Lassoing Current Ketamine Practice

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Conflict of Interest

• I declare the absence of any conflict of interest which might influence the planning of this activity.

Introduction

• Survey developed following 2015 ASPMN Conference
• Discussion and questions during Ketamine presentation spurred interest
• Thank you to the enthusiastic 2015 conference attendees & to members who participated in survey
Objectives

- Identify current Ketamine literature and practice
- Review results of ASPMN Ketamine Practice Survey
- Discuss survey results, gaps and implications for future initiatives

KETAMINE

Current State
Literature Review Update

KETAMINE

Ketamine

- 1962: Developed in 1962 as a safer alternative to PCP
- 1965: Anesthetic properties identified (Niesters, et al.)
- 1970: Approved by US Food and Drug Administration (FDA) for human use
- 1971: First study by Sadove et al. on low dose analgesic properties
- 1970’s: Used in Vietnam War
- 1987: NMDA receptor discovered
- 1999: Designated as a controlled substance
Ketamine

- Commercial forms of Ketamine (Niesters, et. al.)
  - Racemic mixture (Ketalar® by Pfizer);
    - available since 1966 in US
  - S(+) enantiomer (S-ketamine or Ketanest-S®, Pfizer, Inc.)
    - Available in European Community member states since 1994

Ketamine

- US Food and Drug Administration (FDA)
  - Drug class – general anesthetic
  - Dissociative anesthesia
  - Wide margin of safety
  - CSA Schedule 3
  - Studies : >12,000 operative & diagnostic procedures
    - involving over 10,000 patients from 105 separate studies
      - Archived from https://www.drugs.com/pro/ketamine-injection.html

Off-Label Use

- Ketamine for pain
- Considered off-label use
  - By FDA
  - By insurance companies
Literature Updates

- 2012: Ketamine as adjunct for cancer pain - Cochrane Update (Bell, et. al.)
  - Insufficient evidence to assess benefits & harms of ketamine as adjuvant for cancer pain
- 2013: Cochrane Review on Prevention of Pain After Surgery in Adults (Chaparro, et al.)
  - 14 of 40 RCT’s focused on ketamine
  - Noted statistical reduction in incidence of chronic pain following treatment with ketamine

- 2013: Cochrane: Treatment of pain & disability in CRPS (O’Connell, et al.)
  - Low quality evidence for effectiveness of daily IV ketamine when compared to placebo
- 2013: Oral ketamine for children with chronic pain (Brediau, et al.)
  - Small study (n=12)
  - Oral ketamine 0.25 to 1 mg/kg dosing
  - Up to 14 days
  - Safe to administer

- 2013: Study on patients with chronic pain (Barreveld, et al.)
  - n=64
  - Ketamine infusion @ 0.2 mg/kg/hour + opioids
  - Significant reduction in average pain scores
- 2013: Intranasal ketamine in ED (Andolfatto, et.al.)
  - n=40
  - Significant reduction in VAS pain scores in 88% of patients
Literature Updates

- 2015: Widespread use of low-dose ketamine in ED (Ahern, et al.)
  - 500 patients
  - Acute pain, varying types
  - IV & IM ketamine
  - 10-15mg dose
  - Conclusion: low-dose ketamine safe & feasible for treatment of many types of pain

ASPMN KETAMINE PRACTICE SURVEY

Analysis of Results

Survey Design & Review

1. Demographics
2. Multi-modal therapies/alternative therapies
3. Ketamine use
4. Administration/dosing
5. Barriers to use
ASPMN Ketamine Practice Survey

• Data collected from December 2015 to March 2016
• Assessed:
  – Practice setting, administration practices & dosing
  – Other multi-modal therapy options
• Respondent comments individually reviewed
• Total of 146 surveys were submitted electronically via Survey Monkey

Practice Setting

<table>
<thead>
<tr>
<th>Practice Setting</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Care Hospital: 100-200 beds</td>
<td>12 (8.51%)</td>
</tr>
<tr>
<td>Acute Care Hospital: 201-400 beds</td>
<td>33 (23.40%)</td>
</tr>
<tr>
<td>Acute Care Hospital: 401-600 beds</td>
<td>19 (13.48%)</td>
</tr>
<tr>
<td>Acute Care Hospital: &gt;600 beds</td>
<td>6 (4.26%)</td>
</tr>
<tr>
<td>Academic Medical Center: 400-600 beds</td>
<td>17 (12.06%)</td>
</tr>
<tr>
<td>Academic Medical Center: 601-800 beds</td>
<td>12 (8.51%)</td>
</tr>
<tr>
<td>Academic Medical Center: 801-1000 beds</td>
<td>4 (2.84%)</td>
</tr>
<tr>
<td>Academic Medical Center: &gt;1000 beds</td>
<td>2 (1.42%)</td>
</tr>
<tr>
<td>Outpatient Clinics</td>
<td>38 (26.53%)</td>
</tr>
<tr>
<td>Other (Specify): see below</td>
<td>10 (11.35%)</td>
</tr>
</tbody>
</table>

*Other: Includes: Pediatrics (1), Hospital system (1), Ambulatory surgical center (1), others
  pain practice, with (3,200) active patients, Acute care hospital <100 beds = 2, long term care,
  Academic center < 300 beds, Health insurance, Military, Retired, Critical access hospital, Hospital Outpatient Department- Comprehensive Pain Center
Respondent Demographics

- Educational preparation:
  - MSN (70/48.95%)
  - BSN (39/27.27%)
- 68.97% were not prescribers
- Eight-five percent (85.1%) of respondents have direct patient contact
  - 62.5% spending more than 75% of their time in direct patient care
  - Over half (52.94%) of respondents spend 100% of their practice involved in pain management

Specialty Area of Respondents

- Pain service/management (33.6%)
- Chronic pain clinic (25.5%)
- Post anesthesia care unit (PACU; 11%)
- Palliative (11%)
- Pediatrics (5%), anesthesia/operating room (5%)
- Oncology (4.2%)
- Medicine (3.4%)
- Less than 3%: emergency department, intensive care unit, family practice & psych

Pain Management Resources

- Pain Service
- Anesthesia
- Internal Medicine Pain Specialist
- Palliative Care
- Pain Clinical Nurse Specialist
- Pain Nurse Practitioner
- Stress Management
- Aromatherapy
- Other
Interprofessional Pain Resources: Acute Care

- Interdisciplinary Teams
- Integrative & Alternative Therapy:
  - Acupuncture/Massage
  - Music/art therapy
  - Reiki/Healing touch
- Mental Health Resources
  - Pain psychology
  - Biofeedback

Interprofessional Pain Resources: Outpatient

- Pain/Palliative Pharmacist
- Nutrition/dietician
- Integrative & Alternative Therapies
  - Tai Chi, Yoga, Mindfulness, Massage
- Physical Therapy
- Behavioral Health Resources

Multi-Modal Pain Modalities

- Oral Medications:
  - Oral opioids (98.5%)
  - NSAID & acetaminophen (97.8%)
  - Anticonvulsants (81.8%)
  - Anxiolytics (81%)

- Intravenous:
  - Patient controlled analgesia (PCA; 78%)
  - Intravenous opioids (75.6%)
  - Lidocaine infusions
Multi-Modal Pain Modalities

- Regional pain catheters:
  - Epidural catheters (72.3%)
  - Peripheral nerve catheters (60.6%)
  - TAP blocks (53.4%)
- Outpatient procedures,
  - Injections, implantable pumps & spinal cord stimulators.
- Massage 28.5%
- Other modalities (27.8%):
  - Healing touch
  - Reflexology, acupuncture, Reiki, & music
  - Physical therapy
- Behavioral medicine

Ketamine Use

- Sixty-six respondents (63%) reported the use of ketamine in their practice setting
- Practice Setting Factors
  - Acute versus outpatient did not impact utilization
  - Hospital size did not impact
  - Type of provider monitoring administration factor in administration

Practice Setting & Ketamine Use

<table>
<thead>
<tr>
<th>Practice Setting</th>
<th>Ketamine Yes</th>
<th>Ketamine No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Care Hospital: 100-200 beds</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Acute Care Hospital: 201-400 beds</td>
<td>27</td>
<td>6</td>
</tr>
<tr>
<td>Acute Care Hospital: 401-600 beds</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Acute Care Hospital &gt; 600 beds</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Academic Medical Center: 400-600 beds</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Academic Medical Center: 601-800 beds</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Academic Medical Center: &gt;1000 beds</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Outpatient Clinic</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Other (specify)</td>
<td>13</td>
<td>2</td>
</tr>
</tbody>
</table>

Note: Some respondents noted use in both inpatient & outpatient settings of their organizations.
Ketamine Management

- Ketamine Ordering by:
  - Anesthesia (71%)
  - Pain teams (52.9%)
  - ICU/intensivists (24.7%)
  - Palliative Care & Nurse Practitioners (23.7% each)
  - Physician assistants (5.2%)
  - Other: emergency department physicians, clinical nurse specialists & surgeons

- Some require pharmacy consultation or review by anesthesia or an acute pain provider.
- Many areas Ketamine is managed by more than one provider
- Standing orders for Ketamine: 44.4%

Ketamine Monitoring

- Monitoring (oversight) of patients while on ketamine provided by:
  - Anesthesia groups (57.3%)
  - Pain teams (54%)
  - ICU/Intensivists (28%)
  - Palliative care (26%)
  - NPs and Clinical Nurse Specialists (CNSS)
Ketamine Demographics

- Ketamine utilized across the age continuum
  - Majority of patients 18-65 age group (91.3%).
  - >65 years 55.43%
  - 12-18 years (27.2%)
  - 8-12 years (14.1%)
  - 3-8 years (12%)
  - <3 years (5.4%)

Route of Administration

- Continuous Ketamine infusion (65.1%) is the most common route
- Intravenous (IV) bolus (55.1%)
- One-time IV administration (39.8%)
- Oral (30.6%)

Administration Based on Practice Setting

Outpatient Clinics

- Route:
  - Oral
  - IV bolus
  - One-time IV administration.
- Duration of one-time IV administration: 60 to 360 minutes
- One-day intravenous treatment

Inpatient

- Hospice:
  - Oral
  - Continuous infusions
- Acute care hospitals & academic centers
  - One-time IV administration
  - Continuous infusions
# Dosing Duration

<table>
<thead>
<tr>
<th>Route</th>
<th>Length of Therapy</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Bolus</td>
<td>One time</td>
<td>55.78%</td>
</tr>
<tr>
<td>One-time IV Administration</td>
<td>60 minutes</td>
<td>15.57%</td>
</tr>
<tr>
<td>One-time IV Administration</td>
<td>60-120 minutes</td>
<td>10.87%</td>
</tr>
<tr>
<td>One-time IV Administration</td>
<td>120-360 minutes</td>
<td>9.18%</td>
</tr>
<tr>
<td>Continuous infusion</td>
<td>&lt; 24 hours</td>
<td>18.48%</td>
</tr>
<tr>
<td>Continuous infusion</td>
<td>24-48 hours</td>
<td>26.05%</td>
</tr>
<tr>
<td>Continuous infusion</td>
<td>48-72 hours</td>
<td>12.08%</td>
</tr>
<tr>
<td>Continuous infusion</td>
<td>&gt;72 hours</td>
<td>13.04%</td>
</tr>
<tr>
<td>Continuous infusion</td>
<td>Variable; based on patient response</td>
<td>39.13%</td>
</tr>
<tr>
<td>Oral administration</td>
<td>&lt;7 days</td>
<td>15.22%</td>
</tr>
<tr>
<td>Oral administration</td>
<td>7-14 days</td>
<td>8.7%</td>
</tr>
<tr>
<td>Oral administration</td>
<td>&gt;14 days</td>
<td>9.78%</td>
</tr>
</tbody>
</table>

## Dosing: One-Time Bolus

- Provider only bolusing in many areas
- Practice varies
  - One time weight based (*range: 0.05 to 2 mg/kg*)
  - One time mg dosing (*range 5mg to 100mg*)
- Series of one time
  - Weight based
  - Mg
    - Some with max number of doses
    - Some with Mg max

## Dosing: One-Time Infusion

- Provider administration in many situations
- Starting dose varies
  - Weight based (*range: 0.06 to 1mg/kg*)
  - Mg/hr dosing (*range: 5mg to >50mg/hr*)
  - Total mg
  - Time limited (*range: 1-4 hours*)
- Maximum dose varies: (0.5 to 40mg/hr; up to 350mg total)
Dosing: Continuous Infusion

- Variable dosing practices
  - Weight based
    - Mcg/kg/min (range: 1.65 to 200mcg/kg/min)
    - Mg/kg/hr (range: 0.05 to 0.5mg/kg/hr)
  - Mg/hr dosing: (range 3-100 mg/hr)
- Maximum dosing
  - Variable; patient response
  - Range: No max to 20-200 mg/hr

Conditions Necessitating Ketamine

- Acute on Chronic Pain
- Persistent Post-Operative Pain
- Sickle Cell Crisis
- Neuropathic Pain
- Malignant Pain
- Phantom Pain
- Intraoperative
- Preventative
- Other

Side Effects

- Vivid dreams (60.8%)
- Hallucinations (54%)
- Increased sedation (36.5%)
- Feelings of intoxication (35.1%)
- Nausea (28.4%)
- Nystagmus (24.3%)
- Hypertension (20.3%)
- Tachycardia (18.9%)

- Diplopia (12.2%)
- Headache (10.8%)
- Rare occurrences:
  - urinary incontinence
  - frequent urination
  - anxiety
  - tunnel vision
  - dizziness
  - excessive salivation
Management of Side Effects

• Premedication with anti-emetic and/or benzodiazepine
• Stopping infusion or decreasing the rate of infusion
• Ensuring a quiet environment
• Administration of an anti-emetic
• Routine use of anxiolytics = 37.65%
  – Benzodiazepine used in 50% of the practice settings
  – Versed specifically: 46.97%

Barriers to Ketamine Use

- Lack of provider knowledge: 51.61%
- Lack of provider availability: 35.48%
- Practice setting barriers: 27.42%
- Lack of nursing staff to monitor: 20.97%
- Lack of nursing knowledge: 38.71%
- Other: 32.26%

Comments On Barriers

• Individually reviewed
• Categorized into the following areas:
  – Practice setting /monitoring
  – Boards of nursing barriers/regulatory
  – Insurance/reimbursement
  – Knowledge barriers
  – Provider barriers
Practice Setting & Monitoring Barriers

- Outpatient clinic unable to offer conscious or deep sedation
- Time consuming; increased level of care; labor intensive, continuous monitoring
- Interprofessional coordination needed
- Use limited to ICUs & PACUs
- Lack of resources (space, RNs, Providers)

Boards of Nursing/Regulatory Barriers

- State nurse practice acts limit administration of Ketamine by RN
  - Ketamine considered an anesthetic
- BON limitations on administration of Ketamine
- Lack of licensed personnel to administer ketamine (CRNAs, PAs, NPs)
- State law prohibits NPs/PAs from prescribing ketamine

Insurance Barriers

- Insurance coverage academic center regulations vs private practice
- Payment & reimbursement
- Insurance companies procedures resulting in difficulty to obtain authorization
- Insurance stated it was “experimental”.
- Finding a physician to prescribe
Knowledge Barriers

• Nursing knowledge deficit
• Physician knowledge deficit
  – Who can order/monitor
• Organizational knowledge deficit

• Knowledge deficit related to:
  – Benefits/uses
  – Side effects
  – Practice setting

ANALYSIS OF SURVEY RESULTS

Analysis
Gaps/Limitations
Future

• Small, initial analysis of practice related to the use of Ketamine as
  an adjunct for pain management.
• Majority of the respondents devote professional time to caring for
  patients in pain
• Respondents have expertise in pain management
• Non-pharmacologic modalities prevalent
Limitations

- Limitations
  - Relatively small sample size
  - 15 states were not represented.
  - Majority of respondents not prescribers
  - No physicians represented
  - Survey design

Gaps: Survey & Literature

- Lack of standardization in dosing
- Lack of pediatric dosing & administration
- Despite studies noting efficacy of Ketamine for pain, FDA considers this an off-label use
- Knowledge barriers
- Use of anxiolytics

Implications for Future

- Additional data related to prescribing practices.
- Physician & prescriber assessment of knowledge deficits & fears related to utilization of Ketamine as an adjunct for pain management.
- Studies related to pediatric utilization & dosing
- Development of standing orders
Future Implications

- Development of administration & monitoring guidelines
  - Inpatient/Acute Care Guidelines for Malignant Pain
  - Inpatient/Acute Care Guidelines for Non-Malignant Pain including chronic or refractory pain
  - Outpatient & Emergency Department Guidelines
  - Hospice/Home Guidelines
  - Use of anxiolytics
  - Dosing guidelines: bolus, short term infusion & continuous infusion

Future Implications

- Management of side effects
- Education
  - Provider
  - Nursing
  - Patient & family
- Re-evaluation by FDA

Conclusions

- The survey & respondent comments clearly reflected the utilization of the interprofessional approach to pain management.
- Pain is complex & requires a holistic approach to management that extends beyond multi-modal therapy.
- Patient centered approach is critical
Conclusions

• As the US grapples with the ramifications of chronic opioid use and abuse, the need for non-opioid medications to manage pain becomes more urgent.

• An ideal stage for interprofessional groups to examine pain management strategies in general & ketamine specifically.

Questions?

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References


References
