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Comparison Of Contraceptive Injection Between Monthly, Bimonthly And TriMonthly Combination Of Medroxyprogesterone Acetate With Estradiol Cypionate: Hemodynamic Effect, Weight Gain And Compliance Of Multicenter Clinical Trials, Phase III Randomization Study

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Abstract

Background:

Monthly contraceptive injection, which consists of MPA (medroxyprogesterone acetate) mixture with a low-dose estrogen preparate (25 mg MPA and 5 mg estradiol cipionate) is commonly used in Indonesia. It is less practical, because the subjects must visit health services every month. To reduce the impracticality, it has been developed a bi-monthly contraceptive injection of 65 mg MPA and 7.5mg estradiol cypionate and a trimonthly contraceptive injection of 120 mg MPA and 10 mg estradiol cypionate. Method: This is a randomized controlled clinical trial - open-label conducted from March 2013 to May 2017 with a total sample of 1080. The study subjects consist of 3 groups. The first group was treated with bi-monthly injections (Injection A), the second group was treated with trimonthly injections (Injection B) and the third group was treated with monthly injections (Injection C). The blood pressure, pulse rate and body weight were measured since initial treatment and during each visit for 1 year of treatment. This clinical trial has been registered in the National Agency of Drug and Food Control of the Republic of Indonesia with clinical trial number: PN.01.02.1.31.10.12.6669 Result: No significant differences of blood pressure between each group and during 1 year of injection in each group. We found significant differences of weight gain in each group during 1 year of injection ($p<0.01$), but we did not find significant difference of weight gain between each group. Injection B shows the lowest percentage of dropout cases (1,21%).
Conclusion: It can be concluded that bi-monthly injections and trimonthly injections are more effective than monthly injections for 12 months of use. They are safe to use, convenient in reducing doctor visits and have a high acceptability.

Keywords: Contraceptive agents, hemodynamics, progesterone, estradiol

INTRODUCTION

One of the most popular contraceptives in Indonesia is contraceptive injection. The SDKI's (Indonesian Demographic and Health Survey/Survei Demografi dan Kesehatan Indonesia) data shows that the use of contraceptive injections has been increasing from year to year, from 12 percent in 1991, it increased to 15 percent in 1994, 21 percent in 1997, 28 percent in 2003, and increased again to 32 percent in 2007. The result of SDKI's survey in 2012 showed a high rate of 32 percent1,2. The high public interest in contraceptive injections is due to several advantages, among others, high effectiveness, relatively low risk to health, no need for internal checks, easy

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to use, and efficient. Whereas, the disadvantages of contraceptive injections are disruption of menstrual patterns including amenorrhoea, menorrhagia and blood spotting3,4. Contraceptive injection is available in the form of a single compound (only progesterone) and a combination of estrogen and progesterone. Some of the products and trademarks in the form of a single dosage are more varied in terms of the product types, including: Depoprovera® (Depot medroxyprogesterone acetate), Noristerat® (NET-EN), Depogeston®, Depoprogestin®, Planibu®, etc. The combination dosage product is known as the monthly contraceptive injection Cyclofem® or previously known as Cycloprovera®3,5,6. While progestin-only has a higher incident of irregular cycle, progestin combined with estrogen became one of a better choice in maintaining a regular cycle and prevent of other side effect7. To cope with changes in menstrual patterns, a monthly contraceptive injections had been introduced, which consist of a mixture of MPA with a low-dose estrogen preparate, that contains 25 mg MPA and 5 mg estradiol cypionate. However, this preparate is less practical, because subjects must visit health services every month, so it requires more time and costs. Thus, it will certainly affect continuity5,8. Through this study, a bimonthly contraceptive injection of 65 mg MPA and 7.5 mg estradiol cypionate and trimonthly contraceptive injection of 120 mg MPA and 10 mg estradiol cypionate contraceptive injections will be developed with the aim of reducing inconvenience and ineffectiveness of the use of contraceptive injections that have been circulating in the market as mentioned above. Both preparates consisted of 1 ml suspension and are injected intramuscularly. The aim of this injection is to provide protection against pregnancy and complaints of side effects, such as to reduce blood spots, hence increasing its continuity.

RESEARCH METHOD

This study is designed by using an analytic research approach with Randomized Controlled Clinical Trial - open label. The study subjects were divided into 3 (three) groups randomly using the random block permutation method. The first group with the treatment of bi-monthly 65 mg MPA and 7.5mg estradiol cypionate injection (Injection A), the second group with the treatment of trimonthly contraceptive injection of 120 mg MPA and 10 mg estradiol cypionate F3 injection (Injection B) and the third group with the treatment of monthly 25 mg MPA and 5 mg estradiol cipionate injection (Injection C). The effect measured was the haemodynamic effect (blood pressure and pulse rate), weight gain and compliance (acceptability) during the use of contraception. The number of samples needed for each treatment group was 322 subjects. Considering the possibility of "lost to follow-up", the number of samples in each group was added by 10% and rounded up to 360 subjects. Thus, the total subjects for three treatments were as many as 1,080 subjects. The subjects in this study were women of childbearing age aged 18-40 years who were married and fulfilled predetermined inclusion such as normal menstrual cycle, duration and volume and exclusion criteria including such as no gynecologic disease, history of hypertension and other systemic problem. Subjects were allocated into three groups by block, to reduce heterogeneity in the factors that influence efficacy, safety and acceptability. The selected sample will get an injection A (2 months) or Injection B (3 months) or Injection C, according to the random allocation received. Student's t-test with a significance level of 0.05 (5%) was used for the statistical analysis. This research was conducted in five research centers in Indonesia, namely: Bandung, Surabaya, Lampung, Makassar and Medan. Recruitment of subjects was carried out at the KB (Keluarga Berencana) hospital/clinic/Puskesmas which had been determined by each of the center researchers based on the data of the number of subjects interested in the contraceptive injection. The transfer of the study sample was approved by the BKKBN Research Ethics Committee, with consideration regarding the research methodology. This research has been registered in National Agency of Drug and Food Control of the Republic of Indonesia with clinical trial number: PN.01.02.1.31.10.12.6669.

RESULT

GENERAL CHARACTERISTICS

We conduct this research from five research centers in Indonesia that can meet the recruitment of subjects, although they had to have the recruitment time extended and added research

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centers. In this report, as many as 1,080 subjects were able to complete the processes until the return visit for 12 months, the gathered data that could be analyzed consisted of data from 1,079 subjects. Of this number, 259 subjects received injection A, 360 received injection B and 360 subjects received injection C. In this study, Injection C injection was given every month as a comparison. Injection A injections were given every two months compared to Injection C on each use in two months. Both types of injections are given for 12 months of usage.

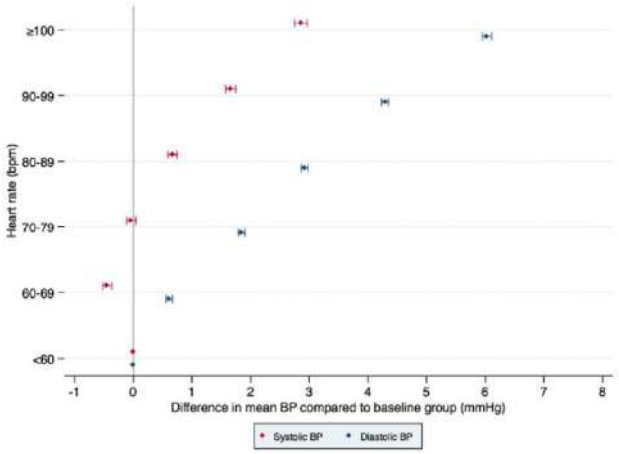

Figure 1. Blood Pressure (systolic and diastolic value) of Injection A (A), Injection B (B), and injection C (C) subjects during 12 months of study with the comparison between the initial treatment measurement and each visit measurement. P: P value.

Hemodynamics system

Change in blood pressure

Table 1 shows the results of systolic and diastolic examinations of the subjects at the initial treatment of Injection A injections compared with Injection C injections. Subjects who received Injection A and Injection C were measured at 112/73 mmHg, there were no significant differences ($p > 0.05$). Table 2 also illustrates the results of systolic and diastolic examination of subjects at the initial treatment of samples receiving Injection B compared with Injection C. The average of systolic and diastolic examination results for subjects of Injection B was 113.0/73.4 mmHg, whereas Injection C subjects' average examination results was 112/73.4 mmHg, there were no significant differences ($p = 0.188$ and $p = 0.942$). In general, there was no significant difference of blood pressure between the start of Injection A (initial treatment) and each visit measurement until the 12th visit as shown in figure 1. Within 12 months of Injection C intrevention, we also found no significant difference between systolic and diastolic blood pressure at the initial treatment compare to each visit measurement (figure 1). During 12 months of injections, there was no significant difference between the average systolic blood pressure at the beginning of the injections B compared to each visit measurement until the end of 12 months. However, there was a significant difference of diastolic blood pressure measurement in 6th months and 9th months of visit compared to the initial treatment, but no difference was found at 12 months of usage (Figure 1).

Parameter	Group	Time Point				
		Baseline	2 w	4 w	12 w	Diff. for Each Group
Systolic BP (mm Hg)	PG	126.3 ± 10.1	129.3 ± 11.5	130.0 ± 13.6	133.7 ± 13.7	NS
	TG	131.9 ± 14.6	131.0 ± 13.4	132.3 ± 12.3	130.5 ± 13.2	NS
	Diff. between group	NS	NS	NS	NS	
Diastolic BP (mm Hg)	PG	72.0 ± 9.2	75.7 ± 11.5	72.7 ± 8.6	73.3 ± 8.8	NS
	TG	76.0 ± 9.2	77.4 ± 10.8	75.7 ± 9.9	74.8 ± 8.6	NS
	Diff. between group	NS	NS	NS	NS	
Body Temp (°C)	PG	36.2 ± 0.3	36.1 ± 0.2	36.2 ± 0.3	36.2 ± 0.3	NS
	TG	36.1 ± 0.3	36.1 ± 0.2	36.0 ± 0.3	36.1 ± 0.3	NS
	Diff. between group	NS	NS	NS	NS	
HR (b/m)	PG	69.1 ± 8.9	68.3 ± 6.2	67.2 ± 6.1	67.5 ± 5.6	NS
	TG	67.5 ± 7.2	69.3 ± 8.7	67.6 ± 7.9	68.2 ± 8.8	NS
	Diff. between group	NS	NS	NS	NS	

Table 1 shows that there were slight changes and fluctuations of the measurement result of systolic and diastolic blood pressure between Injection A subjects compared to Injection C subjects, but the changes in blood pressure of these subjects does not interfere with the health of the subjects. Therefore, it does not affect the daily activities of the subjects.

Month	Injection B	Injection C
0	140/90 mmHg	130/80 mmHg
1	135/85 mmHg	125/75 mmHg
3	130/80 mmHg	120/70 mmHg
6	125/75 mmHg	115/65 mmHg
12	120/70 mmHg	110/60 mmHg

Table 2 shows increasing and decreasing blood pressure of subjects who received Injection B compared to Injection C from the start of injection until 12 months of injections, but after 12 months of injections, it appeared that blood pressure was still in normal condition.

Change in pulse rate

Pulse checks were also performed at each repeat visit, as shown in Table 1. The use of Injection A, and Injection C for 12 months can be concluded to be safe because they have no significant effect on the pulses measurement results of the subjects who use them. Table 2 shows the pulse of subjects who completed the study for up to 12 months of injections and those who received Injection B injections compared to Injection C injections can be said to be normal, which is around 79-80 pulses per minute.

Weight gain

Figure 2 shows that subjects of Injection A at 12 months of use compared with the initial use had significant weight differences. The weight of the Injection A subject up to a 12-month follow-up compared to the beginning of the injection increased significantly. The significant weight gain was found in the 4th, 5th and 6th visit of Injection A. This research also found a statistically difference weight gain in the 3rd and 4th visit of Injection B subjects compare to initial measurement and a tendency of weight increase during 12 months of use amongst the subjects of Injection C (Figure 2).

Month	Injection A	Injection C
1	0.3 kg	0.2 kg
2	0.2 kg	0.1 kg
3	0.1 kg	0.2 kg
4	0.2 kg	0.3 kg
5	0.3 kg	0.4 kg
6	0.4 kg	0.5 kg
7	0.5 kg	0.4 kg
8	0.4 kg	0.3 kg
9	0.3 kg	0.2 kg
10	0.2 kg	0.1 kg
11	0.1 kg	0.2 kg
12	0.2 kg	0.3 kg

Table 3 shows that subjects who received Injection A and Injection C were observed to gain <0.5 kg at each repeat visit, for both subjects who received Injection A and Injection C. The weight gains during 12 months of use, for subjects who took part in the study did not interfere with the subject's activities and are still within normal limits.

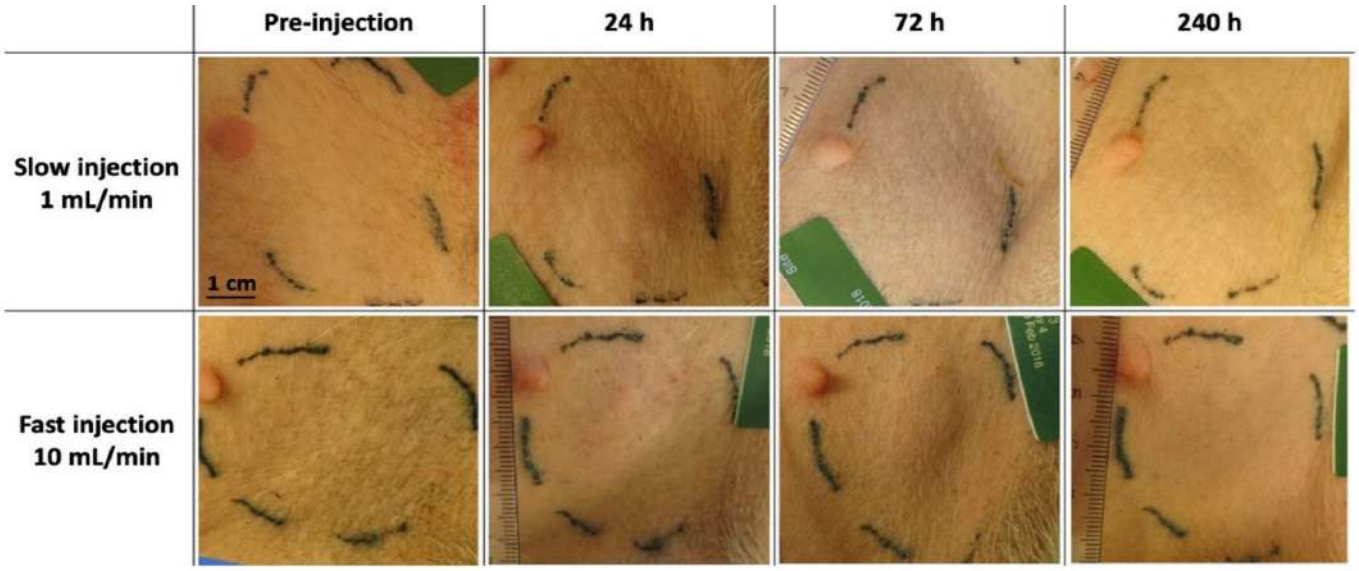

Figure 2. Average weight of Injection A (A), Injection B (B) and Injection C (C) subjects for over 12 months of use with a comparison between initial treatment measurement and each visit measurement. P: P value.

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Time	Injection B	Injection C
0 months	130/80 mmHg	135/85 mmHg
1 month	125/75 mmHg	130/80 mmHg
2 months	120/70 mmHg	125/75 mmHg
3 months	115/65 mmHg	120/70 mmHg
6 months	110/60 mmHg	115/65 mmHg
12 months	105/55 mmHg	110/60 mmHg

Table 4 shows the weight gain in Injection B subjects compared to the Injection C subjects. Weight gain experienced by subjects receiving the Injection B compared to the Injection C subjects ranged from 0.3 to 0.5 kg after each three months of injection.

Compliance

Table 5 illustrates the types of reasons subjects did not continue to complete this study. Injection A has the highest percentage of subjects who stop participating (4.17) followed by Injection B (3.88) and Injection C (3.61). The most common reason is because they moved to other places/cities and cannot be followed up anymore. Health issues, such as headache, nausea, and heartburn, were found to be highest in Injection C users, and it appear to be lower in Injection A and Injection B.

DISCUSSION

It was known that weight gain could be caused by fluid retention, fat deposition, or an increase of muscle mass. Increment of weight is a common phenomenon for women initiating hormonal contraceptives9. Although the existing literature does not provide a clear-cut picture of the mechanism of weight gain, previous studies suggest that weight gain from using hormonal contraception may be due to the deposition of fat rather than fluid retention10. Student's paired t-test showed significant changes in mean weight of each group between the initial treatment and each visit during the 1 year of treatment. This finding was similar to a previous study demonstrated that hormonal contraceptive injection caused significant weight gain and increased BMI as compared to non-hormonal contraception. Another study, conducted to find the association between progestin-only contraceptive use and changes in body weight, found that weight gain was greater in the hormonal group than in the group using a non-hormonal IUCD9,11. Previous studies tried to report the reasons why the use of hormonal contraception can lead to weight increase. In a study by Le at al, an increased of appetite after 6 months of using hormonal contraceptives was found, and this may be the reason leading to weight gain in women using hormonal contraceptive12. Other study reported that the weight gain among progestin only hormonal injection contraceptive users was related to their higher appetite and subsequently, higher dietary ingestion as a result of modifications of the hypothalamic appetite control center by progesterone13. Hircshberg in her review about how sex hormone regulates appetite in normal menstrual cycle, reported that the peak in food intake occurs when the progesterone is in the highest14. Contrary to the prior studies, Lange suggested that hormonal injection contracptive associated weight gain cannot be explained by a simple, direct relationship to the increased food consumption 13. However, the mean weight gain between Injection A and Injection C, and Injection B and Injection C showed no significant differences. This is shown, that even the weight gain was inevitable in each group, but both bi-monthly and trimonthly contraceptive injections were not caused extreme weight gain compared to the monthly contraception that was commonly used. The finding of this study demonstrated that there is no significant effect on blood pressure of the woman using Injection A and Injection B. Altough, there were significant differences of diastolic pressure in the 6th month and 9th month measurement of using Injection B compare to the initial treatment of the same substance, the blood pressure of each sample were still in normal pressure range. The systolic and diastolic pressure between Injection C, Injection A and Injection B users were not significantly different. Change in blood pressure before and during 12 months of injection in each woman of each group were not significantly different. This finding was similar with the previous study11.

CONCLUSION

Bimonthly contraceptive injection of 65 mg MPA and 7.5mg estradiol cypionate (Injection A) and trimonthly contraceptive injection of 120 mg MPA and 10 mg estradiol cypionate contraceptive injections (Injection B) compared with monthly contraceptive injections of 25 mg MPA and 5 mg estradiol cypionate (Injection C) found to be safe, because during 12 months of visit there were no unwanted events that harmed the subjects. Complaints experienced by the subjects during the study were still within normal limits and did not interfere with the subject's health and daily activities. Although the weight gain was inevitable in each group, but both bi-monthly and trimonthly contraceptive injections did not cause extreme weight gain compared to the monthly contraception that was commonly used. The blood pressure of all the subjects also in the normal range since initial treatment, during follow up and after 12 months of injection. The finding of this study demonstrated that there is no significant effect on blood pressure between the women using Injection C, Injection A, and Injection B. We conclude that bi-monthly and trimonthly contraceptive injections in this study could be a safe and convenient alternative in reducing doctor visits, thus enhancing patient compliance.

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Conflict of interest: There are no conflicts of interest in this study.

Authors' Contribution

I.A., A.A.; Study conception and design, analysis and interpretation of data, critical revision and acquisition of data and patient collection. I.A., M.F.S.; Were responsible for overall supervision and helping on drafting I.A., H.P.L; Drafting and editing the manuscript, analysis and interpretation of data, which was revised by I.A. and A.A. All authors read and approved the final manuscript.

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