

# Effect of dexamethasone on morphine consumption after total knee arthroplasty: a statistical analysis plan for post-hoc subgroup analyses of the multicenter, randomized DEX-2-TKA trial

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## Objective

The objective of this study is to assess the intervention effect of the three groups in any of the subgroups according to sex, age, use of paracetamol and/or NSAID prior to surgery, ASA-score, type of anesthesia, level of pain at rest prior to surgery and level of pain when active prior to surgery.

## Subgroups

The subgroups are dichotomized based on the following pre-randomization patient characteristics:

- Sex (male *versus* female)
- Age ( $\leq 65$  years *versus*  $> 65$  years)
- ASA group (ASA I and II *versus* III)
- Preoperative pain at rest measured using visual analogue scale (VAS) ( $\leq 30$  mm *versus*  $> 30$  mm)
- Preoperative pain when active measured using VAS ( $\leq 30$  mm *versus*  $> 30$  mm)
- Type of anesthesia (spinal anesthesia *versus* general anesthesia and converted to general anesthesia)
- Prior daily use of paracetamol and/or NSAID (either paracetamol or NSAID *versus* neither)

## Population

We will include all randomized participants with useful data in all analyses (intention-to treat population).

## Outcome

48-hour morphine consumption as defined as the primary outcome in the original trial.

## Baseline variables

Continuous data will be presented with mean and standard deviations (SD) or median and interquartile range when appropriate; while categorical data will be presented as number and percentage.

## Statistical methods

Statistical analyses will be carried out using R (R Core Team, Vienna, Austria) and Stata (StataCorp LLC, Texas, USA) by two independent statisticians (MHO and JCI). The two statisticians will independently prepare a statistical report, which will be compared for any discrepancies. The discrepancies will be logged, and any changes for the final report will be described. The final report, the two original reports, and the discrepancies log, will be approved by the co-authors. All reports will be added as supplemental material in the final paper.

We will perform pairwise comparisons of the three groups, i.e., three comparisons. We plan to test for subgroup heterogeneity of the intervention effect by assessing whether the interaction between the subgroup and the treatment group is significantly different. We will use quantile regression adjusted for site to test for significant interaction between the predefined dichotomized subgroups and treatment group using a threshold of 0.05 for subsequent Wald test.

We will assess the effects of dexamethasone for each of the predefined subgroups analyzed separately using van Elteren test adjusted for site. As these subgroup analyses will be interpreted as exploratory, and with the purpose of generating hypotheses, we will use the same threshold for significance as used in the main trial. The threshold for significance will therefore be multiplicity corrected using Bonferroni correction and is based on the three groups. Thus, the level of significance will be 0.017. We will quantify and report differences between the groups using Hodges-Lehmann median difference and the corresponding 98.3% confidence intervals.

The subgroup analyses will be presented in forest plots.

Attached is an example of the planned analyses for one subgroup analysis (**Supplemental Material**)

#### Further information

- Clinicaltrials.gov identifier for the main trial: NCT03506789
- Clinicaltrials.gov identifier for this subgroup analyses: NCT05008367
- Published protocol article for the main trial: <https://doi.org/10.1111/aas.13481>
- Published statistical analyses plan for the main trial: <https://doi.org/10.1111/aas.13560>

# DEX2TKA simulations

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## Simulated data

```
#Number of participants
n_part <- 485
df <- NULL

#Random assignment to the three groups
df$group <- as.factor(sample(c(1:3),n_part, replace=TRUE))

#Random assignment to the sites
df$site <- sample(c("A","B","C"),n_part, replace=TRUE)

#Random assignment to age
df$bc_age <- rnorm(n_part, mean=65, sd=8)
df$bc_ASA_above_2 <- sample(c(0,1),n_part, replace=TRUE)
df$bc_High_pain_at_rest <- rnorm(n_part, mean=30, sd=10)
df$bc_High_pain_when_active <- rnorm(n_part, mean=30, sd=10)
df$bc_Only_spinal <- sample(c(0,1),n_part, replace=TRUE)
df$bc_Prior_pain_med <- sample(c(0,1),n_part, replace=TRUE)
df$bc_BMI <- rnorm(n_part, mean=30, sd=4)

df <- data.frame(df)
df$age <- 0
df$age[df$bc_age > 65] <- 1

df_mc <- df

#The simulated outcome depending on the median for each group:
n_dd <- 35
n_dp <- 38
n_pp <- 43
df$outcome[df$group==1] <- rnorm(sum((df$group==1)*1),mean=n_dd,sd=5)
df$outcome[df$group==2] <- rnorm(sum((df$group==2)*1),mean=n_dp,sd=5)
df$outcome[df$group==3] <- rnorm(sum((df$group==3)*1),mean=n_pp,sd=5)

#The simulated RRR of age:
rrr_age <- 0.1
df$outcome[df$age == 1] <- df$outcome[df$age == 1]-df$outcome[df$age == 1]*rrr_age
```

## Baseline characteristics for subgroup

```
library(tableone)
CreateTableOne(c("bc_age", "bc_BMI", "bc_ASA_above_2", "bc_High_pain_at_rest", "bc_High_pain_when_active",
                "bc_Only_spinal", "bc_Prior_pain_med"), strata = c("age", "group"),
              factorVars = c("bc_ASA_above_2", "bc_Only_spinal", "bc_Prior_pain_med"),
              data=df, test=FALSE)
```

```
##                               Stratified by age:group
##                               0:1           1:1
##  n                               81           76
##  bc_age (mean (SD))              58.40 (4.65) 71.01 (4.90)
##  bc_BMI (mean (SD))              30.00 (3.79) 29.30 (3.79)
##  bc_ASA_above_2 = 1 (%)           41 (50.6)  45 (59.2)
##  bc_High_pain_at_rest (mean (SD)) 29.28 (9.40) 30.50 (9.56)
##  bc_High_pain_when_active (mean (SD)) 31.05 (10.00) 29.55 (8.84)
##  bc_Only_spinal = 1 (%)           38 (46.9)  36 (47.4)
##  bc_Prior_pain_med = 1 (%)         39 (48.1)  34 (44.7)
##                               Stratified by age:group
##                               0:2           1:2
##  n                               71           78
##  bc_age (mean (SD))              59.49 (4.42) 70.93 (4.92)
##  bc_BMI (mean (SD))              29.95 (4.24) 29.99 (4.23)
##  bc_ASA_above_2 = 1 (%)           27 (38.0)  38 (48.7)
##  bc_High_pain_at_rest (mean (SD)) 32.68 (12.43) 31.61 (10.56)
##  bc_High_pain_when_active (mean (SD)) 29.73 (9.50) 30.52 (10.82)
##  bc_Only_spinal = 1 (%)           36 (50.7)  35 (44.9)
##  bc_Prior_pain_med = 1 (%)         28 (39.4)  37 (47.4)
##                               Stratified by age:group
##                               0:3           1:3
##  n                               86           93
##  bc_age (mean (SD))              58.59 (4.81) 71.68 (4.97)
##  bc_BMI (mean (SD))              29.53 (3.67) 30.12 (3.97)
##  bc_ASA_above_2 = 1 (%)           41 (47.7)  42 (45.2)
##  bc_High_pain_at_rest (mean (SD)) 31.73 (9.62) 30.29 (9.94)
##  bc_High_pain_when_active (mean (SD)) 30.49 (11.03) 29.38 (9.56)
##  bc_Only_spinal = 1 (%)           41 (47.7)  42 (45.2)
##  bc_Prior_pain_med = 1 (%)         43 (50.0)  47 (50.5)
```

## Quantile regression for interaction only

```
#https://cran.r-project.org/web/packages/quantreg/vignettes/rq.pdf  
#install.packages("quantreg")  
suppressMessages(suppressWarnings(library(quantreg)))  
fit_rq <- rq(outcome ~ group*age,data=df)
```

```
## Warning in rq.fit.br(x, y, tau = tau, ...): Solution may be nonunique
```

```
summary(fit_rq,se="nid")
```

```
##  
## Call: rq(formula = outcome ~ group * age, data = df)  
##  
## tau: [1] 0.5  
##  
## Coefficients:  
##           Value      Std. Error t value Pr(>|t|)  
## (Intercept) 34.64455   0.62947   55.03749 0.00000  
## group2      3.65202   1.23630    2.95398 0.00329  
## group3      8.70705   1.00415    8.67107 0.00000  
## age        -3.10804   0.82288   -3.77702 0.00018  
## group2:age -0.47171   1.46960   -0.32098 0.74837  
## group3:age -1.31063   1.23464   -1.06155 0.28897
```

```
#https://www.rdocumentation.org/packages/aod/versions/1.3.1/topics/wald.test  
#install.packages("aod")  
suppressMessages(suppressWarnings(library(aod)))  
#https://www.rdocumentation.org/packages/Zelig/versions/5.1.7/topics/vcov_rq  
#install.packages("Zelig")  
suppressMessages(suppressWarnings(library(Zelig)))  
wald.test(b = coef(fit_rq), Sigma = vcov_rq(fit_rq), Terms = 5:6)
```

```
## Wald test:  
## -----  
##  
## Chi-squared test:  
## X2 = 1.1, df = 2, P(> X2) = 0.57
```

## Van Elteren p-values

```
#https://cran.r-project.org/web/packages/sanon/sanon.pdf
#install.packages("sanon")
suppressMessages(suppressWarnings(library(sanon)))

df_test <- df[df$age == 0 & (df$group == "1" | df$group == "2"),]
summary(sanon(outcome ~ grp(group, ref="1") + str(site), data=df_test))
```

```
## Call:
## sanon.formula(formula = outcome ~ grp(group, ref = "1") + str(site),
##   data = df_test)
##
##
##      Estimate Std.Err Chisq Pr(>Chisq)
## outcome   0.1707  0.0455  14.1   0.00017 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## Note that the estimates of responses are for the (MW estimate - 0.5).
```

```
df_test <- df[df$age == 0 & (df$group == "1" | df$group == "3"),]
summary(sanon(outcome ~ grp(group, ref="1") + str(site), data=df_test))
```

```
## Call:
## sanon.formula(formula = outcome ~ grp(group, ref = "1") + str(site),
##   data = df_test)
##
##
##      Estimate Std.Err Chisq Pr(>Chisq)
## outcome   0.3992  0.0242   273   <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## Note that the estimates of responses are for the (MW estimate - 0.5).
```

```
df_test <- df[df$age == 0 & (df$group == "2" | df$group == "3"),]
summary(sanon(outcome ~ grp(group, ref="2") + str(site), data=df_test))
```

```
## Call:
## sanon.formula(formula = outcome ~ grp(group, ref = "2") + str(site),
##   data = df_test)
##
##
##      Estimate Std.Err Chisq Pr(>Chisq)
## outcome   0.2663  0.0377   49.8   1.7e-12 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## Note that the estimates of responses are for the (MW estimate - 0.5).
```

```
df_test <- df[df$age == 1 & (df$group == "1" | df$group == "2"),]
summary(sanon(outcome ~ grp(group, ref="1") + str(site), data=df_test))
```

```
## Call:
## sanon.formula(formula = outcome ~ grp(group, ref = "1") + str(site),
##   data = df_test)
##
##
##           Estimate Std.Err Chisq Pr(>Chisq)
## outcome    0.1978  0.0443  19.9    8.1e-06 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## Note that the estimates of responses are for the (MW estimate - 0.5).
```

```
df_test <- df[df$age == 1 & (df$group == "1" | df$group == "3"),]
summary(sanon(outcome ~ grp(group, ref="1") + str(site), data=df_test))
```

```
## Call:
## sanon.formula(formula = outcome ~ grp(group, ref = "1") + str(site),
##   data = df_test)
##
##
##           Estimate Std.Err Chisq Pr(>Chisq)
## outcome    0.4040  0.0234   297    <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## Note that the estimates of responses are for the (MW estimate - 0.5).
```

```
df_test <- df[df$age == 1 & (df$group == "2" | df$group == "3"),]
summary(sanon(outcome ~ grp(group, ref="2") + str(site), data=df_test))
```

```
## Call:
## sanon.formula(formula = outcome ~ grp(group, ref = "2") + str(site),
##   data = df_test)
##
##
##           Estimate Std.Err Chisq Pr(>Chisq)
## outcome    0.2445  0.0392    39    4.2e-10 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## Note that the estimates of responses are for the (MW estimate - 0.5).
```

## Hodges-Lemann median differences

```
#https://rdrr.io/cran/DescTools/man/HodgesLehmann.html  
#install.packages("DescTools")  
suppressMessages(suppressWarnings(library("DescTools")))
```

```
#Sammenligning mellem aldersgrupper i hver gruppe  
HodgesLehmann(df$outcome[df$group == 1 & df$age == 0],  
              df$outcome[df$group == 2 & df$age == 0],  
              conf.level = 0.983)
```

```
##      est      lwr.ci      upr.ci  
## -3.0577938 -5.1431926 -0.9508709
```

```
HodgesLehmann(df$outcome[df$group == 1 & df$age == 0],  
              df$outcome[df$group == 3 & df$age == 0],  
              conf.level = 0.983)
```

```
##      est      lwr.ci      upr.ci  
## -8.405907 -10.300894 -6.602105
```

```
HodgesLehmann(df$outcome[df$group == 2 & df$age == 0],  
              df$outcome[df$group == 3 & df$age == 0],  
              conf.level = 0.983)
```

```
##      est      lwr.ci      upr.ci  
## -5.402509 -7.479059 -3.298164
```

```
HodgesLehmann(df$outcome[df$group == 1 & df$age == 1],  
              df$outcome[df$group == 2 & df$age == 1],  
              conf.level = 0.983)
```

```
##      est      lwr.ci      upr.ci  
## -3.204365 -4.797497 -1.397309
```

```
HodgesLehmann(df$outcome[df$group == 1 & df$age == 1],  
              df$outcome[df$group == 3 & df$age == 1],  
              conf.level = 0.983)
```

```
##      est      lwr.ci      upr.ci  
## -7.287141 -8.749119 -5.665037
```

```
HodgesLehmann(df$outcome[df$group == 2 & df$age == 1],  
              df$outcome[df$group == 3 & df$age == 1],  
              conf.level = 0.983)
```

```
##      est      lwr.ci      upr.ci  
## -4.068798 -5.736961 -2.477672
```