Graphical and Analytical Tools for the Analysis of Two-Period Crossover Clinical Trials

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Abstract
This paper brings together a variety of graphical and analytic tools used in the analysis of two-period crossover clinical trials for continuous data. SAS/GRAPH® is used to construct exploratory analyses for carryover, period, and treatment effects. A number of different SAS® procedures carry out various alternative inferential approaches to crossover studies.

Introduction
Two-period crossover designs are common place in clinical trial research (1,2). A crossover trial is a trial in which subjects are given sequences of treatments with the objective of studying differences between treatments. The most common crossover design is the two-period crossover study where subjects randomly receive one of two treatments and are later crossed over to receive the other treatment (1,2,3).

There are several advantages of crossover trials over parallel group studies (1,2,4). Each patient acts as his/her own control. There is an evaluation of both treatments for each patient, so treatment differences can be based on within-patient comparisons instead of between patient comparisons. Because there is usually less variability within a patient than between patients, there is usually an increase in precision and therefore a decrease in required sample size for a study to detect the same specified effect size.

The disadvantages of using a crossover trial include a greater inconvenience to patients because they are required to submit to multiple treatments and must stay on study longer. Dropouts are a bigger concern than with parallel group studies especially if there is unequal dropout among the two treatments. There can be no carry-over effects, no time trends, and the patients must be in a comparable state at the start of each treatment period in order to be able to draw conclusions regarding treatment comparisons.

Numerous statistical techniques have been suggested for the analysis of crossover designs (1,2,6,7,8,10). In this paper, we pull together a number of these approaches into a hopefully comprehensive analysis using an assortment of SAS tools. The multi-faceted analysis code has been organized so that a single macro call can carry out the various analysis routines involved. We use an example clinical trial involving the application of capsaicin cream for postsurgical pain.

Analytical Approaches: Two-Stage Analysis
The most popular approach to analyzing the two-period crossover study has been to use a two-stage analysis (2,4).

This method first tests for a carryover effect between the two treatment periods in which case the effects of one treatment are still present during the evaluation of the next treatment. The effects of the second treatment are hence confounded with the effects of the first treatment which makes interpretation difficult.

If no carryover effect is detected, the standard analysis is carried out comparing period differences by sequence. If there is a significant carryover effect, the results of the second time period are suspect and are removed from consideration. Comparison is done subsequently using only the between patient scores in the first treatment period.

Analytical Approaches: Senn's Analysis
An alternative method of analysis has been documented by Senn (1993) which assumes that there has been a sufficient wash-out period and therefore no carryover effect present. The primary endpoint for this analysis is the intrapatient difference in efficacy between the two treatments under study. Confidence intervals for treatment effects can then be created and hypothesis testing carried out.

Example Dataset
We demonstrate the results one can obtain from using SAS procedures to carry out the aforementioned analyses on a North Central Cancer Treatment Group (NCCTG) phase III clinical trial which evaluated the efficacy of capsaicin cream in managing surgical neuropathic pain in cancer patients (9). Patients experiencing neuropathic pain after surgery were randomly assigned to receive eight weeks of capsaicin cream followed by eight weeks of a placebo cream or vice-versa. Patients reported their pain level at baseline and weekly thereafter using a visual analog scale rated from 0 (no pain) to 100 (worst pain imaginable).

Descriptive Analysis Results
The SAS code first produces a simple patient listing showing all scores by sequence over time (not shown). This listing is used to make sure the data looks reasonable, to examine the extent of missing values, and for getting a general sense of the data.

SAS/GRAPH is used subsequently to produce simple graphical summaries in order to get a general feel for the data. First the changes in scores over time are plotted for each patient on a template via GREPLAY. An example plot is given for one patient in Figure 1. The vertical line represents the crossover period at week 9. The efficacy of the active treatment versus the placebo is demonstrated for this patient by the fact that the pain scores in the first treatment period are consistently and substantially lower than those obtained during the second (placebo) period. The template displays up to 25 patients' data per page in a 5x5 array. This technique is useful for detecting outliers and examining individual cases. While more graphs can be displayed per page, size limitations make this impractical. These plots show how individual patients responded to the different treatments.

The next method we use for getting a general feeling for the data

are "stream plots" which consist of plotting the changes over time for all patients on one graph. This is also done by treatment sequence and is illustrated in Figure 2. From the picture we can see that while individual variability is present, there is a "current" in the stream for the scores to decrease over time

Overall changes can also be observed by plotting the mean scores over time as shown in Figure 3. Here we get a first glimpse of a beneficial effect (reduction in average pain score) of the capsaicin cream relative to the placebo. Figures 4 and 5 illustrate the use of scatterplots and patient effect plots, respectively, for comparing the results at two time periods. These plots are used to look for trends in the data and for comparisons between the treatments.

Figure 4 produces four different plots of the pain scores for each patient: one for the first and last week of each treatment sequence. A sequence and treatment effect can be detected here by careful inspection of the plots. The 45 degree line on each plot represents the equivalent pain scores for the two treatments. The top left plot (the capsaicin/placebo sequence results for the first week of treatment) has all but four patients with higher pain scores on the capsaicin. This is due to the known capacity for capsaicin to initially induce a burning sensation. By week 8, however, the points (top right plot) have shifted substantially.

The bottom two plots (placebo/capsaicin sequence) show a similar shifting in pain scores from week one to week 8, indicating that by week 8 those receiving a placebo were experiencing greater pain.

Figure 5 gives an indication of treatment success proportions by plotting the final week's pain scores for each patient. The capsaicin pain score is indicated by a asterisk while the score reported by the same patient in the 8th week of the placebo treatment is given by a circle. The two scores are connected by a colored line: green if the patient's score on capsaicin was lower and red if the capsaicin score was higher.

Figure 6 plots the treatment effects from Senn's analysis approach to display effect over time. In this case a positive score (above the zero horizontal reference line) would indicate that the capsaicin pain score was higher than that reported on placebo. Confidence bands give an indication of statistical significance from a zero effect. Figure 6 shows the initial burning impact of capsaicin in that scores are not significantly different from zero in the first two weeks. Once three weeks have elapsed however there is a substantial benefit in pain reduction which carries through to the 8th week of treatment.

Inferential Analysis Results

The SAS code produced to give inferential results relies mainly on SAS/GLM® processing. Standard two stage analysis results confirmed the findings from the graphical displays.

Proc TTEST and NPAR1WAY use the intrapatient difference between the end of period scores to indicate significant benefits of capsaicin (p=0.0002 and p=0.0005, respectively) relative to placebo. The test for a carryover effect indicates that the effect of capsaicin does not extend beyond the crossover period (p=0.7578).

Senn's approach allows for a general linear model to be built based on the individual time point intrapatient differences potentially incorporating baseline and covariate measures (1). Table 1 gives an example display including baseline scores.

Table 1: p-values for Senn's linear model predicting intrapatient treatment effect

TIME	PATIENT	TREATMENT	BASELINE
1	0.0001	0.0215	0.0001
2	0.0002	0.2339	0.0001
3	0.0001	0.2538	0.0001
4	0.0001	0.0271	0.0001
5	0.0001	0.0396	0.0001
6	0.0002	0.0062	0.0001
7	0.0002	0.0022	0.0001
8	0.0001	0.0006	0.0001

The baseline pain scores did impact on subsequent results with all p-values <0.0001. Similarly variability among patients contributed to the pain scores. Finally, the difference in treatment efficacy between capsaicin and placebo described above in the graphical analysis was confirmed. The significant result for treatment effect in the first week is indicative of the initial burning sensation experienced by capsaicin. The subsequent nonsignificant results in weeks 2 and 3 indicate the waning of this effect. The significant p-values for treatment effect in weeks 3 and beyond demonstrate the emergence of a benefit in pain reduction for the capsaicin cream.

Summary

There are a number of options for the analysis of crossover studies. In this paper, we have implemented the most widely used methods via SAS procedures which produces several helpful graphical and analytical tools for crossover analysis.

The SAS code has been collected into a macro and is available from the authors via e-mail at novotny@mayo.edu or jsloan@mayo.edu. A detailed description of the macro call is given in Appendix I.

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APPENDIX I

```
%macro crosseff(dsn,type,score,nbase,n1,nwash,ccovar,dcovar,plot,overall,indiv,glm);

crosseff ==> this code produces treatment effect estimates for a two-period crossover design with two treatments and multiple time points
             per period

authors: Jeff A. Sloan              date created:  9/30/95
         Paul J. Novotny            date modified: 1/16/96
                                                   9/10/96
required variables:
     PATIENT - the patient identifier
     SEQUENCE - a numeric value for the treatment sequence
           1=treatment followed by placebo
           2=placebo followed by treatment
     TX1-TX[N] - one variable for each time the patient reported a score (including baseline and washout scores)

macro parameters:
     dsn    - dataset name of effects with one line per patient
     type   - type of analysis desired:
              'standard' = standard two-step analysis with tests for carryover
              'senn' = Senn's alternative analysis
              'both' = both the standard analysis and Senn's analysis
     score  - prefix of variable names containing all of the scores
     nbase  - number of scores that are baseline scores
     n1     - number of scores in each treatment period
              (there should be the same number of periods for both the active treatment and the placebo)
     nwash  - number of scores that are washout period scores
     ccovar - list of continuous baseline covariates (leave blank if there are no baseline covariates)
     dcovar - list of discrete baseline covariates (leave blank if there are no baseline covariates)
     plot   - type of plots desired                  'g' = 'graphic'     'p' = 'printer'
     overall - print overall model assuming no carryover effects  'y' = 'yes'    'n' = 'no'
     indiv - plot scores over time for individual patients  'y' = 'yes'     'n' = 'no'
     glm - print entire glm output                   'y' = 'yes'     'n' = 'no'

Examples of calling the macro:
     %crosseff(master,senn,tx,0,8,0,  ,p,y,n,n);
     %crosseff(master,standard,tx,1,8,1,base, ,g,n,n,n);
     %crosseff(master,both,tx,1,1,1,base age,gender,p,y,y,n);
```

Figure 1: Scores Over Time
sequence=Active/Placebo patient number=1

Figure 2: Stream Plots
sequence=Active/Placebo

Figure 3: Mean Scores Over Time by Sequence

sequence —— Active/Placebo ···· Placebo/Active

4

Figure 4: Tx by Plac Scores by Sequence
sequence=Active/Placebo

Figure 4: Tx by Plac Scores by Sequence
sequence=Active/Placebo

Figure 4: Tx by Plac Scores by Sequence
sequence=Placebo/Active

Figure 4: Tx by Plac Scores by Sequence
sequence=Placebo/Active

5

Figure 5a: Individual Score Plots: Active/Placebo

Figure 5b: Individual Score Plots: Placebo/Active

Figure 6: Treatment Effects by Time Period and Sequence
sequence – Placebo/Active