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**JUDUL PENGARUH POLYMORPHISM GEN RENIN C-5312T TERHADAP RESPON
TERAPI BERBASIS PENGHAMBAT ANGIOTENSIN PADA PASIEN HIPERTENSI:
IMPLIKASI TERHADAP PEMILIHAN TERAPI HIPERTENSI**

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Ketua/Anggota Tim

dr. M. Saifur Rohman, SpJP, PhD

NIDN. 0031106803

dr. Hidayat Sujuti, SpM, PhD

NIDN. 0023016706

Dibiayai oleh:

Direktorat Jenderal Pendidikan Tinggi,
Kementerian Pendidikan dan Kebudayaan, Melalui DIPA Universitas Brawijaya
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Peneliti / Pelaksana
Nama Lengkap : dr. M. Saifur Rohman, SpJP, PhD
NIDN : 0031106803
Jabatan Fungsional : Lektor
Program Studi : Kardiologi dan Kedokteran Vaskuler
Nomor HP : 085234217292
Alamat surel (e-mail) : ippoenk@yahoo.com atau ippoenk@ub.ac.id
Anggota (1)
Nama Lengkap : dr. Hidayat Sujuti, SpM, PhD
NIDN : 0023016706
Institusi Mitra (jika ada) : -
Nama Institusi Mitra : -
Alamat : -
Penanggung Jawab : -
Tahun Pelaksanaan : Tahun ke 1 dari rencana 2 tahun
Biaya Tahun Berjalan : Rp. 55.000.000,00
Biaya Keseluruhan : Rp. 155.000.000,00



Dr. dr. Karyono Mintaroem, SpPA
NIP. 19501116 198002 1 001

Malang, 30 November 2013
Mengetahui,
Ketua,

dr. M. Saifur Rohman, SpJP, PhD
NIP. 19681031 199702 1 001

Mengetahui
Pjs. Ketua LPPM

(Prof. Dr. Ir. Siti Chuzaemi, MS) K
NIP/NIK 195305141980022001

ABSTRAK

Latar Belakang : Renin memainkan peran penting dalam sistem renin angiotensin aldosteron . Polimorfisme pada gen renin yang mempengaruhi ekspresi akan mempengaruhi kadar angiotensin I dan II , akibatnya kinerja sistem renin angiotensin aldosteron akan diubah . Namun, konsekuensi dari polimorfisme REN C-5391T pada perubahan kadar angiotensin II sebagai respon terapi Angiotensin Receptor Blocker (ARB) masih belum jelas , terutama pada pasien hipertensi di Indonesia.

Metode : 50 pasien hipertensi primer dengan fungsi ginjal normal (serum kreatinin < 2,5 mg / dl) dan kepatuhan terhadap pengobatan yang baik direkrut dalam penelitian ini . Sequencing genomic DNA untuk menentukan adanya varian genetik REN C - 5312T . kadar renin serum awal dan setelah 3 bulan terapi ARB diperiksa menggunakan metode ELISA. Pengukuran tekanan darah ambulatory 24 jam dilakukan pada akhir penelitian .

Hasil : Tidak ada perbedaan yang signifikan antara kadar Renin dan respon tekanan darah 24 jam setelah terapi ARB dengan genotipe REN C - 5312T .

Kesimpulan : Penelitian ini menunjukkan bahwa varian genetik REN C - 5312T tidak mempengaruhi respon tekanan darah dan kadar renin setelah pemberian ARB

ABSTRACT

Background: Renin plays an essential role in RAA system. Polymorphism in renin gene that affect its expression will definitely affect angiotensin I and II levels, consequently the performance of RAA system will be altered. However, the consequences of polymorphism REN C-5391T on angiotensin II level alteration after Angiotensin Receptor Blocker (ARB) therapy response remain unclear, especially in Indonesian hypertensive patients.

Methods: 50 primary hypertensive patients with normal renal function (serum creatinine <2.5 mg/dl) and good medication compliance were recruited in this study. Genomic DNA was sequenced to determine the presence of genetic variant REN C-5312T. Serum renin levels at baseline and after 3 months of ARB therapy were examined using ELISA method. 24 hour ambulatory blood pressure measurement was performed at the end of study.

Results: Renin level after ARB did not achieve any statistical significance among genotypes of REN C-5312T; 24 hour blood pressure response was not achieved any statistical significance.

Conclusion: This study suggested that genetic variant REN C-5312T did not influence the blood pressure response and renin level after ARB administration

RINGKASAN

Hipertensi tidak terkontrol merupakan faktor resiko kejadian kardiovaskuler dan merupakan penyebab dari setengah kejadian penyakit jantung koroner dan sekitar dua pertiga penyakit cerebrovaskuler. Sistem renin angiotensin aldosteron (RAAS) berperan penting dalam terjadinya kerusakan organ sebagai komplikasi hipertensi. Terapi dengan menggunakan angiotensin receptor blocker (ARB) terbukti memberikan banyak manfaat klinis dan banyak digunakan dalam praktek klinis (Mancia et.al 2007). Penelitian kami sebelumnya juga membuktikan tingginya kadar angiotensin I pada pasien hipertensi di Indonesia yang menunjukkan bahwa pasien hipertensi di Indonesia mungkin lebih cocok menggunakan agen penghambat RAAS. Akan tetapi prevalensi hipertensi terkontrol masih rendah, yaitu hanya sekitar 20% yang mencapai tekanan darah target (Lukitasari, Rohman, Hendrawan 2011; Rohman & Hersunarti, 2009a). Hal ini mungkin berhubungan dengan kepatuhan, pilihan kombinasi obat, atau molekul variant genetik yang terlibat dalam RAAS. Penelitian di Jepang menunjukkan bahwa variant renin C-5312T, yang substitusi nukleotida dari C ke T pada urutan nukleotida ke 5312, merupakan prediktor independen terhadap resistensi bagi pengguna ARB di Jepang (Konoshita et.al 2009). Penelitian pendahuluan yang kami lakukan di RS dr. Saiful Anwar Malang menunjukkan adanya polymorphism gen renin C-5312T pada 17 dari 24 pasien hipertensi. Akan tetapi hingga saat ini belum terdapat data mengenai pengaruh polymorphism ini terhadap respon terapi berbasis penghambat angiotensin. Oleh karena itu sangat menarik untuk meneliti fenomena tersebut pada pasien hipertensi di RS dr. Saiful Anwar Malang. Penelitian ini merupakan penelitian kohort prospektif yang dilakukan selama 3 bulan. Populasi dalam penelitian ini adalah pasien dengan hipertensi yang menggunakan terapi golongan *angiotensin receptor blocker* (ARB) di Poliklinik Jantung RS. Saiful Anwar Malang. Sampel dalam penelitian ini adalah 50 orang pasien hipertensi dewasa yang memiliki kepatuhan minum obat dan kontrol yang baik. Pasien dengan hipertensi sekunder, kontrasepsi hormonal, hamil, perdarahan masif, dan gangguan fungsi ginjal dieksklusikan dari penelitian ini. Pasien akan dilakukan pengukuran tekanan darah 24 jam setelah memperoleh terapi ARB. Hasil penelitian menunjukkan tidak ada beda antara kelompok genotip dalam hal capaian tekanan darah dan kadar renin. Hal ini dimungkinkan karena masih kecilnya jumlah sampel. Oleh karena itu penelitian lebih lanjut dengan sampel lebih besar diperlukan untuk menjawab pertanyaan penelitian ini lebih lanjut.

SUMMARY

Uncontrolled hypertension is a risk factor for cardiovascular events and is leads to half of coronary heart disease and two-thirds of cerebrovascular disease. Renin-angiotensin-aldosterone system (RAAS) plays an important role in organ damage as a complication of hypertension. Therapy using angiotensin receptor blockers (ARBs) clinically proven to provide many benefits and are widely used in clinical practice (Mancia et.al, 2007). Our previous studies also show high levels of angiotensin 1 in hypertensive patients in Indonesia. Thus, angiotensin blockade based therapy may provide a great benefit in controlling hypertension. However, the prevalence of uncontrolled hypertension is still low, which is only about 20% hypertensive patients achieved blood pressure target (Lukitasari, Rohman, Hendrawan 2011; Rohman & Hersunarti, 2009a). This may relate to compliance, choices of drug combinations, or molecular genetic variants involved in the RAAS. Research in Japan suggests that the renin C-5312T variant, the nucleotide substitution of C to T at nucleotide sequences to 5312, is an independent predictor of resistance for users of ARBs in Japan (Konoshita et.al 2009). Preliminary study in the dr. Saiful Anwar shows the renin gene polymorphism C-5312T in 17 of 24 hypertensive patient. However, until now there are no data regarding the effect of this polymorphism on the response to angiotensin blokade-based therapy. Therefore, it is very interesting to examine the phenomenon in hypertensive patients in dr. Saiful Anwar hospital Malang. This study is a prospective cohort study conducted over 3 months. The population in this study were patients with hypertension who use therapy of angiotensin receptor blockers (ARBs) in the Cardiology Outpatient Clinic of Saiful Anwar Hospital Malang. A total of 50 adult hypertensive patients with good medication adherence were recruited in this study. Patients with secondary hypertension, hormonal contraception, pregnancy, massive bleeding, and impaired renal function were excluded from this study. Twenty-four hours ambulatory blood pressure measurements were performed at the end of study. The results showed no significantly differences between genotype groups in renin levels and achievement of blood pressure. This is possible because the sample is still small. Therefore, further research with larger samples is needed to answer this research question.

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