The investigation of IL-1β and oxytocin levels among teenager with primary dysmenorrhea

Mukhoirotin*, Kurniawati, Diah Ayu Fatmawati
Unipdu Jombang, Indonesia
mukhoirotin@fik.unipdu.ac.id

Abstract: Primary dysmenorrhea is one of gynecological problems and it commonly occurred among adolescents and reproductive age women during menstruation with some complaints such as pain, cramps and back pain. In primary dysmenorrhea there is an increase of PGF2α levels, vasopressin (VAP), Oxytocin (OT), IL-6 and IL-1β level. The aim of this study was assessed the differences of IL-1β levels and oxytocin among adolescents with primary dysmenorrhea and without primary dysmenorrhea. The research design in this study used Case Control. The population of this study were all students of Health Science Faculty, Unipdu Jombang. The sample of this study was 16 respondents, and they were divided into 2 groups: the case group (n = 8) and the control group (n = 8) that met the inclusion and exclusion criteria. Sampling method used Purposeful Sampling technique. The measurement of IL-1β and Oxytocin levels used ELISA method. The data were analyzed by using Independent Sample T-Test with α ≤ 0.05. The results of this study showed that an average level of IL-1β in case group was 23.830 pg/ml, in control group was 14.715 pg/ml; the average OT levels in case group was 384.662 pg/ml, the control group was 353.262 pg/ml. Independent Sample T-Test showed that there was a significant differences of IL-1β and oxytocin level between case group and control group (p<0.05). IL-1β and Oxytocin (OT) Levels among adolescents with primary dysmenorrhea were higher than adolescents who menstruate without primary dysmenorrhea.

Keywords: IL-1β level, Oksitosin level, Primary Dysmenorrhea

1. Introduction
Primary dysmenorrhoea is one of the gynecological problems that occurred among adolescents and young women with typical complaints like lower abdominal cramps during menstruation without underlying pelvic abnormalities[1-4]. Primary dysmenorrhoea usually begins before menstruation and continues for several days at the beginning of the menstrual cycle[1,5]. The prevalence of dysmenorrhea was reported 60% - 93% occurred among adolescents and decreased among adulthood[6-7]. The severe dysmenorrhea affected the quality of life and daily activities. Several previous studies showed that dysmenorrhoea affected 13.8% - 45% school absenteeism of the students[8-9], work productivity, utilization of health services[10], working absent[11], social and recreational activities[12] and decreased quality of life[13-15]. Several factors that caused primary dysmenorrhea are include increasing of prostaglandins produce, vasopressin (VAP), leukotriene levels and psychological factors[16]. Prostaglandins (PGF2α) was increased uterine muscle tone and contraction, lead to reduced uterine blood flow, uterine hypoxia-ischemia and pain[16,17]. The increasing of interleukins caused spasmodic
contractions in uterine smooth muscle and caused dysmenorrhea\(^{(1,18)}\). Moreover, plasma oxytocin (OT) and IL-6 level among women who got dysmenorrhoea are higher than healthy women during menstruation\(^{(19)}\), these mediators can increase uterine contraction\(^{(20)}\). In menstrual phase, proinflammatory cytokines (IL-1β, TNF, IL-6, and IL8) were increased\(^{(21)}\). IL-1β can stimulate the production of Prostaglandin F2α and oxytocin at the first day of the menstrual phase\(^{(22-24)}\).

The best treatment to reducing pain of primary dysmenorrhea is use NSAIDs, it works by inhibiting the enzyme cyclooxygenase (COX), inhibiting cyclic endoperoxide production and decreasing prostaglandin F2α levels\(^{(25)}\). This drug is useful but also give causes side effects on gastrointestinal system, teenagers / women try to looking for alternatives treatments to reducing pain while got dysmenorrhea. Non-pharmacological treatments for primary dysmenorrhea are include changing the diet by reducing salt and animal fat consumption, increasing fruits consumption and vegetables, also increasing physical activities / exercise\(^{(26-27)}\). Arachidonic acid in animal fats was involved in prostaglandin synthesis\(^{(28)}\). Diets with high fiber can increasing globulin-sex hormones and decrease prostaglandin synthesis\(^{(29)}\). Exercise can improve blood circulation in pelvic area and stimulate the release of endorphins, reduce stress and change the mood\(^{(30-31)}\). In addition, the activities can disturb the prostaglandin accumulation and reduce symptoms of dysmenorrhea\(^{(32)}\). Based on this phenomenon the researchers are interest to conducting a research with the aim of this study to determine the levels of IL-1β and oxytocin (OT) among adolescents with primary dysmenorrhea and without primary dysmenorrhea.

2. Research Methodology
This study used Desaign Case Control. The population in this study were all female students of Faculty of Health Sciences, Unipdu who experienced menstruation, with a total sample is 16 respondents and they were divided into two groups, namely case group (\(n = 8\)), and the control group (\(n = 8\)). The sampling technique used purposive sampling method. Inclusion criteria in this study are include: 1) case group: Students who got primary dysmenorrhoea, who have not received anti-pain medicine and cooperative when giving intervention; 2) Control group: students who experienced menstruation without primary and cooperative dysmenorrhea. Exclusion criteria were female students who experienced secondary dysmenorrhoea. The ELISA (Enzyme Linked Immunosorbent Assay) method was used to assess IL-1β and Oxytocin (OT) levels. Blood sampling for examination of IL-1β levels and Oxytocin (OT) taken on the first day of dysmenorrhea among case group and on the first day of menstruation among the control group. The data were analyzed by using Independent Sample T-Test with \(\alpha \leq 0.05\).

3. Results
In this study, first researcher did normality data of the IL-1β and Oxytocin (OT) variables by using Shapiro-Wilk test, than used Independent T-Test to found the differences of IL-1β and Oxytocin (OT) level. The results of the test found that the data was normal distribution (\(p > 0.05\)). The results showed there were differences of the IL-1β and Oxytocin (OT) level among both control group and case group (\(p <0.05\)), as shown in table 1. below:

| Variable | Case group (Mean ± SD) (pg/ml) | Control group (Mean ± SD) (pg/ml) | Beda Mean (95% CI) | p |
|----------|-------------------------------|-----------------------------------|--------------------|----|
| IL-1β level | 23.830 ± 9.662                | 14.715 ± 6.417                    | 9.115 (0.319 – 17.910) | 0.043 |
| OT level   | 384.662 ± 25.133              | 353.262 ± 24.486                  | 31.400 (4.792 – 58.008) | 0.024 |

3.1 Independent Sample T-Test.
The average of IL-1β and oxytocin levels among adolescents who got dysmenorrhoea were higher than among adolescents without dismenorrhoea. The average value of IL-1β levels among adolescents with dysmenorrhoea were 23,830 pg / ml and adolescents without dismenorrhoea were 14,715 pg / ml. The
average of oxytocin value among adolescents with dysmenorrhea 384,662 pg / ml and adolescents without dysmenorrhea 353,262 pg / ml, as shown in Figure. 1 and Figure. 2.

4. Discussion
The results of this study showed that IL-1β and oxytocin level among intervention group was higher than control group. This is because in menstruation period occurred inflammation in endometrium. This inflammation caused by cytokines pro-Inflammation stimulation and one of those is IL-1β. In primary dismenorrhea has inflammation response higher than menstruation without pain, so among intervention group showed the level of IL-1β higher than control group. The increasing of IL-1β level will followed by the increasing of oxytocin too, the results of this study showed that the level of oxytocin among intervention group was higher than control group. This because IL-1β was in induced F2α Prostaglandin and oxytocin release(21). Oxytosin is an inflammation mediator and had the function for increasing uterus contraction and has importance role in pathophysiology of primary dismenorrhea.
Menstruation occurs due to decreased progesterone, and also complex interactions between ovarian hormones and the immune system\(^{(20)}\). The decreased levels of progesterone at the end of the secretory phase occurred because there is no conception, and it leads entering and activation of leukocytes, followed by the production of proteases (MMPs), which is it causes decay of decidualization in endometrial superficial layer and in the ending by menstruation. The abnormality respond of inflammation in endometrium is induced by proinflammatory cytokines. This condition can be inhibited by progesterone, progesterone is effective inhibit the release of TNFα-induced prostaglandins and oxytocin, activation MMP via NF-kB in endometrial tissue\(^{(33)}\). The decreasing of progesterone in the premenstrual phase has an impact on the loosing of the ability to inhibit the inflammatory response and lead to release of inflammatory mediators including TNF-α, Prostaglandin F2α and oxytocin which followed by menstrual bleeding\(^{(20, 34)}\). The decidual tissue is main source of inflammatory mediators, so when decay of endometrial decidualization in uterus, there will be a decrease the inflammatory response and a decrease the pain\(^{(35)}\).

The results of previous studies conducted by Ma et al (2013), showed that the menstrual phase of pro-inflammatory cytokines among women who got dysmenorrhoea were increased IL-1β, TNF, IL6 and IL8 levels\(^{(21)}\). Other studies also showed that plasma oxytocin was significantly higher among women who experienced dysmenorrhoea than healthy women\(^{(36)}\). A research conducted by Akerlund (2002), also showed that there was an increase of plasma vasopressin and oxytocin levels among women who got primary dysmenorrhoea\(^{(37)}\). The results of some studies indicated that the women who experienced primary dysmenorrhoea there was an increase of pro-inflammatory cytokines (IL-1β) and plasma oxytocin, and in this study also showed the same results, it found an increase of IL-1β levels and plasma levels of oxytocin among adolescents who experienced primary dysmenorrhoea compared to adolescents who got menstruation without primary dysmenorrhoea on the first day of menstrual phase.

Based on these results, an effort is needed to reduce the inflammatory response so that it can reduce symptoms that occur in primary dysmenorrhea. Pharmacological treatment with NSAIDs, although beneficial, can cause side effects that require an alternative safe, effective and efficient action or measure to reduce the symptoms of primary dysmenorrhoea.

5. **Conclusion**

IL-1β and Oxytocin (OT) Levels among adolescents with primary dysmenorrhea were higher than adolescents who menstruate without primary dysmenorrhea, so this need an effort to reducing IL-1β and Oxytocin (OT) level to relieve the symptoms of primary dysmenorrhea. The authors confirmed that this research is original and no conflict of interests regarding the publication of this paper.

6. **Source of Funding**
The Directorate of Research and Community Service, the Directorate General of Research and Development Strengthening, the Ministry of Research, Technology and Higher Education (Kemenristekdikti) had provided funds to support this research process.
References

[1] Harel Z. Dysmenorrhea in adolescents and young adults: an update on pharmacological treatments and management strategies. Expert Opin Pharmacother. 2012 Oct;13(15):2157–70.

[2] Berek JS, Novak E: Berek and Novak’s Gynecology. Wolters Kluwer Health/ Lippincott Williams & Wilkins. 2012.

[3] Osayande AS, Mehulic S. Diagnosis and initial management of dysmenorrhea. Am Fam Phys 2014;89:341–6.

[4] Polat A, Celik H, Gurates B, et al. Prevalence of primary dysmenorrhea in young adult female university students. Arch Gynecol Obstet 2009; 279:527–32.

[5] Sultan C, Gaspari L, Paris F. Adolescent dysmenorrhea. Pediatric and adolescent gynecology, vol. 22. Karger Publishers; 2012. p. 171e80.

[6] Parker MA, Sneddon AE, Arbon P. The menstrual disorder of teenagers (MDOT) study: determining typical menstrual patterns and menstrual disturbance in a large population-based study of Australian teenagers. BJOG. 2010;117:185–92.

[7] Sperró L, Fritz MA. Clinical gynecologic endocrinology and infertility. Lippincott Williams & wilkins, 2011.

[8] Butsripoom B. & Wittayapun Y. Prevalence, Impact and Self-Management of Dysmenorrhea Among Nursing Students. Songklaanaganard Journal of Nursing, Volume 39 No. 1 January - March 2019: 41-52.

[9] Al-Kindi R, Al-Bulushi A. Prevalence and impact of dysmenorrhea among Omani high school students. Sultan Qaboos Univ Med J 2011;11(4):485.

[10] Ju H, Jones M, Mishra G. The prevalence and risk factors of dysmenorrhea. Epidemiol Rev. 2014;36:104–13.

[11] Zahradnik HP, Hanjalic-Beck A, Groth K. Nonsteroidal anti-inflammatory drugs and hormonal contraceptives for pain relief from dysmenorrhea: a review. Contraception. 2010;81(3):185–96.

[12] Iacovides S, Avidon I, Baker FC. What we know about primary dysmenorrhea today: a critical review. Hum Reprod Update. 2015;21(6):762–78.

[13] Unsal A, Ayrranci U, Tozun M, Arslan G, Calik E. Prevalence of dysmenorrhea and its effect on quality of life among a group of female university students. Ups J Med Sci. 2010;115:138–45.

[14] Midilli TS, Yasar E, Baysal E. Dysmenorrhea characteristics of female Students of health school and affecting factors and their knowledge and use of complementary and alternative medicine methods. Holist Nurs Pract. 2015; 29: 194–204.

[15] Rencz F, Pénétke M, Stalmeier PFM, et al. Bleeding out the quality-adjusted life years: evaluating the burden of primary dysmenorrhea using time trade-off and willingness-to-pay methods. Pain. 2017; 158:2259–2267.

[16] DeCherney A, Nathan L, Goodwin TM, et al.: Current Diagnosis and Treatment: Obstetrics and Gynecology 11e Inking Chapter. McGraw Hill Professional. 2012

[17] Letzel H, Me’gard Y, Lamarca R et al: The efficacy and safety of aceclofenac versus placebo and naproxen in women with primary dysmenorrhea. Eur J Obstet Gynecol Reprod Biol, 2006; 129(2):162–68.

[18] Abu JI and Konje JC. Leukotrienes in gynaecology: the hypothetical value of antileukotriene therapy in dysmenorrhea and endometriosis. Hum Reprod Update 2000; 6: 200–205.

[19] Yeh ML, Chen HH, So EC, Liu CF (2004) A study of serum malondialdehyde and interleukin-6 levels in young women with dysmenorrhea in Taiwan. Life Sciences 75: 669–673.

[20] Henriet P, Gaide Chevronnay HP, Marbaix E. The endocrine and paracrine control of menstruation. Mol Cell Endocrinol 2012;358: 197–207.

[21] Ma H, Hong M, Duan J, Liu P, Fan X, Shang E, Su S, Guo J, Qian D, Tang Y. Altered Cytokine Gene Expression in Peripheral Blood Monocytes across the Menstrual Cycle in Primary Dysmenorrhea: A Case-Control Study. PLoS ONE 2013; 8(2): e55200. doi:10.1371/journal.pone.0055200.

[22] Friebe-Hoffmann U, Chiao JP, Rauk PN. Effect of IL-1beta and IL-6 on Oxytocin Secretion in Human Uterine Smooth Muscle Cells. Am J Reprod Immunol 2001;46: 226–231.
[23] Friebe-Hoffmann U, Baston DM, Hoffmann TK, Chiao JP, Rauk PN. The influence of interleukin-1beta on oxytocin signalling in primary cells of human decidua. Regul Pept 2007;142: 78–85.

[24] Tamura M, Sebastian S, Yang S, Gurates B, Fang Z (2002) Interleukin-1beta elevates cyclooxygenase-2 protein level and enzyme activity via increasing its mRNA stability in human endometrial stromal cells: an effect mediated by extracellularly regulated kinases 1 and 2. J Clin Endocrinol Metab 2002;87: 3263–3273.

[25] Dawood MY, Khan-Dawood FS: Clinical efficacy and differential inhibition of menstrual fluid prostaglandin F2alpha in a randomized, double-blind, crossover treatment with placebo, acetaminophen, and ibuprofen in primary dysmenorrhea. Am J Obstet Gynecol, 2007; 196(1): 35.e1–5.

[26] Balbi C, Musone R, Menditto A, et al.: Influence of menstrual factors and dietary habits on menstrual pain in adolescence age. Eur J Obstet Gynecol Reprod Biol. 2000; 91(2): 143–8.

[27] Durain D: Primary dysmenorrhea: assessment and management update. J Midwifery Womens Health. 2004; 49(6): 520–8.

[28] Molazem Z, Alhani F, Anooshe M, et al.: Epidemiology of dysmenorrhea with dietary habits and exercise. Zahedan Journal of Research in Medical Sciences. 2011; 13(3): 41–5

[29] Barnard ND, Scialli AR, Hurlock D, et al.: Diet and Sex-Hormone Binding Globulin, Dysmenorrhea, and Premenstrual Symptoms. Obstet Gynecol. 2000; 95(2): 245–50

[30] Proctor M, Farquhar C: Diagnosis and management of dysmenorrhoea. BMJ. 2006;32(7550): 1134–8.

[31] Kermanshahi S, Hosseinzadeh S, Alhani F: The effect of the group counseling program on the status of primary dysmenorrhea, dietary condition and exercise in Shahreyar Girl’s High School. ZUMS Journal. 2009; 16(65): 49–60.

[32] Salehi F, Marefati H, Mehrabian H, et al.: Effect of pilates exercise on primary dysmenorrhea. Journal of Research in Rehabilitation Sciences. 2012; 1(1): 248–53

[33] Jabbour HN, Kelly RW, Fraser HM, Critchley HO. Endocrine Regulation of menstruation. Endocrine Reviews 2006;27: 17–46.

[34] Maybin JA, Critchley HO, Jabbour HN. Inflammatory pathways in endometrial disorders. Mol Cell Endocrinol 2011;335: 42–51

[35] Szo´stek AZ, Siemieniuch MJ, Deptula K, Woclawek-Potocka I, Majewska M et al. Ovarian steroids modulate tumor necrosis factor-a and nitric oxideregulated prostaglandin secretion by cultured bovine oviductal epithelial cells. Domest Anim Endocrinol 2011;41: 14–23.

[36] Liedman R, Hansson SR, Howe D, Igidbashian S, McLeod A, et al. Reproductive hormones in plasma over the menstrual cycle in primary dysmenorrhea compared with healthy subjects. Gynecol Endocrinol 2008;24: 508–513.

[37] Akerlund M. Involvement of oxytocin and vasopressin in the pathophysiology of preterm labor and primary dysmenorrhea. Prog Brain Res 2002;139: 359–365.