ejpmr, 2020,7(12), 153-157

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

"STUDY ON EVALUATE EFFICACY OF METHOTREXATE SINGLE DOSE FOR MEDICAL TREATMENT OF ETOPIC PREGNANCY"

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Article Received on 12/10/2020 **Article Revised on 02/11/2020** **Article Accepted on 22/11/2020**

ABSTRACT

Background: Ectopic gestation though potentially life threating, timely diagnosis and appropriate treatment can reduce the risk of maternal mortality and morbidity. The benefits of medical therapy particularly with single dose methotrexate and the cure rate are high. **Objective:** The objective of the study was to explore the Efficacy of Methotrexate Single Dose for Medical Treatment of Etopic Pregnancy. **Materials and Methods:** This prospective observational study was conducted on patients diagnosed to have unruptured tubal pregnancy treated as in- patients at Department of Obstetrics and Gynecology, Rajshahi Medical College Hospital, Rajshahi, Bangladesh between January 2016 and December 2019. Women with an ectopic pregnancy, meeting the criteria for medical treatment were included in the study. All the patients were hospitalized. The protocol was a single dose of methotrexate 50mg IM or 1 mg/kg body weight. All the patients were reviewed after 4 days. If the beta-HCG level drops by 15%, then the women were reviewed weekly until the HCG level falls to less than 5 IU/L. The 2nd dose was given if the HCG falls below 15% or if there is no drop. **Results:** The overall success rate of single-dose methotrexate was 64%. 2nd dose methotrexate was required in 11% of patients. In 25% of the cases, surgery was required. Laparoscopic procedure was done in 12% of cases and emergency laparotomy was performed in 13% of the cases. **Conclusion:** Single-dose methotrexate therapy is effective in a selected group of patients.

KEYWORDS: Ectopic Pregnancy, Single Dose Methotrexate, Medical Management, Beta HCG.

I INTRODUCTION

Ectopic pregnancy is the implantation of ovum and its subsequent gestation outside the uterine cavity. In about 95% of such cases, ectopic gestation occurs in the fallopian tube when it is called tubal pregnancy. Other sites of ectopic gestation are ovaries, abdomen, interstitium, rudimentary horn of bicornuate uterus, cervix and cesarean scar. Combined intra-uterine and extrauterine pregnancy in multiple gestations is called heterotopic pregnancy. Ectopic pregnancy is potentially life-threatening and the incidence of it continues to increase day by day from 1:150 to 1:40-1:25 due to increased incidence of pelvic inflammatory disease, use of IUCDs and wider use of Assisted Reproductive Technologies (ART).[1] Ectopic gestation though potentially life-threatening, timely diagnosis, and appropriate treatment can reduce the risk of maternal mortality and morbidity related to ectopic gestation. In acute conditions, the patient may present with haemorrhagic shock, acute pain, a vaginal bleeding with a history of amenorrhea. In sub-acute and chronic conditions, the patient may present with amenorrhea, abdominal pain, vaginal bleeding, retention of urine. Positive urine pregnancy test with a ratio of beta HCG at 48 hours/ beta HCG at 0 hours of less than 2, transvaginal ultrasound,[2] MRI, culdocentesis, and laparoscopy are the diagnostic tests of ectopic pregnancy. Serum progesterone level is not useful in predicting ectopic pregnancy.[3] The principle of use of Methotrexate in the management of ectopic gestation is based on the fact that methotrexate is a folate antagonist that inactivates dihydrofolate reductase enzyme leading to a fall in tetrahydrofolate which is an essential co-factor in the synthesis of DNA and RNA during cell division. Rapidly dividing cells are most vulnerable to methotrexate. This accounts for the drug's effect on trophoblastic tissue.[4] The single dose of methotrexate therapy comprises parenteral administration (intramuscular) of methotrexate in a dose of 50 mg/square meter (approximately 1 mg/kg body wt.), the expected side effects are anaemia, leukopenia, agranulocytosis. The contraindications of methotrexate therapy are serum creatinine more than 1.3 mg%, SGOT && SGPT more than 50 IU/ liter, chronic alcoholism, pre-existing blood lymphomas, acute pulmonary distress, peptic ulcers, breastfeeding. The benefits of medical treatment are- It avoids surgery. High cure rate as surgery, less costly. It is not skilled dependent and higher future fertility rate, than, with surgery. The earlier the ectopic is diagnosed the lower the beta hCG, the smaller

the size of the gestational sac, the better is the fertility rate.

II AIM OF THE STUDY

The aim of the study was to explore the Efficacy of Methotrexate Single Dose for Medical Treatment of Etopic Pregnancy.

III MATERIALS AND METHODS

This prospective observational study was conducted on patients diagnosed to have unruptured tubal pregnancy treated as in- patients at Department of Obstetrics and Gynecology, Rajshahi Medical College Hospital, Rajshahi, Bangladesh between January 2016 and December 2019. Women with an ectopic pregnancy meeting the criteria for medical treatment were counselled to participate in this trial. The diagnosis of ectopic pregnancy was made by quantitative measurement of serum β-hCG, when transabdominal ultrasonography shows no intrauterine pregnancy and with positive urine pregnancy test or any evidence of gestational sac in the tubo-ovarian region. Serum β-hCG was repeated after 48 hours to see the doubling of the hormone. If β-hCG was not doubled or increment was <66%, it was considered an ectopic pregnancy. Inclusion criteria: Patient with ectopic pregnancy who are haemodynamically stable. No signs of intraperitoneal bleeding, free from any severe abdominal pain, a gestational sac of size less than 4 cm with or without any cardiac activity, and serum β-hCG level-up to 5000 IU/L.

Exclusion criteria were acute ruptured ectopic pregnancy, chronic ectopic pregnancy, a patient with hepatic and renal dysfunction. All the patients were advised for hospitalization once it was diagnosed with ectopic pregnancy. Verbal consent was taken. The protocol was a single dose of injection methotrexate 50 mg IM or 1 mg/kg body weight when body weight was less than 50 kg. All the patients were reviewed after 4 days and if the beta hCG level dropped by 15% then women reviewed weekly till β-hCG drops to <5 lU/L. If the drop was less than 15% after 4 days, the second dose of methotrexate was given. Patients were reviewed at 4 days after the last injection and at weekly intervals if needed. Patients were instructed to refrain from intercourse until complete resolution of the ectopic pregnancy and also advised to use contraceptives like oral contraceptive pills for 6 months after completion of treatment. Antibiotics, antispasmodic and analgesics were given to all patients and continued for 7 days for subsidence of inflammatory reactions. Patients were also instructed to notify any complaints like severe abdominal pain and ultrasonogram was repeated for detection of ruptured ectopic pregnancy. Patients were informed about the need for laparotomy or laparoscopy if there is any evidence of intraperitoneal hemorrhage, which is indicated by tachycardia, hypotension, anemia or persistence of pain even after using analgesics. Finally, repeat ultrasonography was done to detect abnormality after cessation of β-hCG. The success rate of medical treatment is defined by the absence of intervention by surgery.

IV OBSERVATION AND RESULTS

Total number of patients recruited for the study was 100. 64 patients (64%) out of 100 had a successful resolution after single dose methotrexate therapy. 45.16% of patients who are primigravida and 72.46% of patients of multigravida had a successful treatment with single dose methotrexate.

Table 1: Age Wise Distribution and the Outcome (N=100).

Age of the Patient in Years	Total no. of Patients (100)	No. of Cases with Successful Single Dose Regime (75)	No. of Patients who had a Laparoscopy (12)	No. of Patients who Landed up in Laparotomy (13)
<20	21	18	1	2
20-30	70	52	9	9
>30	9	5	2	2

Table 2: Socioeconomic Class and Outcome[5] (n=100).

Socioeconomic Class (Modified Kuppuswamy Classification)	Total no. of Patients in the Group	No. of Patients with a Successful Outcome
Upper	Nill	Nill
upper middle	20	15
Lowe middle	22	15
Upper lower	30	16
Lower	28	18

Table 3: Gravidity and Outcome (N=100).

Gravidity	No. of Patients	Patients with a Successful Outcome
Primigravidae	31	14(45.16%)
Multigravidae	69	50(72.46%)

There were 3 cases of repeat ectopic. Out of the 3 patients, one patient underwent salpingectomy and the other 2 patients were treated with multiple dose methotrexate therapies. All 3 patients responded to a single dose regimen. One among 100 patients underwent in vitro fertilization and responded to single drug regime.

Table 4: Body Weight and Outcome (n=100).

Body Weight in kgs	Successful with Single Dose Regime	Laparoscopy	Laparotomy
40-45	21	1	2
45-55	45	6	5
55-65	9	5	6

Out of 100 patients, 28 patients had mild anaemia 10 patients had moderate anaemia and 2 patients had severe anaemia. These 2 patients were given blood transfusions prior to the therapy. Total number units of blood transfusions during the study was 15. Meantime of resolution is 4 weeks.

Table 5: Period of Amenorrhea and Outcome (n=100).

Period of Amenorrhea	Number of Patients	Number of Patients with a Successful Outcome
<1 1/2 months	49	34(69.3%)
>1 1/2 months	51	30(58.8%)

Table 6: Gestational Age by Ultrasound and Outcome (n=100).

Gestational Age by Ultrasound	Number of Patients	Number of Patients with a Successful Outcome
<6 weeks	54	38(70.3%)
>6 weeks	46	38(70.3%)

Table 7: Size of the Gestational Sac and Outcome (n=100).

Gestational Sac Size	Number of Patients	Number of Patients with a Successful Outcome
<3cms	55	40(72.7%)
3-4 cms	45	24(53.35%)

Table 8: Cardiac activity and outcome (n=100).

Cardiac Activity	Number of Patients	Number of Patients with a Successful Outcome
Present	60	43(71.66%)
Absent	40	21(52.5%)

Table 9: Initial β-HCG and Outcome (n=100).

Initial HCG	Number of Patients	Number of Patients with a Successful Outcome
<2000 IU	27	20(71.6%)
>2000 IU	73	44(60.2%)

Table 10: Fall in β-HCG and Outcome (n=100).

Fall in β-HCG	Total Number of Patients	Patients with a Successful Outcome	Laparoscopic Procedure	Laparotomy
>40%	38	34	4	-
40-15%	37	30	2	5
<15%	25	11	6	8

Patients who had less than 15% of the fall in β-HCG were given a 2nd dose of methotrexate and 11 out of 25 patients had resolution with 2nd dose. 6 patients in this group were subjected to laparoscopy and 8 patients landed up in emergency laparotomy. 6 (8%) patients out 75 who had fallen in β-HCG by more than 15% after 1st dose required elective laparoscopy as there was the persistence of mass, symptoms, and delay in further fall in β-HCG. 6 (24%) patients out of 25 patients who required a 2nd dose of methotrexate had a laparoscopy. 5 (6.66%) out of 75 patients who had fallen in β-HCG by more than 15% after the 1st dose required. Emergency laparotomy and 8(32%) patients out 25 after 2nd dose required emergency laparotomy due to acute symptomology and signs of ruptured ectopic gestation.

None of the patients who were given a single dose drug developed side effects.

V DISCUSSION

An ectopic pregnancy occurs in around 1% pregnant woman and may seriously compromise women's health and future fertility. With an increase in the use of ARTs and PIDs incidence of ectopic pregnancy has increased and it remains the great puzzle of gynecology and no other pelvic conditions give rise to more diagnostic errors like this condition. The patients may or may not have symptoms pointing to pregnancy with or without a short period of amenorrhea, pelvic pain and irregular vaginal bleeding. However, only half of the patients with ectopic pregnancy can be correctly diagnosed based on clinical features alone. Ectopic pregnancy can be diagnosed before the patient's condition has deteriorated and the cornerstone of the diagnosis is the use of tram's vaginal ultrasound and serum beta HCG measurement. Surgery and medical management are the two ways to treat ectopic pregnancy. Both are effective, and the choice depends on the technology clinical situation, site if ectopic pregnancy, site of the ectopic and the access to technology, patients who are severely anaemic before therapy and who presented with tubal rupture during the observational period were given a blood transfusion. A total number of units of blood required in the study was 15. Systemic single dose methotrexate seems to offer the greatest benefits in terms of efficacy and tolerability. It has proved to be a good alternative to laparoscopy in selected cases. The success rate of the systemic methotrexate in our study was 64% (n=64). Two doses of methotrexate are required in 11% of patients (n=11). Chang J, Elam-Evans LD, Berg CJ, et al.[5,6] concluded that medical treatment with single dose methotrexate or 2 doses systemic methotrexate seems to be an equal therapeutic option for patients with unruptured ectopic gestation Lipscomb GH, Bran D. McCord ML, Portera JC, Ling FW.[7] in a large series of 315 patients concluded that single-dose methotrexate for treatment of ectopic pregnancy is associated with an excellent overall success rate. In our study, 71.6% of women who had hcg levels less than 2000 in and 60.2% of women who had hcg levels between 2000 and 5000 is, successfully responded to single-dose therapy. Shalev E. Oloffson,[8] recommended multiple doses of methotrexate when beta HCG exceeds 5000 IU/ml. Shalev E, Barnhut KT, Kirk E, Condous V, Haider Z.[9] recommended surgical treatment with beta HCG exceeds 4000 IU/ml KT Barnhart, Nguyen Q, Kaptiz M, Downes K, Silva C[10] proved in a meta-analysis comparing single dose and multiple regimens concluded that women treated with single-dose methotrexate were more likely to fail medical treatment of ectopic pregnancy than those treated with doses. Rozenberg[11] showed that the effect of methotrexate decreases linearly when serum beta HCG level is increased. Stovall TO, Ling FW, Gray LA, Carson SA, and Buster[12] IDE notes that the regimen with single-dose methotrexate requires minimal laboratory follow up and eliminates leucovorin recovery making it the regimen of choice for medical treatment of unruptured ectopic pregnancy. Merisio C, Anfuso S, Berretta R, Gualdi M, Pultrone DC, Melpignano M,[13] in their study provide the evidence of efficacy of methotrexate in ectopic pregnancy treatment both as a therapy and as a form of clinical management. The successful medical management of ectopic pregnancy defined as beta HCG levels becoming negative after the administration of one or multiple doses of methotrexate. In our study 25 (25%), patients out of 100 required surgical intervention. Suliman KB et al., in their study concluded that in 86% of the patient's methotrexate was successful. With pretreatment HCG level of 3000 IU to 4000 IU had a greater probability of requiring either surgical or Multi-Drug therapy. The potential for emergency surgery remains an important risk. In our study single dose regimen is found to be more cost-effective to the patients. Lecuru F.[14] Morlock S, Robin F. Direct in their study concluded that the cost of a single dose of methotrexate unruptured ectopic pregnancy is very cheaper compared to the multi-dose regimen and surgical treatment.

VI CONCLUSION

Methotrexate has proven to be an effective medical management for ectopic pregnancies in a society where tubal conservation is of utmost importance. The medical management by methotrexate seems to offer several benefits over surgical treatment. It is less invasive, less expensive and does not need expertise like laparoscopy. Future reproductive expectations are better with methotrexate with higher intrauterine pregnancy rates and lower ectopic rates. However, the risk of tubal rupture after medical treatment, combined with a prolonged follow-up for an ectopic pregnancy to resolve requires monitoring for rupture and methotrexate side effects making compliance important in patient selection. Single-dose methotrexate offers a safe and effective nonsurgical method of treating selected patients and one important advantage of medical therapy is the potential per considerable savings in treatment costs. This study gave a good impression of single-dose methotrexate therapy as a treatment in selected cases of ectopic gestation. The advent of modern diagnostic and therapeutic modalities had changed the clinical scenario of ectopic pregnancy from one of the possible disaster to one of potential success. An alert woman who has awareness of signs and symptoms of ectopic pregnancy can help the doctors to make the diagnosis earlier and treat the problem with less invasive methods, preserve the fallopian tubes, and greatly increase the hope of achieving a healthy fruitful outcome.

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