A randomized controlled trial on the efficacy of methotrexate in preventing postmolar gestational trophoblastic disease among patients with high-risk complete hydatidiform mole*

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ABSTRACT

Objective: This study aimed to determine the efficacy of methotrexate in preventing postmolar gestational trophoblastic disease (PMGTD) among patients with high-risk complete hydatidiform mole.

Methods: This was a double-blind randomized controlled trial carried out from 2007 to 2013. A total of 99 patients with high-risk complete hydatidiform mole who underwent suction curettage were randomly allocated to either the treatment or control group. The treatment group received methotrexate while the control group received a vitamin B complex. The number of patients who developed PMGTD in each group was recorded. All tests of significance were carried out at a .05 alpha level of significance, 95% confidence interval.

Results: There was no significant difference between the two groups in terms of age, gravidity, baseline ßhCG, age of gestation, and corpus size. The overall incidence of PMGTD was 27.9%. For the per protocol analysis, a total of 30 patients received chemoprophylaxis while 31 patients received placebo treatment. The total incidence of PMGTD was 16.67% for the treatment group and 38.71% for the control group. The computed risk ratio was 0.43 (95% C.I.: 0.17-1.07, p value = 0.07).

Conclusion: Results failed to reach statistical significance but the large fall-out rate may have significantly affected the outcome of the study. Methotrexate chemoprophylaxis may still be useful in preventing PMGTD, particularly in settings where the incidence of hydatidiform mole is high and there is high probability that patients will fail to follow the stringent ßhCG monitoring schedule after molar evacuation.

Keywords: Gestational trophoblastic neoplasia, complete hydatidiform mole, chemoprophylaxis, methotrexate, postmolar gestational trophoblastic disease

INTRODUCTION

A hydatidiform mole is an abnormal placenta characterized by enlarged, edematous and vesicular chorionic villi accompanied by a variable amount of proliferative trophoblasts.[1] It is subdivided into complete hydatidiform mole (CHM) and partial hydatidiform mole (PHM) based on morphologic, cytogenetic, and clinicopathologic features. CHM, in which there is total degeneration of the trophoblast, is the more common type.[2] Broad variations in the distribution of molar pregnancy exist worldwide with higher prevalence is Asia, Africa, China, Latin America, Middle East and Eastern and Central Africa.[2,3] In the local setting, the prevalence of hydatidiform mole is 2.4 per 1000 pregnancies.[4]

The two molar classifications differ in their invasive potential and propensity for malignant transformation. Approximately 8-29% of complete hydatidiform moles and 2-4% of partial hydatidiform moles progress to become persistent gestational trophoblastic disease.[5,6] Studies have shown that the risk of developing the malignant sequelae of the benign disease is higher with a large-for-date uterus, serum ßhCG > 100,000 mIU/ml, theca lutein cysts > 6 cm in diameter, uterine size > 16 weeks, maternal age > 40 years, severe trophoblastic proliferation, a history of molar pregnancy and presence of medical complications associated with molar gestation.[5,7-9]

Identification of high-risk molar pregnancies is important in order to institute measures that would decrease a patient's risk of developing postmolar gestational trophoblastic disease (PMGTD). A strategy that has been utilized to decrease the risk for PMGTD is the administration of prophylactic chemotherapy following the evacuation of molar pregnancy.[8,10,11] Its use was first conceived and implemented in 1966 based on the following premises: (a) that trophoblastic tumor cells are highly sensitive to certain chemotherapeutic agents particularly methotrexate and actinomycin-D, (b) that the development of gestational trophoblastic neoplasia (GTN) after evacuation of a complete hydatidiform mole is

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biologically predetermined, (c) that the mechanism for the development of GTN is hematogenous spread, and (d) that high blood levels of cytotoxic agents at the time of molar evacuation should reduce the incidence of both locally invasive and metastatic GTN.[11] However, the objections for the use of prophylactic chemotherapeutic agents include unnecessary exposure to potent chemotherapy agents in majority of patients, incomplete protection against PMGTD, potential development of resistance to agents used as first line treatment for GTN, potentially lethal toxicity and the risk of inadequate follow-up because of a false sense of security.[8,11]

While several investigators have reported significant reduction in the incidence of PMGTD with chemoprophylaxis, several studies have also reported otherwise.[5,10-13] Because of the proven high cure rate of PMGTD or gestational trophoblastic neoplasia (GTN) with chemotherapy, other authors suggested that prophylactic chemotherapy should be limited to situations in which ßhCG measurements are less available, or when compliance for follow up is poor and the risk to progressing to post molar GTN is high.[14,15]

In the local setting, patients with at least one risk factor are advised chemoprophylaxis, which should be administered within 14 days of molar evacuation.[16] This treatment strategy, however, is based on a limited number of studies dealing with the topic. Currently, the use of methotrexate for chemoprophylaxis remains controversial due to varying results of the available studies in terms of its efficacy and toxicity profile. This study was thus undertaken to evaluate the efficacy of methotrexate in preventing PMGTD among patients with high-risk complete hydatidiform mole. Likewise, this study determined the safety of methotrexate when given as a chemoprophylactic agent.

In 2011, we reported the preliminary results of our study.[17] The computed sample size for this study was 70. In the preliminary study however, only a total of 53 subjects were recruited, with a high attrition rate at 34%. Among the 35 subjects whom we were able to follow-up and determine outcomes, we found that overall, 31.43% developed PMGTD. Among the 17 patients who received methotrexate as chemoprophylaxis, three patients developed PMGTD with an incidence rate of 17.65%. Of the 18 patients in the control group, eight patients developed PMGTD with an incidence rate of 44.44%. The result of the initial study revealed that prophylactic chemotherapy using methotrexate lowered the incidence of postmolar trophoblastic disease but the difference was not statistically significant (risk ratio of 0.39, 95% Confidence Interval (C.I.):0.12-1.25; p-value=0.08). Chemoprophylaxis using a 5-day course of methotrexate was also found to be safe, indicating that the occurrence of toxicity is probably dose related and may be due to individual variability. To offset the high fallout rates of the preliminary study, we pursued the study aimed at achieving the desired sample population to determine if there will be a difference in the results achieved.

MATERIALS AND METHODS

Patients and Trial design

This was a Double Blind Randomized Controlled Trial approved by the institution's technical and ethical review board. The subjects included patients diagnosed with high-risk complete hydatidiform mole who underwent suction curettage for molar evacuation. Patients were qualified for the study if they had at least one of the risk factors for the development of PMGTD, namely uterine size larger than age of gestation of more than 6 weeks, serum βhCG titer more than or equal to 100,000 mIU/ml, theca lutein cysts more than or equal to 6 cms in size, maternal age greater than or equal to 35 years, gravidity of 4 or more, recurrent molar pregnancy, and with medical complications arising from trophoblastic proliferation such as pre-eclampsia, thyrotoxicosis, pulmonary insufficiency and disseminated intravascular coagulopathy. The diagnosis of hydatidiform mole was confirmed histopathologically. Patients were excluded from the study if they had a previous history of gestational trophoblastic neoplasia and if with medical problems or complications that inhibited the administration of methotrexate (i.e. hemoglobin lower than 10 g/L, WBC less than 3.0 x 10 9/L or more than 10.0 x 109/L, absolute neutrophil count less than 1.5, platelet count lower than 100,000/cm3, elevated liver and renal function test and a concurrent infection).

Sample size computation

Based on the study done by Kim, et al, PMGTD developed in 14% of patients who had chemoprophylaxis as opposed to 47% among those who were not treated [11]. Using the formula for sample size by Fleiss, a confidence interval of 95 with power of 80%, and factoring a dropout to follow-up rate of 25%, we computed a sample size of 33 per group.

Randomization and Blinding

Potentially eligible patients were referred to the investigators for inclusion in the study. Eligible patients were enrolled after written informed consent was signed. Patients were then randomly allocated to one of the two study groups using the fish bowl technique. Treatment allocations (e.g. methotrexate or placebo) were written in a paper and sealed in an opaque envelope. Group 1 was the chemoprophylaxis or treatment group and group 2 was the placebo or control group. The patient, statistician

and medical staff involved in the care of the patients were masked to the treatment allocation.

Procedure

Patients who were included in the study underwent routine baseline examination for patients with hydatidiform mole. These examinations included diluted serum ßhCG, complete blood count with platelet count and differential count, urinalysis, BUN, creatinine, ALT, AST, transvaginal ultrasound, and chest x-ray PA upright. Patients underwent suction curettage after management of any medical complication and procurement of appropriate blood products. Specimens obtained from the procedure were sent for histopathologic diagnosis.

Group 1, the chemoprophylaxis or treatment group, was given a single course of methotrexate within fourteen days from molar evacuation. Methotrexate was given at 0.4 mg/kg/day administered intramuscularly for 5 days. On the other hand, Group 2 or the control group received placebo in the form of BeeAll®, a Vitamin B complex drug given intramuscularly for 5 days. This drug was chosen for the study due to its similarity to methotrexate in terms of color, consistency and route of administration. The investigator prepared the drugs just prior to administration. Once the drug was ready for administration, the prepared syringe was endorsed to the physician in-charge for injection. During the treatment days, patients were monitored for toxicities in the form of nausea, vomiting, stomatitis, and rashes. These were graded based on the WHO Toxicity Scoring System.

One week following treatment, complete blood count, liver and kidney function tests were taken for evaluation of any hematologic, hepatic or renal toxicity. Patients were also interviewed and evaluated for other toxicities. These were likewise graded using the WHO toxicity scoring system.

For both groups, patients' serum ßhCG titers were monitored according to standard protocol: ßhCG titer was determined 1 week after molar evacuation and then every 2 weeks until the titers became normal for three consecutive determinations, after which serum ßhCG monitoring was done monthly for 6 months, then every 2 months for the next 6 months to complete one year.[16] All ßhCG determinations were done in a single institution using the Electro-chemiluminescence Immunoassay (ECLIA). During the follow up period, patients were advised to avoid pregnancy and were given a low dose oral contraceptive pill immediately after evacuation.

Outcome Measure

The primary measure of efficacy of Methotrexate was the development of postmolar gestational trophoblastic disease. The criteria used to establish the presence of PMGTD were the following: high level of ßhCG more than 4 weeks post-evacuation (serum level of 20,000mIU/m), progressively increasing or plateauing ßhCG values at any time after evacuation (minimum of 3 weekly determinations), clinical or histologic evidence of metastasis at any site, persistently elevated ßhCG titer at 14 weeks post-evacuation, and elevation of a previously normal ßhCG titer after evacuation provided the diagnosis of pregnancy is ruled out.[13,16,17] Normal ßhCG titer was defined as a value of less than or equal to 5 mIU/ml. The primary measure of safety was the presence and grade of toxicity, which were evaluated using the WHO toxicity scoring system. Data from each patient were recorded in a patient data extraction form.

Data Analysis

Data were encoded using Microsoft Excel 2007 and analyzed using Minitab version 16. Continuous data were expressed as means and standard deviations. Categorical data were expressed as frequencies for populations with and without development of PMGTN. A per-protocol and intention-to-treat analysis was planned and the primary outcome of achievement of three normal ßhCG titers or progression to PMGTN was expressed as relative risks with their corresponding 95% confidence interval. The principle of "last contact, carried forward" was applied for those who did not qualify for the per-protocol analysis. A sensitivity analysis was done to account for all those lost to follow-up to determine if outcome would change due to the drop out. All levels of significance were set at 0.05.

RESULTS

A total of 99 patients were recruited from September 2007 to March 2013. Forty-nine patients received chemoprophylaxis while 50 patients received placebo treatment. Among the 49 patients recruited under the chemoprophylaxis group, 19 were lost to follow-up before achieving normalization of ßhCG titers or being diagnosed with PMGTN. A total of 30 patients were included in the per protocol analysis. Among the 50 patients recruited under the placebo group, 19 were lost to follow up before the final outcome was determined. A total of 31 patients were thus included in the per protocol analysis. The total fallout rate was 38.4% (Figure 1).

Demographic Characteristics

Both treatment groups were similar in terms of baseline serum ßhCG, age, gravidity, as well as actual corpus size and difference between corpus size and age of gestation. Table 1 shows the demographic characteristics of patients included in the per protocol analysis of the study.

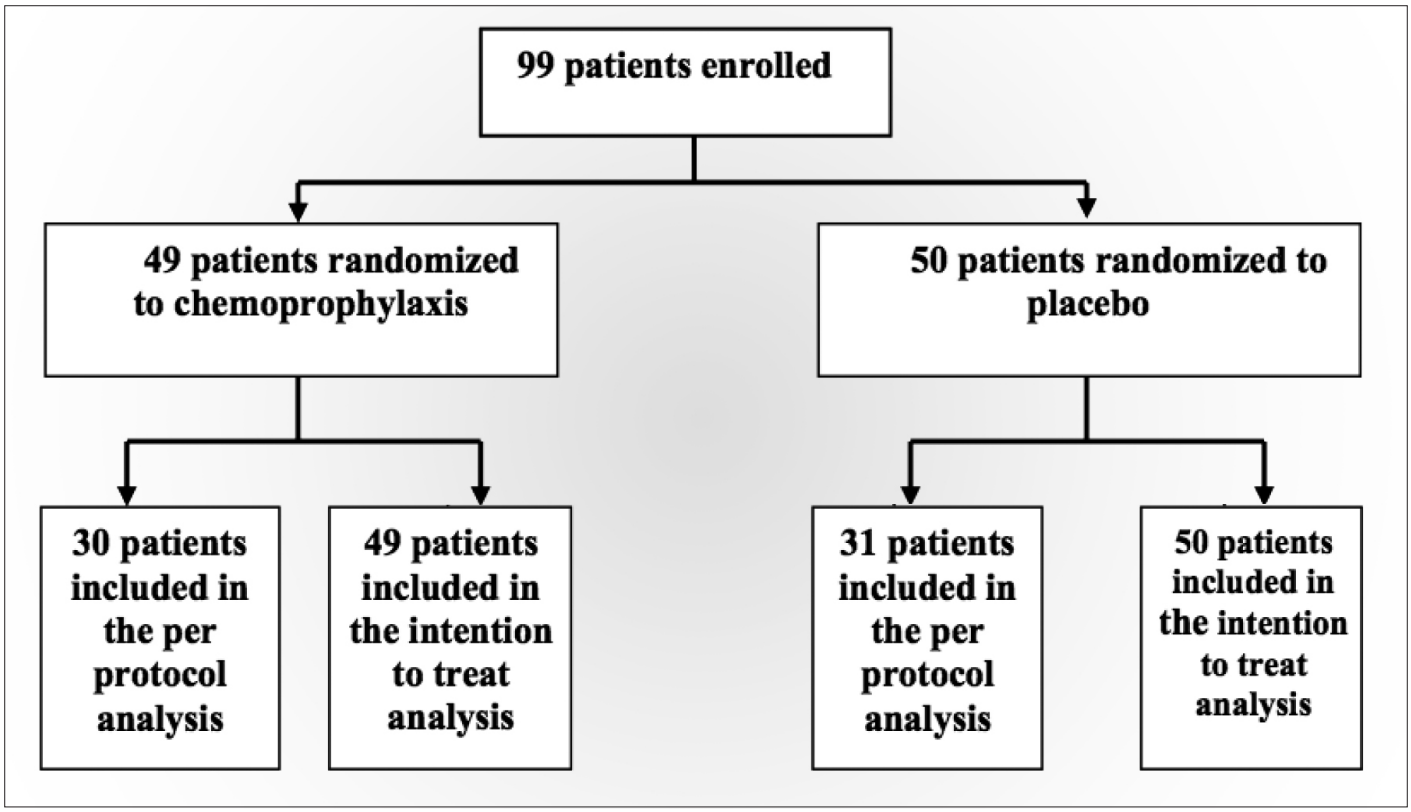

Figure 1. Randomization and allocation of subjects.

Table 1. Demographic characteristics of patients included in the per protocol analysis.

	Methotrexate n = 30	**Placebo n = 31**	***p-value***
Baseline ßhCG (mIU/ml,SD)	370,628.7 +/ 624,074.2	534,925 +/ 236,026.1	0.182*
Age (years; SD)	26.87 +/6.67	26.84 +/6.84	0.984*
Actual corpus size	16.70 +/3.79	16.64 +/3.70	0.952
Actual difference between Corpus size and AOG (weeks)	3.93 +/3.43	4.29 +/3.79	.698*
Age of gestation	14.05 +/4.68	13.53 +/4.48	0.774*
Gravidity, mean +/sd	2.60 +/1.67	2.37 +/1.81	0.612*
Gravidity <G4 >G4	 23 7	 27 4	0.335**
+ theca lutein cyst	2	6	0.159**
+ Co-morbidity	3	2	0.722**

*T-test **Fischer's exact test significant at p<0.05

Development of Postmolar Gestational Trophoblastic Disease

A total of 17 out of 61 patients developed PMGTD for an overall incidence of 27.9%. Five out of the 30 patients who received chemoprophylaxis developed PMGTD for an incidence rate of 16.67%. Out of the five patients (20%), only one had metastatic disease upon diagnosis of PMGTD. On the other hand, 12 of 31 patients in the placebo group developed PMGTD with an incidence rate of 38.71%. Of the 12 patients who developed PMGTD,

three (25%) had metastatic disease.

In the per protocol analysis, the relative risk of using methotrexate in preventing PMGTD was 0.43 (95% CI: 0.17-1.07, p value = 0.07) with a relative risk reduction (RRR) of 56%. The number needed to treat (NNT) to prevent one PMGTD was 5 persons. In the intention to treat analysis, the relative risk of using methotrexate was 0.42 (95% CI: 0.25-1.18, p value = 0.108) with a relative risk reduction of 46%. The number needed to treat was 7.

The sensitivity analysis showed that in the worst-case scenario, the relative risk was 02.04 (95% CI: 1.15-3.6). On the other hand, in the best-case scenario, the relative risk of using methotrexate was 0.16 (95% CI: 0.07-0.39).

Occurrence of Toxicities

There were no recorded mortalities for both treatment and control groups during the duration of the study. Likewise, there were no serious dose-related toxicities that necessitated hospital admission. Under the treatment group, five patients exhibited mild form of toxicities as a result of methotrexate administration. Of these, three patients had grade I stomatitis which resolved after 1 week of treatment while two patients reported occurrence of diarrhea which resolved spontaneously. Only one patient under the control group reported toxicity from administration of placebo, described as mild arm paresthesia after administration of the multivitamin. This symptom likewise resolved spontaneously after one day of observation and required no further treatment.

DISCUSSION

The risk of malignancy after a complete mole is estimated at 15-25%. Patients showing signs and symptoms of marked trophoblastic proliferation are considered at high risk for persistent disease.[16] Described as a strategy in preventing PMGTD among patients with high-risk CHM since 1966 by Lewis et al, the efficacy and safety of chemoprophylaxis has been demonstrated by several randomized studies.[10-12]

In this final report, we found an overall incidence rate of PMGTD that closely reflected the rates reported in literature (27.9 % vs 29%).[2,5,18] Our preliminary report found that prophylactic chemotherapy using methotrexate lowered the incidence of postmolar trophoblastic disease but the difference was not statistically significant.[17] In this final study, the incidence of PMGTD was 16.67% among patients who received chemoprophylaxis and 38.71% for those who received placebo treatment. The incidence rates we obtained were almost similar to those found by Kim et al in 1986, which showed a 14% incidence rate of gestational trophoblastic disease among treated patients and 47% in those who were not treated (p value < 0.05).[11] Our findings were likewise similar with the results found by Park et al in 1996 who strongly advocated the use of chemoprophylaxis, due to a significantly lower incidence rate of PMGTD in the treated group than the untreated group (15.4% vs 31.8%).[8]

In the study of Kim et al, Methotrexate was give as an eight-day regimen alternating with folinic acid while Park et al used Actinomycin-D. Both studies showed a significant difference in the occurrence of PMGTD between the two study groups. In our study, Methotrexate was given as a 5-day regimen and the difference in occurrence of PMGTD between the treatment and control groups failed to reach statistical significance. However, evaluation of the 95% confidence interval for the relative risk showed a larger proportion in favor of using Methotrexate compared to placebo in preventing PMGTD among high-risk CHM. This indicates a trend favoring a protective effect of methotrexate against the development of PMGTD. Moreover, sensitivity analyses of our data, showed a difference in the outcome indicating that the large fall-out rate had a significant impact on the results of the study.

Our results in the per protocol analysis showed that we needed to administer methotrexate to only 5 patients in order to prevent one case of PMGTD from occurring. Therefore, even if our results failed to reach statistical significance, our findings may still have clinical impact particularly in settings where the incidence of hydatidiform mole is high and there is high probability that patients will fail to follow the stringent ßhCG monitoring schedule after molar evacuation. This is attuned with the report of Fu et al in 2012, which stressed that prophylactic chemotherapy may be particularly useful in women with high-risk CHMs who have poor access to health care, for those whom ßhCG monitoring is not available, or where poor compliance may be an issue.[19]

We encountered several problems on the long-term follow-up of subjects during the course of the study, owing mostly to poor patient compliance in terms of clinic visits and monitoring of ßhCG levels despite strong physician advice. In our recent experience, we found that the strongest motivation for follow-up was the patient's desire to recover from illness. Major hindrances to regular follow-up and monitoring include: patients' change of geographic location, financial constraints, and scheduling conflicts, with some of the patients citing inability to leave their home and employment responsibilities as a reason for poor follow-up. The prolonged surveillance period may have also contributed to the large fallout rate encountered in the study. The current study had a total fallout rate of 38.4%, comparable to the attrition rates experienced by other studies, reaching values as high as 40-43%.[5,11,15,19,20]

Some authors argue against the use of chemoprophylaxis due to the possibility of drug toxicity.[8,19]

In this study, mild toxicities were documented in only 8.2% of our subjects, showing a much lower rate as compared to those experienced by other studies with reported toxicities occurring in as much as 16.9% to 70.2% of cases.[8,10,11] There was no mortality or any serious dose-related toxicity that required hospital admission or extensive treatment. We did not observe any hematologic or hepatologic toxicities as compared to those experienced by Park.[8] The known toxicities of methotrexate administration may be dose-related in nature or due to individual variability. The low rates of toxicity we encountered in our study demonstrate the relative safety of using the 5-day course of methotrexate for chemoprophylaxis.

This study showed was a marked difference in the incidence of PMGTD among those who received methotrexate for chemoprophylaxis (16.67%) compared to those who received placebo (38.71%). The difference failed to reach statistical significance however, the large fall-out rate may have significantly affected the outcome of the study. The use of methotrexate is associated with mild toxicities that did not require hospitalization or further treatment. Given the high probability of developing PMGTD following a high-risk complete hydatidiform mole, coupled with a high national incidence and failure of patients in complying with the stringent ßhCG monitoring, as seen in this study, methotrexate chemoprophylaxis may still have a role in the management of patients with molar pregnancy.

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