Research Report

Comparison of administration of estradiol valerat 1 mg and 2 mg to improve squamous epithel maturation of Pap Smear preparation on postmenopausal women

Perbandingan penggunaan estradiol valerat 1 mg dan 2 mg untuk meningkatkan maturasi epitel skuamosa sediaan tes Pap pada perempuan pascamenopause

Ika Sri Purnamaningsih, Dwiana Ocviyanti, Endy Muhardin Moegni

Department of Obstetrics and Gynecology
Medical Faculty of University of Indonesia/
Dr. Cipto Mangunkusumo Hospital
Jakarta

Abstract

Objective: To determine the most effective dose of estradiol valerat (daily oral administration of 1 mg or 2 mg for 14 days) to improve squamous epithel maturation of Pap Smear on postmenopausal women.

Method: Seventy one postmenopausal women with atrophic Pap Smear were participated in this randomized double blind clinical trial. 35 subjects received estradiol valerat 1 mg and the other 36 subjects received estradiol valerat 2 mg. After daily oral administration of estradiol valerat for 14 days, second Pap Smear were performed to evaluate epithel maturation. The side effects were also evaluated in this study.

Result: There were 5 subjects whom lost to follow up due to refused to perform second Pap Smear and 1 subject was drop out due to nausea. 65 subjects were included in final analysis. Estradiol valerat 2 mg was significantly more effective than estradiol valerat 1 mg in improving epithel maturation of Pap Smear preparation on postmenopausal women. There were no complain about nausea and vaginal bleeding. Leukorhea occurred more frequently in the 2 mg group.

Conclusion: Daily oral administration of 2 mg estradiol valerat was more effective than estradiol valerat 1 mg in improving squamous epithel maturation of Pap Smear on postmenopausal women with minimal side effect (leukorhea).

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Keywords: Pap Smear, postmenopausal women, estradiol valerat, epithel maturation of Pap Smear

Abstrak

***Tujuan**: Menentukan dosis estradiol valerat (1 mg atau 2 mg per oral tiap hari selama 14 hari) yang paling efektif untuk meningkatkan maturasi epitel skuamosa sediaan tes Pap pada perempuan pascamenopause.*

***Metode**: Uji klinis tersamar ganda dengan randomisasi ini melibatkan 71 perempuan pascamenopause yang hasil tes Papnya menunjukkan gambaran atrofi. 35 subjek mendapatkan estradiol valerat 1 mg dan sisanya (36 subjek) mendapatkan estradiol valerat 2 mg. Pasca pemberian estradiol valerat per oral selama 14 hari, dilakukan tes Pap ulang untuk menilai peningkatan maturasi epitel dan dinilai efek samping obat.*

***Hasil**: Tercatat 5 subjek lost to follow up karena menolak tes Pap ulang dan 1 subjek drop out karena merasa sangat mual dengan obat yang diberikan. Terdapat 65 subjek yang dimasukkan dalam analisis akhir. Estradiol valerat 2 mg secara bermakna lebih efektif meningkatkan maturasi epitel skuamosa sediaan tes Pap pada perempuan pascamenopause dibandingkan estradiol valerat 1 mg. Tidak terdapat keluhan mual atau perdarahan per vaginam. Leukorhea lebih banyak terjadi secara bermakna pada kelompok dosis estradiol valerat 2 mg.*

***Kesimpulan**: Estradiol valerat 2 mg per oral tiap hari selama 14 hari lebih efektif dibandingkan dosis 1 mg untuk meningkatkan maturasi epitel skuamosa sediaan tes Pap pada perempuan pascamenopause dengan efek samping minimal berupa leukorhea.*

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***Kata kunci**: tes Pap, perempuan pascamenopause, estradiol valerat, maturasi epitel sediaan tes Pap*

Correspondence: Ika Sri Purnamaningsih, Department of Obstetrics and Gynecology Madical Faculty of University of Indonesia.
Jl. Salemba Raya 6, Jakarta Pusat, Telp: 081519016728. Email: ikamoe80@yahoo.com

INTRODUCTION

Demographic study predict that by the year 2020, postmenopausal women will constitute 17.3% of the adult population.[1] With this ageing population, more postmenopausal women are presenting for routine medical care including screening for cervical cancer.

Cervical cytology (Pap Smear) as screening tool face some significant problems and pitfalls when performed to postmenopausal women. The atrophic changes in the genital tract of postmenopausal women may result in cellular changes falsely interpreted as precancerous lesion and can lead to substantial difficulty in recognizing dyskaryotic cells.[2] We reported six cases of postmenopausal women during a 2 years periode (2008-2009) who were referred to colposcopy clinic in Dr. Cipto Mangunkusumo hospital due to abnormal cervical cytology, 2 of them with smear report of ASCUS, 1 with LSIL, and 3 with HSIL. All women had atrophic portio and unsatisfactory colposcopies. After 10-14 days administration of oral estrogen, cervical smear showed benign cellular changes due to atrophy with inflammation. Colposcopy finding showed low grade CIN on 4 women, while the others remain unsatisfactory. The biopsy confirmed cervisitis on all women.

The false information given to the patient will result in psychological, financial burden, and overtreatment of surgery.

Since there are some significant problems and pitfalls of cervical cytology in postmenopausal women, we recommended to all health providers who performed screening to be aware of the atrophic changes. Cytologist and colposcopist should be aware too, and do not in haste judging a woman without concerning the menopause factor. The atrophic changes can be temporarily reserved by short-term administration of estrogen which can improve squamous epithel maturation of Pap Smear preparation on postmenopausal women and increase the acuracy of Pap Smear.

Some study mentioned that estrogen administration could improve genital tract atrophic condition and assist the interpretation of Pap Smear on postmenopausal women.[2-8] But there is still no standard of preparat and dose of estrogen which effective to improve squamous epithel maturation. That is why in this study we compare the effectivity of two dose of estradiol valerat (Progynova® 1 mg and 2 mg) in improving squamous epithel maturation of Pap Smear preparation on postmenopausal women.

METHODS

The study was conducted from December 2009 to January 2010 at Pisangan, Jatinegara and Dr. Cipto Mangunkusumo Hospital. The study population were all postmenopausal women at Jakarta at the time the research perfomed. Subjects were recruited by consecutive sampling method, who fullfill inclusion criteria age less than 65 years old, willing involved in this study and exclusion criteria Pap Smear preparation did not show athrophic smear, diagnosed cervical cancer and precancerous lesion, using hormonal drugs, have history of endometrium and breast malignancy, have history of cerebrovascular and coronary disesase, chronic liver disease, and using tuberculosis drugs. This study had also been approved by the university of Indonesia ethical commission.

Seventy one postmenopausal women with atrophic Pap Smear participated in this randomized double blind clinical trial. At the first visit, we assessed clinical appearance of the portio and sensation of pain during inspeculo insertion was also noted. We divided sample into two groups by simple random sampling. 35 subjects received estradiol valerat (Progynova®) 1 mg and the remaining 36 subjects received estradiol valerat 2 mg. After daily oral administration of estradiol valerat for 14 days, second Pap Smear were performed to evaluate epithel maturation. We also evaluate the side effects, clinical appearance of the portio and sensation of pain when inspeculo performed.

Cytology assessment were performed by two experienced cytologist at the laboratory of cytology at Dr. Cipto Mangunkusumo Hospital.

RESULTS

There were 5 subjects whom lost to follow up due to refusal to perform second Pap Smear and 1 subject was drop out due to nausea. 65 subjects were included in final analysis. Subjects had a mean age of 54 years (range: 46-64 years). The majority were housewife (60%) and had education level at highschool (40%).

Mean parity were 3 (range: 0-8) and mean postmenopausal period were 5 years (range: 1-21 years).

We found that not all postmenopausal women had athropic portio. 4.6% of the subjects still showed squamo-clumnar junction at the portio. All of the first Pap Smear preparation showed inflammatory background, but only one preparat specified as inadequate specimen.

Estradiol valerat 1 mg had effectivity of 84.4% and estradiol valerat 2 mg 100% to improving epithel maturation of Pap Smear on postmenopausal women. Estradiol valerat 2 mg was significantly more effective than estradiol valerat 1 mg (p: 0.024). (Table 1)

Table 1. Bivariat analysis of estradiol valerat dose with epithel maturation improvement.

Dose of Estradiol Valerat	Epithel Maturation Improve		Epithel Maturation Not Improve		p
	n	%	n	%	
1 mg	27	84.4	5	7.7	0.024
2 mg	33	100	0	0	

Other factors which influence quality of Pap Smear preparation are specimen adequation and inflamatory background. On the second Pap Smear, 28% subjects from the dose group of 1 mg and 39% subjects from the dose group of 2 mg showed improvement of inflammatory background. The difference between two group was not significant in improving inflammatory background of Pap Smear preparation (p: 0.337). (Table 2).

Table 2. Bivariat analysis of estradiol valerat dose with improvement of inflammation background on Pap Smear preparation

Dose of Estradiol Valerat	Inflammation Background on Pap Smear Preparation After Administration of Estradiol Valerat				p
	Inflammation +		Inflammation -		
	n	%	n	%	
1 mg	23	72	9	28	0.337
2 mg	20	61	13	39	

There was no complain about nausea and vaginal bleeding. But, we had one subject who drop out due to nausea, this subject had gastritis as predisposing factor. Leukorhea occurred more frequently in the 2 mg group (p: 0.011). (Table 3)

Table 3. Bivariat analysis of estradiol valerat dose with leukorhea

Dose of Estradiol Valerat	Leukorhea		No Leukorhea		p
	n	%	n	%	
1 mg	26	81.25	6	18.75	0.011
2 mg	33	100	0	0	

We noted five subjects who lost to follow up. The concern of lost to follow initially was due to the side

effect which eventually may affect our final analysis. However, after interview with those subjects, we found out that the reason was the pain while inspeculo, it made them afraid to perform second Pap Smear. The pain during inspeculo is an important factor that influence compliance and comfort of the women in performing Pap Smear. About 92% subjects felt uncomfortable and pain during inspeculo at the first Pap Smear, that was due to atrophic vaginitis. But after 14 days administration of estradiol valerat all subjects have no complain of pain during inspeculo because of the leukorhea.

DISCUSSION

Estradiol valerat was proven effective to improve squamous epithel maturation of Pap Smear preparation on postmenopausal women. By statistical analysis in this study, 2 mg dose significantly more effective than 1 mg dose with same administration periode.

Some study mentioned benefit of estrogen administration on postmenopausal women to improve quality of epithel of genital and urinary tract. Main objective of these studies are to manage the signs and symptoms of urogenital atrophy.[4,8] Other studies tried to find benefit of estrogen to allow easy differentiation of areas of dysplasia from the normal mucosa on colposcopy view.[3,5,6]

There has not been any study which directly find estrogen benefit to improve squamous epithel maturation of Pap Smear preparation on postmenopausal women. Marx P[8] used CEE 0.3 mg for 16 weeks for managing atrophic vaginitis and there was highly significant increase in Vaginal Maturation Index compared to placebo treatment.

This study use estradiol valerat because estradiol valerat is group of natural estrogen with high biology activity. It has less effect on endometrial proliferation. Other reasons were drug availability in the market and there were two doses available which are 1 and 2 mg. Most of studies used conjugated equin estrogen to find benefit of estrogen administration on postmenopausal women. There were two preparation, topical and oral estrogen. The topical preparation could be better in term of its less systemic effect. However due to drug availability and consideration of simplicity and comfort of oral preparation we decided to choose oral preparation. It will influence patient compliance to take the medicine.

The duration of administration for 14 days in this study was quite effective to improve epithel maturation. But if we want the effect of eversion of transformation zone in order to get satisfactory colposcopy finding, it seem that we will need longer duration of estrogen administration. Galhardo[4] used CEE 0.625 mg for 3 months to improve epithel quality of genital tract. Marx P[8] used CEE 0.3 mg for 16 weeks to manage atrophic vaginitis. A study from Japan used CEE 1.25 mg for 14 days to allow easy differentiation of areas of dysplasia from the normal mucosa on colposcopy.[6] Spitzer[7] used topical estrogen for 2-3 weeks to achieve the same effect.

There were no side effect nausea and vaginal bleeding on the subject that we analyzed. But patient complained about leukorhea which was not comfortable, and this occured more frequent on 2 mg dose and it statistically significant. Marx P[8] found that on the administration of CEE 0.3 mg for 16 weeks, leukorhea was the most common complain. In our study, lekorhea occured on 81.25% subject of dose 1 mg group and 100% subject of dose 2 mg group.

On the other side leukorhea had benefit to resolve pain during inspeculo, and it will influence the compliance and comfort of postmenopausal women in performing Pap Smear.

Estrogen administration can cause nausea, vaginal bleeding due to endometrium hyperplasia, and leukorhea. The incident of side effect will vary depend on the dose and duration of administration.

On this study we did not find nausea and vaginal bleeding. But we noted 1 subject who dropped out due to heavy nausea. After evaluation, we found that this subject had predispose factor of gastritis and randomly she was on the 2 mg dose. But in this study the correlation between history of gastritis and nausea effect after estrogen administration can not be analyzed. Vaginal bleeding did not occur because the administration duration was only 14 days, and estradiol valerat has low proliferative effect on the endometrium.

CONCLUSION

Daily oral administration of 2 mg estradiol valerat was more effective than estradiol valerat 1 mg in improving squamous epithel maturation of Pap Smear on postmenopausal women with minimal side effect (leukorhea).

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