Impact of One-Rod Levonorgestrel Implant on Blood Chemistry Profile

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Research Article

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Abstract

Objective: The aim of this study is to investigate the effect of one-rod levonorgestrel implant on the blood chemistry profile which include random blood glucose (RBG), hemoglobin (Hb), alanine transferase (ALT), aspartate transferase (AST), and lipid profile such as total cholesterol, High-density lipoprotein (HDL), Low-density lipoprotein (LDL), and triglyceride

Methods: This prospective cohort study was conducted at Raden Saleh Clinic, Jakarta from 2010 to 2012. The implants were inserted subdermally in 30 patients. The subjects were evaluated for 6 months and the blood chemistry profile was followed up to 2 years. Bivariate analysis using t-test or Wilcoxon signed rank test was performed for all variables. The $p < 0.05$ was considered as a significant value.

Results: The level of Hb, RBG, AST, and lipid profile was different significantly before and after 6-months one-rod implant insertion ($p<0.05$). However, in 24 months, all of parameters were still on normal limit and not different clinically.

Conclusion: One-rod levonorgestrel implant insertion shows minimal effect to all blood chemistry profiles.

1. Introduction

One of the long-term contraceptive devices that have been widely used is hormonal implant. Hormonal implant is a contraceptive device which inserted subdermally in the medial aspect of the upper arm and contains steroidal hormone. There are several kinds of progestogens that may be used for hormonal implant, one of them is levonorgestrel.[1]

Levonorgestrel as the second generation of synthetic progestin and gonanes structure derivative, has been widely used as active form of hormonal implant. The hormones will be slowly released into circulation in the same concentration over 5 years period. Levonorgestrel level will rise quickly in the first month after insertion and slowly decreased until the end of expiration. The hormonal level is also influenced by subject's body weight. The side effect of synthetic progestin are edema, abdominal bloating, anxiety, irritability, depression, and myalgia .[2, 3]

Monoplant→ is one of the hormonal implants that contain 160 mg of levonorgestrel which was developed in Indonesia. Monoplant was estimated to have effect of contraception for up to 3 years.[4]

Hormonal contraception, especially combined hormonal contraceptives, were known to affect the metabolism and induce change in lipid, lipoprotein, carbohydrate, and hemostatic factors level.[5] Currently, the metabolic impact of progestin contraceptives has not been investigated thoroughly. The subdermal implant contraception is a type of contraceptive which release low-dose progestin continuously and the implant contraception is a type of contraceptive which is continuously developing. Recently, a one-rod levonorgestrel (LNG) implant contraceptive (Monoplant®) is being developed.[6] The aim of this study is to investigate the effect of one-rod levonorgestrel implant on the blood chemistry

profile which include hemoglobin (Hb), random blood glucose (RBG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lipid profile such as total cholesterol, High-density lipoprotein (HDL), Low-density lipoprotein (LDL), and triglyceride.

2. Methods

This prospective cohort study was conducted at Raden Saleh Clinic, Jakarta as a satellite of Dr. Cipto Mangunkusumo hospital from 2010 to 2012. This analytical study with prospective cohort approach aims to assess the effect of levonorgestrel one rod implant towards chemistry blood profile including Hb, RBG, AST, ALT, and lipid profile (total cholesterol, HDL, LDL, and triglyceride). This study was a second phase of clinical study, which was conducted for the first time in patients. This study was conducted for 24 months.

Minimum sample size was calculated with chosen type I error rate of 0.05 and power of 80%, resulting in 30 minimum samples in each group. The subjects in this study were women in reproductive age (20–40 years old) which planned to delay or space the pregnancy. Every subject was examined to determine the hormonal status especially related to ovulation process. The chemistry blood profile in this study was performed in the Dr. Cipto Mangunkusumo hospital. The technic was guaranteed as international standard procedure. The blood chemistry profile was assessesd before implants insertion. Every subject was then followed and examined the blood chemistry profile in 6th, 12th, 18th, 24th month.

The inclusion criteria were women aged 20–40 years old, which still had regular sexual activities, did not use any hormonal contraceptives for the last 6 months, had informed consent for the study, and able to participate in the routine examination according to the schedule. The exclusion criteria were women which had abortion in the last two weeks, had not menstruated after delivery, had not menstruated after stopping oral or injection contraceptives, or those who participated in other studies during the last 6 months. Other exclusion criteria were the presence of any disease that affects blood chemistry profile (pelvic inflammatory disease since the last delivery, history of ectopic pregnancy, malignancy, abnormal bleeding, abnormal menstrual cycle or amenorrhea, breast abnormalities, thromboembolism, mental illness including depression, headache, or diabetes mellitus). The study was conducted in Raden Saleh Clinic, Jakarta from 2010 to 2012.

The implants were inserted subdermally during the first to seventh day of menstruation. The subjects were followed for 6 months of observation monthly. During those periods, the Hb, RBG, AST, ALT, and lipid profile were tested.

All the method were carried out in accordance with relevance guidelines and regulations. Every subject had been explained about the study and agree to be participants. Every subject that were included in this study were given and signed the informed consent. This study was approved by ethical committee of Faculty of Medicine, University of Indonesia number 176/PT02.FK/ETIK/2009.

Statistical Analysis

Descriptive distribution was shown for frequency and percentage. Bivariate analysis using t-test or Wilcoxon signed rank test was performed for all variables. The p-value < 0.05 was considered significantly.

3. Results

A total of 30 subjects that were following this second phase of clinical study was not pregnant until the end of study. There was no drop out subjects during the follow up. Baseline characteristics of the subject can be seen on Table 1.

Table 1. Baseline characteristics of subjects

Variables	N (%); Mean ± SD; Median (Min-Max)
Age (year)	31.6 ± 5.5
Education	
Elementary	6 (20%)
Junior high school	6 (20%)
Senior high school	16 (53.3%)
College graduate	2 (6.7%)
Parity	2 (1-5)
History of contraception	
Hormonal injection	18 (60%)
Hormonal pill	5 (16.7%)
Hormonal implant	3 (10%)
Intrauterine device	1 (3.3%)
Others	1 (3.3%)
No history	2 (6.7%)
Body mass index (kg/m^2)	22.9 ± 4.4

The mean data of the Hb, RBG, AST, ALT, lipid profile (total cholesterol, HDL, LDL and triglyceride) before and after six months of implant insertion were still in the normal range (Table 2). The level of Hb, RBG, AST, total cholesterol, LDL, and HDL cholesterol was different significantly before and after 6 months one-rod implant insertion ($p<0.05$).

Table 2. The blood chemistry profile before and after 6 months of one-rod implant insertion

Blood Chemistry	Before (n = 30)	After (n = 30)	Normal Range	p
Hb (g/dL)	13.5 ± 1.2	12.8 ± 0.8	12 -14	**0.005**[a]
RBG (mg/mL)	78.6 (55 – 142)	78.5 ± 17	< 160	0.281[b]
AST (mU/mL)	22.4 ± 6.5	30.5 (10 – 94)	< 31	**0.006**[b]
ALT (mU/mL)	16.5 (9 – 53)	20.5 (7 – 93)	< 31	0.128[b]
Total cholesterol (mg/mL)	176.6 ± 22.4	180 ± 23.2	140 – 250	0.460[a]
LDL (mg/mL)	105.9 ± 20.6	95.8 ± 21	<155	**0.023**[a]
HDL (mg/mL)	47.5 (33 – 74)	61.4 ± 11.4	> 35	**<0.001**[b]
Triglyceride (mg/mL)	110.5 (62 – 314)	90.5 (60 – 326)	< 200	0.434[b]

[a]Paired T-test [b]Wilcoxon test

The mean Hb level during the study was normal (12-14 g/dL). The mean RBG level remained in low level, which below <160 mg/mL. The liver function during the observation was normal, including AST and ALT (<31 mU/mL). Similar results were observed in the lipid profile including the total cholesterol, HDL, LDL, and triglyceride could be seen on table 3.

Table 3. The blood chemistry profile during 24 months of follow up

Blood Chemistry	Before (n=30)	6th month (n=30)	12th month (n=30)	18th month (n=30)	24th month (n=30)	Normal Range
Hb (g/dL)	13.5 ± 1.2	12.8 ± 0.8	13.3 ± 0.6	12.6 (10.2–38.2)	13 ± 0.8	12-14
RBG(mg/dL)	78.6 (55–142)	78.5 ± 17	74.8 ± 11.4	83.7 ± 15.5	96.8 ± 16.2	<160
AST (mU/mL)	16.5 (9–53)	20.5 (7–93)	23.8 ± 6.6	19 (10–98)	18 (13–39)	<31
ALT (mU/mL)	22.4 ± 6.5	30.5 (10–94)	20 (8 – 48)	15 (8–43)	16.1 ± 5.3	<31
Cholesterol (mg/mL)	176.6 ± 22.4	180 ± 23.2	169.6 ± 23.9	160 (12–206)	178.5 (133–340)	<200
HDL (mg/mL)	105.9 ± 20.6	95.8 ± 21	51.3 ± 9.4	41 (34–96)	42.7 ± 8.8	>35
LDL (mg/mL)	47.5 (33–74)	61.4 ± 11.4	95.2 ± 22.5	94 (39–140)	114.5 (77–245)	<155
Triglyceride (mg/mL)	110.5 (62–314)	90.5 (60–326)	97.5 (11–295)	102 (60–315)	113.5 (67–307)	140-250

4. Discussion

This study aims to assess the effect of one-rod LNG implant towards the blood chemical profile such as Hb, RBG, AST, ALT, and lipid profile. Based on results, the total cholesterol level was significantly different before and after 6 months of one-rod implant insertion. Observation in two years revealed that there was an increase trend of total cholesterol. However, it was not clinically significant. This result was similar to the study by Affandi which investigated the six-rod 36 mg LNG implant (Norplant©) levels in a cross-sectional study.[3] However, this result found different from most studies which investigated the effect of levonorgestrel on the lipid profile. The total cholesterol level usually decreased significantly during the levonorgestrel implant use.[7–10]

The HDL cholesterol level in this study decreased significantly. Studies investigating the effect of levonorgestrel on the HDL cholesterol level had variable results. Several studies had reported a significant decrease in HDL cholesterol level. Three studies reported no change in HDL cholesterol level. Other studies reported no change during the first 9 months, but there was a slight significant increase on the 12th month. In other studies, they reported a significant increase after 6 months of insertion compared with the control IUD group, however there was a decrease in the 12th to 24th month although it was not significant. Finally, a study with follow-up period of 5 years in Singapore found that the HDL cholesterol level changed variably from time to time. A significant increase was observed on the 12th months after implant insertion and 6 months after extraction, while there was a significant decrease observed in the third and fourth year, and a similar level in the beginning of the second and fifth year.[11] Dilbaz B, et al. stated that etonogestrel implant as derivate of progestogen showed the decrease in total cholesterol and HDL cholesterol.[12] However, the decrease of HDL cholesterol was unlikely be related with increased cardiovascular because in this study the HDL in 2 years was still in normal reference values.

All the blood chemistry parameters in this study were in the normal range after two years of one-rod implant use. This result was not different from similar studies investigating the effect of LNG on the blood chemistry profile, which usually not constant. Taheri, et al. found that the cholesterol and triglyceride levels were unchanged, while the AST and ALT levels increased slightly.[13]

Dorflinger [5] investigated the metabolic effects of several implant contraceptives including LNG, etonorgestrel, nomegestrol acetate, and Nestorone on the liver function, kidney, glucose, insulin, hemostasis, and blood pressure. The overall metabolic effects were reported to be minimal. Every change in the study were still in the normal range for the study population and was not significant clinically. Apart from that, Bender, et al. showed that changes in fasting glucose and insulin sensitivity among obese-progestin only contraceptive method. Therefore, the benefits should be weighed against the risk for this change of metabolic markers.[14]

Based on the result above, we considered that this one-rod LNG implant (Monoplant→) was safe for use because it was not clinically different for follow up until 2 years. The strength of this study is this study was the first to assess the effect of one-rod LNG implant (Monoplant) toward blood chemical profile with prospective cohort approach and similar subjects. However, the factors that influence the metabolic markers such as diet, lifestyle, and medication were not observe so it become the limitation of this study. Furthermore, this study should measure fasting blood glucose or HbA1c because RBG is highly influence by several factors. This study was part of the previous phase II clinical trial and can be used as a basis for phase III clinical trial in the future.

5. Conclusion

The insertion of One-rod levonorgestrel implant can provide an optimal effect in preventing pregnancy. In addition, this One-rod levonorgestrel implant showed minimal effect on all blood chemistry profiles after 2 years of follow-up making it safe to use.

Implications

Levonorgestrel implant has minimal effect to blood chemistry profile

Declarations

Author's Contributions

RE was the leading researcher for this study, with major contribution for statistical analysis for the study.

RS was a major contributor in writing the manuscript, enumerator, and contributor in statistical analysis

IS was contributor in writing the manuscript and contributor in ststistical analysis

YP was a correspondence author that submit the manuscript.

Ethics approval and consent to participate

This study was approved by Ethic Committee of Health Research Medical Faculty University of Indonesia. Number of ethical approval: 176/PT02.FK/ETIK/2009. Informed consent was obtained by written form that was approved by local research committee of Health Research Medical Faculty University of Indonesia and Dr. Cipto Mangunkusumo Hospital.

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