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Evaluation of Predictive Efficacy of β -hCG Levels at 0–4 Days for Single-dose Methotrexate Therapy in Ectopic Pregnancy

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Abstract:

Background: To assess the predictive efficacy of beta-human chorionic gonadotropin (β -hCG) value changes between 0–4 days for single-dose methotrexate (MTX) therapy for ectopic pregnancy (EP). **Materials and Methods:** Between September 2016 and August 2017, the treatment outcomes for patients who received MTX therapy for EP at the Health Sciences University GaziYaşargil Training and Research Hospital were evaluated retrospectively. The efficacy of the cut-off reduction values used in the study was determined through the receiver operator characteristic (ROC) volumetric analysis with $\geq 10\%$ and $>20\%$ reductions in β -hCG values between 0–4 days.

Results: Of the 132 patients who received single-dose MTX treatments, 78.8% (N = 104) had successful outcomes. A sensitivity of 65.3%, specificity of 71.4%, positive predictive value (PPV) of 89.4%, and negative predictive value (NPV) of 35.7% were found to be statistically significant when predictions of treatment success were based on reduced β -hCG values at 0–4 days (AUC:0.690, $p < 0.05$). However, the β -hCG reduction at 0–4 days $>10\%$, $>20\%$ and the ROC was detected in the curve analysis, $>10.4\%$ were found AUC: 0.643 ($p > 0.05$), AUC: 0.614 ($p > 0.05$), AUC: 0.643 ($p > 0.05$) respectively.

Conclusions: In this study, reduced β -hCG values were observed in cases of non-ruptured tubal EP after 0–4 days of single-dose MTX treatment; thus, the efficacy of the therapy was predictive and statistically significant. In addition, the β -hCG values at 0–4 days were reduced by $>10\%$, $>10.4\%$ (cut-off value of current study), or $>20\%$ with a higher PPV for successful treatment outcomes although they were not statistically significant.

Keywords: Ectopic pregnancy, Single dose, Methotrexate, Success rate, Early diagnosis.

Introduction

Ectopic pregnancy (EP) is defined as the implantation of the

fertilized ovum in any part of the body other than the uterine cavity. The frequency of occurrence is 1–2% for all pregnancies [1-3]. Clinically, about 50% of patients present with non-diagnostic complaints, such as abdominal pain, amenorrhea, and irregular vaginal bleeding. The remainder may present with hemodynamic instability because of nonspecific clinical complaints or intraabdominal bleeding resulting in tubal rupture [4]. However, women with delayed menstruation can be diagnosed early by beta-human chorionic gonadotropin (β -hCG), progesterone, and transvaginal ultrasonography (TV-USG) [5,6]. Early episodes of EP can be diagnosed, and a majority of non-ruptured cases can be treated medically [7].

Methotrexate (MTX) has been widely used around the world for this purpose [8]. Despite the use of single-dose or multiple-dose regimens of MTX in the EP treatment protocol, the side effects are fewer with the single-dose protocol, and the compliance with treatment is better, with success rates of 52–94% [9-12]. Single-dose MTX-treated EP has been found to have a 93% positive predictive value (PPV) with a $\geq 15\%$ decrease in human chorionic gonadotropin (hCG) levels at 4–7 days of treatment; however, the accuracy of this treatment has not been fully explained [13]. Having patients wait up to 7 days for a prediction of treatment success and a decision on the continuation of single-dose MTX treatment leads to their experiencing psychological stress and anxiety. Recently, several studies have focused on the changes in β -hCG values at 0–4 days to predict the success of single-dose MTX therapy for early diagnosed EP [14-18]. The results indicate that are reduction in hCG levels at 0–4 days predicts successful outcomes of 80–100% for single-dose MTX treatment [14-16]. Based on a detailed review of these studies, the current research ought to determine the predictive efficacy of single-dose MTX treatment from decreases or increases in hCG levels. Accurately, the study assessed the success of this treatment by using the cut-off value determined by the proportionally reduced hCG values. No consensus was found among the studies [14-16]. The aim of the current study, therefore, was to assess the predictive efficacy of changes in β -hCG values at 0–4 days for single-dose MTX therapy.

Methods

Institutional review board approval was obtained from the Local Ethical Commission. The included cases were 132 patients with tubal EPs who were treated primarily with a single dose of MTX (50 mg/m²) at the Department of Gynecology and Obstetrics of Diyarbakir GaziYaşargil Training and Research Hospital of Health Sciences University between September 2016 and August 2017. This study was performed following the 2008 Declaration of Helsinki principles.

The EPs were diagnosed by standard clinical ultrasonographic with serial β -hCG measurements [19,20]. The indications for the initiation of single-dose MTX (50 mg/m²) therapy in the diagnosed cases were hemodynamic stabilization, no intraabdominal hemorrhage, a transvaginal ultrasound extrauterine EP focus, an extrauterine EP focus of 3.5 cm or less, no fetal cardiac activity, and the non-detection of trophoblastic tissue by endometrial sampling of the transvaginal ultrasound in the absence of an intrauterine gestational sac despite the presence of a normal β -hCG value of 1500–2000mIU/mL. All of the cases were examined for age, gravida, parity, TV-USG, complete blood count (CBC), full metabolic panel ([CMP] renal and hepatic), β -hCG values on days 0, 4, and 7 of treatment, and time until a β -hCG value of <5 mIU/mL. The success of single-dose MTX treatment was defined as a reduction in β -hCG costs of $\geq 15\%$ at 4–7 days and no need for surgery or a second MTX dose before a β -hCG value of <5 mIU/mL was obtained in weekly follow-ups. The failure of single-dose MTX treatment could result in a second MTX dose with a reduction of $\leq 15\%$ of β -hCG levels at 4–7 days. Surgical procedures to treat intraabdominal hemorrhage resulting from tubal rupture, independent of a decrease in β -hCG levels between days, should not be avoided during follow-up visits after treatment.

Comparisons were made concerning all of the parameters used for successful and unsuccessful cases after single-dose MTX treatment. Besides, cases with a decrease in β -Hcg at 0–4 days and a decrease in β -hCG values of >10% and >20% for these two days were also examined. Sensitivity, specificity, positive and negative predictive value of The prediction of treatment success was determined for these values. Besides, a cut-off value was determined by receiver operator characteristic (ROC) value analysis to determine the best proportional decrease in the β -hCG value at 0–4 days for successful single-dose MTX treatment outcomes. The sensitivity, specificity,

NPV, and PPV were determined. Patients with acute abdomen, hemodynamic instability, positive fetal cardiac activity, EP mass of ≥ 4 cm, or abnormal laboratory (hemogram, renal, and hepatic) values were excluded.

Statistical Analysis

Descriptive statistics (mean, standard deviation, minimum, median, and maximum) are used to describe continuous variables. The Mann-Whitney U test was used to compare two independent and non-normal distribution variables. The chi-square test (or Fisher's Exact test at appropriate locations) was used to examine the relationships among the categorical variables. To predict the medical treatment success, the ROC curve analysis (according to Youden's index) was used to determine the proportionally optimal rate of change of the β -hCG level at 0–4 days of treatment. As a result of the ROC analysis, the prediction of treatment success was >10% and >20%, and these values decreased only in cases with the most favorable rate of change at the predicted β -hCG level. Thus, the predictive success of these changes in the specificity, sensitivity, PPV, and negative predictive value (NPV) was assessed. The statistical significance for these values was determined by chi-square test.

Results

Of the 132 patients with non-rupture tubal EP in this study, 104 (78.8%) achieved success with MTX, and 28 (21.2%) experienced failure. The distribution of the characteristic features of the patients is summarized in Table 1. Although there was no statistical difference in median age, weight, parity, previous operations, and free fluid on the TV-USG ratios between the group in which the MTX treatment was successful and the group in which it was not, the β -hCG values were statistically significantly lower on days 0, 4, and 7 in the group that achieved success than in the one that did not. Also, the proportion of patients with decreased β -hCG levels at 0–4 days in the successful group (65.4%) was statistically significantly higher than in the unsuccessful group (28.6%).

The success of MTX therapy was predicted. In the ROC curve analysis, which was performed to determine the most favorable rate of change in the 0–4-day β -hCG values, this ratio was found to be 10.4%. However, as a result of this evaluation in terms of this ratio, sensitivity was determined as 48%, specificity as 78.5%, the PPV as 89.2%, and the NPV as 28.9% (AUC: 0.643, $p = 0.066$ [Figure 1]).

Table 1: Patient characteristics

	Success Group (N=104)	Failure Group (N=28)	p value
Age (year), [mean \pm SD]	29.05 \pm 5.5	29.85 \pm 5.9	0.609
Gravida, [mean \pm SD]	3.44 \pm 1.94	3.64 \pm 1.39	0.509
Parity, [mean \pm SD]	1.87 \pm 1.13	1.92 \pm 0.99	0.267
Free fluid on TV-USG, n (%)	28(26.9)	6(21.4)	0.676
Day 0 β -hCG level, [mean \pm SD], (mIU/mL)	1722 \pm 2005	5277 \pm 5995	0.015
Day 4 β -hCG level, [mean \pm SD], (mIU/mL)	1548 \pm 2060	4606 \pm 3943	0.011
Day 7 β -hCG level, [mean \pm SD], (mIU/mL)	1153 \pm 1728	4455 \pm 3654	0.001
Decreasing β -hCG level on day 4, N (%)	68(65.4)	8(28.6)	0.013

β -hCG: beta-human chorionic gonadotropin, EP: ectopic pregnancy

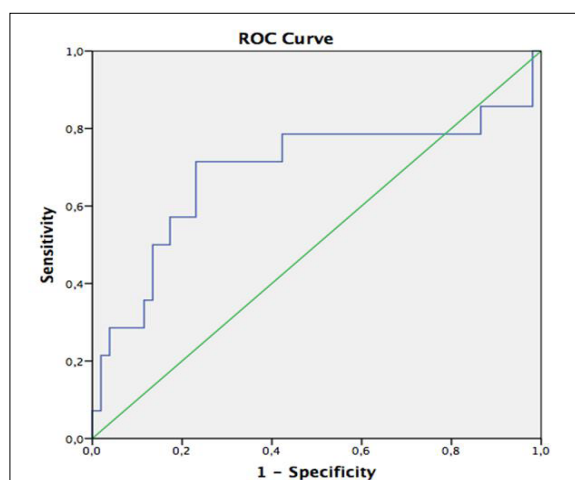


Figure 1: Predicted MTX treatment success based on β -hCG levels of > 10.4% (0–4 days) was assessed through an ROC curve analysis

Table 2 summarizes the success rates of medical treatment with MTX according to the β -hCG exchange rates at 0–4 days. Through an evaluation of the change rates, sensitivity was determined as 65.3%, specificity as 71.4%, the PPV as 89.4%, and the NPV as 35.7% in the cases of with decreased levels of β -hCG at 0–4 days. These results were statistically significant (AUC: 0.690, $p = 0.030$). However, there were no statistically significant differences in the sensitivity, specificity, PPV, and NPV determined for treatment success in the cases with decreases in β -hCG values of >10%, >10.4%, and >20% at 0–4 days.

Discussion

In this study, the success of single-dose MTX therapy for ruptured non-tubal EP was predicted by reduced β -hCG values at 0–4 days. Sensitivity was 65.3%, specificity was 71.4%, the PPV was 89.4%, and the NPV was 35.7%. The results were statistically significant (AUC: 0.690, $p < 0.05$). However, at 0–4 days, the β -hCG values changed by >10% (AUC: 0.643, $p > 0.05$) and >20% (AUC: 0.614, $p > 0.05$), and the ROC detected in the curve analysis was >10.4% (AUC: 0.643, $p > 0.05$). There were no statistically significant differences in the cut-off for sensitivity, specificity, the PPV or the NPV for predicting treatment success.

Skubisz et al. found they decreased β -hCG values to be predictive of treatment success with 73% specificity, 64% specificity, a PPV of 85%, and an NPV of 46%. The results were similar to those of the current study; however, Skubisz et al. did not report statistical significance [16].

The reduced β -hCG values of >10%, >10.4% (cut-off value for current study), or >20% at 0–4 days in all of the patients for predicting treatment success were 89.4%, 89.2%, and 88%, respectively. They are consistent with a PPV of 80–100%, which is related to the prediction of successful treatment outcomes in previous studies [14–16]. At the same time, these values The results of the current study are similar to those of Kirk et al., with 93% PPV for successful treatment of non-rupture tubal EP: 15% decrease in β -hCG levels at 4–7 days of treatment with a single dose of MTX [13].

In this study, the mean β -hCG values at 0, 4, and seven days were significantly lower for the group of patients who were treated successfully with single-dose MTX than for those who were not. These results are similar to those of Girija et al. [21], Ustunyurt et al. [8], and Celik et al. [17]. Indeed, Stika et al. [22] demonstrated that the initial β -hCG value is one of the most important predictors of treatment success. This supports the results of the current study and other studies [8,17,21] with low initial β -hCG values in the successful group. Besides, the β -hCG value decreased at 0–4 days in 65.4% of the cases in the group for which treatment was successful but only in 28.6% of the facts in the group for which treatment was unsuccessful. The difference between the groups was statistically

significant. There was no difference between the groups in the mean age, gravidity, parity, and free fluid as determined by the TV-USG results.

Overall, the success rate for single-dose MTX treatment was 78.8%. This is in line with the 52–94% success rates achieved in previous studies [9–12]. However, predicting successful outcomes for single-dose MTX therapy should be done after seven days of treatment. The high PPV in this study, in which the change in β -hCG seen at 0–4 days predicted successful outcomes, will allow the patient and the physician to determine appropriate treatment without a 7-day waiting period. This will also be instrumental in reducing the patients' stress [21].

The limitation of this study is the retrospective design, relatively low number of cases, and single-centered. Nevertheless, the study is important because of its evaluation of the statistical significance of the β -hCG levels observed at 0–4 days in previous studies for predicting successful treatment outcomes. Indeed, statistical significance had not been investigated in previous studies, although the sensitivity, specificity, PPV, and NPV had been calculated to predict the successful outcomes for the reduction value determined for β -hCG at 0–4 days [8,16,17,21].

Conclusion

This study showed that for non-ruptured tubal EP, reduced β -hCG values at 0–4 days after treatment with a single dose of MTX were predictive of successful outcomes, and this efficacy was statistically significant. In contrast, reduced β -hCG values of >10%, >10.4% (cut-off values for the current study), or >20% with higher a PPV after 0–4 days were not statistically significant. However, there is a need for more extensive prospective studies to establish this relationship.

Abbreviations

AUC: Area under curve;

B-HCG: Beta Human chorionic gonadotropin;

EP: Ectopic Pregnancy;

MTX: Methotrexate;

NPV: Negative predictive value;

PPV: Positive predictive value;

ROC: Receiver operator characteristic;

TV-USG: Transvaginal ultrasonography.

Ethics approval and consent to participate

The ethics committee of Health Science University Gazi Yaşargil Education and Research Hospital approved this study (Committee's

Table 2: Success rates of MTX treatment based on change rates of β -hCG levels at 0–4 days

Day 0–4 β -hCG level	AUC	Sensitivity	Specificity	PPV	NPV	p value
Decreased β -hCG level	0.690	65.3%	71.4%	89.4%	35.7%	0.030
Decreased β -hCG >10%	0.643	48.0%	78.5%	89.2%	28.9%	0.066
Decreased β -hCG >20%	0.614	42.3%	78.5%	88%	26.8%	0.132
Decreased β -hCG (Current study cut-off point >10.4)	0.643	48.0%	78.5%	89.2%	28.9%	0.066

β -hCG: beta-human chorionic gonadotropin, MTX: methotrexate, EP: ectopic pregnancy, AUC: area under curve, NPV: negative predictive value, PPV: positive predictive value

reference number:132).

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MO:acquisition, analysis, interpretation of data regarding ectopic pregnancy;

MHB:design of the work;

SA: interpretation of data;

BK:substantial contributions to the conception;

SCO: acquisition, analysis of study;

İB: data acquisition;

NP: drafting and revising study;

MŞB:acquisition, analysis of study.

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