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The utilization of ANOVA (Analysis of Variance) in investigating therapeutic interventions within medical research

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Abstract
The Analysis of Variance (ANOVA) is a statistical technique widely used in medical research to evaluate the effect of therapeutic interventions. This method enables researchers to determine whether there are statistically significant differences between treatment groups, accounting for change within and between groups to isolate treatment effects. In medical studies, ANOVA is particularly useful for comparing multiple intervention groups, examining interactions between variables (e.g., treatment type and dosage), and tracking changes over time in longitudinal research. This paper reviews the application of different ANOVA types, such as one-way, two-way, and repeated measures ANOVA, and highlights their specific contributions to understanding therapeutic efficacy and patient outcomes. Additionally, the study explores the methodological assumptions necessary for ANOVA, such as normality, homogeneity of variances, and independence, while discussing alternatives and adaptations for non-ideal data conditions. Through case studies and examples, we demonstrate how ANOVA facilitates evidence-based assessments of treatment differences, providing a rigorous foundation for decision-making in clinical and pharmacological research. Ultimately, ANOVA's systematic approach to variance analysis positions it as an essential tool in medical research, supporting more accurate and comprehensive evaluations of therapeutic interventions.

Keywords: Compensation, Performance, Hospital

1. Introduction

Analysis of variance (ANOVA) is a statistical method used to analyze and compare the means of two or more groups or treatments. It helps us draw meaningful conclusions from our data. ANOVA is widely used in many sciences such as psychology, medicine, agriculture, business, and social sciences, to test for differences between groups. Developed by Ronald Fisher in the early 20th century, ANOVA is particularly valuable in experimental and observational studies where the goal is to compare group effects.

Purpose of ANOVA:

ANOVA is apparently your go-to tool when there are multiple groups. Especially when you want to know if there's a real difference in their means.

Specifically, ANOVA answers the question: Are the observed differences in sample means likely due to true differences among groups or simply random variation?

The method partitions the total variability in the data into two components:

Between-Group Variation: Variability caused by differences between the group means.

Within-Group Variation: Variability due to random error or differences among individuals within the same group.

Key features of ANOVA:

Multiple group comparisons: ANOVA is especially useful when comparing more than two groups, as it avoids the accumulation of error rates associated with multiple t-tests.

Hypotheses:
• Null Hypothesis (H0): The group means are equal (μ1=μ2=μ3=…).
• Alternative Hypothesis (Ha): At least one group mean is different.
F statistic: ANOVA produces an F statistic, which is the ratio of the between-group variance to the within-group variance. Larger F statistics indicate more significant differences between group means.
P value: The p value obtained from the F test determines whether to reject the null hypothesis.

Types of ANOVA
One-way ANOVA: Tests for differences between groups based on a single independent variable (factor).
Two-way ANOVA: Extends the analysis to include two independent variables, allowing for testing of interactions between factors.
Repeated Measures ANOVA: Used when the same object is measured under different conditions or over time.
MANOVA (Multivariate Analysis of Variance): For cases with multiple dependent variables.
In this study, we focus on clarifying the method Repeated Measures ANOVA. Standard analysis of variance (ANOVA) (1 or 2 factors) is used to test the means of independent measurements in experiments where each subject is measured only once. In many medical studies where subjects are measured multiple times under different conditions or at different times, measurements are interdependent, previous measurements influence later measurements, so we cannot use standard ANOVA but must use repeated measures analysis of variance (Repeated Measures Analysis of Variance).

2. Methodology
Analysis of variance (ANOVA) is a powerful statistical tool used in medical research to evaluate differences between groups and determine the significance of variations observed in data. Here are some reasons why ANOVA is so important in this field:
1. Assessing treatment effectiveness
ANOVA is widely used to compare the effectiveness of different medical treatments, interventions, or medications. For example:
Comparing blood pressure levels in patients taking three different antihypertensive drugs.
Evaluating differences in weight loss between groups following different diets or exercise regimens.
By determining whether the observed differences between group means are statistically significant, ANOVA helps researchers identify effective treatments.
2. Handling multiple groups
Unlike the t-test, which is limited to comparing only two groups, ANOVA can handle multiple groups at once. This is especially important in medical research when:
There are many different treatment groups or conditions (e.g., different doses, different interventions).
Avoidance of multiple t-tests reduces the risk of Type I errors (false positive results).
3. Testing for interactions
Using two-way or higher-order ANOVA, researchers can study the interaction effects between independent variables. For example:
Investigating how the effects of a drug vary by sex or age group.
Examining how lifestyle factors (e.g., diet and exercise) interact to influence health outcomes.
Understanding these interactions provides greater insight into complex medical phenomena.

4. Identifying sources of variation
ANOVA breaks down the total variation in the data into components:
Between-group variation (e.g., due to treatment effects).
Intra-group variation (e.g., individual differences, measurement error).
This helps determine whether the difference is due to treatment or chance, improving the reliability of the findings.
5. Enables Robust Clinical Trials
ANOVA is essential in the design and analysis of randomized clinical trials (RCTs). It ensures that:
Comparisons between multiple groups are statistically valid.
Variation is properly controlled, increasing the validity of conclusions.
6. Supports Precision Medicine
Medical research often explores differences between subgroups in treatment effectiveness. ANOVA allows:
Detect significant differences between demographic or genetic subgroups.
Insights into personalized medicine by identifying which treatments are most effective for specific patient groups.
7. Efficient and Simple
ANOVA simplifies the analysis of complex data sets, providing a straightforward approach to evaluating hypotheses. It is computationally efficient and forms the basis for advanced statistical techniques such as regression and mixed-effects models.
Example applications:
Comparing vaccine efficacy across demographic groups.
Analyzing recovery times between surgical approaches.

Evaluating the impact of different rehabilitation protocols on physical performance.
In short, ANOVA is a cornerstone of medical research, allowing for robust, reliable, and interpretable comparisons between groups, which is critical to advancing healthcare and improving patient outcome.

3. Case study
Remeasurement designs are often used in longitudinal studies where subjects are measured multiple times (for example, to investigate the interaction of treatment groups over time). This design is also used when the study sample is small with few participants, each subject is measured multiple times under different conditions, thus reducing research costs.
Use remeasured ANOVA to reduce the bias caused by multiple paired tests (T-test, standard ANOVA). If we compare the means of each pair (measurement 1 and 2, measurement 2 and 3, measurement 3 and 4 ...) then the error level will increase significantly because each time we set the null hypothesis, this error level is
5%, if each subject is measured 4 times, we will have 6 pairs of comparisons and the error level will increase to 30%!
The assumption in standard ANOVA analysis is that the variances of the means (independent measures) must be homogeneous (the variances are approximately equal). In remeasurement ANOVA, in addition to the assumption of homogeneity of variances, there must be an assumption of

homogeneity of covariances (because the previous measure has an effect on the following measure), so it is called the assumption of symmetry of the variance-covariance matrix or Mauchly's Sphericity test (in SPSS).

Remeasurement variance analysis in SPSS

Example: In a study of iron chelation in patients with thalassemia, an oral iron chelation drug (Ferrirox) is compared with the subcutaneous infusion drug Desferal. Each treatment group has 10 patients. The researcher wants to know:

1. The effectiveness of iron chelation for both drugs.
2. There is a difference in iron excretion between the 2 injectable and oral drugs or between the 2 treatment groups.
3. There is an interaction between the type of medication and the time it is given.

In remeasurement design, there are two sources of variation to consider:

- Between -subject factors
- Within -subject factors

In this study, treatment group was a between- subject factor and treatment duration was a within -subject factor (by treatment duration).

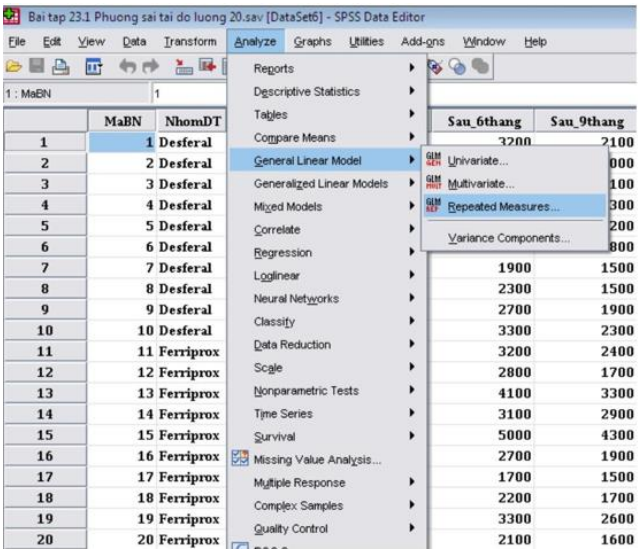
The research data are presented in the following table

Includes 6 columns: Patient code: 1-20 – (MaBN) , Treatment drug group: Desferal and Ferrirox – (Nhom DT), ferritin level (ng/ml) at the beginning of treatment – (Khoidau) , after 3 months – (Sau_3thang), 6 months – (Sau_6thang) and 9 months – (Sau_9thang) of treatment

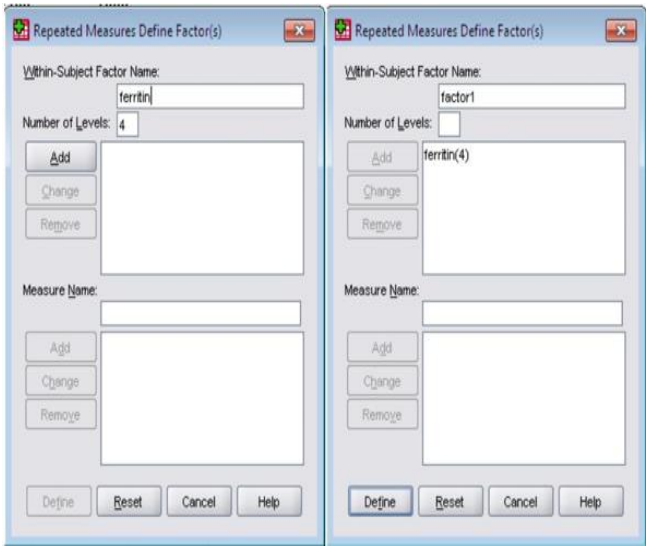
Table 1: Data of 20 patients monitored for iron excretion

MaBN	NhomDI	Khoidau	Sau_3thang	Sau_6thang	Sau_9thang
1	Desferal	5000	4000	3200	2100
2	Desferal	6000	5500	4600	4000
3	Desferal	5500	4500	3800	3100
4	Desferal	4500	3700	3000	2300
5	Desferal	6500	6400	5000	4200
6	Desferal	3500	3200	2400	1800
7	Desferal	3000	2800	1900	1500
8	Desferal	4000	3000	2300	1500
9	Desferal	4500	3400	2700	1900
10	Desferal	5000	4500	3300	2300
11	Ferriprox	5000	4000	3200	2400
12	Ferriprox	4000	3500	2800	1700
13	Ferriprox	5500	5000	4100	3300
14	Ferriprox	4500	4300	3100	2900
15	Ferriprox	6500	6100	5000	4300
16	Ferriprox	3500	3200	2700	1900
17	Ferriprox	3000	2500	1700	1500
18	Ferriprox	4000	3000	2200	1700
19	Ferriprox	4500	4100	3300	2600
20	Ferriprox	3500	2800	2100	1600

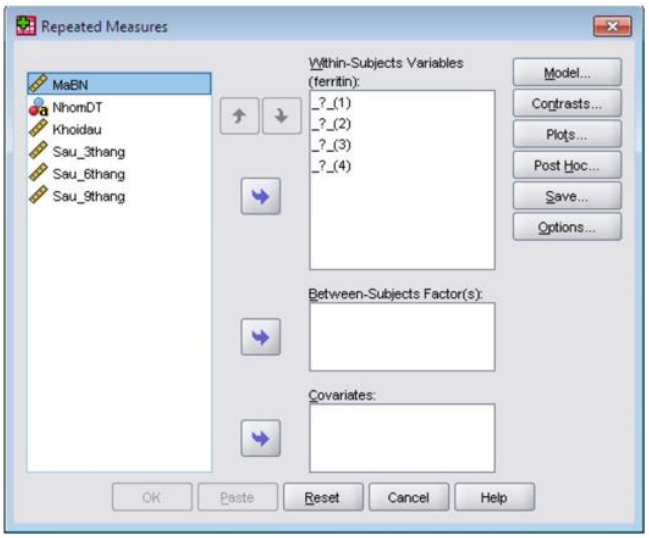
Enter data into SPSS, go to menu: Analyze □ General Linear model □ Repeated Measures as follows



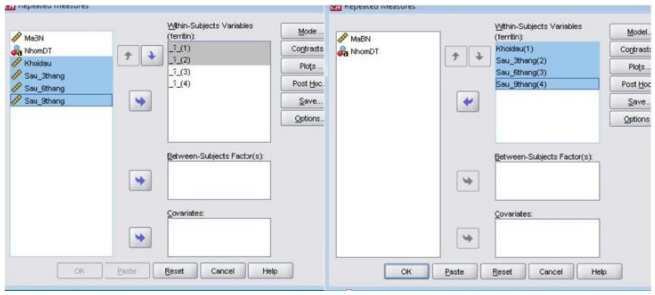
Within-subject Factor Name is ferritin Number of levels: 4 Click the Add button and ferritin (4) will appear in the square box as shown below:



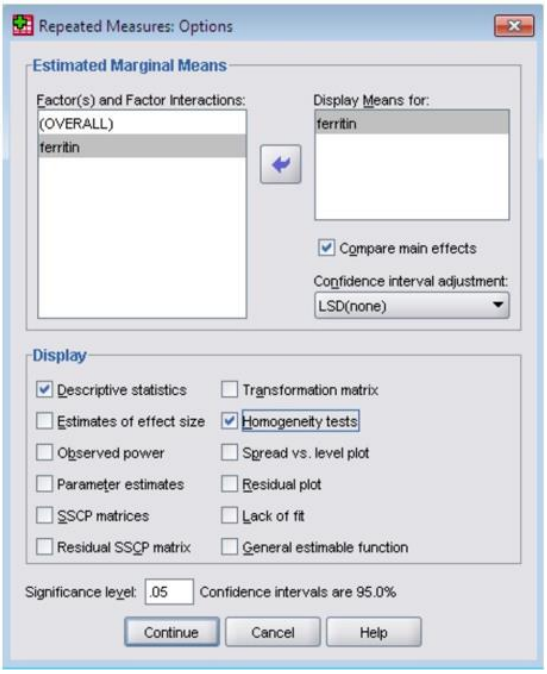
Click the Define button and you get the following screen:



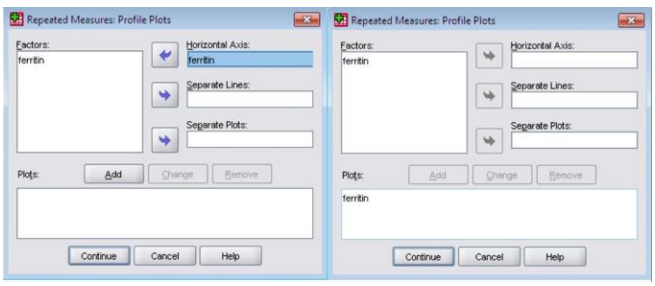
Use the mouse to highlight all 4 variables: Khoidau, Sau_3 Thang, Sau_6 Thang, Sau_9 Thang, click the arrow to move all 4 variables to the right box (Within-subjects variables box) as follows:



Click the Options dialog box below, move ferritin to the right box (Display means for) and click the ÿ checkboxes: Compare main effects, Statistic Descriptives and Homogeneity tests as the following screen:



Click Continue, Click the Plots dialog box (to plot ferritin over time), transfer ferritin into the Horizontal Axis box. Click the Add button, move ferritin into the Plots box below as follows:



Click Continue, then click OK and the result will be as follows:

Table 1. Mean and standard deviation of ferritin at 4 time points Mean Std.

Table 1 shows that the number of treated patients was N=20, the initial serum ferritin level was 4575 and gradually decreased after 3, 6 and 9 months of treatment. The variance (SD squared) between the 4 time points appeared to be heterogeneous (not nearly equal).

Table 2: Mauchly's Test of Sphericity(b)

Mauchly's Test of Sphericity[b]

Measure: MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
ferritin	.485	12.828	5	.025	.703	.793	.333

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

b.
Design: Intercept
Within Subjects Design: ferritin

The results show that Greenhouse-Geisser Epsilon=0.703 and p=0.025, thus rejecting the null hypothesis, meaning that the Sphericity test is violated (there is no homogeneity of variance-covariance). In SPSS, if the Sphericity assumption is violated, we can use one of the following three types of corrections: Greenhouse-Geisser, Huynh-Feldt, Lower-bound.

Table 3: Results of intra-subject validation with three types of corrections (Greenhouse- Geisser, Huynh-Feldt and Lower-bound)

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
ferritin	Sphericity Assumed	53361000.0	3	17787000.00	379.154	.000
	Greenhouse-Geisser	53361000.0	2.109	25300093.02	379.154	.000
	Huynh-Feldt	53361000.0	2.379	22430539.30	379.154	.000
	Lower-bound	53361000.0	1.000	53361000.00	379.154	.000
Error(ferritin)	Sphericity Assumed	2674000.000	57	46912.281		
	Greenhouse-Geisser	2674000.000	40.073	66727.670		
	Huynh-Feldt	2674000.000	45.200	59159.372		
	Lower-bound	2674000.000	19.000	140736.842		

If the sphericity assumption is not violated ($p>0.05$), we read the results in the first row (Sphericity Assumed) with degrees of freedom (df)=3, F=379.154 and p=0.000.
If the sphericity assumption is violated ($p<0.05$), we read the results in row 2 (Greenhouse-Geisser) with adjusted degrees of freedom (df) = 2.109, F=379.154.

Thus, all 3 types of adjustment give the same results (F=379.154 and p=0.000), we can conclude that the blood ferritin level at 4 time points is clearly different. To see the difference at which time point, see the pairwise comparison of each time point in Table 4.

Table 4. Paired comparison

Pairwise Comparisons

Measure: MEASURE_1

(I) ferritin	(J) ferritin	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
1	2	600.000*	72.184	.000	448.917	751.083
	3	1455.000*	63.027	.000	1323.084	1586.916
	4	2145.000*	93.605	.000	1949.083	2340.917
2	1	-600.000*	72.184	.000	-751.083	-448.917
	3	855.000*	48.382	.000	753.736	956.264
	4	1545.000*	69.386	.000	1399.773	1690.227
3	1	-1455.000*	63.027	.000	-1586.916	-1323.084
	2	-855.000*	48.382	.000	-956.264	-753.736
	4	690.000*	55.203	.000	574.459	805.541
4	1	-2145.000*	93.605	.000	-2340.917	-1949.083
	2	-1545.000*	69.386	.000	-1690.227	-1399.773
	3	-690.000*	55.203	.000	-805.541	-574.459

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

a. Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

The results showed that the amount of ferritin at 4 time points were clearly different (1 different from 2, 2 different from 3, 3 different from 4 and 4 different from 1) with p=0.000.
Finally we can view a graph of ferritin levels over time by clicking the Plots dialog box:

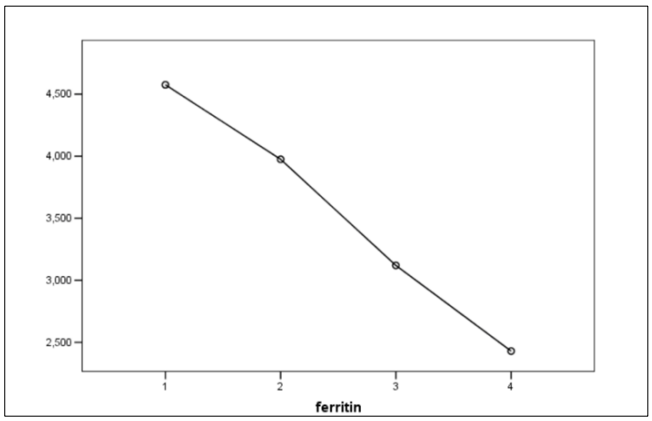
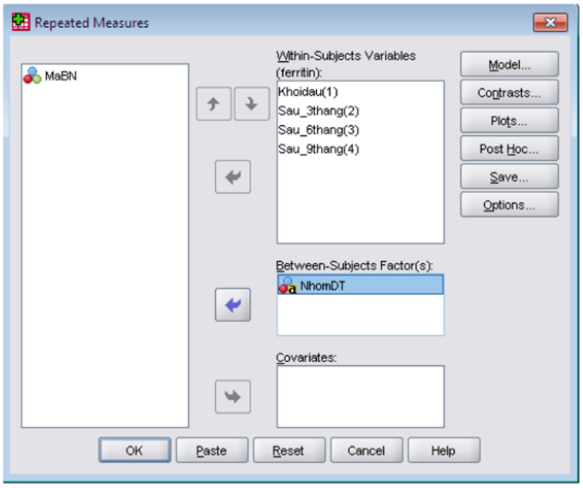


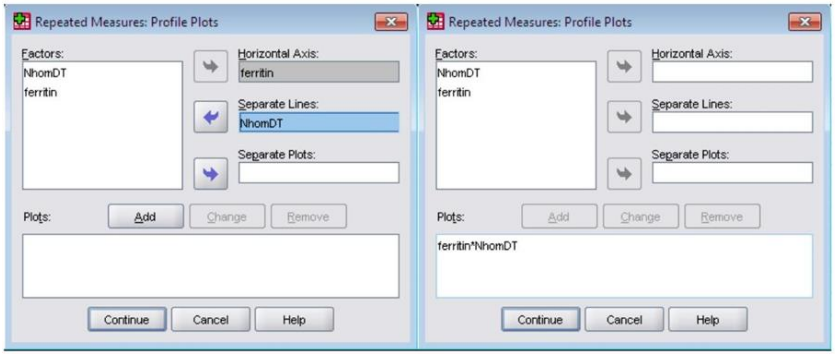
Fig 1: Blood ferritin levels at 4 time points (0, 3, 6, 9 months)

Compare the difference between the 2 treatment groups.

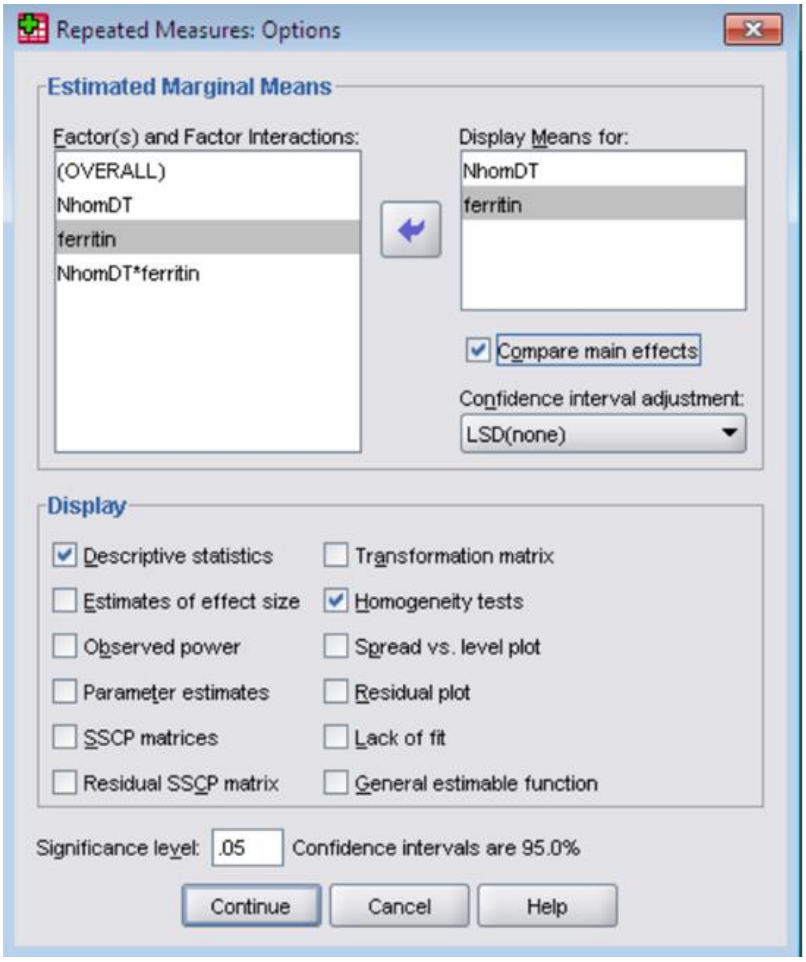
Perform the same procedure as above, but click on the NhomDT switch. Go to the Between-Subjects Factors box.



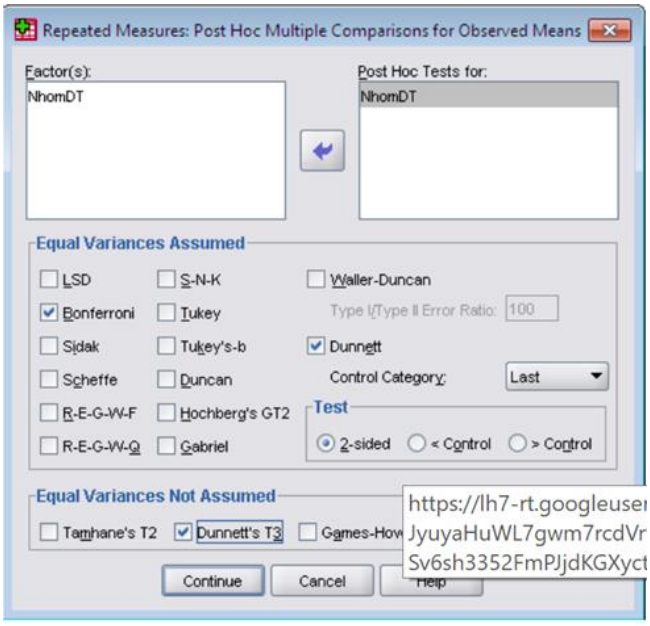
Clicking **the Plots…** dialog opens the following screen:



Transfer ferritin to the Horizontal Axis box and Nhomdt to the Separate Lines box, then click **Add to** transfer to the Plots box below.
Click Continue, click the **Options** dialog box on the following screen:



Click the NhomDT, ferritin variables in the Display Means box, check the Descriptive Statistic box and the Homogeneity tests box. Then click Continue, go to the **Post Hoc** dialog box and check the boxes (Bonferroni, Dunnett, Dunnett's T3) as shown below:



Click Continue to return to the main screen and finally click **OK.**
We get the following results:

Table 5: Mean ferritin levels and standard deviation SD at 4 time points of 2 treatment drugs (Desferal and Ferriprox)

Descriptive Statistics

	Nhomdt	Mean	Std. Deviation	N
Khoidau	Desferal	4750.00	1086.534	10
	Ferriprox	4400.00	1048.809	10
	Total	4575.00	1054.751	20
S3thang	Desferal	4100.00	1151.810	10
	Ferriprox	3850.00	1098.737	10
	Total	3975.00	1103.046	20
S6thang	Desferal	3220.00	999.778	10
	Ferriprox	3020.00	978.434	10
	Total	3120.00	968.232	20
S9thang	Desferal	2470.00	976.445	10
	Ferriprox	2390.00	906.091	10
	Total	2430.00	917.720	20

Table 6: Test for homogeneity of variance and covariance (Sphericity assumption)

Mauchly's Test of Sphericity[b]

Measure:MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
ferritin	.532	10.560	5	.061	.733	.886	.333

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

b. Design: Intercept + NhomDT
Within Subjects Design: ferritin

Table 7. Results of internal testing of subjects

Tests of Within-Subjects Effects

Measure:MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
ferritin	Sphericity Assumed	5.336E7	3	1.779E7	386.518	.000
	Greenhouse-Geisser	5.336E7	2.199	2.427E7	386.518	.000
	Huynh-Feldt	5.336E7	2.657	2.008E7	386.518	.000
	Lower-bound	5.336E7	1.000	5.336E7	386.518	.000
ferritin * NhomDT	Sphericity Assumed	189000.000	3	63000.000	1.369	.262
	Greenhouse-Geisser	189000.000	2.199	85946.386	1.369	.267
	Huynh-Feldt	189000.000	2.657	71136.634	1.369	.265
	Lower-bound	189000.000	1.000	189000.000	1.369	.257
Error(ferritin)	Sphericity Assumed	2485000.000	54	46018.519		
	Greenhouse-Geisser	2485000.000	39.583	62779.767		
	Huynh-Feldt	2485000.000	47.823	51961.945		
	Lower-bound	2485000.000	18.000	138055.556		

Sphericity assumption was not violated (p=0.061). Since the Sphericity assumption is not violated, read the first row of results: Sphericity Assumed: df=3, F=386.518, p=0.000, so ferritin levels differ between the 4 time points. There was no interaction between treatment type and time (ferritin*NhomDT) with p=0.262.

Table 8. Test for homogeneity of variances

Levene's Test of Equality of Error Variances[a]

	F	df1	df2	Sig.
Khoidau	.033	1	18	.859
Sau_3thang	.030	1	18	.864
Sau_6thang	.026	1	18	.873
Sau_9thang	.085	1	18	.774

Tests the null hypothesis that the error variance of the dependent variable is equal across groups.

a. Design: Intercept + NhomDT
Within Subjects Design: ferritin

Levene's test showed no violation of homogeneity of variances (p> 0.05).

Table 9: Test between 2 treatment groups

Tests of Between-Subjects Effects

Measure:MEASURE_1
Transformed Variable:Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	9.940E8	1	9.940E8	240.409	.000
NhomDT	968000.000	1	968000.000	.234	.634
Error	7.443E7	18	4134833.333		

Results: F=0.234 and p=0.634, there was no difference between the 2 treatments.

Table 10: Mean difference between 2 drugs

Estimates

Measure: MEASURE_1

Nhomdt	Mean	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Desferal	3635.000	321.513	2959.526	4310.474
Ferriprox	3415.000	321.513	2739.526	4090.474

Pairwise Comparisons

Measure: MEASURE_1

(I) Nhomdt	(J) Nhomdt	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
Desferal	Ferriprox	220.000	454.689	.634	-735.265	1175.265
Ferriprox	Desferal	-220.000	454.689	.634	-1175.265	735.265

Based on estimated marginal means

a. Adjustment for multiple comparisons: Least Significant Difference (equivalent to no

Mean Difference between the 2 treatment groups =220 and p=0.634. There was no difference between the 2 treatment groups.

The graph shows a gradual decrease in ferritin levels for both treatment groups and no interaction over time (the two lines are nearly parallel).

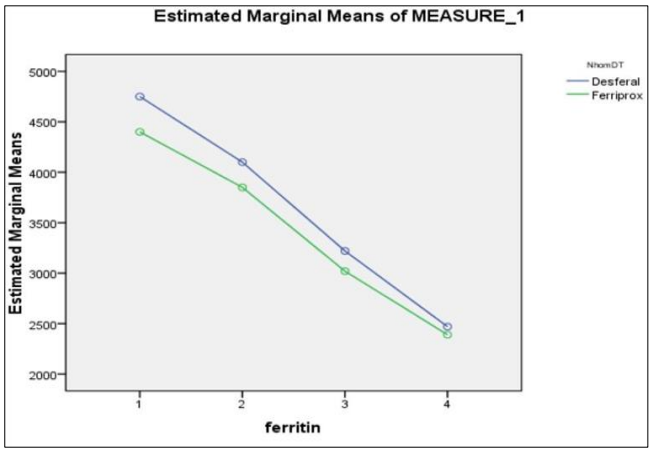


Fig 2: Comparison of blood ferritin levels at 4 time points between the 2 treatment groups

Results and discussion: Both injectable (Desferal) and oral (Ferrirox) iron chelators are effective in treatment (reducing blood ferritin levels) and there is no difference between the two drugs.

4. Conclusion

In summary, ANOVA is a powerful statistical tool in therapeutic research that compares means and detects significant differences between groups, allowing for evidence-based decision-making in clinical practice. It is a versatile tool as it can be used in areas from testing drug efficacy to behavioral interventions and is thus valuable for the progression of medical science. Nonetheless, assumptions about normality and equality of variances can be problematic and require to be noted and planned through the study design in addition to an appropriate method of analysis.

ANOVA is a cornerstone in medical statistics and is always a major pillar of evidence-based treatment. It facilitates innovation and patient-centered care by allowing researchers to make important inferences about the effects of treatments. In this time of modern computation and constant improvement and adaptation of statistical methods, the use of ANOVA and its variants promises even greater potential for the improved evaluation of therapeutics. By adopting these innovations, researchers will be more equipped than ever to solve complex medical problems, leading to better healthcare outcomes.

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