Research Article

Drospirenone–Ethinyl Estradiol and Cyproterone Acetate in Moderate–Severe Acne with Hyperandrogenism: A Randomized Double-Blind Trial

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Abstract

Background: Acne vulgaris is a health problem experienced by 85% of people in Indonesia. The highest prevalence is in women, who attempt to treat acne vulgaris. Unsuccessful acne vulgaris therapy is associated with hormonal influences, the stimulation of the sebaceous glands by androgen hormones. Hyperandrogenism is experienced by 10% of women in Indonesia. The main therapy for hyperandrogens is ciproterone acetate. Drospirenone combined with ethinyl estradiol, apart from sparing pregnancy, is also thought to be effective in treating clinical symptoms of hyperandrogenism. Currently, there is no study on drospirenone for acne and hyperandrogen therapy in Indonesia.

Objective: Determine the efficacy of treatment combination 3-mg drospirenone and 20-microgram ethinyl estradiol as management of choice for moderate-severe acne vulgaris and symptoms of hyperandrogenism (hirsutism, secondary amenorrhea, and oligomenorrhea) for 3 cycles**.**

Method: A randomized clinical trial with a double-blind study was done. Consecutive sampling is based on a random allocation table. A total of 42 subjects were diagnosed with moderate-severe acne vulgaris with hirsutism, secondary amenorrhea and/or oligomenorrhea at RSCM, divided into 2 groups, 21 subjects using drospirenone 3 mg combined with 0.030 mg ethinyl estradiol (DRSP/EE) and 21 subjects using 2 mg ciproterone acetate and 0.035 mg ethinyl estradiol (CRPN/EE), followed with examination of free testosterone check in laboratory. There was 1 subject who dropped out (Cyproterone group). The duration of therapy was 3 months then evaluation of acne lesions, Ferriman Gallwey score (FG score), and menstrual period.

Results: Characteristics of study subjects with the majority of subjects aged 25-35 years, 51,3%. The education level of most subjects about 57,1%, was a bachelor's degree. Testosterone levels at the start of the study were 1,41±0,64 for the DRSP/EE group and 1,32±0,48 for the CRPN/EE group. For the degree of acne, 85.7% of subjects using DRPS/EE and 85% of subjects using CPRN/EE had reduced acne lesions with a P value of 0.645. For hirsutism by calculating the FG score, 61.9% of the subjects using DRSP/EE and 50% of the subjects consumed CPRN/EE had a decreased FG score with a value of P value 0.443, and their menstrual period became regular for 85.7% of the subjects using DRSP/EE and 90% of the subjects using CPRN/EE with P value 0.645.

Conclusion: Drospirenone and ethinyl estradiol are as effective as cyproterone acetate combined with ethyl estradiol as treatment of moderate to severe acne vulgaris, hirsutism, secondary amenorrhea, and oligomenorrhea.

Keywords: acne vulgaris, cyproterone acetate, drospirenone, hirsutism, secondary amenorrhea.

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INTRODUCTION

Acne vulgaris is a skin problem most often experienced by women, around 9.4% of the entire population in the world.[1] In Indonesia, acne vulgaris is a common skin disease that occurs in 85-100% of a lifetime. The highest prevalence is in adolescent girls aged 14-17 years (83-85%).[2] Acne vulgaris can cause psychological problems for society. More than 50% of acne vulgaris sufferers experience stress due to comments or jokes from their family or community. Therefore, women try to treat acne vulgaris. The therapy used is topical treatment and antibiotics.[3] According to

a study, unsuccessful treatment is associated with stimulation of the sebaceous glands by androgen hormones.[3] Hyperandrogenism is experienced by 10% of women in Indonesia and is a collection of symptoms that best describes the state of hyperandrogenemia in women. Other symptoms of hyperandrogenism are acne, hirsutism, alopecia, and menstrual disorders (amenorrhea and oligomenorrhea).[4]

The main therapy for hyperandrogenism is ciproterone acetate. A recent study states that drospirenone can be used to treat hyperandrogenism. Drospirenone combined with ethinyl estradiol, apart from contraception, is thought to be effective in treating clinical symptoms of hyperandrogenism. Maloney et al, in 2008 in America, showed drospirenone and ethinyl estradiol reduced acne by 46.3% compared to placebo 30.6%.[5] In 2009, Jerry Tan, et al in Canada, reported 49% reduced acne lesions using therapy with drospirenone 3 mg and ethinyl estradiol 0.030 mg, compared with a placebo of 33%.[6] Another study using drospirenone and ethinyl estradiol for the treatment of hyperandrogenism was the 2013 study by Caruso et al in Italy, which reported a 78.5% reduction in Gallwey Ferrimen scores in hirsutism patients, reduced acne lesions by 58.7% and 56% reduced seborrhea.[7]

Drospirenone is a synthetic progesterone that has a chemical structure similar to spironolactone and is also structurally similar to progesterone, so drospirenone is an antiandrogen that can occupy androgen receptors, causing a reduction in acne vulgaris lesions, hirsutism, secondary amenorrhea, and oligomenorrhea. When using 20 micrograms of drospirenone it has an anti-mineralocorticoid effect, a hormone produced by the adrenal glands, which plays a role in sodium and water retention. Drospirenone has an anti-mineralocorticoid effect so it does not increase body weight and increase blood pressure.[8] Ciproterone acetate is a more potent antiandrogenic than drospirenone used for standard hyperandrogenism therapy. From a multicenter study, ciproterone acetate reduced moderate-severe acne and seborrheic lesions by up to 80% during 6 months of therapy. But cyproterone acetate can increase body weight and long-term use, increases the risk of thrombosis after 1 year of therapy (RR 6.35; 95% CI: 5.09-7.93), stroke (RR 1.4; 95% CI: 0.97-2.03); and heart infarction (RR 1.47; 95% CI: 0.83-2.61).3 Therefore, this study aimed to determine the effectiveness of drospirenone and ethinyl estradiol in moderate-severe acne vulgaris with symptoms of hyperandrogenism, namely hirsutism, secondary amenorrhea, and oligomenorrhea.

METHODS

A randomized controlled trial (RCT) was done on all of the women who had acne vulgaris and/or hirsutism and/or secondary amenorrhea and/or oligomenorrhea who came to Dermatoveneerology Outpatient Department at Cipto Mangunkusumo Central General Hospital from January 2020 to January 2023. Women with thromboembolism or serious cardiovascular problems, mental disorders, severe headache, or liver disease, using drugs that induce liver enzymes such as Barbiturates, Phenytoin, Carbamazepine, and Rifampicin, high blood pressure (systolic > 160 mmHg, diastolic > 100 mmHg), participation in another clinical study within the last 3 months, and subject refuse participation in the study were excluded. Dropout criteria have not finished the study, died, or infected by COVID-19. The study protocol was approved by the Ethics Committee of the Faculty of Medicine, University of Indonesia on July 8th, 2019 (KET-773 / UN2.F1 / PPM.00.02/ 2019), extended until January 2024. All participating women had signed an informed consent form.

All subjects underwent anamnesis, physical examination, and acne vulgaris examination carried out by a dermatoveneerologist at the Dr. Cipto Mangunkusumo Central General Hospital. Next, the subject had blood drawn in the laboratory to examine free testosterone. Then the subjects were randomly and double blindly allocated into two groups, namely drospirenone 3 mg combined with ethinyl estradiol (YasminR) 0.030 mg (experimental groups) and ciproterone acetate 2 mg combined with ethinyl estradiol (Diane^{R}) 0.035 mg (control group) for 3 months. The drug was given by a general practitioner who was trained before. In the third month, symptoms of hyperandrogenism were evaluated by a trained general practitioner, namely menstrual disorders, hirsutism, and acne vulgaris. The data that has been collected is then verified, coded, and analyzed using the IBM SPSS version 25 program to carry out hypothesis testing in accordance with the Chi-Squared test.

RESULTS

The total sample submitted was 46 subjects, but 42 subjects met the inclusion criteria, 4 subjects did not meet the inclusion criteria. Of the 42 subjects, 1 subject dropped out due to uncomplete laboratorium data and follow-up. At the end of the study, there were 41 subjects across two groups, with 21 subjects in the experimental group and 20 subjects in the control group.

Table 1 shows the characteristics of the study subjects as a whole. Most of the subjects were aged between 25-35 years, namely 20 subjects (51.3%) in the drospirenone group and 19 subjects (48%) in the ciproterone group. The educational level of most subjects, 51.7%, was undergraduate. The baseline free testosterone levels were 1.41 ± 0.64 in the drospirenone group and 1.32 ± 0.48 in the ciproterone group.

At the beginning of this study, 21 subjects were treated with drosperinone-ethinyl estradiol, consisting of 17 subjects (53.1%) with moderate acne vulgaris and 4 subjects (44.4%) with severe acne vulgaris. In the control group, 20 subjects were treated by cyproterone acetate-ethinyl estradiol, 15 subjects (46.3%) had moderate acne vulgaris and 5 subjects had severe acne vulgaris.

Patients with hirsutism have an initial Ferriman Gallwey (FG) score calculated. There is no hirsutism if the FG score is less than 8, moderate hirsutism if the FG score is 8-15, and severe hirsutism if the FG score is less than 15. Of the total of 21 subjects who received the combination of drospirenone and ethinyl estradiol, 16 subjects (53.3%) had hirsutism mild or no hirsutism and 5 subjects (45.5%) had moderate hirsutism. In the control group, 14 subjects (46.7%) had no hirsutism or mild hirsutism, and 6 subjects (54.5%) had moderate hirsutism. The FG score before therapy in the experimental group, drospirenone-ethinyl estradiol, and in the control group, the cyproterone acetate and ethynil estradiol was not statistically significant (p-value = 0.823) and the FG score after therapy in the experimental group and control group was also not statistically significant (p-value = 0.823) Thus, there was no difference in FG scores between the experimental group, drospirenone-ethinyl estradiol and the control group, cyproterone acetate-ethinyl estradiol, before and after therapy. A total of 14 subjects (46.7%) had secondary amenorrhea and 7 subjects with oligomenorrhea, treated with drospirenone therapy. In the control group, 16 subjects received cyproterone acetate and ethinyl estradiol, (53.5%) with secondary amenorrhea and 4 subjects with oligomenorrhea.

Table 1. The characteristic of the study subject.

Variable	Drospirenone + Ethinyl Estradiol (n=21)	Ciproterone acetate + Ethinyl Estradiol (n=20)	*P-value*
Age Group			0.744[f]
25 years – 35 years	20 (51.3)	19 (48.7)	
36 years – 45 years	1 (50)	1 (50)	
Education			0.265[cs]
Completed elementary – high school	5 (38.5)	8 (61.5)	
D3 or Bachelor's degree	16 (57.1)	12 (42.9)	
BMI category			0.393[cs]
Normal	9 (60)	6 (40)	
Overweight & Obesity	12 (46.2)	14 (53.8)	
Free testosterone	1.41 ± 0.64	1.32 ± 0.48	0.629[t]
Acne severity			0.719[f]
Medium	17 (53.1)	15 (46.9)	
Severe	4 (44.4)	5 (55.6)	
Hirsutism (FG score)			0.655[cs]
No hirsutism/mild hirsutism	16 (53.3)	14 (46.7)	
Moderate hirsutism	5 (45.5)	6 (54.5)	
Ferriman Gallwey Score			
Before therapy	5.62 ± 2.89	5.65 ± 2.72	0.823[ww]
After therapy	3.95 ±2.31	3.90 ±2.40	0.968[mw]
Menstrual disorders			0.335[cs]
Secondary amenorrhea	14 (46.7)	16 (53.3)	
Oligomenorrhea	7 (63.6)	4 (36.4)	

f: Fisher's test; cs: Sci-Square Test; t: Unpaired T-Test; mw: Mann-Whitney test

Subjects were given therapy for 3 months. Afterwards, the relationship between drosperinone and cyproterone acetate with acne vulgaris severity, hirsutism, and menstrual disorder

Table 2. The relationship between drosperinone and cyproterone acetate with acne vulgaris severity.

Type of drugs	Post treatment acne vulgaris		*P-value*
	Reduced	Not reduced	
Drospirenone + Ethinyl Estradiol (n=21)	18 (85.7)	3 (14.3)	0.645[f]
Ciproterone acetate + Ethinyl Estradiol (n=20)	17 (85)	3 (15)	

f: Fisher's test; cs: Sci-Square Test; t: Unpaired T-Test; mw: Mann-Whitney test

Table 3. The relationship between drosperinone and cyproterone acetate with hirsutism.

Type of drugs	Post treatment hirsutism		*P-value*
	Reduced	Not reduced	
Drospirenone + Ethinyl Estradiol (n=21)	13 (61.9)	8 (38.1)	0.443[cs]
Ciproterone acetate + Ethinyl Estradiol (n=20)	10 (50)	10 (50)	

f: Fisher's test; cs: Sci-Square Test; t: Unpaired T-Test; mw: Mann-Whitney test.

Table 4. The relationship between drosperinone and cyproterone acetate with menstrual disorder.

Type of drugs	Post treatment menstrual disorder		*P-value*
	Reduced	Not reduced	
Drospirenone + Ethinyl Estradiol (n=21)	18 (85.7)	3 (14.3)	0.645[f]
Ciproterone acetate + Ethinyl Estradiol (n=20)	18 (90)	2 (10)	

f: Fisher's test; cs: Sci-Square Test; t: Unpaired T-Test; mw: Mann-Whitney test.

DISCUSSION

This study was carried out at Dermatoveneerology Outpatient Department at Dr. Cipto Mangunkusumo Central General Hospital. For 1 year the cosmetics clinic was closed due to the COVID-19 pandemic. Therefore, the subjects were taken through social media such as Facebook and Instagram. During the COVID-19 pandemic, March 2020, subjects who met the inclusion criteria came to RSCM for anamnesis, physical examination and laboratory examination, but for acne examination by a dermatovenerologist consultant from Cipto Mangunkusumo Central General Hospital was via telemedicine, then the medicine was sent by delivery service.

In this study, the majority of subjects were aged 25-35 years, with 51.3% in the drospirenone group, in accordance with a study in Turkey, Batukan et al., in 2007, reported that 100 subjects took part in the drospirenone or cyproterone acetate study for hirsutism therapy, the largest age is 25 years from the age range of 18 to 35 years.[9] A study in Thailand, by Chanyachailer, et al., reported that the age of 25-35 years (72.6%) was commonly found in 208 subjects.[10] Postmenopausal women rarely experience hyperandrogenism symptoms. According to a study in Birmingham, by Collier et al, in 2007, the prevalence of acne vulgaris decreased with increasing age, at the age of 50 years or more, the prevalence of acne was 7.3-15.3%,[11] usually associated with metabolic problems such as obesity, insulin resistance, diabetes mellitus type 2. Apart from acne, other symptoms include hirsutism, androgenic alopecia, and clitoromegaly.[12] Women of reproductive age who work have high levels of stress[13], Chiu et al., 2003 stated that increased stress has a significant correlation with an increase in acne severity.[14] The hypothalamus produces Corticotropin-Releasing Hormone (CRH), which increases in stressful situations. CRH stimulates the synthesis of Adrenocorticotropic Hormone (ACTH) by the

adrenal glands, causing an increase in androgen hormones, resulting in increased sebum production, increased sensitivity of hair follicles, and ovulatory dysfunction.[15]

About 60% of our subjects had a normal BMI. This was in accordance with Li Li, et al, in 2020, reporting the characteristics of subjects with normal BMI (22.07 ± 4.09 kg/m^2).[16] Normal free testosterone levels were 0.1-0.9 nmol/liter. In our subjects, the free testosterone levels were examined at the baseline, which was 1.41 ± 0.64 in the drosperinone group. In hyperandrogenism states, the testosterone binding capacity is reduced by androgens, as well as the level of globulin binding which is also reduced. The androgenic effect depends on the unbound testosterone fraction being able to move freely from the vascular compartment into the target cells. Thus, total testosterone concentrations may be within the normal range in women with hirsutism but because the level of globulin binding is suppressed by the effects of androgens, the amount of free and active testosterone is increased.[8]

Acne vulgaris is divided into mild, moderate, and severe degrees. Acne vulgaris is said to be reduced and effective to the treatment if there are 10% reduction in the number of lesions, these includes papules, pustules, or comedo. A total of 85.7 and 85% of subjects from each group had reduced acne lesions. In this study, drospirenone compared with cyproterone acetate did not have a statistically significant difference in the proportion of acne vulgaris (p-value = 0.600), so it can be said that drospirenone is as effective as cyproterone acetate for treating moderate to severe acne vulgaris.

This study follows a previous study in Poland, Stopient, et al., reported Drospirenone (3 mg drospirenone and 0.03 mg ethinyl estradiol) caused a reduction of acne vulgaris after 6 months of treatment and cyproterone acetate (2 mg Cyproterone acetate and 0 .35 ethinyl estradiol) caused a reduction of acne vulgaris after 3 months of treatment by 40%. The duration of therapy in previous studies was longer, which was 6 months.[17]

Van Vloten, et al, in the Netherlands, reported subjects with moderate acne vulgaris who received drospirenone therapy reduced the number of acne by 62.5% from baseline and the cyproterone acetate subject group reduced by 58.8%. Subjects were treated for 9 months. Statistically, there is no difference (non-inferiority margin) of 25%, so it can be concluded that drospirenone has the same effectiveness as cyproterone acetate in the treatment of moderate and severe acne vulgaris.[18] Drospirenone is an anti-mineralocorticoid and antiandrogen, which occupies the androgen receptor in the sebocyte nucleus in sebaceous glands thereby reducing sebum production. This leads to reduced acne formation.[18]

The reduction in FG scores after 3 months of therapy was 61.9% in the experimental group and 50% in the control group. The FG score before therapy in the experimental group was 5.62 ± 2.89 and after therapy, it was reduced to 3.95 ± 2.31, and likewise in the control group the FG score after therapy was 3.90 ± 2.40, which concluded that drospirenone was as effective as cyproterone acetate for treating hirsutism.

This study is inconsistent with that in Poland, which reported that cyproterone acetate (2 mg cyproterone acetate and 0.25 mg ethinyl estradiol) caused an 83% reduction in hirsutism after 6 months of therapy. In another study in Turkey, Batukan, et al., reported 50 patients with moderate and severe hirsutism who were treated with drospirenone combined with ethinyl estradiol for 6 months with FG scores reduced by 67%, and FG scores reduced by 78% after 12 months of therapy.[16] According to Stopient, et al, cyproterone acetate was more potent in reducing FG scores by 83% after 12 months of therapy, but increased the risk of thrombosis after 1 year of therapy (RR 6.35; 95% CI: 5.09-7.93), stroke (RR 1.4; 95% CI: 0.97-2.03); and heart infarction (RR 1.47; 95% CI: 0.83-2.61).[17] The reduction in FG scores in this study was around 60%, which is different from other studies, because the duration of therapy was shorter, namely 3 months. The life cycle of a hair follicle is 6-12 months, so effective treatment for hirsutism is 6 months or more.[19]

After 3 months of therapy, around 85.7% of subjects who received the combination of drospirenone and ethinyl estradiol, and 90% of subjects who received ciproterone acetate and ethinyl estradiol therapy, had regular menstruation. This shows that drospirenone and cyproterone acetate are not statistically significant for menstrual disorders (p-value = 0.645), so it can be said that drospirenone is as effective as cyproterone acetate for the management of secondary amenorrhea and oligomenorrhea. This study is following a study in China, by Li Li et al., which reported 80.71% of subjects (138 in total) with regular menstrual cycles after Drospirenone

therapy combined with ethinyl estradiol for 3 months.[16] Drospirenone and ciproterone acetate combined with ethinyl estradiol cause an increase in sex-hormone binding globulin (SHBG), which will reduce free testosterone, thereby causing a decrease in androgens.[20]

In this study, 3 mg drospirenone was used combined with 20 µg ethinyl estradiol (YasminR) and 2 mg cyproterone acetate combined with 35 µg ethinyl estradiol (Diane). The side effect of using these two drugs was spotting (29%) which occurred in the second month of therapy. Apart from that, headaches, and intestinal tract disorders such as nausea, vomiting, bloating, mood changes, and depression.[21] In this study, no patients reported any side effects from either group.

Medication compliance was monitored by calculating the remaining amount of medication at the end of the month before the next medication was given. There was 1 patient who did not continue therapy because she often forgot to take her medication due to being busy working even though she had been reminded by the study assistant.

This study had several limitations, which were 1) there was no assessment of acne vulgaris and FG score every month; 2) there was no repeated testosterone test at the end of treatment; and 3) the duration of therapy was not long enough to determine the optimal duration of therapy.

CONCLUSION

Drospirenone combined with ethinyl estradiol is as effective as cyproterone acetate combined with ethinyl estradiol for the treatment of moderate to severe acne vulgaris, hirsutism, and menstrual disorders (secondary amenorrhea and oligomenorrhea). Further study is needed with a longer duration to determine the optimal therapy time and evaluate the post-therapy testosterone levels.

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