RESEARCH COMMUNICATION

Prevention of Post-Mole Malignant Trophoblastic Disease with Vitamin A

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Abstract

Objective: Around 15-28% of hydatidiform mole patients suffer from malignant degeneration following evacuation. Since retinoic acid can control cell proliferation and stimulate apoptosis, vitamin A could be used as a therapy for preventing such malignant transformation. The objective of this study was to demonstrate the use of vitamin A as a chemoprevention following hydatidiform mole development. Materials and methods: The study made use of a randomized clinical trial, double blind protocol. Subjects were patients with complete hydatidiform moles, not receiving cytostatics. The intervention was administration of placebo or vitamin A at 200,000 IU per day, performed until the patients were declared as having recovered or having malignant trophoblastic disease (MTD). The outcome variables were the incidence of regression and MTD, established based on WHO criteria. Results: At clinical trial as many as 67 cases met the requirements for the study. Two cases were lost from observation and three experienced pregnancy. The incidence rate of malignant trophoblastic disease in the control group was 28.6%, and in the therapy group was 6.3%. No difference was found in the changes of SGOT and SGPT levels of the therapy group compared with the control group. Conclusion: The rate of malignant trophoblastic disease (MTD) was reduced in the group receiving vitamin A therapy.

Keywords: Hydatidiform mole - retinol - malignant trophoblastic disease

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Introduction

The incidence rates of hydatidiform mole range from 1 to 47/427 deliveries (Martaadisoebrata, 1980), with the majority of affected patients being young women with low parity (Kurowski and Yakoub, 2003). The therapy carried out for hydatidiform mole is the evacuation of mole tissues, which will be followed up with clinical observation and monitoring of blood HCG level to diagnose complete regression or the malignancy after hydatidiform mole at early stage.

Malignancy after hydatidiform mole represents one of the post-hydatidiform mole complications, which normally takes the form of the prolonged proliferation of trophoblastic cells and is clinically recognized as malignant trophoblastic disease (MTD). The incidence rates of MTD range between 15% and 28%, with successful therapy at around 87% overall (Tham et al., 1995; Andrijono et al., 2001; Wolfberg et al., 2005).

The rate of successful therapy for non-metastatic MTD is 95.1%, while for low-risk metastatic MTD it is reported to be 83.3%, and for high-risk metastatic MTD iss only 50%. Overall mortality rates range around 8-9% (Andrijono et al., 2001).

Morbidities caused by MTD include, among others, disorder of reproductive functions such as pregnancy delays, hemorrhage, and other bodily disorders due to the metastasis (Tham et al., 1995; Andrijono et al., 2001; Wolfberget al., 2005).

Vitamin A or pro vitamin A within the body has been shown to be metabolized into retinol, and at a later stage, the retinol is metabolized in the cell into retinoic. Retinoic binds the retinoic receptor, while retinoic complex and retinoic receptor would induce an apoptosis signal and cell cycle termination signal (Sundaram et al.,1998; Chen et al., 1999; Zhang et al., 2000). Enhanced apoptosis would reduce the risk of MTD incidences so that activation of apoptosis induction and cell-cycle termination with retinoic acid might be beneficial as a therapy for the prevention of MTD.

Th present study aimed to demonstrate whether the administration of vitamin A could prevent malignancy following hydatidiform mole development.

Materials and Methods

Samples of this study were the patients with complete hydatidiform mole after the evacuation of mole tissue. These samples were submitted to the administration of either placebo or 200,000 IU vitamin A per day, each of which was produced in the same packages. The treatment was continued until a regression or degeneration of

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MTD was considered to exist, which was specified on the basis of WHO criteria (Tham et al.,1995; RCOG, 2004). The HCG examination as tumor marker was performed with radioimmuno assay (RIA). Deposits of retinol in the liver were examined using relative-dose-response (RDR) method (Stephensen et al., 2002), while vitamin A level was examined with high pressure liquid chromatography (HPLC) method (Hix et al., 2004).

Results

As many as 67 cases met the inclusion criteria of the study. Analysis of the study variables against the incidence of regression and malignancy following hydatidiform mole showed that there was a disparity of malignancy incidence following hydatidiform mole between the control group and the therapy group.

Test of median distribution and mean in the control group and therapy group according to characteristics.

This test was performed to see the distribution of numerical variables in the both groups of study based on the median and mean values. The test results of distribution with equality of populations (Kruskal-Wallis test) and two-sample t test with equal variances, and the results obtained showed an equal distribution of numerical variables in the both groups of study (see Table 1).

Test of proportion disparity of nominal variables in the control and therapy groups

The test of proportion disparity of nominal variables was performed to see the distribution of nominal variables in the both groups of study by using the test of proportion disparity. The test results of the distribution of uterine fundus height using Pearson chi test (meeting the requirements of chi square test) showed an equal distribution of the results (see Table 2).

Correlation of the incidence of malignancy degeneration (MTD) and the time of incidence in the control and terapy groups. This was designed to understand the correlation of MTD incidence and the time the survival test based on Kaplan-Meier test was done. The table of survival analysis was designed to identify the time of MTD occurrence, number or percentage of patients who developed into MTD associated with time unit in the control group and therapy group (see Figure 1).

Table 1. Distribution of median and mean values in each group of intervention according to characteristic variables

Characteristics	Control (N=35)		Therapy (N=32)		P value
	Median (25-75 pct)	Mean (95% IK)	Median (25-75 pct)	Mean (95% IK)	
Age	25 (21;30)	27,03 (24.42;29.64)	26 (23;33)	28.31 (25.63;31.00)	0.488‡
Parity	1 (0;2)	1.23 (0.62;1.84)	1 (0;3,5)	2.06 (1.18;2.95)	0.113‡
Education	9 (6;12)	8.63 (7.40;9.86)	8,5 (6;10,5)	8.00 (6.71;9.29)	0.475¶
Husband education	9 (6;12)	9.40 (8.20;10.60)	9 (6;12)	9.31 (7.88;10.75)	0.924¶
Gestational age	12 (0;16)	11.06 (8.48;13.63)	12,5 (4,5;16)	11.38 (8.73;14.02)	0.863¶
Sounding	16 (12;19)	14.86 (12.95;16.76)	16 (12;20)	16.00 (14.36;17.64)	0.363¶

‡: P value of test results of Equality of populations (Kruskal-Wallis test); ¶: P value of test results of two-sample t test with equal variances

Table 2. Distribution of Proportion in the Control and Therapy Groups according to Characteristic Variables

Characteristic	Control (N=35)		Therapy (N=32)		P value
	n	%	n	%	
Fundus height					0.587‡
< 20 weeks	23	65.71	23	71.88	
> 20 weeks	12	34.29	9	28.13	
Retinol deposit in the liver					0.759¶
No sample	3	8.57	1	3.13	
Sufficient	7	20	7	21.88	
Insufficient	25	71.43	24	75	
End results					0.029¶
Regression	24	68.57	26	81.25	
MTD	10	28.57	2	6.25	
Loss to follow up	0	0.00	2	6.25	
Pregnancy	1	2.86	2	6.25	

‡: P value of test results of proportion disparity with Pearson chi2 test; ¶: P value of the test results of proportion disparity with two direction Fisher's exact test

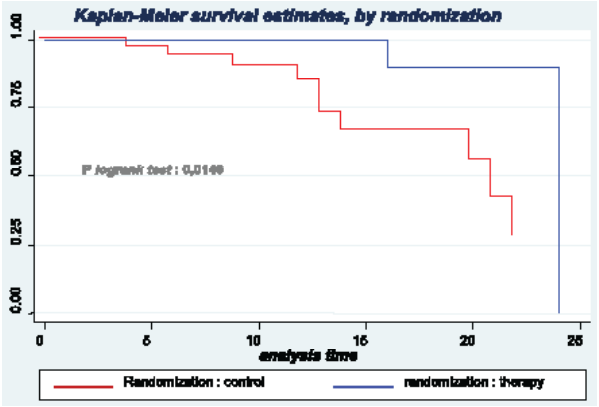

Figure 1. Survival Chart of MTD Incidence of Each Group of Intervention

Side Effects

Mean values of SGOT and SGPT prior to the interventions between the control group and the therapy group did not show any difference. Similarly, no difference was found with respect to mean values after the interventions between the control group and the therapy group. Likewise, no difference was in the changes of the mean values of SGPT before and after the interventions in the therapy group; however, there was a difference in the changes of the mean values of SGOT (p=0.009).

Discussion

Vitamin A would be metabolized in the body into a retinol. Furthermore, the retinol in the cell would be metabolized into retinoic acid, and the latter plays a role in controlling proliferation, increasing cell differentiation, and enhancing apoptosis (Chen et al., 1999; Zhang et al., 2000; Budhu et al., 2002 ; Donato et al., 2005). Hydatidiform mole is an abnormal pregnancy in which the proliferation of trophoblastic cells is found. Trophoblastic cell plays a role of apoptosis (Gang et al., 2000; Dumur et al., 2001). The activity of proliferation and apoptosis represents a connecting link between vitamin A and hydatidiform mole. The relationship between vitamin A and hydatidiform mole was first shown in the epidemiological studies. Vitamin A level in the blood of patients with hydatidiform mole is lower than that in the normal pregnant women (Andrijono et al., 1997).

The low level of vitamin A or retinol might be one of the causal factors in the proliferation of hydatidiform mole trophoblastic cells. The prolonged low level of retinol and might be responsible for the proliferation of trophoblastic cells after the evacuation. The proliferation of trophoblastic cells occurring after the evacuation could clinically develop into MTD.

Low retinol level in the blood in the previous studies was consistent with the data of the incidence of decreased retinol deposit in the liver of patients with hydatidiform mole found in the current study. The data of this study showed that as high as 73.21% (71.43%-75%) of patients with hydatidiform mole had decreased retinol deposit in the liver. This goes to demonstrate that these patients with hydatidiform mole had suffered from vitamin A deficiency in a relatively long period of time.

Vitamin A has an active substance of retinoic acid that plays a role in controlling cell proliferation and enhancing apoptosis (Budhu et al., 2002; Donato et al., 2005). The ability of retinoic acid in controlling proliferation and inducing apoptosis might prevent the persistent proliferation of trophoblastic cells.

A substance such as retinol could enter the cell through an active mechanism with the aid of the receptor. 7 Retinol could enter the trophoblastic cell because there is a retinol receptor in that trophoblastic cell (Andrijono et al., 2007). Furthermore, the retinol which enters cytoplasm of trophoblastic cell would be metabolized into retinoic, and the retinoic in turn is metabolized into retinoic acid. Retinoic acid would increase the apoptosis of trophoblastic cells (Andrijono et al., 2008).

In the clinical trial that we conducted the incidence rate of post- hydatidiform mole malignancies in the control group stood at 28.57%, while in the group receiving the therapy of vitamin A this rate was 6.25%. These results were almost similar to those found in the study of chemo-prevention following hydatidiform mole with actinomycin (in which the control group stood at 29% and the therapy group 6.9%) (Uberti et al., 2006). The risk for developing malignancy following hydatidiform mole, when therapy of vitamin A was not administered, was 8.4 times as high as that for hydatidiform mole patients who received therapy of vitamin A.

Vitamin A at a dose of 200,000 IU constitutes a high dose. The administration of high dose vitamin A would immediately increase the retinol level in the blood. The increase of retinol level would lead to the enhanced retinoic acid level to the extent that the activity of apoptosis is heightened. In addition, the increase in apoptosis activity would raise the incidence of regression and lower the occurrence of MTD.

Thus, vitamin A at a dose of 200,000 IU could be used as a chemo-prevention for the onset of MTD following hydatidiform mole.

In the current study, the administration of 200,000 IU vitamin A (high dose) per day did not give rise to side effects such as the increased SGOT and SGPT levels. Although the administration of high dose vitamin A did not lead to significant side effects, such administration could only be done on the basis of indications as a chemo-prevention of MTD.

The series of studies on vitamin A in hydatidiform mole were of great interest. The first problem encountered in patients with hydatidiform mole was the fact as high as 71.4% of these patients ahd decreased retinol deposits in the liver. A decrease in the retinol deposits in the liver would cause a lower vitamin A or retinol level in the blood. The lower level of retinol would cause the retinol metabolism into retinoic to experience a reduction. A decrease in retinoic in the cell might cause the proliferation of trophoblastic cells to go uncontrollably, which is accompanied by a reduction in the apoptosis activity. Thus, a lower retinol level might indirectly increase the risk of developing MTD following hydatidiform mole The administration of vitamin A would restore the retinol level and increase the apoptosis of trophoblastic cells, such that a regression in the trophoblastic cells could

be boosted. In addition, a lower level of retinol would increase the proliferation of trophoblastic cells, such that it could be one of the causal factors for the occurrence of hydatidiform mole.

In conclusion, a decreased level of retinol deposit was found in 73.21% of patients with hydatidiform mole. The incidence rate of MTD following hydatidiform mole in the group of hydatidiform mole patients receiving vitamin A was 6.25%, while in the control group was 28.57%. The administration of 200,000 IU vitamin A per day did not result in the changes of SGOT and SGPT levels.

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