

Revisiting the cross-over: A two-period design using a treatment and a placebo

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Introduction

- Each subject receives a sequence of experimental treatments.
- The aim is to compare the effects of individual treatments.
- The two-period two-treatments design is the simplest and the most commonly used of all the cross-over trial designs.

Data collection

- The subjects are the patients with asthma.
- The treatments are Salmeterol vs. Placebo and we will label them as S and P, respectively.
- The period includes day21 and day28.
- The response of interest is the forced expired volume in one second (FEV_1).
- The time covariates and self-reported survey data are also included.
- The data set are from Dr. Kemeny in UCSF.
- Id represents subject; order represents sequence(1-SP, 2-PS); group represents treatments.

The linear model

The linear Model is

$$Y_{ijk} = \mu + \pi_j + \tau_{d[i,j]} + S_{ik} + e_{ijk}$$

Where the terms in this model are:

μ : an intercept;

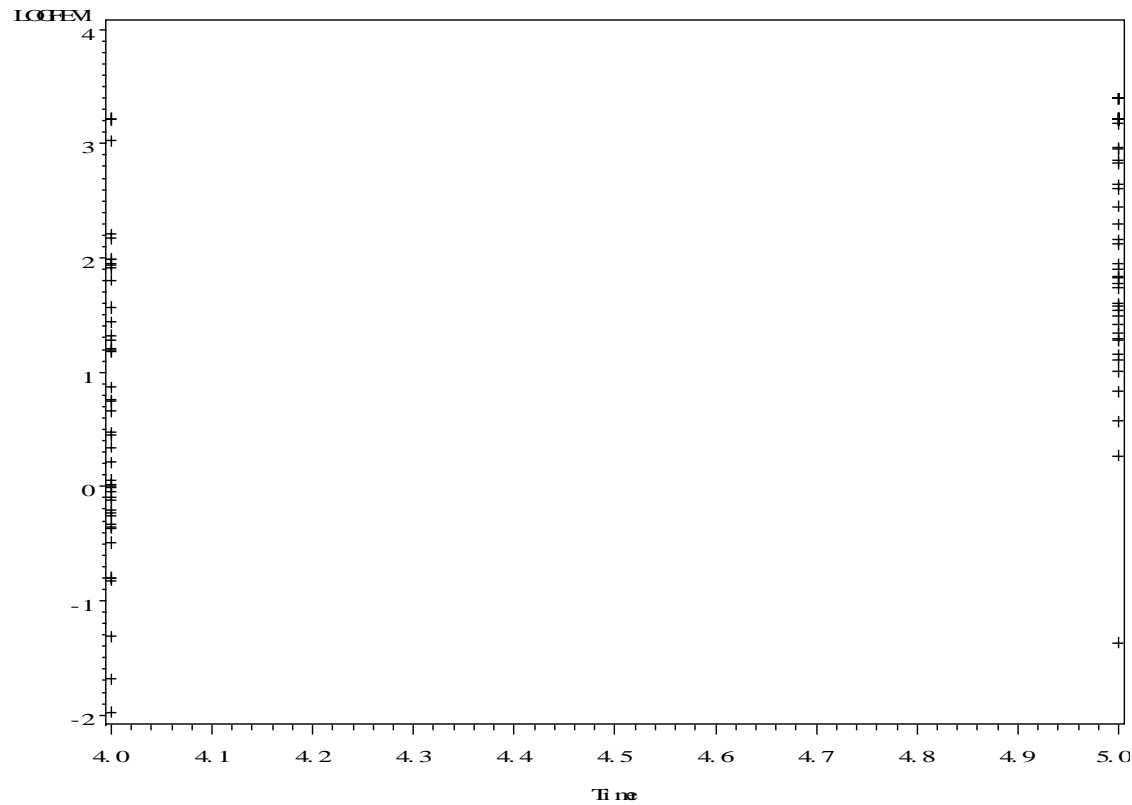
π_i : an effect associated with period

$\tau_{d[i,j]}$: a direct treatment effect associated with treatment applied in period j of sequence i , $d[i,j]=1, \dots, p$

S_{ik} : an effect associated with the k th subject on sequence i , $i=1, \dots, s$,
 $k=1, \dots, n$

e_{ijk} : a random error term, with zero mean and variance

Time difference on response



SAS Code

```
proc contents data =test1 ;
run;
proc freq data = test1 ;
tables time * group / chisq ;
run ;
proc print data = test1 ;
var fev1 time group ;
run ;
proc mixed data = test1 ;
  class id order time group ;
  model logfev1 = order id(order) time group/solution
    ddfm=kenwardroger ;
run ;
proc mixed data = test1 ;
  class id order time group ;
  model logfev1 = order id(order) time group;
  lsmeans group/pdiff;
  estimate 'gr2-gr1' group -1 1;
run ;
```

Output of SAS

1

Type 3 Tests of Fixed Effects

Effect	Num	Den	DF	DF	F Value	Pr > F
ORDER			1	45	0.26	0.6150
ID(ORDER)			45	45	3.41	<.0001
Time			1	45	74.47	<.0001
GROUP			1	45	0.13	0.7168

2

Estimates Standard

Label	Estimate	Error	DF	t Value	Pr > t
gr2-gr1	-0.06594	0.1807	45	-0.36	0.7168

Least Squares Means Standard

Effect	GROUP	Estimate	Error	DF	t Value	Pr > t
GROUP	4	1.4946	0.1225	45	12.20	<.0001
GROUP	5	1.4287	0.1225	45	11.66	<.0001

Differences of Least Squares Means Standard

Effect	GROUP	GROUP	Estimate	Error	DF	t Value	Pr > t
GROUP	4	5	0.06594	0.1807	45	0.36	0.7168

Discussion

- When P-value is less than 0.05, there is strong evidence to reject the null hypothesis.
- P-values of ID(ORDER) and Time are both less than 0.001.
- P-values of Order and Group are both very large.

Conclusions

- There are no significant treatment (Salmeterol vs. Placebo) effects.
- There are no significant order effects.
- For future work, we would take the baseline measurement of day7 and day14 into consideration.

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