


The Efficacy and Safety of Two Depo Medroxyprogesterone Acetate Injection Preparations as Contraception: An Open-Label, Randomized Controlled Study

Dewi Selvina Rosdiana,[1] Suharti K. Suherman,[1] Biran Affandi,[2] Mohammad Baharrudin,[3] E. Rusdianto Gunadi,[2] Dwirani Amelia[3]

[1]Department of Pharmacology & Therapeutic, Faculty of Medicine University of Indonesia, [2]Raden Saleh Clinic, CMG Hospital, [3]Budi Kemuliaan-MCH, Jakarta, Indonesia

ABSTRACT

Background: Injectable hormonal contraceptives remain in extensive use in many developing countries, including Indonesia. This study was intended to compare the efficacy and safety of injectable hormonal contraception containing 150 mg/mL DMPA (drug A), that will be used for national Family Planning Program versus the innovator product (drug B). **Methods**: This study was an open-label, randomized, multicenter, 2-parallel group study, involving 400 women of childbearing age, who received drug A or drug B four times at 3-month interval. **Results**: No pregnancies occur in both groups after 4 injections of drug A or drug B over a period of 12 months, the pearl-index value for each group was zero. The incidence of adverse events between groups was comparable and tolerable, the most common events were amenorrhea, spotting, headache, and prolonged menstruation. **Conclusion**: Injectable DMPA (drug A) produced for National Family Planning program was comparable to the innovator DMPA drug (drug B) in terms of efficacy and safety.

Keywords: Hormonal contraceptives, medroxyprogesterone acetate

ABSTRAK

Latar belakang: Kontrasepsi hormonal injeksi masih banyak digunakan di berbagai negara berkembang, termasuk di Indonesia. Tujuan penelitian ini adalah untuk membandingkan efikasi dan keamanan kontrasepsi hormonal injeksi mengandung 150 mg/mL *medroxyprogesterone acetate* (DMPA) (obat A) yang akan digunakan untuk program Keluarga Berencana Nasional, dibandingkan dengan inovatornya (obat B). **Metode**: Penelitian ini dilakukan secara *open-label*, acak, multisenter, 2 kelompok, melibatkan 400 subjek usia produktif, yang diacak untuk mendapatkan obat A atau obat B. Injeksi diberikan sekali setiap 3 bulan, selama 1 tahun. **Hasil**: Setelah 4 kali injeksi kontrasepsi periode satu tahun, tidak didapatkan kehamilan pada kedua kelompok, nilai *pearl-index* masing-masing kelompok nol. Insidens kejadian tidak diinginkan sebanding pada kedua kelompok dan dapat ditoleransi, dengan kejadian paling sering adalah amenore, *spotting*, sakit kepala, dan menstruasi memanjang. **Simpulan**: Kontrasepsi hormonal injeksi yang akan digunakan untuk program KB nasional (obat A) memiliki efikasi dan keamanan yang sebanding dengan inovatornya (obat B). **Dewi Selvina Rosdiana, Suharti K. Suherman, Biran Affandi, Mohammad Baharrudin, E. Rusdianto Gunadi, Dwirani Amelia. Efikasi dan Keamanan Dua Depo Preparat Injeksi Medroksiprogesteron Asetat sebagai Kontrasepsi: *Open-Label, Randomized Controlled Study.***

Kata kunci: Kontrasepsi hormonal, *medroxyprogesterone acetate*

BACKGROUND

Injectable hormonal contraceptives remain in extensive use in many developing countries, including Indonesia.[1,2] Depot medroxyprogesterone acetate (DMPA) is one of the progesterone-only injectable contraceptives that has been available worldwide since 1980.[1] Its lack of estrogen makes it an excellent choice for women with estrogen contraindication. Its long-acting duration of action (12-week) results in patient convenience, avoiding the need for daily compliance.[2] The efficacy and safety of injectable DMPA had been demonstrated in many clinical trials.[3-6] WHO has also endorsed the use of DMPA as a contraceptive immediately after birth regardless of breastfeeding status.[2]

As a copy drug of DMPA (drug A) is intended for long-term use of contraceptive in the National Family Planning Program, a formal clinical trial comparing the efficacy and safety of the drug to the innovator product (drug B)

Alamat Korespondensi *email: dianaroshtp@yahoo.com*


is needed.

We conducted a clinical trial to compare the efficacy and safety of drug A (test drug) with drug B (reference drug) for the prevention of pregnancy in women of reproductive age.

METHODS

Study Design

We conducted an open-label, randomized, multicentre, 2-parallel group study, involving 400 women of childbearing age, from March 2010 – October 2012. The study was a comparative efficacy and safety study of 150 mg/mL DMPA injection (drug A) versus the reference drug (drug B).

The drug was put in a sealed envelope, labeled with the randomization number, and was kept in a locked cupboard in the custody of the principal investigator. The randomization was balanced, prepared by an independent contract research organization, and the code was kept under controlled access.

On the first visit, subjects were screened according to the eligibility criteria. Subject underwent clinical examination included: anamnesis (interview), blood pressure measurement, body weight measurement, physical examination, laboratory test (liver function, serum creatinine, fasting blood glucose, and total cholesterol), and Pap smear test. Urine HCG test was performed as confirmation test for pregnancy.

The eligible subjects were randomly assigned, in a 1:1 ratio, to receive either 1 mL of the test drug (drug A), or 1 mL of the reference drug (drug B), injected deeply IM into the gluteal muscle. Subject was given a diary, to record any adverse events, and concomitant medication. Subject was instructed to return to the clinic for next visits, each visit was separated by an interval of 12 weeks.

On visits 2, 3, and 4, the drug was injected only if the subject was confirmed not to be pregnant, as shown by the negative result of the urine HCG test, and there were no severe or serious adverse events.

Study outcome evaluated in this study was the occurrence of pregnancy after drug injection shown by urine HCG test result every 12 weeks in 4 cycles of drug administration,

Figure. Subject's disposition

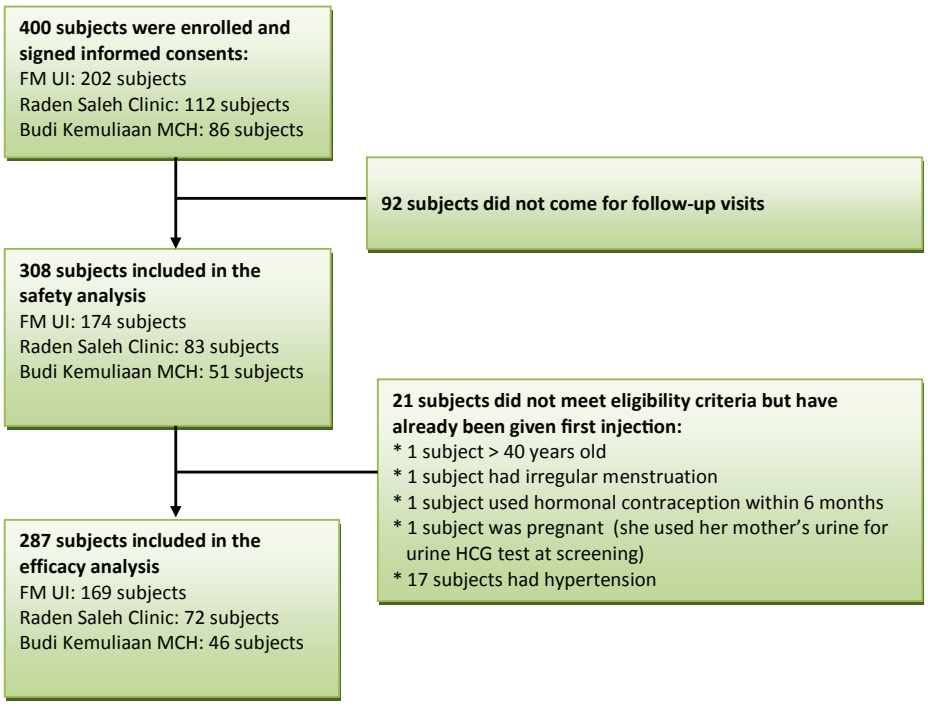

Table 1. Demographic and baseline characteristics of subjects

	Population (n = 308)	
	Drug A (n = 157)	Drug B (n= 151)
Age (years)		
Mean (SD)	30.2 (5.69)	30.1 (5.84)
Median	30.0	31.0
Range	18 – 42	18 – 40
Missing	0	0
Body Weight (kg)		
Mean (SD)	53.2 (10.09)	54.5 (9.51)
Median	53.0	54.0
Range	33 – 86	35 – 78
Missing	0	1
SBP (mmHg)		
Mean (SD)	112.4 (9.40)	112.78 (9.96)
Median	110.0	110.0
Range	90 – 130	90 – 140
Missing	0	0
DBP (mmHg)		
Mean (SD)	74.2 (7.585)	74.04 (7.74)
Median	75.0	75.0
Range	60 – 90	60 – 90
Missing	0	0
Partus (times)		
Mean (SD)	2.35 (1.33)	2.3 (1.10)
Median	2.0	2.0
Range	1 – 8	1 – 5
Missing	0	0
Children		
Mean (SD)	2.3 (1.26)	2.2 (1.08)
Median	2.0	2.0
Range	1 – 8	1 – 5
Missing	0	0

Table 2. Laboratory baseline characteristics of subjects

	Population (n = 308)	
	Drug A (n = 157)	Drug B (n = 151)
AST (IU/L) ≥ 1.5 ULN (Normal: ≤ 46 IU/L)		
Mean (SD)	17.6 (5.77)	18.7 (9.27)
Median	17.0	17.0
Range	6 – 49	6 - 98
Missing	0	0
ALT (IU/L) ≥ 1.5 ULN (Normal: ≤ 46 IU/L)		
Mean (SD)	15.6 (8.28)	18.0 (15.59)
Median	14.0	14.0
Range	1 – 60	5 – 154
Missing	0	1
AP (IU/L) ≥ 1.5 ULN (Normal: 100-240 IU/L)		
Mean (SD)	175.5 (51.90)	176.6 (58.13)
Median	170.0	167.5
Range	91 – 367	100 – 453
Missing	1	1
Creatinine (mg/dL) Normal: 0.6 – 1.4 mg/dL		
Mean (SD)	0.81 (0.145)	0.81 (0.137)
Median	0.80	0.80
Range	0.5 – 1.3	0.1 – 1.2
Missing	1	1
Fasting Blood Glucose (mg/dL) Normal: ≤ 110 mg/dL		
Mean (SD)	89.1 (27.29)	91.5 (34.76)
Median	86.0	85.0
Range	58 – 367	60 – 406
Missing	0	1
Total Cholesterol (mg/dL) Normal: ≤ 200 mg/dL		
Mean (SD)	172.5 (38.18)	179.6 (39.27)
Median	168.0	182.0
Range	97 – 322	94 – 300
Missing	0	1

Table 3. Demographic characteristics of study subjects

	Safety Population (n = 308)	
	Drug A (n = 157)	Drug B (n= 151)
Body Weight (kg)		
Mean (SD)	55.4 (10.96)	56.8 (10.29)
Median	54.0	56.0
Range	35 – 87	35 – 84
Missing	27	30
Sistolic Blood Pressure (mmHg)		
Mean (SD)	108.4 (9.30)	109.1 (9.29)
Median	110.0	110.0
Range	90 – 130	90 – 130
Missing	27	30
Diastolic Blood Pressure (mmHg)		
Mean (SD)	70.8 (7.26)	71.6 (6.99)
Median	70.0	70.0
Range	60 – 90	60 – 90
Missing	27	30

Table 4. Laboratory characteristics of study subjects

	Safety Population (n = 308)	
	Drug A (n = 157)	Drug B (n = 151)
AST (IU/L) ≥ 1.5 Normal (Normal: ≤ 46 IU/L)		
Mean (SD)	18.2 (6.88)	18.7 (6.67)
Median	16.5	17.0
Range	4 – 51	7 - 48
Missing	27	33
ALT (IU/L) ≥ 1.5 Normal (Normal: ≤ 46 IU/L)		
Mean (SD)	14.9 (8.56)	16.1 (12.10)
Median	12.0	13.0
Range	1 – 47	4 – 103
Missing	27	33
AP (IU/L) ≥ 1.5 Normal (Normal: 100-240 IU/L)		
Mean (SD)	177.1 (47.47)	182.1 (52.62)
Median	175.0	176.0
Range	78 – 430	89 – 418
Missing	27	33
Creatinine (mg/dL) Normal: 0.6 – 1.4 mg/dL		
Mean (SD)	0.84 (0.148)	0.85 (0.154)
Median	0.80	0.80
Range	0.6 – 1.3	0.6 – 1.4
Missing	27	33
Fasting Blood Glucose (mg/dL) Normal: ≤ 110 mg/dL		
Mean (SD)	90.1 (32.22)	90.95 (20.21)
Median	86.0	88.0
Range	6 – 374	60 – 218
Missing	27	34
Total Cholesterol (mg/dL) Normal: ≤ 200mg/dL		
Mean (SD)	181.9 (39.48)	184.9 (34.66)
Median	177.5	184.0
Range	94 – 345	90 – 272
Missing	27	33

and the incidence of adverse events.

Study Population

Women 18 to 40 years of age were eligible if they met the following criteria: healthy, married, sexually active, living with her husband and having a minimum of one child, and willing to follow all procedures in the clinical trial and to sign the written informed consent. The exclusion criteria were: use of any hormonal contraceptions within 6 months prior to screening for this study; use of IUD, abstinence, or sterilization contraceptive method including tubectomy; history or presence of infertility; irregular menstruation; blood pressure: systolic ≥140 mmHg, or diastolic ≥90 mmHg; history or presence of contraindication to depo-medroxyprogesterone acetate; pregnant; breast feeding, within 21 days postpartum; and any other known current medical condition, which, was judged by the investigator could jeopardize subject's health or interfere with the study evaluation.

Data Analysis

The data were handled and analyzed by an independent contract research organization (Clinical Study Unit, FMUI). Efficacy analyses were performed according to the intention-to-treat principle. The efficacy of DMPA in the prevention of pregnancy was expressed as pearl index. Pearl index of each treatment group was calculated by dividing the number of pregnancies by the number of months of exposure and number of women, and then multiplied by 1200. The safety analysis was given in tables of adverse events and adverse reactions.

This study was carried out in accordance to the good clinical practice (GCP) standards, with the approval of the Ethics Committee Medical Faculty University of Indonesia.

RESULTS

Subject's disposition was described in figure. Demographic and baseline characteristics of subjects were comparable between the two treatment groups (Table 1 and Table 2).

Efficacy Analysis

Efficacy analysis of injectable DMPA given as drug A or drug B was expressed as pearl index as calculated below.[7]

$$\text{Pearl - Index} = \frac{\text{Number of pregnancies} \times 2}{\text{Number of woman} \times \text{Number of months}} \times 100$$

No patient in each group became pregnant after 4 injections of drug A or drug B over a period of 12 months. Since there was no pregnancy in each group, the pearl-index value for each group was zero.

Safety Analysis

After 1 year period of DMPA injections, demographic and laboratory characteristics were presented in table 3 and table 4 below. In both groups, mean body weight was increased, about +2.2 kg in drug A group and +2.6 kg in drug B group. Total cholesterol levels in both groups were also increased, from 172.5 to 181.9 mg/dL in drug A group, and from 179.6 mg/dL to 184.9 mg/dL in drug B group. For other demographic and laboratory characteristics, the changes appeared to be unremarkable.

Adverse Events

The proportion of subjects with adverse events during the treatment course was 89.8% (141/157) in drug A group and 96.7% (146/151) in drug B group. The most common adverse events were similar in both groups (**Table 5**).

Table 5. Cumulative adverse events in drug A group and drug B group

Adverse Events	Drug A group		Drug B group	
	n	%	n	%
Amenorrhea	363	38.8	346	38.8
Spotting	332	35.4	319	35.7
Headache	96	10.3	96	10.8
Prolonged Menstruation	59	6.3	33	3.7
Upper Respiratory Tract Infection (cough, flu, rhinorhea)	15	1.6	14	1.6
Muscle Stiffness	5	0.5	14	1.6
Dyspepsia	6	0.6	13	1.5
Irregular menstruation	8	0.9	11	1.2
Hypertension	6	0.6	10	1.1
Body weight increase	5	0.5	7	0.8


Serious Adverse Events (SAE)

There was no serious adverse event recorded during study period in both groups.

Discussion

This study was a trial conducted to support the use of drug A - injectable DMPA produced for National Family Planning Program, by comparing its efficacy and safety to the innovator product, drug B, produced by originator. This study enrolled 400 study patients. The number of patients used in this study was the same as used by Salem study prepared by WHO,[6] which compared the safety and efficacy of 150 mg DMPA every 3 months to 200 mg norethistherone-enanthate every 2 months for a period of 1 year. The number of patients with lost to follow up in the Salem study was 32.5%,[6] which was almost the same number as in this study with about 33% lost to follow up.

Our study confirmed the efficacy of DMPA injected every 12 weeks for 1 year. We found no pregnancy in both groups after a period of 1-year, presented as pearl index of zero. The previous trial, conducted by WHO showed more than 99% success rate in women using progesterone-only injectable contraceptives.[1]

Population in the present study included 308 patients for analysis, 157 subjects in drug A group and 151 patients in drug B group. The pattern and frequency of adverse events in both groups were shown to be comparable, the most common adverse events were amenorrhea, spotting, headache and menstruation. These adverse events were tolerable for most study subjects, and most subjects completed the study until 1-year period.

Our findings were consistent with other trials showing that the most common adverse reactions of DMPA were amenorrhea and menstrual bleeding.[1,8-10] Several studies reported that amenorrhea occurred in about 30% of women after 6-months of use and increased to more than 50% after 1 year and 68% after 2 years of use.[8,10] Amenorrhea and menstrual irregularity were the important reasons for discontinuation of DMPA contraceptive.[9] In our study, only a small number of patients withdrew from study due to these adverse events; 0 out of 157 subjects in drug A group and 2 out of 151 subjects in drug B group. Futhermore, even study subjects experienced menstrual irregularity, the intensity was mild and tolerable, which did not cause the subjects to discontinue the drug.

After 1-year period of DMPA injections, either drug A or drug B, an increase in body weight by about 2 kg was seen. This adverse event was also a known undesirable effect of progestin-only contraceptives, including DMPA.[11-13] Their study also showed a BW increase of about 2 kg after 1-year of injectable DMPA use, while other progestin-only contraception such as levonorgesterel caused an increase of body weight up to 5 kg.[13]

Conclusion

Our study confirmed that drug A, injectable DMPA produced for National Family Planning Program, showed a comparable efficacy and safety to the innovator DMPA drug, drug B. No pregnancies occurred up to 1-year period, and the most common adverse events were amenorrhea, spotting, headache, and menstruation, which were consistent with progestin-only contraceptive drug. No serious adverse event occurred during this 1-year study.

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