INTISARI

PENGARUH *CYP2C9*3, GSTM1 NULL*, DAN *GSTT1 NULL* TERHADAP RISIKO PERDARAHAN SALURAN CERNA TERKAIT PENGGUNAAN OBAT ANTI INFLAMASI NON-STEROID

Latar Belakang: Obat anti inflamasi non-steroid (OAINS) dikonsumsi secara luas pada nyeri kronis maupun akut. Meskipun aman untuk penggunaan bebas, penggunaannya memiliki risiko perdarahan saluran cerna. Alel *CYP2C9*3* diasosiasikan dengan aktivitas isoenzim pemetabolisme utama mayoritas OAINS yang menurun, meningkatkan risiko perdarahan. Variasi genetik *GSTM1 null* dan *GSTT1 null* juga dilaporkan berhubungan dengan lesi endoskopik dan premalignan di saluran cerna. Penelitian mengenai marker genetik dari risiko perdarahan saluran cerna terkait penggunaan OAINS di Indonesia masih sangat terbatas.
Tujuan: Penelitian ini bertujuan untuk mengetahui perbedaan distribusi frekuensi alel *CYP2C9*3*, *GSTM1 null*, dan *GSTT1 null* pada individu dengan diagnosis perdarahan saluran cerna dan tidak serta pengaruhnya dengan perdarahan saluran cerna terkait penggunaan OAINS.
Metode: Penelitian observasional analitik dengan rancangan kasus-kontrol tidak berpasangan melibatkan 94 subjek kasus dan 94 subjek kontrol yang terdata pernah melakukan perawatan di RSA UGM atau RSUP Dr. Sardjito, Yogyakarta. Data demografik dan klinis didapat dari wawancara dan dicocokkan dengan sumber data sekunder. Pemeriksaan variasi genetik pada sampel darah dilakukan dengan metode qPCR untuk alel *CYP2C9*3* dan PCR konvensional serta elektroforesis untuk *GSTM1 null* dan *GSTT1 null*. Distribusi genotipe *CYP2C9* diverifikasi dengan Hardy-Weinberg *equilibrium*. Analisis statistik dilakukan dengan *chi square*, Mann-Whitney, estimasi *unadjusted odds ratio* (uOR), serta regresi logistik menggunakan SPSS.
Hasil: Distribusi variasi genetik pada kelompok kasus dan kontrol secara berturut-turut adalah alel *CYP2C9*3* sebesar 7,4% dan 2,1%, *GSTM1 null* sebesar 16% dan 31,9%, dan *GSTT1 null* sebesar 26,6% dan 30,9%. Variasi genetik *GSTM1 null* menurunkan risiko perdarahan (uOR 0,4) dibandingkan *GSTM1 wild-type* (*p* 0,010). Sedangkan alel *CYP2C9*3* dan *GSTT1 null* tidak memiliki nilai bermakna.
Kesimpulan: Variasi genetik *GSTM1 wild-type* memiliki pengaruh terhadap risiko kejadian perdarahan saluran cerna terkait penggunaan OAINS. Alel *CYP2C9*3 dan *GSTT1* tidak berkaitan dengan risiko ini. Temuan ini menunjukkan potensi penggunaan variasi genetik *GSTM1* dalam stratifikasi risiko perdarahan saluran cerna terkait penggunaan OAINS.

Kata Kunci: OAINS; CYP2C9; GSTM1; GSTT1; perdarahan saluran cerna

ABSTRACT

THE INFLUENCE OF CYP2C9*3, GSTM1 NULL, AND GSTT1 NULL GENOTYPES ON THE RISK OF GASTROINTESTINAL BLEEDING ASSOCIATED WITH NON-STEROIDAL ANTI-INFLAMMATORY DRUG USE

Background: Non-steroidal anti-inflammatory drugs (NSAID) are widely used for the management of both chronic and acute pain. Although generally considered safe for over-the-counter use, NSAID consumption carries a risk of gastrointestinal (GI) bleeding. The *CYP2C9**3 allele has been associated with reduced activity of the primary isoenzyme responsible for the metabolism of most NSAID, potentially increasing the risk of bleeding. Additionally, the *GSTM1 null* and *GSTT1 null* genetic variants have been reported to be associated with endoscopic lesions and premalignant changes in the gastrointestinal tract. However, studies investigating genetic markers associated with NSAID-related gastrointestinal bleeding in the Indonesian population remain scarce.
Objective: This study aims to examine the differences in the frequency distribution of the *CYP2C9**3, *GSTM1 null*, and *GSTT1 null* genetic variants between individuals with and without a diagnosis of GI bleeding, as well as to evaluate their influence toward NSAID-related GI bleeding.
Methods: An analytical observational study with an unmatched case-control design was conducted, involving 94 case and 94 control subjects who had previously received care at RSA UGM or RSUP Dr. Sardjito, Yogyakarta. Demographic and clinical data were obtained through interviews and cross-validated with secondary data sources. Genetic variation analysis was performed on blood samples using qPCR for the *CYP2C9**3 allele and conventional PCR followed by electrophoresis for *GSTM1 null* and *GSTT1 null* genetic variants. The genotype distribution of *CYP2C9* was assessed for conformity with Hardy-Weinberg equilibrium. Statistical analyses included chi-square tests, the Mann-Whitney U test, unadjusted odds ratio (uOR) estimation, and logistic regression, conducted using SPSS software.
Results: The genotype distributions in the case and control groups were as follows: *CYP2C9**3 allele, 7.4% and 2.1%; *GSTM1 null*, 16% and 31.9%; and *GSTT1 null*, 26.6% and 30.9%, respectively. The *GSTM1 null* variant was significantly reduced risk of bleeding (uOR 0.4) compared to the *GSTM1* wild-type (*p* 0.010). In contrast, the *CYP2C9**3 and *GSTT1 null* showed no significant value.
Conclusion: The *GSTM1* wild-type genetic variant influence the increased risk of NSAID-related GI bleeding. In contrast, *CYP2C9*3* allele and *GSTT1* genetic variants do not influence this risk. These findings suggest the potential utility of the *GSTM1* genetic variants in risk stratification for NSAID-related GI bleeding.

Keywords: NSAID; CYP2C9; GSTM1; GSTT1; gastrointestinal bleeding