

Ektopik Gebelikte Kullanılan Tek Doz Metotreksat Tedavisinin Başarısını Etkileyen Faktörler

Factors Affecting Success of Single-Dose Methotrexate Treatment in Ectopic Pregnancy

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ÖZ

GİRİŞ ve AMAÇ: Bu çalışmamızın amacı ektopik gebelik tedavisinde uyguladığımız tek doz metotreksat tedavisinin başarı oranını değerlendirmek ve bu başarı oranını etkileyen klinik ve laboratuvar faktörlerini araştırmaktır.

YÖNTEM ve GEREÇLER: Hastanemize 2013 Nisan ile 2018 Nisan arasında ektopik gebelik tanısıyla tek doz metotreksat tedavisi alan hastalar retrospektif olarak değerlendirildi. Hastaların demografik özelliklerinin yanı sıra tanı anındaki serum β -hCG değeri, ektopik odak boyutu ile ektopik odaktaki fetal kardiyak aktivite pozitifliği gibi klinik, laboratuvar ve ultrasonografik bulgular ile metotreksat tedavisi arasındaki ilişki değerlendirildi.

BULGULAR: Ektopik gebelik tanısı ile tek doz metotreksat tedavisi yapılan toplam 123 hasta çalışmaya dahil edildi ve hastalar 2 gruba ayrıldı. Grup 1 (n=97): Tek doz metotreksat ile başarılı tedavi edilen hastalar. Grup 2 (n=26): Tek doz metotreksat ile başarı sağlanamayan ve cerrahi müdahale gereken hastalar. Grup 1'deki hastaların MTX tedavisi öncesi ortalama serum β -hCG değeri 3128 ± 2085 mIU/ml iken Grup 2'deki hastaların ortalama değeri 5813 ± 3858 mIU/ml olarak bulundu ve her iki grup arasında istatistiksel olarak anlamlı fark bulundu ($p=0.0001$). Ektopik odaktaki fetal kardiyak aktivite Grup 1'de 10 (%10.3) hastada, Grup 2'de ise 7 (%26.9) hastada pozitif bulundu. Toplam 123 hastaya MTX tedavisi uygulandı ve genel başarı oranı 97/123 (%78.8) olarak bulundu.

TARTIŞMA ve SONUÇ: Tek doz metotreksat tedavisi ektopik gebeliğin tedavisi için kullanılan etkin ve güvenli bir tedavi seçeneğidir. Metotreksat tedavisinin başarısını öngören en önemli parametre serum β -hCG düzeyi olup tanı anındaki β -hCG değeri ile medikal tedavinin başarı oranı arasında ters orantı söz konusudur. Ektopik odakta kardiyak aktivitenin gözlenmesi de metotreksat tedavisi için kesin bir kontrendikasyon olmasa da tedavi başarısını azaltan önemli bir parametre olarak bulunmuştur.

Anahtar Kelimeler: ektopik gebelik, metotreksat tedavisi, serum β hCG

ABSTRACT

INTRODUCTION: We aimed to evaluate the effectiveness of the single-dose methotrexate used in the treatment of ectopic pregnancy and to identify the clinical and laboratory findings affecting its success.

METHODS: We retrospectively reviewed the patients diagnosed with ectopic pregnancy who received single-dose methotrexate treatment in between April 2013 and April 2018. The associations of the methotrexate treatment with patients' demographic characteristics, clinical and laboratory findings like serum β -Hcg levels, size of ectopic mass, fetal cardiac positivity were evaluated.

RESULTS: Mean serum β -hCG levels of Group 1 (included patients successfully treated with single-dose methotrexate, n=97) and Group 2 (included patients could not treated with single-dose methotrexate, n=26) prior to methotrexate treatment were 3128 ± 2085 mIU/ml and 5813 ± 3858 mIU/ml respectively. In Group 1, fetal cardiac activity was positive in 10 patients (10.3%) and in Group 2. The cardiac fetal activity was positive in 10 patients (10.3%) in Group 1 and 7 patients (26.9%) in Group 2. In total 123 patients who underwent methotrexate treatment the overall success rate of single-dose methotrexate treatment was found as 78.8% (97/123).

DISCUSSION and CONCLUSION: Single-dose methotrexate treatment is a safe and effective option in ectopic pregnancy therapy. The most significant parameter affecting the success of this treatment is the serum β -Hcg levels having an inverse relation with success rate. The observation of cardiac activity in the ectopic focus has been found to be an important parameter that reduces the success of treatment, although not being a definite contraindication to methotrexate therapy.

Keywords: ectopic pregnancy, methotrexate treatment, serum β hCG

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INTRODUCTION

Ectopic pregnancy is defined as the placement of the fertilized ovum outside the uterine cavity (commonly in uterine tubes) and seen in approximately 2% of all pregnancies (1). In modern era, widespread use of transvaginal ultrasonography and precise measurement of serum bhcg levels help diagnose the ectopic pregnancies in an earlier setting. The most commonly used drug in treatment of ectopic pregnancies is methotrexate (MTX) holding a clear advantage over surgery in regards of cost-effectiveness.

MTX; is a folic acid antagonist that inhibits dihydrofolic acid reductase involved in DNA synthesis and repair and in cellular replication. Rapidly proliferating cells such as trophoblasts are highly sensitive to effects of MTX. The success rate of intramuscular single dose MTX (50mg/m²) used in the treatment of ectopic pregnancy has been reported between 63% and 94% (2-5). The main reasons for various curative rates reported in papers are diverse clinical and laboratory characteristics of patients picked and different approaches in disease management.

The most important criteria for choosing between medical or surgical management for an ectopic pregnancy are hemodynamic status, fertility status and pregnancy desire of the patient, size of ectopic focus at ultrasonographic examination, serum bhcg level, fetal heart activity and patient's compliance to treatment and follow-up.

In this study we aimed to identify the success rate of a single dose MTX treatment used in ectopic pregnancy and the correlations between cure rate and certain disease characteristics, particularly pretreatment serum bhcg level.

METHODS

This study was conducted in Obstetrics and Gynecology Clinic at Istanbul Medeniyet University Göztepe Training and Research Hospital with the approval of the ethics committee. We retrospectively evaluated the patients who diagnosed with ectopic pregnancy and treated with a single-dose MTX in between April 2013 and April 2018.

Electronic database of the hospital and conventional patient files were examined in detail and certain demographic and clinical characteristics (age, gravida, abortion or ectopic pregnancy history, gynecologic surgery history, smoking status, intrauterine device (IUD) use, pelvic inflammatory disease history) were recorded.

History of cesarean section, myomectomy and operations for ovaries and uterine tubes were classified under "past gynecologic surgery". Non-abdominal approaches were excluded. Patients treated surgically or with multiple MTX doses were excluded from the study. A total of 123 patients treated with single-dose MTX were divided into two groups. Group 1(n=97): Patient achieved a cure with single-dose MTX. Group 2(n=26): Patients who had treatment failure with single-dose MTX (those required second dose MTX and/or treated surgically).

The diagnosis of ectopic pregnancy was obtained via serial serum bhcg levels and ultrasonographic scans in all patients. Patient's hemodynamic status, fertility status or pregnancy desires, serum bhcg levels and ectopic focus sizes were main factors for deciding on the propriety of MTX therapy. The selection criterias for single dose MTX treatment; initially bhcg levels <10,000 mIU/mL, gestational mass larger than 4cm in size, heterotopic gestation, moderate to severe anemia, leukopenia or thrombocytopenia, immunodeficiency, sensitivity to MTX, peptic ulcer, active or clinically impotent pulmonary/hepatic/renal disease and breast feeding.

All patients who received MTX were admitted to hospital and examined for complete blood count, liver and kidney function tests, direct chest roentgenogram. An informed consent was obtained for MTX treatment from patients. For proper patients, a single-dose MTX (50 mg/m²) was given by intramuscular route. The day of the initiation of MTX was defined as "day 1". The "success" for the treatment was identified as the decline of serum bhcg level by 15% between days 4 and 7 after treatment, or detecting a serum bhcg level less than 5 mIU/ml in three consecutive weeks during follow-up (Group 1). The MTX treatment was

considered “unsuccessful” in patients who underwent surgery in consequence of development of hemodynamic instability and in patients who required multiple doses (Group 2).

SPSS version 22.0 (computer package for Windows) was used for statistical analysis. Variable values were represented as “mean \pm standard deviation”. Categorical variables were expressed as numerical and percentage. Mann-Whitney U test was used for parameters that did not fit the normal distribution. $P < 0.05$ values were accepted as significant.

RESULTS

Demographic and clinical characteristics, serum bhcg levels and ultrasonographic findings of patients in Group 1 and Group 2 are presented in Table 1. The mean serum bhcg level of patients in Group 1 before MTX treatment was 3128 ± 2085 mIU/ml, and in Group 2 was 5813 ± 3858 mIU/ml, indicating a statistically significant difference ($p = 0.0001$). Table 2 represents the risk factors for ectopic pregnancy in each group, not pointing a statistical significance. In ultrasonographic scan mean ectopic mass size was measured as 35.9 ± 10.6 mm for Group 1 and 37.6 ± 8.7 mm for Group 2. In 10 patients (10.3%) in Group 1, a live fetus was detected in ectopic focus and in 7 patients (26.9%) in Group 2. The difference in ratio of live fetuses in two groups indicates a significance ($p=0.03$). Serum bhcg levels before MTX treatment and success rates of two groups are shown in Table 2. Success rate of treatment with MTX in patients with a serum bhcg level between 0-1000 mIU/ml was detected as 93.7%, whereas it was 60% in patients with a serum bhcg level more than 5000 mIU/ml (Table 3).

Character	Group 1 (n:97)	Group 2 (n:26)	pvalue
Age	28.6 \pm 6.6	29.1 \pm 5.7	^a 0.71
Gravida	2.3 \pm 1.4	2.1 \pm 1.1	^b 0.54
Parity	0.7 \pm 0.8	0.7 \pm 0.5	^b 0.55
Abortion	0.3 \pm 0.5	0.3 \pm 0.6	^b 0.91
Weeks of gestation	6.1 \pm 1.7	6.3 \pm 1.7	^a 0.26
β hCGlevel(mIU/ml)	3128 \pm 2085	5813 \pm 3858	^a 0.0001
Ectopicfocus size (mm)	35.9 \pm 10.6	37.6 \pm 8.7	^a 0.36
Presence of fetalheartactivity	10 (%10.3)	7 (%26.9)	^a 0.03

^aStudent t test, ^bMann Whitney U Test

Table 2. Patient’s risk factors for ectopic pregnancy

Risk factor	Group 1 (n:97)	Group 2 (n:26)	P value
Past ectopic pregnancy	6 (%6,1)	4(%15)	^b 0.39
IUD use	8 (%8,2)	2(%7,6)	^b 0.64
Smoking	18(%18,5)	7(%26,9)	^b 0.41
Past gynecologic surgery	32(%32,9)	8(%30)	^b 0.51
Past pelvic inflammatory disease	6(%6,1)	3(%11,5)	^b 0.39
Past ovulation induction	5(%5,1)	2(%7,6)	^b 0.63

^bMann Whitney U Test

Table 3. Successrates of single-dose MTX according to bhcg levels

β hCGlevel (mIU/ml)	Number of patients, n	Number of patient with treatment failure, n	Success rate (%)
0-1000	16	1	93.7
1000-2000	20	2	90.0
2000-3000	22	4	81.8
3000-4000	23	5	78.2
4000-5000	22	6	72.7
>5000	20	8	60.0
Total	123	26	78.8

DISCUSSION

In our study, we detected the overall success rate of single dose MTX used in the treatment of ectopic pregnancy as 78.8% (97/123) regardless of serum bhcg values. The success rates in our study is similar to previous studies. Stoval et al, Glock et al and Corsan et al found the success rates of single-dose MTX in ectopic pregnancy treatment as 94.2%, 85.7% and 75%, respectively.

The first use of MTX in the treatment of ectopic pregnancy dates back to the 1980s (6,7). An effective and safe treatment with MTX has led a considerable reduction in surgery rates for ectopic pregnancy, over time (8). However, medical treatment may not always be the best choice. In our study, serum bhcg levels in patients who achieved cure with MTX was significantly lower than those with treatment failure. In subgroup analysis; we detected an inverse relation between serum bhcg levels and success rates of MTX. In previous studies, pretreatment bhcg level was proposed as the most significant parameter for the prediction of a well-done cure (9,10). Another relevant factor for the efficiency of MTX treatment is the ectopic focus size (11). In cases with an ectopic focus size lesser

than 35-40 mm in sonographic examination, the success of MTX was found to be higher (12,13). We detected the mean ectopic focus size as 35.9 mm in Group 1 and 37.6 mm in Group 2, without a significant difference.

Advances in ultrasonographic technology have led a chance of earlier diagnosis of intra or extrauterine pregnancies. Detection of a live fetus in uterine cavity represents a clear evidence for an intrauterine pregnancy (14). This finding largely excludes an ectopic pregnancy due to the very low incidence of coexistent intrauterine and extrauterine pregnancies (1/30.000). An adnexal gestational sac with a positive fetal cardiac activity, only shown in 10-17% of our cases, is the most definitive finding for an ectopic pregnancy. We detected a significantly higher live fetus rates in patients with treatment failure (26.9% versus 10.3%). Some of the previous studies suggested that the detection of fetal cardiac activity negatively affects the success of single-dose MTX (15).

The relation between tubal obstruction, mainly from pelvic inflammatory disease (PID) and ectopic pregnancy has been proven in many studies. In a study of 415 women with a laparoscopically diagnosed PID, the tubal obstruction rates was found to be increased by 13% after one disease attack, 35% after two and 75% after three disease attacks (16). In our study we not found significant difference between the groups by past pelvic inflammatory disease history

Both the inert and copper IUD prevents intra or extrauterine pregnancies. Women who use an IUD carry a higher risk for tubal pregnancy than others without any contraceptive method. IUDs prevents an intrauterine pregnancy more efficiently than a tubal one.. In one study, the increase in the risk for an ectopic pregnancy was reported as 6-10 times for women using this method (17). There was no difference between the patient groups in our study in regards of intrauterine device use. We believe that intrauterine device use has no significance for the prediction of single dose mtx treatment success.

Some patients diagnosed with ectopic pregnancy have a history of abdominal surgery. The role of

past abdominal surgery in extrauterine pregnancy etiology is unclear. In some studies, no increase in ectopic pregnancy risk was observed with the past cesarean, ovarian or uncomplicated appendicitis surgery (18). Some other papers reported an increase in ectopic pregnancy risk in ovarian cystectomy and wedge resection history, probably from peritubal scarring (19,20). There was no difference between the groups regarding pelvic inflammatory disease or gynecologic surgery history. We believe that history of pelvic inflammatory disease or gynecologic surgery does not confer a risk for the success of medical treatment of ectopic pregnancy.

Although, the incidence of ectopic pregnancy increases with maternal age and parity, nulliparous women who receive infertility treatment carry a high risk. Nulliparous women who do not use any contraceptive method have at least 2.6 times greater risk for tubal pregnancy in a one-year period (21,22). Infertile population have some further risk factors such as history of reversal of tubal sterilization, ovulation induction and in vitro fertilization (23). In many of those women, histerosalphingography does not show any abnormality and one can not detect, intraoperatively any gross tubal pathology.

The tobacco use at least doubles the risk of tubal pregnancy (24). Tubal motility and cilliary activity loss and disruption of blastocyst implantation are probable factors.

In current study, we did not identify any significant differences in two groups created according to the success of MTX treatment, in terms of some proposed risk factors for ectopic pregnancy such as past ectopic pregnancy, IUD use, smoking status, gynecologic surgery or PID history and past ovulation induction.

CONCLUSION

Single dose MTX therapy is an effective and safe treatment option for the treatment of ectopic pregnancy. Serum bhcg level, the most valuable parameter for prediction of an effective treatment, in initial diagnosis has an inverse relation with success rates. Although not being an absolute

contraindication for MTX treatment, the detection of a live fetus in ectopic focus was found to be an important indicator for treatment failure.

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