A Closer Look at the Emergency Medicine PRN

Overview of the PRN

Members of the Emergency Medicine (EMED) PRN are clinical pharmacists who primarily practice in an emergency department (ED) setting or have an interest in the treatment of ED patients. This PRN offers a means to network among members, provides educational opportunities, and uses social media (the PRN runs a Twitter account under the handle @accpemedprn) to facilitate information exchange and promote the professional activities facilitated by PRN members. Over its first year of existence, the PRN's Twitter account has grown to over 500 followers!

Membership Overview

Total members: 1085
Student members: 370
Resident members: 104
Fellow members: 4

Opportunities for Student, Resident, and Fellow Members

The EMED PRN encourages the participation of students, residents, and fellows through service on one of its committees, including the Awards and Recognition, Programming, Media, Research, Student Task Force, and Collaborative Organization for the Development of Emergency Medicine Pharmacists (or CODE) committees. Members can get involved in one of the committees at any time by contacting the current officers or the committee chairs. The PRN has been fortunate enough to offer student and resident travel awards. Awardees receive a monetary award to help support attendance at the Annual Meeting and have the opportunity to present their research at the PRN's business meeting.

Attendance at the PRN's business meeting allows students, residents, and fellows to network with leaders in the field. With over 1000 members and growing, the EMED PRN offers a diverse group of clinicians to network with.

Current Clinical Issue: Sub-dissociative Ketamine for Analgesia in the ED

Pain management in the ED is a challenge for many health care providers. The Institute of Medicine has highlighted the public health concern of opiate abuse and has encouraged a collaborative effort to develop best practices regarding selection of analgesic therapy.[1] The most commonly prescribed pain medications in the ED are opioid analgesics. These agents may be effective for controlling pain in many patients, but their use is associated with serious adverse effects (AEs), including respiratory depression. Adding to the challenge is the increasing rate of opioid abuse, leading to more ED admissions and ultimately fatal overdoses.[2] For these reasons, practitioners must seek additional options to avoid unwanted outcomes.

Ketamine is a NMDA (*N*-methyl-D-aspartate) receptor antagonist that provides analgesia at low doses and dissociative anesthetic effects at higher doses.[2] It has been used for over 20 years for procedural sedation and induction during rapid sequence intubation. Recently, an increasing amount of evidence has been published to suggest that ketamine is effective for acute pain control with opioid-sparing effects.[3-11] Unlike opioids, ketamine does not cause respiratory depression and has a favorable AE profile at low doses. The AEs of ketamine include hypertension, tachycardia, laryngospasm, and dysphoria.[1] Evidence suggests that ketamine doses of 0.1–0.5 mg/kg intravenously provide adequate analgesia. Onset of analgesia with ketamine occurs more rapidly than with most opiates (within 60 seconds); however, it also

wanes more quickly.

Ketamine has been studied in the ED as monotherapy and either against or concomitantly with morphine, hydromorphone, and fentanyl. Given the pharmacokinetic differences between the various agents, some studies have compared ketamine directly with an opiate, whereas others have combined ketamine with a reduced-dose opiate to take advantage of ketamine's more rapid onset. Additional literature exists for the use of ketamine for postoperative pain. The following text will review the evidence for prehospital and ED care. Studies have assessed ketamine for analgesia in adult patients with a mean age younger than 60.

Ketamine Safety and Efficacy Studies

Ahern et al. conducted a retrospective chart review to determine the safety of intravenous or intramuscular ketamine in doses up to 25 mg; 530 ED patients requiring analgesia were evaluated.[4] Only 30 patients (6%) had an AE of hypoxia, emesis, or dysphoric reaction. A few patients required treatment, mainly either administration of oxygen or low doses of lorazepam for dysphoria. These AEs were transient and had no impact on overall disposition. The authors concluded that ketamine for primary or rescue analgesia is safe.

Yeaman et al. and Andolfatto et al. both recently published small prospective trials evaluating intranasal ketamine for analgesia in the ED.[5,6] Initial doses of 0.5–1 mg/kg were used, and both studies found that intranasal ketamine provided rapid analgesia (within as few as 10 minutes) with only mild transient AEs. Yeaman et al. observed only mild AEs, most commonly dizziness. They also observed unwanted sedation and feelings of being "spaced out" or "disconnected." Andolfatto et al. found that subjects had similar AEs, with dizziness as the most common. The authors stated that none of the subjects required treatment for AEs. Both studies concluded that intranasal ketamine is safe and effective in treating moderate to severe pain.

Ketamine vs. Morphine

Ketamine has most commonly been compared with morphine for analgesia in the ED. Ketamine has a more rapid onset of analgesia, but morphine has a longer duration of action.

In 2014, a study by Mijidinejad et al. assessed ketamine 0.5 mg/kg intravenously versus morphine 0.1 mg/kg intravenously in a single-center randomized controlled trial of trauma patients for the treatment of pain related to long bone fractures.[7] The primary end point was pain reduction at 15 minutes post-administration, and the study included 126 patients. Initial pain scores on an analog scale of 0–10 averaged 8.8 and 8.9 in the ketamine and morphine groups, respectively. At 15 minutes, pain scores were reduced to 2.7 (ketamine) and 2.4 (morphine), resulting in statistically significant reduction in pain from baseline but no significant difference between the two groups. More patients required rescue medication in the ketamine group (four) than in the morphine group. Adverse events were more common in the ketamine group; six patients had the emergence phenomenon associated with ketamine.

Two smaller randomized controlled studies assessed ketamine 0.3 mg/kg intravenously compared with morphine 0.1 mg/kg intravenously in non-trauma ED patients.[8] The first, completed in a single ED, included 41 patients who received ketamine and 42 who received morphine, with an initial pain score of 5 or greater associated with abdominal, flank, back, or musculoskeletal pain. Pain scores were assessed at 15, 30, 60, 90, and 120 minutes, with fentanyl available as a rescue analgesic. Resolution of pain occurred more often in the ketamine group at 15 minutes than in the morphine group; however, this advantage was lost at 30 minutes. More patients in the ketamine group required rescue fentanyl at 120 minutes, but not prior. The second study included 45 patients, 24 of whom received ketamine, with the

remainder receiving morphine.[9] Included patients presented with abdominal, flank, lower back, or extremity pain. The primary end point, maximum reduction in pain score from baseline, was 4.9 points in the ketamine group and 5.0 points in the morphine group. Although no different between the two groups, peak reduction in pain occurred 5 minutes after administration in the ketamine group and 100 minutes after administration in the morphine group. Exclusion criteria were a history of ischemic heart disease, history of psychosis, and weight greater than 115 kg, effectively limiting the ketamine dose to 34.5 mg.

Finally, Beaudoin et al. assessed doses of ketamine in combination with morphine by comparing three randomized groups: morphine 0.1 mg/kg intravenously plus placebo, morphine 0.1 mg/kg intravenously plus ketamine 0.15 mg/kg intravenously, and morphine 0.1 mg/kg intravenously plus ketamine 0.3 mg/kg intravenously.[10] Twenty patients were enrolled in each group and were administered a maximum initial morphine dose of 10 mg. Rescue analgesia was available with morphine at prescriber discretion and was allowed no sooner than 30 minutes after initial analgesic administration. Pain scores were assessed at 30 minutes, 1 hour, and 2 hours, and the analgesic efficacy was assessed using the summed pain intensity difference (SPID) over 2 hours. The SPID measures the cumulative reduction in pain over all three tested time intervals. Patients were deemed treatment responders if they had a SPID of at least 33%. All three groups had a significant reduction in pain scores, and both ketamine groups had more treatment responders than the morphine-alone group. The higher-dose ketamine group had more treatment responders at the 2-hour mark, whereas the lower-dose ketamine groups' pain scores were similar to those of the morphine-alone group. There were no differences between rescue analgesia among the groups. Nine patients in the higher-dose ketamine group reported dizziness or lightheadedness at 30 minutes, whereas no patients in the other groups reported this AE. This study confirmed that adding ketamine to morphine provides additional analgesia. However, to provide prolonged analgesia (2 hours), higher doses of ketamine may be needed and would potentially be at the expense of more AEs.

Ketamine with Hydromorphone

Ahern et al. studied the efficacy of low-dose ketamine in combination with hydromorphone in 30 patients with moderate to severe pain.[3] Study participants received ketamine 15 mg intravenously with hydromorphone 0.5 mg intravenously. Rescue analgesia was available at 15 and 30 minutes with additional hydromorphone. Data collected included pain scores, additional hydromorphone doses, and AEs. The authors reported a mean reduction in pain score of 6 points on a visual analog scale at 5 minutes. At 15 minutes, the reduction was 5 points. Thirty-three percent of patients received rescue hydromorphone at 15 minutes, and 40% of patients received rescue hydromorphone at 30 minutes. Although 80% of patients reported dissociative AEs, 73% of patients reported weak or modest AEs, and only 13% reported bothersome or very bothersome AEs. The authors concluded that sub-dissociative dose ketamine with low-dose hydromorphone produced prompt pain relief with minimal significant AEs.

Ketamine vs. Morphine, Fentanyl, and No Analgesia

A process improvement initiative by Shackelford et al. evaluated the impact on vital signs of various prehospital analgesics on U.S. forces in Afghanistan.[11] Ketamine was compared with morphine, fentanyl, and no analgesia. The most common causes of injury were blast injury and gunshot wound. Of 309 patients, 119 received analgesics during point-of-injury care, and 283 received pain medication during TACEVAC (tactical evacuation). There was no difference in vital signs for patients who received pain medication at point of injury and had their vital signs

recorded compared with those who received no analgesic. For patients who received pain medications during TACEVAC, ketamine was associated with increased systolic blood pressure compared with morphine and fentanyl. There was no difference in respiratory rate or decrease in pain scores among the groups. Subsequently, the Tactical Combat Casualty Care guidelines by the U.S. Armed Forces were updated in 2014, placing ketamine as the first-line analgesic for patients at risk of shock or respiratory depression.

Data from this study support current recommendations for use of ketamine in prehospital pain management for combat injuries in the setting of hemodynamic instability because of its increase in systolic blood pressure. Ketamine improves hemodynamics compared with opioids, making it particularly advantageous for patients who are in shock or at risk of shock. Ketamine and fentanyl were both at least as safe as morphine for prehospital pain treatment in this study. The authors admit that these data should not be used as definitive evidence; rather, the authors suggest that fentanyl and ketamine are the future of battlefield pain control, although they admit that more evidence is needed.

Conclusion

None of the reviewed studies can independently conclude the efficacy and safety of ketamine use for analgesia in the ED. Collectively, however, the available evidence is promising that ketamine could evolve into an effective opioid-sparing analgesic. Potential candidates for ketamine include those with opiate-seeking behavior, those requesting not to be given opiates, hemodynamically unstable patients, and those requiring more rapid analgesia. Because most patients enrolled in these studies were younger than 60, more data are needed before using ketamine for analgesia in patients outside this population.

Similarly, evidence is lacking for ketamine use for pediatric acute pain management in the ED. Challenges to widespread use include overcoming negative perceptions of ketamine (street drug), distribution issues (history of backorders), and administration issues (some states only allow physician administration). Caution should be taken for patients with psychological disorders such as schizophrenia because dysphoria may be more detrimental to this population. Future studies should focus on finding the appropriate dose that provides analgesia while avoiding dissociative AEs, establishing the appropriate weight-based dosing in patients with obesity, and ensuring patient/practitioner satisfaction.

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References

1. Institute of Medicine Committee on Advancing Pain Research, Care, and Education. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC: National Academies Press, 2011.
2. Alexander GC, Kruszewski SP, Webster DW. Rethinking opioid prescribing to protect patient safety and public health. JAMA 2012;308:1865-6.
3. Ahern TL, Herring AA, Stone MB, et al. Effective analgesia with low-dose ketamine and reduced-dose hydromorphone in ED patients with severe pain. Am J Emerg Med 2013;31:847-51.
4. Ahern TL, Herring AA, Anderson ES, et al. The first 500: initial experience with widespread use of low-dose ketamine for pain management in the ED. Am J Emerg Med 2015;33:197-201.

5. Yeaman F, Meek R, Egerton-Warburton D, et al. Sub-dissociative-dose intranasal ketamine for moderate-to-severe pain in adult emergency department patients. Emerg Med Australas 2014;26:237-42.
6. Andolfatto G, Willman E, Joo D, et al. Intranasal ketamine for analgesia in the emergency department: a prospective observational series. Acad Emerg Med 2013;20:1050-4.
7. Mijidinejad S, Esmailian M, Emadi M. Comparison of intravenous ketamine with morphine in pain relief of long bone fractures: a double-blind randomized clinical trial. Emerg (Tehran) 2014;2:77-80.
8. Motov S, Rockoff B, Cohen V, et al. Intravenous subdissociative-dose ketamine versus morphine for analgesia in the emergency department: a randomized controlled trial. Ann Emerg Med 2015;66:222-9.
9. Miller JP, Schauer SG, Ganem VJ, et al. Low-dose ketamine vs morphine for acute pain in the ED: a randomized controlled trial. Am J Emerg Med 2015;33:402-8.
10. Beaudoin FL, Lin C, Guan W, et al. Low-dose ketamine improves pain relief in patients receiving intravenous opioids for acute pain in the emergency department: results of a randomized, double-blind, clinical trial. Acad Emerg Med 2014;21:1193-202.
11. Shackelford SA, Fowler M, Schultz K, et al. Prehospital pain medication use by US Forces in Afghanistan. Mil Med 2015;180:304-9.

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