

## **Palliative Chemotherapy and Ibandronic Acid Improves Quality Of Life of Bone Metastasis Breast Cancer Patients**

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### **I. BACKGROUND**

In Indonesia, the prevalence of cancer is quite high. Based on Basic Health Research data of 2013, the prevalence of cancer in Indonesia is 1.4 per 1000 population, or about 330,000 people. The highest cancer in Indonesia in women is breast cancer and cervical cancer. Based on data of Hospital Information System 2010, 12,014 cases of breast cancer cases (28,7%), cervical cancer 5,349 cases (12,8%). Cancer cells can break away from the original tumor and spread to other parts of the body. This can happen by lymph or the circulatory system. Bone metastases are a common complication of cancer patients, occurring in 70% of patients with advanced cancer. Bone metastases can cause severe pain, pathologic fractures, menopausal hypercalcaemia and the risk of spinal cord. Bone metastases are a serious complication and require high medical costs.

Chemotherapy is a treatment process by using drugs intended to destroy or slow the growth of cancer cells. The side effects of chemotherapy arise because chemotherapy drugs not only destroy cancer cells also attack healthy cells, especially distractions that heal quickly. Chemotherapy side effects that attack blood cell counts in the leukocyte marrow, erythrocytes, and platelets. This will increase the chances of getting infected, bruising and bleeding easily, and pregnancy. In addition, the side effects are nausea, vomiting, hair loss, mouth ulcers, appetite drop, diarrhea, constipation, menstrual changes, and eye disorders .

To increase the rate of destruction and excessive bone formation due to metastasis. A study with intravenous administration of intravenous ibandronate for 96 weeks at 3-4 weeks interval was significantly improve the quality of life as well as effective and well tolerated palliative therapy in patients with bone metastases breast cancer.

The impact of breast cancer on quality of life shows that breast cancer sufferers feel helplessness, imperfect, embarrassed by breast shape changes, unhappy, unattractive, feelings of unacceptable acceptance by others, isolation, fear, grief, lingering in bed , functional disability, failing to meet family needs, lack of sleep, difficulty concentrating, anxiety, and depression.

Quality of life is an individual's perception of one's life according to the cultural context and value system it embraces, including its life goals, hopes and intentions.<sup>8</sup> Currently, attention is devoted to developing quality of life among cancer survivors. The prevalence rate of depression increases with the development of cancer, from 11% in the early stages, and develops up to 50% in patients with metastatic breast cancer who are undergoing palliative therapy..

### **II. METHODE**

This study was an observational study with a cohort approach. Which aims to find a palliative chemotherapy relationship to the quality of life of patients with advanced breast cancer.

The research was conducted in Oncology Polyclinic of Saiful Anwar Hospital Malang, conducted between July 2015 until July 2016.

The population of this study subjects were all breast cancer patients with clinically suspicious bone metastases and conducted bone survey obtained a description of bone metastases requiring palliative chemotherapy as well as therapy of Ibandronic Acid and treatment to Polyclinic Oncology Hospital Saiful Anwar Malang.

In this study there is one group of bone metastases breast cancer patients according to inclusion criteria and exclusion criteria. Each patient was given informed consent and obtained ethical clearance from Health Research Ethics Committee of Brawijaya University Malang / Saiful Anwar Hospital Malang. The number of

samples used in this sample is the total sampling of all breast cancer bone metastasis patients who are treated to the oncology polymer Saiful Anwar Hospital Malang. Inclusion criteria in this study were, women aged 40-70 years, Breast Cancer Patients Metastase Bone without other organ metastases.

Patients are willing to follow the research by signing the research informed consent. While the exclusion criteria in this study are being in the presence of a metabolic disease (diabetes mellitus, dyslipidemia, hypo / hyperthyroidism), the patient is in a state of trauma, the patient withdraws from the study, metastases to other organs other than bone.

All female patients with breast lump complaints performed physical examination, breast ultrasound, axilla ultrasound, abdominal ultrasound, histopathologic examination of breast malignancy, thorax and bone surveys obtained evidence of bone metastasis and if it met the inclusion criteria and exclusion criteria diagnosed as breast cancer bone metastases, given informed consent and if agreed to measure quality of life with City of Hope Quality of Life Questionnaire and continued with palliative chemotherapy. After completion of chemotherapy re-measurement of patient's quality of life with City of Hope Quality of Life Questionnaire.

### III. RESULTS

Based on Table 1 of the research data obtained from 23 samples, it can be seen that respondent characteristics include histopathology, grade, CPI, surgery, regimen, fracture location, age, education, and occupation. The following will be described each of the characteristics of respondents.

Based on the results of the research can know the value of the questionnaire score City of Hope and the analysis antarapre and post with paired T-test. There are 4 variables in this questionnaire that are physical, psychological, social and spiritual. Tests conducted using the method of difference test average is paired t test. Prior to the test, there was an underlying assumption of normality using the Shapiro-wilk test. If the data used do not meet the assumptions, then tested a replacement, the test wilcoxon. The hypothesis of analysis used is as follows:

H0: There is no significant mean difference between pre and post

H1: There is a significant average difference between pre and post.

With the following test criteria:

if the significance value is  $<0.05$ , then H0 is rejected;

if the value of significance  $> 0.05$ , then H0 is accepted.

Table 1 Summary of Histologic Respondents' Characteristics

Characteristic	F	%
<b>Histopathology</b>		
- INVASIVE DUCTAL CARCINOMA	21	91.3
- INVASIVE PAPILLARY CARCINOMA	1	4.3
- INFILTRATING LOBULAR CARCINOMA	1	4.3
<b>Grade</b>		
- I	1	4.3
- II	11	47.8
- III	11	47.8
<b>Immunohystokimia (ER)</b>		
- (+)	17	73.9
- (-)	6	26.1
<b>Immunohystokimia (PR)</b>		
- (+)	14	60.9
- (-)	9	39.1
<b>Immunohystokimia (HER 2)</b>		
- (-)	13	56.5
- (+)	2	8.7
- (++)	2	8.7
- (+++)	6	26.1
<b>History of Operation</b>		
- Yes	15	65.2
- No	8	34.8
<b>Chemotherapy regimen</b>		
PACLITAXEL/CYCLOPHOSPHAMID	4	17.4
-	11	47.8

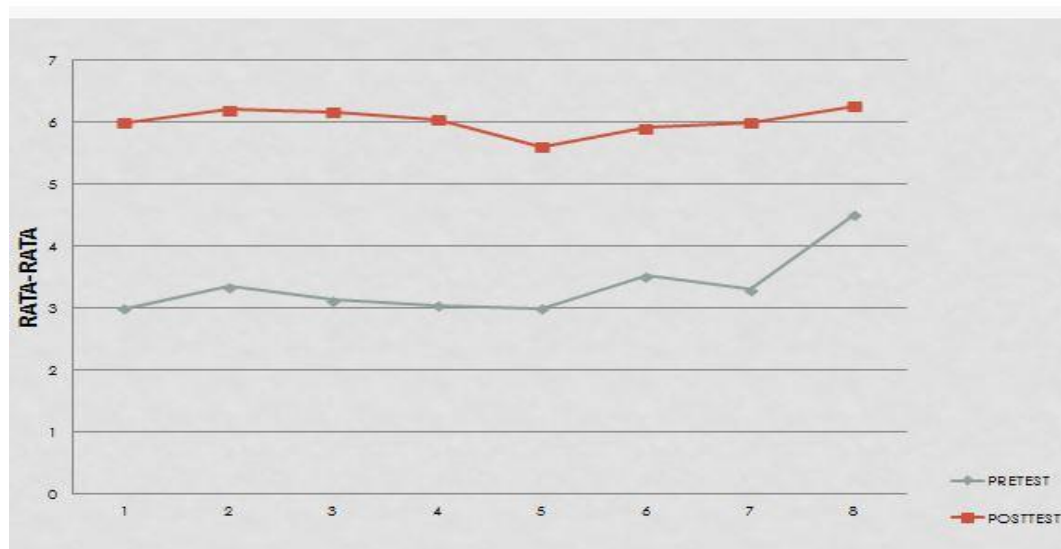
	CYCLOPHOSPHAMIDE/DOXORUBICIN/5-FU		
	- PACLITAXEL/DOXORUBICIN	1	4.3
	- CYCLOPHOSPHAMIDE/METOTREXATE/5-FU	2	8.7
	- CYCLOPHOSPHAMIDE/EPIRUBICIN/5-FU	2	8.7
	- DOCETAXEL/CARBOPLATIN	2	8.7
	- PACLITAXEL/CARBOPLATIN	1	4.3
<b>Location of Fracture</b>			
	- HUMERUS	1	4.3
	- VERTEBRA + FEMUR	1	4.3
	- PELVIS + VERTEBRA	2	8.7
	- FEMUR + PELVIS	1	4.3
	- VERTEBRA	11	47.8
	- COSTAE + HUMERUS	1	4.3
	- COSTAE + PELVIS + FEMUR	1	4.3
	- PELVIS	1	4.3
	- COSTAE	2	8.7
	- CALVARIA + VERTEBRA	1	4.3
	- PELVIS + COSTAE	1	4.3
	Total	23	100.0

The result of Shapiro-wilk normality test shows that post data has normal distribution of significance value more than  $\alpha$  5%, but pre-data is not normally distributed with significance less than 0.05. Then use a replacement test with wilcoxon.

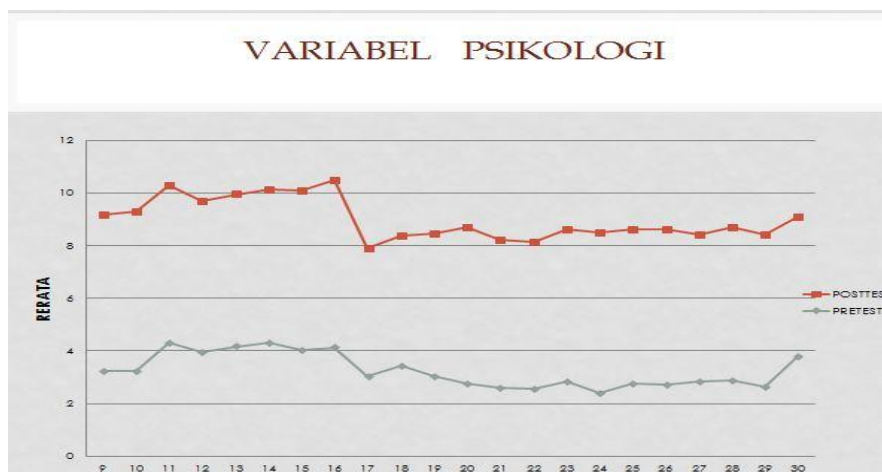
From the test of wilcoxon, the significance value is less than  $\alpha$  (0.000 < 0.05). H0 decision is rejected, which means there is significant mean difference between pre and post based on the physical variable score (Diagram 1) measured. The results of the wilcoxon test showed significantly different for overall physical variables.

**Diagram 1. Physical Variables**

### VARIABEL FISIK



**Diagram 2. Psychology Diagram**



The result of Shapiro-wilk normality test shows that pre and post data have normal distribution of significance value more than  $\alpha$  5%. Then paired t test is used.

From paired t test, the significance value less than  $\alpha$  (0.000 < 0.05), H0 decision is rejected which means there is significant mean difference between pre and post based on the measured psychological score. Seen from Table 5.4 shows a high average increase in scores, supported by t test results that show significantly different in total for the psychological variable group.

When a different test of each group of psychological variables was obtained, significant differences were found among all the questions in this group, including: coping with the outcome of the disease, overcoming the outcomes of therapy, quality of life, perceived joy, controlling situations, life satisfaction, ability to concentrate and memory, feelings useful to others, appearance change, self-perspective, stress on early diagnosis, stress on cancer chemotherapy, stress on cancer radiation, stress on cancer surgery, stress on complete therapy completion, anxiety, depression, fears of further diagnostic tests, fear of second cancer, fear of cancer recurrence, fear of cancer spreading and the degree of life to return to normal as before.

### 3. The Social Diagram

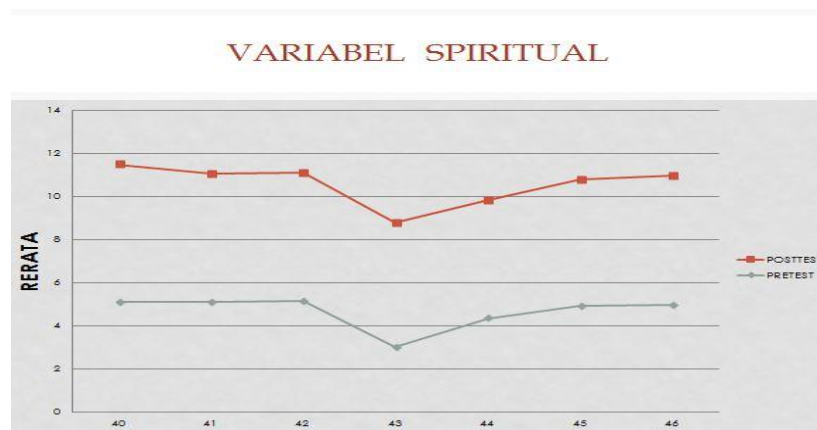


The result of Shapiro-wilk normality test shows that pre and post data have normal distribution of significance value more than  $\alpha$  5%. Then paired t test is used.

From paired t-test, the significance value less than  $\alpha$  (0.000 < 0.05), H0 decision was rejected, which means there was significant mean difference between pre and post based on measured social score. Seen from table 5.5 shows a high average increase in scores, supported by t test results that show significantly different for overall social variables.

From the test results of each question component of the social variables group, there were significant differences in how the disease had a stressful impact on the family, the adequacy of support gained from others, personal relationships relating to ongoing care, the impact of sexuality, the impact on the work, impacts on home activities, feelings of isolation, attention from girls or sisters and the financial burden on illness.

#### 4. Spiritual Diagram



The result of Shapiro-wilk normality test shows that the pre distribution data has a normal significance value greater than  $\alpha$  5%, but post data is not normally distributed with significance less than 0.05. Then use a replacement test with wilcoxon.

From the test of wilcoxon, the significance value less than  $\alpha$  ( $0.007 < 0.05$ ),  $H_0$  decision is rejected, which means there is significant mean difference between pre and post based on measured spiritual score. Seen from table 5.6 shows a fairly high increase in average score, supported by wilcoxon test results that show significantly different.

There are significant differences from the spiritual questionnaire group, among others, uncertainty about the future and positive changes in life. From the table above also found no significant differences in religious activities, spiritual activities, changes in spiritual life, perspective on the reasons for life and hope.

#### IV. DISCUSSION

Quality of life is a perceived state of one's state according to its cultural context and value system, including life goals and expectations.<sup>21</sup> They include physical symptoms, functional ability, family welfare, spiritual, social function, treatment satisfaction, future orientation, Sexual life includes self-image and function in work.<sup>7,17</sup>

The impact of breast cancer on the bio-psycho-socio-spiritual aspect shows that breast cancer sufferers feel helplessness, imperfect, embarrassed by breast changes, unhappy, unattractive, feelings of unacceptable acceptance, isolation, fear, grief, lingering in bed, functional disability, failing to meet family needs, lack of sleep, difficulty concentrating, anxiety, and depression.<sup>7</sup>

In this study, from 23 samples, it was found that the most histopathologic result was invasive ductal carcinoma as many as 21 people or 91.3%, the highest grading was grade II and III which were 11 people or 47.8% and immunohistochemistry ER (+) was obtained at 17 people, PR (+) on 14 people and strong positive HER2 (+++) in 6 people. This corresponds to the theory that about 70-80% of all breast cancers are the most common type of invasive ductal carcinoma.<sup>25</sup>

Of the 23 samples found that 15 people or 65.2% of patients had previously performed mastectomy surgery. The most used regimen for chemotherapy in these 23 samples was the combination of Cyclophosphamide / Doxorubicin / 5-FU, which were 11 patients, and the location of the most metastases in the bone was vertebrae with 15 patients or 47.8% of the total. Several factors play a role in the occurrence of metastases of cancer to the bone, among others, blood flow in the bone marrow and cancer cells to produce adhesion molecules that cause attachment of cancer cells in bone marrow stromal cells and bone matrix where this adhesion process causes increased production of angiogenic factors and factors bone resorption factor that will increase the growth of cancer in the bone. Clinical features of metastatic breast cancer to bone may be bone pain caused by periosteal stretching and nerve stimulation of the endosteum by tumor cells, fractures due to osteolytic lesions of the bone, spinal cord compression due to compression fractures in the vertebrae, elevated levels of calcium in the blood caused by release of calcium from bone, as well as manifestations of blood disorders when the metastases to the vertebral bone reach the marrow.<sup>13</sup>

In this study of 23 respondents, the highest number of respondents is age between 41 to 50 years as many as 10 people or 43.5% of the total. This is similar to the research conducted by Leong et al (2010) in Sabah Malaysia and Oktaviana et al (2012) in Dharmais Cancer Hospital Jakarta stated that breast cancer is found in the age group 40-49 years.<sup>26,27</sup> In women aged > 30 years or reproductive age of breast cancer incidence will increase rapidly, doubling every 10 years and will decline after menopause.<sup>25,28</sup> Each 1 year

increase over the age of 40 years has a new incidence rate of 1-2% for the risk of breast cancer. This is thought to be related to the effects of long-term hormonal exposure as well as exposure to other risk factors that trigger cancer. 29

From the results of research based on the level of education, found that most breast cancer respondents have high school education level of 9 people from 23 respondents or 39.1% of the total. This is similar to the results of research by Sirait AM (2011) in Indonesia states that there is a significant relationship between education with tumor / breast cancer, where the risk of tumor / breast cancer in higher education 2.22 times greater than with low education, this probably because an increase in educational status will improve the socioeconomic status, which will then alter the pattern of life.<sup>30</sup> The pattern of community life with high socioeconomic good in the form of higher fat intake and unhealthy lifestyle will increase exposure to breast cancer risk factors.<sup>29</sup>

Based on the results of the research can know the score score of the questionnaire City of Hope and in the analysis between pre and post with paired T-test. There are 4 variables in this questionnaire that are physical, psychological, social and spiritual. Variables of physical activity include: fatigue, appetite changes, pain, changes in sleep patterns, weight gain, menopausal symptoms and changes in menstrual or fertility patterns. Psychological variables include difficulty to overcome daily activities, quality of life, joy, control of the situation, life satisfaction, concentration, memory, appearance and perspective on self. Social variables include: family relationships, support, personal relationships, sexuality, work, home activities, sense of isolation, understanding of family and financial needs. Spiritual variables include: religious, spiritual activities, changes in spiritual life and hope.<sup>21</sup>

Based on the results of research on physical variables, the average pre average of 26,826 is lower than the post average of 48,348. It appears that there is an increase in pre-post average. While the psychological variables obtained the average pre of 71.478 lower than the average post of 126.348, also seen that there is an increase in average pre to post. Similarly, the social and spiritual variables in this study also showed an average increase from pre to post. This suggests that palliative chemotherapy and Ibandronic Acid significantly improve the quality of life of breast cancer patients with bone metastases on physical, psychological, social and spiritual aspects .

Psychologically the subject shows that he is not getting worse in the sadness and able to foster positive feelings in him. In social relations, the subject revealed that the great social support of the family made an important contribution. Efforts are made in achieving the quality of life of the spiritual aspect of positive thinking and closer to God by multiplying worship and prayer, and undergoing treatment procedures well. It is like the respondent considers that his illness is God's plan for him so that he has been able to accept and be strong to live his life despite having to wrestle with cancer.<sup>28</sup>

In patients with breast cancer, Ibandronic Acid has several uses: preventing or inhibiting the occurrence of skeletal complications in patients with bone metastases, reducing bone pain, hypercalcemia therapy, delaying bone metastasis in patients with early-stage breast cancer with high risk (as adjuvant therapy) prevent the occurrence of bone mass loss that accompanies systemic adjuvant therapy and direct cytotoxic effects on cancer cells.<sup>15</sup>

In this study it was found that body fatigue increased significantly between before and after chemotherapy. This indicates that administration of chemotherapy triggers side effects of body weakness or does not reduce symptoms of fatigue before chemotherapy is given. This is consistent with the literature that cancer-related fatigue is the most frequent symptom before and after therapy.<sup>31,32,36</sup> One of the mechanisms that causes fatigue is muscle mass changes, although it is still controversial.<sup>33,34</sup>

In this study also obtained decreased appetite significantly between before and after chemotherapy. This indicates that the administration of chemotherapy triggers side effects such as decreased appetite than before chemotherapy. This corresponds to the literature of decreased appetite in patients receiving chemotherapy.<sup>35</sup>

In this study, there was a significant increase of pain between before and after chemotherapy. This indicates that the administration of chemotherapy triggers side effects of increased pain than before chemotherapy. This is consistent with the literature that there is an increase in pain in patients receiving chemotherapy.<sup>36,37,39</sup> Pain in this can not be distinguished by the effects of palliative chemotherapy alone or ibandronic acid itself because of the treatment protocols of palliative chemotherapy and ibandronic acid entering simultaneously and some are given separately with palliative chemotherapy given first. This is a weakness in this study.

In this study we found a significant increase in sleep disorder between before and after chemotherapy. This indicates that the administration of chemotherapy triggers side effects of increased pain than before chemotherapy. This is consistent with the literature that there is an increase in pain in patients receiving chemotherapy.<sup>37</sup>

In this study showed an increase in menopausal symptoms (vaginal dryness and changes in menstrual pattern) significantly between before and after chemotherapy. This indicates that the administration of chemotherapy triggers side effects such as increased symptoms of menopause (vaginal dryness and changes in menstrual pattern) than before chemotherapy. 40

Limitations to this study on several research subjects, chemotherapy regimens did not coincide with ibandronic acid because bone metastases in the subject were only known after the chemotherapy process was already under way.

In this study, protocols for the use of chemotherapy regimens were not limited. So it is not specific which regimen is really effective in improving the quality of life of breast cancer patients bone metastases. For the location of bone metastases, this study is also not limited. So it can be known also where the location of the most bone metastases in breast cancer patients.

In this study there was no control group, so the intervention that researchers did on this study became less homogeneous. This study is a preliminary study, so that this study is expected to develop to be more specific in studying the quality of life of breast cancer patients in general and breast cancer bone metastases in particular.

The sample in this study is not homogeneous, both respondent age and therapy protocol given. This is a weakness in this study. For the next age will be grouped into 2 groups of age group <40 years and  $\geq 40$  years. From the age group <40 years, a sample of 3 patients, and 1 patient (33%) of the sample had a history of previous mastectomy surgery. From the age group > 40 years, 20 people were sampled and 12 of them (60%) had previously performed the previous mastectomy surgery.

In this study can not specifically evaluate the unfavorable effects of the sample is the effect of palliative chemotherapy therapy or the effect of ibandronic acid because in some samples palliative chemotherapy and ibandronic acid are given simultaneously.

If grouped by age <50 years and  $\geq 50$  years, then get 14 samples in the age group <50 years with the youngest age of 29 years and the oldest age 45 years with an average age of 42.7 years. Of these age groups, 7 samples had undergone a previous history of mastectomy surgery with an average span of 25 months between mastectomy surgery and the presence of bone metastases. Still in the patient group <50 years, 7 samples obtained no history of previous mastectomy surgery action and immediately given palliative chemotherapy and ibandronic acid.

In the age range group  $\geq 50$  years, a sample of 9 patients with an average age of 55.78 years was obtained. Of this age group, 7 samples had a history of previous mastectomy surgery with mean of 27.28 months after it was found that there was bone metastasis. Still in this age group, as many as 2 samples were not performed before surgery and performed palliative and ibandronic acid chemotherapy.

If the evaluation of t-test for the questionnaire score in the age group <50 years and  $\geq 50$  years, in the normality test with Shapiro-wilk found that the data age group <50 years and  $\geq 50$  years of normal distribution with significance of each greater from 0.05. Tests of homogeneity of various data with levene's test showed a homogeneous variety of data with a significance value greater than  $\alpha 0.05$ . Then proceed with unpaired t test.

From the unpaired t test, the significance value was greater than  $\alpha (0.541 > 0.05)$ , H0 decision was taken, which means there was an unambiguous average difference between the groups based on the measured post score. Seen from table 3, the mean post-age <50 years old score was slightly lower than the post-age group score  $\geq 50$  years but not too far away, or in other words, the age of the respondents had no effect on the measured post score.

By age group <50 years and  $\geq 50$  years it can be seen that the mean post score was highest in the age group <50 years of nonoperative history of 273.71, and the lowest post-prevalence score in the <50 years age group of surgical history was 251.00. Based on the average, it can be seen that there is a difference between post group mean score. To verify whether the initial conclusions are statistically significant, one-time anova statistical analysis will be conducted, but first tested for normality and homogeneity.

Normality test results with one Shapiro Wilk test showed the significance value of each group is greater than  $\alpha (0.05)$ , then the data is normally distributed. The value of significance on homogeneity test of data range of 0.108 greater than  $\alpha (0.05)$  proved homogeneous data. Because the data used already meet the assumption, then the next one-way anova test.

Based on the test results with one way anova obtained greater significance value of  $\alpha (0.383 > 0.05)$ , so it can be concluded that there are differences in average post scores are not real in each group, in other words the history of operation and age have no effect on post scores are measured.

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