# Ketamine for Pre-hospital Control of Agitated Delirious Patients: Promising but Not yet Ready for Prime Time

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Providing acute medical care to severely agitated patients in the pre-hospital setting is a significant challenge. These patients often pose a serious safety threat to themselves and emergency medical services (EMS) providers. The dilemma confronting paramedics is they can't provide medical care until the can restrain the individual and they can't restrain the individual until they provide sedation. This is a bit reminiscent of the dilemma confronting individuals seeking their first job – you know how the phrase goes. Currently, no real solution to this problem exists. Most agents currently available act too slowly or require establishing an intravenous (IV) line. Of course, if you can establish an IV, you probably don't need to sedate the patient in the first place.

The use of ketamine in the field by paramedics for chemical restraint could be an important new development. This is a relatively new concept, but if it proves safe and effective, it would absolutely change medical practice. This alone makes the article by Scheppke et al. published in this issue of the journal worth reading.[1]

The authors of this manuscript describe a retrospective chart review of patients who received intramuscular (IM) ketamine for chemical restraint in the field by EMS providers. The study covered a 39-month period and included patients from five different catchment areas who received ketamine solely for chemical restraint in the field per a paramedic protocol (standing order). Researchers abstracted the patients' pre-hospital medical record looking for specific endpoints. The primary outcome was the adequacy and duration of field sedation. Secondary outcomes included the elapsed time to achieve medical control of patients, any airway or respiratory side effects, and the presence of hemodynamic compromise. The authors conclude that ketamine was both safe and effective in sedating 50 out of 52 patients. The average time to sedation and medical control was just over 2 minutes for the 50 patients successfully sedated. No hemodynamic complications occurred, and paramedics recorded only 3 cases of respiratory compromise requiring intervention. Tastes great, less filling. So what's not to like?

Before you go out and begin buying stock in pre-hospital ketamine use, however, a more detailed review of the company is warranted. I do understand the authors' exuberance over their findings, but stating ketamine is safe and effective based solely on a sample size of 52 patients is probably a bit premature. While potentially promising, significant reservations remain.

The major problem with this study is that the number of patients enrolled is too small to advance the authors' hypothesis. While providing a trend, the data lack the statistical power to provide real evidence of ketamine's safety and efficacy. In fact, the authors offer no real statistical analysis of their work. They state only 6% of patients required airway intervention but offer no confidence intervals around this number. If you do the math, the upper level of the 95% CI is 16%. Hmmm, this changes things a bit. If one out of seven patient receiving IM ketamine required airway intervention, it would probably be back to the drawing board. Even the 50/52 proportion for successful sedation has a lower confidence limit of 87%.

Another important issue is that significant other data are missing. Complications from ketamine administration that occurred after the patient arrived in the emergency department (ED) were not recorded. Even if pre-hospital ketamine use was 100% effective with no complications, it would be unusable if 40-50% of patients then required intubation in the ED or suffered cardiovascular compromise. It would only require a few ED deaths from this practice to make pre-hospital ketamine as popular as the military anti-shock trousers.

The authors offer no measurement of patient agitation and did not control for alcohol consumption or other drugs and conditions. So it makes it more difficult to interpret the data. How many patients may have used other substances that

could explain the complications? Even the inclusion criteria are somewhat vague. The medics had to state in the narrative that the patient was agitated. It is easy to see how medics could have easily missed these items during a difficult patient encounter since they would be unaware of the future study and would not necessarily know they had to make these entries in the record. While it appears the paramedics use of ketamine was reliably captured, identifying the indications for its use may have been less robust.

The basic methodology for data abstraction was retrospective chart review. Therefore, the authors should have made some comments regarding their adherence to the standard methods of chart review. I don't want to get too anal about this, but no reference was made to any of these criteria and the article by Gilbert and Lowenstein does not appear in the references. They do not address who abstracted the charts, if they used a standard tool, how discrepancies between abstractors were resolved, etc. The definition for an agitated patient that would initiate the ketamine protocol is absent and seems patient selection for treatment was totally by paramedic discretion.

The use of midazolam by the paramedics also seems somewhat confusing. In the methods section, the authors state midazolam was given after IM ketamine, if IV access was obtained after securing sedation. However, in the results section, they comment that nearly half of the patients received IV or IM midazolam. This seems to imply that paramedics could have administered midazolam either IV or IM. If midazolam could be given IM, it is unclear why only 50% of subjects received the drug. In addition, the conclusion that midazolam may have been responsible for the respiratory complications is in doubt. Assuming half of the subjects received midazolam (the authors suggest this in the article), the incidence of respiratory depression is approximately 3 out of 25 for those receiving the drug and 0 out of 25 for those that did not. The 95% CI for the difference in these proportions crosses zero (-3% to 30%), meaning there is no statistical significance between these groups. Recent evidence is fairly convincing that the use of midazolam in adults significantly reduces the incidence of recovery agitation (emergence reaction).[2] As such, the use of midazolam would be considered an important adjunct to pre-hospital ketamine use unless clearly contraindicated. Unfortunately, this pilot study does not provide a clear answer.

Lastly, the authors are a bit optimistic regarding the safety profile for ketamine. In several sections of the manuscript, they state ketamine is safe and effective in the pre-hospital setting. However, they simply don't have the data to support this. While I do actually believe this is true, the investigation by Scheppke et al. is preliminary and does not have the power to support this statement. In fact, ketamine is primarily a myocardial depressant. This effect is generally not seen due to the immediate release of catecholamines that accompany drug administration. In individuals who are catecholamine depleted, however, ketamine can cause cardiovascular compromise and rarely transient cardiac arrest. Given the results from this study are also consistent with the need for intubation or bag-valve-make ventilation in as many as 16% of individuals receiving pre-hospital IM ketamine, a blanket statement that ketamine is safe may be inconsistent with the data.

In summary, I think the authors should be congratulated for providing preliminary evidence for the use of ketamine in the pre-hospital setting. While not definitive, these data can provide support to justify larger, randomized trials which can establish the safety and efficacy of ketamine and further clarify the risks of midazolam, if any. If the data in this study are ultimately proven correct, the standard of care for pre-hospital management of agitation would change, and those who adopted this practice early will look as brilliant as the investors who purchased stock in a small company called Microsoft in 1985.

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