Research Article

A Randomized Five-Year Comparative Study of Two Levonorgestrel-Releasing Implant Systems: Norplant® Capsules and Jadena® Rods

Penelitian Komparatif Acak Lima Tahun antara Dua Implan Levonogestrel: Kapsul Norplant© dan Batang Jadena©

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Abstract

Objective: To provide a randomized comparison between Jadena® and Norplant® in terms of efficacy and acceptability among Indonesian women.

Method: This study was a phase IV, open label, randomized, multicenter study throughout Indonesia. Subjects were Indonesian adult women who were randomized to receive Jadena® or Norplant® as their contraceptive method. The subjects were recruited from 6 large cities in Indonesia, such as Medan, Palembang, Jakarta, Semarang, Surabaya, and Makassar.

Result: Of 600 subjects, 301 women getting to Jadena® and 299 women to Norplant® were enrolled between August 1998 and February 1999. The mean age was 29.8 (SD 5.3) years old, ranging from 18 to 40 years old. We did not find the pregnancy during the study. Non-pregnancy probability at the end of one year was similar between Jadena® (0.920 (SD 0.016)) and Norplant® users (0.916 (SD 0.084)). The continuation rates of Jadena® at one and three-year were 95.3% and 66.8%; whereas, the continuation rates of Norplant® was 94.3% at year-1 and 70.2% at year-3.

Conclusion: The new two rod levonorgestrel subdermal system (Jadena®) showed similar efficacy with the old six capsule levonorgestrel subdermal system (Norplant®) in term of birth control. Both implant systems also have similar tolerability profile. Jadena® is easier to insert and remove than Norplant®.

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Keywords: birth control, efficacy, implant

Abstrak

***Tujuan**: Untuk mengetahui efikasi dan akseptabilitas antara Jadena© dan Norplant© di antara perempuan Indonesia.*

***Metode**: Penelitian ini merupakan fase 4, terbuka, acak, dan multisenter di Indonesia. Subjek penelitian merupakan perempuan dewasa Indonesia yang teracak untuk menerima Jadena© atau Norplant© sebagai metode kontrasepsi. Penelitian ini diambil dari 6 kota besar di Indonesia yaitu Medan, Palembang, Jakarta, Semarang, Surabaya, dan Makassar.*

***Hasil**: Dari total 600 subjek, 301 menggunakan Jadena© dan 299 mengunakan Norplant© pada periode Agustus 1998 hingga Februari 1999. Rerata usia ialah 29,8 (SD 5,3) tahun berkisar antara 18 hingga 40 tahun. Tidak ada kehamilan yang terjadi selama periode observasi. Kemungkinan hamil setelah 1 tahun antara Jadena© (0,920 (SD 0,016)) dan Norplant© (0,916 (SD 0,084)). Angka kebertahanan penggunaan Jadena© pada tahun 1 dan tahun 3 ialah 95,3% dan 66,8%, sementara pada Norplant© ialah 94,3% dan 70,2%.*

***Kesimpulan**: Sistem subdermal levonogestrel 2 batang (Jadena©) memiliki efikasi yang mirip dengan sistem subdermal lama menggunakan 6 kapsul (Norplant©) dalam mengontrol kehamilan. Kedua sistem implan memiliki profil tolerabilitas yang serupa. Jadena© lebih mudah dimasukkan dan dikeluarkan daripada Norplant©.*

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***Kata kunci**: efikasi,implan, kontrol kehamilan*

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INTRODUCTION

Levonorgestrel (LNG) is a synthetic progestin used for contraception either alone or in combination with ethynyl estradiol. The preparation in LNG administered alone is progestin only contraceptive pills (known as mini pills), Norplant® and Jadena® subdermal implant, and the intrauterine LNG system (Levonova® or Mirena®).

Levonorgestrel primarily acts through thickening the cervical mucus; thus, it will obstruct the sperm penetration into the uterus.[1,2] Besides, it also inhibits ovulation in over 50% of the menstrual cycles[3,4] and has a suppressive effect on the endometrium to reduce the likelihood of nidation.[5] Both mechanism of action above provide protection against pregnancy efficiently.

The beneficial features of Norplant® include long contraceptive activity, high contraceptive efficacy, absence of estrogen side effects, and convenience due to no daily attention needed. Furthermore, it is completely reversible and the side-effects are mainly mild and transient. Norplant® capsules have been studied extensively for clinical efficacy and safety by independent clinicians and agencies throughout the world for many years. However, insertion and removal of the implant needs sufficient training.

On the other hand, Jadena® is developed as two implantable rods in order to make insertion and removal of the contraceptive device easier. Both the release rate of LNG from Jadena® rods and plasma hormone concentrations achieved are comparable to those of the Norplant® capsules.[6,7] The two preparations are similar in terms of contraceptive efficacy for three years and the occurrence of side effects.[8-10]

Jadena® is a subdermal tube implant containing 75 mg of LNG each, whereas Norplant® is a subdermal capsule containing 36 mg LNG each. Jadena® implant consists of two rods sizing nine millimeters longer than the Norplant® capsules. The period of Jadena® rod user is for three years; meanwhile, the Norplant® capsules provide longer period for five years of effective contraceptive protection.

Norplant® was introduced into the Family Planning Program (FPP) in Indonesia since 1981. It becomes popular among Indonesian community.[9] By March 1997, there were 2.4 million women using Norplant® as their contraceptive method in Indonesia. This represents about three quarters of Norplant® users all over the world. Recently, Jadena® was also registered in Indonesia and it had already been used by about 2,000 Indonesian women. However, data comparing the efficacy and acceptability of Norplant® and Jadena® are still not available in Indonesia. Therefore, this study aims to provide a randomized comparison between Jadena® and Norplant® in terms of efficacy and acceptability among Indonesian women.

METHODS

This study was a phase IV, open label, randomized, and multicenter studies throughout Indonesia. Subjects were recruited from 6 large cities in Indonesia, namely Medan (Universitas Sumatera Utara), Palembang (Universitas Sriwijaya), Jakarta (Universitas Indonesia), Semarang (Universitas Diponegoro), Surabaya (Universitas Airlangga) and Makassar (Universitas Hasanuddin) between August 1998 and February 1999.

Subjects were Indonesian adult women having been randomized to receive Jadena® or Norplant® as their contraceptive method. The sample size was determined through formula proposed by Pocock. To demonstrate a ten-fold increase in cumulative 3-year pregnancy rate (0.5 per 100 women-years), the minimum sample size was 272 subjects per treatment group.

A total of 600 women were needed which meant 100 women recruited from each center. This study was the first design to be followed-up for three years; however, another 2 years were added to complete 5-year observation and follow-up. Subjects were followed every year in 12 visits, such as at month-1, 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60. We recruited 18-40-year old women, not currently pregnant, be regularly exposed to the risk of pregnancy, without exposure to injectable steroid in the predicting 6 months, be willing to rely solely on the implant randomly assigned for her contraceptive method, be willing to return the clinic for regular follow-up. All the participants were informed of the purpose, risk, and benefits of the study and they had to sign the written informed consent.

Subjects were excluded from the study if there was any kind of cancers, undiagnosed abnormal uterine bleeding (AUB); thromboembolism or severe cardiovascular problem; mental illness, depression or epilepsy; severe and frequent headaches; diabetes mellitus; active liver disease or jaundice; regular treatment with enzyme-inducing drugs, such as barbiturates, phenytoin, carbamazepine or rifampicin; blood pressure greater than 160 mmHg systolic or 100 mmHg diastolic; bloody breast discharge; severe hirsutism; pregnancy or suspected pregnancy; current evidence of pelvic

inflammatory disease; and participation in another clinical study on the previous three months.

Study Endpoints

The primary efficacy variable was the pregnancy rate calculated using the Kaplan-Meier product limit method. Secondary efficacy parameters were the alteration in menstrual cycles, discontinuation or continuation rates, rates of implant removal due to menstrual problems and/or medical reasons, and the duration of implant insertion and removal from asepsis to wound closure. All data were based on the information reported by the women using Jadena® or Norplant®. We also investigated several safety parameters including laboratory parameters, general state of health, adverse events, concomitant medications, body weight, and vital signs.

Data Management and Analyses

All variables were described according to their types using univariate statistics (mean and standard deviation for continuous data, frequency and percentage for categorical data). The primary efficacy variable in this trial was the pregnancy rate estimated using the Kaplan-Meir product limit method. The two treatment groups were compared using the Wilcoxon rank-sum test. A significance level (α-level) of 0.05 was used for all statistical tests. Secondary and safety variables were presented descriptively.

RESULTS

There were 600 women enrolled in this study. They were randomized to receive Jadena® (301 women) or Norplant® (299 women). Their mean age was 29.8 (SD 5.3) years old, ranging from 18 to 40 years old. Subjects using Norplant® were older than subjects using Jadena® (p=0.008). On the average; however, the women from both implant groups were relatively similar to the demographic characteristics, such as body weight, body mass index (BMI), and blood pressure (Table 1). All subjects had normal body weight and BMI. All subjects had been pregnant and/or had delivered at least once. The mean number of previous pregnancies were 2.8 (SD 1.5). The mean number of live birth were 2.6 (SD 1.4). Higher parity was observed in women on Jadena® than Norplant® (p=0.04). At baseline, most women (87.6%) reported normal or usual menstrual pattern. Five-point four percent of these women had amenorrhea. Almost one-third (32.5%) of the subjects wanted more children. The most popular (49.8%) contraceptive method used prior to the study enrollment was the combination of oral contraceptive and majority of them (38.7%) had their last contraceptive used less than 31 days before. More than half of the women (60.3%) did not practice breastfeeding. Almost all subjects (95%) reported vaginal delivery at the last pregnancy. Cytological examination data were available in 591 subjects. The results were mostly classified into CI (75.1%), while CII was found in 24.2% of women. None was classified as CIII.

Efficacy Assessment

Primary end point

No pregnancy was observed in both contraceptive users. However, an intrauterine pregnancy was found in Norplant® group which had been confirmed that it started before her enrollment into the study. The implant was removed immediately and she delivered a baby spontaneously at term gestational age. The Kaplan-Meier product limit method showed that non-pregnancy probabilities were not different between the two implants (Table 2). Therefore, both contraceptive methods showed similar efficacy in controlling pregnancy over 5 years.

Secondary endpoints

The prevalence of dysmenorrhea was considered low. The prevalence was not significantly different between baseline and after 5 years both in women using Jadena® (2.0% vs. 2.5%; p=0.812) and Norplant® (2.4% vs. 2.0%; p=0.977). The menstrual changes occurred in majority of subjects in the first two years. Improvement of menstrual irregularities increased after three years. The pattern of menstrual changes was similar between Jadena® and Norplant® users (Figure 1).

Discontinuation or continuation rates

At the end of the third year and after obtaining written consent to extend the observation period by an additional 2-year, 411 of the 600 women (68.5%) agreed to continue the study; consisting of 210 women using Norplant® (70.2%) and 201

women using Jadena® (66.8%). Continuation rates per year were shown on Table 3. The difference in discontinuation rates between the two contraceptive methods from year-1 to year-5 was not significantly different (p=0.746).

Rates of implant removal due to menstrual problems and/or medical reasons

Premature removal of the implant was decided by 154 out of 217 women. The reason mostly was because of the desire to get pregnant (19.4%). Others had menstrual problems, such as metrorrhagia (4.1%), amenorrhea (3.2%), spotting (2.3%), prolonged menstrual flow (1.8%), and heavy menstrual flow (1.4%). The details on the primary reasons for implant removal in both groups were given on Table 4.

Duration of the implant placement and removal

Nearly all subjects (99.2%) had their implant placed on their left upper arm. There were neither reported complications nor difficulties encountered during implant placement. From aseptic to skin closure, the surgical procedure took an average of 3.1 (SD 1.5) minutes, varied from as short as 1 minute to as long as 10 minutes. The procedure for Jadena® placement was shorter than NorplantS® (2.2 (SD 0.9) vs. 4.1 (SD 1.3) minutes; p<0.001).

The surgical procedure for implant removal took an average of 8.7 (SD 4.9) minutes. Procedures for Jadena® removal was significantly shorter than Norplant® removal (6.4 (SD 4.1) vs. 10.5 (SD 4.7) minutes; p<0.001). Most subjects (89.5%) did not feel any complication during the procedure.

Safety Assessment

During the 5-year period, 37 (6.2%) of subjects experienced at least one adverse event (AE), comprising 20 (6.6%) women on Jadena® and 17 (5.9%) women on Norplant®. Most AEs (64.9%) was mild; however, 6 women (16.2%) experienced moderate AEs, which all belonged to Jadena® group. Two patients had severe AEs; one on Norplant® was diagnosed with severe hypertension during visit-11 and the another one on Jadena® experienced severe cramping on the arm at visit-11 which requested to be removed. One woman on Jadena® died due to dengue hemorrhagic fever (DHF) and it was not related to the contraceptive method.

Adverse events reported by women using Jadena® included spotting (5 women), bleeding (3 women), influenza (2 women), dizziness (2 women), expulsion (1 woman), cardiomegaly (1 woman), cramp at the implant site (1 woman), death due to DHF (1 woman), headache (1 woman), local infection (1 woman), menometrorrhagia (1 woman), metrorhagia (1 woman), and numbness (1 woman). In women using Norplant®, the adverse events were headache (5 women), spotting (3 women), hypertension (2 women), influenza (2 women), local infection (2 women), abscess (1 woman), bleeding (1 woman), dizziness (1 woman), emesis gravidarum (1 woman), irregular bleeding (1 woman), numbness (1 woman), palpitation (1 woman), pelvic pain/dyspareunia (1 woman), and sweating (1 woman).

DISCUSSION

In the beginning, this study was designed for 3 years, but it was extended for another 2-year to complete a 5-year observation of both implant system. The first study on extended use (5 years) of the two-rod implants (Norplant II®) was conducted in China, with a failure rate of 0.65 per 100 users and continuation rate of 65.3 per 100 users. These rates were similar to that of the capsule implant users.[8] Continuation of two-rod LNG implants has also been tried in US study when the 3-year cumulative pregnancy rate was 0.8 per 100.[10] For a 5-year period, the 2-rod LNG implants were equivalent to the 6-capsule LNG implants regarding to safety and efficacy parameters. It offers the advantage to insert more easily and remove more rapidly.[10] The cumulative 5-year pregnancy rate of LNG implants was comparable to that of tubal ligation.[11]

Our study subjects were older (29.8 years old) than the US study, which had the mean age at baseline of 25.5 years old.[10] This could be because all subjects in our study was married women who had given delivering at least once. It also reflects that contraceptive use is uncommon in young, unmarried women adults in Indonesia. Other characteristics in this study were the subjects' body weight and BMI, which showed the normal range. On the contrary, subjects in the US study showed much higher body weight with a mean of 62.4 kg at baseline.[10] Weight gain is an important problem

during implant use; thus, it should be considered since the beginning.

The primary reason for discontinuation after three years of use was the subjects' plan for pregnancy. However, a substantial number of subjects (more than 70%) also experienced menstrual problems. Menstrual irregularities (lighter or heavier menstrual flow and amenorrhea) were occurred in most subjects at the first year of use. Although menstrual change was common, most subjects decided to continue the implants. The overall level of satisfaction was high and even the continuation rates at the end of the first year were better than combined oral contraception.[12] Menstrual change was also reported as the common AE during the first year of Norplant® use in Singapore. However, these menstrual irregularities appeared to be reduced as the time and they were tolerated since 97% of the women continued at the end of the first year.[13] Study on bleeding patterns on 234 Norplant® users for 5 years showed that a substantial number of subjects (66.3%) had irregular cycles during the first year and 7.1% were amenorrhea. However, by the fifth year of use, only 37.5% subjects had irregular cycles and none had amenorrhea. Thus, the menstrual irregularity improved after the first year of use.[14]

In a minority of subjects, prolonged bleeding/spotting (8.2%) and irregular bleeding (5.6%) were the primary reasons for removal.[10] A study among Norplant® users in Europe found that discontinuation before 5 years of implant was related mostly to irregular bleeding.[15] Risk factors for Norplant® discontinuation for perceived menstrual problems were higher education level (more than 12 years), had used no contraceptive in the preceding month before Norplant® insertion, or had a relatively long duration of menstrual flow at admission.[16] Discontinuation rate due to menstrual problems increased from 9.4 per 100 women at the end of year-2 to 16.4 per 100 women at the end of year-5.[16]

In a phase III clinical trial, the 2-rod subdermal implants showed high continuation rates, such as 88.1% at 1 year of use and 73.5% after 2 years. The main reason for discontinuation was menstrual disturbance, mainly prolonged bleeding.[17] Menstrual irregularity with the 2-rod system was not significantly different from that observed with Norplant®. Normal menstrual bleeding was uncommon during the first three months of use, but the prevalence increased to almost 70% at the end of five years. Amenorrhea was uncommon after two years of use.[18]

Removal due to headache (4.7%) and weight gain (4.0%) were the next most frequent medical reasons after menstrual problem in US study.[10] In our study, only three subjects asked the implants remove for headache and one subject for having weight gain. Increased body weight of 1 kg per year on average was observed in implant users.[11] Higher body weight gain of 2.9 kg was observed in intrauterine LNG device at 12 months.[19]

Other rare adverse effects that might be a medical concern were local infection and hypertension. Local infection was rare (0.4 per 100 users at 24 months) in the phase III clinical trial of 2-rod implant.[17] A study among 2,674 Norplant® acceptors from 7 countries and followed for one year showed that the incidence rate of infection was low (0.8%). Insertion site infection and implant expulsion were reported after the first two months of use.[20] A study on 267 Norplant® users showed that neither systolic nor diastolic blood pressures were affected. Increasing blood pressure was more likely to be associated with the women's age, obesity and family history of hypertension.[21]

In this study, Jadena® use was associated with significant shorter time of insertion and removal. In a 3-year randomized, controlled study, implant removal of the 2-rod system took about half the time required for 6-capsule implants ($p<0.001$).[22] Difficult implants removal might be occurred in about 3% subjects due to deeply placed or poorly aligned implant or severe reaction to local anesthetic agent.[11] Implant removal was more difficult than insertion because in step of time, fat and fibrous tissue could develop around the capsules. Delayed removal of implant could be seen in many Norplant® users in Indonesia. A large study involving 2,979 Indonesian women using Norplant® in 14 provinces showed that 66% of the women had implant removal by the end of the fifth year (90% by sixth year).[23] Therefore, the 2-rod implant system which was easier to insert could potentially reduce the difficulties during implant removal after a long period of use.

Cervical cytology might be a concern among women who used long-term hormonal contraception. However, subdermal LNG implant has been proved to be safe during five years of use.[24] In this study, there was no abnormal cytology or cervical

Table 1. The Characteristics of the Study Subjects (n=600)

	Jadena® (n=301)	**Norplant® (n=299)**
Age, years (mean (SD))	28.8 (1.3)	30.0 (1.7)
Body weight, kg (mean (SD))	50.7 (2.3)	50.9 (2.1)
Body mass index, kg/m2 (mean (SD))	21.9 (0.6)	22.1 (0.6)
Systolic blood pressure, mmHg (mean (SD))	112.9 (0.9)	113.4 (2.0)
Diastolic blood pressure, mmHg (mean (SD))	73.8 (1.9)	73.6 (2.3)
Number of previous pregnancies (mean (SD))	2.7 (0.4)	2.9 (0.4)
Parity (mean (SD))	2.5 (0.4)	2.7 (0.3)

SD=standard deviation

Table 2. Kaplan-Meier Estimates for non-Pregnancy Probabilities*

	Jadena® (n=301)		**Norplant® (n=299)**	
	Probability	SD	Probability	SD
Year 1	0.920	0.016	0.916	0.084
Year 2	0.890	0.018	0.886	0.018
Year 3	0.664	0.027	0.702	0.026
Year 4	0.651	0.027	0.692	0.027
Year 5	0.000	0.000	0.000	0.000
Median time	60 months		60 months	

**Not significant at alpha 0.05; SD=standard deviation*

Table 3. Continuation Rates of using Levonorgestrel Contraceptive Implant

	Year 1		**Year 2**		**Year 3**		**Year 4**		**Year 5**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Jadena® (n=301)	287	95.3	274	91.1	201	66.8	199	66.1	185	61.5
Norplant® (n=299)	282	94.3	273	91.3	210	70.2	208	69.6	198	66.2

Table 4. Primary Reasons for Discontinuation (Implant Removal) after Three Years*

Primary reason	**Jadena®**	**Norplant®**	**Total**
No reason indicated	25	32	57
Intrauterine pregnancy	0	1	1
Menstrual problems			
Frequent irregular bleeding	4	4	8
Heavy menstrual flow	2	1	3
Prolonged menstrual flow	1	2	3
Amenorrhea	3	4	7
Spotting	4	1	5
Placement problems			
Infection at site	1	4	5
Expulsion of 1 or more implants	1	2	3

Primary reason	Jadena®	Norplant®	Total
Cardiovascular			
Hypertension	0	1	1
Not specified	2	0	2
Other medical problems			
Headache	1	2	3
Pain at the implant site	1	0	1
Weight change	1	0	1
Personal			
Planning of pregnancy	24	12	36
Widowed/divorced/separated	2	1	3
Moving	6	6	12
Other personal reasons			
Subject objection	3	6	9
Husband objection	1	2	3
Death of the husband	1	0	1
Not specified	10	5	15
Other removal problems	0	1	1

**multiple response*

change to lead to premature removal or discontinuation of both implant systems.

CONCLUSION

The new 2-rod LNG subdermal system (Jadena®) showed similar efficacy with the old 6-capsule LNG subdermal system (Norplant®) in term of birth control. Both implants system also have similar tolerability profile. Jadena® is easier to insert and remove than Norplant®.

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