IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

COMPARE THE SUCCESS RATES OF SINGLE AND FOUR DOSE METHOTREXATE PROTOCOLS FOR THE TREATMENT OF UNRUPTURED TUBAL ECTOPIC PREGNANCY.

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❖ ABSTRACT

OBJECTIVE: To compare the success rates of single and four dose methotrexate protocols for the treatment of unruptured tubal ectopic pregnancy.

DESIGN: Retrospective randomized controlled trial.

SETTING: obstetrics and gynaecology department ,GGG hospital , Jamnagar

POPULATION: Thirty women treated with methotrexate therapy for unruptured tubal ectopic pregnancy.

METHODS: 20 received a single dose and 10 received a four dose methotrexate regimen.

MAIN OUTCOME MEASURES: Success rate of methotrexate therapy (women successfully treated with one injection and women who completed four doses).

RESULTS: In the single dose group, treatment was considered successful in 16 women (80%), whereas in the four dose group, 9 women (90%) responded to treatment . In the single dose group 4 women (20%) experienced side-effects compared to 3 (30%) of those who had four doses .

CONCLUSION: A result of four dose methotrexate regimen and single dose methotrexate regime was comparable. If we compare side effects , four dose regimen has more side effects .

❖ INTRODUCTION

Incidence of ectopic pregnancy is around 1 in 150 normal pregnancy in INDIA (Around 2% in USA and 1% in UK. The Incidence is about 2% in patient undergoing Assisted reproductive technique. The Rising tendency is thought to have been related to increased incidence of pelvic inflammatory disease. Patient with ectopic pregnancy present with amenorrhoea first trimester bleeding and lower abdominal pain. Diagnosis made by measurement of human chorionic gonadotrophin by ELISA/RIA and Transvaginal ultrasonography.Due to above diagnostic modalities ,early detection can be possible .Accurate diagnosis is essentional for operative , medical , or epectant management. With early diagnosis , we can manage patient by conservative/medical management.

Treatment with methotrexate in properly selected patient has paramount importance in management of tubal ectopic pregnancy. The success rate has been reported has between 75 to 96percentage

Methotrexate desturbes de novo synthesis of purine and pyrimidine by competitively inhibiting th.e binding of dihydrofolic acid to the dihydrofolate reductase enzyme. Thus reduction to folinic acid, an important cofactor in cell growth pathways, is inhibited.

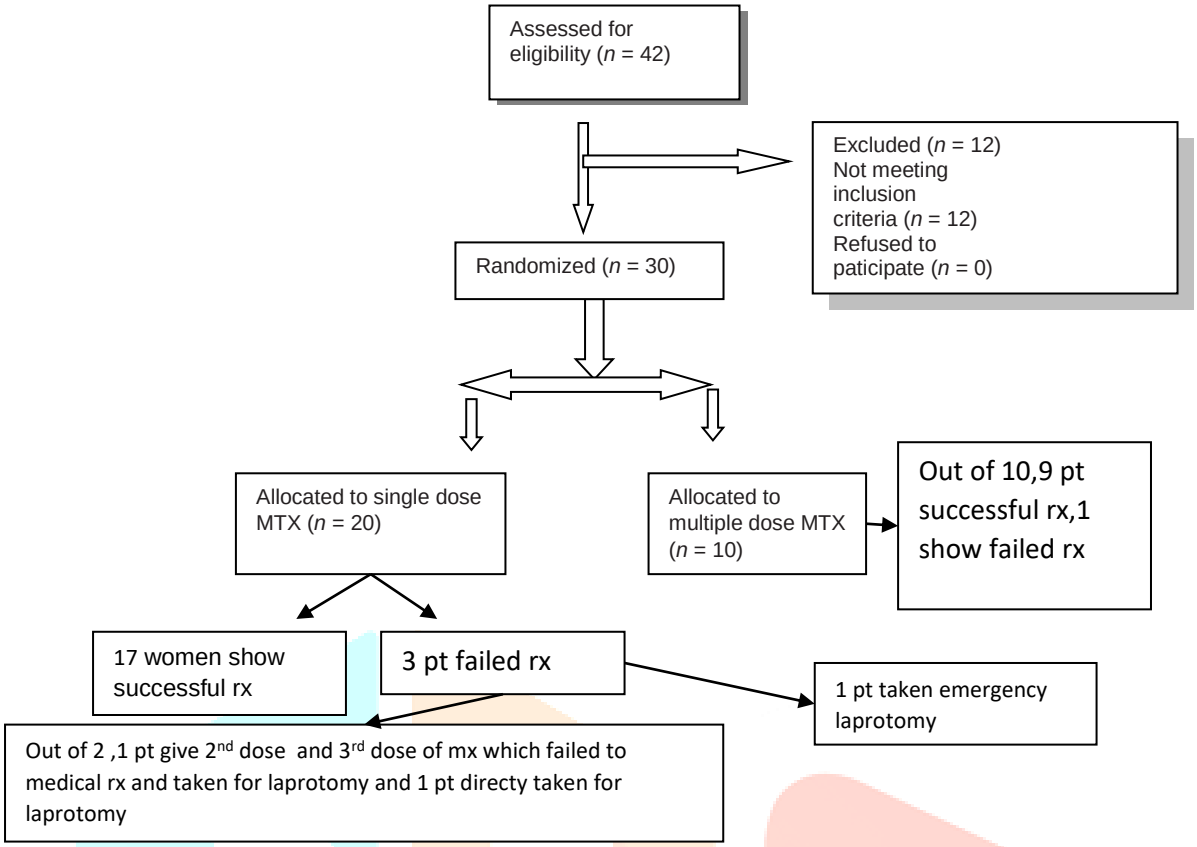
Two types of regimen are commonly used ; single dose methotrexate and four dose methotraxate.Recently two dose protocol was suggested to decrese number of hospital visits as well as side effects.Recent metanalysis suggests no difference between single dose and four dose success rate. Barnhart et al suggests higher failure rate with single dose therapy.

❖ MATERIAL AND METHODS

A Total of 42 women admitted in hospitalised have suspected ectopic pregnancy were enrolled during the period excending from August 2019 to August 2020.

Iniatlly all women were evaluated by TVS and hCG measurement , and those diagnosed with ectopic pregnancy were recrited. Out of which 12 women were found to have ruptured ectopic pregnancy , so were excluded from study.

Following criterias were taken into consideration :-hemodynamic stability, serum hCG levels reaching a plateau or increased by £50% in 48-hour intervals, detection of an adnexal mass 3.5 cm or less in diameter, no history of previous tubal surgery, the patient's desire for a future pregnancy, and willingness to participate in the study.



Patients satisfying the selection criteria (n = 30) were retrospectively randomized into two groups as Group I (treated with single intramuscular dose of 50 mg/m2 methotrexate n = 20) and Group II (treated with four dose methotrexate therapy, n = 10).

we obtained hCG levels 0, 4, and 7 days after the methotrexate injection. Patients with a decline of 15% in hCG levels between days 4 and 7 were accepted as having a positive response and monitored on an outpatient basis weekly until their hCG levels were below 5 mU/mL. A repeat dose of methotrexate was given if hCG levels did not fall 15% between days 4 and 7 after the initial dose or if an hCG level fall of 15% was not observed during the subsequent weekly hCG level follow-up . Group II was treated with methotrexate 1 mg/kg/day intramuscularly on days 1, 3, 5, and 7, and leucovorin (0.1 mg/kg) on days 2, 4, 6, and 8). In the follow-up period, serum hCG levels were obtained at baseline (day 0), and on days 1, 3, 5, and 7 until hCG declined 15% from the previous value. A positive response was defined as an hCG level decrease of 15% in 48 hours or after four doses of methotrexate were given (14). Patients with positive response rates were regarded as successfully treated. In all women, subsequent weekly hCG levels were obtained. In all successfully treated women the time in days until the levels of hCG became less than 5 mU/mL was assessed. Only successfully treated patients (women who needed only one methotrexate injection in group I and women who completed the four doses of methotrexate injections in group II) were considered successfully treated (hCG< 5 mU/mL)in the single dose group or additional doses in the four dose group (10 women) or who needed surgical therapy (laparotomy, n = 12) were considered unsuccessfully treated.

❖ RANDOMIZATION

Women were allocated randomly to the groups 1 or group 2 on the first treatment day following diagnosis of ectopic pregnancy

❖ STATASTICAL ANALYSIS

On the basis of previous study results (9) and the estimated success rates of single dose therapy (the lowest success rate, 75%; proportion positive for group I) and multiple dose therapy (the highest success rate, 96%; proportion positive for group II) as the primary end point, a sample size of 58 patients in each group would have a 90.5% power to detect a difference in success rate of 21.0%, using a Z-test withpooled variance, and a = 0.05 two-sided significance level (using the Power and Precision (tm) program, Biostat, USA). The results are given as proportions and mean ± standard deviations. Fisher's exact chisquared test, Student's t-test, and Mann–Whitney U test were used for statistical analysis using SPSS software, version 12.0 for Windows. Statistical significance was set at $p < 0.05$.

❖ RESULTS

The final analysis included 30 women . The main complaint on admission was pelvic pain and abnormal vaginal bleeding with a missed period (78.2% of cases).There were no significant differences between groups I and II with regard to demographic, clinical, and laboratory characteristics .

The medical treatment was successful in 26 patients (86%). Of the 20 patients in the single dose group, treatment was considered successful in 17(85%). Of the 10 patients in the multiple dose group, 9 were considered to have responded to the treatment (90%). The comparison of the clinical (age, gravidity, parity, gestational age, and side-effects) or laboratory (hCG, progesterone on admission, and size of mass on ultrasonography) population profile for the 'failed medical treatment' single (group I) and multiple dose (group II) methotrexate therapy of unruptured ectopic pregnancy revealed no significant differences. The success rates in all age categories, gravidity, gestational age, size of mass on ultrasonography, transvaginal ultrasound findings, and hCG values on admission were higher in the single dose group than in the multiple dose group, although significant values were not obtained.

Out Of the 3 patients in whom treatment failed in the single dose group, 2 received a second dose (50 mg/m2) and the remaining 1 women underwent surgical treatment (either laparoscopy or laparotomy). One responded to a second dose, whereas one patient in whom the second dose treatment failed responded to a third dose (50 mg/m2). The remaining woman, in whom the second dosed treatment failed, underwent surgery directly. Of the onewomen in whom multiple dose treatment failed, surgery were done. For both groups only the clinically significant sideeffects during the initial treatment were included. Side-effects were seen in 7 patients (23.5%) and consisted of abdominal pain, nausea, diarrhea, elevated liver enzymes (serum AST or ALT > 40 IU/L), stomatitis, and dermatitis. In the single dose and multiple dose groups, 4 (20%) and3(30%) patients, respectively, experienced side effect.

❖ DISCUSSION

This retrospective randomized study focused on a comparison of the success rate of single and multiple dose methotrexate regimens for unruptured tubal ectopic pregnancy, since there is no true consensus regarding which protocol, surveillance, and frequency of administration should be used.

Our results suggest that the multiple dose regimen is not superior to the single dose one as a conservative treatment modality for EP, and they indicate a higher rate of side-effects but a shorter number of days for hCG levels to drop below 5 mU/mL in the multiple dose regimen. The single dose administration of methotrexate is a more practical approach to the multiple dose one (19), although Barnhart et al. found that a single dose was associated with a high failure rate (9). By contrast, in a recent retrospective analysis, Lipscomb et al. stated that there was no significant difference between the two protocols (8). These results were attributed to the clinicians' tendency to choose a single dose for the patients with good prognosis while reserving the multiple dose for patients with a high probability of failure. Moreover, they stated that in meta-analysis the patient population of the multiple dose regimen is from an earlier era of medical treatment and so the patients were chosen strictly; thus the

multiple dose treatment could have appeared successful. These selection criteria may have influenced the results of the meta-analysis in the multiple dose regimen. Medical therapy for ectopic pregnancy 893 Since there is disagreement in the literature about the most efficient regimen, randomized blinded clinical trials are needed to reduce potential confounders and biases.

A randomized clinical trial designed by Alleyasin et al. revealed no significant differences between the two treatment regimens and concluded that there was a need for larger clinical trials (14). Their study implies that single dose treatment should be the first line treatment in selected group of patients (14). A recent Cochrane review also reported that there were no significant differences between the two treatment regimens in terms of primary treatment success rates (20). The current prospective randomized study may contribute to this ongoing debate since it includes more patients in order to reduce statistical errors

The overall methotrexate success rate was 53% for our study. In the literature, the overall success rate of methotrexate therapy is 75–96% independent of the method of administration. In our analysis, the success rates of the single dose regimen (85%) and multiple dose regimen (90%) did not differ significantly, which was consistent with the results of two previous studies (8,14), although a rising tendency was observed in the success rate of the multiple dose regimen compared with the single dose one. The results of our study suggest that the multiple dose regimen is more effective in disrupting the well organized trophoblastic proliferation. This may explain the shorter detriment time for the multiple dose treated group. The main limitations of the multiple dose regimen is the need for leucovorin rescue treatment, the high frequency of side-effects, and the requirement of intensive monitoring. By contrast, the single dose is practical in application but the term ‘single dose’ is a misnomer since 11–20.6% of patients require a second dose (8,9,13,14,21).

In our study only about 10% of patients in the single dose group and 3.5% of those in the multiple dose group required a second dose. The optimal and practical treatment of choice could be other than one dose administration. In a recent study a new methotrexate regimen was proposed (11). To increase the success rate of the single dose regimen, the two dose regimen was also reported to be a reasonable choice, since it optimized convenience and efficiency for patients, and only 10% of patients were reported to need an additional methotrexate dose.

In this study a total of 26 women (86.1%) were treated successfully with medical treatment. A total of 10 women with the success rate of 90% needed one course (2 doses) of methotrexate and a total of 2 women (20%) reported adverse events during the course of treatment.

In our study, a similar success rate of medical treatment of EP and a lower adverse events rate are reported. This recent study also highlights the effectiveness of additional methotrexate administration and the need for new methotrexate regimens similar to the multiple dose one (11). The aim of the current study was to examine whether it was appropriate to choose multiple dose therapy for all patients when there was a chance to offer only one dose. This randomized clinical trial was designed to help clinicians in deciding whether to choose a single dose or multiple doses; thus the treatment failure rate was assessed.

It was demonstrated that the rate of failure of the single dose treatment (19.3%) was higher than that of the multiple dose regimen (15%). in a randomized controlled trial it was noted that single dose therapy has a high failure rate (14). Our results also support these findings. Based on this, it should be emphasized that single dose therapy could be a first line of treatment in well selected patients. Potentially life-threatening nephrotoxicity, hepatotoxicity, pulmonary damage, and myelosuppression are sometimes seen with the use of methotrexate and can occur with either highdose therapy as used for malignant diseases or with low-dose therapy as used in other disorders such as rheumatoid arthritis and psoriasis (22). Adverse reactions to methotrexate for EP are usually mild and self-limited. The most common are stomatitis and conjunctivitis. Rare side-effects include gastritis, enteritis, dermatitis, pneumonitis, alopecia, elevated liver enzymes, and bone marrow suppression. Our prospective randomized study also emphasized the high side-effects rate in the multiple dose group compared with the single dose one. This may be attributed to the high cumulative dose of methotrexate used in the multiple dose regimen. According to the current results, it is not easy to define the target population to benefit from the single dose regimen as the first line of treatment, since the subgroup analysis of factors affecting the success rates in both

groups revealed no clinical and laboratory parameters predicting the success rate in group I. Our findings do not suggest the superiority of the multiple dose methotrexate regimen over the single dose one. One of the limitations of this study was the absence of blinding. The other one is that the 894 E.S. GuvendagGuven et al. power calculation was based on a large anticipated difference. This study highlights the need for further research before deciding on which medical treatment is best for unruptured tubal ectopic pregnancy, as multiple dose methotrexate therapy had a significantly higher rate of side-effects and shorter number of days for hCG levels to drop below 5 mU/mL.

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