Comparison of single and multiple-dose methotrexate therapy for ectopic pregnancy: a clinical trail

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Abstract: Introduction: Ectopic pregnancy (EP) is potentially life threatening condition. Methotrexate (MTX)is widely used in treatment of EP. The aim of current study is to compare single dose and multiple doses of MTX in treatment of EP. **Methods:** In this randomized controlled trial 78 patients with unruptured EP who were hemodynamically stable and had EP size less than 4 cm were enrolled in the study during 2008-2011. All patients were undergone transvaginal sonography and β-HCG titration. Patients were randomly assigned into two groups either to receive 50mg/m^2 intramuscular Methotrexate(MTX)or 1mg/kg/day intramuscular MTX in days one, three, five and seven till β-HCG decreases at least 15%. Data were analysed using SPSS 20.0 software. **Results:** Baseline characteristics were similar in both groups. There was no significant difference between teo groups in treatment response.(P=0.255). β-HCG decreased percentage was significantly higher in single dose group in comparison with multiple dose group.(P=0.046). β-HCG decreased percentage wasn't significantly different in two groups. No difference was seen in two groups in drug side effect rate. **Conclusion:** Treatment of EP with single dose MTX is recommended because of lower costs and time needed.

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1. Introduction

Over the past decades, the occurrence of ectopic pregnancy (EP) has been noteworthy all over the world; currently the rate is nearly 2% of all pregnancies (1). It is reported to be the major cause of early pregnancy maternal deaths (2). Risk of death due to EP is higher than pregnancies resulting in live births or those voluntarily aborted. Moreover, after an EP, the chance of subsequent successful pregnancy is reduced. However, the advances in diagnostic methods and treatment of EP has decreased mortality rates of ectopic pregnancy (3). With early diagnosis and treatment, definite therapy of unruptured EP is feasible even before the onset of symptoms (4). There are two treatment modalities for EP, surgical and non-surgical intervention. Surgical treatments include salpingotomy, salpingostomy, salpingectomy, segmentala resection, and anastomosis. Methotrexate (direct local injection or systemic) has been used successfully to treat EP. Methotrexate is a folic acid antagonist that inhibits the enzyme dihydrofolate reductase and reduces the supplies of tetrahydrofolate which is a cofactor in the synthesis of DNA and RNA and necessary for cell division. Due to adverse effects, if necessary, higher dose can be used with leukoverin. Moreover, the risk of tubal rupture due to methotrexate has been reported to be from 7% to 14% (4). MTX is currently administered either via single does or multiple dose regimens to treat EP. Although, the single-dose treatment is easier to administer and monitor, it elevates the risk of treatment failure which is defined as remained in place EP. The most common side effects of methotrexate are reported to be liver problems (12%), followed by osteomatitis (6%) and gastroenteritis (1%) (5). Srivichai and others (6) in a study on 106 patients demonstrated the success of medical treatment in 90% of patients. But patients with higher βhCG level and larger adnexal mass in ultrasonography report were more likely to require surgical intervention. Many studies compared the therapeutic effects of MTX single dose and multiple dose regimens. Some studies have shown that compared to multiple dose regimen, single dose MTX has the same therapeutic effect with less side effects (3, 7). The purpose of this study was to compare the two methods of EP medical treatment (single dose and multiple dose) regarding their effectiveness and side effects.

2. Methods and Materials

This study was a single-blind clinical trial conducted during18 months period from April 15, 2008 to April 15, 2011 at Specialized Hospital of Obstetrics and Gynecology of Dr. Ali Shariati,

Bandar Abbas, Iran. The study was approved by the ethical committee of Hormozgan University of Medical Sciences. Institutional Review Board approval was also achieved before starting the trial. All patients and their husbands provided their written informed consent. The diagnosis of EP in all cases was confirmed by initial β-hCG level, transvaginal ultrasonography, and uterine sampling.

3. Patient Selection

The population of this prospective study consisted of 87 patients with unruptured tubal EP, gestational mass of less than or equal to 3.5 cm in ultrasonography report, no contraindications related to the use of MTX, and no hemodynamic instability. Exclusion criteria were hepatic, renal and active pulmonary diseases; peptic ulcer; immune deficiency status; alcohol abuse, and blood dyscreasia (8). Moreover, data was recorded regarding the patients' age, positive history of infertility, recent pregnancy through ovulation stimulation, gravidity, abortions, parity, previous history of EP and patient complaints like delayed menstruation, irregular bleeding, abdominal and pelvic pain. Patients were alternatively selected to be treated either with a single-dose or multiple- dose of MTX (9).

4. Protocol of Treatment

The two methods used for MTX administration for EP were as follows:

Single dose regimen: Informed consent was obtained from the patients after explaining the efficacy and side effects of the treatment. In the single dose regimen, 50 mg/m^2 intramuscular methotrexate was given on day one and hCG level was measured on days four and seven. If the hCG level did not decrease by 15% between day four and seven, a second dose of methotrexate was injected on day seven, hCG level was measured weekly until a level of 15 mlU/ml or less was achieved (10-11).

multiple dose regimen: In the multiple dose regimen, 1 mg/kg/day intramuscular methotrexate was given on days one, three, five and seven and 0.1 mg/kg/day intramuscular Citrovoram factor was administered on days two, four, six and eight until serum hCG level decreased 15% in 48 hours or four doses of methotrexate was given weekly until serum hCG level of 15 mlU/ml or less was obtained (12-13).

5. Statistical Analysis

The results are presented as frequencies, percentages, and mean ± standard deviation. Odd Ratio (OR) of main outcome with 95% CI, Kolmogrov-Smirnov test for normality, Student's t-test, were used for statistical analysis. Data analysis was carried out using SPSS software, version 12.0 (SPSS, Inc., Chicago, IL). P<.05 was considered statistically significant.

6. Results

Of 87 patients 41 (47.1%) were medically treated using the single-dose methotrexate protocol, and 46 (52.9%) were treated with multiple doses of methotrexate. The average age of the single-dose group was found to be 29.15±5.63 and for those treated with multiple-doses was 27.85±5.27. No statistically significant difference has been observed in age between the two groups.

Analysis revealed that 11patients in single-dose group and 4 patients in the multiple-dose group had a history of cesarean section, representing 26.8% and 8.7% respectively. Chi-Squared test results showed significantly higher rates of cesarean section among single-dose group compared to multiple-group (p= .025). Seventy patients (41.5%) in single-dose group and 4 patients (13.3%) in multiple-dose group had a history of EP. Statistically, single-dose group showed significantly greater history of EP (p= .003). Only one patient (2.4%) in single-dose group had a positive bulging cul-de-sac, while in multiple-dose group no case with a positive bulging cul-de-sac was observed. No statistically difference was observed between the two groups in this regard.

In this study Kolmogrov-Smirnov test, which is used to examine the normality of observations, was performed on the qualitative variables of βhCG at three different times, the size of EP mass, and the endometrial thickness. The initial review of normal variables revealed that some observations were not normal, after logarithmic transformation all of them followed normal distribution (p>.05). Hence, parametric tests such as independent samples t-test might be used to compare the groups.

As shown in table 1 the mean endometrial thickness in multiple-dose treatment group was significantly higher than single-dose group (p= .037). The mean value of initial β-hCG level found to be significantly higher in multiple-dose group than single dose group (p=.037).

The percent of the drop in βhCG levels in one period compared to the prior one was calculated as follows:

$$\frac{\text{Third day serum hCG} - \text{first day serum hCG}}{\text{first day serum hCG}} \times 100 = \text{percent of the drop in } \beta\text{hCG levels}$$

$$\frac{\text{Seventh day serum hCG} - \text{third day serum hCG}}{\text{third day serum hCG}} \times 100 = \text{percent of the drop in } \beta\text{hCG levels}$$

After calculating the percent of the drop in βhCG levels in the single and multiple-dose groups, they were compared in two groups using the independent samples t-test. As shown in table 2 it can be noticed that, in single-dose group the percent of drop in serum hCG levels on the seventh day

compared to the third day is significantly higher than multiple-dose group (p= .046). However, no significant difference was observed between the two groups regarding the percent of the drop in serum hCG levels on the third day compared to the first day.

The Chi-Squared test result (Table 3) detected no statistically significant difference between single-dose and multiple-dose regimens regarding response rate to treatment (p=0.255).

The results indicated fewer complications among patients in single-dose group than those in multiple-dose group. One patient in single-dose group experienced leukopenia. But the treatment continued and this complication did not cause exclusion of the patient from the treatment process. No significant difference was detected between the two groups in this regard.

Table 1 Comparison of mass size, endometrial thickness and initial βhCG in both groups

Day	Group	SD±mean	t	P-Value
Size of EP Mass(mm)	Single-dose	26.96±11.20	0.487	0.672
	Multiple-dose	25.84±9.74		
Endometrial thickness (mm)	Single-dose	8.61±3.20	-2.13	0.037*
	Multiple-dose	10.58±4.76		
Baseline βhCG	Single-dose	1176.01±1.38	-3.38	0.001*
	Multiple-dose	4990.37±1.81		

p<.05 is statistically Significant

Table 2 Comparison of percent of serum hCG drop changes

Percent of βhCG drop changes	Group	SD±mean	t-Value	p-Value
Third day to the first day	Single-dose	-28.76±24.68	-0.346	0.731
	Multiple-dose	-26.53±23.74		
Seventh day to the third day	Single-dose	-50.15±24.78	-2.13	0.046*
	Multiple-dose	-38.99±24.67		

The test is considered significant at the level of 0.05

Table 3 Comparison of response to treatment between single-dose and multiple-dose protocols

	Single-dose Group	Multiple-dose group	P-Value
Response to treatment	36 (87.8%)	35(76.1%)	0.255
Laparotomy due to pain	2(4.9%)	2(4.3%)	
Laparotomy due to tube rupture	3(7.3%)	9(19.6%)	

7. Discussion

This study compared single-dose and multiple-dose regimens of methotrexate in treating ectopic pregnancy. In our study no significant difference was observed between the two groups regarding the efficacy of two regimens of methotrexate for medical treatment of ectopic pregnancy. Although it was observed to be 87.8% and 76.1% for single-dose group and multiple-dose group, respectively. In spite of the fact that the significant results of this study is somewhat different from similar studies, yet considering factors such as differences in sample size, it can be concluded that the results of this study is consistent with the previous studies. Hence, the results of this study and most previous studies favor the use of single-dose methotrexate for the treatment of ectopic pregnancy. Guvendag and others (1) found a higher rate of treatment success in both groups. In their study no significant difference was detected between the two groups regarding the treatment success rate. But due to fewer side effects, single-dose therapy is recommended. The success rate in single-dose group has been reported to be 80.6%, whereas in our study it was found to be 87.8 percent. In multiple-dose group the success rate was 89.7% which was significantly more than our study (76.1%). Comparing these two studies, several points should be considered. The first point is related to the sample size, in Guvendag's study 120 women have been enrolled, which is higher than the sample size of our study. However, studies with small sample size (61 patients) has also been conducted (14). Another point is the success rate of treatment, although the difference between the two groups was not significant in none of the two studies, but in Guvendag's study the success rate in multiple-dose was found to be higher than single-dose group. These are inconsistent with our study (1). In another study by Guven and colleagues the success rates in multiple-dose and single-dose groups has been reported to be 56.7% and 83.9%, respectively (14). In this study the sample size is smaller than ours and the

differences that favor single-dose methotrexate therapy, unlike our study, was significant. Alleyassin and others conducted a study on a sample size bigger than our study. They found that the success rates in multiple-dose group to be slightly higher than single-dose group (15). The rates are 92.6% and 88.9%, respectively which are higher than the rates obtained in our study. Moreover, unlike our study, the higher rate is related to the multiple-dose group. Although, in this study no significant difference was observed regarding the success rates and complications in two groups, the use of single-dose methotrexate therapy has been suggested. The small sample size can be mentioned as the limitation of the study, although many studies have also been reported with lower sample size (14). Overall, given the results of our study single-dose methotrexate is recommended to be used for the medical treatment of ectopic pregnancy to save time and costs. However, it is suggested that more studies should be conducted on tubal patency in EP patients 6-4 months after being managed successfully with methotrexate. Also, given the methotrexate teratogenicity studies should be done on the minimum amount of time required to avoid pregnancy after the completion of the treatment.

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