INPLASY PROTOCOL

To cite: Wolf et al. Efficacy and effectiveness of Oliceridine in acute postoperative pain, a systematic review and meta-analysis. Inplasy protocol 202310063. doi: 10.37766/inplasy2023.1.0063

Received: 18 January 2023

Published: 19 January 2023

Corresponding author:
Alexander Wolf

alexander.wolf-x5i@ruhr-uni-bochum.de

Author Affiliation:
University Hospital Knappschaftskrankenhaus Bochum

Support: **Departmental resources only.**

Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None declared.

Efficacy and effectiveness of Oliceridine in acute postoperative pain, a systematic review and meta-analysis

Wolf, A[1]; Unterberg, M[2]; Witowski, A[3]; Adamzik, M[4]; Wolf, A[5].

Review question / Objective: **Oliceridine is a relatively novel so called bias opioid which is approved for severe opioid requiring pain. Due to its biased agonism, it is said to have fewer side effects than conventional opioids. This systematic review and meta-analysis will analyze the efficacy and effectiveness of oliceridine compared to placebo or morphine in acute postoperative pain for up to 72 hours. This will be the first meta-analysis on this topic. Our aim with this work is to evaluate the clinical utility of this relatively new substance in a broad postoperative context.**
The lead questions of this systematic review and meta-analysis are:
1. Does Oliceridine demonstrate comparable analgesia to morphine with an improved side effect profile?
2. Does oliceridine demonstrate a superior analgesia compared to placebo with a comparable side effect profile?
Transfered to PICOS, the study questions present as follows:
Patients: Postoperative (up to 72hours) patients with moderate to severe pain
Intervention: Oliceridine (TRV130)
Comparison: Morphine and Placebo
Outcome: Efficacy (pain reduction), effectiveness (side effects, adverse events)
Study: Randomized controlled trials, at least single-blind.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 January 2023 and was last updated on 19 January 2023 (registration number INPLASY202310063).

INTRODUCTION

Review question / Objective: **Oliceridine is a relatively novel so called bias opioid which is approved for severe opioid requiring pain. Due to its biased agonism, it is said to have fewer side effects than conventional opioids. This systematic review and meta-analysis will analyze the efficacy and effectiveness of oliceridine**

compared to placebo or morphine in acute postoperative pain for up to 72 hours. This will be the first meta-analysis on this topic. Our aim with this work is to evaluate the clinical utility of this relatively new substance in a broad postoperative context.
The lead questions of this systematic review and meta-analysis are:
1. Does Oliceridine demonstrate comparable analgesia to morphine with an improved side effect profile?
2. Does oliceridine demonstrate a superior analgesia compared to placebo with a comparable side effect profile?
Transfered to PICOS, the study questions present as follows:
Patients: Postoperative (up to 72hours) patients with moderate to severe pain
Intervention: Oliceridine (TRV130)
Comparison: Morphine and Placebo
Outcome: Efficacy (pain reduction), effectiveness (side effects, adverse events)
Study: Randomized controlled trials, at least single-blind.

Rationale: Oliceridine is a relatively new opioid that is characterized by what is known as "biased agonism." This means that after activation of the μ-receptor by the pharmacone, the intracellular cascade via G-protein is activated, but with significantly reduced activation of the beta-arrestin pathway, which is responsible for the side effects.
Opioids are regularly used for postoperative analgesia. The classic opioids such as morphine have a pronounced side effect profile ranging from itching, nausea and vomiting to respiratory depression. Oliceridine is expected to cause significantly fewer side effects due to the mechanism described above.
This is of great clinical relevance. For this reason, efficacy and effectiveness of oliceridine against the reference substance morphine and against placebo in moderate to severe postoperative pain will be investigated in this meta-analysis. To date, no meta-analysis has been conducted on this substance with a sufficient number of clinical studies.

Condition being studied: Acute postoperative moderate to severe pain therapy with opioids. Pain reduction and side-effects.

METHODS

Search strategy: Databases: Pubmed/ Medline, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL; covering Pubmed, Embase, CINAHL, ClinicalTrials.gov, ICTRP), Web of Science, and Google Scholar
Restrictions: None
Search terms: oliceridine, TRV130, TRV-130.

Participant or population: Postoperative patients with moderate to severe pain.

Intervention: Analgesia with the opioid oliceridine.

Comparator: Morphine, placebo.

Study designs to be included: Randomized, controlled trials, at least single-blinded.

Eligibility criteria: N/A.

Information sources: Electronic databases (Pubmed/Medline, Scopus, CENTRAL (covering Embase and CINAHL), Web of Science, Google Scholar) Trial registers via CENTRAL (covering ClinicalTrials.gov and WHO's ICTRP).

Main outcome(s): Efficacy - pain reduction.

Additional outcome(s): Effectiveness - side effects (adverse events, serious adverse events, mortality, nausea, vomiting, constipation, dizziness, headache, somnolence, sedation, pruritus, hyperhydrosis, respiratory safety) Dose dependent efficacy/effectiveness (via subgroups and meta-regression).

Data management: All references will be imported into the reference management program Endnote 20. Duplicates will be removed. The remaining references will be further screened by reading title and

abstract for eligability by two independent researcher. Commentaries, reviews, or animal studies will be directly excluded. For the remaining references, the respective manuscript is screened with respect to the inclusion criteria. The manuscripts that meet the inclusion criteria will be read in detail by two independent investigators and the corresponding data will be extracted and transferred to an individual Excel spreadsheet. In case of discrepancies, a third investigator will verify the data.
The collected data will be included in the meta-analytic calculation.

Quality assessment / Risk of bias analysis: For quality assessment the Risk of Bias 2 (RoB 2) tool of the Conchrane collaboration will be used. This covers the following seven domains:
-Random sequence generation
-Allocation concealment
-Blinding of participants and personnel
-Blinding of outcome assessment
-Incomplete outcome data (attrition bias)
-Selective reporting (reporting bias)*
-Other bias.

Strategy of data synthesis: For data synthesis we will use the software Comprehensive Meta-Analysis Version 4.0 Professional (Biostat Inc, Englewood, NJ; USA).
Statistical heterogeneity will be assessed using the I^2 statistics. For analysis of the pooled data, we will use the random effects model. Dichotomous data will be delivered as risk ratio (RR) with a 95% confidence interval, continuous data or mixed data will be displayed in as standardized mean differences (SMD) based on Hedges's adjusted g or RR where appropriate and their 95% confidence interval.
Publication bias will be examined using funnel plot and the Egger test.

Subgroup analysis: For an assessment of dose dependent effects of the intervention drug the initial dose as well as the time dependent cumulative dose will enter in subgroup analysis and a meta regression correlating dosing with efficacy and effectiveness against morphine and placebo.

Sensitivity analysis: The sensitivity analysis will be done as a "Remove-One" analysis to gauge each study's impact.

Language restriction: No.

Country(ies) involved: Germany.

Keywords: TRV130, oliceridine, postoperative pain, analgesia, morphine, meta-analysis.

Dissemination plans: The goal is to summarize the results in a manuscript and publish it in an international, English-language medical journal focusing on anesthesiology, pain, or pharmacology.

Contributions of each author:
Author 1 - Anne Wolf - The author contributed to conceptualization, manuscript draft, literature research.
Email: anne.wolf@uni-wh.de
Author 2 - Matthias Unterberg - The author contributed to manuscript draft, data extraction, and risk of bias assessment.
Email: matthias.unterberg@kk-bochum.de
Author 3 - Andrea Witowski - The author contributed to review and editing of the manuscript and references/literature screening.
Email: andrea.witowski@kk-bochum.de
Author 4 - Michael Adamzik - The author contributed to conceptualization, reviewing and editing of the manuscript.
Email: michael.adamzik@kk-bochum.de
Author 5 - Alexander Wolf - The author contributed to conceptualization, literature search, reference/manuscript screening, data extraction, meta-analytic calculation, and writing of the manuscript.
Email: alexander.wolf-x5i@ruhr-uni-bochum.de