Maine Medical Center
Department of Emergency Medicine

Journal Club / Research Article Summary - (Adapted from Schultz Table)

Date: 11/28/12
Presenter: Matthew Kerr PGY2

ARTICLE:
- Country: USA

PURPOSE:
- Research Question(s):
  Amongst the most commonly used medications for chemical restraint in the ED with regard to violent and agitated patients, is there a single agent available that has rapid onset thus ensuring patient and staff safety in addition to having duration of action short enough to avoid delays in diagnosis resulting from excessive sedation.

- Hypothesis:
  Midazolam is superior in time to sedation and arousal than other commonly used agents (haloperidol and lorazepam) when used as a single agent for sedation of violent and severely agitated patients.

DESIGN:
- Study Design:
  A randomized prospective double-blinded study

- Dependent / outcome Variable(s):
  The length of time to sedation
  The time to arousal

- Independent / research Variable:
  The intramuscular injection of midazolam, haloperidol, or lorazepam

SETTING / SUBJECTS:
- Research Setting:
  The study was performed in a university affiliated county teaching ED with a residency program (Highland, Almeda County Medical Center), annual census 64,000 patients annually. Study December 1997-December 1999.
Subjects:
- Study population:
  Patients who required emergency sedation for the control of violent behavior or severe agitation, after physical restraints were deemed insufficient to provide safe setting for the patient and staff respectively.
- Inclusion / Exclusion criteria:
  Patients were excluded if they had; allergies to medications being studied, hypotensive (sBP < 90), unable to protect own airway, tachycardia (>140 bpm), bradycardia (< 60 bpm), respiratory distress (RR > 40 ), < 18 yo, pregnant.
- Number (control / intervention groups):
  111 agitated patients were enrolled
  No placebo/control group
- Demographics:
  Across all three study groups (lorazepam, midazolam, haloperidol)
  Lorazepam
  Age 39.5 +/- 12
  African American 48%, White 10%, Hispanic 11%, Asian 4%
  Midazolam
  Age 39.8 +/- 10
  African American 55%, White 38%, Hispanic 5%, Asian 2.5%
  Haloperidol
  Age 42.4 +/- 16
  African American 55%, White 36%, Hispanic 7%, Asian 2.5%
- Attrition:
  Any patients who received “rescue medication” (additional sedation medications, whether additional doses of single medication, or combination therapy were removed from the study group.

METHODS:
- Interventions: Any patients deemed violent and/or agitated in need of chemical restraint by medical practitioners per institutional protocols were given an IM injection of 1 of 3 medications (5 mg midazolam, 5 mg haloperidol, 2 mg lorazepam). The medications were all given in a volume of 1 ml and none of the medical practitioners were aware of which medication was being used. This decision was made by a computer generated random number generator.
Starting at “time zero” (initial IM injection) a trained research coordinator (available 0800-2300) monitored the patient every hour for the duration of the study period and/or discharge from the ED. A modified Thomas Combativeness Scale was used for documentation. This is a not validated scale rating patients on a 1 to 3 scale from severely agitated to no agitation respectively.

- **Study Groups:**
  1. Receiving 5 mg midazolam – based on PDR dosing of 70 kg patient
  2. Receiving 5 mg haloperidol – based on published guidelines
  3. Receiving 2 mg lorazepam – based on published guidelines

- **Instruments:**
  Modified Thomas Combativeness Scale
  1 – violently agitated, fully restrained, requires constant attention
  2 – decreasing agitation, partially restrained, intermittent attention
  3 – no agitation, no supervision required, may be asleep

- **Data Collection:**
  A convenience sample of patients were enrolled when a trained research coordinator was available 0800-2300. They were trained to record time of sedation, time of patient recovery to an interview-able state, and apply the sedation and arousal scales.

**DATA ANALYSIS:**

- **Level of Data:**
  x Categorical  ´ Ordinal  ´ Interval

- **Statistics Used:**
  Categorical data was reported as absolute number and percentage with differences in time to sedation and times to awakening reported as mean differences with 95% confidence intervals. Differences were analyzed with chi square test for categorical data and analysis variance for continuous data.
  A priori sample was not initially calculated – after 95 individuals enrolled a sample size was calculated. Pocock tables were used to adjust sample size and Bonferroni correction employed for multiple comparisons of data.

- **What, if any, confounding variables were controlled for / adjusted for:**
  none

**RESULTS:**

- **Brief answers to research questions:**
  The interim data analysis demonstrated a statistically longer time to sedation and time to awakening than lorazepam, and was dropped from the remainder of the study.
  42 patients received midazolam, 42 patients received haloperidol
Time to sedation:
Midazolam – 18.3 min +/- 14 min
Haloperidol – 28.3 min +/- 25 min

Time to arousal
Midazolam – 81.9 min +/- 66 min
Haloperidol – 126 min +/- 85 min

- Additional findings:
  No difference in regard to changes in blood pressure, heart rate, respiratory rate, oxygen saturation between study groups.

- Other possible explanation for findings:
  There is significant overlap of time between the two study groups. Since the dosages of medications did not take into account the weights of individual patients and their co-ingestions, it is possible the differences are not as significant as demonstrated by the study findings.

- Limitations?:
  1. The study group is quite small, 111 patients, and only from one single emergency room.
  2. Patients were enrolled only when coordinators were available, 0800-2300.
  3. Droperidol was excluded from study
  4. Sedation/arousal scale – Modified Thomas Combativeness Scale was not validated
  5. No placebo group
  6. Dosing was not adjusted for weight
  7. Dosing not adjusted for co-ingestions

IMPLICATIONS FOR PRACTICE:
- Applicable to this clinical practice:
  Midazolam is a frequently used medication for restrain with agitated/combative patients. It is often combined with other medications, not necessarily as a single agent. In our institution most individuals utilize a combination of haloperidol and lorazepam, Physicians and nurses are comfortable with this combination, and studies have demonstrated its effectiveness. Many of our psychiatry colleagues prefer zypraxa. Midazolam is not a wrong choice, however, its efficacy and advantages over other medications and/or combinations of medications may need to be researched further before midazolam becomes a first line single agent choice.

- Feasibility (cost, resources, etc):
  Cheap, available, in our armamentarium
Clinically Relevant:
Midazolam is a medication used daily in the emergency room, however it is not often chosen as a first line single agent medication for the acute chemical restraint of a violent patient. It may certainly be effective, but individuals are currently more comfortable with other medications and combinations, therefore I imagine it will take more investigation than this study provides before our medication patterns change.

LEVEL OF EVIDENCE / DECISION FOR USE:
- x Background 
  - Consider Replication 
  - Ready for use

Level of Evidence:
- Ia Evidence obtained from meta-analysis of randomized controlled trials
- Ib Evidence obtained from at least one RCT
- IIA Evidence obtained from at least one well-designed controlled study without randomization
- X IIb Evidence obtained from at least one other type of well-designed quasi-experimental study
- III Well-designed non-experimental studies
- IV Expert committee reports, opinions of experts