Original Research Paper Gynaecology

A Comparative Study of Efficacy of Methotrexate and Mife-Pristone with Methotrexate in Medical Management of Ec-Topic Pregnancy

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ABSTRACT

OBJECTIVE: Our goal was to compare the use of a combination of methotrexate and mifepristone with methotrexate alone in the medical management of ectopic pregnancy.

STUDY DESIGN: This was a randomised control trial. Patients with progressing ectopic pregnancy meeting cri-teria for medical management were included in the study. Patients were assigned into two groups based on random selection.Group 1 was given a combination of 200 mg mifepristone and inj Methotrexate IM (50 mg/m2).Group 2 received only injection methotrexate.The dose of methotrexate was repeated depending on the individual patient response.

RESULTS & CONCLUSION: There was no statistically significant difference in terms of success rate and the need for a second dose of methotrexate in both the groups.However there was an earlier resolution of ectopic pregnancy and reduced duration of hospital stay when a combined therapy was used as against using methotrexate alone for medical management.p=0.002275

Combination therapy did not significantly decrease the need for laparotomy.

KEYWORDS Ectopic pregnancy,Mifepristone,methotrexate,Laparotomy

INTRODUCTION

The World wide incidence of ectopic gestation is 1-2%(1).In india it is around 0.3 to 0.7% .Now a days ectopic pregnancy is on a raising trend.Increase in number of patients with infertility going for assisted reproductive techniques and increasing sterilisation procedure and tubal reanastomosis procedures have contributed to this rise.With the advent of transvaginal ultrasound and beta hCG measurement early diagnosis of ectopic pregnancy is possible.The diagnosis of ectopic pregnancy is done by Serum beta hcg and USG

A transvaginal ultrasound can detect gestational sac at serum beta HCG of 1500-1800 mIU/ml.For multiple pregnancy it can diagnose at a level of about 2300 mIU/ml.A doubling titre of serum beta Hcg in 48-72 hrs as seen in intrauterine pregnancy is not evident in ectopic pregnancy.(2)

In a non-randomized phase II study (Perdu et al., 1998), the failure rate was significantly more reduced in patients treated with mifepristone and methotrexate than in patients previously treated by methotrexate alone. In a randomized controlled trial (Gazvani et al., 1998), unruptured ectopic pregnancy appeared to resolve significantly faster with the combination of methotrexate and mifepristone when compared to methotrexate alone, as assessed by the interval to resolution of b-hCG levels.

Hence this study was done to determine the efficacy of combination therapy for successful medical management of ectopic pregnancy.

MATERIAL AND METHODS

The study was conducted between 2013-2015 at the Institute of obstetrics and gynaecology chennai.40 women with ectopic pregnancy meeting the criteria for medical management were counselled to participate in this study.

INCLUSION CRITERIA

- Haemodynamically stable patient
- -Gestational sac <4 cm on USG
- -Serum beta hcg <10,000 mIU/ml(3)
- Absent cardiac activity in the sac
- Patient willing for follow up

EXCLUSION CRITERIA

- Haemodynamically unstable patients,Ectopic of diameter >4cm on USG
- Patients with hepatic and renal dysfunction,haemorrhagic disorder
- Baseline serum beta hcg level,UPT and USG was done for all the patientsA detailed history of symptoms and past medical history was recorded.Physical exam findings and vitals recorded..Complete haemogram,RFT,LFT was done.
- Blood grouping typing was done for all the patients and those who were RH negative were given Rh isoimmunoglobulin
- All patients received IM Injection of Methotrexate 50 mg/sqm of Body surface area and a single dose of oral mifepristone 200 mg for patients in group 1 and a placebo for the patients in group 2 .
- Patients were under close follow up.They were reviewed at day 4 and day 7. All women had serial serum b-hCG, hepatic and renal function tests and full blood counts on each visit.
- If b-hCG levels dropped by >15% between days 4 and 7, the women were then reviewed weekly until serum b-hCG concentrations fell to <10 mIU/ml. If the decrease was <15% between days 4 and 7, a second injection of methotrexate (50 mg/m2) was given i.m. In these cases, b-hCG levels were also checked on days 11 and 14.
- A repeated dose of methotrexate was also given if gestational cardiac activity was still present on day 7 after the first or the subsequent dose of methotrexate.

- Patients were instructed to refrain from alcohol and intercourse and to avoid vitamin preparations containing folic acid until complete resolution of the ectopic pregnancy, and to use either oral contraceptive pills or barrier contraception for 3 months after treatment completion.
- Repeat transvaginal scanning was performed to rule out rupture of ectopic pregnancy if the patient presented with increasing abdominal pain. When gestational cardiac activity was seen at treatment initiation, transvaginal scanning was performed on alternate days until cardiac activity disappeared. Repeated clinical pelvic examinations were not performed in any patients to avoid the potential of iatrogenic tubal rupture after treatment initiation.
- Surgical treatment was indicated if the b-hCG level had not decreased sufficiently after day 14 and if pelvic pain was not controlled by non-opiate analgesics or if signs of internal haemorrhage developed.

OUTCOME

The primary outcome was the success rate of the medical treatment, defined by the absence of indication for surgical intervention before serum b-hCG levels were below 10 mIU/ml irrespective of the number of injections of methotrexate.

The secondary outcomes were: (i) efficacy criteria: indications for surgical intervention, surgical modalities, need for a second dose of methotrexate, number of days in hospital, time-interval from randomization to fall in b-hCG levels to <10 mIU/ml; (ii) safety and tolerance criteria: gastritis, stomatitis, reversible alopecia, increase in serum aminotransferase concentrations, severe neutropenia or thrombocytopenia.

RESULTS

GROUP 1

Out the 20 cases treated with mifepristone and methotrexate 17 cases resolved completely.The success rate was 85%.Three patients required surgical intervention due to failure of medical management.(15%). 3 patients required a second dose of methotrexate.The average time taken for a complete resolution was 21 days.The average duration of hospital stay was 7 days.

GROUP 2

- Out of the 20 cases in group 2 fourteen cases were successfully managed with methotrexate with a success rate of 70 %.6 cases needed surgical intervention .Failure rate of 30%.5 out of the fourteen cases required a second dose of methotrexate.The average time taken for complete resolution was 28 days.Average duration of hospital stay was 12 days.

ANALYSIS OF STUDY

TABLE 1-SUCCESS RATE

	SUCCESS	FAILED MEDICAL MANAGEMENT
GROUP 1	17 (85%)	3 (15%)
GROUP 2	14(70%)	6(30%)

Chi square value -1.2903 and P value of 0.255989 which was not significant statistically at p<0.05.Thus the combination of mifepristone and methotrexate in medical management was not statistically significant .

TABLE 2 NEED FOR SECOND DOSE OF METHOTREXATE

	2 ND DOSE METHOTREXATE	FIRST DOSE OF METHOTREXATE
GROUP 1	3	14
GROUP 2	5	9

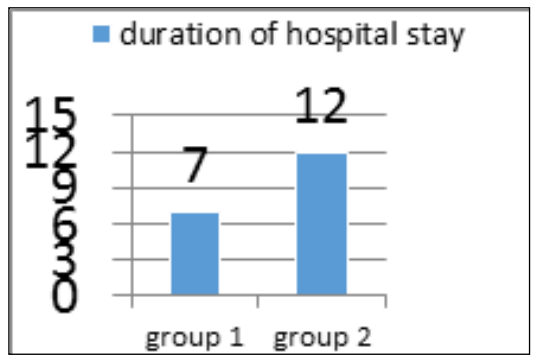
Chi square- 1.3089 p value-0.252595 not statistically significant at p<0.05.The combination of drugs did not alter the requirement of 2nd dose methotrexate

TABLE 3-TIME TAKEN FOR RESOLUTION

	<3 WEEKS FOR RESOLUTION	>3 WEEKS FOR RESOLUTION
GROUP 1	13	4
GROUP 2	3	11

The chi square test -9.3136 P=0.002275.Highly significant.65% of patients in group 1 showed complete resolution in less than 3 weeks as compared to 15% in group 2

TABLE 4-DURATION OF HOSPITAL STAY



The average duration of hospital stay in group 1 was 7 days whereas in group 2 it was 12 days.The difference was statistically significant

DISCUSSION

In_this study combination therapy for the medical management of ectopic did not show significant success rate when compared to methotrexate only supported by another study published by Patrick et al(4)

-USG is the most important tool for the diagnosis of ectopic pregnancy .

Colour flow doppler usg helps in better detection of ectopic by increasing the sensitivity or specificity.Ectopic pregnancy can be treated by medically or surgically.(5)

MEDICAL MANAGEMENT

Only methotrexate has been extensively studied as an alternate to surgical therapy(6).De novo purine and pyrimidine synthesis is halted,which leads to arrested DNA,RNA and protein synthesis.Thus,methotrexate is highly effective against rapidly proliferating tissue such as trophoblast,and overall ectopic tubal pregnancy resolution rates approximate 90% with its use.

For ease and efficacy IM Injection of methotrexate is used most frequently for ectopic pregnancy resolution .Single dose and multi dose protocols regimen are available.Single dose therapy offers simplicity,less expense and less intensive post therapy monitoring and does not require leucovorin rescue. However some but not all studies report a higher success rate for the multi dose regime

Treatment Regimen:

Day 1- Give methotrexate 50mg/m2 IM Day 4 -Measure Quantitative hCG level (it is common to see a rise in serum hCG levels from Day 1)

Day 7 -Measure Quantitative hCG level

If there has been a decline of > or = to 15% from the Day 4 level, follow serum hCG levels weekly until <5mIU/ml (or)

If there has NOT been a decline of > or = to 15% from the Day 4 level, a second dose of methotrexate 50mg/m2 IM should be given to the patient (new Day 1) and hCG levels should be measured again on Day 4 and Day 7 after the second dose. If values decline by > or = to 15%, follow serum levels weekly until <5mIU/ml

If there is an inappropriate decline in serum hCG levels after a second dose of methotrexate, the patient should be re-evaluated and therapy either with additional methotrexate or surgical intervention is required.

MULTIDOSE METHOTREXATE

-Administer_methotrexate 1mg/kg IM on days1,3,5,7

Administer leucovorin 0.1 mg/kg on days 2,4,6,8

Measure serum beta hcg level on day 1,3,5,7 until a 15% decrease between two measurements.

-Once beta hcg levels drop by 15% then stop methotrexate and monitor beta hug weekly until non pregnant level.

ABSOLUTE CONTRAINDICATIONS TO METHOTREXATE TREATMENT

-Haemodynamically unstable

-Ruptured ectopic pregnancy.

-Preexisting blood dycrasias,active pulmonary disease,hepatic,-renal or haematological disorder,immunodeficiency

RELATIVE CONTRAINDICATIONS

-Gestational sac larger than 3.5 cm

-Embryonic cardiac motion.

Role of mifepristone in managing ectopic gestation

Mifepristone is a 19 norsteroid with potent competitive antiprogestational as well as antiandrogenic activity.It blocks progesterone support to the endometrium,and stimulates uterine contractions.If implantation has occurred it blocks decidualization,the conceptus is dislodged

The combination therapy has been found to hasten the time taken for resolution of beta hcg as well as duration of hospital stay as supported by our study but failed to demonstrate a superior success rate when compared with methotrexate alone.However larger trials are required to prove the efficacy of combination therapy versus methotrexate alone for a successful management of ectopic pregnancy.

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