Medical Ethics in Public View: Managing and Researching Agitation Under Media and Public Scrutiny

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- Jon Cole, MD, Medical Director, MN Poison Control
- Lauren Klein, MD, MS, Faculty and Investigator
- Jim Miner, MD, Chief of Emergency Medicine
• Ethics Background (Westgard)
• Study of Prehospital Agitation (Cole)
• Study of Agitation in the ED (Klein)
• Public Impressions and Media Portrayal (All)
• Responses (Miner)
• Lessons Learned and Discussion
Burden of Agitation for EM

• 2.6% of visits in an urban ED
• 23% of agitated patients with delirium sx
• Clinical event
  – Low BP, vomiting, monitoring, O2, airway
  – Delirium symptoms (OR 1.6, 1.2-2.4)
  – Drug other than alcohol (OR 1.7, 1.1-2.9)
  – Nondrug-induced agitation (OR 3.5; 2.3-5.6)

Caring for the Agitated Patient

• Capacity
  – Different from competency, more complex, legal
  – *Understand information*
  – *Reason and deliberate about choices*
  – *Make and communicate choices*
  – Question arises when choices differ from what a provider deems reasonable
Caring for the Agitated Patient

• Capacity
  – Dependent abilities, context, consequences
  – Guardian
  – Agent – Power of attorney
  – Surrogate
  – Standards
Caring for the Agitated Patient

- Assessment of degree of agitation
- Verbal de-escalation
- Trained security response when safety is concern
- Safe and effective physical restraints
- Chemical restraint or sedation
- Treatment of immediate life threats and diagnoses
Research for Altered and Agitated

• Belmont Report
  – beneficence, justice, respect for persons
• Respect for persons right to determine what happens to them, special protections for those with diminished autonomy
• Informed consent for research participation
  – Method to secure ethical rights for potential research participants
Exception from Informed Consent

- 21 CFR 50.24
- Applicable under narrow clinical circumstances
- Critical condition of the patient and rapidity of intervention
- Impracticable to obtain prospective informed consent from the patient or his/her legally authorized representative (LAR)
- Other criteria
  - lack of adequate alternatives, acceptable risk/benefit profile, direct benefit to patient are also required
- Informed consent process in case consent can be obtained from individuals or LAR within the established treatment window
Exception from Informed Consent

• Community Consultation

• Concerns of relevant “community” regarding a proposed study research study are solicited and considered before the research

• 2-way conversation to enhance protection, benefits, legitimacy and respect in research

• Examples: literature, variation, formality, efficacy
Waiver of Informed Consent

- 45 CFR 46.116
- 21st Century Cures Act, 2016
- Research involves no more than minimal risk to the subjects
- Waiver will not adversely affect rights/welfare of subjects
- Research could not practically be done without waivers or alterations
- Whenever appropriate, subjects provided with additional information after enrollment/participation
<table>
<thead>
<tr>
<th>Antipsychotics</th>
<th>Benzodiazepines</th>
<th>Ketamine</th>
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<tbody>
<tr>
<td>Haloperidol</td>
<td>Midazolam</td>
<td>IM or IV</td>
</tr>
<tr>
<td>Droperidol</td>
<td>Lorazepam</td>
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Ketamine

- Fast onset
- Tremendous safety profile
- Duration ideal for reassessment
The combative multitrauma patient: a protocol for prehospital management
Eitan Melamed, Yahav Oron, Ron Ben-Avraham, Amir Blumenfeld and Guy Lin


Clinical Notes

Ketamine for prehospital use: new look at an old drug

James E. Svenson MD, MS*, Michael K. Abernathy MD
Our EFIC plan: 2013-2014

A Randomized Double Blinded Trial Comparing Ketamine and Haloperidol for Severe Agitation in the Pre-Hospital Setting

Principal Investigator: Jon B Cole, MD

Plan for Community Consultation, Public Disclosure, and Contact of Legally Authorized Representatives

Department of Emergency Medicine
Hennepin County Medical Center
5 Elements of EFIC (completed)

• Community Consultation
• Public Disclosure before & after the trial
  – including methods by which patients can “opt-out”
• Plan for contact of Legally Authorized Representatives (LAR) to seek informed consent
• Formation of a Data Safety Monitoring Board
• FDA Investigational New Drug (IND) application
FDA phone meeting

• FDA group decides the study does not qualify for EFIC because, due to the large number of patients in our system, we should be able to obtain consent.
  – Either from the patient themselves or
  – From a legally authorized representative
    • Appointed health care surrogate, judicially appointed guardian, or closest adult relative in absence of the former (MN definition).
CLINICAL TOXICOLOGY, 2016
VOL. 54, NO. 7, 556–562
http://dx.doi.org/10.1080/015563650.2016.1177652

CLINICAL RESEARCH

A prospective study of ketamine versus haloperidol for severe prehospital agitation

Jon B. Cole, Johanna C. Moore, Paul C. Nystrom, Benjamin S. Orozco, Samuel J. Stellpflug, Rebecca L. Kornas, Brandon J. Fryza, Lila W. Steinberg, Alex O’Brien-Lambert, Peter Bache-Wiig, Kristin M. Engebretsen, and Jeffrey D. Ho

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ABSTRACT

**Context:** Ketamine is an emerging drug for the treatment of acute undifferentiated agitation in the prehospital environment, however no prospective comparative studies have evaluated its effectiveness or safety in this clinical setting. **Objective:** We hypothesized 5 mg/kg of intramuscular ketamine would be superior to 10 mg of intramuscular haloperidol for severe prehospital agitation, with time to adequate sedation as the primary outcome measure. **Methods:** This was a prospective open label study of all

ARTICLE HISTORY

Received 5 February 2016
Revised 3 April 2016
Accepted 7 April 2016
Published online 21 April 2016
And the Follow-up: 2017-2018

Ketamine Versus Midazolam for Out-of-Hospital Agitation: A Prospective Study

Cole J, Klein LR, Scharber SK, Simpson NS, Driver BE, Arens AM, Nystrom PC, Olives TD, Moore JC, Ho JD/Hennepin County Medical Center, Minneapolis, MN; Duke University School of Medicine, Durham, NC

Olanzapine, Haloperidol, Ziprasidone, or Midazolam for Treating Agitation in the ED

Randomized Trial using EFIC

Clinical Treatment Protocol
Olanzapine, Haloperidol, Ziprasidone, or Midazolam for Treating Agitation in the ED

Waiver of Consent

ONLY study procedures:

Stopwatch

Standardized Agitation Scales

Data Collection Form
Olanzapine, Haloperidol, Ziprasidone, or Midazolam for Treating Agitation in the ED

SAEM Plenary Session, 2018

Intramuscular Midazolam, Olanzapine, Ziprasidone, or Haloperidol for Treating Acute Agitation in the Emergency Department
And the Trouble with the Media

Ketamine cases raise questions over boundaries between police and paramedics

Nature

Controversial US ketamine trial sparks ethics complaint

Advocacy group alleges that emergency medical workers in Minnes injections without consent, despite known risks.

Ketamine study at Hennepin Healthcare suspended after criticism from politicians

Politicians called study of sedative "unconscionable and unethical."

Patients sedated by ketamine were enrolled in Hennepin Healthcare study.

To Your Health

Hospital's experiment in sedating patients without consent raises ethical concerns.
What we did

• Crisis Team Formed
  – Researchers
  – EM and EMS leadership
  – IRB Chair
  – Hospital Public Relations
  – Hospital Leadership
  – Hospital Legal
What We did Next

• Community Forums
  – Multiple venues
• Engage community leaders
• Engage hospital employees
Public Advisory Board

• Research Advisory Board
  – Views research/concurrent with before IRB review

• Public Research Advisory Board
  – Views research after IRB approval
  – Makes recommendations on community notification
Things We Learned

• Press interviews require intense preparation
  – Practice questions with community input
  – Control time and place as much as possible
  – Carefully consider who will answer what questions
Things We Learned

• Engaging social media attacks increases their penetration

• The first version told might be the only one heard, regardless of accuracy
Importance for Emergency Medicine

• Convey critical nature of care for altered and violent patients prehospital and in the ED
• Need for ongoing engagement with the communities we serve (not just detox, shelters)
• Public and policy engagement is necessary to protect the space for research in EM
The Hennepin Ketamine Study

Jeffrey D. Ho,1,2 Jon B. Cole,3 Lauren R. Klein,1 Travis D. Oliver,1 John E. Driver,4 Johanna C. Moore,5 Paul C. Nystrom,6,7 Annzie M. Arens,1 Nicholas S. Simpson,1 John L. Hick,3,8 Ross A. Chavez,9 Wendy L. Lynch,6,10 James R. Miner4

The Hennepin Ketamine Study Investigators’ Reply

We read with interest the recent editorial, ”The Hennepin Ketamine Study,” by Dr. Samuel Stratton commenting on the research ethics, methodology, and the current public controversy surrounding this study. As researchers and investigators of this study, we strongly agree that prospective clinical research in the prehospital environment is necessary to advance the science of Emergency Medical Services (EMS) and emergency medicine. We also agree that accomplishing this is challenging in the prehospital environment because it often encounters patient populations which cannot provide meaningful informed consent due to their emergent conditions. To ensure that follow emergency medicine researchers understand the facts of our work so they may plan future studies, and to address some of the questions and concerns in Dr. Stratton’s editorial, the lay press, and social media, we would like to call attention to some inaccuracies in Dr. Stratton’s editorial, and to the lay media stories on which it appears to be based.

First, a brief overview of the study in question. This was a prospective, observational study of an EMS protocol change over a 12-month period regarding two medications commonly used in the sedation within our EMS system: ketamine and midazolam. For the first six-month period, the EMS protocol recommended ketamine as a first line agent for sedation of agitated patients; for the second six-month period, midazolam was the recommended first line agent. There was no randomization. If a patient was deemed to need sedation based on the clinical judgment of the paramedic, the patient was given the medication per protocol. Importantly, no patients received medication for the sake of research; all sedatives were administered as part of usual clinical care. The only aspect of this work that was considered research was the careful observation of the effects of the sedative agents, and paramedic use of stopwatches to record the primary outcome (time to adequate sedation). We also recorded