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Literature Review

Articles That May Change Your Practice: Chemical Restraint of Agitated Patients

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The management of acutely agitated patients represents a challenge in the prehospital and transport setting. Agitated patients are not only a threat to themselves but also to the providers and the transport vehicle in which they travel. There are a variety of techniques that can be used to manage agitated behavior. These include verbal management techniques, physical restraints, pharmacologic interventions, or a combination of these. A drug is considered a restraint when it is used with the intent to manage or restrict the patient's behavior or freedom of movement and is not a standard treatment or dosage for the patient's condition.

The aim of chemical restraint is to rapidly and safely sedate patients to control symptoms and allow them to be safely managed without providing a threat to themselves or staff. Once the decision has been made to chemically restrain a patient, several factors may affect doses and the dosing interval. These include the level of agitation, response to treatment, body size, age, medical history, medication history (eg, drug dependence), and previous response to sedative drugs. The intramuscular (IM) route is frequently preferred if there is a significant risk of harm to staff in attempting intravenous (IV) access. However, caution is needed before giving additional doses if there is apparent failure to respond after IM administration because onset may be slow and erratic. IV access may be used if appropriate physical restraints are in place because IV administration typically provides a more rapid, predictable, reliable delivery method that can be more readily titrated to achieve the desired effect.

Pharmacologic agents typically used to provide chemical restraint include benzodiazepines, typical and atypical antipsychotics, and ketamine. Lorazepam and midazolam are benzodiazepines commonly used for the control of agitated patients. Lorazepam has a longer duration of action when compared with midazolam, does not undergo hepatic metabolism using the cytochrome P450 system, and has no active metabolites. This makes lorazepam preferred in patients requiring longer control of agitation without repeat dosing, those with liver disease, and those with potential drug interactions. Diazepam is an alternative but has a slower onset of action and cannot be administered intramuscularly because of poor, erratic absorption. All benzodiazepines may cause respiratory depression and compromise airway protective reflexes, particularly in elderly patients.

Antipsychotics are used to reduce or relieve the symptoms of psychosis including delusions, hallucinations, paranoia, and disordered thought. These agents are classified as first generation (typical) or second generation (atypical). The former include haloperidol, droperidol, loxapine, and chlorpromazine. The latter include risperidone, olanzapine, quetiapine, and clozapine. The main difference between the 2 types of antipsychotics is that the first-generation drugs act by blocking dopamine receptors in the brain and interfering with dopaminergic transmission, whereas the second-generation drugs block dopamine and affect serotonin levels. Although many of these agents can be administered intramuscularly for rapid control of patients with acute psychosis, they have a number of potential side effects that may be life-threatening. These can include acute dystonic reactions, neuroleptic malignant syndrome, and QT interval prolongation.

Ketamine is an N-methyl-D-aspartate and glutamate receptor antagonist that decreases central sensitization and pain memory. It is well-known for its amnestic and dissociative properties, similar to phencyclidine. Ketamine produces profound and rapid anesthesia and analgesia with minimal to no respiratory or hemodynamic compromise and has a predictable duration of action and a short elimination half-life. This makes it suitable for rapid pharmacologic control of an acutely agitated patient.

There is a growing focus on patient and provider safety and with it comes a renewed interest in the use of pharmacologic agents to provide chemical restraint in situations with acutely agitated patients. Given the myriad of choices, this issue provides a summary of recent publications that examine and compare the various agents available.

Isenberg DL, Jacobs D. Prehospital agitation and sedation trial (PhAST): a randomized control trial of intramuscular haloperidol versus intramuscular midazolam for the sedation of the agitated or violent patient in the prehospital environment. *Prehosp Disaster Med*. 2015;30:491-495.

This prospective, randomized, observational trial compared the effect of IM haloperidol versus IM midazolam in the control of agitated patients in the prehospital setting. Agitation was quantified using the Richmond Agitation and Sedation Scale (RASS). Paramedics recorded vital signs and RASS every 5 minutes during transport and again upon arrival to the emergency department (ED). The primary outcome was the mean time to achieve an RASS score less than +1, indicating a patient who is alert and calm or sedated to a lesser or greater extent. Secondary outcomes included the

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mean time for patients to return to baseline mental status and adverse events. Five patients were enrolled in each study group. In the haloperidol group, the mean time to achieve an RASS score of less than +1 was 24.8 minutes (95% confidence interval [CI], 8-49 minutes), and the mean time for the return of a normal mental status was 84 minutes (95% CI, 0-202 minutes). Two patients required additional prehospital doses for adequate sedation. There were no adverse events recorded in the patients administered haloperidol. In the midazolam group, the mean time to achieve an RASS score of less than +1 was 13.5 minutes (95% CI, 8-19 minutes), and the mean time for the return of normal mental status was 105 minutes (95% CI, 0-178 minutes). One patient required additional sedation in the ED. There were no adverse events recorded among the patients administered midazolam. The authors concluded that midazolam and haloperidol administered intramuscularly appear equally effective for sedating an agitated patient in the prehospital setting.

This was the first randomized controlled trial comparing 2 intramuscular sedative agents in the prehospital environment. The goal of the study was to enroll 63 patients in each arm of the study, but it was discontinued after 2 years because of poor enrollment. This limits the study's power to detect any differences between the 2 agents or any adverse events, but its findings showed results similar to other studies in terms of the mean time to achieve adequate sedation.

Taylor DM, Yap CYL, Knott JC, et al. Midazolam-droperidol, droperidol, or olanzapine for acute agitation: a randomized clinical trial. *Ann Emerg Med*. 2017;69:318-326.

This randomized, controlled, double-blind, triple-dummy, clinical trial took place in 2 metropolitan EDs between October 2014 and August 2015. Patients were included if they were between 18 and 65 years of age and required IV medication for acute agitation. Those who had been previously enrolled, had a known hypersensitivity or contraindication to a study medication, had a reversible cause for their agitation (hypotension, hypoxia, or hypoglycemia), were experiencing acute alcohol withdrawal, or were pregnant were excluded. Eligible patients were randomized to an IV bolus of midazolam 5 mg plus droperidol 5 mg, droperidol 10 mg, or olanzapine 10 mg. Two additional doses were administered if required (midazolam 5 mg, droperidol 5 mg, or olanzapine 5 mg), blinded and in keeping with the initial randomization. The outcome measure was the proportion of patients adequately sedated at 10 minutes.

The study randomized 361 patients and analyzed 349 patients who completed the protocol. Ten minutes after the first dose, 25% (95% CI, 12.0%-38.1%) more patients in the midazolam-droperidol group were adequately sedated compared with the droperidol and olanzapine groups. For times to sedation, the differences in medians between the midazolam-droperidol group and the droperidol and olanzapine groups were 6 minutes (95% CI, 3-8 minutes) and 6 minutes (95% CI, 3-7 minutes), respectively. Patients in the midazolam-droperidol group required fewer additional doses or alternative drugs to achieve adequate sedation. The adverse event rates and lengths of stay did not differ among the 3 groups. The authors concluded that midazolam-droperidol combination therapy is superior in the doses studied to either droperidol or olanzapine monotherapy for IV sedation of the acutely agitated ED patient. However, the authors did note that almost half of all patients did not have an electrocardiogram recorded, and this may have introduced selection bias. Although unlikely, it is possible that some patients with substantial QT abnormalities were not identified.

Korczak V, Kirby A, Gunja N. Chemical agents for the sedation of agitated patients in the ED: a systematic review. *Am J Emerg Med*. 2016;34:2426-2431.

The authors performed a systematic review and meta-analysis of the available medical literature regarding chemical agents for the sedation of agitated patients in the ED to help determine which agents are more effective and which class of drugs has fewer adverse events, making them better options for this cohort of patients. To be included, the study had to compare 2 or more chemical agents for sedation of agitated patients in the ED. Meta-analyses for pair-wise comparisons of drug class (benzodiazepine, antipsychotic, or a combination) were performed for each outcome (ie, proportion sedated, need for repeat sedation, and adverse events).

Seven studies with 1,135 patients were included. At 15 to 20 minutes, the proportion of patients sedated was greater with combination therapy (benzodiazepine plus antipsychotic) than benzodiazepines alone (risk ratio [RR] = 1.31, $P < .0001$). Antipsychotics and combination therapies required significantly less repeat sedations than benzodiazepines alone (RR = 0.49, $P = .0001$ and RR = 0.64, $P = .002$, respectively). There was significant heterogeneity in adverse event data, with respiratory system adverse events (desaturation and the need for airway and ventilatory support) being the most commonly reported. A higher incidence of adverse events was attributed to benzodiazepines compared with antipsychotics and combination therapy, with these events typically involving the respiratory system.

The authors concluded that a greater proportion of patients at 15 to 20 minutes were sedated by the combination therapy than benzodiazepines alone. Antipsychotics and combination therapy were more effective, requiring less repeat doses for sedation than benzodiazepines. The risk of any adverse event was higher with benzodiazepines. Like prior studies, the authors indicate the main limitation of their review was the relative paucity of literature on this subject, yielding only 7 articles.

Perkins J, Ho JD, Vilke GM, DeMers D. American Academy of Emergency Medicine position statement: safety of droperidol use in the emergency department. *J Emerg Med*. 2015;49:91-97.

Droperidol is commonly used for the control of psychosis and agitation. In 2001, the Food and Drug Administration (FDA) issued a black box warning for droperidol over concerns of QT prolongation and the potential for torsades de pointes. The FDA stated that an electrocardiogram should be obtained before droperidol administration and it should not be used if the QTc is > 440 milliseconds in males or > 450 milliseconds in females. The FDA also recommended cardiac monitoring for 2 to 3 hours after droperidol administration.

Clinicians familiar with droperidol questioned this warning. The authors of this review conducted a literature search and structured review to determine the safety of droperidol use in the ED. They screened 542 articles, yielding 35 articles from which to base their recommendations. Among their conclusions regarding droperidol for several indications, including nausea and headache, the authors concluded that it is an effective and safe medication in the treatment of agitation, with intramuscular doses of up to 10 mg as safe and as effective as other medications used for sedation of agitated patients (class B recommendation).

The authors further recommend a clarification of the FDA black box warning to address the dosage of droperidol regarding their recommendation because the initial FDA warning was related to a few isolated cases of torsade de pointes, typically after exceedingly large (25-600 mg) doses of droperidol.

Kishi T, Matsunaga S, Iwata N. Intramuscular olanzapine for agitated patients: a systematic review and meta-analysis of