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COMPARISON OF BETA-HCG TITRATION AT BASELINE AND 4TH DAY AFTER SINGLE DOSE OF METHOTREXATE IN PATIENTS WITH ECTOPIC PREGNANCY IN PREDICTING THE SUCCESS OF PHARMACOTHERAPY

TAYEBEH JAHED BOZORGAN, BEHNAZ AMIRNAZARI*,MAHTAB MOTEVASELIAN, SARAH BAHRAMZADEH AND MARAL BALESH

Department of Gynecology, Mahdieh Hospital, Shahid Beheshti University, Tehran, Iran.

ABSTRACT

Recent studies have shown that ectopic pregnancy is a potentially life-threatening emergency, accounting for 1% of prevalence. Methotrexate is a folic acid antagonist used as an option for treating ectopic pregnancy. Considering that the drug also has significant side effects, this study tended to treat patients with single-dose regimens and compare beta-hCG titration at baseline and 4th day of receiving the drug in predicting the success or failure of pharmacotherapy. The population of this study included EP patients without rupture referring to the Mahdieh Hospital during 2010-2015. This study was designed as a cohort study. First, EP patients without rupture were enrolled in the study. Serum beta-HCG level was examined at baseline and 4th day in all patients treated by single dose methotrexate (50 mg/m^2). T-test was used to compare parametric variables. To compare non-parametric variables in two groups, Mann-Whitney U test and Chi-square test were used and Fisher exact test was used, if necessary. Moreover, multi-variable regression analysis was used to predict hCG level for success. The results showed no significant difference in βhCG titration at baseline between two successful and unsuccessful groups in response to single dose methotrexate. There were interesting results in reducing βhCG titration between baseline and 4th day; this means that 81 (84%) out of 97 patients of the successful group had a decrease in βhCG level on the 4th day compared to baseline; therefore, single dose methotrexate was successful in 84% of patients with a 4th day beta drop. This study showed that βhCG level decreased on 4th day compared to baseline in 84% of patients who were successful in responding to a single dose methotrexate. However, βhCG level at baseline did not predict successful response to treatment.

KEYWORDS: ***beta-hCG titration, methotrexate, ectopic pregnancy***

BEHNAZ AMIRNAZARI*

Department of Gynecology, Mahdieh Hospital, Shahid Beheshti University, Tehran, Iran.

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INTRODUCTION

Recent studies have shown that ectopic pregnancy is a potentially life-threatening emergency, accounting for 1% of prevalence. Methotrexate is a folic acid antagonist used as an option for treating ectopic pregnancy. Although the drug is mainly used intramuscularly, gynecologists use this drug as a direct injection into the ectopic fetus guided by ultrasound. This drug is mainly based on blocking of dihydrofolate reductase.[1] In fact, this drug prevents cell division in the ectopic fetus. The decision to use methotrexate in an ectopic pregnancy is based on conditions of pregnancy and the patient herself. Accordingly, the major indications for administration of methotrexate are:[2] 1) hemodynamic stability and lack of evidence of ectopic pregnancy rupture; 2) pregnancy mass<4cm in the case of cardiac failure; 3) fully aware and reliable patient able to follow and do consecutive and continuous tests; 4) βhCG<5000 ml units per ml. A notable point about the use of methotrexate is the relationship between its failure frequency and βhCG level, so that the percentage of patients requiring surgery after administration of methotrexate is significantly related to beta-hCG levels. For patients with baseline βhCG<1000munit/ml, a single dose methotrexate will be associated with 1.5% failure rate. However, when beta-hCG level rises from 1000 to 5000, failure rate of pharmacotherapy increases by 4%. In cases where beta-hCG levels range from 5000 to 9999 munit/ml, failure rate of pharmacotherapy will rise to 14%; if βhCG increases by 10000 to 15000 munit/ml, this failure will also increase to 18%.[3] In contrast, methotrexate treatment regimens will also be in two forms, including single dose administration with a success rate of about 88.1% and multiple dose treatment with a success rate of about 92.7%.[4,5] Given that the drug also has significant side effects, single dose treatment is generally more concerned. Based on above, it can be concluded that predictors of success rate of methotrexate in treating ectopic pregnancy include the type of administration (single dose or multiple dose) and baseline βhCG hormone, mass size and presence of FHR effective factors in predicting success rate of treatment. Few studies have been conducted to compare the time of measuring beta-HCG titration as a predictor of success rate of treatment. In some studies, it has been shown that comparison of titration at baseline and titration on the 4th day after treatment with methotrexate could play a role in predicting therapeutic success of a single-drug regimen.[6] Therefore, this study tended to do this comparison in patients treated with a single-dose regimen and titration of beta-hCG at baseline and 4th day of administration in predicting success rate or failure rate of pharmacotherapy.

MATERIALS AND METHODS

This study was designed as a cohort study. First, patients with an ectopic pregnancy without rupture enrolled in the study. EP diagnosis was given in two ways: 1) viewing the ectopic gestational sac by transvaginal ultrasound; 2) constant or increasing rate of beta titration without viewing gestational sac. Inclusion criteria included: 1) hemodynamic stability and lack of evidence of ectopic pregnancy rupture; 2) gestational mass<4 cm in the presence of cardiac failure; 3) fully aware and reliable patient able to follow up and do continuous tests; 4) beta-hCG<5000munit/ml. Patients with methotrexate contraindications were not enrolled. Exclusion criteria included Beta>5000 units per liter, fetal heart rate and fluid in choledosac, sensitivity to methotrexate, lactation, immune deficiency, leukopenia, thrombocytopenia, anemia, active pulmonary disease, peptic ulcer, liver failure, kidney and blood disease, and patients who could not be followed up. The serum beta-HCG level at baseline and 4th day was examined in all patients treated with single-dose 50 mg/m^2 methotrexate. Changes in two groups and in success or failure of ectopic pregnancy treatment were determined. Demographics and physiological data of patients was recorded in pre-prepared information forms filled by a gynaecologist resident. Patient checklist archived in the hospital records was used to extract information. To analyze data, all quantitative variables were expressed as mean and standard deviation; qualitative variables were expressed as numbers (percentages). Normality of quantitative variables was investigated by Kolmogorov-Smirnov test and box diagrams. T-test was used to compare parametric variables. In order to compare non-parametric variables in two groups, Mann-Whitney U test and Chi-square tests as well as Fisher exact test was used, if necessary. A multivariable regression analysis was used to predict success of beta-hCG. All statistical tests were performed in two tails ($p<0.05$). The sample size was calculated based on the first type error α = 5% and test power (power = 80%).

STATITICAL ANALYSIS

Comparison of age, BMI and parity of patients showed no significant difference between the two

groups (p>0.05) (Table 1). However, there was a significant difference in EP history and gravidity between the two groups (p<0.05).

RESULTS

In this study, 194 patients with ectopic pregnancy were enrolled. This study was done in the form of a cohort study. By referring to their records, successful response of patients to a methotrexate dose was based on treatment or that the patient had to continue treatment or administration of next dose of methotrexate or laparotomy. Among these patients, 97 cases responded to single dose methotrexate successfully and 97 cases did not respond successfully.

Table 1
Demographic variables and gravid and parity of patients in two groups

	Successful (n=97)	Unsuccessful (n=97)	p-value
Age	28.6±5.4	30.9±3.9	0.27
BMI	24.5±3.63	24.3±3.54	0.34
History of EP	0%	27 (28%)	<0.001
Gravid			
G1	25	9	
G2	43	25	
G3	21	43	0.015
>G3	8	20	
Parity			
P1	45	48	
P2	28	27	0.067
>P2	24	22	

**P<0.001*

Comparison of βhCG at Baseline

Comparison of beta-hCG at baseline between two successful and unsuccessful groups in response to a single dose methotrexate showed no significant difference in baseline beta-hCG between successful group (2048 ± 1383) and unsuccessful group (1226 ± 2006; p = 0.87) (Figure 1).

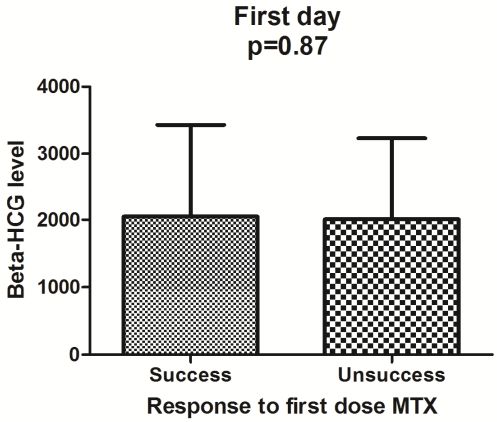

Figure 1
Beta-hCG level at baseline after administration of single dose methotraxate in two groups of successful and unsuccessful responses

Comparison of βhCG on 4th Day

Comparison of beta-hCG on 4th day between two successful and unsuccessful groups in response to a single dose methotrexate showed a significant difference in beta-hCG on 4th day between successful group (081 ± 665) and unsuccessful group (2308 ± 857; p = 0.0001) (Figure 2).

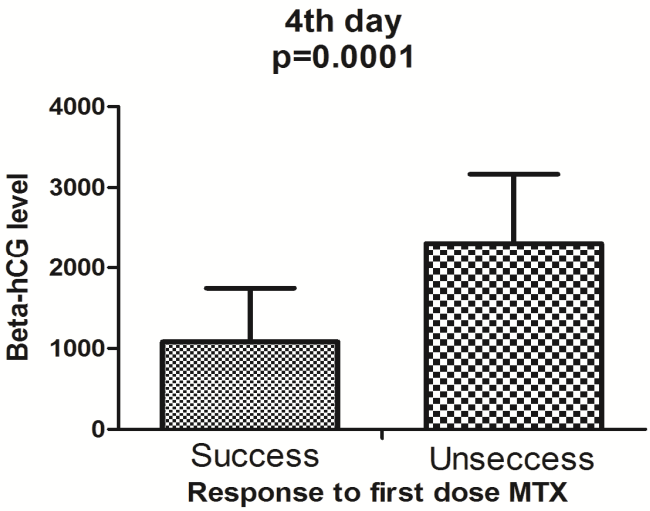

Figure 2
Beta-hCG level on 4th day after administration of single dose methotrexate in two groups of successful and unsuccessful responses

Comparison of βhCG on 7th Day
Comparison of beta-hCG on 7th day between two successful and unsuccessful groups in response to a single dose methotrexate showed a significant difference in beta-hCG on 7th day between successful group (1275 ± 939) and unsuccessful group (2719 ± 1276; p = 0.0001) (Figure 3).

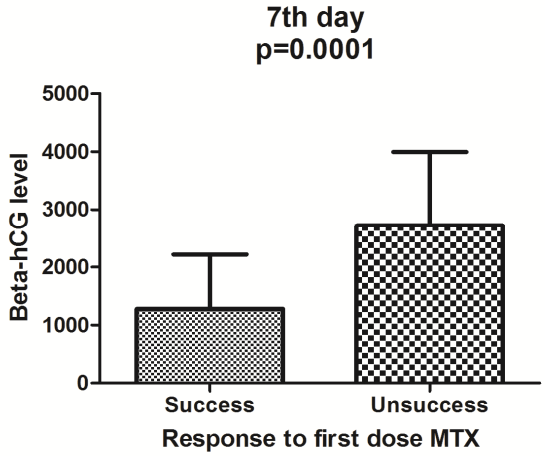

Figure 3
Beta-hCG level on 7th day after administration of single dose methotrexate in two groups of successful and unsuccessful responses

Reduction in βhCG Titration on 4th Day Compared to Baseline
In 81 patients (84%) out of 97 patients in the successful group, there was a drop in βhCG level on the 4th day compared to baseline. Therefore, single dose methotrexate was successful in 84% of patients with a 4th day beta drop, while βhCG level decreased in only 10% of unsuccessful patients on 4th day compared to baseline; this difference was significant (p = 0.0001) (Figure 4).

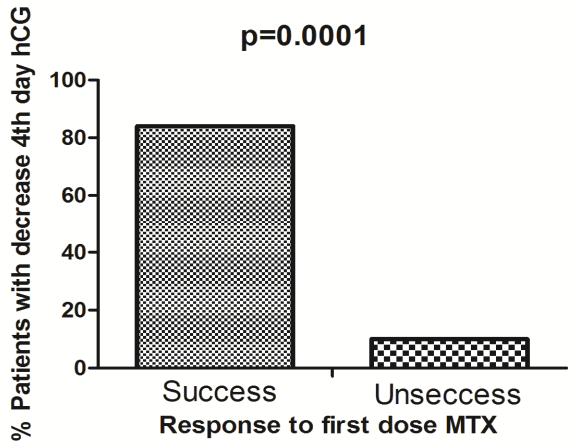

Figure 4
4th day drop in βhCG in successful and unsuccessful patients

Reduction in βhCG Titration on 7th Day Compared to Baseline

In 85 patients (87%) out of 97 patients in the successful group, there was a drop in βhCG level on the 7th day compared to baseline. Therefore, single dose methotrexate was successful in 87% of patients with a 7th day beta drop, while βhCG level decreased in only 5% of unsuccessful patients on 7th day compared to baseline; this difference was significant (p = 0.0001) (Figure 5).

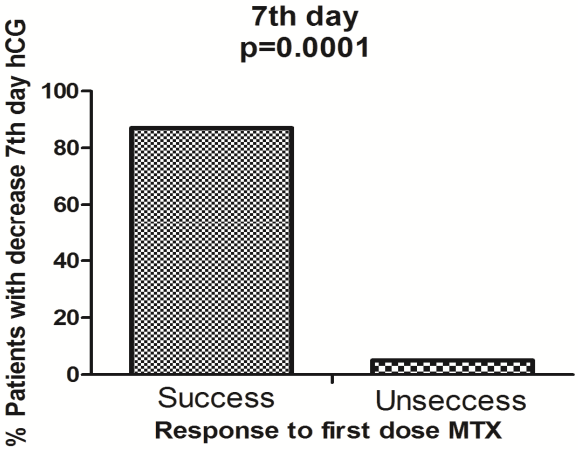

Figure 5
7th day drop in βhCG in successful and unsuccessful patients

Prediction of Success Using βhCG Changes at Baseline and 4th Day

Next, effects of different variables were evaluated on successful response to treatment. These results are listed in Table 2. In patients with successful response, one unit decrease in βhCG concentration on 4th day compared to baseline increased chance of success by 4%, which is significant (p = 0.025). In patients with unsuccessful response, one unit increase in βhCG concentration on 4th day compared to baseline increased chance of failure by 9%, which is significant (p = 0.031) (Table 1).

Table 2
Effects of one unit increase and decrease in βhCG on 4th day compared to baseline on prediction of success and failure of response to treatment

variables	RR	95% CI	p-value
βhCG decrease	1.04	1.00-1.25	0.025
βhCG increase	0.91	0.45-0.99	0.031

Reduction in βhCG in Percent

The mean percentage of reduction in βhCG on 4th day compared to baseline was 39±6% in the successful group and 9.5±5% in the unsuccessful group; this difference was significant (P = 0.0001) (Figure 6).

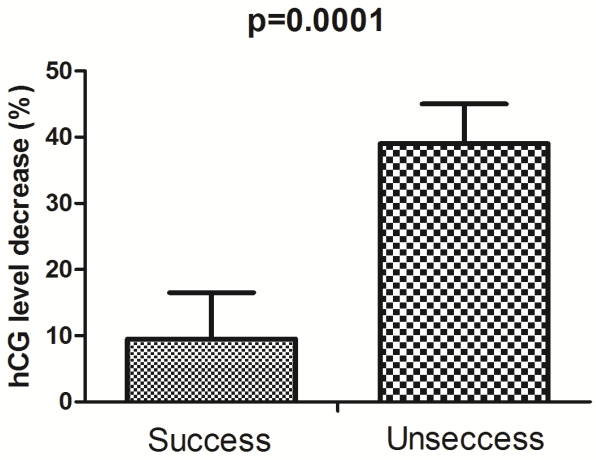

Figure 6

Reduction in βhCg level on 4th day between successful and unsuccessful groups

DISCUSSION AND CONCLUSION

This study evaluated the rate of beta-hCG titration at baseline and 4th days after receiving the drug and percentage of changes in βhCG between baseline and 4th days in predicting success or failure of pharmacotherapy in ectopic pregnancy patients treated with methotrexate. The results well showed that βhCG titration in the first days is not so predictive of success or failure of treatment. Instead, the change in βhCG titration at baseline and 4th day is significantly predictive of these changes. At first, the results showed no significant difference in βhCG titration in the first days between two successful and unsuccessful groups in response to single dose methotrexate. This meant that βhCG level itself did not differ between two successful or unsuccessful groups on the first or fourth day. However, βhCG level did not differ between the two groups on 7th day, which could be predicted. Interesting results were obtained regarding the decrease in βhCG titration at baseline and 4th day. In 81 patients (84%) out of 97 patients in the successful group, there was a drop in βhCG level on the 4th day compared to baseline. Therefore, single dose methotrexate was successful in 84% of patients with a 4th day beta drop, while βhCG level decreased in only 10% of unsuccessful patients on 4th day compared to baseline. In similar studies, such as Uztunyurt, the number of cases with a decrease in βhCG on the 4th day was significantly higher in the successful treatment group than the unsuccessful treatment group (61.9% vs. 37.5%); in cases where βhCG ranged from 1000 to 1999, it was 85.7%. Azargoon showed that treatment success rate was 77.1%, and <15% reduction in β titration in the first and fourth days was associated with increased failure of treatment. These are consistent with results of current study, which showed that 84% of successful patients had reduction in hCG and only 15% had no hCG reduction. However, βhCG increased on the 4th day in all unsuccessful patients. Many previous studies have emphasized a cut-off point in hCG level in predicting the response to treatment; for example, Erden[8] or Nowak-Markwitz[7] determined 1800 for hCG as predictor of response to treatment. However the results of this study showed that in fact the most important predictor of response to treatment was decrease in hCG titration on day 4 compared to baseline. Based on these results, a regression analysis with the reference of successful group showed that βhCG titration at baseline or 4th day was not a significant predictor of failure of the treatment. Mirbolouk et al reported similar results, which had a predictive value for reducing hCG on the 4th day.[9] Finally, the results indicated a significant difference in gravid of the successful patients in response to treatment compared to the failure group; in the failure group, the majority of patients were greater than G3, while in the success group, the majority of patients were less than G2. Moeini and Bowman, however, confirmed the results that higher gravid results in a lower success

rate in response to treatment. Finally, the results of this study showed that 84% of patients who were successful in responding to a single dose methotrexate experienced drop in βhCG levels on day 4 compared to baseline. However, βhCG level at baseline did not predict the success of response to treatment.

CONFLICT OF INTEREST

Conflict of interest declared none.

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