ~ pain_mea_bas + tratt, data = data)
result = Anova(fit.ancova, type=3) # Type III
print(result)
```

```
## Anova Table (Type III tests)
##
## Response: pain_mea_30
##           Sum Sq Df F value    Pr(>F)
## (Intercept)  24.426  1  9.9081  0.002118 **
## pain_mea_bas 207.658  1 84.2329 2.989e-15 ***
## tratt         6.914  1  2.8047  0.096830 .
## Residuals    271.182 110
## ---
```

```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

The paper used ANCOVA to to a non-inferiority analysis. We calculate ANCOVA adjusted means and 95%-CI.

```
n = summary(data$stratt)
means.adj = effect("tratt", fit.ancova, se=T)
MD = means.adj$fit[1] - means.adj$fit[2]
# variance assumed unequal
SE = sqrt(means.adj$se[1]^2 + means.adj$se[2]^2)
#ci95 = c(MD - 1.96*SE, MD + 1.96*SE)
# SE based on t-distribution because n1 and n2 < 60
myt = qt(.975, df= n[1] + n[2] - 2)
ci95 = c(MD - myt*SE, MD + myt*SE)

sprintf("%.2f (%.2f, %.2f)", MD, ci95[1], ci95[2])

## [1] "-0.49 (-1.08, 0.09)"
```

Comparing ANCOVA in original study with reanalysis

Independant variable

```
tab.IV = rbind(stats.orig.IV, stats.rep.IV)
rownames(tab.IV) = c("original Study", "reanalysis")
print(t(tab.IV))
```

##	original Study	reanalysis
## Fvalue	NA	"2.80"
## df1	NA	" 1"
## df2	NA	"110"
## pvalue	NA	"0.097"
## MD	"-0.49"	"-0.49"
## lowerCI	"-1.1"	"-1.08"
## upperCI	"0.09"	"0.09"

Covariate

```
tab.CV = rbind(stats.orig.CV, stats.rep.CV)
rownames(tab.CV) = c("original Study", "reanalysis")
print(t(tab.CV))
```

##	original Study	reanalysis
## Fvalue	NA	"84.23"
## df1	NA	" 1"
## df2	NA	"110"
## pvalue	NA	"< 0.0001"
## MD	NA	NA
## lowerCI	NA	NA
## upperCI	NA	NA

Assumptions

1. Homogeneity of variance

- ANOVA/ANCOVA is fairly robust in terms of the error rate when sample sizes are equal.
- When groups with larger sample sizes have larger variances than the groups with smaller sample sizes, the resulting F-ratio tends to be conservative. That is, it's more likely to produce a non-significant result when a genuine difference does exist in the population.
- Conversely, when the groups with larger sample sizes have smaller variances than the groups with smaller sample sizes, the resulting F-ratio tends to be liberal and can inflate the false positive rate.

```
tapply(data$pain_mea_30, data$tratt, sd)

##          SCM          SLF
## 2.030992 2.121189

leveneTest(pain_mea_30 ~ tratt, data = data)

## Levene's Test for Homogeneity of Variance (center = median)
##           Df F value Pr(>F)
## group    1  0.3764 0.5408
##           111
```

2. Independence between covariate and IV

When the covariate and the experimental effect (independent variable) are not independent the treatment effect is obscured, spurious treatment effects can arise and the interpretation of the ANCOVA is seriously compromised.

We test whether our groups differ on the CV. If the groups do not significantly differ then is appropriate to use the covariate.

```
fit.cv = aov(pain_mea_bas ~ tratt, data = data)
Anova(fit.cv, type=3)

## Anova Table (Type III tests)
##
## Response: pain_mea_bas
##           Sum Sq Df   F value Pr(>F)
## (Intercept) 6408.4  1 3180.7293 <2e-16 ***
## tratt         0.0  1   0.0012  0.972
## Residuals    223.6 111
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

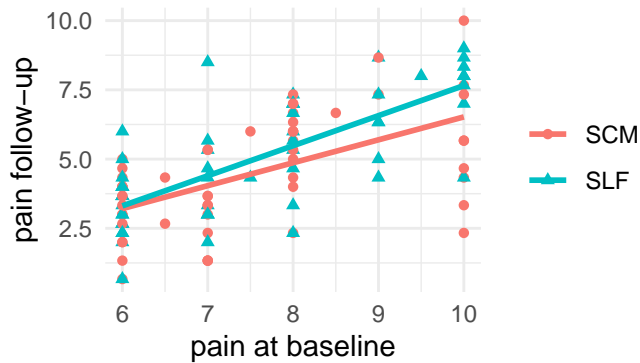
3. Homogeneity of regression slopes

```
fit.hrs = aov(pain_mea_30 ~ pain_mea_bas*tratt, data = data)
Anova(fit.hrs, type=3)

## Anova Table (Type III tests)
##
## Response: pain_mea_30
##           Sum Sq Df F value    Pr(>F)
```

```
## (Intercept)      23.374    1  9.5251    0.00257 **
## pain_mea_bas     204.174    1 83.2032 4.304e-15 ***
## tratt           1.988     1  0.8100    0.37011
## pain_mea_bas:tratt 3.704    1  1.5096    0.22185
## Residuals       267.477 109
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
ggplot(data, aes(y=pain_mea_30, x=pain_mea_bas, color=tratt, shape=tratt)) +
  geom_point() +
  geom_smooth(formula = y ~ x, method=lm, se=FALSE, fullrange=TRUE) +
  theme_minimal() +
  theme(legend.title = element_blank()) +
  xlab("pain at baseline") + ylab("pain follow-up")
```



Notes

- Non-inferiority intervention study, ANCOVA is used to calculate adjusted means for the two groups (corrected for baseline pain)
- Main finding partly reproduced, lower bound of the 95%-CI was wrong, probably a typo.
- Our analysis was consistent with SAS output from authors
- One assumptions not met, baseline pain (CV) not independent from treatment groups (IV)

Data was analyzed according to recommendations by Field, Miles, & Field (2012).