INTISARI

Perbedaan Ekspresi Protein *Bcl-2 Family* sebagai Regulator Aktivitas *Caspase* Trofoblas pada Kehamilan dengan Preeklamsia dibandingkan dengan Kehamilan Normotensi

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Latar Belakang: Apoptosis ditemukan pada plasenta dari kehamilan normal dan meningkat pada kehamilan dengan komplikasi preeklamsia dan pertumbuhan janin terhambat (PJT). Mekanisme apoptosis molekuler pada manusia sangat kompleks dan melibatkan berbagai sinyal molekuler, termasuk yang dimediasi sistem imun melalui ligan ekstraseluler dan reseptor-reseptor seperti *Fas ligand* dan *Fas receptor*, serta sinyal kematian endogen oleh gen *Bcl-2 family*, yang bertemu untuk mengaktivasi eksekutor sentral kaskade *caspase*. Protein *Bcl-2 family* terdiri atas kelompok proapoptosis (misalnya Bax dan Bak) dan yang menghambat apoptosis atau kelompok antiapoptosis (misalnya Bcl-2 dan Bcl-xL).
Tujuan: Membandingkan ekspresi protein proapoptosis (Bax dan Bak) dan protein antiapoptosis (Bcl-xL dan Bcl-2) pada sel trofoblas plasenta dari kehamilan dengan preeklamsia berat dengan kehamilan normotensi.
Metode: Menggunakan metode penelitian potong lintang (*cross sectional study)* untuk membandingkan ekspresi protein Bak, Bax, Bcl-2, dan Bcl-xL dari plasenta preeklamsia berat dibandingkan kehamilan normotensi. Penelitian dilakukan di RSUP Dr. Sardjito, Yogyakarta. Kriteria inklusi adalah pasien preeklamsia berat dengan umur kehamilan 28-40 minggu dan setuju untuk masuk dalam penelitian. Kriteria eksklusi adalah pasien dengan penyakit penyerta yaitu: korioamnionitis, hipertensi kronis, diabetes, sistemik lupus eritematosus, kejang oleh karena sebab lain, HIV/AIDS, janin dengan kelainan kongenital mayor, serta kehamilan kembar. Sampel diambil dari plasenta segera setelah bayi lahir dari pasien yang sebelumnya telah menyetujui untuk mengikuti penelitian secara tertulis. Sampel kemudian dikirim ke Laboratorium Histologi FK UGM, Yogyakarta untuk dilakukan pewarnaan imunohistokimia dengan antibodi anti protein yang diperiksa. Ekspresi protein diukur dengan sistem skor imunohistokimia semikuantitatif yaitu HSCORE (*histological score*).
Hasil: Didapatkan sampel penelitian sebanyak 79 plasenta, yaitu 38 plasenta dari kehamilan dengan preeklamsia berat dan 41 plasenta dari kehamilan normotensi. Rerata ekspresi protein Bak pada kelompok normotensi lebih rendah dibandingkan kelompok preeklamsia namun tidak bermakna ($p>0,05$). Rerata ekspresi protein Bax pada kelompok normotensi lebih rendah dibandingkan kelompok preeklamsia dan bermakna secara statistik ($p<0,05$). Rerata ekspresi protein Bcl-2 dan Bcl-xL pada kelompok normotensi lebih tinggi dibanding kelompok preeklamsia dan bermakna secara statistik ($p<0,05$). Pada uji multivariat, diperoleh efek multivariat yang signifikan dari kelompok normotensi/preeklamsia terhadap keseluruhan ekspresi protein dengan Wilk's $\lambda=0,480$, $F(4, 72)=19,466$, $p=0,000$, partial $\eta^2=0,997$. Pada uji efek antar subjek,

ekspresi protein Bcl-xL memiliki perbedaan paling bermakna dan efek ukuran yang paling besar ($p=0,000$, partial $\eta^2=0,410$) dibanding protein lainnya.
Kesimpulan: Terdapat peningkatan ekspresi protein proapoptosis, Bax, dan penurunan ekspresi protein antiapoptosis, Bcl-xL dan Bcl-2, pada pasien PEB bila dibandingkan dengan kontrol. Di antara protein *Bcl-2 family*, protein Bcl-xL memiliki memiliki peran yang paling besar dalam kejadian preeklamsia berat. Hasil ini konsisten dan tidak dipengaruhi oleh paritas dan usia kehamilan subjek penelitian.

Kata Kunci: Preeklamsia, Apoptosis, Bak, Bax, Bcl-2, Bcl-xL

ABSTRACT

Difference in Expression of Bcl-2 Family Protein as Trophoblast *Caspase* Activity Regulator in Preeclamptic and Normotensive Pregnancy

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Background: Apoptosis is found in placenta of normal pregnancy and is increasing in pregnancy complicated by preeclampsia or intrauterine growth restriction (IUGR). Mechanism of molecular apoptosis in human is a complicated process and involving numerous molecular signals, including immune-mediated extracellular ligand and receptors such as Fas ligand and Fas receptor, and also endogenous death signals by Bcl-2 family genes, which are then communicated to activate the executor *caspase*s. Bcl-2 family protein consists of proapoptotic group (such as Bax and Bak) and antiapoptotic group (such as Bcl-2 and Bcl-xL)
Purposes: To compare the expression of proapoptotic protein (Bax and Bak) and antiapoptotic protein (Bcl-xL and Bxl-2) in placental trophoblastic cells from pregnancy complicated by severe preeclampsia and normotensive pregnancy.
Methods: The research was conducted in was cross sectional design in order to compare the expressions of Bak, Bax, Bcl-2, and Bcl-xL in placenta from pregnancy complicated with severe preeclampsia and normotensive pregnancy. The research was conducted at RSUP Dr. Sardjito, Yogyakarta. The inclusion criteria were patients with severe preeclampsia with age of 28-40 weeks and agree to parcipate in the research. The exclusion criteria were patients with comorbid conditions such as chorioamnionitis, chronic hypertension, diabetes, systemic lupus erythematosus, seizure from another cause, HIV/AIDS, fetus with major congenital disorder, and multiple pregnancy. Samples were taken immediately after the baby was born from the patients which previously agreed to participate in the research. The samples were sent to Histology Laboratory and Anatomical Pathology Laboratory Faculty of Medicine, UGM, Yogyakarta, in order to perform immunohistochemistry with monoclonal antibodies tested. Protein expression was measured using semiquantitative immunohistochemistry scoring system (HSCORE/histological score).
Results: Total samples were 79 placentas, which consisted of 38 placentas from severe preeclamptic patients and 41 placentas from normotensive patients. Mean of Bak expression in normotensive group was lower than severe preeclamptic group but was not statistically significant ($p>0,05$). Mean of Bax expression in normotensive group was lower than severe preeclamptic group and was statistically significant ($p>0,05$). Means of Bcl-2 and Bcl-xL expressions in normotensive group was higher than severe preeclamptic group and were statistically significant ($p>0,05$). In multivariate test, normotensive/preeclamptic group had significant effect towards overall protein expression with Wilk's $\lambda=0,480$, $F(4, 72)=19,466$, $p=0,000$, partial $\eta^2=0,997$. In test of between-subjects effects, Bcl-xL protein expression had the highest significant difference and size effect ($p=0,000$, partial $\eta^2=0,410$) compared to other proteins.

Conclusions: There is an increase in expression of proapoptosis protein, Bax, and a decrease in expression of antiapoptosis protein Bcl-xL and Bcl-2, in severe preeclamptic patient compared to control. Between member of Bcl-2 family protein, Bcl-xL has the highest effect on the occurence of severe preeclampsia. The result is consistent with multivariate test and is not affected by parity and gestasional age.

Keywords: Preeclampsia, Apoptosis, Bak, Bax, Bcl-2, Bcl-xL