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Submission date: 06-Oct-2022 11:31AM (UTC+0700)
Submission ID: 1917978366
File name: 047_-_3629_-_Syarief_Thaufik_Hidayat_-_Galley.pdf (346.58K)
Word count: 5001
Character count: 24578

ORIGINAL ARTICLE

Bali Medical Journal (*Bali MedJ*) 2022, Volume 11, Number 3: 1290-1300
P-ISSN.2089-1180, E-ISSN: 2302-2914

A study of efficacy, safety, and acceptance of two combined oral contraceptive pills containing 150 mcg Levonorgestrel and 30 mcg Ethinyl Estradiol at Dr. Kariadi Hospital, Semarang, Indonesia

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Received: 2022-07-08
Accepted: 2022-08-14
Published: 2022-09-27

ABSTRACT

Background: Combine Oral Contraceptives (COCs) pills is one of the many popular contraceptives worldwide, with 100 million women who use contraceptive pills. To increase the choice of oral contraceptives, COCs Novadiol® (Pill A) domestic production, which has the same dosage as Microgynon® (Pill B), are still imported drugs. This study aims to determine Pill A's efficacy, safety and acceptance level compared to Pill B for 3 months.

Methods: The study was a randomized control clinical trial, an open-label trial in 200 women of childbearing age who met the inclusion and exclusion criteria from July to November 2015. Data were analyzed using SPSS version 20 for Windows.

Results: About 300 participants were selected and 200 met the inclusion and exclusion criteria who participated study from the beginning to the end of the study period. In the first month of observation, 1 complaint of dizziness in pill A and 2 from pill B. One nausea complaint was found in the participant from Pill A. These differences were not statistically significant ($p>0.05$). In the second month of observation, 1 complained of dizziness from pill B and 1 nausea from Pill A. In the third month, observation found no complaints about using Pill A and pill B. There were changes in menstrual patterns in both pills and bleeding outside the cycle during the use of 3 months, but they were not statistically significant ($p>0.05$).

Conclusion: Pills A has the same efficacy, safety and acceptance when compared to the use of birth control pills B for 3 months.

Keywords: COCs, Safety, Efficacy, Acceptance.
Cite This Article: Hidayat, S.T., Tjahjanto, H., Eria, R., Gozali, Y.K. 2022. A study of efficacy, safety, and acceptance of two combined oral contraceptive pills containing 150 mcg Levonorgestrel and 30 mcg Ethinyl Estradiol at Dr. Kariadi Hospital, Semarang, Indonesia. *Bali Medical Journal* 11(3): 1293-1300. DOI: 10.15562/bmj.v11i3.3269

INTRODUCTION

Family planning is important in reducing population control, poverty reduction, and human development.[1] In developing countries, such as Indonesia, the prevalence of contraceptive use among married women is still low and varies between provinces, economic status, education level, and residential location. Problems that often arise in the community include the difficulty of access to contraception and the cost, which is still considered expensive for most people.[1]

Contraceptive pills are a popular contraceptive method worldwide, 100 million women are using contraceptive pills.[2,3] Oral contraceptives are relatively safe and effective when used for years. In the United States, the risk of death in an oral contraceptive user (nonsmoker) is less than the risk of death from pregnancy: 1 in 63,000 vs. 1 in 11,000.[4] In Indonesia, the contraceptive prevalence rate increased from 50% in 1991 to 64% in 2017. Oral contraceptives are also popular in Indonesia, where about one-fifth of women use pills as their contraceptive method.[5,6]

Contraceptive pills are convenient to use because they enable women to be in control of fertility, improve menstrual regularity, do not interfere with sexual activity and can decrease dysmenorrhea.[2,7] It can also reduce the incidence of pelvic inflammatory disease, ovarian cancer, endometrial cancer, and benign breast neoplasm.[8,9]

There are 2 kinds of oral contraceptives, Combined Oral Contraceptives or COCs (containing the hormones progesterone and estrogen) and the mini-pill (progesterone only), on the market today. COCs pill containing 150 mcg levonorgestrel (LNG) and 30 mcg Ethinyl estradiol (EE) has long been used worldwide, including in Indonesia.[10-12] Compared to combination oral contraceptives, the mini-pill has been associated with a higher pregnancy rate in adolescents, but its efficacy is similar to combination oral contraceptives in older women. Incidence of spotting or bleeding days is also higher on Mini-pill than on COCs.[4,13]

As it had been widely circulated, Microgynon®, one of the COCs' brands, is becoming the gold standard of the contraceptive pill in the National Family Planning program. Microgynon® oral contraceptives are still imported from

Brazil.[14,15] To increase the choice of oral contraceptives, it has been introduced Novadiol®, made domestically, has the same dose combination as Microgynon®.

This study aims to evaluate the comparison level of efficacy (efficacy), security (safety) and acceptance (acceptability) of Novadiol® and Microgynon® as alternative combined oral contraceptive pills.

METHODS

Research Design and Population

The sampling technique used in this research is random sampling. The authors found 4 midwives who joined the sampling study in the Tugurejo district, Pedurungan, East Semarang and West Semarang, to collect participants and the local family planning cadre. This study also used an open-label method, so the researchers and the subjects knew the investigated drug of this study. This open-label, multicenter randomized control study enrolled 200 women recruited from several health centers and family planning cadres through Bapermasper Semarang.

The inclusion criteria included the following: healthy women who were aged 20-35 years, knew exactly the last date of menstrual period, had normal menstrual cycle (21-31 days), not using hormonal contraception in the last 3 months, and were willing to fill out a card menstrual bleeding and take combination oral contraceptives to delay pregnancy were recruited. An early PAP test result showed no cell abnormalities in all the participants.

Exclusion criteria included the following: currently nursing; have not menstruated within 6 months after using contraceptive implants, injections or pills; place of residence was not fixed; routinely used drugs that could influence the way progesterone drugs work (hydantoins, barbiturates, primidone, carbamazepine, rifampicin and griseofulvin); had a history of cerebrovascular, coronary heart disease history, a history of migraine head disease, uncontrolled hypertension, severely impaired liver function (malignancy, hepatoma, liver cirrhosis); suffering from gynecologic tumors or tumor; chronic hemolytic disease.

Procedure

Participants were divided into two groups by using permutation random 10 blocks. This was to reduce the heterogeneity of the factors that could influence the variables that would be measured. Every 10 women were recruited and divided into two groups, i.e., five (5) subjects would get the Novadiol® (referred to as Pill A) and 5 (five) participants were given Microgynon® (referred to as Pill B). The participants were monitored for three months (September to November 2015). The monitoring was conducted following a predetermined time period by writing in the card control bleeding time, through short messages to patients with a cell phone or home visits if the patient cannot be reached through existing communication facilities. Acceptance was the number of participants that had been using the pills during the study after deducted by the number of participants that stopped taking the pills because of medical reasons or pregnancy.

Instruments

All participants were monitored monthly to evaluate Pill A's and Pill B's side effects. The measures that the author collected for monitoring the safety included the following: increase of weight; blood pressure; menstruation cycle; menstruation pattern change; duration of menstruation; tampon change for a day; incidence of metrorrhagia; dizziness; nausea or vomiting; dyspnea; fluor or vaginal discharge; and depression. The efficacy of the Pills would be assessed by the number of unwanted pregnancies while using the Pills. Acceptance by the participants would be measured by using the questionnaire to assess the number of discontinuations in using the pills.

Statistical Analysis

Descriptive statistical analysis was done to compare the two groups. The data were calculated using life table analysis to assess both pills' efficacy, safety and acceptance. Bivariate analysis to analyze the dependent variables (efficacy, acceptance and safety) and the independent variables (Pills A and B) was performed using the Chi-Square test for nominal data and Mann Whitney if numerical data distribution was not normal; when p> 0.05 was declared no statistically different. Data analysis was evaluated by Statistical Package for the Social Science (SPSS) version 20 for Windows.

RESULTS

This clinical trial was conducted from July to November 2015. Within 2 months (from July to August), 300 participants were selected and 200 met the inclusion and exclusion criteria. Participants were monitored for three months, from September to November 2015 (Table 1).

In the first month of observation, the authors found one complaint of dizziness in pill A and two participants from pill B. One nausea complaint was found in the participant from Pill A. However, these differences were not statistically significant. There were changes in menstrual patterns in both pill and bleeding outside the cycle, but they were not statistically significant (p>0.05) (Table 2).

In the second month of observation, the authors found one dizziness complaint on pill B and one nausea complaint on Pill A. There were changes in menstrual patterns in both pills and bleeding outside the cycle in pill A, but the difference was not statistically significant (p>0.05) (Table 2).

In the third month of observation, there was no complaint about the use of Pill A and pill B. Changes in menstrual patterns in both pills were found, but the difference was not statistically significant (p>0.05) (Table 2).

DISCUSSION

The research site selection was based on data from the Agency for Community Empowerment, Women (BAPERMASPER) and Semarang family planning organization. The authors found 4 midwives who joined the sampling study in the Tugurejo district, Pedurungan, East Semarang and West Semarang, to collect participants and the local family planning cadre. The combined oral contraceptive pill is one of the methods commonly

used by women in Indonesia. IDHS 2012 indicated that the contraceptive pill is used by 15.6% of married women and the knowledge of the family planning pill is 97.3%.[16] Thus, since the start of the subject election, patients quickly understood the combined oral pills and signed informed consent of research through the provision of research information. Once the patient agreed, anamnesis was performed to obtain identity data in the form of initials with 3-digit letters, the criteria for inclusion, exclusion, a random number with a block 10, a history of the disease, a history of drug use, obstetric history and menstrual history. Before patients got random numbers, they needed a physical inspection, inspeculo examination and pap smear. Once a patient met the criteria, the patient started the first pill on menstruation between day 1 to 5.[7,17] Due

Table 1. Participants Characteristic.

Variables	Type of Pills						p
	Mean±SD	Median (Min-Max)	N (%)	Mean±SD	Median (Min-Max)	N (%)	
Age (Years)	30.0±4.0	31.0 (21.0-35.0)		31.0±4.0	32.0 (21.0-35.0)		0.67[a]
< 25			9 (9.0)			10 (10)	
25-29			64 (64.0)			65 (65)	
30-35			27 (27.0)			25 (25)	
BMI (kg/m²)	23.2±3.1	22.7 (18.2-32.5)		22.8±3.8	22.2 (15.2-38.7)		
Underweight			1 (1.0)			9 (9.0)	0.35[a]
Normoweight			56 (56.0)			53 (53.0)	
Overweight			22 (22.0)			20 (20.0)	
Obese			21 (21.0)			17 (17.0)	
Blood Pressure (mmHg)							
Normotensive			100 (100.0)			100 (100.0)	
Hypertensive			0 (0.0)			0 (0.0)	
Systole	114.0±7.0	110.0 (100.0-		116.0±8.0	120.0 (100.0-		0.20[a]
Diastole	75.0±5.0	130.0)		75.0±6.0	130.0)		0.59[a]
Education		70.0 (70.0-80.0)			80.0 (60.0-80.0)		
Uneducated			1 (1.0)			0 (0.0)	0.99[b]
Primary School			8 (8.0)			10 (12.4)	
Junior High			27 (27.0)			29 (27.6)	
High school			52 (27.0)			41 (41.3)	
University			12 (12.0)			20 (19.0)	
Occupation							
Unemployment			36 (36.0)			41 (41.0)	0.99[b]
Civil-worker			3 (3.0)			0 (0.0)	
Private-worker			49 (49.0)			51 (51.0)	
TNI/POLRI			0 (0.0)			0 (0.0)	
Farmer			0 (0.0)			0 (0.0)	
Laborer			10 (10.0)			4 (4.0)	
Trader			2 (2.0)			4 (4.0)	
Parity							
1	2.0±1.0		41 (41.0)	2.0±1.0		38 (38.0)	0.47[a]
>1		2.0 (1.0-3.0)	59 (59.0)		2.0 (0.0-5.0)	62 (62.0)	
Menstruation Period	4.0±1.2			4±1,3			
≤ 8 days		5.0 (1.0-8.0)	100 (100.0)		5(1-8)	100 (100.0)	0.64[a]
> 8 days			0 (0.0)			0 (0.0)	
Menstruation cycle	28.0±1.0			28.0±2.0			0.65[a]
Normal		28 (25.0-34.0)	100 (100.0)		28 (21.0-35.0)	100 (100.0)	
Not normal			0 (0.0)			0 (0.0)	
Tampon Used	1.0±0.0			1.0±0.0			0.85[a]
≤ 3		1 (1.0-2.0)	100 (100.0)		1 (1.0-2.0)	100 (100.0)	
> 3			0 (0.0)			0 (0.0)	
Last Contraception							
IUD			3 (3.0)			8 (8.0)	0.99[b]
1-month injection			14 (14.0)			17 (17.0)	
3-month injection			40 (40.0)			39 (39.0)	
Pill			19 (19.0)			14 (14.0)	
Condom			17 (17.0)			10 (10.0)	
Implantation			0 (0.0)			2 (2.0)	
Not using contraception			7 (7.0)			10 (10.0)	

[a]Mann Whitney Test; [b]Chi-Square Test; *Statistically significant if p-value less than 0.05

to the effectiveness of birth control pills available on the 7th day of taking the pill, the patient was advised not to perform sexual ties or when it did, it was recommended to use additional contraception such as condoms.[10,18-20]

Combined oral pills have some side effects that vary from mild to severe.[3,21] Mild reactions include nausea, bleeding between menstruation, mild headaches, weight changes and edema. Generally, the state of the drug does not need to be stopped unless it is considered very disturbing. This research found that minor complaints such as nausea, mild headaches and changes in body weight in both pills were obtained. Still, the difference was not statistically significant and the complaints could go away without medicine. Headaches could be a migraine associated with vascular disorders. Weight gain was caused by anabolic progestin derivatives, while edema was associated with water retention and electrolyte effects of estrogen. Bleeding between menstruation usually occurs in the use of small doses of estrogen.[22-26] In this study, body weight changed in the use of both pills and there was no significant difference. Menstrual disorders were found, such as changes in the pattern of menstrual bleeding and the length of the menstrual cycle in both pills. Still, there was no significant difference or discontinuation due to these changes.

Another side effect was the change of psychic connection with a sense of security because there are no fears of becoming pregnant, a sense of quick offense such circumstances of premenstrual, sometimes depressive or aggressive, and changes in libido.[27] Hyperpigmentation of the skin, especially the face area, was generally difficult to overcome. Worsening of acne could occur with the use of androgenic progestin, but this side effect was rarely treated using medicine because the estrogen used in combination with hormonal contraceptives can increase the production of sex hormone binding globulin (SHBG) by the liver so that the effect of androgenic progestin can be prevented.[28,29] In this study, psychiatric disorders such as depression, aggression, and changes in libido, acne or hyperpigmentation were not obtained during the 3 months observation.[30,31]

These Pill's effect on the liver study examination was not conducted, but from literature, a liver function test is recommended at a regular check-up every six months on hormonal contraception.[32] Cardiovascular disorders in this study were indicated by a change in blood pressure, and blood pressure variation was obtained for each control, but cases of hypertension that made the participants need to stop taking the medication were not found.[33,34]

There was no rejection of Pill A and B from the participants. This study used an open-label method, so the researchers and the subjects knew the investigated drug of this study. This could affect the perception of the subject and the researcher so it might be the limitation of the study. To reduce the perception of open-label, this research used permutation random sampling with 10 blocks, in which the sequence was based on the sequence of arrival of the subject, so the researchers nor the subjects could not choose the drugs that would be used.

The second reception of the combination pill is 100% because there was no discontinuation of the pill for 3 months and the incidence of pregnancy was not acquired in using both of these pills. It demonstrated that the pill's efficacy for 3 months of usage was 100%.

CONCLUSION

Pill A birth control has the same efficacy, safety and acceptance when compared to the use of birth control pills B for 3 months. Pill A can be used as an additional choice of birth control pills in Indonesia, given the same content as the innovator who had undergone previous studies. To be more accurate in assessing the efficacy, safety and acceptance of Pill A, further studies are needed for a longer period time of study, at least 12 months. For further research, Double-blind studies should be performed in choosing the subjects to reduce bias.

CONFLICT OF INTEREST

All authors declare there was no conflict of interest in this study.

ETHICS APPROVAL

This study has been approved by the Ethics Committee of Kariadi Hospital. All participants agreed to participate in this study prior to trial.

FUNDING

PT Catur Dakwah Crane funded this research.

AUTHOR CONTRIBUTION

All authors have contributed to this research process, including preparation, data collection, analysis, compilation, and approval to publish the manuscript.

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Table 2. **First, second-, and third-month Observation.**

Variable	Pill Type						p
	A-Pill			B-Pill			
	Mean±SD	Median (Min-Max)	N (%)	Mean±SD	Median (Min-Max)	N (%)	
Increase in weight (kg)							
1st Month	0.0±4.0	0.0 (-25.0-16.0)		1.0±4.0	0.0 (-13.0-13.0)		0.350[a]
Stable			36 (36.0)			40 (40,0)	
Up			39 (39.0)			40 (40.0)	
Down			25 (25.0)			20 (20.0)	
2nd Month	-1.0±11.0	-1.0 (-27.0-30.0)		1.0±12.0	1.0 (-43.0-39.0)		0.370[a]
Stable			6 (6.0)			3 (3.0)	
Up			45 (45.0)			54 (54.0)	
Down			49 (49.0)			48 (48.0)	
3rd Month	-1.0±11.0	-1.0 (-27.0-30.0)		1.0±12.0	1.0 (-43.0-39.0)		0.370[a]
Stable			5 (5.0)			5 (5.0)	
Up			47 (47.0)			47 (47.0)	
Down			48 (48.0)			48 (48.0)	
Blood Pressure							
1st Month (mmHg)							
Normotensive			100 (100.0)			100 (100.0)	-
Hypertensive			0 (0.0)			0 (0.0)	
Systole	115.0±7.0	120.0 (100.0-		115.0±7.0	120.0 (100.0-		0.690[a]
Diastole	75.0±6.0	130.0)		75.0±5.0	130.0)		0.620[a]
2nd Month (mmHg)		80.0 (60.0-80.0)			80.0 (60.0-80.0)		
Normotensive			100 (100.0)			100 (100.0)	-
Hypertensive			0 (0.0)			0 (0.0)	
Systole	115.0±7.0			115.0±7.0			0.840[a]
Diastole	76.0±6.0	120.0 (100.0-		75.0±5.0	120.0 (100.0-		0.260[a]
3rd Month (mmHg)		130.0)			130.0)		
Normotensive		80.0 (60.0-80.0)	100 (100.0)		80.0 (60.0-80.0)	100 (100.0)	-
Hypertensive			0 (0.0)			0 (0.0)	
Systole	115.0±7.0			115.0±7.0			0.840[a]
Diastole	76.0±6.0			75.0±5.0			0.260[a]
Menstruation Cycle		120.0 (100.0-			120.0 (100.0-		
1st Month (Days)	28.0±1.0	130.0)		28.0±2.0	130.0)		-
2nd Month (Days)	28.0±1.0	80.0 (60.0-80.0)		28.0±2.0	80.0 (60.0-80.0)		-
3rd Month (Days)	28.0±1.0			28.0±2.0			-
Menstruation Change		28.0 (24.0-34.0)			28.0 (21.0-35.0)		
1st Month		28.0 (24.0-34.0)			28.0 (21.0-35.0)		
Yes		28.0 (24.0-34.0)	5 (5.0)		28.0 (21.0-35.0)	6 (6.0)	0.890[b]
No			95 (95.0)			94 (94.0)	
2nd Month							
Yes			7 (7.0)			4 (4.0)	0.270[b]
No			93 (93.0)			96 (96.0)	
3rd Month							
Yes			7 (7.0)			4 (4.0)	0.270[b]
No			93 (93.0)			96 (96.0)	
Duration of Menstruation							
1st Month							
≤ 8 days			98 (98.0)			99 (99.0)	0.610[a]
> 8 days			2 (2.0)			1 (1.0)	
2nd Month							
≤ 8 days			98 (98.0)			99 (99.0)	0.610[a]
> 8 days			2 (2.0)			1 (1.0)	
3rd Month							
≤ 8 days			98 (98.0)			99 (99.0)	0.610[a]
> 8 days			2 (2.0)			1 (1.0)	

Variable	Pill Type						p
	A-Pill			B-Pill			
	Mean±SD	Median (Min-Max)	N (%)	Mean±SD	Median (Min-Max)	N (%)	
Tampon Change							
1st Month			98 (98.0)			96 (96.0)	0.690[b]
≤ 3 times			2 (2.0)			4 (4.0)	
> 3 times							
2nd Month			97 (97.0)			97 (97.0)	1.000[b]
≤ 3 times			3 (3.0)			3 (3.0)	
> 3 times							
3rd Month			97 (97.0)			97 (97.0)	1.000[b]
≤ 3 times			3 (3.0)			3 (3.0)	
> 3 times							
Metrorrhagia							
1st Month			1 (1.0)			3 (3.0)	0.620[b]
Yes			99 (99.0)			97 (97.0)	
No							
2nd Month			4 (4.0)			0 (0.0)	0.050[b]
Yes			96 (96.0)			100 (100.0)	
No							
3rd Month			0 (0.0)			0 (0.0)	-
Yes			100 (100.0)			100 (100.0)	
No							
Dizziness							
1st Month			1 (1.0)			2 (2.0)	1.000[b]
Yes			99 (99.0)			98 (98.0)	
No							
2nd Month			0 (0.0)			1 (1.0)	1.000[b]
Yes			100 (100.0)			99 (99.0)	
No							
3rd Month			0 (0.0)			0 (0.0)	-
Yes			100 (100.0)			100 (100.0)	
No							
Nausea and Vomiting							
1st Month			1 (1.0)			0 (0.0)	0.480[b]
Yes			99 (99.0)			100 (100.0)	
No							
2nd Month			1 (1.0)			0 (0.0)	0.480[b]
Yes			99 (99.0)			100 (100.0)	
No							
3rd Month			0 (0.0)			0 (0.0)	-
Yes			100 (100.0)			100 (100.0)	
No							
Dyspnea							
1st Month			0 (0.0)			0 (0.0)	-
Yes			100 (100.0)			100 (100.0)	
No							
2nd Month			0 (0.0)			0 (0.0)	-
Yes			100 (100.0)			100 (100.0)	
No							
3rd Month			0 (0.0)			0 (0.0)	-
Yes			100 (100.0)			100 (100.0)	
No							
Fluor							
1st Month			0 (0.0)			0 (0.0)	-
Yes			100 (100.0)			100 (100.0)	
No							
							-

Variable	Pill Type						p
	A-Pill			B-Pill			
	Mean±SD	Median (Min-Max)	N (%)	Mean±SD	Median (Min-Max)	N (%)	
2nd Month							
Yes			0 (0.0)			0 (0.0)	-
No			100 (100.0)			100 (100.0)	
3rd Month							
Yes			0 (0.0)			0 (0.0)	-
No			100 (100.0)			100 (100.0)	
Bleeding							
2nd Month							
Yes			1 (1.0)			3 (3.0)	0.620[b]
No			99 (99.0)			97 (97.0)	
3rd Month							
Yes							
No							
Depression							
1st Month							
Yes			0 (0.0)			0 (0.0)	-
No			100 (100.0)			100 (100.0)	
2nd Month							
Yes			0 (0.0)			0 (0.0)	-
No			100 (100.0)			100 (100.0)	
3rd Month							
Yes			0 (0.0)			0 (0.0)	-
No			100 (100.0)			100 (100.0)	

[a]Mann Whitney test; [b]Chi-Square test; *Statistically significant if p-value less than 0.05

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FINAL GRADE

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GENERAL COMMENTS

Instructor

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