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The Role of Curcumin to PGF2a and the Primary Dysmenorrhea Pain Intensity

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ABSTRACT--- *The aims of the research is to rate the effectiveness of giving curcumin 7 days before menstruation in* ***order*** *to decrease the pain Intensity of women with primary Dysmenorrhea. The research is using randomized controlled trial method analysis with block permutation to women with Primary dysmenorrhea. The statistic data then processed by using SPSS 21. The level of PGF2a on women that consume curcumin decreased significantly from 677.31 ± 387.27 became 419 ± 234.58 with the ratio P 0.001 compared to control group. The average scale of visual analogue scale (VAS) also decreased significantly to women that were given curcumin supplementation which was from 5.33 ± 1.56 became 2.67 ± 1.15 with the ratio P 0.000. The research has shown that supplementation of curcumin has certain role in decreasing the pain Intensity and the prostaglandin F2a content to women with Primary dysmenorrhea.*

Keywords--- Primary dysmenorrhea*, Curcumin, Prostaglandin F2α (PGF2α)*

I. INTRODUCTION

Dysmenorrhea or menstruation pain is gynecological problem that often found in reproduction age of women with the manifestation of cramp on the lower stomach. Generally, dysmenorrhea is classified into primary and secondary. Primary dysmenorrhea is the menstrual pain that happens to women with normal pelvic anatomy. Primary dysmenorrhea usually happens to teenagers with regular ovulatory cycle and cause myometrium contraction (Speroff L. Fritz, 2011). There are 20%-45% of teenagers with ovulatory cycle 2 years after menarche, and 80% after 4-5 years. Secondary dysmenorrhea is menstrual pain relates to pathology of the pelvic organ which happens several years after menarche, such as endometriosis, adenomyosis, or even uteri myoma (Gebeheyu MB et al, 2017).

The prevalence of dysmenorrhea can vary (16,8% to 81%) and tends to increase when one gets older. The Primary Dysmenorrhea prevalence in the United States of Amerika in 2012 was 59.7% to women aged 12-17 years, which consist of Light dysmenorrhea, medium dysmenorrhea, and heavy dysmenorrhea, each has the percentage of 49%, 37%, and 12% (Osayande, 2017). The number of primary dysmenorrhea in Indonesia comes to 54.89% and 45.11% for the secondary dysmenorrhea (Narsih et al, 2017).

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It is suspected that primary dysmenorrhea appears as the effect of uterus contraction that cause the ischemic process in the myometrium. The uterus contraction is stimulated by PGF2a. PGF2a is also the main mediator of primary dysmenorrhea. Prostaglandin F2a (PGF2a), prostaglandin E (PGE2) and increasing leukotriene during menstruation come from arachidonic acid secreted by endometrium. The concentration of PGF2a and PGE2 relate to how severe the symptoms of dysmenorrhea (Speroff L. Fritz, 2011). The prostaglandin, especially in PGF2a and PGE2 will increase during menstruation cycle. The concentration of both prostaglandins previously low on the proliferation phase, but on the phase of secretion the PGF2 concentration is higher compare to the concentration of PGE2 (Fortier MA et al, 2008).

Prostaglandin is the mediator that has important role on inflammation of cancer. The prostaglandin biosynthesis from arachidonic acid needs cyclooxygenase (COX) enzyme. There are several clinical experiments show the effectiveness of COX inhibition from prostaglandin on menstrual secretion (Speroff L. Fritz, 2011).

Curcumin (*Curcuma longa*) is one of the herbal plants that contains phytochemical. Curcumin is anti inflammation, antioxidant, antiangiogenic, strong anti neoplastic, and widely used as therapeutic agent in the medicine in India and China (Clutterbuck AL et al, 2013). Curcumin is commonly used traditional therapy for stomachache, abdomen colic, and dysmenorrhea. Several experiments have shown the pharmacology of curcumin that is safe and well tolerated (Ravindran RN et al, 2007). As alternatitive therapy, curcumin is considered to be safer and the reason is essential due to this research.

The pharmacology and non pharmacology therapy like NSAID (non steroidal anti-inflammation dugs), herbal, diet therapy, yoga, meditation, and acupuncture have been used to decrease the effect of dysmenorrhea (Clutterbuck AL et al, 2013). Herbal therapy and anti inflammation can be the alternative for dysmenorrhea therapy for the low cost and minimum side effect compare to non steroidal anti inflammation dugs. Those reason shave been the basic idea of the researcher to rate the curcumin effectiveness as one of the alternative for those who suffer primary Dysmenorrhea.

II. METHODOLOGY

The research used randomized controlled trial which was conducted Medical Faculty of Indonesia Muslim University in Makassar since February 2019 to July 2019. The samples of the research are the woman students of Medical Faculty of Indonesia Muslim University that suffer primary menstrual pain, were then Intensity of pain is measured by using Visual Analog Scale and the samples of the research are taken by using randomized mutated block technique with inclusion criteria and exclusion criteria. Inclusion criteria: they who suffer primary menstrual pain with the age 17-21, suffer the Light to medium pain (1-7 VAS score) for the past 3 months, have regular menstrual cycle for the past 3 months (24-35 days), voluntarily join the research. Exclusion criteria: women with other complaints around the womb and pelvic area, had been under medication, still suffer pain in some parts of their body, still consuming pain killers, have undergone surgery around abdomen and pelvic, using any type of contraception and other drugs, have history of gastritis.

Determining the samples is by taking the Population of the woman students of Medical Faculty of UMI Makassar, by using total sampling technique to get the dysmenorrhea based on the inclusion and exclusion criteria. After that, informed consent is performed in order to notify the students are voluntarily join the research. The

process of samples recruitment is through research questionnaire. After they are required, notes are taken based on their period dates, body height, menarche age, and menstrual pain intensity, which is done by the subject by using VAS.

From the screening, 59 woman students suffer dysmenorrhea and 42 of the required the qualification as subject in this research. Subject of the research are divided into two groups, the intervention group, which are provided with curcumin supplement, and the control group (placebo). Samples groups will be treated with curcumin supplement that is consume for 7 days before the first period on the next cycle. The data is recorded on the research form, and Will be analyzed by using couple Sample test. And the result will be served in tables and narration as well as explanations. SPSS program is used with 95% degree of trust and the score of $p< 0.05$.

III. RESULTS

Research has been conducted to those who suffer primary dysmenorrhea, who are Medical Faculty woman students from Indonesia Muslim University, from the screening 59 woman students suffer dysmenorrhea and 42 participants are grouped as the subject of the research. There are 17 students excluded, 2 of the with the history of ovarian cyst, 2 of them still undergo therapy, the rest have gastritis and refuse to participate on this research.

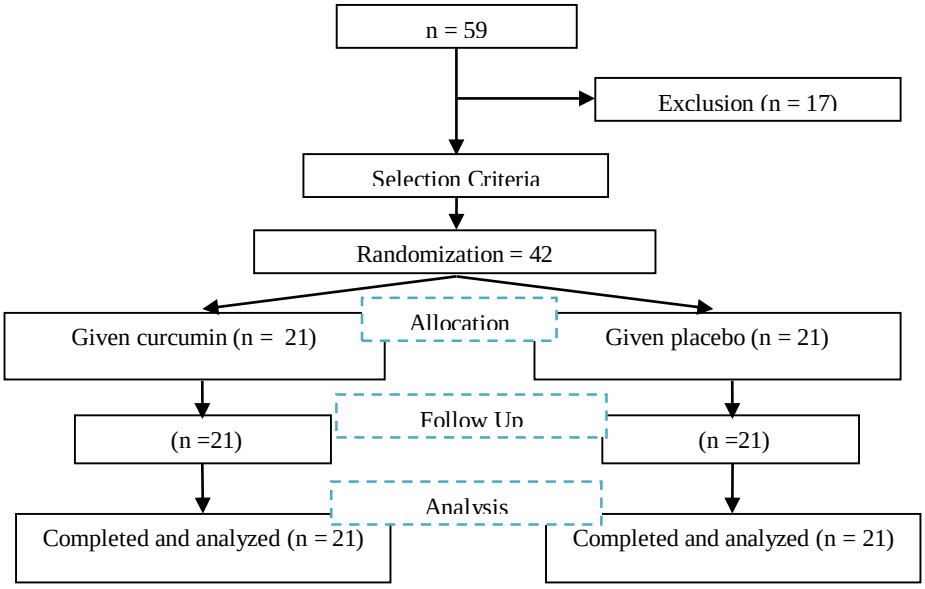

Figure 1 Flow chart

Table 1 The Characteristic of Research Subject From Intervention Group and Control Group

Variable	Intervention	Control	P Value
	Mean±SD	Mean±SD	
Age	18.86±0.73	18.48±0.87	0.102
Age of Menarche	12.90±1.34	13.33±1.35	0.267
BMI	20.34±1.29	20.81±1.55	0.290
Menstrual Cycle	28.86±2.435	29.14±4.078	0.149

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Long Period	5.52±0.87	6.00±0.84	0.049
PGF2a Pre	677.31±387.27	504.31±139.83	0.068
VAS Pre	5.33±1.56	4.95±1.69	0.548

*Mann Whitney Test; Source: Primary Data

Tabel 1 shows 42 woman students aged 17-21 suffer primary Dysmenorrhea and divided into two groups, the intervention group, which is given curcumin supplement and control group, which is given placebo, with total of 21 subjects. Homogeneity test comes UP with the result of score p on the age variable, menarche age, IMT, menstrual cycle, menstrual duration, consent of prostaglandin and VAS score before the treatment is bigger than 0.05 ($p > 0.05$), which means there are no significant differences between the two groups.

Table 2 The Consent of PGF2a Between The Groups of Samples with Curcumin and Placebo Treatment

Group	PGF2α Pre	PGF2α Post	Nilai p
Intervention	677.31±387.27	419.76±234.58	0.001
Control	504.31±139.83	546.30±170.47	0.122

*Paired t test

Table 2 shows average prostaglandin consent on the group of intervention before the treatment is 677.31 and after the treatment is 419.76. The meaning analysis is conducted by using t coupled test show the score $p = 0.00001$. This shows the meaningful correlation between the consent of prostaglandin before and after intervention of the groups ($p > 0.05$). While on the control group, the prostaglandin before the treatment is 504.31 and after the treatment is 546.30 with the score $p = 0.122$ ($p > 0.005$) which describes no meaningful correlation between the consent of prostaglandin before and after the treatment to the intervention group.

Table 3 VAS Score Between Sample Groups Treated with Curcumin and Plabo

Group	VAS Pre	VAS Post	Nilai p
Intervention	5.33±1.56	2.67±1.15	0.000
Control	4.95±1.69	5.19±1.86	0.159

*Paired t test

Table 3, it can be seen that the average Intensity of menstrual pain before treatment on the intervention group is 5.33 and control group 4.95. The changes of pain Intensity for the intervention group is the decrease of score to 2,67 with the score p 0.000 ($p < 0.05$). This describes a meaningful correlation between pain Intensity in the intervention group during the treatment. While in the control group, the score is increasing to 5,19 with the score p 0.19 ($p>0.05$). This describes no meaningful correlation in the control group after treatment is given.

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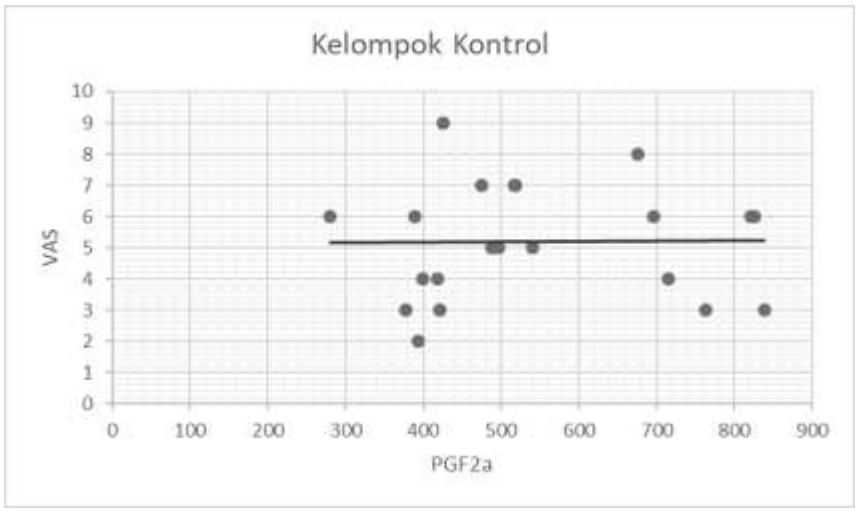
Table 4 Relation of Consent PGF2a and VAS on Intervention And Control Sample Groups

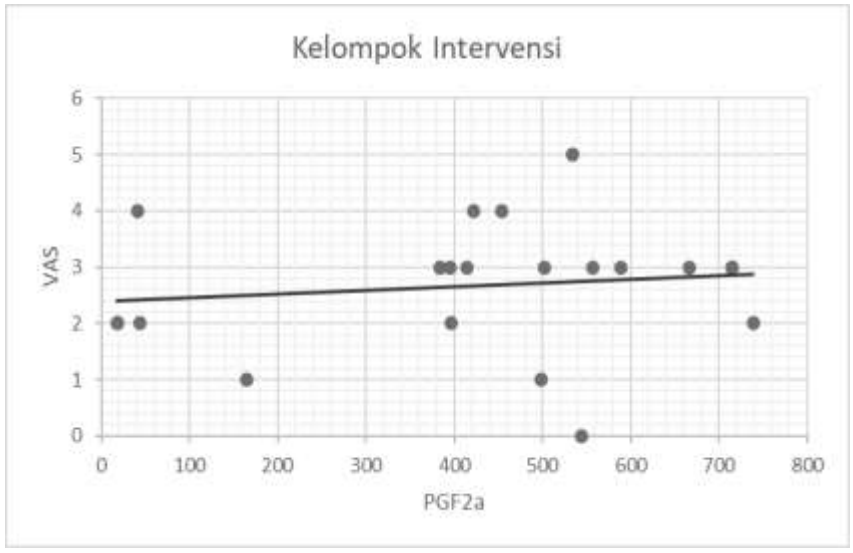
Group	PGF2α Levels to VAS Scores	
	r	p
Intervention	0.147	0.526
Control	0.109	0.637

* Spearman correlation test

Table 4 describes relation analysis between PGF2a and VAS score that is taken before the treatment. On intervention group it is known the score is p 0.526 (score r 0.147) and control group, score p 0.637 (score r 0.109). P score on both groups show p>0.05. This shows no meaningful correlation between PGF2a and VAS score on those who suffer primary Dysmenorrhea. This can also be seen on picture 2 (a) and 2 (b).



(a)



(b)

Figure 2. (a) VAS correlation and PGF2a on control group

(b) VAS correlation and PGF2a on intervention group.

This research involves 42 woman students of Medical Faculty Indonesia Muslim University with the age of 17-21 who suffer primary menstrual pain with the degree light-heavy. Choosing the Sample from that range of age

is with the reason of those who suffer primary menstrual pain come from the age of teenagers to early adulthood (20%-90%). This relates with normal ovulatory cycle without any pathological abnormalities in the pelvic. The criteria for other selection on this research are age, other factors such as period of the cycle, IMT, duration of menstruation, and Medical history.

Based on the previous research, it is shown that the dysmenorrhea intensity is higher for having younger age. (Habibi et al, 2015) This suits the research where the average age of the subjects are younger, for intervention group and control group, each are 18,86 ± 0.73 years and 18.48 ± 0.47 years. Primary dysmenorrhea Intensity is decreasing when the get older (Burnet M, Lemyre M., 2017). That fact cannot be measured in this research because age correlation and pain Intensity cannot be scored in this research.

Research with large number of samples and stated that primary dysmenorrhea does not relate to onset menarche (p 0.15) (Akbarzadeh M., et al, 2017). This is suitable to the research we conducted, which showed no significant difference between primary Dysmenorrhea and onset menarche. Body mass index has significant relation with primary dysmenorrhea, especially with underweight women (Rafique N., Al-Sheikh MH., 2018). This research also stated women with body mass index tend to suffer primary Dysmenorrhea (Chauhan M., Kala J., 2012).

The dose of curcumin used in this research is 3 x 2 capsules (each capsule contain of 100 mg curcumin) 7 times ± 1 day before second day of menstruation. Based on the statistic analysis result on this research, the comparison test after the treatment shows the decrease of prostaglandin in the blood on the intervention group (score $p<0.05$), yet the PG is increase in the control group ($p>0.05$). The influence of curcumin on the pain Intensity to the intervention group shows the increasing of the pain Intensity from the curcumin supplement ($p <0.05$). This means the zero hypothesis (H01 and H02) is refuse and the alternative hypothesis (Ha1 and Ha2) is accepted which is because the decrease of prostaglandin and pain Intensity on those who suffer primary Dysmenorrhea after treated with curcumin.

Research on curcumin anti-inflammation effect on pregnant woman's myometrium cell shows curcumin inhibition effect to the COX-2 expression, and the decrease of the prostaglandin (PGF2a and PGE2) after providing the curcumin (Lim R., at al, 2013) This suits the research we have done. Other research shows giving curcumin extract supplement 100mg/12 hours for 7 days before until the third Day of menstruation can reduce the menstrual pain syndrome symptoms to the research samples who suffer menstrual pain. The curcumin mecanism in reducing the pain intensity is by inhibition COX-2 (synthetic prostaglandin) (Khayat et al, 2015).

Prostaglandin is also said to be the cause of menstrual pain. Therefore, there are many research were done to block the release of prostaglandin. OAINS is the medicine that reacts blocking the production of prostaglandin. OAINS blocks the works of enzyme COX (responsible to form prostaglandin). Some other intervention to dysmenorrhea has been rated in cochrane systematic review (Marjoribanks J., et al, 2015).

The research that compare curcumin analgesic effect and NSAID on the People who suffer osteoartistic (OA) concludes that curcumin extract can be as effective as ibuprofen in reducing pain. Curcumin extract shows better security profil than ibuprofen, rated based on the symptoms such as stomachache/distention (Kuptniratsaikul V., et al, 2014)

The average concentration of PGF2a on the research subjects before the treatment is 677.31 pg/ml on intervention group and 503.31 pg/ml on the control group. PGF2a is a potent stimulant on the pain muscles of the vascular wall, intestine, and myometrium. Some literatures say that women with dysmenorrhea have higher PGF2a

and PGE2 concentration in their menstruation liquid compare to women with no dysmenorrhea. The highest level prostaglandin can be found on the first Day of menstruation (Smith RP, 2018)

Spearman correlation test does not show any meaningful relation between prostaglandin level and pain Intensity on both groups. This different from the research that say there are meaningful relation between prostaglandin and menstrual pain on primary dysmenorrhea (Nulanda M., et al, 2019).

A cochrane study says that even through most primary dysmenorrhea women have higher PGF2a level and sestradiol, some women with heavy dysmenorrhea do not show the increase of prostaglandin. The cause are still unknow. Pain Intensity changes can be affected by many factore, hormonal, nutrition, stress, body physiology, sport activity, and diet (Marjoribanks J., et al, 2015; Dawood M., 2006).

There are some limitations in this research, some factors that can affect the level of prostaglandin are not measured in this reseacr, like the PGE2, thrombosis and other mediators. The way curcumin works in LOX path is not searched in this research. In addition, primary Dysmenorrhea complaints such as nausea, vomit, diarrhea, and headache are not searched in this research

IV. CONCLUSION

Based on the research conducted to women with Primary menstrual pain, can be concludes that providing curcumin for 7 days before period Time can reduce the level of prostaglandin (PGF2a) on primary menstrual pain case. Providing curcumin for 7 days before period Time and reduce the pain Intensity in menstrual primary pain.

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