Journal of Research in Medical and Dental Science
Volume 5, Issue 6, Page No: 20-24

Available Online at: www.jrmds.in
eISSN No. 2347-2367: pISSN No. 2347-2545

Evaluation of hepatic, renal and hematologic parameters during single, double and multiple treatment with Methotrexate in patients with ectopic pregnancy hospitalized in AL Zahra hospital

Maryam Asgharnia[1], Apameh Azarpira[2]*, Soudabeh Kazemi[3], Zahra Atar-Kar-Roushan[4], Davood Pourmarzi[5]

[1]Professor of obstetrics & Gynecology, Reproductive Health Research center, Guilan University of Medical Sciences, Rasht, Iran
[2,] Gynecologist, Reproductive Health Research Center, Al-zahra Hospital, Medical School, Guilan University of Medical Sciences, Rasht, Iran
[3]Assistant Professor of Obstetrics & Gynecology, Reproductive Health Research center, Guilan University of Medical Sciences, Rasht, Iran
[4] PhD, Assistant Professor in biostatistics, Faculty member of Guilan University of Medical Sciences, Rasht, Iran
[5]MSc in Epidemiology, Reproductive health research center, Guilan University of Medical Sciences, Rasht, Iran

DOI: 10.24896/jrmds.2017564

ABSTRACT

Treatment of ectopic pregnancy with Methotrexate (MTX) is very common. Nowadays available principles include repeated hematologic, hepatic and renal tests a week after administration of MTX but the importance of these tests in healthy woman with no previous history is not clear. The aim of this study was the evaluation of alternation patterns of CBC, LFT and RFT in 1, 7 and 14 days after treatment with single, double and multiple dose of MTX in healthy women with ectopic pregnancy. So that the necessity of performing these tests during MTX treatment in healthy women was determined. Material and Methods: study performed on 275 patients with ectopic pregnancy which hospitalized in AL-Zahra hospital and treated with MTX. Patients divided in three groups according to prescription of single, double and multiple doses of MTX and hepatic and renal functional tests and hematologic cell count evaluated for all patients in 1,7 and 14 days after MTX administration. Demographic data include: age, BMI, gravidity, parity and type of ectopic pregnancy were recorded for all patients. Overall data from three groups were compared. Homogeneity of age and BMI between three groups confirmed. Analysis of hepatic and renal function test and hematologic parameters showed that in single and double treatment route mean of AST, ALT, total and direct bilirubin, white hematologic cell and platelet count were significantly different in 1 and 7 days. However, there was no significant difference observed in multiple dose route. According to results, hepatic, renal and hematologic parameters in different treatment routs were significantly different. However, means in normal range and toxicity was not observed. It seems that measurement of hepatic, renal and hematologic parameters in 0 and 7 days after administration of MTX in healthy woman with no medical history of hepatic, renal or hematologic disorders is not necessary.

Keywords: Ectopic Pregnancy, Hospitalized patients, Methotrexate, Treatment

HOW TO CITE THIS ARTICLE: Maryam Asgharnia, Apameh Azarpira, Soudabeh Kazemi, Zahra Atar-Kar-Roushan, Davood Pourmarzi, Evaluation of hepatic, renal and hematologic parameters during single, double and multiple treatment with Methotrexate in patients with ectopic pregnancy hospitalized in AL Zahra hospital, J Res Med Dent Sci, 2017, 5 (6): 20-24, DOI: 10.24896/jrmds.2017564

Corresponding author: Apameh Azarpira
e-mail✉aram_407@yahoo.com
Received: 05/05/2017
Accepted: 20/10/2017

INTRODUCTION

Ectopic pregnancy comprises 1-2% of all pregnancy in US and Methotrexate (MTX) is

widely used as a first line therapy in these patients. Protocols for MTX administration differ according to dosage and prescribing [1]. The overall success rate of treatment in the ectopic pregnancy with MTX estimated around 89% [3].

MTX in folate antagonist which inhibits dihydrofolate activity [4] and subsequently causes depletion of Tetrahydrofolate resources, Tetrahydrofolate is crucial cofactors in DNA and RNA synthesis during cell proliferation. Tissues with high proliferation rate like trophoblast, bone marrow, lung epithelium and intestine mucosa are very susceptible to MTX [4-6]. Therefore complications of MTX include inhibition of cell proliferation and gastrointestinal movements with nausea, vomiting and abdominal pain [1, 4].

MTX also have direct toxic effect on liver and kidney. Rare complication associated with MTX administration include leukopenia, thrombocytopenia, renal failure, azotemia, nephropathy, hepatic atrophy, hepatic cirrhosis, necrosis or fibrosis, elevation of hepatic enzyme and hepatic failure which dependent to dose [6].
For this reason, most professional organizations like American College of Obstetricians and Gynecologists (ACOG) recommend hepatic, renal and hematologic screening tests in women received MTX which accompanied by liver functional testes (LFTs), Renal functional tests (RFTs) and cell blood count (CBC) [1, 6]. Nowadays protocols recommend these tests repeated a weed after MTX administration, however the necessity of these tests in healthy women treated with MTX is not clear [1].

Recent years, few studies conducted about complication and toxic effects of different MTX protocols and different results are also obtained from these studies [1, 7, 8]. Small sample size and selection of high risk patients are some of the limitation of these studies, also previous study were not evaluate multiple doses of MTX [7-9].

Therefore the aim of this study was to evaluate the alternation pattern of CBC, LFT and RFT during 1 and 7 days after treatment with single, double and multiple doses of MTX in healthy women with ectopic pregnancy, so that the need for these tests can be determined during treatment with MTX in healthy women.

MATERIAL AND METHODS

This is sectional prospective studies which performed on 275 patients with ectopic pregnancy which hospitalized in Al-Zahra hospital and treated with MTX. Transvaginal sonography followed by abnormal increase of β-hCG was performed to definitive diagnosis of ectopic pregnancy. Sonographic criteria used for diagnose include ectopic pregnancy sac, adnexal cyst with hypoechoic ring around pregnancy sac or adnexal cyst apart with ovary [2].

Patients divided according single, double or multiple administration of MTX.
In a single dose group, patients received 50 mg/m^2 MTX in day 1 and repeated on days 7 if reduction of β-hCG between 1-7 days was blew 15%.

In double dose groups, 50 mg/m^2 MTX administrated on days 1 and 4.
In multiple dose group, 1 mg/kg MTX administrated on 1,3,5 and 7 days and on days 2, 4, 6 and 8 0.1 mg/kg folinic acid prescribed.

Patients with failure in MTX treatment and need for surgery were excluded from study. Liver functional tests (AST, ALT, total and direct bilirubin) renal functional test (BUN, creatinine) and cell blood count (CBC) performed for all patients in first day of treatment with MTX and repeated in day 7. In multiple dose groups, tests evaluated a week after completion treatment on days 14. All analysis performed in laboratory section of Al-Zahra hospital, Rasht-Iran. Demographic data include age; BMI, gravidity and type of ectopic pregnancy were recorded for all patients. Data were analyzed using SPSS 21 software. Kolmogorov–Smirnov test was used to evaluate the normality of data. One way ANOVA with post Hoc LSD, Chi-square and paired t-test were performed to compression of data within and between groups on days 1 and 7.

RESULTS

Study performed on 275 patients with ectopic pregnancy which hospitalized in Al-Zahra hospital and treated with MTX. According to ANOVA analysis mean of age and BMI were not different significantly between groups (table 1).

Table 1: Compression of age and BMI in studied groups

Variable	Single dose (n=123)	double dose (n=119)	multiple dose (n=23)	p value
age	30.40±6.32	31.30±6.23	32.96±6.01	0.10
BMI	26.99±3.98	27.49±4.20	27.21±3.61	0.62

Table 2: Alternation of liver and renal functional test and hematologic parameters before and after treatment with single dose of MTX

Variable	before treatment (Mean±S.D)	after treatment (Mean±S.D)	p value
AST	21.56±5.78	23.34±9.32	0.009
ALT	19.30±8.71	23.99±14.95	0.001
Bili total	0.61±0.23	0.63±0.26	0.04
Bili direct	0.14±0.08	0.15±0.07	0.02
BUN	9.49±0.65	9.60±2.64	0.55
Cr	0.73±0.10	0.80±0.75	0.29
WBC	9043.08±2424.29	7896.74±2076.72	0.0001
Hb	13.10±9.91	11.92±1.29	0.18
Plt	251260±58819.10	243788±57840.54	0.006

Table 3: Alternation of liver and renal functional test and hematologic parameters before and after treatment with double dose of MTX

Variable	before treatment (Mean±S.D)	after treatment (Mean±S.D)	p value
AST	22.28±6.57	22.28±6.57	0.002
ALT	1950±9.32	26.94±19.04	0.0001
Bili total	0.59±0.17	0.62±0.18	0.001
Bili direct	0.14±0.06	0.15±0.06	0.008
BUN	10.03±2.75	10.23±3.14	0.37
Cr	0.73±0.08	0.73±0.10	0.52
WBC	9305.88±2518.14	7850.42±2260.03	0.0001
Hb	12.13±1.09	12.48±9.91	0.69
Plt	247798±50778.44	239470.58±52290.39	0.002

Table 3: Alternation of liver and renal functional test and hematologic parameters before, 1 and 2 week after treatment with multiple dose of MTX

Variable	before treatment (Mean±S.D)	after 1 week (Mean±S.D)	after 2 week (Mean±S.D)	p value
AST	21.56±5.78	23.34±9.32	27.78±13.40	0.802
ALT	19.30±8.71	23.99±14.95	28.55±15.66	0.868
Bili total	0.61±0.23	0.63±0.26	0.68±0.34	0.749
Bili direct	0.14±0.08	0.15±0.07	0.17±0.09	0.938
BUN	9.49±0.65	9.60±2.64	9.47±2.70	0.913
Cr	0.73±0.10	0.80±0.75	0.70±0.07	0.077
WBC	9043.08±2424.29	7896±2076.72	8094.44±3125.46	0.271
Hb	13.10±9.91	11.92±1.29	11.35±1.46	0.882
Plt	251260±58869.10	243788±57840.54	269527±2122.31	0.890

Paired t-test analysis showed that within single dose group mean of AST, ALT, total and direct bilirubin, WBC and platelet were significantly different between days 1 and 7 (table 2).

Paired t-test analysis showed that within double dose group mean of AST, ALT, total and direct bilirubin, WBC and platelet were significantly different between days 1 and 7 (Table 3).

According to results of variance analysis in multiple treatments with MTX, hepatic, renal and hematologic parameters were not significantly different between before, 1 and 2 week after administration of MTX (Table 4).

DISCUSSION

Hepatic and renal failure and hematologic disorders are known as life-threating complication of MTX. Therefore American College

of Obstetricians and Gynecologists (ACOG) recommend hepatic, renal and hematologic screening tests in women who's received MTX [1,6]. Nowadays protocols recommend these tests repeated a weed after MTX administration, however the necessity of these tests in healthy women treated with MTX is not clear [1].

Recent years, few studies conducted about complication and toxic effects of different MTX protocols and different results are also obtained from these studies [1, 7-9]. In our study mean of AST, ALT, total and direct bilirubin, WBC and platelet count in single and double dose groups were significantly different before and after administration of MTX and hepatic and hematologic parameters decrease after administration of MTX. These results was in contradictory with Pereira studies. However, study population in Pereira studies was small and groups were not identical (n=89 and 18 for single and double dose respectively) [7]. They reported that repetition of test in patients with normal results in day 1 is not necessary [7]. In the study conducted by Clark, hepatic and renal parameters slightly increased but not significantly different. In this study 320 patients received single dose of MTX and effect of double dose administration was not evaluated. Clark reported that measurement of creatinine and AST in the beginning of treatment with single dose of MTX is not necessary, but for other dose must be done [8]. Darbhama examined 68 patients after MTX administration and no alternation in hepatic, renal or hematologic parameters were reported [9].

In the present study, in multiple dose group, compression of mean AST, ALT, BUN, Hb and WBC before and 1 week after MTX administration were significantly different. In compression of before and 2 weeks after MTX administration (day 14) mean of ALT, BUN, Hb, WBC, total and direct bilirubin and creatinine were significantly different. According to the results, hepatic and renal enzymes elevated and hematologic parameters significantly decrease. About effect of multiple dose of MTX no studies were found [7-9]. This contradiction in results can be explained by small sample size of other studies. For example, Pereira examined 107 high risk patients (89 single dose, 18 double dose) which underwent IVF treatment [7]. In retrospective study performed by Clark, 320 patients which received single dose of MTX evaluated, but there was no evaluation performed for double or multiple dose administration [8].

Although the results of hepatic, renal and hematologic parameters alternations were significantly different, the means of these parameters in normal range and no toxicity or complication reported. However, according to mechanism of action of MTX, liver, renal and hematologic complications are possible and therefore exact history of hepatic, renal of hematologic disorders must be obtained before MTX administration. Willner reported intense toxicity in hemodialysis patients which received MTX and concluded that even low dose of MTX must not be administrated for treatment of EP in patients with inefficiency of renal function [11]. Isaacs reported two patients with ectopic pregnancy who's received MTX (single and triple dose) and life-threating neutropenia observed due to suppression of bone marrow. They concluded that due to these complications of MTX, monitoring and tests for control and early diagnosis of complication must be done [12]. Song et al examined single and double dose among 46 patients with EP, but there are no difference between the success of the treatment, as well as the incidence of complications, cost, and satisfaction were observed [13].

CONCLUSION

Although the results of hepatic, renal and hematologic parameters alternations were significantly different, the means of these parameters in normal range and no toxicity or complication reported. It seems that measurement of hepatic and renal functional tests and hematologic parameters before and a week after treatment by MTX in not necessary, However, according to mechanism of action of MTX, liver, renal and hematologic complications are possible and therefore exact history of hepatic, renal of hematologic disorders must be obtained before MTX administration and in the case of impairment in these organs, measurements of parameters performed before MTX administration.

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