# Pencegahan keganasan pascamolahidatidosa dengan vitamin A dosis tinggi

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Abstrak

Pendahuluan
Molahidatidosa merupakan kehamilan abnormal yang secara histologi ditandai dengan proliferasi sel trofoblas, degenerasi hidrofik vili korialis dan degenerasi avaskular vili korialis. Sejumlah 15-28% penderita molahidatidosa menderita degenerasi keganasan pascamolahidatidosa. Vitamin A atau retinol dimetabolisme menjadi asam retinoat di dalam sel. Asam retinoat mempunyai aktivitas mengontrol proliferasi sel dan merangsang apoptosis. Aktivitas proliferasi dan apoptosis merupakan aktivitas yang dimiliki oleh sel trofoblas molahidatidosa dan juga vitamin A. Mungkin terdapat hubungan antara molahidatidosa dengan vitamin A. Penelitian epidemiologi mendapatkan kadar vitamin A penderita molahidatidosa lebih rendah jika dibandingkan dengan wanita hamil normal.

Risiko menderita molahidatidosa pada wanita yang berusia kurang dari 24 tahun dan menderita defisiensi vitamin A sebesar 6,29-7 kali. Kadar vitamin A yang rendah mungkin merupakan salah satu bagian dari patofisiologi terjadinya molahidatidosa dan atau bagian dari patofisiologi terjadinya degenerasi keganasan pascamolahidatidosa. Bila vitamin A merupakan bagian dari patofisiologi terjadinya degenerasi keganasan pascamolahidatidosa, maka vitamin A dapat digunakan sebagai salah satu terapi pencegahan keganasan pascamolahidatidosa. Penelitian ini bertujuan membuktikan penggunaan vitamin A sebagai kemoprevensi keganasan pascamolahidatidosa. Penelitian ini memberi manfaat menurunkan kej adian, morbiditas dan mortalitas Penyakit Trofoblas Ganas (PTG).

Bahan dan cara kerja
Rangkaian penelitian
Penelitian ini merupakan bagian dari rangkaian penelitian. Dua penelitian penunjang yaitu penelitian ekspresi reseptor RBP (retinal binding protein), dan penelitian aktivitas apoptosis sel trofoblas yang diberi asam retinoat. Penelitian utama adalah penelitian uji klinik pencegahan keganasan pascamolahidatidosa dengan vitamin A. <br /><br />Penelitian ekfpresi reseptor RBP pada sel trofobias.

Penelitian ini bertujuan membuktikan bahwa sel trofoblas mempunyai reseptor RBP. Sampel penelitian ekspresi reseptor RBP adalah blok paratin molahidatidosa. Ekspresi reseptor retinol diperiksa dengan imunohistokimia tidak langsung menggunakan antibodi RBP. Sementara itu ada atau tidaknya ekspresi dan letak ekspresi reseptor RBP pada sei trofoblas dinilai bersama dokter spesialis Patologi Anatomi.

Penelitian aktivitas apoprosis sel trofoblas yang diberi asam retinoat. Penelitian aktivitas apoptosis sel trofoblas molahidatidosa pada pemberian asam retinoat bertujuan untuk membuktikan adanya induksi apoptosis pada sel trofoblas yang diberi retinoat. (ATRAI all trans retinoic acid). Sampel penelitian aktivitas

apoptosis sel trofoblas yang diberi asam retinoat adalah sel trofoblas yang dilakukan kultur. Kultur sel trofoblas diberi ATRA dengan dosis 50 pg/mL, 100 pg/mL, 150 pg/mL, dan 200 pg/mL. Penilaian dilakukan 24 jam pascaperlakuan dengan pemeriksaan flow cytometry. Hasil sitogram jlow cytometry pada kultur sel trofoblas yang mendapat ATRA dibandingkan dengan kultur sel trofoblas tanpa perlakuan (DMSOl dimethyl sulfoxide) sebagai kontrol.

Penelitian pencegahan keganasan pascamolahidatidasa dengan vitamin A.
Penelitian menggunakan uji klinik tersamar ganda (randomized clinical trial, double blind study). Sampel adalah penderita molahidatidosa komplet, tidak mendapat terapi sitostatika. Perlakuan adalah pmberian plasebo atau vitamin A 200.000 IU per hari (dosis tinggi) yang dibuat dalam bentuk kemasan yang sama, perlakuan diberikan sampai dinyatzikan sembuh atau PTG. Variabel keluaran adalah kejadian regresi dan PTG yang ditetapkan berdasarkan kriteria WHO. Variabel pengganggu antara lain umur, pendidikan, usia kehamilan, besar uterus, deposit retinol di hati.

Hasil
Penelitian ekspresi resepror RBP pada sel trofoblas. Didapatkan ekspresi reseptor RBP pada sel irofoblas. Reseptor RBP dijumpai pada membran sel bagian luar, rnembran sei bagian dalam dan sitoplasma.

Penelitian aktivitas apoptosis sel trofabias yang diberi asam retinoat. Jumlah sel yang mengalami apoptosis pada kontrol 6O,64%, pada ATRA 50 pg/mL sebesar 89,54%, 100 pg/mL sebesar 87,23%, 150 pg/mL sebesar 94,63% dan pada 200 pg/mL sebesar 94,83%. Jumlah sel yang hidup pada kontrol 7,09%, pada ATRA 50 pg/mL sebesar 5,04%, 100 pg/mL sebesar 5,71%, 150 pg/mL sebesar 3,l4% dan pada 200 pg/mL sebesar 2,66%.

Penelitian pencegahan keganasan pascamolahidatidosa dengan vitamin A.
Pada uji klinik, didapatkan sejumlah 67 kasus yang masuk penelitian. Sejumlah 2 kasus hilang pada pengamatan dan 3 kasus mengalami kehamilan saat pengamatan. Kejadian PTG (Penyakit Trofoblas Ganas) pada kelompok kontrol 28,57%, dan pada kelompok terapi 6,25%. Tidak dijumpai perbedaan perubahan kadar SGOT dan SGPT kelompok terapi jika dibandingkan dengan kelompok terapi.

Kesimpulan
Sel trofoblas molahidatidosa mempunyai reseptor RBP di mernbran sel dan sitoplasma. Pemberian asam retinoat pada sel trofoblas menginduksi aktivitas apoptosis. Kejadian Penyakit Trofoblas Ganas (PTG) pada kelompok kontrol 28,57% dan pada kelompok terapi vitamin A 6,25%. Tidak dijumpai efek samping berupa perubahan kadar SGOT dan SGPT.
<hr><i>Introduction
Histologically, hydatidiform mole is an abnormal pregnancy characterized by the proliferation of trophoblastic cells, hydropic degeneration of chorionic villi and degeneration of avasculdar chorionic villi. Around 15-28% of hydatidiform mole patients suffered from malignant degeneration following hydatidiform mole. Vitamin A or retinol is metabolized into retinoic acid in the cell. Retinoic acid has the activity of controlling cell proliferation and stimulating apoptosis. The activity of proliferation and apoptosis constitutes the main activity exercised by hydatidiform mole trophoblastic cells and vitamin A. There might

be a relationship between hydatidiform mole and vitamin A.

Epidemiological studies showed that vitamin A level in patients with hydatidiforrn mole was lower than that in normal pregnant women. The risk for developing hydatidifoml mole in women less than 24 years and suffering from vitamin A deficiency was 6.29-7 times higher as compared to older age without vitamin A deficiency. The low level of vitamin A might be a part of pathophysiology for the occurence of malignant degeneration following hydatidiform mole. If vitamin A is a part of pathophysiology for the occurence of hydatidiform mole, then vitamin A could be used as one of the therapies for preventing malignancy following hydatidiform mole. The objective of this study was to demonstrate the use of vita.rr|in A as a chemoprevention for malignancy following hydatidiform mole. This study would be beneficial in terms of reducing the incidence, morbidity and mortality rates of malignant trophoblastic disease (MTD).

Material and methods

Series of studies

This study constituted part of a series of studies. The supporting studies, comprise the study of the expression of RBP (retinol binding protein) receptor, the study on the apoptosis activity of trophoblastic cells receiving retinoic acid. The main study was a clinical trial on tl1e prevention of malignancy following hydatidiform mole with vitamin A.

Study on Ike expression of RHP receptor in trophoblastic cells.

This study was aimed to demonstrate that trophoblastic cells had RBP receptor. Samples of the study on the expression of RBP receptor were paraffin blocks of hydatidiform mole. The expression of retinol receptor was examined with indirect immunohistochemistry using RBP antibody. The presence or absence of the expression and location of RBP receptor expression in trophoblastic cells was evaluated together with the specialist of anatomy pathology.

Study on the apoptosis activity of trophoblastic cells receiving retinoic acid

The study on the apoptosis activity of hydatidifom mole trophoblastic cells receiving retinoic acid was aimed to demonstrate the presence of apoptosis induction in trophoblastic cells receiving retinoic (ATRA/ all trans retinoic acid). Samples of the study on the apoptosis activity of trophoblastic cells receiving retinoic acid were the trophoblastic cells undergoing culture. The culture of trophoblastic cells received ATRA at doses of 50 pg/mL, 100 pg/mL, l50 pg/mL, and 200 pg/mL. The evaluation was made in 24 hours after the intervention with flow cytometry examination . The results of flow cytometry cytogram in the culture of trophoblastic cells receiving ATRA were compared with the culture of trophoblastic cells without intervention (DMSO/ dimethyl sulfoxide) as control.

Study of the prevention of malignancy jhllowing hydatidiform mole with vitamin A.

This study made use of randomized clinical trial, double blind study. Samples of the study were the patients with complete hydatidifomt mole, not receiving cytostatics. The intervention was the administration of placebo and vitamin A 200,000 IU per day (high dose), both of which were made in the similar packages. The intervention was 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 which were

established based on WHO criteria. The intervening variables were, among others, age, education, gestational age, uterus size, retinol deposit in the liver.

Results

Study on the expression of RBP receptor in trophoblastic cells. e found the presence of RBP receptor expression in trophoblastic cells. RBP receptors were found in the outer cell membrane, inner cell membrane, and cytoplasm.

Study on the apoptosis activity oftrophoblatic cells receiving retinoic acid.

The activities of apoptosis in the control group was 60,64%, in ATRA of 50 pg/ml was 39.54%, in 100 ug/ml was 8'7.23%, in 150 ug/ml was 94.63%, and in 200 ug/ml was 94.83%. The alive cells in t.he control group was 7.09%, in ATRA of 50 pg/ml was 5.04%, in 100 pg/ml was 5.71%, in 150 pg/ml was 3.14%, and in 200 pg/ml was 2.66%.

Study on the prevention of malignancy following hydatidpform mole with vitamin A.

At clinical trial as many as 67 cases met the requirements for the study. Two cases were lost from observation and three cases experienced pregnancy during observation. The incidence rate of malignant trophoblastic disease in the control group was 28.57%, and in the therapy group was 6.25%. No difference was found in the changes of SGOT and SGPT levels of the therapy group compared with the control group.

Conclusion

Trophoblastic cells of hydatidiform mole had RBP receptor in the cell membranes and cytoplasm. The administration of retinoic acid in the trophoblastic cells induced the activity of apoptosis. The rate of malignant trophoblastic disease (MTD) in the control group was 28.57% and in the group receiving vitamin A therapy was 6.25%. No side effects were found in the form of changed SGOT and SGPT levels.</i>