Study protocol and statistical analysis plan

The Influence of Systemic Inflammation on the Analgesic Effect of Tramadol After Major Abdominal Surgery

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Background

Tramadol is a commonly used opioid analgesic for the treatment of moderate to severe acute and chronic pain. It is metabolized in the liver by O- and N-demethylation (phase I) and conjugation (phase II). O-demethylation of tramadol to the active metabolite O-demethyltramadol (ODT) is catalyzed by cytochrome CYP2D6, and N-demethylation to N-demethyltramadol (NDT) occurs via CYP2B6 and CYP3A4. The ODT metabolite of tramadol is an active metabolite that has 200-fold higher affinity for opioid receptors than tramadol itself and is thought to be responsible for the bulk of the analgesic effect of tramadol. The expression and activity of CYP2D6 is regulated by a number of physiological, pathological and environmental factors. CYP2D6 expression is susceptible to changes in infection states or systemic inflammatory response associated with elevated cytokine values. Systemic inflammation reduces the activity of CYP2D6, and possibly reduces the synthesis of ODT-

Design of a research

The research will be designed as a prospective observational research. The research will include patients hospitalized at the Department anaesthesiology and intensive care unit (ICU) of the Clinical Hospital Osijek, and after the signed informed consent. Informed consent will be signed by the legal guardian if the patient is unable to do so alone for various reasons.

Objectives

1. examine the analgesic effect of tramadol in ICU patients after major abdominal surgery
2. examine differences in analgesic effect of tramadol with respect to postoperative systemic inflammation

Patients and methods:

All patients included in the study will sign informed consent. Patients undergoing major abdominal surgery will be included in the study. A major surgical procedure in the abdomen will be considered all procedures that require a surgical approach by laparotomy, which include resections of parts of the organs of the digestive system. A systemic inflammatory response will involve the perioperative presence of two or more of the following factors: body temperature> 38 oC or <36 oC, leukocytes> 12,000 or <4,000 mm3, pCO2 <4.3 kPa, and pulse> 90 / min.

The analgesic effect of tramadol will be measured in patients who are conscious on the NRS scale (0 - no pain, 10 - most severe pain) 30 minutes before and 30 minutes after tramadol administration. An NRS value of 3 or less will be considered adequate analgesia, and in case of inadequate analgesia, an additional analgesic will be used - morphine 2 mg.

Statistical analysis plan:

Category data will be presented in absolute and relative frequencies. Numerical data will be described by the arithmetic mean and standard deviation in the case of distributions following the normal, and in other cases by the median and limits of the interquartile range. Differences in category variables will be tested by the $\chi 2$ test and, if necessary, the Fisher exact test. The normality of the distribution of numerical variables will be tested by the Shapiro-Wilk test. Differences of normally distributed numerical variables between two independent groups will be tested by Student's t test, and in case of deviation from normal

distribution by Mann-Whitney U test. The correlation of continuous numerical variables will be evaluated by Pearson's correlation coefficient r, and in the case of ordinal distribution variables by Spearman's correlation coefficient ρ (rho). Wilcoxon's test will be used to measure differences in NRS score before and after tramadol administration. The significance level will be set to Alpha = 0.05. MedCalc Statistical Software version 19.0.5 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2019) and SPSS (version 16.0, SPSS Inc., Chicago, IL, USA) will be used for statistical analysis.