Effectiveness and safety of pharmacological sedation for aggressive or agitated adult patients in a prehospital emergency situation: a systematic review protocol

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Review question/objective: The objective of this systematic review is to identify, evaluate and synthesize evidence on the effectiveness and safety of pharmacological sedation for aggressive or agitated adult patients in a prehospital emergency situation.

Keywords Aggression; agitation; emergency; prehospital; sedation


Introduction

Aggression and agitation are commonly encountered behaviors in a prehospital emergency situation. There are various medical, neurologic and psychiatric conditions that can cause or present these behaviors. Cerebral insult as a result of stroke, tumor, trauma or meningitis, alcohol intoxication, sepsis, dementia, substance abuse and mental health conditions such as excited delirium syndrome and schizophrenia are common causes of aggression or agitation.1-3 Uncontrollable and uncontained aggression and agitation in the prehospital environment pose considerable risks to not only patients but also their attending health practitioners, most commonly the paramedics or emergency services personnel. Severe agitation in patients, for example, which is common in excited delirium syndrome, can cause metabolic abnormalities that can lead to cardiac arrest and death.4 Uncontrolled agitation or aggression can also preclude accurate assessment of the patient’s medical condition and therefore make administration of appropriate treatment impossible.5 Conversely, paramedics or emergency services personnel may experience patient-related physical and emotional harm including verbal threats, actual body harm, and even assault causing death.6 Frequent exposure to aggressive and violent behavior may lead to increased stress, poor job satisfaction, and unsatisfactory performance and functioning.7

Paramedics or emergency services personnel attending to aggressive or agitated patients in a prehospital environment must apply strategies promptly to achieve control of these patients and allow assessment and treatment of their medical condition and minimize potential harm for both patients and health personnel. Various jurisdictions and professional bodies promote the use of strategies that are based on the principle of using the lowest impact intervention first.7 In a consensus statement from the American Association for Emergency Psychiatry Project BETA De-escalation Workgroup, the main goals of managing aggression were described as follows: “(1) ensure the safety of the patient, staff, and others in the area; (2) help the patient manage his emotions and distress and maintain or regain control of his behaviour; (3) avoid the use of restraint when at all possible; and (4) avoid coercive interventions that escalate agitation.”8 The use of de-escalating techniques as an initial approach and restraints as a last resort is already common practice for paramedics. However, in a prehospital setting, an often-uncontrolled environment (e.g. patient’s residence, public places, unknown crowds, etc.) with unknown patient history, unknown intoxication status and confined space not being uncommon, “talk down” techniques are not likely to be
Pharmacological sedation of aggressive or agitated patients in a prehospital environment can facilitate safe transport as well as efficient monitoring of vital signs and other assessments, and further medical intervention, as deemed necessary. The ideal pharmacological profile of such a sedation agent would be an immediate onset, wide toxicity, good safety profile (e.g. no associated respiratory depression or cardio-vascular compromise), not requiring repeat dosages, and intramuscular administration.10-11 Sedative agents that are commonly used to manage agitation and aggression in emergency situations include benzodiazepines, such as midazolam,12 antipsychotics such as olanzapine, droperidol and haloperidol,13-14 and anesthetics such as ketamine.10,12,15-17 A number of studies have examined the effectiveness of these drugs in the prehospital environment.12 Isenberg et al., for example, compared the effects of midazolam to haloperidol on controlling agitation in patients seen in the prehospital setting and found both agents to be equally effective.12 Although this trial showed promising results, only five patients participated in the study. In another study, Scheppke et al. reviewed paramedic records for cases of violent, aggressive behavior secondary to a psychiatric condition or substance abuse and found that intramuscular ketamine may be used safely and effectively as a prehospital emergency agent; however, the study called for more rigorous studies comparing commonly used pharmacological agents, including ketamine, to determine which agent is best for rapid sedation and control of difficult-to-manage patients in the prehospital setting.10 A recent systematic review investigated the effectiveness of chemical agents for the sedation of agitated patients including the use of antipsychotics, benzodiazepines and a combination of both antipsychotics and benzodiazepines.18 The review found that combination therapy was associated with a greater proportion of patients sedated at 15–20 minutes than benzodiazepines alone; no difference was observed between those who were sedated with antipsychotics and those who were given benzodiazepines. The review focused on patients presenting to emergency department settings rather than prehospital settings and considered both intramuscular and intravenous administration of sedatives. As such, the findings may not be applicable to a prehospital environment.

A preliminary overview of studies around the pharmacological management of aggressive or agitated adult patients in a prehospital setting shows an inconclusive picture of the effectiveness and safety of the commonly used sedation agents. Previous studies refer to one or a comparison between two pharmacological agents, mainly antipsychotics,15-14 and none of the studies have comprehensively reviewed all of the commonly used pharmacological agents including ketamine, midazolam, droperidol, olanzapine and haloperidol in regard to sedation in a prehospital emergency setting. There is no consensus in the literature on what drug to administer, what the optimal dosage is and the potential harm that might be associated with their use. Currently, there are no evidence-based recommendations regarding the optimal pharmacological approach to prehospital sedation of aggressive or agitated adult patients.

A search of the Cochrane Database of Systematic Reviews, PROSPERO and the JBI Database of Systematic Reviews and Implementation Reports failed to identify a systematic review on pharmacological sedation in a prehospital setting. This review will therefore investigate the effectiveness and harm of pharmacological sedation for aggressive or agitated adult patients in a prehospital emergency situation.

**Inclusion criteria**

**Participants**

This review will consider studies that include adult patients (18 years or over) in need of a sedation in a prehospital emergency setting due to the presence of unmanageable (through de-escalating techniques) aggression, agitation or both. The cause of aggression and agitation can be, but is not limited to, stroke, brain tumor, head trauma, meningitis, alcohol intoxication, sepsis, dementia, substance abuse, alcohol intoxication, excited delirium syndrome, mental conditions (e.g. schizophrenia) or any other medical conditions.

**Intervention**

This review will consider studies that examine the effect of pharmacological sedation administered...
in a prehospital setting, specifically the use of intramuscular administration of any or a combination of the following drugs, commonly used by paramedics or emergency medical personnel: benzodiazepines (midazolam), ketamine, and antipsychotic agents such as haloperidol, droperidol and olanzapine, irrespective of dosage. Studies that examine intravascular sedation, which is not appropriate in a prehospital environment (inability to safely place an intravenous cannula), will not be considered in this systematic review.

Comparator
This review will consider studies with no comparator interventions, in addition to those that compare pharmacological interventions with non-pharmacological interventions (e.g. de-escalating techniques) and those that compare different types of pharmacological sedation.

Outcomes
This review will consider a range of outcome measures for agitation and aggression including level of sedation, need for repeat sedation dose, time of onset of sufficient sedation, and change in behavior as perceived by the emergency medical personnel or measured using available tools and scales. The level of sedation can be measured using validated scales such as, but not limited to: Richmond Agitation Sedation Score, Sedation Assessment Tool and Glasgow Coma Scale.

This review will also consider safety outcomes including occurrence of respiratory depression (e.g. needing supplementary oxygen or ventilation) and cardiovascular compromise (e.g. blood pressure <90 mmHg systolic).

Types of studies
This review will consider experimental studies including randomized controlled trials, pseudo-randomized controlled trials and quasi-experimental studies. This review will also consider observational studies such as prospective and retrospective cohort studies and case control studies.

Methods
Search strategy
The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of MEDLINE and CINAHL will be undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, the reference list of all identified articles will be searched for additional studies. Only studies published in the English language will be considered for inclusion in this review. No publication date restrictions will be applied due to the different availability dates of the relevant pharmacological agents for prehospital sedation.

Information sources
The sources/databases to be searched via EBSCO and Ovid platforms will include: MEDLINE, CINAHL, Embase, PsycINFO, Web of Science and Cochrane Central Register of Controlled Trials.

The search for unpublished studies will include: ProQuest Dissertations and Theses, ClinicalTrials.gov and Google Scholar using the following keywords: prehospital, sedation, agitation, aggression, ketamine, midazolam, olanzapine, droperidol, haloperidol.

A proposed MEDLINE (on Ovid platform) search strategy is included in Appendix I.

Study selection
Following the search, all identified citations will be collated and uploaded into EndNote (Clarivate Analytics, PA, USA) and duplicates removed. Two independent reviewers will then screen titles and abstracts for assessment against the inclusion criteria of the review. Studies that meet the inclusion criteria will be retrieved in full and their details imported into the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI). The full text of selected studies will be retrieved and assessed in detail against the inclusion criteria. Full text studies that do not meet the inclusion criteria will be excluded and reasons for exclusion will be provided in an appendix in the final systematic review report. Included studies will undergo a process of critical appraisal. The results of the search will be reported in full in the final report and presented in a PRISMA flow diagram. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.
Assessment of methodological quality
Papers selected for retrieval will be assessed by two independent reviewers using standardized critical appraisal instruments from JBI SUMARI. Any disagreements between reviewers will be resolved through discussion, or with a third reviewer.

Data extraction
Data will be extracted from papers included in the review using the standardized data extraction tool from JBI SUMARI. The data extracted will include specific details about the participants, interventions (e.g., type of pharmacological agent, dose), outcomes and study methods. In addition, attempts will be made to obtain missing data from the study report(s) by contacting the authors of the included studies. Data extraction will be carried out by one reviewer with verification by another reviewer to minimize bias and potential errors in data extraction.

Data synthesis
Results from individual studies, where possible, will be pooled in statistical meta-analysis using JBI SUMARI. All results will be subject to double data entry. Effect sizes expressed either as odds ratio (for categorical data) or weighted mean difference (for continuous data) will be calculated for analysis. Heterogeneity will be assessed statistically using the standard Chi-square test and I-squared tests. Subgroup analyses (e.g., patient group, component drugs), if appropriate, will also be considered. Where statistical pooling is not possible, the findings will be presented in narrative form to address the review questions. Tables and figures will be used as appropriate to aid in data presentation.

Assessing certainty in the findings
A Summary of Findings will be created using GRADEPro GDT software. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for grading the quality of evidence will be followed. The Summary of Findings will present the following information where appropriate: absolute risks for treatment and control, estimates of relative risk, and a ranking of the quality of the evidence based on study limitations (risk of bias), indirectness, inconsistency, imprecision and publication bias.

References


**Appendix I: Search strategy**

**PubMed**

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<tr>
<th>Search</th>
<th>Query</th>
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</thead>
<tbody>
<tr>
<td>#6</td>
<td>#1 AND #2 AND (#3 OR #4 OR #5)</td>
</tr>
<tr>
<td>#7</td>
<td>limit to English language</td>
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