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Genetic polymorphisms associated with upper gastrointestinal bleeding: A systematic review protocol

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ABSTRACT

Gastrointestinal bleedings (GIB) are one of the most frequent adverse drug reactions. Among the GIB upper gastrointestinal bleeding (UGIB) stands out due to their high mortality. The different idiosyncratic responses related to UGIB in medication users may be due to the presence of genetic variants in the genes that encode enzymes that are targets of pharmacokinetic and pharmacodynamic activity of the metabolism of the drugs, such as cyclooxygenase 1, endothelial nitric oxide synthase, cytochrome P450, among others. Although a review has focused on assessment whether the presence of CYP2C9*2 and CYP2C9*3 could increase UGIB diagnosis, the search is outdated, and more evidence can be identified regarding both CYP polymorphisms and other genes potentially involved with UGIB. The objective of the systematic review is to explore case-control or case-case studies to assess the epidemiological association between genetic polymorphisms and UGIB. This review will consider genetic polymorphisms of case-control and case-case studies and their association with the UGIB, in the presence or absence of drugs exposure. Electronic searches will be performed in PubMed, Scopus and the Cochrane Library with no time limit. Two researchers will select registries and extract data on study and population characteristics, exposure, covariates, and outcomes. Critical appraisal will consider Joanna Briggs tool for case-control studies. Studies will, where possible, be pooled with statistical meta-analysis. Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation, where appropriate.

Keywords: Drug-Related Side Effects and Adverse Reactions. Hemorrhage. Pharmacogenetics. Polymorphism, Genetic. Systematic Review. Upper Gastrointestinal Bleeding.

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INTRODUCTION

Gastrointestinal bleeding (GIB) is one of the most frequent and potentially more serious adverse drug reactions, with an estimated incidence of about 50 to 100 cases per 100,000 people/ year (El-Tawil, 2012). Among the GIB, upper gastrointestinal bleeding (UGIB) stands out and the rate of death can vary from 10% to 35% depending on the origin of UGIB and acute and chronic comorbidities (Rockall et al., 1995; Zimmerman et al., 1995; Christensen et al., 2007).

UGIB is a bleeding resulting from lesions proximal to the Treitz ligament and is classified as varicose or non-varicose (Feinman & Haut, 2014). Non-varicose etiology is the most frequent, with the main cause being peptic ulcer (duodenal or gastric), which is often associated with reactivity to *Helicobacter pylori* and exposure to non-steroidal anti-inflammatory drugs and antiplatelet agents, while varicose etiology is often associated with esophageal and gastric varices (Feinman & Haut, 2014).

The existence of a genetic susceptibility to UGIB associated with drug exposure has been suggested (Shiotani et al., 2015; Figueiras et al., 2016). These variations could be explained in part through polymorphisms in genes that encode enzymes involved in their activity in the pharmacokinetics and pharmacodynamics of drugs, such as endothelial nitric oxide synthase, cytochrome P450, P-glycoprotein transporter, among others. And yet, other polymorphisms related to the coagulation cascade may be involved with the development of UGIB not related to drugs and, therefore, are relevant to the exclusion of causality with drugs (Groza et al., 2017).

A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews and the *JBI Evidence Synthesis* in November 2019 was conducted and revealed that there is no systematic review regarding our propose. However, a review was identified, whose objective was to assess whether the presence of CYP2C9*2 and CYP2C9*3 could increase UGIB diagnosis (Estany-Gestal et al., 2011). In addition to the strict inclusion criteria, the search for the review carried out by Estany-Gestal et al. was completed in June 2010 and, therefore, more evidence can be identified regarding the polymorphisms of CYP and other genes potentially involved with UGIB. Estany-Gestal et al. (2011) provided an excellent clinical perspective, but had a major limitation in the absence of a comprehensive search and systematic data summary.

Therefore, we aim to conduct a systematic review of case-control and case-case studies to assess the epidemiological association between genetic polymorphisms and UGIB diagnosis.

REVIEW QUESTIONS

Two main questions will be addressed in this review:

i) What are the genetic polymorphisms associated with UGIB diagnosis?

ii) What are the genetic polymorphisms and drug therapy associated with UGIB as an adverse drug reaction?

METHODS

The proposed systematic review will be conducted in accordance with the Cochrane Collaboration (Higgins et al., 2019) and Joanna Briggs Institute methodology for systematic reviews of etiology and risk evidence (Munn et al., 2017).

Inclusion criteria

Participants: This review will consider studies that include participants with UGIB (as diagnosed using any recognized diagnostic criteria), regardless of the diagnostic criteria, sex, age or ethnicity. Studies that explicitly include participants with UGIB of varicose etiology will be excluded;

Exposure: This review will consider studies that evaluated genetic polymorphisms (etiology or exposure) associated with the diagnosis of UGIB;

Comparator: This review will consider studies that compare the exposure to absence of genetic polymorphism;

Outcome: This review will consider studies that include the following outcomes: UGIB.

Types of studies: This review will consider studies reported as case-control or case-case or following a case-control or case-case design. Studies published in non-roman alphabet languages (e.g. Arabic, Chinese, Russian) will be excluded. Studies published from database inception to the February 2020 will be included.

Search strategy

The search strategy will aim to locate both published and unpublished studies. An initial limited search of PubMed was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles were used to develop a full search strategy for PubMed, which includes MEDLINE and PubMed Central databases, Scopus, Cochrane Central databases (see Appendix I). The search strategy, including all identified keywords and index terms, will be adapted for each included information source. The reference list of all studies selected for critical appraisal, as well as systematic reviews recovered in the search, will be screened to identify any additional papers.

Study selection

Following the search, all identified records will be collated and uploaded into EndNote X7.2.1 (Clarivate Analytics, PA, USA) and duplicates will be removed. Titles and abstracts will then be exported to sheets of Microsoft Excel and screened by two independent reviewers against the inclusion criteria for the review. Potentially relevant papers will be retrieved in full. The full text of selected citations will be assessed in detail against the inclusion criteria by two independent reviewers. Reasons for exclusion of full text studies that do not meet the inclusion criteria will be recorded and reported in the systematic review. Any disagreements that arise between the reviewers at each stage of the study selection process will be resolved through discussion, or with a third reviewer. The results of the search will be reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram (Moher et al., 2009).

Assessment of methodological quality

Eligible studies will be critically appraised by two independent reviewers at the study level for methodological quality in the review using standardized critical appraisal instruments from the Joanna Briggs Institute for case-control studies. Authors of papers will be contacted to request missing or additional data for clarification, where required. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer. The results of critical appraisal will be reported in narrative form and in a table.

All studies, regardless of the results of their methodological quality, will undergo data extraction and synthesis (where possible). The synthesis will consider studies subgroups regarding methodological quality.

Data extraction

Data will be extracted from studies included in the review by two independent reviewers using a data extraction tool developed by the reviewers in Microsoft Excel and Microsoft Word (Redmond, Washington, USA). The extracted data will include specific details about: i) baseline study characteristics (author names, year of publication, country, inclusion and exclusion criteria study, sample size, groups definition (i.e. case or control), gene and polymorphism information, patient sex and age, conflict of interest and funding, covariates evaluated in adjusted analysis. A draft extraction tool is provided in Appendix II. The draft data extraction tool will be modified and revised as necessary during the process of extracting data from each included paper. Modifications will be detailed in the full scoping review. Any disagreements that arise between the reviewers will be resolved through discussion or by a third reviewer. Authors of papers will be contacted to request missing or additional data where required.

Data synthesis

Studies will, where possible, be pooled with statistical meta-analysis. Effect sizes will be expressed as odds ratios (for dichotomous data) and their 95% confidence intervals and prediction interval will be calculated for analysis. Statistical analyses will be performed using the R v. 3.4.1/ R studio 1.0.153 (R Foundation, 2019) software – packages READR (Wickham et al., 2017), META (Schwarzer, 2007) and METAFOR (Viechtbauer, 2010). A meta-analysis of the main analyses will be conducted using a random model by Hartung-Knapp and the τ^2 estimator from the Sidik-Jonjman, due to the high expected heterogeneity for observational studies, and Higgins inconsistency test (I^2) being used for the evaluation of heterogeneity. In cases of meta-analyses containing 10 or more studies, the probability of publication bias will be evaluated, with a statistical test based on the Harbor test and visual analysis of the presence of asymmetry in the funnel plot. The main analysis will consider adjusted estimates for confounding variables, when available. Sensitivity analyses will be conducted to test decisions made regarding adjustment of the random effects model Mantel-Haenszel method, with DerSimonian-Laird estimator for τ^2, presence of adjustment for confounding factors, as well as modification of the effect estimation (relative risk instead of OR). In addition, arbitrary exclusion from studies will be performed. Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation, where appropriate.

ACKNOWLEDGMENTS

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RESUMO

Polimorfismos genéticos associados à hemorragia digestiva alta: um protocolo de revisão sistemática

As hemorragias gastrointestinais (HGI) são uma das reações adversas a medicamento mais frequentes. Dentre as HGI, destaca-se a hemorragia digestiva alta (HDA) devido a sua alta mortalidade. As diferentes respostas idiossincráticas relacionadas ao diagnóstico de HDA em usuários de medicamentos podem ser devido à presença de variantes genéticas nos genes que codificam enzimas alvos de atividade farmacocinética e farmacodinâmica do metabolismo de medicamentos, tais como a ciclo-oxigenase 1, a óxido nítrico sintase endotelial, citocromo P450, entre outros. O objetivo desta revisão sistemática é explorar estudos de caso-controle ou caso-caso para avaliar a associação epidemiológica entre polimorfismos genéticos e diagnóstico de HDA. Esta revisão considerará polimorfismos genéticos identificados em estudos de caso-controle e caso-caso e sua associação com a HDA, na presença ou ausência de medicamentos. As pesquisas eletrônicas serão conduzidas no PubMed, Scopus e Cochrane Library, sem limite de data de publicação. Dois pesquisadores selecionarão registros e extrairão dados sobre as características do estudo e da população, exposição, covariáveis e resultados. A avaliação crítica considerará a ferramenta do *Joanna Briggs Institute* para estudos de caso-controle. Os estudos serão, sempre que possível, agrupados estatisticamente com meta-análise. Quando o agrupamento estatístico não for possível, os achados serão apresentados em forma narrativa, incluindo tabelas e figuras para auxiliar na apresentação dos dados, quando apropriado.

Palavras-chave: Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos. Farmacogenética. Hemorragia; Hemorragia digestiva alta. Polimorfismo Genético; Revisão Sistemática.

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APPENDIX I: SEARCH STRATEGY

PubMed (MEDLINE and PubMed Central)

Search	Query
#1	Upper[TIAB]
#2	(gastrointestinal[TIAB] OR GI[TIAB] OR esophageal[TIAB] OR duodenal[TIAB])
#3	(bleeding [TIAB] OR hemorrhage*[TIAB] OR haemorrhage*[TIAB] OR injury[TIAB] OR blood[TIAB])
#4	("Gastrointestinal Hemorrhage"[MH] AND upper)
#5	(UGIB[TIAB] OR "peptic ulcer"[TIAB] OR "Stomach Ulcer"[TIAB] OR "Duodenal Ulcer"[TIAB] OR "Peptic Ulcer"[MH])
#6	polymorphism*[TIAB] OR Polymorphism, Genetic[MH] OR (genetic[TIAB] AND variant*[TIAB]) OR "genetic risk factor"[TIAB]
#7	(letter[PT] OR editorial[PT] OR historical article[PT])
#8	(animals[MH:noexp] NOT (animals[MH:noexp] AND humans[MH]))

Search: ((#1 AND #2 AND #3) OR #4 OR #5) AND #6 NOT #7 NOT #8

SCOPUS

Search	Query
#1	TITLE-ABS-KEY(Upper)
#2	TITLE-ABS-KEY(gastrointestinal OR GI OR esophageal OR duodenal)
#3	TITLE-ABS-KEY(bleeding OR hemorrhage* OR haemorrhage* OR injury OR blood)
#4	TITLE-ABS-KEY(UGIB OR "peptic ulcer" OR "Stomach Ulcer" OR "Duodenal Ulcer")
#5	TITLE-ABS-KEY(polymorphism* OR (genetic AND variant*) OR "genetic risk factor")
#6	DOCTYPE(le OR ed)
#7	TITLE-ABS-KEY(animals AND NOT (animals AND NOT humans))
#8	INDEX(MEDLINE)

Search: ((#1 AND #2 AND #3) OR #4) AND #5 AND NOT #6 AND NOT #7 AND NOT #8

COCHRANE CENTRAL

Search	Query
#1	(upper):ti,ab,kw
#2	(gastrointestinal OR GI OR esophageal OR duodenal:ti,ab,kw)
#3	(bleeding OR hemorrhage* OR haemorrhage* OR injury OR blood):ti,ab,kw
#4	(UGIB OR "peptic ulcer" OR "Stomach Ulcer" OR "Duodenal Ulcer"):ti,ab,kw
#5	(polymorphism* OR (genetic AND variant*) OR "genetic risk factor"):ti,ab,kw
#6	(letter:pt OR editorial:pt OR "historical article":pt)
#7	MeSH descriptor: [Gastrointestinal Hemorrhage] this term only
#8	MeSH descriptor: [Peptic Ulcer] this term only
#9	MeSH descriptor: [Polymorphism, Genetic] this term only
#10	(animal*:ti,ab,kw) NOT (animal*:ti,ab,kw AND human*:ti,ab,kw)

Search: ((#1 AND #2 AND #3) OR #4) AND #5 NOT #6 NOT #7

APPENDIX II: DATA EXTRACTION INSTRUMENT

Sheets in Microsoft Excel with the following columns:

- Study code
- Surname of first author
- Year
- Country
- Study design
- Setting
- Sample size (number of men)
- Ethnicity
- Age (median ± standard deviation or median plus quartiles)
- Genetic polymorphism (gene and allele)
- Odds ratio (OR), 95% confidence interval (CI), number of patients in analysis for adjusted analysis for upper gastrointestinal bleeding, and covariate (e.g. drugs, comorbidity, sex, age)
- OR, 95% CI, number of patients in analysis for non-adjusted analysis for upper gastrointestinal bleeding
- Summary of results and p-value if OR not reported

Document in Microsoft Word with:

- Study code
- Surname of first author
- Inclusion and exclusion criteria