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Study Protocol

Intramuscular pharmacological treatments for agitation in adults: a multiple treatment meta analysis

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Chapter 1

Background

Agitation is an emergency clinical condition characterized by an intense anxiety and increased motor activity occurring in the context of psychiatric disorders, intoxication or other medical disorders with an impact on psychic functioning. Many agitated patients could not respond to verbal de-escalation or accept other therapeutic interventions as for example oral medications. The primary treatment goal being to tranquilize the patient, a heterogeneous set of substances with sedative properties, mainly antipsychotics and benzodiazepines are used in clinical practice. Despite the growing number of published recommendations for the treatment of agitation based on experts' opinions, there is to our knowledge no review taking into consideration all the existing recent evidence concerning the multiple treatments used in practice. The lack of universally admitted indicator of treatment response and the use of many different clinical scores could make treatment comparisons difficult. For that reason we will analyze the availability of data on different treatment outcomes before defining outcomes of interest. Useful and already validated statistical methods could provide us with the methodological framework to overcome that problem and this by using the indirect information available in the data network. Besides, we could estimate the effect sizes of treatment comparisons that were never analyzed directly.

Chapter 2

Objectives

To compare the existing intramuscular treatments in terms of effectiveness and tolerability. To provide an evidence-based framework for intramuscular treatments of acute agitation.

Chapter 3

Methods

3.1 Criteria for considering studies for review

3.1.1 Types of studies

Randomized controlled trials (RCTs) comparing one or more active drugs with other drugs or placebo administered via intramuscular administration will be included. Studies including drug combinations will also be considered. Studies published in the last 40 years (i.e. since 1981) will be reviewed. The main reason of this choice is that many of the currently used drugs against agitation are available since decades.

3.1.2 Participant characteristics and PICO-criteria

Adults (at least 18-years-old) acutely agitated or having a violent behavior in the context of a psychiatric condition. Statistics on the clinical agitation context will be provided. PICO-criteria applied for searches: agitation in adults, intramuscular pharmacological treatments, active substances or placebo, effectiveness, and tolerability.

3.1.3 Length of the follow up

Treatment administration to patients with violent behavior implying risks to themselves or others is an emergency intervention by default and effectiveness evaluation time seems more immediate after the intervention than tolerability. Data on effectiveness is generally available at 2 hours post-injection. We have decided to include studies on substances that have comparable pharmacokinetic profiles. Adverse events are generally recorded within 24 hours.

3.2 Outcomes of interest

Based on the availability of effectiveness and tolerability outcomes of different pharmacological treatment interventions, we have defined clinically relevant primary and secondary outcomes of interest and their time for assessment. For effectiveness, we have selected the outcome “*Needed a second injection 2 hours after the intervention”*. If this outcome is unavailable, other dichotomic outcomes will be considered, such as relevant agitation scores (for example reduction on PANSS-Excited after 2 hours of the intervention).

For the tolerability outcome, we have chosen the number of "*Any adverse event"*, ideally at 24 hours. Comparison between the treatments will be realized by calculating the odd ratios and their 95% confidence intervals.

3.3 Search strategy

Systematic bibliographic searches will be conducted among English and non-English, published, and unpublished articles concerning randomized controlled trials initiated since 1981. These searches will be done in Cochrane-CENTRAL-Register, Embase, Pubmed and ClinicalTrials.gov, by manual search and upon request from abstracts authors and manufacturers. Supplementary data requests will be sent to the authors and drug manufacturers and replies will be considered within a three-months period.

3.4 Study selection and data extraction

All potentially articles will be independently reviewed for inclusion by three authors (AC, FV and SC). The primary criteria for selection are the correspondence to the PICO-target and a minimum total sample size of 20 patients. In case of disagreement among the three authors regarding study's inclusion, a fourth person for arbitrage (CE) was considered and the final decision will be then taken by the four parties. We will use the Cochrane Review Manager software package v. 5.4 (RevMan, The Cochrane Collaboration) to create masks for data extraction and for bias assessment. Microsoft Office package will be used to construct tables summarizing relevant study characteristics and a PRISMA-Flowchart.

3.5 Study quality assessment

We will use the quality criteria systematized in the Cochrane Handbook for Systematic Reviews of Interventions. Dose ranges will be described and compared. Bias assessments will be summarized using RevMan 5.4.

Chapter 4

Statistical analysis

4.1 Descriptive statistics

A flowchart of our study will be constructed with details of the study selection process, the number of records, articles assessed, included studies, participants, and treatment arms. Demographic data about study samples, including gender, age, primary diagnosis, and ethnicity will be presented in a table. Additional information such as year of study and publication status will also be presented. The structure network of the included studies will be presented graphically.

4.2 Direct effects meta-analysis

Odds ratios (OR) and their 95% confidence interval will be determined by conducting a pairwise meta-analysis with a random effects model (because of the multiple treatments and different study settings, we assume that the effect size between the studies will be different). The variance between studies (heterogeneity) will be assessed using the I^2 and tau statistics. In the case of high heterogeneity (I^2>75%), the data are analyzed by reviewing the publication(s) but also by performing sensitivity analysis if feasible.

4.3 Bias assessment

Details of the methodology biases of the included studies are described individually and by an overall approximation by bias type. Publication bias will be assessed graphically, using funnel-plots and regression tests (following the different methods proposed by Abbe, with modifications and regression-tests proposed by Egger, Peters and Harbord) if the sample size if large enough. The study quality assessment will supply data tables (Summary of findings) about every comparison of treatment arm, including the number of participants, the estimate of treatment effects as OR(CI)/Risk Difference and the quality of the evidence based on study-bias assessment and the risks of imprecision, inconsistence, indirectness, and publication-bias.

4.4 Indirect information and indirect calculation of treatment effects

A network meta-analysis with frequentist method will be conducted. Network consistency will be assessed by comparing every direct and indirect effect sizes of different treatment arms [Salanti et al. 2009]. To rank all treatments according to their probability of being the most

effective and tolerable, we will calculate the Surface under the cumulative ranking curve (SUCRA) and P-scores.

4.5 Software use

Analyses will be carried out utilising the most recent R version. Published packages for conducting network meta-analysis will be used.

Chapter 5

Data protection and financial support

The data in our study is already published or, if unpublished, available to public on search or upon request. Financial support: none.

Chapter 6

Study timeline

01.08.2021- 30.10.2022 : Study selection and data extraction

01.11.2022-31.12.2022 : Frequentist meta analysis, outcome choice, bias evaluation, network evaluation

01.01.2023- 28.10.2023 : Inconsistency analysis, bayesian modelling and multiple treatment meta analysis

01.11.2023- 31.05.2024: Article writing and manuscript submission

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