Use of Bioequivalence Tests and Its Properties under Different Sampling Techniques

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Authors' contributions

This work was carried out in collaboration among all authors. Author FB designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors NJ and MH managed the analyses of the study. Author US managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Bioequivalence testing is the initial approach for the analysis of quantitative determination of drugs and their metabolism in biological samples. In this research work its applications was tested and reviewed under different sampling techniques. The basic concept of bioequivalence testing crossover design was used to make assessment of medicine for breast cancer methotrexate and tamoxifen. Effectiveness of methotrexate at initial stage was 2.38 and at advance stage it was 1.85 which means it was 43% effective at initial stage while 38% effective in advance stage. Effectiveness of tamoxifen at initial stage 3.19 at advance stage 3.68 which means it was 52% effective at initial stage while 57% effective in advance stage. The relation of bioequivalence testing and distance base inference was highlighted. An attempt was made to analyze the efficiency of both medicines at initial and advance stage of diagnostic of breast cancer.

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1. INTRODUCTION

Two approaches that are generally using in the bioequivalence studies are interval hypothesis testing and confidence interval approach. In the confidence interval approach, a 90% interval is calculated for the ratio of geometric means of some main pharmacokinetic responses are calculated under cross over design. In case of interval hypothesis testing, the bioequivalence is rejected in favor of alternate hypothesis of bioequivalence. Generally, this method is used by decomposing into two sets of hypotheses. The first set that the bioavailability of a medicine is not as well low whereas the second set bioavailability of the medicine is not too high.

Bioavailability of drugs is an amount of the rate and amount to which a drug reaches at the site of action. Bioequivalence is a term used to evaluate the biological equivalence of two medicines in pharmacokinetics. When two products are bioequivalent it means that they would be same for all intents and purposes. Bioavailability and bioequivalence (BE) have turned into the foundations for the approval of efficiency of drugs use for the treatment of cancer. It was urged to realize that there was proceeding with endeavors by administrative experts and established researchers, both generally and globally, to comprehend and grow more dynamic and logically significant ways to deal with the consideration of BE of different measurements shapes including a section of the extreme complex incredible measurements shaped [1].

The basic role of a bioequivalence testing is frequently to meet the requirement necessity of comparable normal bioavailability. This is normally done by estimating the mean difference between formulations in a crossover design. Consequently, it can be contended that this association ought to be a piece of the foundation of compatibility. To have the capacity to think about this association the standard simple crossover design is not appropriate. Rather, a plan where every detailing is directed no less than twice to each subject is attractive. Such a design is obtained by repeating a simple crossover layout is evaluated.

Two sources of variety in information experimental designs with repeated measures are the within-subject and between-subjects variations. So, the greater part of the data for treatment comparisons is contained in the within subject variation. Hence, to attain sufficient precision from little trials for treatment correlations are desirable to reduce or eliminate the between-subject variation got from each subject to maximize the information. In crossover designs, each subject receives a sequence of treatments over different periods of time i.e. before and after half-life of treatment. Although the major purpose of crossover trial is to compare the effects of two treatments. Indeed, even two treatments have equal effects. A large difference between two measurements on a subject might be obtained. The measurements in one treatment period were significantly lower or higher than those in the other treatment period. To avoid treatment effects and confounding period, more than one sequence must be used to obtain unbiased estimates of the treatment effects.

Carry over is the important impact of a treatment into the resulting time frame in crossover studies. Carryover impacts are differences in the degree of the carry-over between the treatments under consideration. It is well realized that the test for carry-over impacts in individual studies has low power. Carry-over impacts could be helpful for investigators considering the design. Here we create strategies for expressing the power to distinguish carry-over as an element of the power to identify a clinically relevant treatment effect. Two-treatment, two-period cross-over studies the power to recognize clinically relevant carry-over impacts for bioequivalence [2].

We use inverse sampling technique in our research because it gives us more precise estimate then simple random sampling. Selection of sample becomes impossible in simple random sampling, if the units or items are widely dispersed. So inverse sampling is a good method for detecting differences between two different treatments for a rare disease and dispersed data.

Purposive sampling technique is a non-probability sampling method. it occurs when elements selected for the sample are chosen by the judgment of the researcher and is specially use for rare disease. Purposive sampling (also known as judgment, subjective or selective sampling) is a sampling technique in which members of population chosen to participate in the study when researcher relies on her or his own judgment. Researchers believe that sample by using a sound judgment can be obtaining by representative, which will result in saving money and time. Judgment sampling is a non-probability

sampling method that occurs when elements selected for the sample are chosen by the judgment of the researcher for rare disease. This technique is more convenient when chosen sample is truly representative of the entire population [3].

In inverse sampling (some of the time called standard inverse sampling), you keep on choosing things until the point when an event has occurred a specified number of times. It is regularly utilized when you don't have the exact idea about the correct size of the sample you need to take. We keen on occasions happening in a specific time and age group. In our research we use inverse sampling for collecting the data of breast cancer patients. Inverse sampling is frequently performed when a specific characteristic is rare. For instance, it is a decent technique for recognizing contrasts between two distinct medicines for a rare disease i.e. breast cancer.

Statistics based on degree of bioequivalence of two medicines were considered bioequivalent where variance of its components and squares of mean for miscellaneous linear model. There were a practical and technical issues related with these proposals primarily they were required in more complicated design i.e. 2 × 2 crossover design. Westlake analyzed an approach for standard 2 × 2 crossover designs. The valuations of population and individual bioequivalence were provided that should be sufficient for all practical and clinical purposes [4].

BA/BE idea for huge acknowledgment everywhere throughout the world, enormous progressions were made by the FDA and diverse national, worldwide, supranational administrative specialists. Evaluation of BE in parallel to pharmaceutical industry and the scholarly world was additionally contributed. There were accessible ways to deal with deciding BE of bland items were to a great extent institutionalized due to dialog and concurrence along with different partners at various national workshops, meetings and gatherings.

Tamoxifen creates certain side effects like swelling or pain in any part of body. Change in vision, weakness and headache. Chest pain and coughing is the most important symptom of breast cancer. After recovery of patient depends upon the stage of patient if he or she is treated at initial level chances of recovery is more and side effects of tamoxifen is less than methotrexate.

Both medicines are not beneficial at advance live Redness in legs or any part of body is also symptom of breast cancer. Blood clot in lungs can be cause if we don't use proper diet and not consult with doctor when feel any of this type of symptoms during treatment [5].

The objective of our study is

- To study the bioequivalence tests and its properties under different Sampling techniques.
- To study the application of bioequivalence tests and their properties.

2. REVIEW OF LITERATURE

Anderson and Hauck [6] explored elective plans to hybrid outline for leading bioequivalence contemplates. Three appropriate investigations were utilized. The primary inspected the benefits of hybrid plan over parallel ones. The second case was a pooled factual inspection of some bioequivalent item. The third appropriate analysis concern the assessable pooled investigation of two bioequivalent investigation for the same products.

Haidar [7] analyzed the bioequivalence approaches for the especially factor of medications and medical items. An approach of scaling a normal BE model to the inside subject variation of the reference item in a hybrid BE examination. Collectively with a point evaluate constraint forced on proportion of geometric mean among the test and reference substance. A partial duplicated treatment outline with new in rank analysis technique will consequently give a more skilled plan to BE ponders with extremely factor medications and medical items.

Alvan [8] analyzed that two different details of a medication were considered bioequivalent if their normal bio availabilities are equivalent. The assessment of this similarity is typically in light of an acting estimate of the mean distinction of values. This emphasis on implies was an inadequate rule, since a little comparison and to calculate a somewhat limit confidence for short-term, may be acquired as well detailing contrasts demonstrate a wide variation among subjects.

Hwang et al. [9] Proposed subject by assistance was talked about, for instance. In this cooperation they recommend a plan where every variable was managed at Minimum twice and show their effect on each subject. The operation

of a reference-scaling approach includes the declaration of instability of the reference item, which requires duplication of the reference treatment in every person.

Armitage et al. [10] examined the unpredictability of the dynamic substances utilized to recognize the two periods of hybrid (500 mg) drug. In two-period hybrid inconstancy was utilized to evaluate the subjects for the fundamental significant analysis. The two examinations were dissected to consider configuration was changed over into a planed the information mutually as a two-period hybrid chart. The primary information of the investigations was used to in like manner which shows its positive impacts in both periods i.e. before and after washout.

Chow [11] considered medication compatibility under a repeated bioavailability and bioequivalence. There were some factual issues that generally confronted in the evaluation of bioequivalence were talked about. Bioavailability and bioequivalence (BE) have turned into the foundations for the approval of medicine. Proposals with respect to feasible resolutions were made at whatever point feasibility. Some finishing up comments on the plausibility of the consumption of current strategies for bioequivalence to the assessment of bio closeness of take after on bioavailability was as well displayed.

Putt [12] proposed the prospective for carry-over impacts was a significant consideration in the plan of any cross-over think plan. It was responsible for an investigator to clear out the design altogether. In cross-over studies, carry-over is the important impact of a treatment into the resulting time frame. Carry-over impacts are differences in the degree of the carry-over between the treatments under consideration. It is well realized that the test for carry-over impacts in individual studies has low power. For investigators allowing for the design carryover impacts were helpful. Here we create strategies for expressing the power to distinguish carry-over as an element of the power to identify a clinically relevant treatment effect. Power to be familiar with clinically significant carry-over impacts for bioequivalence two treatments and two-periods cross-over studies was used.

Bhupathi and Vajjha [13] analyzed the comprehensive criterion of population selection for utilizing same distributional parameter from a reference for scaling the squared separation between the averages difference in variability and bioequivalence prescribed in the new FDA direction for *in vivo* bioavailability thinks about was condemned. Keeping in mind the end goal to evade this and different troubles characteristic in the way to deal have been tested. For testing the statistical hypotheses coupled with this criteria basis, a correct ideal strategy in light of the common two-sample t-statistic.

Welsh et al. [14] analyzed cure and prediction of result for men with breast tumor progressively relies upon a molecular consideration of cancer conduct and expansion. That observation characterized by expression levels of in more than 8900 genes in normal and malignant tissues of tumor. Way of gene crosswise over tissues uncovered an exact refinement amongst ordinary and tumor tests, and uncovered a striking gathering of around 400 genes that were over expressed in tumor tissues. We positioned these genes as indicated by their differential articulation in typical and growth of tissues by choosing for mass of cancers with deficient expression in usual tissues.

Al-Mohizea et al. [15] investigated to contrast the bioavailability of an innovative tablet formulation of (gemifloxacin 320 mg/tablet) with that of the reference item (factive 320 mg/tablet). The bioequivalence of a particular measurement (320 mg) was assessed by analyzing the pharmacokinetic parameters got from the plasma absorption time profiles included in the test and reference items for Gemifloxacin. Following administration to 24 healthy male volunteers in a balanced, two periods, two sequence, two way crossover design were performed to analyze Gemifloxacin plasma levels of the two formulations at each sampling time and statistical differences between the two formulations.

Mandallaz [16] examined the idea of bioavailability of time and degree by which the medication was accessible at its location of activity was presented. This was a difficult and multi-dimensional idea. Quantitatively it was communicated by a few trial acquired from the bend of the centralization of medication in blood or plasma opposed to time, seen in each subject matter after a single-dosage association. The bioavailability measured at primary level, the time until the most of medicine was dissolve in the body.

Chow and Liu [17] researched on life probability of patients from the last three decades have

increased globally the new treatment discovered with drugs production. According to health care examination (HCE) interventions occurred through medication. When medication cost increased that contributed to the total charge of health care that receives significant value. Without sacrificing quality this approach has been effective in dropping total cost. The medicines that have captured more than 66% in the global market and account for 67% of prescriptions filled in the United States but for less than 12% of the cost.

Mastan [18] described bioavailability (BA) and bioequivalence (BE) have significant along with the most recent three decades as a result of their function to new brand name drugs, and in addition to nonspecific medications. Thus, gigantic advanced have been made in the utilization of appraisal way to deal with these logical ideas. He used logistic regression for the medicine determination.

3. MATERIALS AND METHODS

The present study is conducted of twin's cities i.e. Islamabad and Rawalpindi. That is mainly consisting of different type of hospitals private as well as public hospitals lab. The reason behind the selecting that area is breast cancer rate is 68% increases in this area [19]. Population rapidly using medicine to control baby birth and dirty water is one of the major causes of breast cancer in this area. One of the major things is lake of awareness and delay in treatment due to which patients are quickly moving from initial stage toward advance stage of breast cancer.

Patient data is collected through questionnaire. The Physical data collection criteria was used as follows; Gender, Age (20-60), Stage of diagnoses breast cancer of patients, Examination done by doctor at initial stage, Examination done by doctor at advance stage, Drug use for patient at initial stage, Drug use for patient at advance stage, Half-life of both medicine use for the treatment of breast cancer i.e. (Methotrexate and Tamoxifen), Treatment period of both medicines, Patient cure by both medicine, Patient not cure by both medicine, Efficiency of both medicines, Prognosis of both medicines. In physical data collection all of the above points play very important role while we are going to study about the patients of breast cancer.

The way toward deciding breast cancer stage has a number of important parameters of tumor

development: Its circulation to the surrounding tissue, its mass, regardless of whether it has increase to the lymph nodes in the breast or around it, regardless of whether it has extended to different organs. Based on these information, the stage is found and also a treatment procedure. The continued existence rate is constantly calculated in view of interpretation of individuals who have been treated for disease.

The initial stage of breast cancer implies that tumor estimate is fewer than 2 cm. Also, that the tumor has not yet widen to the lymph hubs or to different organs or could frame just micro metastases in 1-3 lymph hubs in the underarm territory. On the initial stage, the survival rate during 5 years is right around 100%.

Advance Stage demonstrates that tumor is more prominent than 2 cm in diameter across, but less than 5 cm and has not spread to the lymph hubs or different organs or little cancer cells were found in close to three lymph hubs in the axilla and/or lymph hubs in mammary organ, however not found in the interior organs; Or on the other hand the tumor is bigger than 5 cm in diameter, however has not developed into the chest. Wall or skin and did not frame metastases in the lymph hubs or inward organs [20].

Research will conduct on breast cancer in males and females of Rawalpindi and Islamabad. The research for selecting this are that focus of the study is on breast cancer that is second leading cause of death not only in females but also in males. All this happens due to lack of knowledge and carelessness. There researcher will be concentrating to provide basic knowledge about breast cancer and assessment about treatment according to age [21].

The statistical analysis of a crossover trial requires additional assumptions and is more difficult than a parallel group experiment. The treatment effect difficultly separate from the time effect and previous treatment effects are carryover in it. It is more complex to keep patients enrolled in the study because subjects must be considered at least twice. It is perhaps simpler to assess a subject once than to obtain their measurement twice. This is predominantly true when the measurement process is uncomfortable, uncomfortable, painful or time-consuming process. The t trial of details (medicines) might be thought of as a preparatory appraisal of bioequivalence. Be that as it may, this t test explores whether the two medicines

are unique. It doesn't evaluate whether the two medicines are the same bioequivalent. That is, inability to dismiss the speculation of equivalent means does not infer bioequivalence. Keeping in mind the end goal to build up bioequivalence, distinctive factual tests must be utilized.

Before examining these tests, it is imperative to comprehend that, dissimilar to most measurable speculation tests, while testing bioequivalence, you need to build up that the reaction to the two medicines is the same. Henceforth, the invalid speculation is that the mean reactions are extraordinary, and the option theory is that the mean reactions are square with. This is the polar opposite from the standard t test. This is the reason bioequivalence testing requires the unique factual methods examined here. When utilizing a traverse configuration to test for bioequivalence, a washout phase between the first and second time spans must be utilized that is sufficiently long to dispose of the lingering impacts of the main treatment from the reaction to the second treatment. On account of this washout period, there is no remainder impact. Without a remainder impact, the general straight model diminishes to there are many sorts of bioequivalence. The 2x2 traverse configuration is utilized to survey normal bioequivalence. Keep in mind that normal bioequivalence is an announcement about the populace normal.

The universal linear model issue for the average 2x2 crossover design

$$Y_{ijk} = \mu + s_{ik} + P_j + F_{(j,k)} + C_{(j-1,k)} + \varepsilon_{ijk}$$

where i is representing a subject (1 to n_k), j representing the time of using both medicine (1 or 2), and k representing the sequence of treatment (1 or 2). The S_{ik} represent the random effects of both medicine on patients. The P_j represent the effects of the two drugs period and comparative examination for measurement of various doses under certain conditions. The $F_{(j,k)}$ is representing the effects of the two treatments. In the case of the 2x2 crossover design

$$F_{(j,k)} = F \begin{cases} F_R & K = j \\ F_T & K \neq j \end{cases} \text{ if}$$

where the subscripts R and T represent are the treatment and reference correspondingly. The

$C_{(j-1,k)}$ represents the carry-over effect of medicines. In the case of the 2x2 cross-over design

$$C_{(j-,k)} = \begin{cases} C_R & j = 2, k = 1 \\ C_T & \text{if } j = 2, k = 2 \\ 0 & otherwise \end{cases}$$

where the subscripts T and R represents the treatment and reference correspondingly. It was assuming that the average effect of the subjects is zero and four means from the 2x2 crossover design can be summarized using the following

1(RT) $\quad \mu_{11} = \mu + P_1 + F_R \quad \mu_{21} = \mu + P_2 + F_T + C_R$

2(TR) $\quad \mu_{12} = \mu + P_1 + F_T \quad \mu_{22} = \mu + P_2 + F_R + C_T$

Where $P_1 + P_2 = 0$ $F_T + F_R = 0$ and $C_T + C_R = 0$

Treatment effect of drugs may studied through testing whether $F_T = F_R = 0$ using t test. The test is calculated as follows

$$T_d = \frac{\hat{F}}{\hat{\sigma}_d \sqrt{\frac{1}{n_1}} + \sqrt{\frac{2}{n_2}}}$$

Hypothesis Testing:

H$_o$: Both medicines have equal effects
H$_1$: Both medicines do not have equal effects

Two Cross Two Crossovers Design: In two cross two Crossovers design trials in which the repeated measure method is used. The essential features distinguishing from conventional equivalent group trial contain crossover trial that each patient serves as his/her own control. Then further prevalence of subjects had also been identified separately in male and female population. This statistical method is use for analyzing a data set in which one or two independent variables that determine an outcome. The outcome is calculated with a dichotomous variable (there are only two possible outcomes in which).

4. RESULTS AND DICUSSION

The current study includes data collection of two hundred subjects under treatment of breast cancer by visiting hospitals lab of Rawalpindi and

Islamabad. Addition criteria of conclusion were focused on subjects, whom were diagnosed and under treatment of breast cancer. This research reviews the comparison study of breast cancer patients to assist patients to help the clinician with the lead and assessment of such examinations. Patient data from one subject are utilized to outline the treatment techniques. Although one would not settle on choices in view of the findings from one subject, the extensive number of paired estimations in the informational collection allows its utilization for examination purposes. To analyze such sorts of information Repeated Measure method is used.

4.1 Medicine Efficiency on Different Stages and Ages

Age factor plays very important role in breast cancer because its risk increases when person getting older. Medicine tendency also depend upon age factor because dose of medicine is different for every age group. The most complex challenge in executing both medicines is the amount of medicine required to reach meaningful results. As a result of the fully factorial nature of these tests, the number of variations in a test can add up promptly. Comparison between initial and advance stage of breast cancer is by using medicine tamoxifen. Here we make analysis by giving that drug to 50 patients of initial and 50 of advance stage of breast cancer are treated with tamoxifen and then made its analysis. Medicine 1 is methotrexate and medicine 2 is tamoxifen. In first age group medicine 1 is used 15% while medicine 2 is 3%. In second age group medicine 1 is used 51% while medicine 2 is 29%. In third age group medicine 1 is used 47% while medicine 2 is 61%. In fourth age group medicine 1 is used 8% and medicine 2 is 18%.

4.2 Efficiency of Methotrexate at Different Stages

One of the important things is that by using methotrexate patient suffers less by its side effects at initial stage and vice versa. We also focused to check the examination prefer in adult subjects additionally after completion of its half-life. But using methotrexate at age group 21 to 40 mean values is 2.42 and for age group 41 to 60 mean value is 2.27 at advance stage. While, standard deviation is 0.56 and .67 respectively and standard mean error is 0.80 and 0.12 respectively. For first age group efficiency is 44%

whole for second is 42%. Methotrexate creates side effects at initial stage of breast cancer than advance stage.

By using methotrexate at age 21 to 40 is 3.67 and 41 to 60 is 3.55 at initial stage. While, standard deviation is 0.59 and 0.54 respectively and standard mean error is 0.8 and 0.10 respectively. Here 25 patients of age group 21 to 40 and 25 of age group 41 to 60 were taken on both stages of methotrexate and made their analysis. For first age group efficiency is 57% whole for second is 55%. When, age increases from 40 years there are more chance of advance stage of breast cancer diagnosis in female. These results show that methotrexate is more convenient for patients of age 20 to 40 years to use.

4.3 Efficiency of Tamoxifen at Different Stages

Efficiency of medicine is depending upon its half-life of tamoxifen. Because after completion of its half-life effects of medicine are examine. Comparison between initial and advance stage of breast cancer is by using medicine tamoxifen. mean value of using tamoxifen at age 41 to 50 is 2.46 and 51 to 60 is 2.63. But using tamoxifen at age group 41 to 50 mean values is 1.66 and for age group 51 to 60 mean value is 2.20.

4.4 Analysis of Effectiveness of Two Drugs

Methotrexate is more efficient at initial stage with respect to advance stage. Analysis the effect of medicine by giving that drug to patients of initial and advance stage and check its effect on patient. Mean value of using methotrexate at age 41 to 60 is 3.55 and 21 to 40 is 3.67. Tamoxifen is more efficient for the age group of 51 to 60 years old. But using tamoxifen at age group 41 to 50 mean values is 1.66 and for age group 51 to 60 mean values is 2.20 describe in Table 1. Effectiveness of methotrexate at initial stages 2.38 and at advance stage is 1.85 which means it is 43% effective at initial stage while 38% effective in advance stage. Effectiveness of tamoxifen at initial stage3.19at advance stage 3.68which means it is 52% effective at initial stage while 57% effective in advance stages shown in Table 2. So we can say that we can use this medicine at advance stage is more efficient then initial stage.

Table 1. Analysis of effectiveness of two drugs

	Mean	Std. deviation	N
Effectiveness of methotrexate at initial stage	2.38	1.052	200
Effectiveness of methotrexate at advance stage	1.85	1.048	200
Effectiveness of tamoxifen at initial stage	3.19	.545	200
Effectiveness of tamoxifen at advance stage	3.68	.589	200

Table 2. Prognosis of drugs

	Age	N	Mean	Std. deviation	Std. error mean
Prognosis of methotrexate	21 to 40	50	3.46	.788	.111
	41 to 60	50	2.63	.765	.140
Prognosis of Tamoxifen	21 to 40	50	2.64	.485	.069
	41 to 60	50	3.87	.346	.063

4.5 Prognosis of Drugs

Prognosis of using both drugs i.e. methotrexate and tamoxifen for different age groups for the treatment of breast cancer. Here we make analysis of 50 patients of initial and 50 of advance stage of breast cancer are treated with tamoxifen. Here we make analysis of 50 patients of initial and 50 of advance stage of breast cancer are treated with methotrexate. Prognosis of methotrexate for the age group of 21 to 40 years mean value of prognosis is 3.46 and for 41 to 60 is 2.63 which means prognosis percentage is 34% and 46% respectively. One of the important thing is that by using tamoxifen patient suffer less by its side effects at advance stage and vice versa. Prognosis of tamoxifen for the age group of 21 to 40 years mean value of prognosis is 2.64 and for 41 to 60 is 3.87 which means prognosis percentage is 46% and 59% respectively.

4.6 Cross over Design (Repeated Measures Method)

Given the sample sizes are sufficiently large; the inverse sampling is a procedure ought to guarantee that gathering contrasts in factors that may impact result of the intervention of significance (e.g. age, sex) each other. There is no distinction between the medications tried

these variables may themselves be subjected to statistical analysis and the null hypothesis. A case would be a comparison of the efficacy of two unique medications for the treatment of breast cancer. Firstly, the table shows detail of both medicines used in initial stage of diagnostic of breast cancer i.e. patients are selected that are using methotrexate and tamoxifen. Therefore, effectiveness of the predicted classification against the actual classification can be assessed by this method.

4.7 Tests of Within-Subjects Contrasts

Every statistical tests start with the premise of the null hypothesis. This is tested by calculating the probability that the differences observations between the sample groups are because of occurring (the P-value). Give us a chance to consider examination comparison two sample methods for two unique medications of breast cancer. This test shows the within subject contrasts of both medicines. Sum of mean squares of methotrexate is 231.040, F is 341.591 and p-value is. Sum of mean squares of tamoxifen is 10.240, F is 14.327 and p-value is highly significant in both cases shown in Table 3. When examining such information, we clearly don't know whether the medications are equally effective. Where drug A is more effective than drug B or vice versa.

Table 3. Tests of within-subjects contrasts

Source	Type III sum of squares	Df	Mean square	F	Sig.
Methotrexate	231.040	1	231.040	341.591	.01
Error(methotrexat)	66.960	199	.676		
Tamoxifen	10.240	1	10.240	14.327	.000
Error(tamoxifen)	70.760	199	.715		
methotrexate * tamoxifen	4.410	1	4.410	5.223	.024
Error(methotrexate*tamoxifen)	83.590	99	.844		

5. CONCLUSION

Breast cancer is the second leading cause of death in females which is quickly spreading. Breast cancer is present not only in female but also in males. In our study population of Rawalpindi and Islamabad is considered for observation of breast cancer treatment. All patients are included which are taking treatments at different stages and levels. Two medicines that are methotrexate and tamoxifen used for the treatment of breast cancer at both initial and advance level are considered in our research. Mean value of initial stage of treatment A is 2.38, while mean value of advance stage of same treatment is 1.85 whereas, mean value of treatment B in at initial stage is 2.01 and in advance stage is 3.58. After analyzing our data by applying independent t test and cross over design we concluded that methotrexate is more beneficial at initial level of diagnostic and its side effects are less in this stage. But its side effects in advance level is more so it is not beneficial to use in this stage. Tamoxifen for age group 41 to 50 mean values is 1.66 and for age group 51 to 60 mean values are 2.20 but for using methotrexate at age 41 to 50 is 2.40 and 51 to 60 is 2.26. Methotrexate is more beneficial for age 41 to 50 but tamoxifen is more efficient for the age group of 51 to 60 years old and shows its significant results and beneficial in advance level of diagnostic. Side effects of tamoxifen are lesser in advance stage of diagnostic as compare to methotrexate. Effectiveness of methotrexate at initial stage is 2.38 and at advance stage is 1.85 which means it is 43% effective at initial stage while 38% effective in advance stage. Effectiveness of tamoxifen at initial stage 3.19 at advance stage 3.68 which means it is 52% effective at initial stage while 57% effective in advance stage.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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