ARTICLE

The efficacy of oral Micronized Progesterone versus Medroxyprogesterone Acetate in the control of mild to moderate abnormal uterine bleeding – ovulatory Dysfunction (AUB-O) in Adolescents: An Open Label Randomized Controlled Trial

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OBJECTIVES: To determine the efficacy of micronized oral progesterone (OMP) versus Medroxyprogesterone Acetate (MPA) in the control and regulation of mild to moderate abnormal uterine bleeding in adolescents with ovulatory dysfunction.

MATERIALS AND METHODS: This is an open labelled Randomized Controlled Trial. Fifty patients with mild to moderate abnormal uterine bleeding were randomized to treatment with Medroxyprogesterone Acetate or Oral Micronized Progesterone.

RESULTS: There was no significant difference in the control of bleeding for patients with moderate abnormal bleeding. There was no significant difference in the regularity of cycles and length of bleeding once the patients were started on cyclic dosing. There was a difference in amount of bleeding (1-3 pads versus 2-4 pads for MPA and OMP respectively), but both were within normal amount. The adverse effects experienced for patients taking OMP was significantly more compared to MPA.

CONCLUSION: Oral Micronized Progesterone is just as effective as Medroxyprogesterone Acetate in the control and regulation of mild to moderate abnormal uterine bleeding in adolescents with ovulatory dysfunction. However, it was associated with more adverse effects.

KEYWORDS: *Abnormal Uterine Bleeding, Combined Oral Contraceptive Pills, Oral Micronized Progesterone, Medroxyprogesterone Acetate*

INTRODUCTION

Abnormal uterine bleeding is one of the most common reasons for consultation in the adolescent gynecology clinic. Sixty percent of these adolescents will have bleeding caused by anovulatory cycles secondary to immature Hypothalamic-Pituitary-Ovarian axis, while the rest would be caused by bleeding disorders and other non-structural causes[1]. The current treatment regimen for these patients is to give a combined oral contraceptive regimen, or a progestogen, usually in the form of medroxyprogesterone acetate (MPA).

However, both regimens may have significant side effects[2]. In the recent years, a newer preparation of progesterone, oral micronized progesterone (OMP), has been introduced in the market. It is said to be closer to the natural form of progesterone, which is produced by the ovary, rather than the current synthetic progestogens being used. It is already a part of the options for management in the Clinical Practice Guidelines for Abnormal Uterine Bleeding from the Philippine Obstetrical and Gynecological Society, [3,] but these guidelines do not state if they can also be used for adolescents. In this age group there has been no actual study regarding its efficacy, although some treatment guidelines abroad have already included its use in AUB. Thus, we wanted to find a safer alternative for the adolescent age group.

Abnormal uterine bleeding (AUB) has a myriad of possible causes. It is defined as the "departure from a normal menstrual cycle pattern". The FIGO has classified them into 2 categories, the first having structural causes (PALM), and the second having structurally normal anatomy (COEIN) but with abnormal bleeding. For our purposes, the study focused on the category of non-structural causes, because structural causes are very rare in the adolescent age group[4]. We focused specifically on ovulatory dysfunction as a cause for AUB. The normal menstrual cycle in adolescents is typically around 21-45 days, lasting 3-7 days, consuming 3-4 pads per day. A departure from this cycle would be classified as abnormal. In terms of classification of severity of bleeding, we adapted the following classification:

Mild	Longer menses (>7 days) or shorter cycles < 3 weeks for 2 months in succession, with slightly or moderately increased bleeding, a usually normal (>12 g/dL) or mildly decreased (10-12 g/dL) hemoglobin value
Moderate	Moderately prolonged or frequent (every 1-3 weeks) menses, with moderate to heavy bleeding and a hemoglobin level of ≥10 g/dL
Severe	Heavy bleeding with a hemoglobin level of<10 g/dL

There is really no consensus on the treatment for AUB-O for adolescents[1]. Anovulatory AUB can be treated with progestogens alone or oral contraceptive pills (OCPs). There is a paucity of data from randomized trials regarding the treatment of HMB in adolescents. Nonetheless, there are a variety of regimens that appear to be equally effective[5]. Most clinicians utilize combined oral contraceptive pills or progestins/ progestogens for the control of AUB-O. In a study by Munro et al, they compared combined oral contraceptive pills and medroxyprogesterone acetate, and concluded that both medications may be effective and well tolerated[12]. In some treatment protocols for management of acute bleeding in adolescents, oral micronized progesterone is included as well. For adults, it is an accepted part of the treatment protocol. However, there is no evidence on the efficacy of micronized progesterone in the adolescent age group.

Progestogens differ in structure from the natural progesterone produced by the body but is designed to act on progesterone receptors[6]. The effect that is aimed in the uterus is achieved for both, which is stabilization of the endometrium. Progestational agents are an ideal alternative for women who have a contraindication to estrogen. They quickly treat AUB by stabilizing endometrial fragility; inhibiting the growth of the endometrium by triggering apoptosis; inhibiting angiogenesis; and stimulating the conversion of estradiol to the less active estrone. It prevents ovulation and ovarian steroidogenesis, interrupting the production of estrogen receptors and the estrogen-dependent stimulation of the endometrium, leading to an atrophic endometrium[7]. However, side effects for progestogens include irregular bleeding, decrease in bone density, androgenic affects, fluid retention, headache, and mood disturbance. Some studies have shown an increased risk for breast cancer when given in combination with estrogen as hormone replacement therapy for menopausal women[6]. On the other hand, micronized progesterone is progesterone, which is plant based, usually extracted from yams and soybeans[8], unlike the more commonly used progestins which are synthetic progesterone-like compounds. Micronization of progesterone to particle sizes of 10 mm increases the available surface area of the drug and enhances the aqueous dissolution rate and intestinal absorption of progesterone. To enhance intestinal absorption, it is suspended in peanut oil[10]. In studies with adolescents, some current treatment guidelines have included oral micronized progesterone in their algorithms. However, there are no studies documenting its' actual effect on this population.

The main objective of this study is to determine the efficacy of micronized oral progesterone versus medroxyprogesterone acetate in the control and regulation of mild to moderate abnormal uterine bleeding in adolescents with ovulatory dysfunction. The specific objectives were as follows: 1) to describe the demographic profile of adolescents with abnormal uterine bleeding with ovulatory dysfunction in relation to[13] age, menarche, menstrual bleeding patterns and severity of bleeding; 2) to determine the efficacy of progesterone (oral micronized progesterone) versus Medroxyprogesterone Acetate in terms of percentage of adolescents whose bleeding stopped within 5 days (for moderate AUB), mean days until bleeding stopped for those with moderate AUB, timing of next menstrual cycle when cyclic dosing is started (mean interval), number of pads used when cyclic dosing is started (amount of blood, and mean duration of bleeding when cyclic dosing is started. Lastly, we wanted to determine the adverse effects following treatment with oral micronized progesterone and medroxyprogesterone acetate.

METHODOLOGY

This was an open labelled randomized trial that compared the efficacy of micronized oral progesterone versus Medroxyprogesterone Acetate in the control and regulation of mild to moderate abnormal uterine bleeding in adolescents with ovulatory dysfunction seen in the Pediatric and Adolescent Gynecology in the Philippine Children's Medical Center from July 2021-July 2022.

Inclusion criteria included all adolescent girls aged 10-18 complaining of mild to moderate abnormal menstrual bleeding who were assessed and interviewed by the pediatric and adolescent gynecology fellows in the clinic from July 2021-July 2022. Patients who had a probable coagulation disorder (with history of gum bleeding, epistaxis, prolonged bleeding from minor wounds or for dental extractions), were hemodynamically unstable, tagged as with severe bleeding or those who needed admission were excluded from the study. Micronized progesterone contains peanut oil, so those with allergies were not included.

The minimum number of participants was determined at 48 to achieve 80% power to detect a difference in regularity of cycles between the 2 groups using a two-sided two sample t-test. Twenty-five patients who received micronized oral progesterone (OMP) and twenty-five who had taken Medroxyprogesterone Acetate (MPA) were included in the study.

The informed consent/assent was presented to all eligible patients and their guardians. Those whose guardians agreed and signed the informed consent were randomized to one of two groups: oral micronized progesterone and medroxyprogesterone acetate. Randomization sequence was prepared by a third party, the allocation of the eligible patients was placed in sequentially numbered sealed envelopes with specific interventions. Only the co-investigator knew which intervention corresponded to the specific number. Depending on the severity of bleeding, the dosing was as follows. If mild, she received cyclic micronized oral progesterone at 200 mg per capsule on day 16 -25 of the menstrual cycle or started on medroxyprogesterone acetate 10 mg/tab on day 16-25 of the menstrual cycle. If bleeding is moderate, she was started on oral micronized progesterone 1 capsule until the bleeding stopped for at least one month, then was started on cyclic dosing once the bleeding has been controlled. For medroxyprogesterone acetate, she took 1 tablet daily for 1 month then started on cyclic regimen on day 16-25 of each cycle. Dosing was the same regardless of the age of the patient.

The baseline characteristics obtained from the patient are as follows: the age of the patient at present, the age of menarche, the menstrual bleeding pattern which led to the consult (prolonged bleeding, intermenstrual bleeding, heavy bleeding, amenorrhea, irregular menses), and the severity of bleeding.

Patient and mother were instructed to take the capsule on the same time each day, and to take note of when the bleeding stopped, the date of her next menstrual cycle, number of pads used per day, the number of days for the cycle and if there were any adverse effects noted. They were also given instructions on how to fill out a menstrual diary and to fill out the information during the duration of the study. They were given the medications for free after the process has been explained and the consent and assent forms have been signed. Medications were distributed by the Co-Investigator.

The primary investigator kept in touch with the mother and patient to monitor progress thru phone call or social media messengers. Re-evaluation was done if the bleeding persisted or increased in severity. They were contacted every month for two months via phone call. The third month marked their follow up in the clinic where data was reviewed by the investigator. A travel allowance of Php 500 for their return visit was given after the 3rd month of medication.

The costs of the medications were shouldered by 3 parties: Medroxyprogester-one Acetate was shouldered by Philippine Children's Medical Center; Oral Micronized Progesterone cost was shouldered by the main investigator, since it is not in the Philippine National Drug Formulary. Drug samples of Oral Micronized Progesterone from Besins Healthcare were also utilized for 10 of the participants.

The patient and the mother were asked to record information in a menstrual diary. For moderate bleeding, outcomes were measured as follows. First, how many days it took until the bleeding stopped, and the percentage of those whose bleeding stopped within 5 days. After one month, medication was stopped, and patients were instructed to wait for the start of the next cycle (Day 1 of menses). The patient and mother were asked to record when the first day of menses started, the number of pads per day, and how many days the menses lasted. Cyclic dosing was then started on Day 16-25 of the cycle.

For mild bleeding, cyclic dosing was started, meaning the tablets were taken on day 16-25 of each cycle. As in the protocol for moderate bleeding, patient and mother were asked to record when the first day of next menses started, the number of pads per day, and how many days the menses lasted.

Patients were also instructed to take note of perceived adverse effects in the menstrual diary. They were also instructed to note any other symptom that they perceive which is not included in the list of possible adverse effects.

The primary outcomes for the intervention were as follows: the days until the bleeding stopped for moderate bleeding

and the interval until the next menstrual cycle once cyclic dosing is started. Compliance to the medication was monitored thru the information they will log in their menstrual diary. The study was started once it was approved by the Institutional Research - Ethics Committee of this institution.

RESULTS

Out of the 25 patients per arm that were randomized, some were lost to follow up. For the MPA group, 3 patients were lost to follow up, and 1 patient had to be shifted to another medication as the bleeding did not stop after 5 days. For the OMP group, 5 patients were lost to follow up, 1 was shifted to severe dizziness after intake of the medication, and 1 had to be shifted to another medication as bleeding did not stop after 5 days of OMP. All in all, the drop out rate was 16%. Patients who were shifted to another medication were withdrawn from the study and not included in the calculation of the drop out rate. This can be seen in Figure 1.

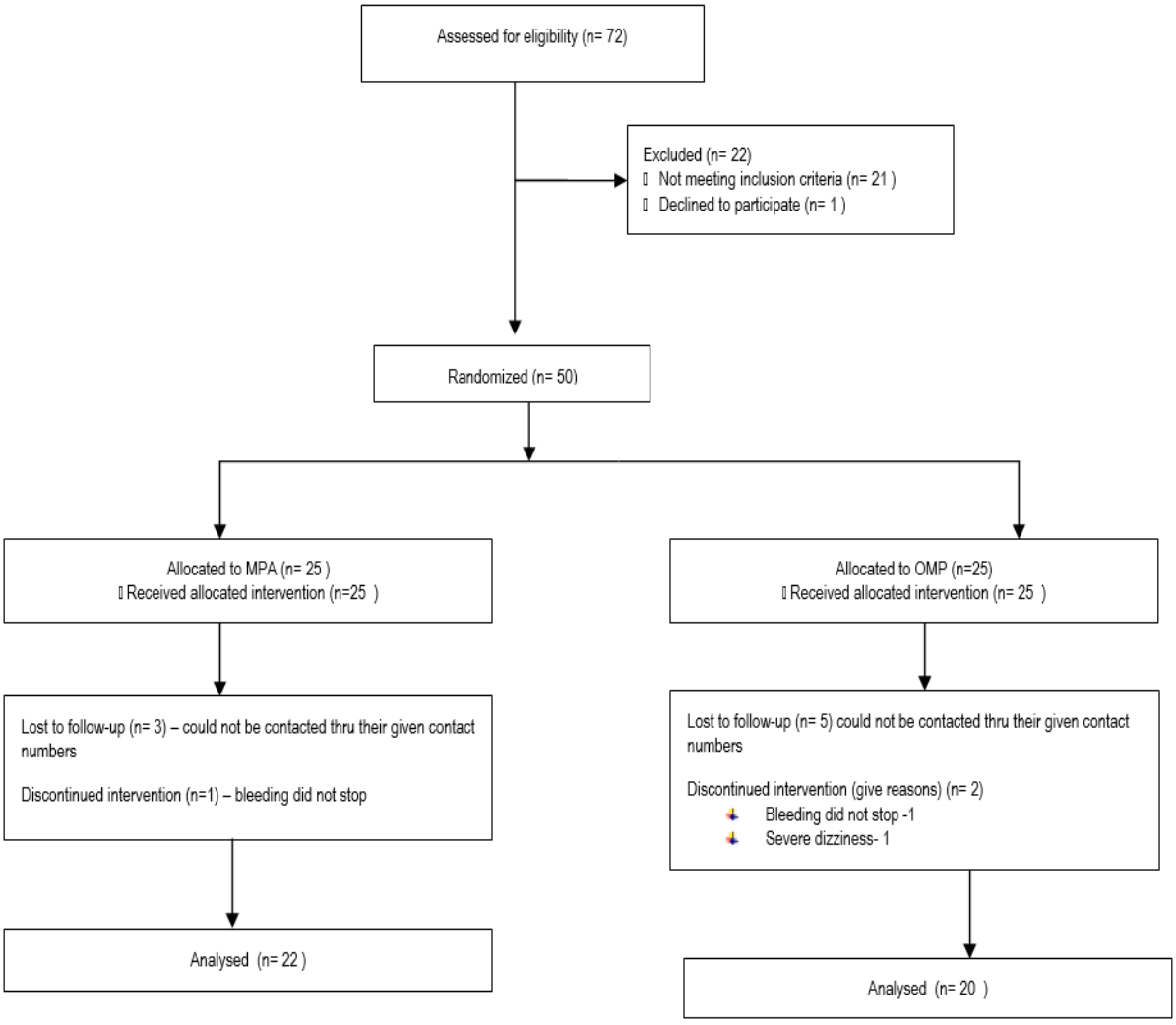

Figure I. *CONSORT Diagram*

Twenty-five patients who received micronized oral progesterone (OMP) and 25 who took Medroxyprogesterone Acetate (MPA) were included in the study. Though there were some who dropped out from the study, the information regarding their demographics was still used for the demographic profile. Table 1 shows that the two groups have no significant difference on their characteristics as both groups are around 15 years old with a mean age of menarche at around 11 years old. For both groups, the most common presentation was irregular menses and prolonged menses. On severity of AUB, we included 33 patients with mild bleeding, and 17 patients for moderate bleeding. For both groups, there was no significant difference in the number per group, per treatment arm. The study population was homogenous.

Table 2. Presence of Adverse Effects for Oral Micronized Progesterone (OMP) Versus Medroxy-progesterone Acetate (MPA) and Breakdown

	OMP (n=20)	**MPA (n=22)**	**p value**
Bleeding stops in 5 days, n, %			
Yes	5 (83.0)	8 (88.9)	1.000^{ns}
No	1 (16.0)	1 (11.1)	
Days until bleeding stop, mean ± SD	4.5 ± 1.0	4.4 ± 1.5	0.939 ^{ns}
Timing of next cycle (interval)			
Regular	15 (88.2)	17 (77.3)	0.438 ^{ns}
Irregular	2 (11.8)	5 (22.7)	
Number of Pads, n, %			
1 to 2 / 1 to 3	1 (5.3)	10 (45.5)	0.009*
2 to 3 / 2 to 4	12 (63.2)	6 (27.3)	
3 to 4/ 3 to 5	6 (31.6)	6 (27.3)	
Duration of Bleeding, mean ± SD	4.8 ± 1.4	5.4 ± 2.6	0.448 ^{ns}

*Significant, ns not significant

Table 3 shows the presence of adverse effects was significantly higher in OMP group as 56% of them experienced it, as compared to only 12% in the MPA group. Some of the adverse effects felt in the OMP group are dizziness, sleepiness, weakness, and headache, while the patients with adverse effects in MPA group all experienced sleepiness.

TABLE 3. *Efficacy of Oral Micronized Progesterone (OMP) Versus Medroxyprogesterone Acetate (MPA)*

	OMP (n=20)	MPA (n=22)	p value
Adverse effects, n, %			
Yes	14 (56.0)	3 (12.0)	0.001*
No	11 (44.0)	22 (88.0)	
Adverse effects breakdown			
Sleepiness	8	3	
Dizziness	11	0	
Weakness	2	0	
Headache	1	0	

DISCUSSION

Out of the 50 patients included in this study, the mean age was 14-15 years old. Most of them had their menarche at a mean age of 11-12 years old. There has been a decreasing trend of age at menarche over the years due to several factors. According to Tey et al, in the Philippines, the mean and median ages at menarche declined from 13.2 years and 12.6 years, respectively, among young women born in 1973-1977, to 12.9 years and 12.3 years, respectively, among those born in 1993-1997". [15] This is comparable to age of menarche in other Asian countries, with studies stating that Korean girls have menarche at an average age of 12.27 years and Chinese girls at 11.38 years old.

The most common presentation of abnormal bleeding in adolescents was irregular menses at 34 percent, which was followed by prolonged menses in 26% of the patients. This is comparable to a prospective cohort study done by Chung et al, where they reviewed menstrual disorders in 577 adolescents. Out of these, 47% presented with menorrhagia, prolonged menstruation, and short menstrual cycles, while the rest presented with amenorrhea or oligomenorrhea. [18]

In adolescents, structural causes of abnormal uterine bleeding are rare. Out of the non-structural causes, the most common reason of AUB in adolescents would be immaturity of the hypothalamic-pituitary-ovarian axis and associated anovulatory cycles. Usually, regular cycles are achieved within 2-3 years from menarche[4]. The pathophysiology during an anovulatory cycle is that estrogen continuously stimulates the endometrium but there is no ovulation, hence no progesterone production occurs. Progesterone is needed for stabilizing the endometrium, hence leading to unpredictable and heavy bleeding.[14] Aside from immaturity of the HPO Axis, other conditions which influence ovulation such as PCOS, systemic diseases and stress can cause ovulatory AUB [4].

There is really no consensus on the treatment for AUB-O for adolescents[1]. There is a paucity of data from randomized trials regarding the treatment of HMB in adolescents. Most clinicians utilize combined oral contraceptive pills or progestins/ progestogens for the control of AUB-O. Both progesterone and OCPS seem to be equally effective in treating the condition[5,12]. Whatever the treatment plan chosen, the main goals are the same. These are: to stop the acute episode of bleeding, prevent anemia, prevent absences from school and other activities, and to prevent the recurrence of heavy, prolonged or irregular bleeding[4]. In this study we chose to focus on progesterone as the treatment modality as other studies have already compared OCPs and synthetic progesterone.

Among the progesterones used to treat AUB, Micronized progesterone is one of the newer modalities. It is a progesterone which is plant based, usually extracted from yams and soybeans[8], unlike the more commonly used progestins which are synthetic "progesterone-like" compounds. Currently, OMP is utilized for conditions such as secondary amenorrhea, treatment for dysfunctional uterine bleeding, support for luteal phase deficiency, hormone replacement therapy, treatment for endometrial hyperplasia and other clinical conditions which would need progesterone[11] which makes it ideal for treatment of anovulatory AUB.

On studies with adolescents, some current treatment guidelines have included oral micronized progesterone in their algorithms. However, a search for studies documenting its' actual effect on this population was unsuccessful. In our study, there was no significant difference in the results for both the moderate and mild groups who were randomized to OMP and MPA. For moderate bleeding, OMP was just as effective as MPA in stopping acute bleeding within five days, as both were able to stop bleeding in 4.5 and 4.4 days respectively.

The data for cyclicity, bleeding duration and amount of bleeding was also comparable. For those on OMP, 88.2% were

able to achieve regular cycles while on the medication, lasting for a mean of 4.8 days consuming 2-4 pads per day. On the other hand, those on MPA had regular cycles in 77.3% of patients, lasting for 5.4 days and consuming 1-3 pads per day. Though not statistically significant, patients in the MPA group experienced more irregular cycles. Progestogens are different in structure from natural progesterone produced by the body but the effect of stabilizing the endometrium is there.[6] However, it is also known that progestogens such as MPA do have a tendency to cause irregular bleeding.[6,19] Various studies and articles comparing treatment for abnormal uterine bleeding in adults show that Oral Micronized Progesterone is just as effective in regulating menses by helping patients achieve a more predictable cycle and reducing menstrual flow[20,21]. Review of literature did not show specific studies on exact amount of bleeding or number of pads used for MPA and OMP, though the results still showed that bleeding was controlled and pads used were still within normal amount.

There was a significant difference in adverse effects, as patients in the OMP group complained more of dizziness and sleepiness, which was one of the expected adverse effects for OMP, even in the adult population.[8,21] Out of all the participants, only one dropped out because she was unable to tolerate the dizziness after taking the medication. No participant had to be brought to the emergency room for treatment due to adverse effects.

According to Carswell et al, micronized oral progesterone is one of the options in ensuring that there is no uterine bleeding for adolescent patients using the dose of 100-200 mg of micronized progesterone per day[9]. They also state that the adverse effects for OMP may be limited to sedation and fatigue hence the rationale for giving the dosage at night[9]. One of the recommendations of this study is to utilize a dose of 100 mg instead of 200 mg since this was also effective for patients in the study of Carswell.

Adverse effects for Medroxyprogesterone Acetate include decrease in bone density (which can be reversed), androgenic effects, fluid retention, headache, and mood disturbance[7,19]. These adverse effects were mostly not reported by the patients using Medroxyprogesterone Acetate in this study. Instead, they noted sleepiness as an adverse effect. A review of literature did not come up with sleepiness as a adverse effect for MPA. This leads us to believe that this is a possible side effect for younger patients, although the percentage who complained of this was not significant. A greater study population is needed to make this conclusion. Another possibility is that since it was once the adverse effects listed in the menstrual diary, the patients may have been influenced by the existing chart of adverse effects.

Conclusion and Recommendation

Both oral micronized progesterone and Medroxyprogesterone acetate are effective in the control and regulation of menses for patients with Mild to Moderate Abnormal Uterine Bleeding. Our study showed that there was a comparable effect on stopping acute AUB within 5 days and helping in achieving regular cycles with normal duration and amount of flow. Significantly, there were more complaints of adverse effects for the OMP group.

Limitations of the study include the small sample size and follow up period of 3 months. Since this was done in the time of the pandemic, the sample size was expected to be small and just barely reached the minimum. Also, some of the data collected was subjective such as the assessment of the napkins used, and the adverse effects noted. A more systematic approach in recording, such as use of the Pictorial Blood Assessment Chart may be recommended. Also, since there are no studies utilizing OMP in the adolescent, we recommend that a lower dose such as 100 mg might also be favourable to this population and may bring about less adverse effects. Lastly, further studies should focus on one group (mild or moderate) rather than combining them both in one study.

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