Nature and Science

Websites:
http://www.sciencepub.net/nature
http://www.sciencepub.net

Emails:
naturesciencej@gmail.com
editor@sciencepub.net

MARSLAND PRESS
Multidisciplinary Academic Journal Publisher

Comparison of Double & Single-dose Methotrexate Protocols for Treatment of Ectopic Pregnancy

Hossam Aldin Hussein Kamel[1], Adel Aly Elboghdady[2] and Hamza Mohamed Elkilany Hamza[3]

[1]Professor, Obstetrics and Gynecology Department - Faculty of Medicine – Al Azhar University, Egypt
[2]Lecturer, Obstetrics and Gynecology Department - Faculty of Medicine – Al Azhar University, Egypt
[3] Resident Obstetrics and Gynecology - Kafr El-Zayat General Hospital, Egypt
hossam626@yahoo.com,elboghdadyd8@gmail.com, dr.mezo8008@gmail.com

Abstract: Background: Approximately 19.6% of all pregnancy-related deaths and 45.6% of early pregnancy deaths in the UK during 2006–2008 were associated with ectopic pregnancy. **Objective:** To comparison efficacy and safety of double dose of methotrexate at day 0 and day 4 versus single dose of methotrexate at day 0 in patient with tubal ectopic pregnancy. **Patients and methods:** This prospective randomized controlled clinical study was done at Sayed Galal University Hospital, Faculty of Medicine Al-Azhar University, between period March 2018 to March 2019, included 60 patients with a tubal ectopic pregnancy whom were be divided into two groups: Group A (n=30): received single dose (50mg/m^2) intramuscularly on day 0). Group B (n=30): received double dose (50mg/m^2) intramuscularly on day 0 and 4). **Results:** The overall success rate in this study was 93.3% where the success rate in group A was 90% while it was 96.7% in group B with significant difference (p=0.046). Three participants (two in group **A** and one in group **B**) had failed response to methotrexate treatment followed by surgical treatment. In group A, both patients' quantitative β-hCG titers at day 7 didn't not decline more than 15% than day 4 of the treatment. The third patient in group B had shown signs of disturbed ectopic pregnancy where urgent surgical interference (laparotomy) was done for her. **Conclusion:** Methotrexate therapy is a safe and effective alternative for the management of undisturbed ectopic pregnancy with mild side effects and associated advantage of avoiding invasive surgery provided that the criteria of medical management are strictly fulfilled.

[Hossam Aldin Hussein Kamel, Adel Aly Elboghdadyand Hamza Mohamed Elkilany Hamza. **Comparison of Double & Single-dose Methotrexate Protocols for Treatment of Ectopic Pregnancy.** *Nat Sci* 2020;18(5):1-6]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 1. doi:10.7537/marsnsj180520.01.

Keywords: Double & Single-dose Methotrexate Protocols, Ectopic Pregnancy

1. Introduction

Three methotrexate protocols, fixed multi-dose, single-dose and two-dose regimens, have been reported for the treatment of ectopic pregnancy. [1]

Of these protocols, the fixed multi-dose protocol involves the administration of four doses of methotrexate alternating with leucovorin (rescue regimen). As a result of the multiple dosing of methotrexate, side effects are more common, [2] and therefore, this protocol treatment protocol is rarely used for ectopic pregnancy treatment. [3]

The single-dose protocol has advantages, including the non-necessity of a rescue regimen, a lower incidence of adverse effects and better compliance, [4] but is associated with a higher treatment failure rate than the fixed multi-dose protocol. [5]

A new regimen called the 'two-dose' protocol was first introduced by ***Barnhart et al., 2007*** in an attempt to combine the efficacy and convenience of the fixed multi-dose and single dose protocols. [6]

Among multiple methotrexate protocols, multidose regimen includes IM administration of 4 methotrexate doses alternating with folinic acid in a course that extends for 8 days. While single dose protocol comprises single dose administration which could be repeated weekly up to 4 weeks in poor-responders. [7]

The potential advantages of single protocol over multi-dose one are elimination of folinic acid use, lower incidence of side effects, and better compliance and convenience. [8]

The single-dose protocol in a large meta-analysis conducted by ***Barnhart et al., 2003*** was associated with significantly lower success rate compared with multi-dose regimen (88% vs. 93%). [5] But, these data were not proved in multiple subsequent studies which showed comparable success rates in both regimens. [4]

The challenge to develop an optimum regimen that balance between efficacy and safety in one side and convenience in other side was attempted by ***Barnhart et al., 2007***, who first described what is called double-dose protocol. [6]

Although their reported rate is comparable to that of single-dose regimen, there are no clinical trials in literature have compared both regimens. [9]We hypothesize that efficacy of double-dose protocol could be more effective than nonrepeated single-dose regimen especially in patients with high baseline β-hCG and large gestational mass. [2]

The aim of this study to comparison efficacy and safety of double dose of methotrexate at day 0 and day 4 versus single dose of methotrexate at day 0 in patient with tubal ectopic pregnancy.

2. Patients and Methods

This prospective randomized controlled clinical study was done at Sayed Galal University Hospital, Faculty of Medicine Al-Azhar University, between period March 2018 to March 2019, included 60 patients with a tubal ectopic pregnancy whom were be divided into two groups: Group A (n=30): received single dose (50mg/m^2) intramuscularly on day 0). Group B (n=30): received double dose (50mg/m^2) intramuscularly on day 0 and 4).

Inclusion criteria:

Ectopic pregnancy was diagnosed with non-laparoscopic algorithm [9]**:** Gestational mass in adnexa with maximum diameter ≤ 4 cm. Baseline β-hCG<15000 mIU/ml. Hemodynamically stable patients. Absence of gestational cardiac activity, and patients agreed to methotrexate therapy and follow-up.

Exclusion criteria:

Non-tubal ectopic pregnancy. Clinically suspected tubal rupture. Free fluid at TVS extending beyond Douglas pouch. Low platelet count or abnormal liver or kidney functions, and heterotrophic pregnancy (co-existing intrauterine and ectopic pregnancies).

All patients taken an informed consent and investigated:

Investigation:

Laboratory test: CBC, liver enzyme, kidney function test and beta-human chorionic gonadotropin. *Imaging:* Transvaginal ultrasound.

All patients were followed up in Sayed Galal University Hospital in patient department:

Quantitative beta-human chorionic gonadotropin concentrations will be measured on day 4,7 if s. beta-human chorionic gonadotropin concentrations decline at least 15% on day 7. The measurement repeated weekly until the concentrations reach 15 miu/ml or less. If concentrations didn't decline by at least 15 at day 7 second dose of methotrexate will be given in this case the dose of administration considered day 1. Endo vaginal ultrasound done at day 4 and 7. Treatment success of s. beta-human chorionic gonadotropin concentration reach 15 miu/ml or less without need for surgical intervention. In case of failure of treatment, patient will be resorted to surgical treatment.

Precautions during the use of MTX:

To avoid the intercourse until hCG is undetectable. To avoid pelvic exams during surveillance of MTX therapy. To avoid sun exposure to limit risk of MTX dermatitis, and to avoid gas- forming foods because they produce pain.

During medical treatment in both regimens, surgical treatment was indicated in case of any signs of disturbed ectopic pregnancy. The primary outcome in this study was treatment success in both regimens.

Table (1): Comparison between group A single dose and group B double dose according to demographic data.

Demographic data	Group		t/x2#	p-value
	Group A: Single dose *(n=30)*	Group B: Double dose *(n=30)*		
Age (year)				
Range	21-37	19-45	0.083	0.664
Mean±SD	31.24±4.47	31.89±5.80		
Weight (Kg)				
Range	50-132	65-85	0.783	0.353
Mean±SD	84.96±18.24	80.36±5.99		
Menstrual GA (wk)				
Range	5-9	4-8	0.593	0.185
Mean±SD	6.54±0.55	6.41±1.04		
BMI (Kg/m2)				
Range	18-38.9	23-29	2.075	0.160
Mean±SD	30.07±4.56	27.93±2.00		
BSA (m2)				
Range	1.5-2.56	1.72-2	0.129	0.622
Mean±SD	1.99±0.24	1.94±0.09		
Parity				
0	11 (36.7%)	8 (26.7%)	3.377#	0.210
1	6 (20.0%)	6 (20.0%)		
>2	13 (43.3%)	16 (53.3%)		

t-Independent Sample t-test; #x^2: Chi-square test

*p-value>0.05 NS; *p-value <0.05 S; **p-value <0.001HS*

Statistical analysis:

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Independent-samples t-test of significance was used when comparing between two means. Chi-square (x^2) test of significance was used in order to compare proportions between two qualitative parameters. The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following: P-value <0.05 was considered significant. P-value <0.001 was considered as highly significant. P-value >0.05 was considered insignificant.

3. Results

This table presents a comparison between the two studied groups according to their demographic data. There was no statistical significant difference between studied groups regarding their demographic data as shown table 1.

This table shows a significant statistical difference regarding 7th day quantitative P hCG titre in both regimens groups (p = 0.016) as shown Table 2.

Table (2): Comparison between 7th day quantitative β-hCG titre in both groups.

β-HCG level (mIU/mL) at 7th day of treatment	Group		t-test	p-value
	Group A: Single dose *(n=30)*	Group B: Double dose *(n=30)*		
Range	2-2100	14-840	4.214	0.016*
Mean±SD	547.95±161.79	343.36±90.44		

*t-Independent Sample t-test; *p-value <0.05 S*

This table shows the success and failure rates of both regimens which were 90% in group A versus 93.3% in group B while failure rates in group A and B were 10% and 6.7% respectively with a significant statistical differences (p= 0.046) as shown table 3.

Table (3): Comparison between group A single dose and group B double dose according to outcome of treatment.

Success of TTT	Group				χ^2	p value
	Group A: Single dose *(n=30)*		Group B: Double dose *(n=30)*			
	N	%	N	%		
Success	27	90	29	96.7	4.146	0.046*
Failed treatment	3	**10**	**1**	3.3		

*x^2: Chi-square test*p-value <0.05 S; **p-value <0.001HS*

This table depicts a comparison between success and failure groups in overall studied cases showing a statistical significant difference with PID (p=0.025), IUD users (p=0.011), previous ectopic (p=0.010), and previous chemotherapy (p=0.018) as shown table 4.

Table (4): Comparison between success group and failure group according to Age (year), BMI (Kg/m2), parity, PID, IUD, previous ectopic and previous chemotherapy in overall studied cases.

		Outcome of TTT		t/2#	p-value
		Success group *(n=56)*	Failure group *(n=4)*		
Age (year)		32.21±5.67	26.75±4.39	2.356	0.126
BMI (Kg/m2)		29.19±4.13	27.21±2.65	1.498	0.621
	0	18 (32.1%)	1 (25%)		
Parity	1	10 (17.9%)	2 (50%)	2.558#	0.087
	>2	28 (50.0%)	1 (25%)		
PID	YES	10 (17.9%)	4 (100%)	3.659#	0.025*
	No	46 (82.1%)	0 (0%)		
IUD	Yes	12 (21.4%)	4 (100%)	2.814#	0.011*
	No	36 (64.3%)	0 (0%)		
Previous Ectopic	Yes	2 (3.6%)	0 (0%)	6.443#	0.010*
	No	54 (96.4%)	4 (100%)		
Previous Chemotherapy	Yes	2 (3.6%)	0 (0%)	4.242#	0.018*
	No	54 (96.4%)	4 (100%)		

BMI=Body Mass Index *t-Independent Sample t-test; #x^2: Chi-square test*
*p-value>0.05 NS; *p-value <0.05 S;*

Receiver operating characteristics (ROC) curve shows that a quantitative P hCG level of 3960 mIU/mL had sensitivity of 92.6%, specificity of 90.7%, PPV of 89.4% and NPV of 87.6% with accuracy of 91.3% for the success of the medical treatment as shown table 5.

Table (5): The sensitivity and specificity of quantitative β-hCG level in the follow up of both regimens as an indicator of success.

Success of TTT					
Cut off	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
3960.0	92.6	90.7	87.6	91.3	88.7

PPV= positive predictive value NPV= negative predictive data

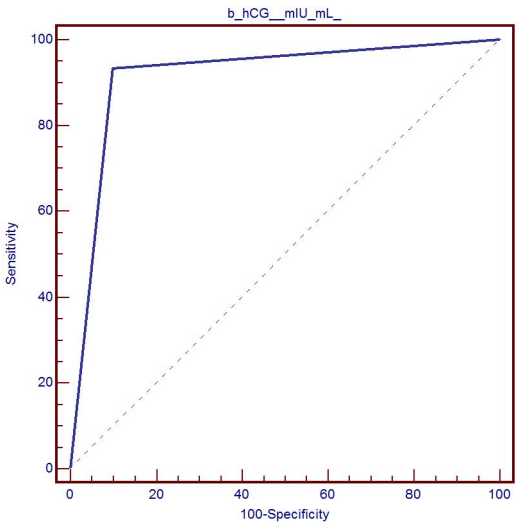

Figure (1): The Receiver operator curve (ROC) shows the accuracy of P-hCG mIU/mL levels in prediction of success of the medical treatment.

This table shows statistically significant increase mean of success group compared to mean of failure group according to endometrial thickness, with p-value 0.038*, also significant decrease mean of success group compared to mean of failure group according to pretreatment β-hCG level, with p-value 0.007* as shown table 6.

Table (6): Comparison between success group and failure group according to endometrial thickness and pretreatment β-hCG level (mIU/mL) of the study group.

	Outcome of TTT		**t-test**	**p value**
	Success group *(n=56)*	**Failure group *(n=4)***		
Endometrial thickness	12.56±1.29	11.78±0.58	2.558	0.038*
Pretreatment β-hCG level (mIU/mL)	1419.66±355.72	2406.12±475.61	5.859	0.007*

4. Discussion

Our study had shown that the double doses regimen of methotrexate therapy (group B) was significantly superior to methotrexate single dose regimen therapy (group A), with success rate of 90% in group **A** while 95% in group **B** with overall success rate of 92.5% for all studied cases, three cases only failed all over the study (two in group A and one in group B) where surgical interference was done. The failed cases in group (A) showed unsatisfied descent in B- hCG level between day 4 and day 7 while the failed case in group (B) showed signs of disturbed ectopic pregnancy. There was no plateau or rising titre in the quantitative level of B-hCG during follow up.

Our data agrees with ***Barnhart et al.,2003,*** who reported in his meta-analytic study that the crude overall success rate for women managed with the single dose therapy was 88.1% while it was 92.7% in the multiple doses therapy. [5]

Alleyassin et al., 2006 who performed a study comparing the treatment of ectopic pregnancy using multiple doses regimen versus single dose regimen of methotrexate therapy have reported success rate of 88% and 82% in multiple doses and single dose regimen respectively. [4]

In accordance with our results, ***Guvendag et al., 2010*** have shown that the success rate of multiple doses regimen was 89.7% while it was 80.6% in the single dose regimen. [10]

In addition, ***Gungorduk et al.,2011*** have reported in a retrospective study that the success rates of the single dose and multiple doses methotrexate regimens were 87% and 90.2% respectively. [11]

Guven et al., 2007 also reported that the success rate in the multiple doses regimen was inferior to the success rate in the single dose regimen (56.7% and 83.9% respectively). [12]

In addition, ***Malihe et al., 2013*** also reported that single dose regimen is better than multiple doses regimen with success rate of 87.8% and 76.1% respectively. [13]

The previous recommendations of RCOG were based on several studies demonstrating that only 15%-25% of women will require more than 1 dose. [14]

Klauser et al., 2005 in a trial comparing the single dose versus the fixed multiple doses methotrexate regimens, involving a total of 159 women, showed that no significant difference in treatment success between the two regimens. [15]

Similarly, ***Hajenius et al., 2007*** have reported that there is no significant difference between the two protocols of methotrexate therapy in treatment of unruptured ectopic pregnancy. [16]

Considering the previous debate on both methotrexate regimens, ***Barnhart et al., 2007*** reported that the two doses protocol had been proposed to provide the convenience of the single dose protocol and efficacy of the multiple doses protocol as it minimizes the number of injections and surveillance visits compared with the multiple doses regimen. [6]

In our study, the most common side effect during the course of treatment was the gastric upset constituting 60% in group (A) and 75% in group (B) with insignificant statistical difference. The other side effects as epigastric and pelvic pain, hair loss, gastric upset and oral ulcers had shown no significant statistical difference. The only statistically significant difference was in vomiting (p= 0.020).

On contrast, in the study of ***Barnhart et al., 2007*** they reported that the most frequent adverse effect was pelvic pain 27% for the double-dose and 20% for the single-dose protocols which was most propably caused by resolution of EP rather than methotrexate itself. [6]

The next common adverse effect for the double-dose regimen was nausea and vomiting (16%), a value that was in contrast to the single dose protocol which was (5.1%).

Gungorduk et al., 2011 reported that the side effects were minor, self-limited and generally included mild stomatitis and gastrointestinal upset but the most common side effects seen in their study was nausea and low grade fever (< 37.8°C). In addition, abdominal pain had been found in 17% of single dose group and 26.8% of multiple doses group. [11]

Another important part of our study was the evaluation of both risk factors as well as signs and symptoms of presentation for EP. Our study population was conducted to women who admitted with the symptoms and signs suggestive of an ectopic pregnancy, pelvic pain (90%), bleeding per vagina (75%) and / or amenorrhea (100%), in the first trimester of pregnancy.

Majhi et al., 2007 in his prospective study that was carried out among consecutive 180 patients of ectopic pregnancy have found that infertility (12.2%), pelvic inflammatory diseases (PID) (12.8%) and history of previous surgery (11.1%) were the important risk factors. He also found that amenorrhea (76.1%), abdominal pain (86.1%) and vaginal bleeding (42.2%) were the frequent presenting complaints. [17]

The receiver operator curve (ROC Curve) analysis in our study demonstrated that the cut off level 3600 mIU/mL of P-hCG level (area under curve, 0.533) has a sensitivity and specificity of 94.5% and 92.6% respectively for prediction of treatment success.

Hossam et al., 2012, in their prospective randomized study, the ROC curve analysis showed that the sensitivity and specificity of success were 81% and 89% at a P-hCG cut-off level of 5500mIU/mL (area under curve, 0.882). [18]

There was a statistically significant negative correlation between the pre-interference (pre-treatment) B-hCG level and the rate of success in the treatment with (p value = 0.008) which means that the higher pre-interference B-hCG level, the lower will be the success rate.

Our data was consistent with ***Lipscomb et al., 2004*** who had reported that the higher initial beta hCG was identified as a predictor of treatment failure. [19]

Also there was a statistically significant negative correlation between the pretreatment endometrial thickness detected with ultrasonographic scanning and the overall success rate (p value= 0.05).

In accordance with our results, a cohort study which was performed by ***da Costa et al., 2004***, on 73 cases of ectopic pregnancy have reported that the endometrial stripe thicker than 12 mm increases the risk of treatment failure with p value= 0.01. [20]

Conclusions

Methotrexate therapy is a safe and effective alternative for the management of undisturbed ectopic pregnancy with mild side effects and associated advantage of avoiding invasive surgery provided that the criteria of medical management are strictly fulfilled.

Multiple doses regimen of methotrexate is more effective in treatment of ectopic pregnancy than single dose regimen. However, the availability of leucovorin for the former is required in addition to its higher cost concern.

The prediction of methotrexate therapy success is concerned with the initial ectopic pregnancy titres of phCG where at cutoff titres of 3600 mIU/mL, the sensitivity of successful methotrexate therapy is more than 90%. When the diagnosis of EP is made early, conservative medical approach can be done.

References

1 American college of Obstetricians and Gynecologists: Medical Management of Ectopic Pregnancy. Obstet Gynecol. 2008; 111:1479-1485.

2 Lipscomb G, Stovall T and Ling F: Nonsurgical treatment of ectopic pregnancy. N Engl J Med. 2000; 343(18):1325-9.

3 Alkatout I, Honemeyer U, Strauss A, Tinelli A, Malvasi A, Jonat W, et al.: Clinical diagnosis and treatment of ectopic pregnancy. Obstet Gynecol Surv. 2013; 68:571–581.

4 Alleyassin A, Khademi A, Aghahosseini M, Safdarian L, Badenoosh B and Hamed EA: Comparison of success rates in the medical management of ectopic pregnancy with single-dose and multiple-dose administration of methotrexate: a prospective, randomized clinical trial. Fertil Steril. 2006; 85(6):1661–6.

5 Barnhart K, Gosman G, Sammel M and Sammel M: The medical management of ectopic Pregnancy: a Meta analysis comparing 'single and multidose' regimens. Obstet Gynecol. 2003; 101:778-84.

6 Barnhart K, Hummel AC, Sammel MD, Menon S, Jain J and Chakhtoura N: Use of a "2-dose" regimen of methotrexate to treat ectopic pregnancy, Fertil Steril. 2007; 87(2):250-6.

7 Rodi IA, Sauer MV, Gorrill MJ, Bustillo M, Gunning JE, Marshall JR, et al.: The medical treatment of unruptured ectopic pregnancy with methotrexate and citrovorum rescue: preliminary experience. Fertil Steril. 1986; 46(5):811–3.

8 Stovall T, Ling F and Gray L: Single dose methotrexate for treatment of ectopic pregnancy, Obstet Gynecol. 1991; 77:754-7.

9 Tawfiq A, Agameya A and Claman P: Predictors of treatment failure for ectopic pregnancy treated with single dose methotrexate. Fertil Sertil. 2000; 74:877-80.

10 Guvendag G, Dilbaz S, Dilbaz B, Aykan Yildirim B, Akdag D and Haberal A: Comparison ofsingle and multiple dose methotrexate therapy for unruptured tubal ectopic pregnancy: a prospective randomized study. Acta Obstet Gynecol Scand. 2010; 89(7):889-95.

11 Gungorduk K, Asicioglu O, Yildirim G, Gungorduk OC, Besimoglu B and Ark C: Comparison of single-dose and two-dose methotrexate protocols for the treatment of unruptured ectopic pregnancy. Journal of Obstetrics and Gynecology, 2011; 31(4):330-334.

12 Guven ES, Dilbaz S, Dilbaz B, Ozdemir DS, Akdag D and Haberal A: methotrexate therapy on tubalpatency. Fertility and Sterility. 2007; 88(5): 1288-92.

13 Malihe A, Minoo R, Usha M, Mohammadi F and Hosseini S: Comparison of single and multiple dose methotrexate therapy for ectopic pregnancy. Life Science Journal. 2013; 10(6s): 564-567.

14 Lipscomb G, Givens V, Meyer N and Bran D: Comparison of multidose and single-dose methotrexate protocols in the treatment of ectopic pregnancy. Am J Obstet Gynecol. 2005; 192:1844-8.

15 Klauser C, May W, Johnson V, Cowan B, Bryan D and Hines R: Methotrexate for ectopic pregnancy: a randomized single dose compared with multiple doses. Obstet Gynecol. 2005; 105:64S.

16 Hajenius PJ, Mol F, Mol BW, Bossuyt PM, Ankum WM and van der Veen F: Intervention for tubal ectopic pregnancy. Cochrane Database of Syst Rev. 2007; 1: CD000324.

17 Majhi AK, Roy N, Karmakar KS and Banerjee PK: Ectopic pregnancy - an analysis of 180 cases. J Indian Med Assoc. 2007; 105:308-12.

18 Hossam O, Salah R and Abdullah A: Comparison of double and single dose methotrexate protocols for treatment of ectopic pregnancy. International Journal of Gynecology and Obstetrics.2012; 116: 67-71.

19 Lipscomb GH, Givens VA, Meyer NL, Bran D: Previous ectopic pregnancy as a predictor of failure of systemic methotrexate therapy. Fertil Steril. 2004; 81:1221-1224.

20 Da Costa Soares R, Elito J, Han KK and Camano L: Endometrial thickness as an orienting factor for the medical treatment of unruptured tubal pregnancy. Acta Obstet Gynecol Scand. 2004; 83(3):289-292.

4/25/2020