ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Ektopik Gebeliklerde Tek Doz Metotreksat Tedavisinin Etkinliğinin Değerlendirilmesi: 5 Yıllık Deneyim

Evaluation of Medical Treatment Success in Ectopic Pregnancy with Single Dose Methotrexate: 5 Year Experience

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ABSTRACT

Aim: *The aim of this study was to evaluate the predictive factors of success or failure of treatment of Ectopic Pregnancy with single dose Methotrexate (MTX).*

Material and Method: *In this retrospective study, records of 351 patients who were treated for ectopic pregnancy with single dose of MTX were reviewed during five years. Patients were divided into two groups; the first group or "success group" are the patients who were successfully treated with MTX. The second group or "failure group" consist the patients who did not respond to the MTX therapy.*

Results: *Of 351 patients, 240 (68.3%) were successfully treated with single dose MTX. 111 patients (31.7%) required second dose MTX or a surgery. The mean initial BHCG level was significantly lower in the treatment success group than in the treatment failure group (1265 mIU/ml versus 5751 mIU/ml, p<0.001). The number of cases with decreasing BHCG level on day 4 was significantly more in the success group compared to failure group (62.5% and 36.9% respectively, p<0.0001). The success rate was 95% when the levels were <1000 mIU/ml, 87.5% when the levels were between 1000–1999 mIU/ml and 35.5% when the levels were >5000 mIU/ml.*

Conclusion: *Medical treatment with single dose systemic MTX may be an acceptable therapeutic option for ectopic pregnancy and MTX therapy is a safe and effective treatment modality for ectopic pregnancies with a serum BHCG levels below 3000 mIU/ml.*

Key words: *ectopic pregnancy; methotrexate; medical treatment*

ÖZET

Amaç: *Bu çalışmada ektopik gebeliklerde tek doz metotreksat tedavisinin başarı ve başarısızlık oranlarını değerlendirmesi amaçlandı.*

Materyal ve Metot: *Çalışmada ektopik gebelik tanısı konulup tek doz metotreksat uygulanan 351 hastanın tıbbi kayıtlarının retrospektif olarak incelenmiştir. Hastalar tek doz metotreksat ile başarılı olarak tedavi edilen ve edilemeyen olmak üzere 2 gruba ayrılarak değerlendirilmiştir.*

Bulgular: *351 hastanın 240 (%68,3) tek doz MTX ile başarılı olarak tedavi edilmiştir. 111 (%31,7) hasta ikinci bir MTX dozuna ya da cerrahi tedaviye ihtiyaç duymuştur. Ortalama BHCG seviyeleri tek doz MTX tedavisine başarılı olarak yanıt veren grupta, başarısız olunan gruba göre belirgin olarak düşük saptandı. (1265 mIU/ml-5751 mIU/ml, p<0,001). Tedaviye başarılı olarak yanıt veren grupla başarısız olunan grup arasında 4. gün BHCG seviyelerindeki düşüş oranı arasında istatistiksel olarak anlamlı fark saptandı. (%62,5 ve %36,9 istatiksel anlamlı, p<0,0001). Tek doz MTX tedavisine başarılı yanıt BHCG seviyeleri <1000 olduğunda %95, 1000–1999 arasında %87,5, >5000 olduğunda %35,5 olarak saptandı.*

Sonuç: *Tek doz MTX uygulamaları ektopik gebeliklerin medikal tedavisinde kabul edilebilir, güvenli ve efektif bir yöntemdir, özellikle BHCG seviyeleri 3000 altında olan hastalarda ilk seçenek olarak düşünülmelidir.*

Anahtar kelimeler: *ektoik gebelik; metotreksat; medikal tedavi*

Introduction

An ectopic pregnancy (EP) is one of the major causes of maternal morbidity and mortality. Late diagnosis leads to rupture and cause internal hemorrhage[1]. Today, due to scientific, laboratory and imaging technologies advances, EP diagnosed at an early stage with transvaginal ultrasonography and serum Beta-human chorionic gonadotropin (BHCG) assay[2,3]. Compared to previous treatment, although instead of laparotomy, laparoscopy is preferred, medical treatment with methotrexate (MTX) seems to be more attractive to doctors. The use of methotrexate (MTX) for medical treatment of women with tubal ectopic pregnancy was first introduced in 1982, and has now come to be widely accepted. Additionally, the role of MTX has become more

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important as a consequence of the current wide spread availability of the early diagnosis of ectopic pregnancy. Medical management of unruptured EP with intramuscular MTX is common and cost effective[4]. Although there is still controversy regarding the appropriate treatment protocol. A meta-analysis estimated the overall success rate of single dose protocol to be 88.1% with a 95% CI: 86–90%. The failure rate of single dose administration of MTX was estimated to be 1.96 times higher than the use of multi dose treatment[5].

Several studies to determine factors associated with the success or failure of response to treatment was done. Women most likely to respond to MTX therapy are thought to be those with small gestational masses, lower serum concentrations of human chorionic gonadotropin and progesterone, and the absence of blood in the peritoneal cavity, but there is controversy in previous studies to determine the true effect of these characteristics on successrates[6]. For example, one of the factors associated with successful treatment response is BHCG level at the beginning of treatment but the value of the determinant or the Cut off in different studies is varied.

In this study it was aimed to find the predictive factors of success and failure of treatment of unruptured EP with single dose of MTX

Material and Method

In this study, medical records of 351 women admitted with the diagnosis of EP in Sisli Etfal Education and Research Hospital, during the five year period from 2009 to 2014 were reviewed. The Ethics Committee of the Hospital approved the study. Inclusion criteria were: women with unruptured tubal EP diagnosis, hemodynamically stable, BHCG titrage under 10000 IU, absent fetal cardiac activity, and who treated with single dose of MTX and have days 0, 4 and 7 BHCG values appropriately recorded after MTX administration. Women who treated with double dose protocol of MTX or unstable patients who had surgery before medical treatment, women who had abnormal baseline hematologic, renal, or hepatic laboratory values, and fetal cardiac activity were excluded from study by single dose MTX in accordance with the published guidelines. Demographic data such as age, marital duration, gravidity, last menstrual period date (LMP), history of abortion, size of EP, infertility, contraceptive use and clinical presentation such as abdominal pain, vaginal bleeding, and amenorrhea were taken by a check list from patients documents. Treatment success was defined as 15% decrease in BCHG levels between days 4 and 7, followed by weekly BHCG level measurement until it was negative. Treatment failure was defined as the need for a second dose of MTX and/or surgery. Patients were divided into two groups; the first group or "success group" are the patients who were successfully treated with single dose MTX. The second group or "failure group" were the patients who did not respond to the single dose MTX therapy. These women were initially being treated with MTX but underwent surgery after they had shown no positive response to the medical therapy or had a tubal rupture.

Statistical analysis was done via SPSS software (SPSS, Chicago, IL, USA). Student t test was used to compare means; Chi square test was used for categorical variables. A probability value of <0.05 was considered statistically significant.

Results

The Mean age of women was 31.35±5.24 years old (range 18–45). The presenting symptoms were abdominal pain with vaginal bleeding (55.4%), vaginal bleeding (19.2%), abdominal pain (18.4%), and amenorrhea (5.9%). Of 351 patients, 240 (68.3%) were successfully treated with single dose MTX treatment. 111 patients (31.7%) required a second dose MTX or surgery. In both the success and failure groups, the age of the patients (mean 31.05 and 31.75 years, respectively), the week of gestation (mean 6.81 and 7.02 weeks, respectively), the size of EP (mean 29.71 and 30.51 mm, respectively), the location of tubal EP (right or left), number of gravidity, infertility or EP history, contraceptive use, revealed no statistically significant differences (Table 1).

The medians of β-hCG levels on days 1, 4, and 7 were significantly higher in the "failure group" (5751 vs. 1265, 5988 vs. 1209, and 5834 vs. 911 mIU/mL, respectively) ($p=0.0001$). The BHCG levels increased between days 0 and 4 in 45.01% of cases. BHCG levels decreased between days 0 and 4 in 54.9% of cases. (193/351). The number of cases with decreasing BHCG level on day 4 was significantly more in the success group than failure group (62.5% and 36.9% respectively, $p<0.0001$).

The success rate was 95% when BHCG levels were < 1000 mIU/mL, 87.5% when the levels were between 1000 and 1999 mIU/mL and 75.5% when the levels

were between 2000 and 2999 mIU/mL, and 45.6% when the levels were between 3000 and 3999 mIU/mL (Table 2).

Discussion

The systemic use of MTX for ectopic pregnancy is not a new therapeutic modality. Although a single dose MTX protocol of 50 mg/m^2, with subsequent doses where necessary, has recently been accepted as the most appropriate treatment option, there is still debate not only on the success rates but on the patient characteristics which were thought to influence the response to single dose MTX. In selected patients, single dose MTX regimen constitutes a safe and effective treatment modality for ectopic pregnancy. This regimen is the most commonly used regimen with reported of 52–94%[7]. Stoval et al.[8] reported a complete resolution of EP in 94.2% of their patients. Gamzu et al.[9] reproted 88% success rate with the use of single dose of MTX. Other studies reported relatively lower success rates. Corsan et al.[10] reported a success rate 75%. Nazac et al.[11] only noted a 67.1% success rate. In our study the success rate of single dose MTX treatment was 68.3% and this result is in accordance with the studies published earlier[12,13].

Through many studies, initial BHCG level, size of an ectopic gestational mass, the presence of fetal cardiac activity, the presence of free peritoneal fluid and the presence of pelvic pain or vaginal spotting have been accepted as predictors of success for single dose regimen[14,17]. BHCG level was one of the first variables found to be associated with successful treatment. Corsan et al.[12] found that BHCG left alone or combined with serum progesterone levels have an important predictive value. Also a meta-analysis published by Kirk and Bourne[18] reported that only BHCG level might be a predictor of the successful or unsuccessful outcome of the ectopic pregnancy after MTX treatment. In our study, we found that the initial BHCG level was the only predictor of success for repeated injections, particularly in the cases with initial BHCG levels lower than 3000iu/ml. The β-hCG level on days 1, 4 and 7 in our study were significantly higher in the failure group

Table 1. *Patient characteristics*

Characteristics	Success group (n=240)	Failure group (n=111)	P value
Age (year)	31.05±5.56	31.75±5.65	NS
Parity	1.2±0.7	1.1±0.9	NS
Abortion (n)	% 25.4	% 30.1	NS
Ectopic pregnancy (n)	% 10.1	% 12.2	NS
Infertility history (%)	% 25	% 28.3	NS
Gestational age (week)	6.81±0.82	7.02±1.74	NS
Size of Ectopic pregnancy (mm)	29.71±10.33	30.51±10.71	NS
Endometrial thickness (mm)	7.78±3.87	8.04±4.98	NS
Hcg 1 day (mean)	1265	5751	0.0001
Hcg 4 day (mean)	1209	5988	0.0001
Hcg 7 day (mean)	911	5834	0.0001
Cases with decreasing BHCG level on day 4 (n)	150 (% 62.5)	41	0.001

Continuous data presented as mean ± SD with p-values obtained from Independent-Samples t-test; Categorical data presented as n (%) with p-value obtained from Chi-Square test
NS: non spesific HCG: human chorionic gonadotropin

Table 2. *Treatment outcome results of five B-HCG ranges*

HCG (mIU/mL)	Number of patients	Success (%)	Failure (%)
<1000	81	95	5
1000–1999	75	87.5	12.5
2000–2999	79	75.5	24.5
3000–3999	46	45.6	54.4
4000–4999	37	49.5	50.5
>5000	33	35.5	64.5

which was similar to Cohen et al.'s study[19]. In Potter et al study the median pretreatment serum beta-human chorionic gonadotropin level was lower in those women in whom treatment was successful compared with those women with treatment failure (793 vs. 3804 mIU/mL, p<0.002), similar to Ustunyurt et al.'s study, (1.417 mIU/mL vs. 5.995 mIU/mL, p<0.001).[20,21] Based on our findings number of cases with decreasing β-hCG level on day 4 was significantly more in the success group compared to the failure group (62.5% and 36.9% respectively, p<0.0001).) similar to Ustunyurt et al. (61.9 and 37.5%, respectively) Nguyen et al., Vaswani et al., and Skubisz et al.[3,12,21,22].

In our study, the mean initial BHCG level was significantly lower in the treatment success group than in the treatment failure group. The success rate of a single MTX dose for EP in patients with a BHCG serum concentration below 1000 mIU/ml resulted 95%. As it was reported in recent studies, expectant management of ectopic pregnancy seems to be an approach for these patients with very low BHCG levels[23,25]. In our study, we found that when the initial BHCG levels was higher than 3000 mIU/ml, the treatment failure rate was increasing significantly. Similarly, the success rate was significantly lower in patients whose serum BHCG levels above 5000 mIU/ml before MTX treatment. These results are similar to those reported by Sagiv et al.[7] and Ustunyurt et al.[21].

In our study there was no significant difference between groups about age of patients, gravidity, history of EP, infertility, contraceptive use, and size and location of ectopic mass similar to Barnhart et al. and Lipscomb et al. None of these variables would predicted the success of MTX treatment in this population study[26,27]. Logistic regression analysis demonstrated that day-1 and fall in 1–4 days β-hCG level was the significant independent variables for prediction of MTX treatment outcome.

In conclusion, this study showed that medical treatment with single dose systemic MTX may be an acceptable therapeutic option for ectopic pregnancy and MTX therapy is a safe and effective treatment modality for ectopic pregnancies with a serum BHCG levels below 3000 mIU/ml.

Compliance with Ethical Standards

The local ethics committee of the hospital approved the study. The authors of the study were committed to the principles of the Helsinki Convention. This article does not contain any studies with animals performed by any of the authors.

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