# STATISTICAL ANALYSIS OF A CONTROLLED CLINICAL TRIAL IN PATIENTS WITH METASTATIC BONE PAIN

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A Project

Submitted to the School of Graduate Studies

in Partial Fulfilment of the Requirements

for the Degree

Master of Science

McMaster University



November 1995

MASTER OF SCIENCE (1995) MCMASTER UNIVERSITY

(Statistics) Hamilton, Ontario, Canada

TITLE: Statistical Analysis of a Controlled Clinical Trial in Patients with Metastatic Bone Pain

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NUMBER OF PAGES: ix, 52

# ACKNOWLEDGEMENTS

I would like to take this opportunity to express my sincere appreciation to Dr. R. Viveros-Aguilera, my supervisor, for his guidance, encouragement, and patience throughout this project work.

I would like to thank Prof. C.H. Goldsmith for his valuable suggestions and especially his willingness to share with me his wealth of experience and knowledge in the statistical analysis of clinical trial.

I would like to thank all the Professors at McMaster University who have ever taught me. Appreciation is also expressed to McMaster University for providing financial assistance.

I would like to thank the Statistical Society of Canada through Dr. Rollin Brant from the Department of Community Health Sciences of University of Calgary for providing the data.

I also would like to thank my friends Dr. Xiaodong Gu and Tian Lin for their help.

Finally, I would like to thank my parents, my husband, Dr. Qinan Wang, and our children, Doris and Brian, for their love, support and understanding.

# ABSTRACT

The analgesic effect of 600 mg and 1500 mg of a pain killing drug to metastatic bone pain, and associated side effects, were assessed. The experimental design was a double-blind cross over clinical trial involving 44 patients known to suffer from metastatic bone pain. Each patient received the active drug in one of two dosages and the placebo in a random order, each lasting about 14 consecutive days. The data consisted of daily measurements of several pain and side effect variables. A few covariates were available. It was found that the patient and the investigator achieved a high degree of agreement on the blinded preference of the active drug to the placebo. A multivariate analysis of variance (MANOVA) on three different summary scores (mean, median, trmean) calculated on the daily measurements for which the patient received the active drug and on those for which the patient received the placebo was conducted. It was found that for the group of pain variables the order of application and the treatment do not have a significant effect marginally, but that they interact significantly. Variation between subjects was also significant. For the group of side effect variables, however, only significant variation between subjects was found. This suggests that the drug does not have noticeable overall side effects. To account for correlations among the response measurements within each patient, the methodology of generalized estimating equations was used to assess the significance of the effects of the predictors. Although the results are less reliable as they depend on the asymptotic behaviour of statistics, it was found that regardless of the level of correlation within patient response measurements, only the interaction of order of application with treatment has a significant effect on each of the pain variables. All the statistical analyses were carried out using Minitab, SAS, Matlab and Splus.

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# Chapter 1

# Background and Study Description

## 1.1 Background on Metastatic Bone Pain

Bone pain is the commonest form of pain experienced by many cancer patients with metastatic bone disease (Hanks, 1988). By its very nature, bone pain has a substantial incidental component, and therefore the degree of pain experienced in any period of time would vary from day to day. Involvement of bone by primary or secondary tumours is the commonest cause of pain in patients with cancer. In patients with primary bone tumours the prevalence of pain is as high as 85% (Bonica, 1982). For patients with bone metastases from other primary sites, pain may arise directly from bone, from nerve compression (associated particularly with vertebral collapse) or from muscle spasm surrounding an area of bone disease. Radiotherapy or other tumoricidal treatments may relieve pain by shrinking the tumour. Today radiotherapy remains a most effective treatment for localized bone pain due to metastatic cancer, and may also have an important role in the management of more widespread bone pain. Despite considerable advances in the technical aspects of radiotherapy with the advent of megavoltage X-ray machines, treatment simulators and computerized tumour localization and planning, the treatment of bone pain remains largely empirical. To effectively relieve pain and allow the patient to function as normally as possible are the main objectives in the management of pain in cancer patients.

## 1.2 Research Objectives

The main objectives of this study are:

(a) to test a pain killing drug to assess its effectiveness on the control of metastatic bone pain, and

(b) to assess the possible side effects of the drug.

For commercial reasons, information of the drug is not released in this report. A double-blind cross over clinical trial was conducted to compare the active drug (coded as drug 1 in the study) with placebo (coded as drug 2 in the study). Two different doses (600 mg, 1500 mg) of the active drug were used.

## 1.3 Pretest

In a preliminary trial, the effect of 600 mg active drug in reducing bone pain in patients with known metastatic bone pain was investigated. A double-blind cross over trial was conducted on 21 patients. Either 600 mg active drug or placebo was given to the patient randomly. Patients crossed over to the alternative treatment after 1 week. At the end of the second week, a blinded choice was made by each patient and the investigator between the active drug and placebo. They were asked which drug, the drug in week 1 or week 2, was preferred. Of the 21 patients, 12 (57%) patients preferred the active drug, 4 (19%) the placebo and 5 (24%) had no preference. The investigator selected the active drug in 14 (67%) cases, placebo in 6 (29%) and was unable to discern a difference in 1 (5%) cases. The preliminary findings suggest that active drug may be useful in the management of metastatic bone pain.

## 1.4 The Sample

The sample for the study was selected from a roster of cancer patients who were actually undergoing therapy in the associated hospitals. Forty-four patients with known metastatic bone pain were selected for the study. The age and number of painful localizations for each patient were recorded prior to entry into the trial. This information is reported in Table 1.1.

Table 1.1: Characteristics of Patients Prior to Entry to the Trial

| Patient (ID) | Age (Years) | Number of Painful Sites | Patient (ID) | Age (Years) | Number of Painful Sites |
|---|---|---|---|---|---|
| 101 | 59.7 | 2 | 132 | 76.6 | 3 |
| 103 | 45.4 | 3 | 133 | 68.3 | 3 |
| 104 | 48.2 | 3 | 134 | 45.8 | 1 |
| 105 | 48.0 | 2 | 135 | 55.2 | 2 |
| 107 | 77.0 | 1 | 136 | 61.5 | 1 |
| 108 | 83.0 | 4 | 137 | 67.0 | 2 |
| 109 | 46.7 | 2 | 139 | 60.8 | 2 |
| 111 | 49.1 | 3 | 140 | 67.0 | 2 |
| 113 | 50.9 | 4 | 141 | 71.7 | 9 |
| 114 | 48.5 | 4 | 142 | 54.1 | 4 |
| 115 | 69.3 | 6 | 143 | 69.5 | 4 |
| 116 | 52.8 | 4 | 144 | 73.3 | 2 |
| 119 | 68.5 | 5 | 146 | 67.3 | 1 |
| 120 | 73.9 | 1 | 147 | 68.7 | 5 |
| 121 | 55.8 | 1 | 148 | 60.0 | 4 |
| 123 | 63.7 | 2 | 150 | 65.2 | 1 |
| 126 | 37.5 | 3 | 151 | 85.7 | 3 |
| 127 | 67.2 | 2 | 152 | 78.0 | 3 |
| 128 | 71.4 | 3 | 154 | 64.1 | 3 |
| 129 | 45.7 | 3 | 157 | 65.0 | 1 |
| 130 | 70.5 | 1 | 158 | 76.6 | 1 |
| 131 | 67.5 | 1 | 159 | 58.8 | 2 |

Looking at the ID numbers, it appears that the roster of 44 patients for which data were reported, was part of a bigger group. The original investigators did not provide any information on the remaining patients.

The sample consisted mostly of elderly people, with a mean age of 62.7 years. The age of the patients varied from 38 to 86 years. Each patient had at least one painful site but no more than nine painful sites at the time of entering the study. There was one patient having nine painful sites; eleven patients having one painful site. The mean number of painful sites per patient is 2.7. The frequency of the number of painful sites is summarized in Table 1.2.

Table 1.2: Frequency of Painful Sites

| Number of Painful Sites | Frequency | Percentage |
|---|---|---|
| 1 | 11 | 25.0 |
| 2 | 11 | 25.0 |
| 3 | 11 | 25.0 |
| 4 | 7 | 15.9 |
| 5 | 2 | 4.5 |
| 6 | 1 | 2.3 |
| 9 | 1 | 2.3 |
| Total | 44 | 100.0 |

## 1.5 Design of the Experiment

A double-blinded cross over randomized clinical trial was used in the study. Each patient was to receive the active drug in one of two dosages. All patients were treated with an infusion of one drug, either the active drug or the placebo, on day 1, and scheduled to cross over to receive the alternative drug after two weeks. The order to receive the two drugs, either the active drug or the placebo, and the dosage to be received by each patient

were randomized. Both the patient and investigator were blinded to the assignment until completion of the study period.

Upon entering the study, each patient was randomly assigned to one of the following groups:

Group 1 = receiving 600 mg active drug followed by placebo;
Group 2 = receiving 1500 mg active drug followed by placebo;
Group 3 = receiving placebo followed by 600 mg active drug;
Group 4 = receiving placebo followed by 1500 mg active drug.

Table 1.3 summarizes the group composition in relation to size and mean age. Note that the largest difference in mean age is about 5.6 years among four groups. Of the 44 patients, 24 patients were treated with 600 mg active drug and 20 patients were treated with 1500 mg active drug; 25 patients were treated with the active drug first, followed by placebo, and 19 patients were treated with the placebo first, followed by the active drug.

Table 1.3: Summary of Patient Groups

| | | Mean Age | Drug | |
|---|---|---|---|---|
| Group | Size | (Years) | First Period | Second Period |
| 1 | 14 | 64.0 | 600 mg Active Drug | Placebo |
| 2 | 11 | 65.1 | 1500 mg Active Drug | Placebo |
| 3 | 10 | 61.3 | Placebo | 600 mg Active Drug |
| 4 | 9 | 59.5 | Placebo | 1500 mg Active Drug |

Three variables were used to measure a patient's pain level during the study: pain, pain while at rest, and pain with movement. The first variable measures the overall pain level and the second and third variables measure the pain when the patient is in a resting position and when the patient is moving, respectively. Because side effects are often associated with pain killers, the following variables were also recorded: nausea, depression, anxiety, drowsiness, and appetite. A relative degree of physical activity level

performed each day was also measured. In addition, the number of times in each 24-hour period a patient required an extra dose of pain killer medication and the total morphine equivalent dose of this medication were also recorded.

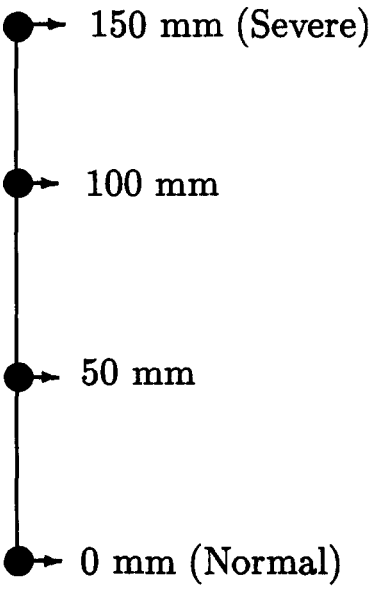


Figure 1.1: Visual Analog Scale

Each variable was measured on a visual analog scale (see Figure 1.1). A visual analog scale is a visual aid for respondents to measure each variable in a numerical scale. The scale varies from 0 at the bottom to 150 mm on the top. For the pain variables (pain, pain while at rest, and pain with movement), 0 represents no pain and 150 represents severe pain; for the variables nausea, depression, anxiety, drowsiness, 0 represents normal condition or no symptom and 150 represents very severe condition, e.g., very depressed for the depression variable; for the variables activity and appetite, 0 represents no activity or no appetite and 150 represents very active or very good appetite, respectively. Each patient indicated the severity of his/her condition on a variable on the scale relative to the two anchor conditions, i.e., the bottom and the top conditions, on the visual analog scale.

Throughout the study a daily analgesic log was established for each patient. Each patient was instructed regarding the daily completion of the 150 mm visual analogue scales evaluating the presence and severity of his/her symptoms. The drug of all analgesics was recorded every day by the investigator.

## 1.6 Literature Review

In recent years, some studies (Ernst *et al.*, 1992; Paterson *et al.*, 1993; Purohit *et al.*, 1994) on treatment of metastatic bone pain have been conducted. The aim of these studies was to assess the effect of various drugs on the control of metastatic bone pain.

The analgesic benefit of the bisphosphonates to metastatic bone pain, and the associated side effects were evaluated by Ernst *et al.* (1992) and Purohit *et al.* (1994). Ernst *et al.* (1992) studied the analgesic effect of 2-dichloromethylene bisphosphonate ($CL_2MDP$) to the metastatic bone pain in a double-blind cross over trial. 24 patients with metastatic bone pain were randomized to receive either a 4-hr intravenous infusion of $CL_2MDP$, 600 mg in 500 mL of normal saline, or a 4-hr placebo infusion, 500 mL of normal saline. The administration was double blind. After 1 week, the patients were crossed over to the alternative treatment for 1 more week. No observations were missing in the study of $CL_2MDP$.

The method of repeated measurements was used in the analysis. The statistical analyses show that $CL_2MDP$ had a beneficial effect in patients with known metastatic bone pain and the side effects of $CL_2MDP$ were not important to the patient.

## 1.7 The Data Set

The data set studied in this project was provided by Dr. Rollin Brant, from the Department of Community Health Sciences at University of Calgary. It was one of two data sets proposed for analysis in the Case Studies Session at the Annual Meeting of the Statistical

Society of Canada held in Banff, Alberta, 7-12 May 1994. No team presented an analysis on this data set. Contact with the original investigators was not possible.

## 1.8 Organization of the Report

The rest of this report is organized as follows. A preliminary analysis of the data on the clinical trial is presented in Chapter 2. The focus is on an analysis per response variable by treatment primarily on the pain and side effect responses. An assessment of the agreement between patients and investigators on the blinded preference of the active drug to the placebo is also presented. A multivariate analysis of variance on the group of pain variables and the group of side effect variables is presented in Chapter 3. The sources of variability accounted for are: subject (patient), observing period, treatment, and interaction of observing period and treatment. The recently developed methodology of generalized estimating equations is used in Chapter 4 in an attempt to account for correlation among the response measurements within each patient. The objective here is to assess the statistical significance of the explanatory variables (age, observing period, treatment, and interaction of observing period and treatment) in a linear model for each of the pain variables and side effect variables. Some conclusions, implications and suggestions are summarized in Chapter 5.

# Chapter 2

# Statistical Analysis per Response Variable

## 2.1 Introduction

The objective of this chapter is to present a preliminary analysis of the data. The focus is on an analysis per response variable by treatment primarily on the pain and side effect responses. An assessment of the agreement between patient and investigator on the blinded preference of the active drug to the placebo is also presented. Some plots that exhibit the time-dependent feature of the response pain within each patient are displayed. A summary of the response variables is made for each treatment in each group. The calculations were done in SAS (SAS, 1985) on a UNIX machine. and the plots were produced in Splus (Splus, 1993) on a SPARC 10 machine.

## 2.2 Observing Period

It was mentioned in Section 1.5 that all patients were treated with an infusion of one drug, either the active drug or placebo, on day 1, and scheduled to cross over to receive the alternative drug after two weeks. However, due to logistics not all patients were observed

for exactly 14 days after the administration of the first drug and before the infusion of the second drug. Some periods were longer, some shorter. Of the 44 patients, 23 (52.3%) patients were observed for exactly 14 days after the first drug administration and before the crossover to the alternate drug. For the remaining 21 patients, 14 (31.8%) were crossed over to the second drug less than two weeks and 7 patients (15.9%) were crossed over to the second drug more than two weeks after the first administration. The mean length of the period from the first administration to the crossover to the second drug is 14 days, varying from 6 days to 35 days. The length of the first observing period of the 44 patients is summarized in Table 2.1.

Table 2.1: Length of the First Observing Period

| Length | Frequency | Percentage |
|---|---|---|
| 6 | 1 | 2.3 |
| 7 | 3 | 6.8 |
| 8 | 2 | 4.5 |
| 11 | 1 | 2.3 |
| 13 | 7 | 15.9 |
| 14 | 23 | 52.3 |
| 15 | 2 | 4.5 |
| 18 | 2 | 4.5 |
| 21 | 1 | 2.3 |
| 29 | 1 | 2.3 |
| 35 | 1 | 2.3 |
| Toal | 44 | 100.0 |

For the second observing period from the administration of the second drug to the completion of the study, 3 patients had no observations to all response variables, 36 patients were observed for exactly 14 days, and 1 patient was observed for more than 14 days.

## 2.3 Blinded Preference of Active Drug to Placebo

At the end of the study period, the patient and the investigator made blinded choices as to which drug, either the active drug or the placebo, was preferred. If they could not discern a differential effect between the two infusions, this was recorded as the third choice. The investigator's choice was based on clinical impression. The assessments by patients and investigators are recorded in Table 2.2.

Table 2.2: Cross-Frequency of Drug Preference by Patient and Investigator

| | | Investigator | | | | |
|---|---|---|---|---|---|---|
| | Frequency | 1* | 2 | 3 | Total | (Percentage) |
| Patient | 1 | 23 | 0 | 2 | 25 | (56.8) |
| | 2 | 3 | 8 | 0 | 11 | (25.0) |
| | 3 | 3 | 1 | 4 | 8 | (18.2) |
| | Total | 29 | 9 | 6 | 44 | |
| | (Percentage) | (65.9) | (20.5) | (13.6) | | (100.0) |

*1 = active drug; 2 = placebo; 3 = no preference.

Of the 44 patients, 25 preferred the active drug, 11 preferred placebo, and 8 had no preference between the two choices. The investigator selected the active drug in 29 cases and placebo in 9 cases, but could not differentiate between the two drugs in 6 cases. These results are consistent with the observations in the pretest.

Based on the results of Table 2.2, the observed value of Cohen's measure of agreement $K$ is

$$\hat{K} = \frac{n\sum_i x_{ii} - \sum_i x_{i+}x_{+i}}{n^2 - \sum_i x_{i+}x_{+i}} = 0.6333,$$

where $n = 44$. Its estimated asymptotic variance $\hat{V}(\hat{K})$ is

$$\hat{V}(\hat{K}) = \frac{[\sum_i \hat{p}_{i+}\hat{p}_{+i} + (\sum_i \hat{p}_{i+}\hat{p}_{+i})^2 - \sum_i \hat{p}_{i+}\hat{p}_{+i}(\hat{p}_{i+} + \hat{p}_{+i})]}{n(1 - \sum_i \hat{p}_{i+}\hat{p}_{+i})^2} = 0.012.$$

Based on the asymptotic normal distribution of $\hat{K}$, a 95% confidence interval for the true value of $K$ is thus [0.42, 0.85]. This indicates that the patient and investigator had relatively high agreement regarding the preference of the active drug and the placebo. For more details on the methodology, see Bishop, Fienberg and Holland (1991, pp. 395-397).

## 2.4 Data Screening

Before analysis, the data for the 44 patients were examined. Of the 44 patients, 3 patients had observations in the first period but not in the second and 1 patient had no observations in the first period on all response variables except the equivalent dose of morphine and number of breakthroughs. Observations were also missed for several other patients. However, no recording mistakes were spotted. All the patients were included in the study.

## 2.5 Summary of Response Scores

To get some feeling for the time-dependent nature of the responses within each patient, one patient was picked up in each group. The pain measurement for four patients were plotted and the results are displayed in Figure 2.1. The four patients are Patient #130 in Group 1, Patient #133 in Group 2, Patient #108 in Group 3, and Patient #146 in Group 4. The vertical line on each time sequence plot separates the observations of the patient when receiving the active drug from observations when receiving the placebo. The missing observations can be seen from break points on the time sequence plots.

The time sequence plot of the pain score of Patient #130 in Figure 2.1 shows that this patient was observed for 27 days in the study, and had no observations on pain score in the first period when receiving 600 mg active drug, and some missing observations in the second period. The responses of Patient #130 to the pain are quite small.

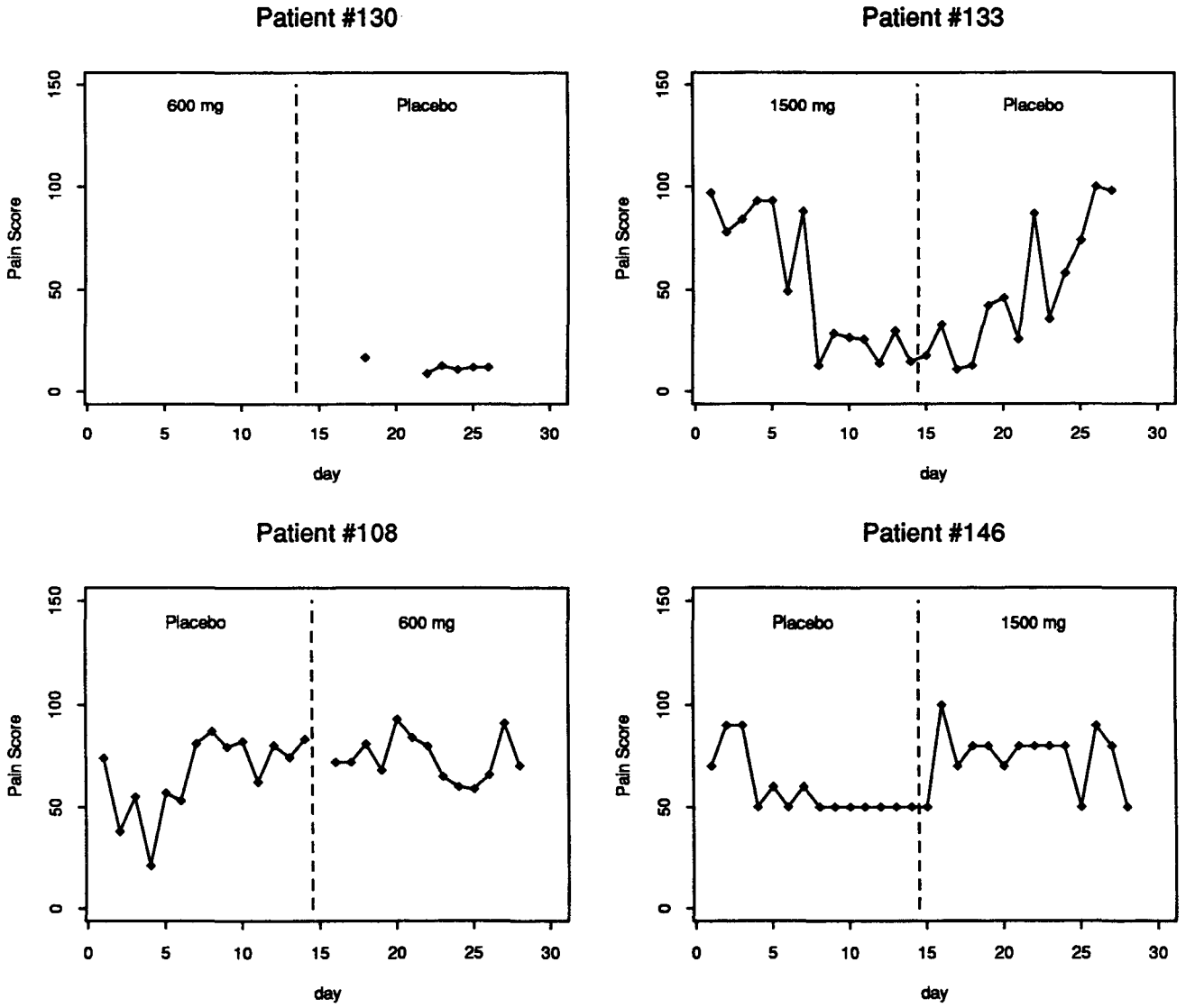


Figure 2.1: Time Sequence Plots of Pain

From the time sequence plot of the pain score of Patient #108 in Figure 2.1, One missing observation at day 15 can be seen, and this patient was observed for 28 days in the study.

The time sequence plots of the pain variable of Patient #133 and Patient #146 are

also displayed in Figure 2.1. It can be seen that both patients were crossed over to the alternate drug at day 15, and observed for 28 days throughout the study. But the observation of Patient #133 on last day was missing.

Generally it can be seen from Figure 2.1 that the number of observations of each patient and the length of the period for every patient may be different. Due to missing data, the number of observations on each patient for different variables may also be different. The large difference in the response on the variable pain among the patient can also be seen from Figure 2.1. The subject (patient) should be considered as an important factor in the statistical analysis.

Throughout the study, three treatments: placebo, 600 mg active drug and 1500 mg active drug were randomly assigned to the 44 patients. The three treatments were coded as treatment 0, treatment 1 and treatment 2, respectively, in the analysis. The responses were first summarized by treatments.

Table 2.3: Summary on Pain Variables by Treatment

| Variable | Treatment | Size | Mean | Standard Deviation | Minimum | Maximum |
|---|---|---|---|---|---|---|
| Pain | 0* | 538 | 41.25 | 28.07 | 0 | 129 |
| | 1 | 320 | 35.90 | 29.38 | 0 | 130 |
| | 2 | 259 | 42.51 | 26.61 | 0 | 111 |
| Pain while | 0 | 546 | 32.86 | 24.64 | 0 | 126 |
| at Rest | 1 | 321 | 29.49 | 26.31 | 0 | 130 |
| | 2 | 257 | 36.53 | 24.00 | 0 | 112 |
| Pain with | 0 | 545 | 48.82 | 27.39 | 0 | 117 |
| Movement | 1 | 320 | 42.51 | 30.24 | 0 | 130 |
| | 2 | 256 | 48.31 | 25.04 | 0 | 110 |

*0 = placebo; 1 = 600 mg active drug; 2 = 1500 mg active drug

Table 2.4: Summary on Activity Level by Treatment

| Treatment | Size | Mean | Standard Deviation | Minimum | Maximum |
|---|---|---|---|---|---|
| 0 | 546 | 38.59 | 21.38 | 0 | 117 |
| 1 | 318 | 39.11 | 23.98 | 0 | 116 |
| 2 | 257 | 38.89 | 18.50 | 0 | 93 |

The response summary scores for the three variables measuring pain are summarized in Table 2.3, and the summary scores of activity level is outlined in Table 2.4. The plot of means of pain variables and activity level by Treatment is displayed in Figure 2.2.

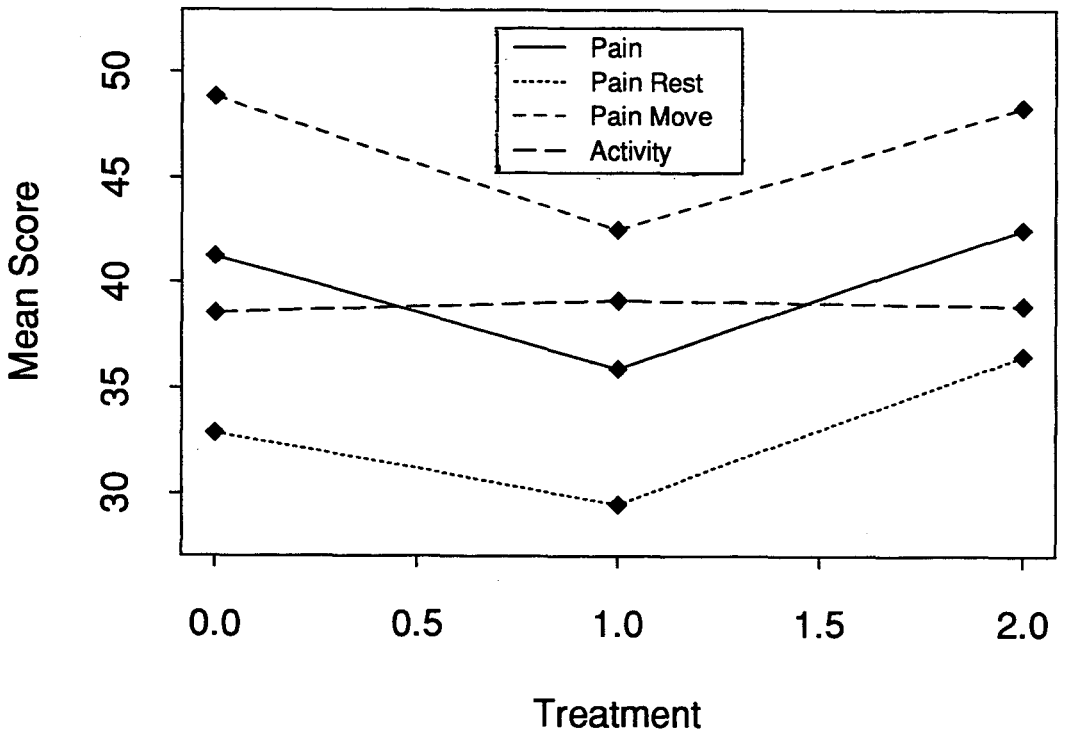


Figure 2.2: Plot of Means of Pain Variables and Activity Level by Treatment

The mean scores on the pain variables reflect little difference between the treatments. For all the three variables measuring pain (Table 2.3), treatment 1 has the lowest mean

scores. Mean scores for treatments 0 and 2 are relatively close. However the mean scores on Activity level (Table 2.4) are almost the same across the treatments. This also can be seen from Figure 2.2. Note that the number of observations for different treatment are not same.

The overall scores for the other response variables are summarized in Table 2.5. Note that the mean scores on the other response variables are very similar across the treatments except for the response variable nausea.

Table 2.5: Summary on Side-Effect Variables by Treatment

| Variable | Treatment | Size | Mean | Standard Deviation | Minimum | Maximum |
|---|---|---|---|---|---|---|
| Nausea | 0 | 544 | 26.16 | 24.75 | 0 | 117 |
| | 1 | 319 | 18.62 | 21.70 | 0 | 100 |
| | 2 | 257 | 27.77 | 21.86 | 0 | 115 |
| Depress | 0 | 547 | 30.97 | 27.72 | 0 | 130 |
| | 1 | 320 | 27.15 | 30.43 | 0 | 130 |
| | 2 | 257 | 30.12 | 23.45 | 0 | 114 |
| Anxiety | 0 | 545 | 32.85 | 27.28 | 0 | 130 |
| | 1 | 320 | 31.60 | 29.70 | 0 | 130 |
| | 2 | 258 | 30.83 | 23.38 | 0 | 110 |
| Drowsy | 0 | 541 | 40.34 | 26.62 | 0 | 130 |
| | 1 | 320 | 39.37 | 28.88 | 0 | 121 |
| | 2 | 248 | 36.66 | 24.82 | 0 | 112 |
| Appetite | 0 | 546 | 56.89 | 29.47 | 0 | 130 |
| | 1 | 320 | 56.62 | 32.51 | 0 | 120 |
| | 2 | 258 | 63.84 | 28.41 | 0 | 126 |

Boxplots of the responses on the variables of pain and activity level for the three different treatments after removing patient effects are displayed in Figure 2.3. The patient effects were removed by subtracting the average patient response from all the observations

for each patient. The medians of the response variable for the three treatments are very close. Some unusually large values can be seen from both boxplots in Figure 2.3. The number of unusually large values for 1500 mg active drug is quite few.

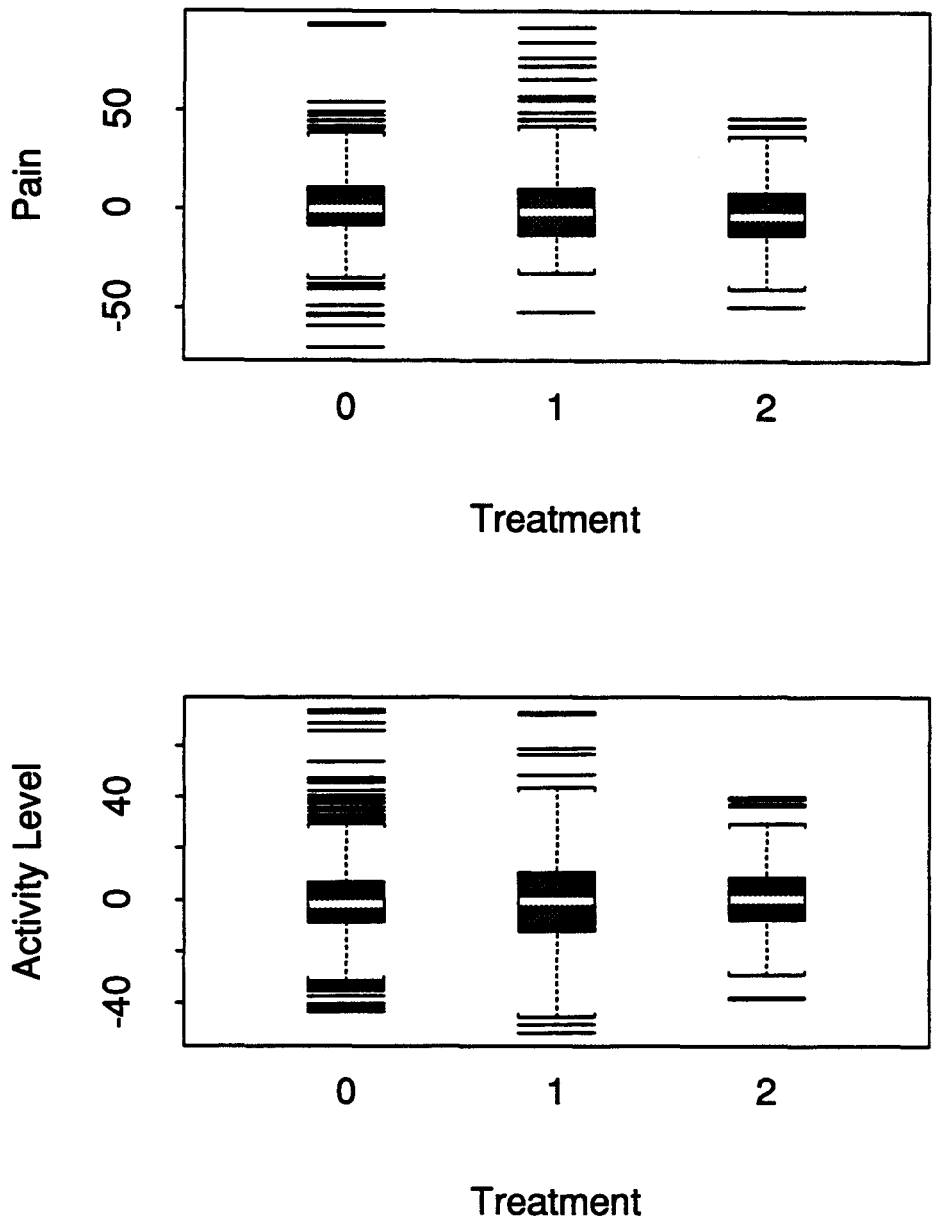


Figure 2.3: Boxplots of Pain and Activity Level by Treatment

The order of administration of the two drugs, i.e. period, on each patient was also considered to be an important factor in the analysis. This is because, if the drug is effective, the pain level should be lower after the administration of the drug than before the administration of the drug. Note that both order of administration and dosage are reflected in the groups assigned in the clinical trial. The measurement scores on the response variables are then summarized by group and treatment.

Table 2.6: Summary of Pain Variables by Group and Treatment

| Variable | Group | Treatment | Size | Mean | Standard Deviation | Minimum | Maximum |
|---|---|---|---|---|---|---|---|
| Pain | 1 | 1 | 185 | 31.67 | 24.68 | 0 | 100 |
| | | 0 | 141 | 24.78 | 23.54 | 0 | 100 |
| | 2 | 2 | 144 | 38.26 | 20.53 | 0 | 97 |
| | | 0 | 149 | 49.21 | 22.03 | 10 | 109 |
| | 3 | 0 | 129 | 46.41 | 32.33 | 0 | 129 |
| | | 1 | 135 | 41.70 | 34.05 | 0 | 130 |
| | 4 | 0 | 119 | 45.18 | 27.13 | 2 | 105 |
| | | 2 | 115 | 47.83 | 31.97 | 3 | 111 |
| Pain while at Rest | 1 | 1 | 186 | 26.34 | 21.44 | 0 | 100 |
| | | 0 | 149 | 19.47 | 19.30 | 0 | 95 |
| | 2 | 2 | 144 | 31.52 | 17.24 | 0 | 112 |
| | | 0 | 148 | 43.02 | 24.47 | 5 | 117 |
| | 3 | 0 | 130 | 30.86 | 24.91 | 0 | 126 |
| | | 1 | 135 | 33.84 | 31.40 | 0 | 130 |
| | 4 | 0 | 119 | 39.19 | 22.61 | 4 | 92 |
| | | 2 | 113 | 42.90 | 29.40 | 1 | 107 |
| Pain with Movement | 1 | 1 | 185 | 40.15 | 25.23 | 0 | 105 |
| | | 0 | 147 | 37.57 | 27.25 | 0 | 99 |
| | 2 | 2 | 142 | 41.58 | 21.37 | 0 | 110 |
| | | 0 | 149 | 54.30 | 20.98 | 16 | 105 |
| | 3 | 0 | 130 | 52.72 | 33.11 | 0 | 117 |
| | | 1 | 135 | 45.74 | 35.83 | 0 | 130 |
| | 4 | 0 | 119 | 51.59 | 23.84 | 5 | 95 |
| | | 2 | 114 | 56.69 | 26.79 | 8 | 100 |

The response scores on the pain variables for the three treatments in the four different groups are summarized in Table 2.6.

The mean scores, the minimum scores, and the maximum scores for the pain variables are generally lower after the administration of the active drug than after placebo for group 2 (patients receiving 1500 mg active drug followed by placebo) and group 3 (patients receiving placebo followed by 600 mg active drug); and higher after the administration of the active drug than after placebo for group 1 (patients receiving 600 mg active drug followed by placebo) and group 4 (patients receiving placebo followed by 1500 mg active drug). For the same treatment between groups, the mean scores for treatment 2, i.e. 1500 mg active drug, are lower when the active drug was administered before the placebo; the mean scores for treatment 0 or placebo are generally lower when 600 mg active drug was administered before the placebo.

The summary scores on the variable of activity level are in Table 2.7. The mean scores are very close between treatments within group.

Table 2.7: Summary of Activity Level by Group and Treatment

| Group | Treatment | Size | Mean | Standard Deviation | Minimum | Maximum |
|---|---|---|---|---|---|---|
| 1 | 1 | 183 | 38.93 | 21.90 | 0 | 100 |
| | 0 | 148 | 35.36 | 22.95 | 0 | 105 |
| 2 | 2 | 143 | 39.46 | 18.12 | 7 | 93 |
| | 0 | 149 | 38.48 | 17.83 | 9 | 80 |
| 3 | 0 | 130 | 42.22 | 25.49 | 0 | 117 |
| | 1 | 135 | 39.36 | 26.62 | 0 | 116 |
| 4 | 0 | 119 | 38.76 | 17.85 | 1 | 98 |
| | 2 | 114 | 38.18 | 19.03 | 0 | 80 |

For the side effect variables, the measurement scores by treatment and group are summarized in Table 2.8. The differences between treatments within group are generally small for all the side-effect variables in Table 2.8. However, the variations between groups

are relatively large for some variables, e.g., anxiety.

The marginal summaries (by response variable) presented in this chapter address only partial features of the case study. They form part of a preliminary data analysis and should be treated with caution. One of the difficulties for interpretations is that the response values coming from any particular individual are very likely correlated. Additionally, because of the presence of the other factors, a good degree of mixing may be occurring in the marginal analysis. These issues serve as motivation to consider statistical models that account for the issues raised and that permit a more thorough look at the data.

Table 2.8: Summary of Side-Effect Variables by Group and Treatment

| Variable | Group | Treatment | Size | Mean | Standard Deviation | Minimum | Maximum |
|---|---|---|---|---|---|---|---|
| Nausea | 1 | 1 | 185 | 16.53 | 19.53 | 0 | 100 |
| | | 0 | 149 | 19.68 | 19.22 | 0 | 99 |
| | 2 | 2 | 142 | 29.00 | 20.00 | 0 | 106 |
| | | 0 | 147 | 35.24 | 25.89 | 0 | 113 |
| | 3 | 0 | 129 | 26.02 | 30.62 | 0 | 117 |
| | | 1 | 134 | 21.51 | 24.16 | 0 | 95 |
| | 4 | 0 | 119 | 23.19 | 18.53 | 0 | 77 |
| | | 2 | 115 | 26.25 | 23.25 | 0 | 115 |
| Depress | 1 | 1 | 185 | 21.51 | 20.74 | 0 | 95 |
| | | 0 | 149 | 22.29 | 19.45 | 0 | 85 |
| | 2 | 2 | 142 | 31.42 | 22.60 | 0 | 110 |
| | | 0 | 149 | 38.74 | 25.75 | 0 | 107 |
| | 3 | 0 | 130 | 32.08 | 35.55 | 0 | 130 |
| | | 1 | 135 | 34.89 | 38.84 | 0 | 130 |
| | 4 | 0 | 119 | 30.90 | 26.36 | 0 | 99 |
| | | 2 | 115 | 28.53 | 24.47 | 0 | 114 |

Table 2.8: **Con't**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Anxiety | 1 | 1 | 185 | 24.23 | 22.71 | 0 | 103 |
| | | 0 | 148 | 22.20 | 19.21 | 0 | 97 |
| | 2 | 2 | 143 | 32.37 | 23.09 | 0 | 110 |
| | | 0 | 149 | 37.60 | 26.24 | 0 | 110 |
| | 3 | 0 | 130 | 40.99 | 31.92 | 0 | 130 |
| | | 1 | 135 | 41.70 | 34.83 | 0 | 130 |
| | 4 | 0 | 118 | 31.22 | 27.45 | 0 | 100 |
| | | 2 | 115 | 28.92 | 23.69 | 0 | 101 |
| Drowsy | 1 | 1 | 185 | 35.82 | 28.91 | 0 | 107 |
| | | 0 | 149 | 33.97 | 25.44 | 0 | 107 |
| | 2 | 2 | 143 | 41.20 | 21.56 | 0 | 89 |
| | | 0 | 149 | 49.72 | 22.84 | 0 | 103 |
| | 3 | 0 | 129 | 40.05 | 31.36 | 0 | 130 |
| | | 1 | 135 | 44.23 | 28.22 | 0 | 121 |
| | 4 | 0 | 114 | 36.74 | 23.64 | 0 | 100 |
| | | 2 | 105 | 30.47 | 27.59 | 0 | 112 |
| Appetite | 1 | 1 | 185 | 54.20 | 35.55 | 0 | 117 |
| | | 0 | 148 | 43.74 | 25.41 | 1 | 91 |
| | 2 | 2 | 145 | 65.83 | 29.82 | 12 | 126 |
| | | 0 | 149 | 61.30 | 30.31 | 3 | 120 |
| | 3 | 0 | 130 | 57.62 | 33.66 | 0 | 130 |
| | | 1 | 135 | 59.93 | 27.60 | 4 | 120 |
| | 4 | 0 | 119 | 66.92 | 21.70 | 22 | 120 |
| | | 2 | 113 | 61.29 | 26.41 | 0 | 120 |

# Chapter 3

# Multivariate Analysis of Variance by Summary Scores

## 3.1 Introduction

Because the observations on each patient in our data set have been gathered sequentially, the experiment belongs to the subclass of longitudinal studies commonly referred to as repeated measure experiments. Hoke, Lavori and Perry (1992) provided an interesting discussion on the applied aspects of statistical methods for longitudinal studies.

For repeated experimental designs with the same number of repeated observations per subject, measured at the same time intervals and with no missing data, the standard linear model methods, such as repeated measures analysis of variance (RM ANOVA) and multivariate analysis of variance (MANOVA), are highly efficient and work optimally (Lavori, 1990). However the present data set does not fall within these constraints. On one hand, not every patient was observed for the same number of days before crossing over to the second drug. Thus, the number of observations and the time period of observation are different for the subjects. On the other hand, and perhaps more importantly, the observations on each subject are likely to be dependent on each other. Thus, an ordinary (repeated measures) linear statistical model with the full data set seems inappropriate for

the analysis of the data.

## 3.2 Use of Summary Scores

In situations where different number of observations are made on each subject in different periods, a simpler way to handle repeated observations is to use single summary scores, such as means and medians of each individual in each period (Hoke, Lavori and Perry, 1992). These summary scores can be analyzed by using ordinary statistical methods. The use of summary statistics has advantages of simplicity.

The summary scores: mean, median, and trmean of each response variable in each observing period were used in the analysis. The trmean is a 5% trimmed mean obtained by removing the smallest 5% (rounded to the nearest integer) and the largest 5% of the values, and then computing the mean of the middle 90%. These summary scores represent the overall levels of the response for each subject. The means, medians, and trmeans of each response variable were calculated using Minitab (1994) on Windows.

The objective of the analysis is to test if the drug is effective and the two doses are significantly different as well as if there is any side effect to the patients. The following nine variables

$$\begin{pmatrix} \text{pain} \\ \text{pain while at rest} \\ \text{pain with movement} \\ \text{activity level} \\ \text{nausea} \\ \text{depression} \\ \text{anxiety} \\ \text{drowsiness} \\ \text{appetite.} \end{pmatrix}$$

were used to measure the responses of the subject in the study. There are three variables measuring pain of the patient (pain, pain while at rest, and pain with movement), one variable measuring the activity level of the patient, and five variables measuring side effects of the drug to the patient (nausea, depression, anxiety, drowsiness, and appetite).

When a summary score is used, the problem may be analyzed by a three-way ANOVA for a single response variable or a three-way MANOVA for more than one response variables with three factors: subject, period, and treatment.

## 3.3 Multivariate Analysis of Variance (MANOVA) for Pain Variables

For the three response variables measuring pain, namely

$$\underset{(3\times 1)}{\boldsymbol{Y}} = \begin{pmatrix} \text{pain} \\ \text{pain while at rest} \\ \text{pain with movement} \end{pmatrix}$$

the problem may be analyzed as a three-way MANOVA with unequal number (1 or 0) of observations per cell. The data were fitted by the model

$$\begin{array}{ccccccccc} \mathbf{Y}_{ijkl} & = & \boldsymbol{\mu} & + & \boldsymbol{\alpha}_i & + & \boldsymbol{\beta}_j & \left\{ \begin{array}{l} i = 1, 2, \ldots, 44 \\ j = 1, 2 \\ k = 1, 2, 3 \\ l = 0, 1, \ldots, n_{ijk} \end{array} \right. \\ (3\times 1) & & (3\times 1) & & (3\times 1) & & (3\times 1) & & \\ & + & \boldsymbol{\gamma}_k & + & (\boldsymbol{\beta\gamma})_{jk} & + & \boldsymbol{e}_{ijkl} & & \\ & & (3\times 1) & & (3\times 1) & & (3\times 1) & & \end{array} \tag{3.1}$$

where $\boldsymbol{\mu}$ is the overall mean, $\boldsymbol{\alpha}_i$ is the effect of the $i$th subject, $\boldsymbol{\beta}_j$ is the effect of the $j$th period, $\boldsymbol{\gamma}_k$ is the effect of the $k$th treatment, and $(\boldsymbol{\beta\gamma})_{jk}$ is the interaction of the $j$th period and the $k$th treatment.

Assume:

$$\sum_{i=1}^{44} \alpha_i = \sum_{j=1}^{2} \beta_j = \sum_{k=1}^{3} \gamma_k = 0,$$

$$\sum_{j=1}^{2} (\beta\gamma)_{jk} = \sum_{k=1}^{3} (\beta\gamma)_{jk} = 0$$

and $e_{ijkl} \sim$ iid $N_3(\mathbf{0}, \Sigma)$, where $\Sigma$ is positive definite. The analysis was performed by Procedure GLM in SAS (see SAS, 1985, pp. 433-506 for details).

Tables 3.1-3.3 present the summary statistics required for the testing of the hypothesis of no overall effect to the pain when the summary scores: mean, median and trmean were used in the analysis, respectively.

Table 3.1: MANOVA Summary on Pain Variables by Mean ($p = 3$)

| | Effect | | | |
|---|---|---|---|---|
| | Patient | Period | Treatment | Interaction of Period and Treatment |
| Degrees of Freedom under Hypothesis | 43 | 1 | 2 | 1 |
| Degrees of Freedom for Error | 36 | 36 | 36 | 36 |
| Wilks' Lambda Criterion | 0.001 | 0.800 | 0.727 | 0.716 |
| Degrees of Freedom | 129, 103 | 3, 34 | 6, 68 | 3, 34 |
| F-Value | 7.090 | 2.839 | 1.956 | 4.506 |
| $Pr > F$ | 0.0001 | 0.052 | 0.084 | 0.009 |
| Pillai's Trace Criterion | 2.678 | 0.200 | 0.281 | 0.284 |
| $Pr > F$ | 0.0001 | 0.052 | 0.091 | 0.009 |
| Hotelling-Lawley Trace | 28.655 | 0.251 | 0.363 | 0.398 |
| $Pr > F$ | 0.0001 | 0.052 | 0.079 | 0.009 |
| Roy's Greatest Root | 15.277 | 0.251 | 0.327 | 0.398 |
| $Pr > F$ | 0.0001 | 0.052 | 0.018 | 0.009 |

Table 3.2: MANOVA Summary on Pain Variables by Median ($p = 3$)

| | Effect | | | |
|---|---|---|---|---|
| | Patient | Period | Treatment | Interaction of Period and Treatment |
| Degrees of Freedom under Hypothesis | 43 | 1 | 2 | 1 |
| Degrees of Freedom for Error | 36 | 36 | 36 | 36 |
| Wilks' Lambda Criterion | 0.002 | 0.871 | 0.774 | 0.646 |
| Degrees of Freedom | 129, 103 | 3, 34 | 6, 68 | 4, 34 |
| F-Value | 5.219 | 1.671 | 1.545 | 6.203 |
| $Pr > F$ | 0.0001 | 0.192 | 0.177 | 0.002 |
| Pillai's Trace Criterion | 2.583 | 0.129 | 0.230 | 0.354 |
| $Pr > F$ | 0.0001 | 0.192 | 0.186 | 0.002 |
| Hotelling-Lawley Trace | 20.804 | 0.147 | 0.286 | 0.547 |
| $Pr > F$ | 0.0001 | 0.192 | 0.169 | 0.002 |
| Roy's Greatest Root | 10.706 | 0.147 | 0.265 | 0.547 |
| $Pr > F$ | 0.0001 | 0.192 | 0.040 | 0.002 |

Table 3.3: MANOVA Summary on Pain Variables by Trmean ($p = 3$)

| | Effect | | | |
|---|---|---|---|---|
| | Patient | Period | Treatment | Interaction of Period and Treatment |
| Degrees of Freedom under Hypothesis | 43 | 1 | 2 | 1 |
| Degrees of Freedom for Error | 36 | 36 | 36 | 36 |
| Wilks' Lambda Criterion | 0.001 | 0.834 | 0.738 | 0.707 |
| Degrees of Freedom | 129, 103 | 3, 34 | 6, 68 | 3, 34 |
| F-Value | 6.667 | 2.263 | 1.862 | 4.695 |
| $Pr > F$ | 0.0001 | 0.099 | 0.100 | 0.008 |
| Pillai's Trace Criterion | 2.655 | 0.166 | 0.271 | 0.293 |
| $Pr > F$ | 0.0001 | 0.099 | 0.106 | 0.008 |
| Hotelling-Lawley Trace | 27.497 | 0.200 | 0.344 | 0.414 |
| $Pr > F$ | 0.0001 | 0.099 | 0.096 | 0.008 |
| Roy's Greatest Root | 15.379 | 0.200 | 0.305 | 0.414 |
| $Pr > F$ | 0.0001 | 0.099 | 0.024 | 0.008 |

The four statistical tests used, namely Wilks' Lambda, Pillai's Trace, Hotelling-Lawley Trace and Roy's Greatest Root, are the most widely accepted methods because of their good power. Complete details on these methods can be found in Rao (1973, p. 555), Pillai (1960, Tables 2 and 3) and Heck (1960). As an illustration of the calculations involved, we describe in some detail Wilks' Lambda.

The statistical test of Wilks' Lambda is

$$\text{Wilks' Lambda} = \frac{\det(\mathrm{E})}{\det(\mathrm{H}+\mathrm{E})} = \frac{1}{\prod_{j=1}^{p}(1+\lambda_j)}$$

where $E$ is the multivariate error sum of squares, $H$ are the total sample variance between columns and between rows, and $\lambda_j$ is the $j$th latent root of $HE^{-1}$.

These tests do not always yield the same results when more than one response variables ($p > 1$) are used in the analysis (Press, 1972, pp. 253-254). If contradictory results are obtained, interpreting the results should be with extreme caution.

When the means, medians, and trmeans of the patient were used in the analysis, it can be seen from Tables 3.1-3.3 that for Wilks' lambda criterion, Pillai's Trace Criterion, and Hotelling-Lawley Trace, the conclusions are the same, that is, there is no significant treatment effect at 5% significance level. Roy's Greatest Root criterion yields a significant treatment effect at the significance level of 5%.

Note that all the criteria agree in showing that patients do have a significant effect, and the order of application does not have a significant effect marginally. However, the order of application and treatment interact significantly. This is also reflected in Figure 3.1.

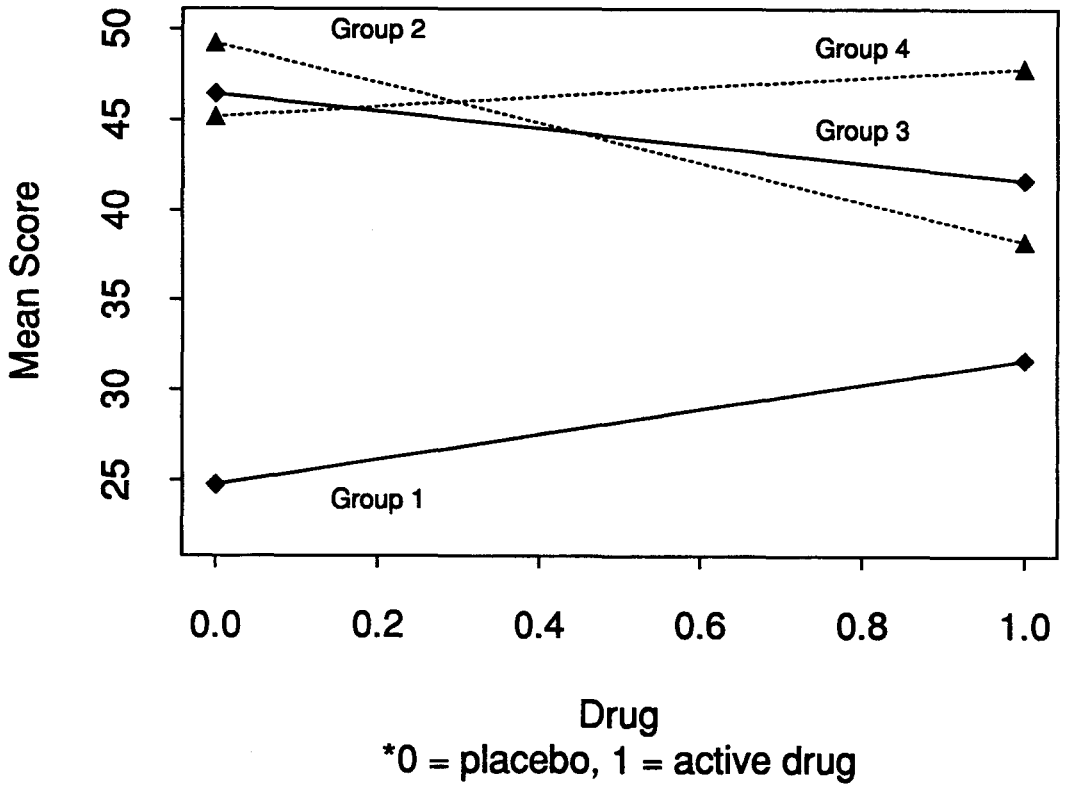


Figure 3.1: Mean Pain in Each Group by Treatment

An indication of the nature of the interaction between the order of application and treatment is exhibited in Figure 3.1. The main feature is a receiving of trends with a change in the order of application.

Unfortunately, there is very litter methodology for checking the goodness-of-fit of MANOVA (see Press, 1976, p. 262).

## 3.4 Multivariate Analysis of Variance (MANOVA) for Side Effects Variables

To test the side effects of the drug, the problem may be also analyzed as a three-way MANOVA with unequal number (1 or 0) of observations per cell for the response variables

$$\underset{(5\times 1)}{\mathbf{Y}} = \begin{pmatrix} \text{nausea} \\ \text{depression} \\ \text{anxiety} \\ \text{drowsiness} \\ \text{appetite} \end{pmatrix}$$

measuring side effects. The data were fitted by the model

$$\begin{array}{ccccccccc} \underset{(5\times 1)}{\mathbf{Y}_{ijkl}} & = & \underset{(5\times 1)}{\boldsymbol{\mu}} & + & \underset{(5\times 1)}{\boldsymbol{\alpha}_i} & + & \underset{(5\times 1)}{\boldsymbol{\beta}_j} & \left\{ \begin{array}{l} i=1,2,\ldots,44 \\ j=1,2 \\ k=1,2,3 \\ l=0,1,\ldots,n_{ijk} \end{array} \right. \\ & + & \underset{(5\times 1)}{\boldsymbol{\gamma}_k} & + & \underset{(5\times 1)}{(\boldsymbol{\beta\gamma})_{jk}} & + & \underset{(5\times 1)}{\boldsymbol{e}_{ijkl}} & \end{array} \tag{3.2}$$

The assumption about $\boldsymbol{\alpha}_i$, $\boldsymbol{\beta}_j$, $\boldsymbol{\gamma}_k$, $(\boldsymbol{\beta\gamma})_{jk}$ in model (3.2) are exactly the same as in model (3.1). But $\boldsymbol{e}_{ijkl} \sim$ iid $N_5(\mathbf{0}, \boldsymbol{\Sigma})$, where $\boldsymbol{\Sigma}$ is positive definite, in this problem. The analysis was performed by the exactly same Procedure GLM in SAS (see SAS, 1985, pp. 433-506 for details).

Table 3.4: MANOVA Summary on Side Effects by Mean ($p = 5$)

| | Effect | | | |
|---|---|---|---|---|
| | Patient | Period | Treatment | Interaction of Period and Treatment |
| Degrees of Freedom under Hypothesis | 43 | 1 | 2 | 1 |
| Degrees of Freedom for Error | 36 | 36 | 36 | 36 |
| Wilks' Lambda Criterion | 0.000003 | 0.823 | 0.853 | 0.863 |
| Degrees of Freedom | 215, 164 | 5, 32 | 10, 64 | 5, 32 |
| F-Value | 9.341 | 1.375 | 0.530 | 1.02 |
| $Pr > F$ | 0.0001 | 0.260 | 0.862 | 0.422 |
| Pillai's Trace Criterion | 4.554 | 0.177 | 0.150 | 0.137 |
| $Pr > F$ | 0.0001 | 0.260 | 0.860 | 0.422 |
| Hotelling-Lawley Trace | 74.207 | 0.215 | 0.170 | 0.159 |
| $Pr > F$ | 0.0001 | 0.260 | 0.865 | 0.422 |
| Roy's Greatest Root | 35.543 | 0.215 | 0.152 | 0.159 |
| $Pr > F$ | 0.0001 | 0.260 | 0.433 | 0.422 |

Table 3.5: MANOVA Summary on Side Effects by Median ($p = 5$)

| | Effect | | | |
|---|---|---|---|---|
| | Patient | Period | Treatment | Interaction of Period and Treatment |
| Degrees of Freedom under Hypothesis | 43 | 1 | 2 | 1 |
| Degrees of Freedom for Error | 36 | 36 | 36 | 36 |
| Wilks' Lambda Criterion | 0.000003 | 0.806 | 0.779 | 0.855 |
| Degrees of Freedom | 215, 164 | 5, 32 | 10, 64 | 5, 32 |
| F-Value | 9.000 | 1.526 | 0.850 | 1.087 |
| $Pr > F$ | 0.0001 | 0.210 | 0.583 | 0.386 |
| Pillai's Trace Criterion | 4.540 | 0.192 | 0.224 | 0.145 |
| $Pr > F$ | 0.0001 | 0.210 | 0.598 | 0.386 |
| Hotelling-Lawley Trace | 69.935 | 0.238 | 0.279 | 0.170 |
| $Pr > F$ | 0.0001 | 0.210 | 0.570 | 0.386 |
| Roy's Greatest Root | 31.864 | 0.238 | 0.262 | 0.170 |
| $Pr > F$ | 0.0001 | 0.210 | 0.156 | 0.386 |

Table 3.6: MANOVA Summary on Side Effects by Trmean ($p = 5$)

| | Effect | | | |
|---|---|---|---|---|
| | Patient | Period | Treatment | Interaction of Period and Treatment |
| Degrees of Freedom under Hypothesis | 43 | 1 | 2 | 1 |
| Degrees of Freedom for Error | 36 | 36 | 36 | 36 |
| Wilks' Lambda Criterion | 0.000002 | 0.814 | 0.839 | 0.867 |
| Degrees of Freedom | 215, 164 | 5, 32 | 10, 64 | 5, 32 |
| F-Value | 9.882 | 1.463 | 0.587 | 0.978 |
| $Pr > F$ | 0.0001 | 0.229 | 0.819 | 0.446 |
| Pillai's Trace Criterion | 4.573 | 0.186 | 0.164 | 0.133 |
| $Pr > F$ | 0.0001 | 0.229 | 0.818 | 0.446 |
| Hotelling-Lawley Trace | 79.491 | 0.229 | 0.189 | 0.153 |
| $Pr > F$ | 0.0001 | 0.229 | 0.820 | 0.446 |
| Roy's Greatest Root | 38.614 | 0.229 | 0.171 | 0.153 |
| $Pr > F$ | 0.0001 | 0.229 | 0.366 | 0.446 |

The summary statistics required for the hypothesis testing of no effects to the side effects of the drug are outlined in Tables 3.4-3.6 when the summary scores: mean, median and trmean were used in the analysis.

At this time all the criteria agree in showing that treatments do not have a significant effect at a 5% significance level, and the order of application and the interaction of order and treatment do not have a significant effect either. Patients have a significant effect.

## 3.5 Analysis of Variance (ANOVA) for Activity Level

For the testing of hypothesis of no effect to the activity level of the patient, the problem may be analyzed as a three way ANOVA for the response of activity level. The data were fitted by the model

$$\mathbf{Y}_{ijkl} = \boldsymbol{\mu} + \boldsymbol{\alpha}_i + \boldsymbol{\beta}_j + \boldsymbol{\gamma}_k + (\boldsymbol{\beta\gamma})_{jk} + \boldsymbol{e}_{ijkl} \begin{cases} i = 1, 2, \ldots, 44 \\ j = 1, 2 \\ k = 1, 2, 3 \\ l = 0, 1, \ldots, n_{ijk} \end{cases} \tag{3.3}$$

The assumption about $\alpha_i$, $\beta_j$, $\gamma_k$, and $(\beta\gamma)_{jk}$ in model (3.3) are exactly the same as before. Note $e_{ijkl} \sim$ iid N(0, $\sigma^2$), and $\alpha_i$, $\beta_j$, $\gamma_k$, and $(\beta\gamma)_{jk}$ are not vectors in this problem.

By the same Procedure GLM in SAS, the analysis of variance are summarized in Tables 3.7-3.9 for the summary scores of mean, median, and trmean, respectively.

Table 3.7: ANOVA on Activity Level by Mean

| Source of Variation | Degree of Freedom | Sum of Square | Mean Square | F-Value | $Pr > F$ | R-Square |
|---|---|---|---|---|---|---|
| Model | 47 | 15738.9 | 334.9 | 5.16 | 0.0001 | 0.87 |
| Patient | 43 | 15642.1 | 363.8 | 5.60 | 0.0001 | |
| Period | 1 | 23.5 | 23.5 | 0.36 | 0.5508 | |
| Treatment | 2 | 54.1 | 27.0 | 0.42 | 0.6625 | |
| Period* Treatment | 1 | 19.2 | 19.2 | 0.30 | 0.5902 | |
| Error | 36 | 2336.6 | 64.9 | | | |
| Total | 83 | 18075.5 | | | | |

Table 3.8: ANOVA on Activity Level by Median

| Source of Variation | Degree of Freedom | Sum of Square | Mean Square | F-Value | $Pr > F$ | R-Square |
|---|---|---|---|---|---|---|
| Model | 47 | 19381.9 | 412.4 | 4.77 | 0.0001 | 0.86 |
| Patient | 43 | 19244.8 | 447.6 | 5.17 | 0.0001 | |
| Period | 1 | 53.6 | 53.6 | 0.62 | 0.4362 | |
| Treatment | 2 | 19.0 | 9.5 | 0.11 | 0.8964 | |
| Period* Treatment | 1 | 64.5 | 64.5 | 0.75 | 0.3934 | |
| Error | 36 | 3113.5 | 86.5 | | | |
| Total | 83 | 22495.4 | | | | |

Table 3.9: ANOVA on Activity Level by Trmean

| Source of Variation | Degree of Freedom | Sum of Square | Mean Square | F-Value | $Pr > F$ | R-Square |
|---|---|---|---|---|---|---|
| Model | 47 | 16745.5 | 356.3 | 5.16 | 0.0001 | 0.87 |
| Patient | 43 | 16605.5 | 386.2 | 5.60 | 0.0001 | |
| Period | 1 | 36.1 | 36.1 | 0.52 | 0.4744 | |
| Treatment | 2 | 56.6 | 28.3 | 0.41 | 0.6664 | |
| Period* Treatment | 1 | 47.2 | 47.2 | 0.68 | 0.4134 | |
| Error | 36 | 2484.2 | 69.0 | | | |
| Total | 83 | 19229.7 | | | | |

To the activity level of the patient, the treatment effect are not significant, and the patient effect are significant at 1% significance level when the mean, median and trmean were used in the analysis, respectively. The R-Square are about 0.86. The residual plots of mean activity level, median activity level and trmean activity level against the predict

values of response are presented in Figures 3.2-3.4, respectively. None of these plots shows any clear pattern among the residuals.

From the analysis above, it can be seen that whatever the type of the summary scores was used in the analysis, at 5% significance level the conclusions from the analysis of the variance by three different summary scores are consistent.

Generally speaking, when the data were analyzed by the summary scores: mean, median or trmean, by Wilks' lambda criterion, the difference among the patients are always significant at a 1% significance level, and the treatment effect are not significant at 5% significance level to the pain, activity level and associated side effects.

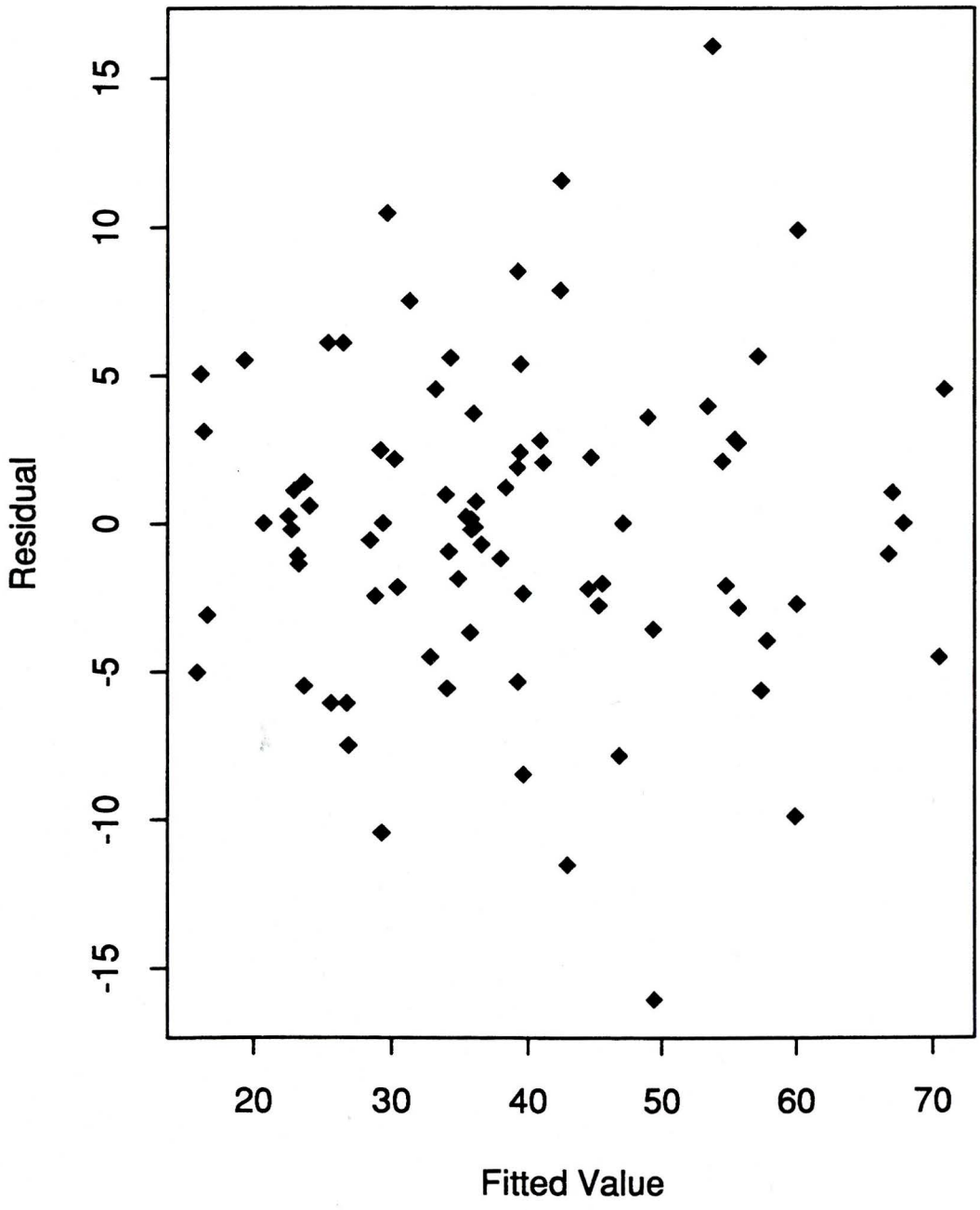


Figure 3.2: Residual Plot of Mean Activity Level

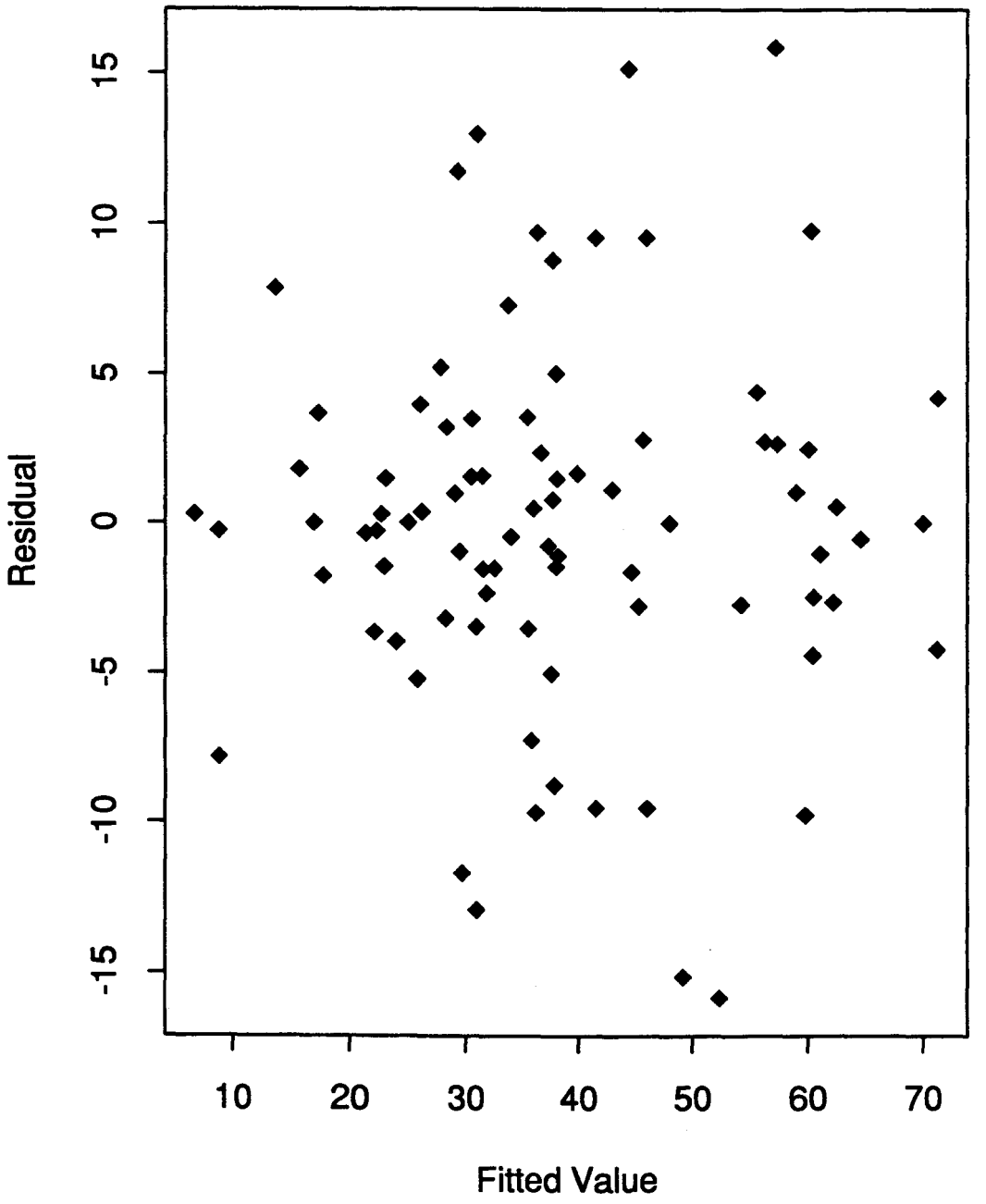


Figure 3.3: Residual Plot of Median Activity Level

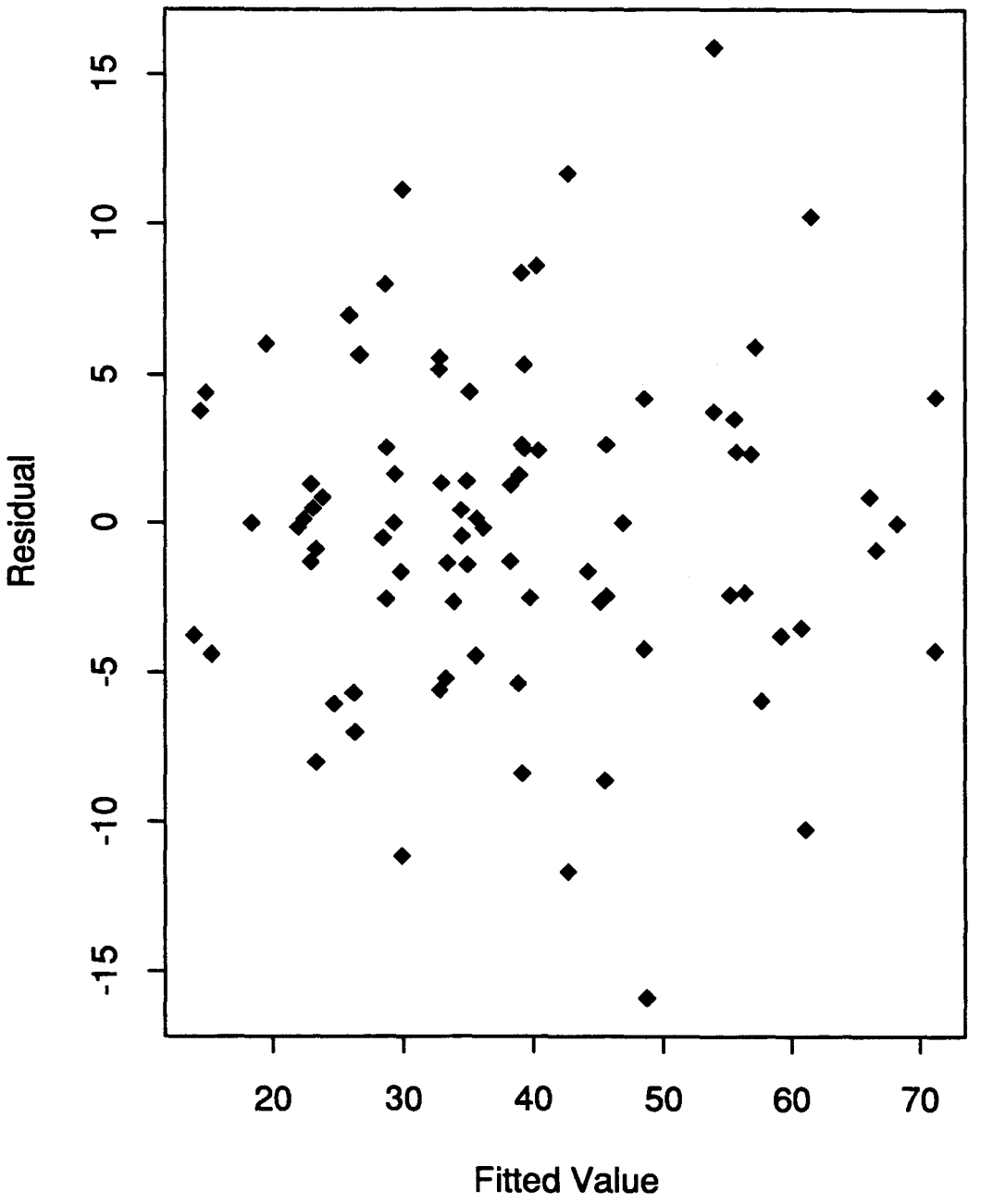


Figure 3.4: Residual Plot of Trmean Activity Level

# Chapter 4

# Accounting for Correlation: Generalized Estimating Equations

## 4.1 Introduction

In Chapter 3 we presented the analysis of the data using the mean, median and trmean as summary scores. This analysis avoids consideration of any possible correlation of the observations within each patient. Because repeated observations are made on the same individual, the measurements of each response variable are usually correlated. The correlation among observations for each subject are taken into account in the approach of the generalized estimating equations (GEEs). This method will be used in this chapter to analyze the data.

The generalized estimating equations method was developed to facilitate the analysis of repeated measurement data (Zeger and Liang, 1986; Liang and Zeger, 1986). Generalized estimating equations are based on moments of the response vector and only require the specification of the form of the first two moments of the response vector for each individual. The estimates of the regression parameters and of their variance obtained from GEEs are consistent and asymptotically Gaussian under mild assumptions about the time dependence, even when the "working" correlation matrix is incorrectly specified.

In this chapter, a marginal model was specified for each response variable. The estimates of the regression parameters, and related asymptotic standard normal statistics obtained by applying GEEs under various assumptions are presented. The results for the response variable pain are discussed in detail in the following. The results for response variables of pain while at rest and pain with movement are also summarized. For other response variables, the results can be obtained similarly.

## 4.2 Marginal Model

Let $y_{it}$ be the response of patient $i$ at day $t$, $t = 1, 2, \ldots, n_i$, for the measurement pain, where $n_i$ may be different for all $K = 44$ patients. In most of our cases, $n_i = 28$. With a continuous response $y_{it}$ we form a $n_i \times 1$ vector

$$\mathbf{Y}_i = [y_{i1},\ y_{i2},\ \ldots,\ y_{in_i}]'$$

for the $i$th patient, $i = 1, 2, \ldots, K$. The missing data are assumed to be missing completely at random (Rubin, 1976). Therefore, all missing data are removed from the analysis before the model is fitted. There are two time-dependent covariates: period and treatment, and one time-independent covariate: age. Since the response variable $y_{it}$ is continuous, a natural choice of link function is the identity and a marginal regression model should be

$$E(y_{it}) = \mu_{it},$$

$$\mu_{it} = \beta_0 + \beta_1 \text{age} + \beta_2 \text{period} + \beta_3 \text{treatment} + \beta_4 \text{period*treatment},$$

and

$$Var(y_{it}) = 1.$$

The marginal model can be rewritten as

$$E(y_{it}) = \mathbf{x}_{it}\boldsymbol{\beta} \tag{4.1}$$

where $\boldsymbol{\beta} = [\beta_0, \beta_1, \beta_2, \beta_3, \beta_4]'$, and $\mathbf{x}_{it}$ = [1, age, period, treatment, period*treatment].

## 4.3 Generalized Estimating Equations

Consider the generalized estimating equations proposed by Liang and Zeger (1986):

$$\sum_{i=1}^{K} D_i' V_i^{-1} (Y_i - \mu_i) = 0, \tag{4.2}$$

where $D_i = \dfrac{\partial \boldsymbol{\mu}_i}{\partial \boldsymbol{\beta}}$, $V_i$ is the "working" covariance matrix of $\boldsymbol{Y}_i$, and $\mu_i = [\mu_{i1}, \mu_{i2}, \ldots, \mu_{in_i}]'$.

Let $\mathbf{X}_i = (x_{i1}, x_{i2}, \ldots, x_{in_i})'$ be the $n_i \times 5$ matrix for the $i$th subject $(i = 1, \ldots, K)$. Therefore, $\boldsymbol{\mu}_i = X_i \boldsymbol{\beta}$. The working covariance matrix in (4.2) has the form

$$V_i = A_i^{\frac{1}{2}} R_i(\alpha) A_i^{\frac{1}{2}}$$

where $A_i$ is $n_i \times n_i$ diagonal matrix with diagonal elements $\mathrm{Var}(y_{it})$ and $R_i(\alpha) = \mathrm{corr}(Y_i)$ is $n_i \times n_i$ working correlation matrix, which is assumed to be fully specified by the $s \times 1$ vector of unknown parameter $\boldsymbol{\alpha}$, $\boldsymbol{\alpha}$ is the same for all the subjects.

Under mild regularity conditions, Liang and Zeger (1986) have shown that as $K \to \infty$, the estimate $\hat{\boldsymbol{\beta}}_G$ of $\boldsymbol{\beta}$ obtained from GEEs (4.2) is a consistent estimator of $\boldsymbol{\beta}$ and $K^{\frac{1}{2}}(\hat{\boldsymbol{\beta}}_G - \boldsymbol{\beta})$ is asymptotically multivariate Gaussian with zero mean and covariance matrix $V_G$ given by

$$V_G = \lim_{K \to \infty} K \Big(\sum_{i=1}^{K} D_i' V_i^{-1} D_i\Big)^{-1} \Big[\sum_{i=1}^{K} D_i' V_i^{-1} \mathrm{cov}(Y_i) V_i^{-1} D_i\Big] \Big(\sum_{i=1}^{K} D_i' V_i^{-1} D_i\Big)^{-1} \tag{4.3}$$

The variance estimate $\hat{V}_G$ of $\hat{\boldsymbol{\beta}}_G$ can be obtained by

$$\hat{V}_G = K \Big(\sum_{i=1}^{K} D_i' V_i^{-1} D_i\Big)^{-1} \Big[\sum_{i=1}^{K} D_i' V_i^{-1} (y_i - \mu_i)(y_i - \mu_i)' V_i^{-1} D_i\Big] \Big(\sum_{i=1}^{K} D_i' V_i^{-1} D_i\Big)^{-1}. \tag{4.4}$$

Thus asymptotically

$$\frac{K^{\frac{1}{2}}(\hat{\boldsymbol{\beta}}_{G_i} - \boldsymbol{\beta}_i)}{\sqrt{\hat{V}_{G_{ii}}}} \sim \mathrm{N}(0, 1)$$

where $\hat{\beta}_{G_i}$ is the $i$th element of $\hat{\beta}_G$ and $\hat{V}_{G_{ii}}$ is the $i$th diagonal element of $\hat{V}_G$.

A useful feature of the GEE approach developed by Zeger and Liang (1986) is that a consistent and asymptotically Gaussian estimate, $\hat{\beta}_G$, can be obtained even when the "working" correlation matrix $R_i(\alpha)$ is not correctly specified.

## 4.4 Estimated Regression Coefficients for Pain Variables

Here

$$\mu_i = X_i\beta, \quad A_i = I_{n_i}$$

where $I_{n_i}$ is the $n_i \times n_i$ identity matrix, and

$$D_i = \frac{\partial \mu_i}{\partial \beta} = X_i, \quad V_i = R_i(\alpha).$$

To get a solution from GEE (4.2), a program was written in Matlab (1994) on a UNIX machine, and the related asymptotic standard normal statistics when $\beta = 0$ were also obtained by using three different choices of $R_i(\alpha)$:

- $R_i(\alpha) = I_{n_i}$, i.e. that repeated observations of each patient are uncorrelated,
- $[R_i]_{jk} = \begin{cases} \alpha^{|j-k|} & j-k = -1, 0, 1 \\ 0 & \text{else} \end{cases}$ i.e. $R_i(\alpha)$ is a tridiagonal matrix. This is equivalent to the 1-dependent model. In this model the observations of each subject are assumed to be correlated with those immediately before or after,
- $[R_i]_{jk} = \alpha^{|j-k|}$, This is the correlation structure for a stationary $n_i$-dependent process. By this assumption, all the observations of each subject are correlated.

When $\alpha = 0.3$, and $\alpha = 0.7$, the estimated regression coefficients for three different choices of $R_i(\alpha)$ on variable pain are summarized in Table 4.1. Table 4.2 displays the

Table 4.1: Estimated Regression Coefficients on Response Pain

| | | $\alpha = 0.3$ | | $\alpha = 0.7$ | |
|---|---|---|---|---|---|
| | Indep. | 1-Depend. | $n_i$-Depend. | 1-Depend. | $n_i$-Depend. |
| Intercept | 60.160 | 59.845 | 59.914 | 60.009 | 56.188 |
| Age | -0.177 | -0.177 | -0.179 | -0.057 | -0.181 |
| Period | -5.851 | -5.510 | -5.414 | -10.501 | -2.142 |
| Treatment | -13.479 | -13.209 | -13.210 | -13.131 | -12.585 |
| Period* Treatment | 9.112 | 8.961 | 8.933 | 7.332 | 8.467 |

Table 4.2: Asymptotic Standard Normal Statistics on Response Pain

| | | $\alpha = 0.3$ | | $\alpha = 0.7$ | |
|---|---|---|---|---|---|
| | Indep. | 1-Depend. | $n_i$-Depend. | 1-Depend. | $n_i$-Depend. |
| Intercept | 2.783 | 2.810 | 2.826 | 2.427 | 2.904 |
| Age | -0.630 | -0.635 | -0.643 | -0.219 | -0.667 |
| Period | -0.915 | -0.870 | -0.860 | -0.900 | -0.354 |
| Treatment | -1.200 | -1.185 | -1.188 | -1.120 | -1.198 |
| Period* Treatment | 1.147 | 1.137 | 1.135 | 0.847 | 1.137 |

standardized counterparts which have an asymptotic $N(0,1)$ distribution when each $\beta_i$ is 0.

From Table 4.1, it can be seen that when $\alpha = 0.3$, the difference between the estimated regression coefficients $\hat{\boldsymbol{\beta}}_I$ (obtained under independent assumption) and $\hat{\boldsymbol{\beta}}_G$ (obtained under dependent assumption) is very very small. When $\alpha = 0.7$, there are some difference between $\hat{\boldsymbol{\beta}}_I$ and $\hat{\boldsymbol{\beta}}_G$, but the coefficient of treatment and interaction do not change much. Whatever the form of $R_i(\alpha)$ is, the asymptotic standard normal statistics (Table 4.2) show similar results. Note the asymptotic standard normal statistics are very small for

all the factors. Since 44 patients are included in the data set, the number of the patients is quite small, the inference based on the asymptotic theory should be made with care.

When $R_i(\alpha) = I_{n_i}$, i.e. the observation of each subject are assumed to be independent, the solution of GEEs (4.2) can be obtained by existing software (McCullagh and Nelder, 1983). The estimated regression coefficients obtained by S-plus (1993) are exactly the same as the results obtained by programming in Matlab (1994). The analysis of deviance when the observation of each subject are assumed to be independent, is summarized in Table 4.3.

Table 4.3: Analysis of Deviance on Response Pain

| Term | DF | Deviance | Resid. DF | Resid. Dev | F-Value | $Pr > F$ |
|---|---|---|---|---|---|---|
| Null | | | 1116 | 888831.0 | | |
| Age | 1 | 7289.77 | 1115 | 881541.2 | 9.3529 | 0.00228 |
| Period | 1 | 197.77 | 1114 | 881343.4 | 0.2537 | 0.61456 |
| Treatment | 1 | 0.56 | 1113 | 881342.9 | 0.0007 | 0.97870 |
| Period* Treatment | 1 | 14624.94 | 1112 | 866717.9 | 18.7638 | 0.00002 |

When the observation of each subject are assumed to be independent, Table 4.3 indicated that at 1% significance level the effect of age and the effect of interaction of period and treatment are significant for pain. The effect of treatment and the effect of period are not significant at 5% significance level. These results are consistent with the analysis of variance.

The estimated regression coefficients for three different choices of $R_i(\alpha)$ on response variable pain while at rest is displayed in Table 4.4. Table 4.5 displays the standardized counterparts which have an asymptotic $N(0,1)$ distribution when each $\beta_i$ is 0. Similar results can be seen from Tables 4.4 and 4.5 for the response variable pain while at rest.

When the measurements of response pain while at rest within each subject are assumed to be independent, the analysis of deviance table on response variable pain while at rest

Table 4.4: Estimated Regression Coefficients on Response Pain while at Rest

| | | $\alpha = 0.3$ | | $\alpha = 0.7$ | |
|---|---|---|---|---|---|
| | Indep. | 1-Depend. | $n_i$-Depend. | 1-Depend. | $n_i$-Depend. |
| Intercept | 52.698 | 52.347 | 52.232 | 41.441 | 48.506 |
| Age | -0.280 | -0.279 | -0.277 | -0.236 | -0.266 |
| Period | -2.065 | -1.864 | -1.807 | 4.741 | 0.356 |
| Treatment | -8.238 | -7.972 | -7.907 | -8.998 | -6.031 |
| Period* Treatment | 6.506 | 6.413 | 6.361 | 3.584 | 5.495 |

Table 4.5: Asymptotic Standard Normal Statistics on Response Pain while at Rest

| | | $\alpha = 0.3$ | | $\alpha = 0.7$ | |
|---|---|---|---|---|---|
| | Indep. | 1-Depend. | $n_i$-Depend. | 1-Depend. | $n_i$-Depend. |
| Intercept | 2.744 | 2.745 | 2.747 | 1.856 | 2.667 |
| Age | -1.238 | -1.236 | -1.230 | -1.231 | -1.180 |
| Period | -0.403 | -0.366 | -0.357 | 0.407 | 0.071 |
| Treatment | -0.979 | -0.953 | -0.945 | -0.901 | -0.734 |
| Period* Treatment | 1.038 | 1.030 | 1.023 | 0.475 | 0.930 |

Table 4.6: Analysis of Deviance on Response Pain while at Rest

| Term | DF | Deviance | Resid. DF | Resid. Dev | F-Value | $Pr > F$ |
|---|---|---|---|---|---|---|
| Null | | | 1123 | 706875.1 | | |
| Age | 1 | 14765.92 | 1122 | 692109.2 | 24.24 | $< 0.0001$ |
| Period | 1 | 1677.03 | 1121 | 690432.1 | 2.75 | 0.0973 |
| Treatment | 1 | 1413.93 | 1120 | 689018.2 | 2.32 | 0.1279 |
| Period* Treatment | 1 | 7446.68 | 1119 | 681571.5 | 12.23 | 0.0005 |

is presented in Table 4.6. The effect of treatment are not significant to the pain while at rest at 5% significance level. At 5% significance level the effect of age is significant to the pain while at rest.

The estimated regression coefficients for three different choices of $R_i(\alpha)$ on response variable pain with movement are also displayed in Table 4.7. Table 4.8 displays the standardized counterparts which have an asymptotic $N(0,1)$ distribution when each $\beta_i$ is 0. Similar results also can be seen from Tables 4.7 and 4.8 for the response variable pain with movement.

Table 4.7: Estimated Regression Coefficients on Response Pain with Movement

| | | $\alpha = 0.3$ | | $\alpha = 0.7$ | |
|---|---|---|---|---|---|
| | Indep. | 1-Depend. | $n_i$-Depend. | 1-Depend. | $n_i$-Depend. |
| Intercept | 57.682 | 57.514 | 57.685 | 50.286 | 55.292 |
| Age | -0.028 | -0.025 | -0.025 | 0.106 | -0.010 |
| Period | -5.393 | -5.382 | -5.438 | -5.210 | -4.200 |
| Treatment | -16.297 | -15.961 | -15.895 | -14.652 | -14.263 |
| Period* Treatment | 10.429 | 10.293 | 10.256 | 7.898 | 9.562 |

Table 4.8: Asymptotic Standard Normal Statistics on Response Pain with Movement

| | | $\alpha = 0.3$ | | $\alpha = 0.7$ | |
|---|---|---|---|---|---|
| | Indep. | 1-Depend. | $n_i$-Depend. | 1-Depend. | $n_i$-Depend. |
| Intercept | 2.658 | 2.679 | 2.698 | 2.188 | 2.756 |
| Age | -0.099 | -0.089 | -0.090 | 0.389 | -0.037 |
| Period | -0.891 | -0.891 | -0.905 | -0.529 | -0.684 |
| Treatment | -1.486 | -1.464 | -1.462 | -1.282 | -1.374 |
| Period* Treatment | 1.377 | 1.368 | 1.367 | 0.970 | 1.341 |

Table 4.9: Analysis of Deviance on Response Pain with Movement

| Term | DF | Deviance | Resid. DF | Resid. Dev | F-Value | $Pr > F$ |
|---|---|---|---|---|---|---|
| Null | | | 1120 | 868274.8 | | |
| Age | 1 | 1212.11 | 1119 | 867062.7 | 1.60 | 0.21 |
| Period | 1 | 1510.46 | 1118 | 865552.2 | 1.99 | 0.16 |
| Treatment | 1 | 485.62 | 1117 | 865066.6 | 0.64 | 0.42 |
| Period* Treatment | 1 | 19101.86 | 1116 | 845964.8 | 25.20 | $< 0.01$ |

The analysis of deviance table on response variable pain with movement when the observation of each subject are assumed to be independent, is also presented in Table 4.9. The effect of treatment are not significant to the pain with movement at 5% significance level. However, at 5% significance level the effect of age is not significant to the pain with movement.

Generally, we can see that the estimated regression coefficients and the variance of the parameter are robust to the choices of the working correlation matrix $R_i(\alpha)$.

# Chapter 5

# Conclusions and Discussion

(1) This project presents the statistical analysis of a longitudinal study on the effectiveness of a pain killing drug on the control of metastatic bone pain and its side effects. The data were collected in a randomized clinical trial from 44 patients with known metastatic bone pain. The active drug was compared with a placebo. A double-blind cross over design was used in the study. Each patient received the active drug in one of two doses or placebo first and was scheduled to cross over to the other drug after 14 days. The patient was observed for another 14 days after the second administration. The order to receive the active drug and placebo was randomized. Both the patient and investigator were blinded to the assignment until the completion of the study.

(2) An assessment of the agreement between patient and investigator on the blinded preference of the active drug to the placebo was conducted. It was found that the patient and the investigator achieved a high degree of agreement on the blinded preference of the active drug to the placebo.

(3) An ordinary repeated measures linear statistical model might be used for the analysis of data with the original design of experiment. However, the task was highly complicated by the fact that, due to logistics, not every patient was actually observed

for exactly 14 days before the second administration.

(4) Two statistical methods were then used for the data analysis of the study:

(a) multivariate analysis of variance by summary scores: mean, median and trmean; and

(b) generalized estimating equations.

(5) According to the results of the multivariate analysis of variance by the summary scores: mean, median, and trmean, the active drug did not produce a statistically significant effect on the control of pain on patients with known metastatic bone pain. It did not produce any significant side effects, evaluated by variables of nausea, depression, anxiety, drowsiness, and appetite, either.

(6) The generalized estimating equations yielded consistent results with the multivariate analysis of variance regarding the effectiveness of the drug. The estimated regression coefficients are robust to the choice of working correlation matrix and the asymptotical standard normal statistics under various assumptions show that the treatment effects were not significant. However, the analysis did not consider all the related response variables simultaneously. Further analysis might be done to include all the response variables in one analysis. Nevertheless, considering the consistency of results from various analyses in our study, this may not be worthwhile.

(7) Because the results from GEEs depend on the asymptotic behaviour of statistics and 44 patients were included in the analysis, the interpretation of the results should be made with caution.

(8) In this study, three treatments were involved and two periods were used in the trial. Therefore, the number of observations under placebo is almost double the number of observations under 600 mg active drug or 1500 mg active drug. If another trial is conducted, it might be useful to use three or more periods. That is, each patient

receives the three treatments. In this way, each treatment will have approximately equal number of observations.

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