Original Article

Effect of single-dose methotrexate injection to prevent neoplastic changes in high risk complete hydatidiform mole: A randomised control trial

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Abstract

Background: Complete hydatidiform mole affects women in their reproductive age. About 15-20% develops persistent molar gestational trophoblastic neoplasia (GTN), which is linked with delayed (beyond 56 days) normalization of serum βHCG after surgical evacuation. **Objective:** The objective of the article is to shorten the duration of normalization time of βHCG with single-dose methotrexate injection in women with high risk complete hydatidiform mole (CHM) after suction evacuation. **Methods:** Total 76 women with CHM were randomized into intervention and control groups. In the intervention arm (n = 34) women received single dose 100 mg intramuscular methotrexate injection post evacuation and the control group (n = 42) had standard care. Surveillance was done in both groups at two weeks intervals for next six months and duration of normalization of βHCG level was recorded. **Results:** Total 94.7% women completed follow-up. Mean of normalization time was significantly lower in the intervention group compared to controls (9.7 weeks versus 14.7 week; $P < 0.01$). Time to event curve showed significantly earlier cumulative normalization time for the intervention group. **Conclusion:** Single-dose 100 mg methotrexate injection is a low-cost, simple intervention to help one out of three women with CHM with high-risk features to achieve normalization of βHCG within 56 days. This might be helpful for people in resource-poor countries where adherence to prolonged surveillance is poor.

Keywords: Hydatidiform mole, India, uterine neoplasm

Introduction

Hydatidiform mole (HM) is a type of gestational trophoblastic disease (GTD) arising from placenta with an ability to locally invade the uterus and metastasize.[1] HM is classified into complete hydatidiform mole (CHM) and partial hydatidiform mole (PHM) with the former having a higher potential to develop persistent molar gestational trophoblastic neoplasia (GTN), at approximately 15 to 20% as reported in global literature.[1] This happens more frequently in patients with CHM with one or more high-risk features including enlarged uterine size more than date, elevated beta subunit of human chorionic gonadotrophin (β HCG) >1,00,000 mIU/ml, bilateral theca lutein cysts and previous caesarean section.[2,3] With the advent of chemotherapy (CT) metastatic GTN has a much-improved prognosis.[4-6] Following normalization

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of β HCG level to <5 mIU/ml after surgical evacuation the risk of developing GTN is 0.35% in CHM and 90% of this adverse outcome occurs when normalization happens beyond 56 days window period.[7] Risk is considerably lowered even with a single measurement of β HCG <5 mIU/ml.[1] This can reduce surveillance duration which is particularly important in resource-poor countries where patient adherence to repeated office visits is poor. Low patient education and their understanding about the requirement for prolonged surveillance, wage loss and travelling cost are important factors for low adherence to repeated follow-up visits.

Fall in β HCG level is not influenced by age, ethnicity, race, body mass index and hormonal contraception.[8] However, prophylactic chemotherapy with methotrexate and leucovorin rescue is associated with earlier normalization time (NT).[9] Single-dose methotrexate without leucovorin rescue is an established treatment for low-risk GTN. With this regimen, significant side effect is not reported.[10] In this trial the objective was to determine the effect of single-dose methotrexate injection in shortening the NT in high-risk GTN. The study hypothesis was single-dose methotrexate injection will significantly reduce NT among women with high-risk CHM.

Methods

This was an open-labeled, two-group, randomized controlled trial, with parallel arms conducted at Bankura Sammilani Medical College and Hospital (BSMCH), West Bengal, India. Patients were enrolled between September 2017 and October 2019 with inclusion criteria of molar pregnancy diagnosed by ultrasonography with or without clinical symptoms. Exclusion criteria were patients with partial mole, choriocarcinoma (CCA), opacity in chest X-ray, and previous history of molar pregnancy. Withdrawal criteria were persistent GTN and pregnancy occurring while on follow-up. All eligible patients were approached for recruitment. Participants were assessed for the presence of one or more of the following high-risk features: Pre evacuation serum β HCG > 1,00000 mIU/ml, enlarged uterine size more than the date and bilateral theca lutein cysts. Blood parameters including complete blood count, liver function test (LFT), renal function test (RFT), thyroid profile, and chest radiograph were done. Serum β HCG was measured by immunoassay method using Calbiotek β HCG kit. All cases of CHM were treated by surgical evacuation within first trimester of gestation. A histopathology (HP) report was obtained by five days after surgical evacuation. Randomization with 1:1 allocation ratio using computer-generated random numbers was conducted after getting the HP report. Sample was calculated by the online statistical calculator ClinCalc.[11] Anticipated means were extracted from a similar study comparing prophylactic (CT) and spontaneous normalization of β HCG in months, with $\alpha = 0.05$ and $\beta = 60\%$.[9] The calculated sample size was 35 in each arm. The recruitment and follow-up of participants have been shown in [Figure 1], CONSORT flow diagram.

The study was conducted in the department of gynecology and obstetrics, BSMCH, with trial registration number CTRI/2017/09/009723 registered on clinical trials registry of India. This study was compliant with Helsinki declaration on bioethics policy and was approved by Institutional ethics committee of Bankura Sammilani Medical College and Hospital with approval No. BSMC/Aca/1740 dated 1.6.2016.

Intervention

In the intervention group, all women received 100 mg methotrexate intramuscular injection before discharge from the hospital. Women in the control group received standard care. In both groups, participants were advised to attend the outpatient department with β HCG report at two weeks intervals for a maximum duration of six months. Women were advised to use barrier method of contraception during follow-up. They were released from surveillance once they achieved normalization. Transvaginal sonography (specifications - GE logic P9; model BE 9CS with 9 nano Hz frequency) was done for any abnormal bleeding to exclude invasive mole during follow-up. Those having β HCG >20,000 mIU/ml at four weeks or elevated β HCG even if falling beyond six months since surgical procedure were given chemotherapy (CT).[12] Informed consent was taken from all participants, data collection was anonymous and blinded analysis was performed.

Study variables and outcome measure

Variables included in the study were demographic and clinical information including age, parity, mode of delivery, interval since last child birth, side effects of methotrexate, β HCG levels at specific time points and NT. β HCG normalization was defined as β HCG level <5 mIU/ml.[1] Data were captured by clinical and radiological examination, review of laboratory reports and interview of patients.

Statistical analysis

All data elements were recorded in a structured data collection proforma which was later entered and coded in a Microsoft excel spreadsheet version 2010. Data for women who did not complete surveillance or were withdrawn from study was analyzed up to the point till they participated (intention to treat analysis-ITT). Mean, median and standard deviation was calculated for continuous variables while frequencies and percentages were calculated for the categorical ones. Standard error and confidence interval for difference of mean β HCG level between intervention and control group was calculated. Significance level was $P < 0.05$. Kaplan-Meier survival function, for time to event was compared for two arms. β HCG NT was the outcome of interest, right censoring was done for those women who did not complete follow-up till β HCG normalization or were excluded as per exclusion criteria (persistent GTN or pregnancy). Statistical Package for Social Sciences (SPSS) IBM Corp. Released 2010 [IBM SPSS Statistics for Windows, Version 19. 0. Armonk, NY: IBM Corp. United States of America] was used for analysis.

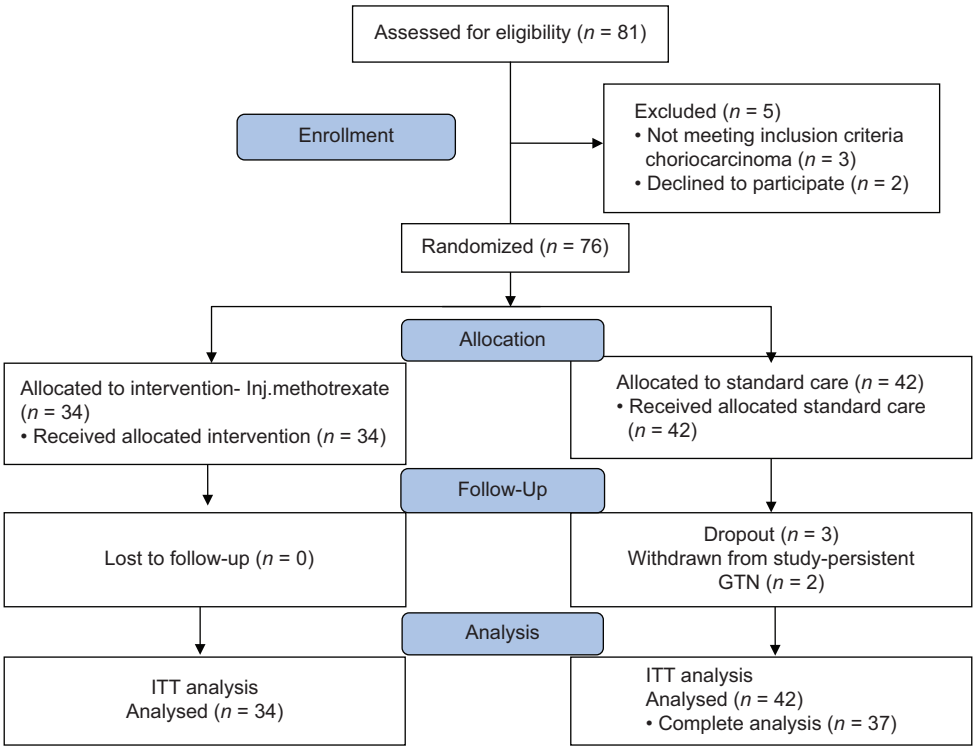

Figure 1: CONSORT flow diagram

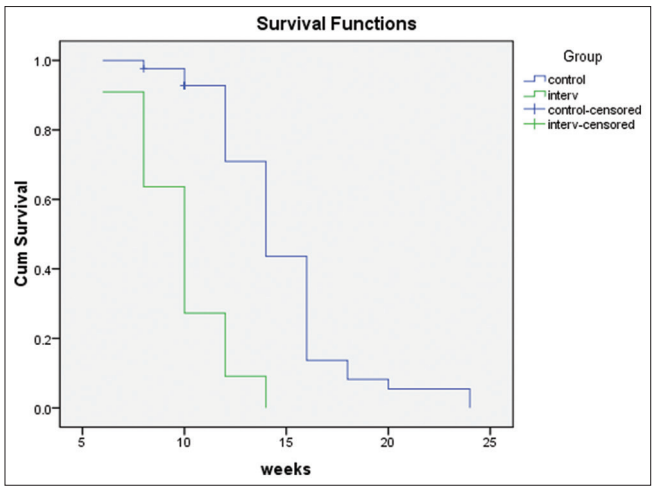

Figure 2: Kaplan-Meier Survival (time to event- B HCG normalisation) curve for intervention and control groups

Results

During the study period, 81 patients were encountered who fulfilled inclusion criteria, among them 79 (97.5%) provided informed consent to participate in the study. Three patients were excluded before randomization (one PHM, two CCA). Remaining 76 women were randomized to 34 in intervention group and 42 in control group. Mean age of the study population was 22.38 years and 32 (42.1%) women were nulliparous. Range of pre-evacuation β HCG level was from 22,918 to 360,000 mIU/ml. The distribution of pre-evacuation β HCG was checked for normality by Kolmogorov-Smirnov normality test with Lilliefors significance correction and was found to be normally distributed. Table 1 shows baseline characteristics of women enrolled in the intervention and control arms. Groups were comparable in terms of age, parity, history of abortion, past caesarean section, and last child birth to CHM diagnosis interval. Median uterine height was 20 weeks for both groups. Pre-evacuation β HCG level and hemoglobin level between the groups did not show any significant difference. In this study, 73 (96.1%) women completed follow-up. All women in the intervention arm had normalization of β HCG level by the 14th week of follow-up. Table 2 shows comparison of β HCG levels between the groups during this 14-week time period. Mean of β HCG level was significantly different for first eight weeks with lower values in the intervention group. Between 10th and 14th weeks, though the intervention group continued to have lower mean β HCG, it was not significantly different from the control group. The mean duration for normalization in the intervention group was 9.7 weeks which was significantly lower from 14.7 weeks in the control group. By 12 weeks, 31 (91.2%) women in the intervention group had normalization in β HCG levels which was only 11 (29.7%) in the control group. By the standard cut-off time of 8 weeks only 1 (2.4%) woman in the control group and 13 (38.2%) women in the intervention group had normalization in β HCG values. The median duration for normalization in the intervention group was 10 weeks (inter-quartile range of 8-12 weeks) while that for the control group was a month more, 14 weeks with inter-quartile range of 12-16 weeks.

In the control group, two women achieved normalization at 24th week, three women dropped out from the trial before achieving

Table 1: Baseline characteristics of intervention and control groups

Variable	intervention group *n*=34	Control group *n*=42	Difference of proportion/mean (*P*)
Number (%)			
Parity			
Nullipara	15 (44.1)	17 (40.5)	1.00
Primipara	14 (41.2)	15 (35.7)	0.72
Multipara	5 (14.7)	10 (23.8)	0.48
H/O abortion	8 (23.5)	10 (23.8)	1.00
Proportion of CS	5 (11.9)	8 (19.0)	0.50
Central tendencies & Dispersion			
Age (mean±SD)	22.09±3.28	22.67±3.56	0.46
Interval since last child birth in years (mean±SD)	1.53±1.8	1.95±2.2	0.37
Uterine height in weeks (median and inter-quartile range)	20 (18-24)	20 (16-22)	----
Haemoglobin level in gm% (mean±SD)	10.7±0.94	10.7±1.06	1.00
Pre-evacuation β HCG (mean±SD)	215130±60917.5	196650±51682.5	0.16

Table 2: Mean β HCG values at follow-up visits for cases and controls

Weeks of follow-up	Intervention group [follow-up/total] Mean & SD of β HCG values (mIU/ml)	Control group [follow-up/total] Mean & SD of β HCG values (mIU/ml)	SE of difference	95% CI
Time to normalise in weeks	*n*=34 9.7 (2.2)	*n*=42 14.7 (3.3)	0.67	3.6 to 6.3**
2nd	34/34 25608 (25723)	42/42 53025 (25207)	5868.5	15723.6 to 39110.0**
4th	34/34 4361 (4839)	39/42 11244 (6292)	1305.3	4276.8 to 9489.1**
6th	34/34 735 (810)	38/42 3853 (3465)	609.0	1903.3 to 4332.6**
8th	31/34 195 (259)	39/42 1350 (1888)	342.0	472.3 to 1837.6**
10th	21/34 54.3 (86)	37/42 481 (1028)	225.6	-25.3 to 878.7
12th	9/34 13.7 (27.4)	37/42 208.2 (465.6)	156.6	-121.1 to 510.1
14th	3/34 1.4 (2.24)	27/42 115.5 (248.2)	145.5	-184.1 to 412.2

**Significant at *P*<0.01

normalization and two women developed persistent GTN who were withdrawn. Kaplan-Meier Survival analysis was performed for comparing time to event (i.e. β HCG normalization) for the two groups. The survival function was NT. NT was significantly different for intervention and control groups. Figure 2 shows the cumulative β HCG normalization curve.

Discussion

This trial examines a novel intervention that has the advantage of low cost and high benefit. The study result lends support to the hypothesis that single-dose methotrexate injection will significantly reduce NT among women with high-risk CHM. Mean age of participants in this study was about five years lower than two other studies conducted at Tehran and Ankara.[9,13] The Ankara study had 39% primigravid women, which is quite close to the present study. Pre evacuation β HCG level had wider dispersion in the Ankara study (minimum 551 mIU/ml- maximum 844,441 mIU/ml) compared to present study (22,918 to 360,000 mIU/ml) which can be attributed to the enrolment of both high-risk and low-risk CHM.[13]

Reported time for spontaneous remission of β HCG was 3.2 ± 1.21 months and it was 2.5 ± 1.33 for women with high-risk CHM treated with methotrexate-leucovorin prophylactic CT.[9] Post evacuation β HCG values and NT as prognostic markers

has been explored in several studies. A meta-analysis reports only 0.3% incidence of post-molar GTN following β HCG normalization in CHM.[14] When β HCG is not at detectable level, the risk of developing GTN is reduced to less than 1% and higher for CHM.[15-25] A study in Charing Cross Hospital, England, demonstrated that rapidity of normalization was predictive of likelihood of cure versus developing GTN.[5] The study by Sebire *et al.*[21] showed NT within 56 days of evacuation reduced the risk of GTN to 1 in 1159 versus 1 in 308 when normalization happened beyond 56 days in patients with CHM. A β HCG level ≥20,000 IU/L four weeks after uterine evacuation for CHM, was the most important risk factor for the development of post molar GTN with an adjusted risk ratio of 5.83. Wolfberg *et al.*[16] found in their study, risk of persistent GTN was less than 9% when β HCG value was less than 200 mIU/ml at 4th week following evacuation compared to 64% risk when β HCG level was more than 2000 mIU/ml at 4th week in CHM.NT ≥8 weeks had 7.7 times higher odds of developing post molar GTN. The risk was even higher with women being 19.5 times more likely to develop GTN for NT ≥17 weeks.[15] Use of cut-off period for 8 weeks of NT for a continuously distributed variable can overestimate risk for those women falling closely outside the cut-off limit. Research lacunae are still present regarding different durations of NT beyond 8 weeks, when risk of GTN gradually increases. One way to understand this risk can be survival curves comparing NTs. Kizaki *et al.*[26] reported survival curves to be good estimator of GTN risk. A meta-analysis conducted in 2017 incorporating three randomized trials concluded prophylactic CT could reduce the risk of GTN by 63% but it might invite drug resistance and toxic side effects and presently this practice is not recommended.[27] The present study utilized the unique property of methotrexate to inhibit the trophoblastic activity of molar tissue in an attempt to shorten the window period between suction evacuation to normalization of β HCG level while minimizing the side effects by giving single dose methotrexate injection. In this trial, single-dose methotrexate was able to achieve normalization in most women in <12 weeks and in 38% women in <8 weeks. Mean β HCG level for the intervention group was 4361 mIU/ml and it was significantly lower than the control group. This intervention has comparable NT to those reported by prophylactic CT in high-risk CHM.[9]

After surgical evacuation of HM, women may prefer to visit their primary care physicians for β HCG surveillance, and thus this study should be of interest to both primary care physicians and gynaecologists alike.

Limitation of this study is the arbitrary dose of methotrexate. It is not known if 100 mg methotrexate as chemoprophylaxis was adequate dosage or lower/higher doses were required. Novelty lies in the simple approach in preventing an invasive disease.

Conclusion

It can be concluded that single-dose methotrexate injection can help one out of three women to achieve normalization of β HCG within the cut-off period of 8 weeks. This simple, low-cost intervention can reduce office visits and associated expenditures, by at least a month earlier suppression of chorionic activity compared to standard care.

Key points and take-home messages

Risk of development of GTN after the evacuation of CHM is high for delayed normalisation of β HCG beyond 8 weeks window period. Prophylactic chemotherapy with methotrexate can achieve earlier normalisation and lowers the risk of GTN but it is not free from side effects.

Single-dose methotrexate has no major side effects and has been successfully used in low-risk CHM.

Novel use of single-dose methotrexate in women with high-risk CHM in the present trial was able to achieve NT within 8 weeks for 30% of women in the intervention group as opposed to only 2.4% among the controls. Mean NT was significantly lower for the intervention group at 9.7 weeks.

It is recommended that women with high-risk CHM should be given single-dose methotrexate, especially in situations where poor compliance to β HCG surveillance is anticipated.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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