INPLASY

Pharmacogenetics of opioid therapy for management of labor pain and post-cesarean pain: a systematic review and meta-analysis

INPLASY202410040
doi: 10.37766/inplasy2024.1.0040
Received: 10 January 2024
Published: 10 January 2024

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202410040

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 January 2024 and was last updated on 10 January 2024.

INTRODUCTION

Review question / Objective To qualitatively and quantitatively summarize the evidence on the association between gene polymorphisms and clinical response to opioid therapy for management of labor pain and post-cesarean pain.

Rationale Opioids represent the gold standard for pain relief and are among the most commonly administered medications for systemic analgesia in labor pain management. The analgesic effect and adverse event profiles of these agents exhibit large inter-individual variability due to various factors, including age, ethnicity, comorbidities, and genetics. In the last decades, an increasing number of pharmacogenetic studies have investigated the role of genetic polymorphisms in drug-metabolizing enzymes, drug-transporters and target receptors as factors potentially affecting individual variability in opioid response, in terms of their efficacy and/or safety. The aim of the present study is to conduct a systematic review and meta-analysis to qualitatively and quantitatively assess the impact of genetic polymorphic variants on opioid analgesia and opioid-induced adverse reactions in the context of labor pain and post-cesarean pain.

Condition being studied Labor pain and post-cesarean pain.

METHODS

Search strategy A comprehensive literature search (PubMed, Web of Knowledge,Cochrane Library and OpenGrey databases) will be conducted to identify all potential eligible studies. The combination of the following key terms will be used: (opioid* OR opiate* OR analges*) AND (polymorphism* OR SNP OR SNPs OR variant* OR pharmacogenetic* OR pharmacogenomic*) AND (labor OR labour OR *birth OR delivery OR *partum OR *natal). The retrieved studies will be read in their entirety to assess their appropriateness for inclusion in the meta-analysis. If two or more studies share part of the same patient population, the more complete or the one with the larger sample size will be included. Manual search to

identify additional primary studies not initially retrieved from the literature search will be performed by checking reference lists of identified articles.

Participant or population Women receiving opioid treatment for relief of labor pain or post-cesarean pain.

Intervention If genotype data for a given genetic variant are available as separate three groups, analyses will be done using both a dominant and recessive genetic inheritance model. For the dominant model, results will be grouped as AB+BB vs AA, where A is the major allele and B is the minor allele. For the recessive model, results will be grouped as BB vs AA+AB. Thus, the intervention group will be AB+BB for the dominant model, and BB for the recessive model. As regard to CYP alleles, if data are presented as phenotype metabolizer categories (i.e. ultrarapid metabolizer, normal metabolizer, intermediate metabolizer and poor metabolizer), the intervention group will be chosen in accordance with the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for that specific gene (e.g. intermediate metabolizer + poor metabolizer for CYP2D6).

Comparator If genotype data are available as separate three groups, the comparator will be the AA group for the dominant model and the AA+AB group for the recessive model. For CYP alleles, the comparator will be chosen in accordance with the CPIC guidelines (e.g. ultrarapid metabolizer + normal metabolizer for CYP2D6).

Study designs to be included This systematic review will include case-control studies, cohort studies or randomized clinical trials.

Eligibility criteria Studies meeting the following inclusion criteria will be selected: 1) studies including women treated with opioids by any route of administration for relief of labor pain or post-cesarean pain; 2) studies evaluating the association of any gene polymorphism with at least one of the following outcomes: a) pain score after opioid administration based on any patient-reported scale; b) total opioid consumption; c) 50% effective opioid dose (ED50); d) analgesic satisfaction based on any patient-reported scale; e) studies with sufficient data to calculate the above-mentioned continuous outcomes (pain score, total opioid consumption, ED50 and analgesic satisfaction) as mean ± standard deviation; f) incidence of any specific adverse effect of opioid therapy. The review exclusion criteria will be the following: 1) not human studies; 2) studies not related to the research topics; 3) reports, case series, meeting abstract, editorials, letters to the editor, review articles and meta-analyses; 4) studies not evaluating the association of gene polymorphisms with at least one of the outcomes of interest; 5) article written in a language other than English. In cases where data for a given outcome of interest cannot be extracted from an eligible study, the missing data will be requested by email to the corresponding author of the study. The study will be excluded from the systematic review or from the pooled analysis, depending from availability of other outcomes of interest, if the corresponding author will not respond to the email or will not provide the data requested for calculation of the effect size.

Information sources PubMed, Web of Knowledge, Cochrane Library and OpenGrey databases.

Main outcome(s) Primary outcomes will be pain score after opioid therapy.

Additional outcome(s) Secondary outcomes include a) ED50; b) total opioid consumption; c) analgesic satisfaction; and d) incidence of any specific adverse effect to opioid treatment.

Data management Two investigators (M.G. and S.C.) will independently review titles and abstracts and select the articles for full text evaluation. Potentially eligible studies will be then read in their entirety to assess their appropriateness for inclusion in the meta-analysis. Any disagreements will be resolved through discussion or with a third reviewer (S.T.). For each study included in the meta-analysis, the following data will be extracted: the first author's last name, year of publication, study location, patient's ethnicity, type of pain (i.e. labor pain or post-cesarean pain), time of pain assessment, the opioid administered and its administration route, total number of opioid-treated patients, the reported outcome of interest, the scale used for pain score evaluation, the gene polymorphism investigated and the method used for genotyping. Means and standard deviations for continuous outcomes (pain score, analgesic satisfaction, ED50 and total opioid consumption), as well as incidence of adverse events following opioid treatment will be extracted (or calculated) from each study for the three genotypes when available as separate groups (homozygous major allele, heterozygous, and homozygous minor allele) or for combined groups as indicated in the primary study. For continuous outcomes, regrouping heterozygous data to either homozygous group will

be done by combining means and standard deviations from each group, using an online tool available at https://www.statstodo.com/CombineMeansSDs.php. If median, minimum and maximum value are reported for continuous outcomes, the median ± standard deviation will be calculated by an online tool available at https://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html, which will be also used to verify lack of data skewness. In case of studies with skewed data, the log-transformed values of geometric mean and geometric SD will be calculated from the respective arithmetic values for all the studies included in the pooled analysis, according to the conversion equations described by Higgins et al., 2008 (doi: 10.1002/sim.3427).

Quality assessment / Risk of bias analysis The risk of bias will be assessed independently by two reviewers (M.G. and S.C.) by the ROBINS-I tool for observational or non-randomized studies (https://methods.cochrane.org/robins-i), while the RoB 2 tool will be used for randomized controlled trials (https://www.riskofbias.info/welcome/rob-2-0-tool). Disagreements will be resolved by discussion or with a third reviewer (S.T.). For meta-analyses including at least ten studies, publication bias will be assessed graphically by drawing funnel plots and analysed statistically using the Egger's test. If there will be statistical evidence of asymmetry in the funnel plot (Egger's p-value <0.10), the "trim-and-fill" method will be used to determine the stability of the results.

Strategy of data synthesis The mean difference (MD) and its 95% confidence intervals will be used as a summary statistic in meta-analyses of continuous variables when outcome measurements in all studies are made on the same scale, otherwise the standard mean difference (SMD) and its 95% confidence intervals will be derived for each study and used for pooling results. For studies evaluating post-cesarean pain, if presenting repeated time observations, the data referring at the most frequent time point among studies (e.g. 24h) or the nearest time available (e.g. 12h) will be used to determine the respective study effect size. For analyses of any specific type of adverse effect, the odds ratio (OR) with 95% confidence intervals will be calculated for each study and used as a summary effect size. Studies, irrespectively from the effect size, will be pooled with random-effect model, which assumes that the true effect size may differ from study to study due to included population, surgical type, or any other variables. The inverse variance-weighted average statistical method will be used for all comparisons of MD or SMD, while the Mantel-Haenszel statistical method will be used for pooling of ORs. Between-study heterogeneity will be estimated by using either the chi-square–based Cochran's Q statistic and the I2 index, which quantifies heterogeneity irrespective of the number of included studies. Meta-analysis will be performed for each gene polymorphism and outcome of interest when data are reported in at least three studies. All meta-analyses will be performed using Review Manager (RevMan) 5.4.1 software.

Subgroup analysis For each gene polymorphism and outcome of interest, subgroup analyses will be conducted based on type of pain (i.e. labor pain or post-cesarean pain).

Sensitivity analysis Leave-one-out sensitive meta-analyses will be performed to assess the contribution of each study to the pooled estimate by excluding individual results one at a time and recalculating the pooled effect size for the remaining results.

Language restriction Article written in a language other than English will be excluded from the systematic review.Article written in a language other than English will be excluded.

Country(ies) involved Italy.

Keywords Opioids; labor pain; post-cesarean pain; gene polymorphisms; meta-analysis.

Dissemination plans The findings will be disseminated via oral/poster presentations at conferences, seminars, workshops and peer-reviewed publications.

Contributions of each author

Author 1 - Martina Giacon - Contribution: data extraction and analysis, results interpretation, substantial contribution to manuscript writing.
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