CLINICAL STUDY

Single Dose Levonorgestrel and Two Regimens of Centchroman for Emergency Contraception

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Abstract

Objective: To investigate centchroman as an effective method of emergency contraception and to compare its efficacy and side effects with single and double dose of levonorgestrel regimen.

Materials and Methods: Hundred and fifty healthy women in reproductive age group seeking post coital contraception advice within 120 hours of single unprotected intercourse from Outpatient Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, New Delhi. The three regimens of emergency contraception given on random basis were 1.5 mg single dose levonorgestrel tablet-Group I, single 60 mg dose of centchroman-Group II, and 30 mg centchroman twice a day at an interval of 12 hours-Group III. The outcome measures were unintended pregnancy, pregnancy rates, prevented fraction, side effects and the timing of the first menstruation after treatment.

Results: The baseline characteristics of women were similar. Four women (2.7%) were lost to follow up and 146 women remained in the investigation. The pregnancy rate and the prevented fraction was 4% (2/50) and 50% in Group I, 2.1% (1/47) and 75% in Group II, and 6.1% (3/49) and 25% in Group III ($p>0.05$). There were no serious side effects and more than 90% women in all groups had menses within 2 days of the expected date.

Discussion: Single dose (60 mg) of centchroman is comparable to a single dose (1.5 mg) of levonorgestrel as a measure of emergency contraception.

Keywords: emergency contraception, levonorgestrel, centchroman, pregnancy rates

Özet

Acil Kontrasepsiyon İçin Tek Doz Levonorgestrel ile İki Centchroman Rejiminin Karşılaştırılması

Amaç: Centchromanın acil kontrasepsiyondaki etkinliğinin araştırılması ve tek veya iki doz olarak verilen centchromanın etkisinin levonorgestrel rejimleri ile karşılaştırılması.

Materyal ve Metot: Üreme çağında olan ve postkoital kontrasepsiyon amacıyla ayaktan merkezimize başvuran 150 sağlıklı kadın çalışmaya alındı. Randomize olarak verilen acil kontrasepsiyon yöntemleri şunlardı: Grup I, tek doz 1.5 mg levonorgestrel tablet; Grup II, tek doz 60 mg centchroman ve Grup III, 12 saat arayla iki dozda verilen 30 mg centchroman. Araştırılan sonuçlar istenmeyen gebelik oranı, engelleme oranı, yan etkiler ve tedavi sonrası ilk menstrüasyonun zamanı idi.

Sonuçlar: Kadınların temel değişkenleri benzerdi. Dört kadın (%2.7) kontrollere gelmediğinden, analiz 146 kadın üzerinden yapıldı. Gebelik oranı ve engelleme oranı sırasıyla Grup I' de %4 (2/50) ve %50, Grup II'de %2.1 (1/47) ve %75, Grup II'de ise %6.1 (3/49) ve %25 idi ($p>0.05$). Hiçbir olguda ciddi bir yan etki görülmezken, kadınların %90'ından fazlası beklenen menstrüasyon tarihinin iki gün öncesi veya sonrası menstrüasyon oldu.

Tartışma: Tek doz 60 mg centchroman acil kontraseptif olarak tek doz 1.5 mg levonorgestrel ile benzer etkinliğe sahiptir.

Anahtar sözcükler: acil kontrasepsiyon, levonorgestrel, centchroman, gebelik oranı

Introduction

The need for emergency contraception is increasing because of changing lifestyle, fear of unwanted pregnancies and complications from termination of pregnancies. Greater use of emergency contraception can potentially reduce the number of unplanned pregnancies.

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Methods of emergency contraception include administration of progestin only or combination estrogen progestin oral contraceptives, synthetic estrogen and conjugated estrogen, or antiprogestins and insertion of a copper intrauterine device (1); no mechanism having been singled out as specific for emergency contraception. Levonorgestrel is the preferred method over Yuzpe regimen due to its higher efficacy and fewer side effects. Levonorgestrel-only regimen has been shown to inhibit or delay ovulation. A 1.5 mg single levonorgestrel dose taken within 120 hours of single unprotected coitus is a very efficacious emergency contraception and can be substituted with two 0.75 mg doses 12 hours apart as reported in the World Health Organization (WHO) randomized multicentre trial in 2002 (2).

Centchroman, 3, 4 trans-2, 2-dimethyl-3-phenyl 4-p (β-pyrrolidinoethoxy) phenyl 7-methoxychroman, is a synthetic non steroidal estrogen. It is a safe and effective non hormonal oral contraception developed by Central Drug Research Institute, Lucknow but it has not been used as an emergency contraceptive. It is a unique, need-oriented contraceptive with long terminal half life of 168 hours in women, when exhibiting anti-implantation; and, despite a short half life in rats, exhibiting an estrogen antagonistic action of 120 hours (3-5). It prevents pregnancy by increasing the transport of zygote through oviducts, accelerating blastocyst formation and suppressing endometrial proliferation and decidualization (6-8). In phase II and III multicentric trials, it was shown that children born despite the use of this contraceptive method as well as the user failure pregnancies have shown normal milestones without any congenital anomaly (6). If it can be reasonably established that centchroman can be an effective emergency contraceptive in humans, then we can make a dedicated product specially packaged and labeled for use as an emergency contraceptive.

The aim of the present study was to investigate the use of centchroman as an effective method of emergency contraception and to compare its efficacy and side effects with single and double dose regimen of levonorgestrel.

Materials and Methods

One hundred and fifty women of reproductive age attending the Gynaecology Outpatient Department of Obstetrics and Gynecology, All India Institute of Medical Sciences and seeking post coital contraception advice were selected for the study. Clearance from the Institute's Ethics Committee was obtained before starting the present study. The women included in this investigation were those who had a single unprotected intercourse in the last 120 hours, were healthy and with menstrual cycles of 24-42 days duration. Women who were uncertain of their last menstrual period, were lactating, had used hormonal contraception within the current menstrual cycle and with contraindications to hormonal contraception were excluded from the study. A detailed history, the date and time of unprotected intercourse and also the date of last menses was recorded. A through general physical and local examination was done before recruitment. The subjects after informed written consent were then randomly allocated to one of the study groups. The three different regimens of emergency contraception taken in the study were 1.5 mg single dose of levonorgestrel tablet Group I, single 60 mg (2 tablets of 30 mg each) dose of centchroman Group II, and 30 mg centchroman (1 tablet of 30 mg) twice a day at an interval of 12 hours Group III. Each woman recruited was willing for termination of pregnancy in case of failure.

All of the women were asked to abstain from intercourse or use condoms till the next period; and, each was given a menstrual card to record all the events till the follow up visit which included date and time of tablets taken, dates of intercourse and any symptoms like vomiting, nausea, headache, dizziness, abdominal pain or spotting in between. Detailed records of subsequent menstruation were also to be noted. All women were advised to report after seven days of expected date of next period. Women who had not menstruated till then were subjected to urine pregnancy test and followed up till pregnancy termination.

Outcome measures

The primary outcome measure was an unintended pregnancy, confirmed by a positive pregnancy test or by ultrasound at follow up or both. Pregnancy rates as well as the estimated reduction in expected pregnancies or prevented fraction (1 minus observed pregnancies/expected pregnancies) were measured in the study. We estimated the expected number of pregnancies in each group by multiplying the number of women having unprotected intercourse on each day of the menstrual cycle by the probability of conception on that cycle day. Other outcome measures were side effects in the week after the start of treatment and the timing of the first menstruation after treatment.

Statistical analysis

The proposed sample size for the trial was 50 women per treatment group. To compare the efficacy of the 3 treatments, we calculated rates and relative risks by standard methods and their 95% confidence intervals (CI) with the Taylor series. The efficacy of the three groups at different intervals and of Group II and III with Group I were compared. We calculated the ratio of observed to expected pregnancies, the prevented fraction, their 95% CI using the Poisson distribution. The Stata 8.0 Software was used to test interactions between the treatment regimens and other variables like delay in treatment, timing of coitus and additional acts of intercourse. The women who were lost to follow up were excluded from the efficacy analysis because the respective outcomes were unknown. Data collection, interpretation and writing of the report were done by the authors.

Results

The total number of women enrolled were 150, assigned to 3 different groups of 50 women each, with Group I

receiving 1.5 mg levonorgestrel regimen, Group II receiving a single dose of 60 mg centchroman, and Group III receiving two doses of 30 mg centchroman. Each eligible woman coming for emergency contraception received one of these three regimens on a random basis. In all, outcome was unknown for 4 women (2.7%) who were lost to follow up despite attempts to reach them. The data of 50 women in Group I, 47 in Group II and 49 in Group III have been analysed.

As shown in Table 1, the baseline characteristics of women in the 3 treatment groups were similar. The mean age of the participants was 28.8 years in Group I, 28.7 years in Group II, and 27.9 years in Group III. A small number (20/146, 13.7%) had used emergency contraception in the past. Almost three fourths of subjects had used some contraception in the past (78%, 74.5%, 79.6% in Groups I, II and III respectively). About 70% of the women (68.4%, 100/146) cited failure of the barrier method, 25% had not used any contraception and 5.5% (8/146) had other contraception method failures as the reason for requesting emergency contraception. Treatment started within 24 hours of unprotected coitus in 20%, 27.7% and 40.8% and within 48 hours in 60%, 68.1%, 75.5% in Groups I, II and III respectively.

Of the 146 women included in analysis, 6 women (4.1%) were found to be pregnant after treatment (Table 2). All pregnancies were intrauterine, confirmed by transabdominal ultrasound and all 6 women went in for an induced abortion. The pregnancy rates in Group I, II and III were 2/50 (4%), 1/47 (2.1%) and 3/49 (6.1%), respectively. The number of expected pregnancies if no treatment had been given and proportions prevented by treatment are also given in Table 2. There was no statistically significant difference in the pregnancy rates between the three groups. The crude relative risk of pregnancy with single and double dose of centchroman and with single dose of levonorgestrel was 0.41 (0.05-3.51) and 1.98 (0.41-9.45), respectively. Three women who became pregnant, 1 each in Group I, II and Group III gave a history of unprotected intercourse after treatment in the same cycle. However we decided to keep them in the study as failures. When we reanalysed the results after excluding these failure cases as protocol violation, the crude pregnancy rate and prevented fraction were 2% and 75%, 0 and 100%, 4.08% and 75%, respectively, for Group I, II and III (data not shown). There was no significant difference in the results obtained for pregnancy rate after adjustment in turn for age, BMI and the reason for requesting emergency contraception between the three regimens ($p>0.05$, data not shown).

As shown in Table 3, there was no significant difference between the individual pregnancy rates in all three groups on the bases of the time interval between coitus and treatment within 72 hours and beyond ($p>0.05$). However, the combined pregnancy rate for all women was 3.35% vs 7.7% in women receiving treatment within 72 hours and beyond ($p=0.3$); 1/41 versus 1/9 in Group I, 1/38 versus 0/9 in Group II, and 2/41 versus 1/8 for Group III.

Side effects were uncommon in the seven days after starting the treatments (Table 4). No serious side effects were reported. Also, there was no significant difference in the proportion of

Table 1. Demographic profile

Characteristics	Group I (n=50)	Group II (n=47)	Group III (n=49)	*p*
Mean (±SD)				
Age (years)	28.8±4.9	28.7±6.1	27.9±4.5	0.68
BMI (kg/m^2)	21.9±3.6	22.6±4.7	22.4±2.8	0.57
Menstrual cycle (days)	29.1±2.1	29.6±2.4	29.3±3.1	0.58
Obstetric history				
Previous pregnancy	39 (78%)	33 (70.2%)	22 (44.9%)	0.002
Previous EC use	2 (4%)	8 (17%)	10 (20.4%)	0.04
Previous other contraception use	39 (78%)	35 (74.5%)	39 (79.6%)	0.83
Reason for EC				
No method	10 (20%)	11 (23.4%)	16 (32.6%)	No method vs
Condom failure	37 (74%)	34 (72.3%)	29 (59.2%)	method failure
Other method failure	3 (6%)	1 (2.1%)	4 (8.2%)	0.32
Time from coitus to treatment				
<24 hours	10 (20%)	13 (27.7%)	20 (40.8%)	0.27
25-48 hours	20 (40%)	19 (40.4%)	17 (34.7%)	
49-72 hours	11 (22%)	6 (12.8%)	4 (8.2%)	
>72 hours	9 (18%)	9 (19.1%)	8 (16.3%)	

EC: emergency contraception; BMI: body mass index.

women with each side effect among the three regimens. The side effects were more on day 2 and day 3 after the start of the treatments (data not shown). Unreported pregnancies in women lost to follow up could bias the results. However, this situation is unlikely to have happened. Having intercourse between treatment and the expected menses resulted in higher pregnancy rate in all three groups. More than 90% women in all groups had menses within 2 days of expected date.

Discussion

To the best of our knowledge the present trial is the first to study centchroman as an emergency contraceptive. This trial was initiated with the objective of establishing centchroman as an effective emergency contraception and comparing the efficacy of two different regimens of centchroman with that of 1.5 mg single dose levonorgestrel. Our study is limited by the small number of subjects enrolled. To prove statistically significant equivalence a larger trial is required.

Majority of women seeking emergency contraception in our study were young as also seen in previous multicentric trials (2,7). In our trial the failure rate within 120 hours of unprotected intercourse was 4%, 2.1% and 6.1% for Groups I, II and III respectively. In an earlier multicentric international trial a lower pregnancy rate of 1.47% with levonorgestrel single dose regimen has been reported compared to 4% as in present trial (2). After adjusting the expected pregnancies with the same conception probabilities, the single dose levonorgestrel regimen in the WHO trial prevented 82% whereas in the present study the prevented fraction was 50% (2). The difference could be due to the small sample size in this study and the differences in the inclusion and exclusion criteria of the two studies.

Table 2. Pregnancy rates and prevented fraction

Emergency contraception	Rate			Prevented fraction	Relative risk
	n	Pregnancies n (%)	Expected pregnancies		
Group 1	50	2 (4)	4	50% (0.01-0.09)	1.0
Group 2	47	1 2.1)	4	75% (0.02-0.06)	0.42 (0.05-3.51)
Group 3	49	3 (6.1)	4	25% (0.02-0.13)	1.98 (0.41-9.45)

Table 3. Pregnancy rates in treatment groups and time since unprotected coitus

Coitus to treatment interval	Group I n/N (%)	Group II n/N (%)	Group III n/N (%)	*p*	All women		
					n/N	Pregnancy rate	*p*
<24 hours	1/10 (10)	1/13 (7)	-/20 (0)	-	<72 hours	3.3	0.31
24-48 hours	-/20 (0)	-/19 (0)	2/17 (11.8)	-	4/120	(RR 1.0)	
48-72 hours	-/11 (0)	-/6 (0)	-/4 (0)	-			
>72 hours	1/9 (11.1)	-/9 (0)	1/8 (12.5)	-	2/26	7.7 (RR 2.31: 0.45-11.94)	

*RR: relative risk.

Table 4. Side effects within 7 days and the delay of menses

Symptoms	Group I n (%)	Group II n (%)	Group III n (%)	*p*
Nausea	7 (14)	2 (4.25)	2 (4.1)	0.10
Fatigue	1 (2)	1 (2.1)	4 (8.2)	0.21
Dizziness	5 (10)	-	-	0.01
Headache	4 (8)	5 (10.6)	7 (14.3)	0.60
Breast tenderness	1 (2)	-	1 (2)	0.62
Lower abdominal pain	1 (2)	3 (6.3)	4 (8.2)	0.38
Weakness	2 (4)	-	3 (6.1)	0.25
Delay of menses >7 days	3 (6)	3 (6.3)	1 (2)	0.54

Unprotected intercourse after starting the treatments in one woman each in three groups were included as failures in our study. As reported in earlier large multicentric trials, there are increased chances of failure with a delay in the intake for all emergency contraceptives. We also found that a trend towards a lower efficacy with longer duration after unprotected intercourse before the treatment was present for all three regimens combined. Centchroman regimens were also associated with higher pregnancy rates if there was intercourse between treatment and expected menstruation (2).

The side effects were rare and comparable in all three regimens. Overall, in our study the women reported comparable side-effects with those shown in previous trials with emergency contraception. The occurence of nausea were, respectively, 14%, 4.25% and 4.1% and of lower abdominal pain were, respectively, 2%, 6.3% and 8.2% for Group I, Group II and Group III compared to 14% in previous trials (2). More than 90% of women in all groups had menses within 2 days of expected date and only 6%, 6.3% and 2% in Group I, Group II and Group III, respectively, had delay of menses for more than 7 days. It is comparable to 5% for levonorgestrel regimen reported in an earlier trial (2).

Our findings support the earlier studies that levonorgestrel single dose regimen is a safe and efficacious emergency contraceptive. The centchroman regimen, especially the single dose regimen compared well with levonorgestrel single dose regimen both in terms of efficacy, safety and occurrence of side effects. Centchroman single dose regimen proved to be the most efficacious and with minimal side effects although, due to limited sample size, the observation was statistically insignificant. The pregnancy rate and the prevented fraction for single dose centchroman was 2.1% and 75% respectively compared to 4% and 50% with single dose levonorgestrel regimen. The relative risk of pregnancy with single dose centchroman compared to single dose levonorgestrel regimen was 0.41%.

Centchroman single dose regimen compared to the levonorgestrel single dose regimen, is safe and more efficacious if given as soon as possible after unprotected intercourse (1,2,9,10). Centchroman, with its unique combination of weak estrogenic and potent antiestrogenic properties, has, therefore, the ability to reduce the number of unwanted pregnancies safely. It acts as an anti-implantation agent by disrupting the balance between estrogen and progesterone and inhibiting the fertilized ovum from nidation. Centchroman is reported to accelerate ovum transport causing asynchrony between ovum transport and uterine receptivity preventing implantation (3,6). Centchroman as emergency contraceptive has a potential dual advantage of providing regular contraception if continued in the same cycle. As with levonorgestrel single dose regimen, there is no need for a scheduled follow up after centchroman single dose emergency contraceptive. The woman needs to be counselled to come for a follow up if the menses are delayed for a period of one week or more.

Conclusion

The preliminary observation made by our study suggests that centchroman single dose regimen is an alternative to hormonal emergency contraception with equal efficacy. This preliminary observation can be utilized to design future clinical trials and pharmacological studies with sufficient power to confirm or refute the efficacy of this alternative regimen. A wider choice of emergency contraceptive methods has the possibility of popularization of this form of emergency contraception. At the same time information about other contraceptive methods should be made available at the time of emergency contraception.

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