

Topical *Laporteadecumana* Leaves Extract Could Increase IL-6 Levels and PG-E2 Levels among Women in Active Phase of the First Stage of Labor

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ABSTRACT---The study aims to explain the effect of *Laporteadecumana* (LD) on IL-6 levels and PG-E2 levels among women in active phase of the first stage of labor. The mean age of respondents was 23-26 years, most from the ethnic group of 70%. They had an occupation as housewives of 92.5%, and given birth more than once of 67.5%. There were no significant differences (p -value > 0.05). The characteristics could be controlled and did not have a biased effect on the results. There was an increase in IL-6 levels and PG-E2 levels after treatment. The variable of IL-6 levels, the sequence of the increase in IL-6 levels from the highest value was SP+V (18.34 ± 22.26), LD+SP (16.21 ± 23.12), LD+KS (12.81 ± 20.56) and the lowest increase was in KS+V (5.76 ± 6.59). Overall given treatment to all groups did not affect IL-6 levels ($p=0.541$). The highest difference in mean increase was in the SP+V group (802.50 ± 444.16) and the lowest was in the LD+SP group (491.90 ± 475.25). Overall given treatment to all groups did not affect PG-E2 levels ($p=0.623$). *L. decumana* could increase the levels of IL-6 and PG-E2 according to the labor progress.

Keywords---IL-6 levels, *L. decumana*, labor, PG-E2 level, treatment.

I INTRODUCTION

Pain during labor makes pregnant women prefer to avoid spontaneous labor with a cesarean section. On the other hand, the cesarean section procedure is an obstetric intervention that has a significant risk, cesarean section is significantly associated with maternal and neonatal morbidity. In Papua Province, people have traditionally used itching leaves (*Laporteadecumana*) to reduce labor pain. Preliminary animal studies comparing *L. decumana* with Sodium diclofenac have provided substantial (not yet published) results. One biomarker that initiates the onset of labor is interleukin 6 (IL-6), in response to the stimulation of IL-1 β and TNF α which are secreted by decidual and chorion cells which will increase the formation of prostaglandins. There was no previous study that correlated *Laporteadecumana* as a pain killer agent with the biomarkers that initiate labor.

Pain is an integral part of labor and is considered to be the worst type of physical suffering of a human being during life. The intensity of pain affects the psychological condition of the mother, labor and fetal well-being.

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Post-delivery trauma due to pain has been shown to increase the risk of having no further children or delaying subsequent pregnancies (Garthus-Niegelet *et al.*, 2014; Caurel & Sánchez, 2019). Pain during labor makes pregnant women prefer to avoid spontaneous labor with cesarean section (Rahnama *et al.*, 2015; Arnawa *et al.*, 2019). The results of Basic Health Research (Riskesdas) in 2013 showed that cesarean births incidence was 9.8% of the total 49,603 births from 2010 to 2013, cesarean section without labor complications was 8.5% (Sihombing *et al.*, 2017; Jain *et al.*, 2017). On the other hand, cesarean section procedure is an obstetric intervention that has a significant risk, this is an important public health problem because the caesarean section is significantly associated with maternal and neonatal morbidity (Loke *et al.*, 2015; Cedeño *et al.*, 2019).

Labor pain arises due to contractions in the myometrium caused by the interaction/union of actin and myosin which are components of contraction. The interaction occurred because of the activity of magnesium-dependent myosin ATP-ase which causes the head of myosin to bind to actin and forms a bridge between the thin and thick plates of myosin to form an angle and cause uterine contractions (Rosa *et al.*, 2002; Manuaba *et al.*, 2011; Giri, 2019).

One factor that initiates the onset of labor is interleukin 6 (IL-6), in response to the stimulation of IL-1 β and TNF α which are secreted by decidual and chorion cells. IL-6 can be found in the placenta, decidua, chorion, and amniotic fluid. There is a positive correlation between IL-6 levels and the intensity of uterine contractions (Cierny *et al.*, 2014; Narasimhulu, 2019). It has been reported in an experimental trial that the administration of IL-6 to human amnion and decidual cell culture could increase prostaglandin formation (Gulati *et al.*, 2012; Rodriguez *et al.*, 2020). Cervicovaginal fluid (CVF) is a reflection of the local biochemical environment that is affected by physical changes that occur in the vagina, cervix and fetal membranes so that it is a biomarker for predicting the onset of labor (Henget *et al.*, 2015; Zambrano *et al.*, 2018). Opioids such as pethidine are associated with a decrease in labor pain, but these drugs can increase drowsiness, nausea, vomiting and can cause respiratory depression in newborns (Makkaret *et al.*, 2015; Primatanti & Jawi, 2019). In Papua Province people have traditionally used Papuan native plants known as Itching Leaves (*Laportea decumana*) to reduce pain (Simaremare, 2014; Holle *et al.*, 2015).

Preliminary animal studies comparing *L. decumana* with Sodium diclofenac have provided substantial (not yet published) results. It's a shrub containing Acetamida/Acetaminophen (N-(4-Hydroxyphenyl), Acetamida/Acetaminophen (N-(4-Hydroxyphenyl) that is a p-aminophenol derivative with antipyretic/analgesic properties (Aribawa, 2017). The skin irritation test did not show any side effects (Vázquez *et al.*, 2019). Decrease in labor pain using *L. decumana* has been passed down from generation to generation and there are no reports of side effects of the use of this plant, but the use of *L. decumana* as an anti-pain and scientific evidence underlying its effect on biomarkers that initiate labor (IL-6 and PG-E2) have not been found.

II METHODS

This was a true experimental with pre post-test control group design. This study was registered in the Health Research Ethics Commission of the Faculty of Medicine of the University of Diponegoro with Ethical Clearance

number: 514/EC/FK-RSDK/VII/2018 and obtained a research recommendation was obtained from the National Unity and Politics Agency of Mimika Regency with the number: 070/368/209.4/2018.

The samples in this study were 40 women in active phase of the first stage of labor at Mitra Timika Papua Hospital. The selection of study subjects was conducted by consecutive sampling and randomization was carried out to assign the study subjects into 4 groups according to the treatment given.

- a) Group I: 5 gram *L. decumana* and Placebo Suppository.
- b) Group II: 5 gram *L. decumana* and 2 gram Ketoprofen Suppository
- a) Group III: 2 gram Ketoprofen Suppository and Vaseline
- b) Group IV: Vaseline and Placebo Suppository

L. decumana or vaseline was administered by 40x sedation acupressure at SP6, SP8 and SP9 points. Measurements were made twice, namely before treatment and 60 minutes after treatment. Measurement of IL-6 levels and PG-E2 levels was performed by collecting 1ml of cervical mucus. Then it was put into a deep freezer of -80° C until the required number of examination samples was met. Examination of IL-6 levels and PG-E2 levels was performed in GAKI laboratory of Semarang Diponegoro National Hospital.

III RESULTS

This study was conducted for five months, from September 2018 to February 2019 and there were no respondents dropped out. 80 samples for IL-6 levels examination and 80 samples for PG-E2 levels examination were obtained from 40 respondents. The characteristics of respondents can be seen in Table 1.

Table 1: Characteristics of respondents

Patient Characteristics	LD+SP	LD+KS	KS+V	SP+V	p-Value
	n (%)	n (%)	n (%)	n (%)	
Age	26,10 ±4,84	23,40 ±7,76	25,30 ±8,06	25,70 ±5,79	0,815 ^a
Suku					
a. AOP	7 (70,7)	6 (60,0)	7 (70,0)	10 (100,0)	0,187 ^a
b. Non AOP	3 (30,0)	4 (40,0)	3 (30,0)	0 (0,0)	
Education					
a. None	3 (30,0)	2 (20,0)	3 (30,0)	5 (50,0)	0,444 ^a
b. SD	2 (20,0)	5 (50,0)	2 (20,0)	1 (10,0)	
c. SMP	1 (10,0)	1 (10,0)	1 (10,0)	1 (10,0)	
d. SMA	2 (20,0)	0 (0,0)	2 (20,0)	3 (30,0)	
e. Diploma	0 (0,0)	1 (10,0)	2 (20,0)	0 (0,0)	
f. Scholar	2 (20,0)	1 (10,0)	0 (0,0)	0 (0,0)	
Occupation					
a. Teacher	1 (10,0)	0 (0,0)	0 (0,0)	0 (0,0)	0,410 ^a
b. Honorer	0 (0,0)	1 (10,0)	0 (0,0)	0 (0,0)	

c. Housewife	8 (80,0)	9 (90,0)	10 (100,0)	10 (100,0)	
d. Private employee	1 (10,0)	0 (0,0)	0 (0,0)	0 (0,0)	
Gravida					
a. Primipara	3 (30,0)	4 (40,0)	3 (30,0)	3 (30,0)	0,952 ^a
b. Multipara	7 (70,0)	6 (60,0)	7 (70,0)	7 (70,0)	

Chi-square test, (b) one-way ANOVA, OAP (Papua Indigenous People)

Table 1 showed the mean age of the subjects studied ranged from 23 years to 26 years. Most respondents came from the ethnic group of Papuans (OAP tribe) as many as 30 people (70%), while the rest came from Non-Papuan (30%). Most of them did not have formal education as many as 13 people. Most respondents had an occupation as housewives as many as 37 people (92.5%). Based on the gravida, most respondents had given birth more than once as many as 27 people with a percentage of 67.5%, while the remaining 32.5% gave birth for the first time.

Difference test results showed no significant differences in the characteristics of age, ethnicity, education, occupation and parity in each group (p -value > 0.05). This indicated that the researcher could control the existing characteristics so that they did not have a biased effect on the results of the analysis.

Table 2 showed that the lowest IL-6 levels before treatment was in the KS+V group of 10.70 pg/ml and the highest was in the LD+KS group of 18.66 pg/ml, the lowest IL-6 levels after treatment was in the KS+V group of 11.16 pg/ml and the highest was in the SP+V group of 29.37 pg/ml. Overall, there was an increase in the mean values before and after treatment, and the highest increases was in the SP+V group. Difference test results after treatment did not show differences between the four groups with a p -value of 0.163.

Table 2: Data distribution and effect of *L. decumana* administration on IL-6 levels and PG-E2 levels among women in active phase of the first stage of labor

Variable			Group				<i>p-value</i>	
			LD+SP (n=10)	LD+KS (n=10)	KS+V (n=10)	SP+VP (n=10)	(difference test)	
IL-6 levels	Pre	$\bar{X} \pm SD$	10.96 ± 17.75	18.66 ± 24.71	10.70 ± 8.26	18.11 ± 17.16	0.163 ^b	
		Min - max	1.10-57.6	2.20-81.9	2.9-27.8	4.9-55.6		
		<i>p-value</i> (normality)	0.000	0.000	0.007	0.003		
	Pos	$\bar{X} \pm SD$	19.55 ± 24.02	19.49 ± 45.20	11.16 ± 8.60	29.37 ± 31.95	0.101 ^b	
		Min - max	1.20-75.80	0.80-147.8	0.40-27.9	5.6-111.9		
		<i>p-value</i> (normality)	0.005	0.000	0.354	0.002		
	<i>p-value</i> (difference test)		0.445 ^b	0.241 ^b	0.799 ^b	0.386 ^b		
	PG-	Pre	$\bar{X} \pm SD$	1362.50 ±	1069.20 ±	1517.90 ±	1231.80 ±	0.349 ^a

E2levels		641.76	398.28	670.71	518.23	
	Min – max	409.0-2267.0	550.0-1849.9	659.0-2427	290.0-1887.0	
	<i>p-value</i> (normality)	0.417	0.499	0.345	0.344	
Pos t	$\bar{X} \pm SD$	1642.80 ± 605.59	1738.10 ± 570.54	1802.40 ± 632.54	1565.50 ± 552.61	0.817 ^b
	Min – max	596.0-2453.0	921.0-2480.0	627.0-2556.0	767.0-2379.0	
	<i>p-value</i> (normality)	0.333	0.400	0.349	0.702	
	<i>p-value</i> (difference test)	0.200 ^a	0.020 ^a	0.212 ^a	0.265 ^a	

a superscript = one-way ANOVA test, b superscript = Kruskal Wallis test

In the variable of PG-E2 levels, the lowest mean value before treatment was in the LD+KS group of 1069.20 and the highest was in the KS+V group of 1517.90. The lowest mean value after treatment was in the SP+V group of 1565.50 and the highest was in the KS+V group of 1802.40. Overall, there was an increase in the mean PG-E2 levels before and after treatment and the highest increase was in the LD+KS group. Difference test results after treatment did not show differences between the four groups with a p-value of 0.817. Further analysis of the difference in mean changes in IL-6 levels and PG-E2 levels can be seen in Table 3.

Table 3: Differences in mean changes in IL-6 levels and PG-E2 levels among women in active phase of the first stage of labor

Variable	Group				<i>p-value</i> (Difference test)
	LD+SP (n=10)	LD+KS (n=10)	KS+V (n=10)	SP+VP (n=10)	
	$\bar{X} \pm SD$	$\bar{X} \pm SD$	$\bar{X} \pm SD$	$\bar{X} \pm SD$	
IL-6 levels	16.21 ± 23.12	12.81 ± 20.56	5.76 ± 6.59	18.34 ± 22.26	0.541
PG-E2 levels	491.90 ± 475.25	723.30 ± 690.09	611.70 ± 350.89	802.50 ± 444.16	0.623

**)Kruskal Wallis test*

In the variable of IL-6 levels, the highest difference in mean increase was in the SP+V group (18.34 ± 22.26) and the lowest was in the KS+V group (5.76 ± 6.59). Overall the treatment given to all groups did not have a significant effect with a p value=0.541, meaning that the treatment given did not affect IL-6 levels. In the variable of PG-E2 levels, the highest difference in mean increase was in the SP+V group (802.50 ± 444.16) and the lowest was in the LD+SP group (491.90 ± 475.25). Overall the treatment given to all groups did not have a significant effect with a p-value of 0.623, meaning that the treatment given did not affect PG-E2 levels.

IV DISCUSSION

IL-6 is a proinflammatory cytokine that is the main mediator of the body's response to inflammation and infection, can stimulate prostaglandin in labor so that it is used as a biomarker for the onset of labor (Rhee *et al.*, 2015; Katzung & Trevor, 2015). This cytokine plays a central role in prostaglandin stimulation of the amnion and decidua and it is the start of the acute phase response. Clinical studies have shown that in preterm labor with premature rupture of membranes, an increase in serum C-reactive protein occurred first before the clinical symptoms of chorioamnionitis. Since IL-6 plays an important role in the induction of C-reactive protein formation, there is a hypothesis that this cytokine is the main mediator of the body's response to infection and tissue damage, it is also important in the body's response to intrauterine infection.

PG-E2 is the most powerful prostaglandin in cervical maturation by inducing changes in connective tissues (Evronet *et al.*, 2005; Ratniet *et al.*, 2019). Pharmacologically and physiologically, prostaglandin has two direct actions related to labor, namely cervical ripening and myometrial stimulation. Prostaglandins and increased myometrial sensitivity cause intra uterine pressure up to 400 mmHg and cause severe myometrial contractions. Prostaglandins produced by the uterus apparently play a role in causing hyperactivity (contraction) of the myometrium (Harel, 2006).

The results of this study indicated that there was an increase in PG-E2 levels in the four treatment groups between before and after treatment. The highest difference in mean increase was in the SP+V group (802.50 ± 444.16) and the lowest was in the LD+SP group (491.90 ± 475.25). Overall the treatment given to all groups did not have a significant effect with a p value of 0.623. Clinically the treatments given namely LD+SP, LD+KS, KS+V and KS+V could increase IL-6 levels, however, the results of the study evidenced that *L. decumana* did not affect IL-6 production which functions in stimulating PG-E2, so it did not inhibit labor process. An increase in prostaglandin levels after being treated is in line with a study conducted by Liu *et al.*, that the prostaglandin hormone is a hormone that triggers contractions or increases the intensity of contractions and is responsible for stimulating labor. Women produce this hormone when the fetus is ready to be born. The impact of reduced levels of this hormone in the woman's body may cause postterm pregnancy (Liu *et al.*, 2017).

V FINDINGS

The study findings illustrated an increase in IL-6 levels in all groups between before and after treatment. The lowest mean IL-6 level before treatment was in the KS+V group of 10.70 pg/ml and the highest was in the LD+KS group of 18.66 pg/ml. The lowest mean IL-6 level after treatment was in the KS+V group of 11.16 pg/ml and the highest was in the SP+V group of 29.37 pg/ml. Overall there was an increase in the mean values before and after treatment, and the highest increase was in the SP+V group. In the variable of IL-6 levels, the sequence of the increase in IL-6 levels from the highest value was SP+V combination group (18.34 ± 22.26), LD+SP combination group (16.21 ± 23.12), LD+KS (12.81 ± 20.56) and the lowest increase was in KS+V combination group (5.76 ± 6.59). Overall the treatment given to all groups did not have a significant effect with a p value=0.541 meaning that the treatment is given not affect IL-6 levels.

VI CONCLUSION

It is in accordance with the theory that IL-6 plays a role in stimulating PG-E2 which plays a role in causing uterine contractions and it can be found in the placenta, decidua, chorion and amniotic fluid. It was reported in vitro trials that the administration of IL-6 to human decidua amnion cell cultures would increase prostaglandin formation. So based on this theory, a decrease in IL-6 levels during labor should not exist (Kang et al., 2011; Gulati et al., 2012).

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