Randomizing Patients without Consent: Waiver vs Exception from Informed Consent

Jon B. Cole, MD;[1] Jeffrey D. Ho, MD;[2] Michelle H. Biros, MD, MS[3]

1. Minnesota Poison Control System, Hennepin County Medical Center, Minneapolis, Minnesota USA
2. Hennepin Emergency Medical Services, Hennepin County Medical Center, Minneapolis, Minnesota USA
3. Department of Emergency Medicine, University of Minnesota, Minneapolis, Minnesota USA

Correspondence:
Jon B. Cole, MD
Medical Director
Minnesota Poison Control System
Hennepin County Medical Center
Minneapolis, Minnesota USA
E-mail: jon.cole@hcmed.org

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To the Editor:
We read with great interest the article by Isenberg and Jacobs entitled "Prehospital Agitation and Sedation Trial (PhAST): A Randomized Controlled Trial of Intramuscular Haloperidol versus Intramuscular Midazolam for the Sedation of the Agitated or Violent Patient in the Prehospital Environment."[1] We agree their goal of conducting the first randomized controlled trial comparing two intramuscular sedative agents in the prehospital environment is a worthy one. We have endeavored ourselves to conduct a similar trial, the results of which were published recently.[2]

We are puzzled, however, by several aspects of their methodology that lacked clarity. The authors themselves note patients were enrolled and randomized without their consent, and that patients "met very specific inclusion criteria." However, other than excluding children, pregnant women, patients with intravenous access, and including patients who met their agitation protocol, no mention is made regarding inclusion criteria. Most concerning, there is no mention in the article how these patients were ethically enrolled and randomized without their consent.

Prospective studies that enroll patients without consent in the United States may be conducted under one of two federal regulations. Studies may qualify for "Waiver of Consent" (46 CFR 45.116)[3] if they involve no more than minimal risk, the waiver will not adversely affect the rights or welfare of the subjects, and the research could not be practicably carried out in any other manner. Subjects also should be notified immediately of their participation. Certainly, randomizing patients without their consent into a trial of two medications with significant side effects, including torsade de pointes, respiratory depression, and apnea, is not minimal risk.

Higher risk studies of this nature require "Exception from Informed Consent" (21 CFR 50.24),[4] a far more robust process consisting of five critical elements, including: community consultation; public disclosure before and after the trial; plans for contacting legally authorized representatives to seek consent; formation of a data safety monitoring board; and completion of an Investigational New Drug Application with the US Food and Drug Administration (Silver Spring, Maryland USA).

As researchers on agitated patients, by definition a vulnerable population of potentially critically ill patients, we are concerned neither of these codes were addressed in the article by Isenberg and Jacobs. While addressing consent is challenging in this patient population,[5] it is vital for the protection of patient autonomy, as well as the future of agitation research.

References

1. 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(5):491-495.
2. Cole JB, Nystrom PC, Orozco BS, et al. A prospective study of ketamine versus haloperidol for severe prehospital agitation. *Clin Toxicol*. 2016 Apr 22;1-7. [Epub ahead of print].
3. 45 CFR 46.116(d) - General requirements for informed consent.
4. 21 CFR 50.24 - Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors Exception from Informed Consent Requirements for Emergency Research.
5. Biros MH, Dickert NW, Wright DW, et al. Balancing ethical goals in challenging individual participant scenarios occurring in a trial conducted with exception from informed consent. *Acad Emerg Med*. 2015;22(3):340-346.

Author Reply:

Derek L. Isenberg, MD; Dorian Jacobs, MD

Department of Emergency Medicine, Crozer-Chester Medical Center, Upland, Pennsylvania USA

Correspondence:
Derek Isenberg, MD
Crozer-Chester Medical Center
Department of Emergency Medicine
1 Medical Center Boulevard
Upland, Pennsylvania 19013 USA
E-mail: Derek.isenberg@crozer.org

Thank you for your comments about our article entitled "Prehospital Agitation and Sedation Trial (PhAST): A Randomized Controlled Trial of Intramuscular Haloperidol versus Intramuscular Midazolam for the Sedation of the Agitated or Violent Patient in the Prehospital Environment." We look forward to reading your upcoming manuscript on a similar topic.

You have raised the very important topic of patient protection in emergency care research. In response to your questions, the inclusion criteria for our study corresponded to the Commonwealth of Pennsylvania Emergency Medical Services (EMS) Protocol for Agitated Patients. This protocol was listed in the article.

Our study was approved by the Investigational Review Board (IRB) of Mercy Catholic Medical Center (Philadelphia, Pennsylvania USA). We cannot speak to the reasoning of the IRB regarding the approval of this study; however, we believe that the IRB felt that this study met the definition for approval under the minimal risk clause. Firstly, midazolam is currently used by our EMS providers under Commonwealth Protocols, and therefore represented no additional risk to the patient. Haloperidol, though carrying a black box warning from the US Food and Drug Administration (Silver Spring, Maryland USA), has a long track record of safe use in the emergency department. In addition, the black box warning only applies to high dose and intravenous haloperidol, neither of which were used in this study.

We join you in emphasizing the importance of patient safety, autonomy, and beneficence in emergency care research.

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