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AHC Media

Alternatives to Opioids for Acute Pain Management in the Emergency Department: Part II

This is part II in the series on non-opioid alternatives and adjuvants for pain treatment in the ED. Part I covered nitrous oxide, trigger point injections, and intravenous lidocaine. This issue discusses ultrasound-guided nerve blocks and sub-dissociative doses of ketamine.

As emergency physicians, we want to ensure our patients are not suffering severe pain. But, at the same time, we clearly need to reduce the use of opioids. Balancing these two priorities is difficult but important to our patients and society as a whole.

— Sandra M. Schneider, MD, Editor

Ultrasound-guided Regional Anesthesia

Background

Ultrasound-guided regional anesthesia rapidly has become the standard of care for intra-operative pain control over the past decade.[91] As emergency ultrasonography expertise has increased in recent years, ultrasound-guided nerve blocks, without the aid of nerve stimulators, have been adopted within emergency medicine. This practice has been shown to be effective in lieu of procedural sedation for joint reduction as well as an alternative to parenteral opioids for the pain associated with extremity trauma. Emergency medicine physicians were able, with minimal training, to achieve effective anesthesia by performing ultrasound-guided nerve blocks of the forearm in the emergency department for hand procedures.[92] Additionally, following brief hands-on ultrasound-guided regional anesthesia training, emergency physicians were successfully able to perform ultrasound-guided upper and lower extremity nerve blocks for the management of joint/fracture reduction and traumatic limb pain.[93] Ultrasound guidance allows clinicians to fully visualize nerves, blood vessels, and targeted muscle groups for accurate deposition of local anesthetic, resulting in reliable and rapid anesthesia and analgesia. Ultrasound-guided regional anesthesia is a reliable and safe alternative to procedural sedation and an effective intervention for the management of traumatic limb pain in the ED setting.

Indications

Trauma. Ultrasound-guided regional anesthesia has gained popularity in emergency medicine for the management of limb pain and joint reduction, due to its minimal monitoring requirements, safety, and reliability. One of the

EXECUTIVE SUMMARY

- Ultrasound guided nerve blocks can provide regional anesthesia for procedures, but also provide relieve from the pain of fractures. They are safe and effective in adults and children.
- The maximum dose of lidocaine is 5 mg/kg. Lidocaine toxicity can range from minor CNS effects including tinnitus and lightheadedness, to seizures or cardiopulmonary collapse. A lipid infusion is used to treat lidocaine toxicity.
- Subdissociative doses of ketamine are effective in reducing pain from a variety of causes. Because ketamine in much higher doses is used as an anesthetic, hospitals often restrict the use of the drug in this setting. However in the small doses used for pain, ketamine is a very safe and effective drug.
- Side effects are commonly see with sub dissociative doses of ketamine. These include dizziness, nausea and a feeling of unreality. However these side effects are nearly always mild and short lived,

first publications highlighting its role in emergency medicine reported four cases of successful shoulder reduction, without complication, after ultrasound-guided interscalene nerve block.[94] This was followed by a study of 11 patients who underwent ultrasound-guided forearm nerve blocks for hand procedures in the ED with desired anesthesia and without complication.[92] Additionally, a report was published highlighting the use of an ultrasound-guided supraclavicular block in the management of five patients for treatment of upper extremity fracture, dislocation, and abscess management.[95] Evidence continues to support the safe and effective treatment of joint reduction and traumatic limb pain with ultrasound-guided nerve blocks in the ED.

The management of acute pain secondary to trauma has many barriers. The first priority in trauma care is to resuscitate and stabilize the patient with attention to life-threatening injuries. These patients can have unstable vital signs and require extensive imaging; however, once stabilized, patients still may not receive adequate analgesia for a variety of reasons. The oral route of administration for medications is discouraged, and non-steroidal anti-inflammatory medication is not preferred. Typically, the medication of choice is systemic opioids. Although opioids are a rational choice, because of their rapid onset and effectiveness, clinicians must consider potential side effects. Opioid medications may cause respiratory depression, airway compromise, nausea and vomiting, hemodynamic instability, obscured neurological re-assessment, and delirium in a labile trauma patient. The management of pain may not seem a top priority in this setting; however, studies have shown that the intensity of acute pain upon presentation may be an important risk factor in predicting the development of chronic pain in the future.[96,97] Therefore, clinicians must familiarize themselves with viable options for managing pain in this group of patients.

Ultrasound-guided regional anesthesia can significantly reduce the intensity of acute pain associated with trauma.[98] Although there is very limited evidence that regional anesthesia performed early can impede the progression to chronic pain, it should be considered in the management of traumatic injuries, as it has significant advantages over systemic medications.[99] These advantages include decreased opioid requirements, decreased length of stay in the ED, superior comfort during transfer and transport, less staff necessary at bedside for monitoring, and decreased risk of adverse events as compared to procedural sedation.[100]

Geriatrics. Management of traumatic pain in the geriatric patient population can be even more challenging. In the United States in 2003, hip fracture was the cause of 30% of all hospitalizations, and by 2050, hip fracture is expected to exceed 6 million worldwide.[101,102] The desire to control geriatric fracture pain adequately, while balancing the risks associated with parenteral opioid administration, presents a management dilemma. There is a delicate balance between over-sedation and adequate analgesia that must be found when titrating opioids in geriatric patients. One of the complicating issues with geriatric pain management is that undertreated pain has as much risk as "overtreated" pain (e.g., sedation, respiratory depression, and hemodynamic instability).

Morrison et al evaluated the risk of delirium and pain in geriatric hip fracture patients treated with opioids while in an inpatient setting. The authors concluded that cognitively intact patients with undertreated pain (i.e., patients who received less than 10 mg of intravenous morphine equivalents per days) were nine times more likely to develop delirium compared to patients whose pain was controlled adequately.[103] Ultrasound-guided regional anesthesia was the only intervention found to be effective in controlling acute hip fracture pain in a systematic review of 83 studies, when compared to multimodal pain management, traction, systemic analgesia, and neurostimulation.[104]

Early studies evaluating the effectiveness of ED ultrasound-guided femoral nerve blocks for the management of pain in geriatric hip fracture patients were compelling. Beaudoin et al reported no procedural complications, first attempt success for all patients, significant pain relief at 15 and 30 minutes, and a median time to perform the procedure of eight minutes in 13 elderly patients with hip fracture.[105] Continued research in this population found a 76% reduction in pain score at 120 minutes without complications in 20 geriatric patients who underwent ultrasound-guided fascia iliaca compartment block for isolated hip fracture.[106]

More recent randomized controlled studies and systematic reviews have continued to show the benefits of ultrasound-guided nerve blocks in geriatric hip fractures, with significant reduction in pain score, improved mobility

Table 1. Contraindications to Brachial Plexus Regional Anesthesia[120]

Absolute Contraindications	Relative Contraindications
• Patient refusal • Infection over needle insertion site • Allergy to local anesthetics	• Severe pulmonary disease • Ipsilateral neuromuscular disease • Contralateral phrenic nerve damage • Anticoagulation or bleeding disorder • Sepsis or untreated bacteremia • Contralateral pneumothorax • Cervical hardware

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Table 2. Side and Effects and Complications of Brachial Plexus Regional Anesthesia[120]

Side Effects	Complications
• Horner's syndrome • Phrenic nerve block • Recurrent laryngeal nerve block • Motor and sensory blockage of the arm	• Subarachnoid/epidural spread • Pneumothorax • Hoarseness

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Table 3. Contraindications to Lower Extremity Regional Anesthesia[120]

Absolute Contraindications	Relative Contraindications
• Patient refusal • Infection over site of needle insertion • Allergy to local anesthetics	• Ipsilateral neuromuscular disease • Contralateral neuromuscular disease in ambulatory patient • Anticoagulation or bleeding disorder

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while awaiting surgery, decreased opioid requirements pre- and post-operatively, no difference in morbidity and mortality, and more frequent discharge home.[105, 107-111]

Pediatrics. Ultrasound-guided regional anesthesia in the pediatric trauma patient population can play an important role in successfully managing pain associated with fractures. A pediatric study comparing pain control with intravenous morphine compared to a fascia iliaca compartment block in 55 patients ages 16 months to 15 years found fascia iliaca block to be superior. Patients who received a nerve block had an 18% greater reduction at 30 minutes post-block that lasted up to six hours. Mean time of analgesia in the nerve block group was significantly longer at 313 minutes compared to the 60-minute duration of the morphine group. There were no complications in the nerve block group and medical staff satisfaction was higher.[112] A more recent study compared pain score and need for systemic analgesia in 259 pediatric femur fracture patients who received fascia iliaca compartment block compared to systemic analgesics alone. Authors found a statistically significant decrease in pain score and requirement of systemic analgesic in the fascia iliaca group, with no difference in adverse events.[113] Turner et al evaluated duration of analgesia and need for morphine in 81 patients who received either an ultrasound-guided femoral nerve block or systemic analgesia alone for pain associated with femur fracture in patients 1-18 years of age. The group that received ultrasound-guided femoral nerve block had a two to three times longer duration of analgesia after initial treatment, required less than 50% of the total dose of morphine, and needed few nursing interventions as compared to the systemic analgesic alone group.[114]

Frenkel et al evaluated the use of ultrasound-guided forearm nerve blocks in the management of traumatic hand pain in patients 9-17 years of age. In this study, a single physician performed all blocks. This physician had performed approximately 30 forearm blocks prior to the start of the study. The median initial pain score for patients was 5.8 and the post-block pain score was 0.8, with seven out of 10 patients reporting a score of 0 on a 0-10 pain scale. Although this physician was experienced in ultrasound-guided forearm blocks, median procedure time was between 69 and 79 seconds. There were no immediate complications, and at 1 year followup, no adverse events were discovered.[115]

Joint Dislocation. Joint dislocation is another challenging injury to manage in the ED. Typically, successfully reducing a joint requires procedural sedation for the patient. Although emergency physicians are trained and well equipped to provide procedural sedation, the process can be cumbersome. Procedural sedation requires airway monitoring with a complete intubation set up available, significant resource utilization with

Table 4. Side Effects and Complications of Lower Extremity Regional Anesthesia[120]

Side Effects	Complications
• Motor blockage of targeted area of lower extremity • Fall may be at fall risk for proximal lower extremity block	

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Table 5. Factors Affecting Systemic Toxicity of Local Anesthetics

- Volume of local anesthetic used
- Choice of local anesthetic
- Site of block
- Low protein state (e.g., malnutrition, liver/renal failure)
- Acidemia
- Peripheral vasoconstriction

Table 6. Emergency Department Ultrasound-guided Regional Anesthesia Safety Check List

- Check patient identifiers
- Verify block location
- Calculate weight-based dose of local anesthetic
- Verify volume of local anesthetic is under toxic level
- Verify availability of Intra-lipid and expiration date
- Check patient is on cardiac monitor
- Verify past medical history, current medications, and allergies
- Aspirate frequently during procedure

assistance by staff during and after the procedure, and a post-procedural observation period. Procedural sedation patients are at risk for airway compromise and hypotension and may have increased length of stay in the ED. One study found a statistically significant difference in ED length of stay when comparing procedural sedation to ultrasound-guided brachial plexus block for shoulder reduction. The procedural sedation group had a 285-minute stay in the ED compared to a 106-minute stay for the nerve block group. For patients with joint dislocation, ultrasound-guided regional anesthesia is a safe and effective alternative in the ED. There was no difference in adverse events, and both groups had high patient satisfaction.[116]

A second study also found a significant reduction in ED length of stay when comparing procedural sedation to ultrasound-guided interscalene nerve block for shoulder reduction: 177 minutes compared to 100 minutes, respectively. Additionally, this study highlights a statistically significant decrease in one-on-one provider time when comparing these two interventions. The procedural sedation group required, on average, 47 minutes of one-on-one provider time, compared to an average of five minutes with the nerve block. There was no difference in complications between groups.[117]

A more recent study found suprascapular nerve block in the ED to be safer and quicker compared to procedural sedation. This study of 41 patients revealed a statistically significant reduction in ED length of stay: 125 minutes in the procedural sedation group compared to 25 minutes in the nerve block group. There was no difference in the rate of success of reduction or patient satisfaction in either group; however, there was a difference in adverse events. The nerve block group had no adverse events, but the procedural sedation group had 15% nausea/vomiting, 10% hypoxia, and 15% post-procedural agitation. Overall, suprascapular nerve block was the superior intervention when compared to procedural sedation.[118]

Heflin et al recently published a case report of a successful reduction of a posterior elbow dislocation in a 29-year-old male after infraclavicular nerve block. The infraclavicular nerve block allowed clinicians to avoid procedural sedation as well as achieve analgesia without concerns for Horner's syndrome or other post-block side effects that can be seen with more proximal brachial plexus blockade. The patient reported no pain during reduction and there were no complications reported.[119]

Cointraindications/Complications/Toxicity

There are a variety of unique considerations, dependent on location, that should be addressed and understood prior to the decision to perform regional anesthesia. (*See Tables 1–4.*) Local anesthetic systemic toxicity, infection, bleeding, and nerve damage are potential complications that can be see with all blocks.[120] The incidence of peripheral nerve injury after ultrasound-guided regional anesthesia is rare, and, therefore, difficult to quantify. The rate may be between 0.18-8%; however, there are a variety of definitions used between studies. Most of the nerve injuries reported are transient, lasting only days to months, and described as tingling or paresthesia. Permanent nerve injuries, lasting longer than six months have been reported between 0.015-0.09%.[121-125]

Acute compartment syndrome is a known complication after traumatic limb injury, most commonly seen in tibial and forearm fractures or with crush injuries. The classic symptoms of compartment syndrome are severe pain and paresthesia, out of proportion to the injury, or distal to it, raising the concern

that pain management with regional anesthesia may blunt these signs and symptoms and, thus, lead to a delay in diagnosis.[126] However, there have been a variety of case reports and review articles highlighting no significant delay in the diagnosis of acute compartment syndrome after pain management with ultrasound-guided regional anesthesia.[126-130] Although clinicians should fully evaluate the risks and benefits prior to implication of a block, diligent monitoring of pain with frequent and thorough neurovascular exams should allow clinicians to discern when acute compartment syndrome is developing despite regional anesthesia.

Lastly, when performing regional anesthesia, clinicians should be aware of the signs and symptoms of local anesthetic systemic toxicity. Although rare, it can be devastating. Toxicity can occur from peripheral infiltration as well as accidental intravenous or intra-arterial injection.[131] The maximum recommended dose of lidocaine is 5 mg/kg without epinephrine; for bupivacaine and ropivacaine the maximum recommended dose is 3 mg/kg without epinephrine.[120] Toxicity manifests as a spectrum of disease from minor neurological symptoms such as tinnitus to more significant symptoms such as seizure. If toxicity is severe, patients can have respiratory and cardiovascular collapse. Cardiovascular collapse is related to the local anesthetic's ability to bind to voltage-gated sodium channels in channels having a pro-arrhythmic effect. Bupivacaine readily binds to these channels; therefore, it is more cardiotoxic compared to ropivacaine, which has a broader therapeutic window.[131] Depending on a variety of factors such as volume, site, and route of administration, toxicity can take minutes to hours to develop. When local anesthetic systemic toxicity is suspected, clinicians should initiate treatment and supportive care. Patients should be given benzodiazepines if they develop seizures. Their airway and oxygenation should be monitored, and in advanced cases of cardiovascular collapse, advanced life support should be initiated.[132] There are studies supporting the use of intralipid infusions to counteract the cardio-toxic effects of local anesthetics. Recommended dosing is administration of a 20% lipid solution at 1-3 mL/kg given every five minutes up to 3 mL/kg. This should be followed by an infusion of a 20% lipid solution at 0.25 mL/kg/min for up to three hours.[120] Morbidity and mortality are high once patients have cardiovascular compromise, so treatment should never be delayed. Cardiopulmonary bypass should be considered in refractory cases. Local anesthetic systemic toxicity is rare, and by performing a pre-injection safety check list and using ultrasound guidance, clinicians can minimize patient risk.[133] (*See Table 6.*)

Administration and Dosing

The choice of local anesthetic is important based on the duration of anesthesia and analgesia required. In the ED, short-acting lidocaine 1-2% is preferred for joint reduction, and longer-acting ropivacaine 0.2-0.5% is preferred in the management of traumatic limb pain. The smallest volume possible to achieve analgesia is recommended.

Sub-Dissociative Dose Ketamine

Background

Ketamine possesses anesthetic, amnesic, and analgesic properties. Since the discovery of N-methyl-D-aspartate (NMDA) receptors' role in processing of painful stimuli, ketamine analgesia has gained a great deal of attention in anesthesia, surgery, palliative care, and emergency medicine.[134] Ketamine given in sub-dissociative doses (≤ 0.3 mg/kg IV) provides effective analgesia with minimal effects on hemodynamics, cognition, or consciousness.[135,136] A growing number of clinical trials support the use of sub-dissociative dose ketamine (SDK) in the ED for a variety of acute and chronic painful conditions as an adjunct to opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), or local anesthetics, as well as a single agent.

Pharmacology

Ketamine is a non-competitive NMDA and glutamate receptor antagonist that decreases central sensitization, "wind-up" phenomenon, and pain memory at the level of the spinal cord (dorsal ganglion) and central nervous system.[136,137] It consists of two pure optical isomers, *S*- and *R*-ketamine, with the former being three to four times more potent. In addition, *S*(+)-isomer has a shorter duration of action and more rapid clearance.[137,138]

In the United States, only *R*(–)-enantiomer is used. Ketamine is absorbed rapidly after intravenous, intramuscular, and intranasal administration, with the oral bioavailability of ketamine of about 20%. Once absorbed, ketamine undergoes extensive hepatic metabolism (via cytochrome P450 enzymes), with norketamine being an active metabolite with one-third of the potency of ketamine. Ninety percent of the drug is excreted in urine in the form of metabolites, with 2-4% of the drug remaining unchanged.[136-138] Theoretically, patients with severe liver and renal insufficiency may have prolonged clearance and accumulation of the metabolites; however, there are no data to suggest that SDK is unsafe in patients with liver or renal dysfunction.[139] Ketamine is both hydrophilic and lipophilic, which allows administration via various routes (IV, IM, SQ, IN, PO, and via nebulization), with IV and IN routes [AUTHORS: IV AND IN CORRECT OR SHOULD THIS BE IM HERE?] being the most commonly used for sub-dissociative dosing.

Clinically, the NMDA receptor blockade translates into a decrease in acute pain, opioid tolerance, opioid-induced hyperalgesia, as well as a decrease in persistent chronic (allodynia) and neuropathic pain.[138] Indications, contraindications, dosing regimens, and side effects of SDK are listed in Tables 7-9.

Clinical Applications

There is a significant amount of evidence that SDK is effective and safe for control of acute and chronic painful conditions in the pre-hospital arena and in the adult and pediatric ED.

Pre-hospital Setting. In pre-hospital setting, Johansson et al evaluated the analgesic effect of ketamine by comparing intravenous morphine (0.2 mg/kg) alone to the combination of intravenous morphine and ketamine (0.1 mg/kg and 0.2 mg/kg) given to

Table 7. Indications and Contraindications to Sub-dissociative Dose Ketamine

Indications	Contraindications
Acute pain • Traumatic • Non-traumatic • Brief painful procedures • Post-operative pain	Absolute • Allergy to ketamine • Pregnancy • Age < 2 months • History of schizophrenia
Chronic pain • Central pain (post stroke pain) • Phantom pain • Neuropathic pain • Cancer pain	Relative • Severe coronary artery disease • Uncontrolled hypertension • Severe hepatic insufficiency • Severe renal insufficiency
Opioid-tolerant pain	
Opioid-induced hyperalgesia	

Table 8. Dosing Regimen/Routes of Administration of Sub-dissociative Dose Ketamine

Route of Administration	Comments
Intravenous route 0.3 mg/kg over 10 minutes (bolus dose)	• Dilute in 100 mL NS for short infusion • IV pump is preferred • No monitoring necessary
Intravenous route 0.15-0.2 mg/kg/hr (continuous infusion)	• 100 mg ketamine in 100 mL NS • IV pump is necessary • Titrate q30 min by 5 mg until pain is optimized • No monitoring necessary
Intranasal route 0.5-1 mg/kg	• Optimum volume 0.3--0.5 mL per nostril • Titrate q15 minutes • Use high concentration solution (50 mg/mL for pediatrics or 100 mg/mL for adults)
Subcutaneous route • 0.3 mg/kg over 10 minutes (bolus dose)	• Dilute in 100 mL NS for short infusion • IV pump is preferred • No monitoring necessary
Subcutaneous route 0.15-0.2 mg/kg/hr (continuous infusion) [AUTHORS: IS THIS CORRECT? OUR PHYSICIAN EDITOR SAYS CONTINUOUS INFUSION SUBQ MEDICATIONS ARE NOT GIVEN]	• 100 mg ketamine in 100 mL NS • IV pump is necessary • Titrate q30 minutes by 5 mg until pain is optimized • No monitoring necessary

Table 9. Side Effects of Sub-dissociative Dose Ketamine

- Nausea
- Vomiting
- Dizziness
- Lightheadedness
- Feeling of unreality
- Mild dysphoria

patients with acute traumatic injuries. The trial demonstrated a significantly greater improvement in pain scores upon patients' arrival to the hospital in the morphine-ketamine group (3.1 vs. 5.4), as well as nearly 50% decrease in morphine requirements (7 mg vs. 13.5 mg). Fourteen percent of the patients had minor adverse side effects related to ketamine administration (dizziness and feeling of "unreality").[140]

Similarly, Jennings et al compared the analgesic efficacy of SDK (given in 10-20 mg IV pushes every 5 minutes) co-administered with morphine to IV morphine alone (given at 5 mg dose every 5 minutes) in patients with traumatic pain. Results demonstrated better pain relief and greater change in the pain score with the ketamine-morphine combination (3.2 vs. 5.6). There were higher rates of minor adverse side effects in the ketamine/morphine treatment group, mainly nausea and dizziness (39% vs. 14%).[141]

A pre-hospital trial by Galinski et al evaluating the opioid-sparing ability and analgesic efficacy of low-dose ketamine given at 0.2 mg/kg to patients with traumatic pain, demonstrated a 29% decrease in morphine consumption and high rates (54%) of dysphoria, nausea, and feeling of unreality. These adverse side effects were brief in duration and weak in intensity and did not require interventions.[142] Another randomized controlled trial of 308 patients with acute traumatic injuries demonstrated similar changes in pain score between IV SDK (0.2-0.3 mg/kg) and IM morphine (10 mg) upon arrival to the hospital, with patients in the ketamine group experiencing more hallucinations and agitations. Of note, 57 patients with closed head injuries who received ketamine did not experience major adverse effects.[143] A systematic review of ketamine analgesia in the pre-hospital setting demonstrated good analgesic efficacy and opioid-sparing effect of ketamine but high rates of minor side effects, notably nausea, dizziness, and feeling of unreality.[144]

Adult ED. In the adult ED, numerous observational and randomized trials compared the analgesic efficacy, safety, and opioid-sparing effects of SDK as an adjunct to opioid analgesia and/or as a single agent (in comparison to opioids). A retrospective case series of 35 patients

presenting with acute traumatic (fractures) and non-traumatic (abscesses) painful conditions who received SDK (range 5-35 mg) demonstrated good pain relief in 54% of patients, with only one patient experiencing mild dysphoria.[145] Richards et al evaluated the efficacy and safety of SDK analgesia in the ED by conducting a survey of patients and physicians regarding their experience with ketamine. Results of the survey demonstrated a decrease in pain by 63%, patient satisfaction of 55%, and physician satisfaction of 72%. Notably, 96% of physicians believed that ketamine is underused in the ED for analgesia, citing the emergence phenomenon as a limiting factor.[146]

Ahern et al, in a prospective observational study of adult patients with severe pain who received intravenous SDK (15 mg) and half-dose IV hydromorphone (0.5 mg), demonstrated complete pain relief at 5 minutes in 46% of patients, with 80% of patients reporting minimal or modest side effects of nausea, dizziness, and a feeling of unreality.[147] A prospective randomized double-blind, placebo-controlled trial by Beaudoin et al, evaluating the analgesic efficacy and safety of low-dose IV ketamine (0.15 mg/kg and 0.3 mg/kg) as an adjunct to morphine (0.1 mg/kg) for patients with acute moderate to severe pain, reported significantly greater pain relief with the ketamine/morphine combinations than morphine alone. Patients receiving ketamine/morphine combination reported a sustained reduction in pain intensity for up to two hours (in 0.3 mg/kg ketamine group), but more of these patients reported a feeling of "unreality" (15%) and dizziness (45%).[148] The largest retrospective case series conducted to date is by Ahern et al of 530 consecutive patients receiving SDK (10-15 mg per dose in 92% of patients). This study demonstrated overall good safety, with only 6% of patients experiencing side effects, and 3.5% of patients experiencing mild dysphoria.[149]

Two randomized controlled trials directly compared IV SDK (0.3 mg/kg) to IV morphine (0.1 mg/kg) in ED patients with acute abdominal, flank, and back pain. A trial by Miller et al demonstrated comparable short-term analgesia (up to 20 minutes) in both groups, as well as similar rates of adverse effects between the two groups (58% vs. 57%).[150] Motov et al demonstrated no significant difference in mean pain scores from the baseline (8.6 vs. 8.5) to a 30-minute mark (4.1 vs. 3.9) between the two groups, as well as similar rates of rescue analgesia. Importantly, more patients in the ketamine group reported complete resolution of pain at 15 minutes (44% vs. 13%). However, a significant percentage of patients in the ketamine group had side effects at five minutes (73% vs. 51%) and 15 minutes (69% vs. 31%), which included nausea, dizziness, and a feeling of unreality. These adverse effects were noted to be short-lived and did not require any treatment or interventions.[151]

All of the above-mentioned studies demonstrated significant rates (14-80%) of minor but bothersome side effects associated with SDK analgesia, mainly nausea, vomiting, dizziness, and feeling of unreality. These side effects occurred in the first several minutes after intravenous push administration and were typically short-lived. Thus, it is reasonable to assume that the rate (speed) of administration of ketamine is directly related to onset and severity of psychomimetic side effects due to the high lipophilicity.

There are several trials that specifically evaluated role of short-term (more than 10 minutes) SDK versus continuous infusion on frequency of side effects and analgesic efficacy. Goltser et al utilized a short-infusion of SDK analgesia in 14 ED patients with acute and chronic painful conditions by administering 0.3 mg/kg over 10 minutes and demonstrated acceptable pain relief in 11 patients (NRS > 3) and minor side effects in only two patients (dizziness and tinnitus).[152] Similarly, Ahern et al prospectively administered 15 mg of IV ketamine that was immediately followed by a continuous infusion of 20 mg/hour for one hour in 38 patients with acute pain. By 10 minutes, seven patients were pain-free, and 25 patients had significant pain relief (NRS > 3) at 60 minutes. However, 87% of patients experienced side effects of nausea, fatigue, headache, and feeling of unreality.[153] The high rates of side effects might be explained by the initial bolus of ketamine.

Literature supporting the use of continuous SDK infusion revolves primarily around patients with sickle cell disease and chronic intractable pain.[154-156] However, a trial by Gurnani et al, randomized patients with acute fractures to receive either subcutaneous SDK with initial bolus of 0.25 mg/kg and subsequent continuous infusion of 0.1 mg/kg/hour or IV morphine at 0.1 mg/kg given every four hours. This study demonstrated greater change in pain score, less sedation, less rescue analgesia, early ambulation, and minimal rates of side effects in the ketamine group.[157]

Intranasal Sub-dissociative Dose Ketamine

Intranasal (IN) ketamine delivery via atomizer results in rapid medication absorption with serum and cerebral spinal fluid (CSF) levels approaching those comparable to the intravenous route due to the large surface area and rich blood supply of the nasal mucosa. Advantages of IN ketamine analgesia include rapid onset, high medication bioavailability, titratability, painless and easy delivery, and great patient and staff satisfaction. One of the pressing issues with IN ketamine administration for analgesia, however, is finding the optimum dosing regimen that will provide effective pain control with minimal rates of adverse effects.

Several research papers evaluated the analgesic efficacy and rates of side effects of IN ketamine in the ED given in sub-dissociative doses. Yeaman et al in a pilot study evaluated the efficacy of IN ketamine given at an average dose of 1 mg/kg (0.84-1.38 mg/kg) in children with acute traumatic limb injury, and demonstrated a 60% decrease in pain score from baseline at 30 minutes (75 mm to 30 mm), with 33% of patients requiring rescue opioids, 30% of patients requiring ketamine re-dosing, and 100% of patients experiencing side effects (nausea and dizziness).[158]

Graudins et al compared IN SDK (1 mg/kg) to IN fentanyl (1.5 mcg/kg) for children in the ED with isolated musculoskeletal limb injuries in a randomized controlled fashion and demonstrated similar analgesic efficacy and satisfaction rates between the two groups at 30

minutes. However, there were significantly higher rates of side effects noted in the ketamine group (78% vs. 40%), which were mild in intensity and transient in duration.[159]

Andolfatto et al, in a prospective observational study of 40 ED patients with acute musculoskeletal trauma receiving IN ketamine at 0.5-0.75 mg/kg, demonstrated significant pain relief in 88% of patients at 30 minutes, with rates of side effects (dizziness, nausea, mood changes, and hearing changes) in up to 67% of patients. All adverse effects were transient and none required intervention.[160] Yeaman et al evaluated the effectiveness of IN SDK given at a median dose of 0.98 mg/kg (0.6-1.6 mg/kg) to adults and demonstrated significant changes in pain score at 30 minutes in 56% of patients.[161]

Despite the documented safety of SDK administration in acute care settings such as the ED, ketamine use, even in non-dissociative doses, often is classified erroneously as sedation. Therefore, it is recommended that patients receiving short-term and/or continuous SDK infusions be placed on a cardiac monitor and pulse oxymetry. In addition, structured assessments of sedation and agitation for patients receiving ketamine analgesia may be recorded in the chart by utilizing Richmond Agitation-Sedation Scales (RASS) and Side Effects Rating Scale for Dissociative Anesthetics (SERSDA).[172,173] It is prudent to emphasize that individual facilities (departments and hospitals) should have a set of guidelines and policies on safety parameters as well as established nursing competencies related to SDK administration in the ED.[174,175]

The use of SDK (via IV, IN, and even SQ routes) administered either alone or in combination with opioids is safe and effective for the treatment of acute pain in the ED and may result in opioid sparing. Its use has been associated with relatively high rates of minor and short-lived adverse side effects that might be reduced by utilizing a short-infusion of ketamine via IV and SQ routes and smaller initial dosing with frequent titration for IN route.

Conclusion

The management of acute pain in the ED can be challenging. However, with advanced research and access to alternative medications, clinicians today can use a multi-modal approach, tailoring pain management needs on a case-by-case basis. Opioids are an important part of acute pain management, but should be reserved as a rescue medication, or for cancer pain, end of life pain, and refractory pain. Opioids mask pain, whereas some alternatives can treat the underlying cause of pain. Alternatives should be what clinicians reach for first in an attempt address the source of patients' pain and avoid unnecessary exposure to opioids. Trigger point injection, for example, is an intervention that targets the cause of musculoskeletal pain and can provide immediate relief otherwise impossible to achieve in the ED. Additionally, nitrous oxide allows clinicians to perform otherwise painful procedures with ease as patients experience analgesia and anxiolysis, with minimal to no side effects. Nitrous oxide has broad applications in the ED, and due to its exceptional safety profile and rapid onset and elimination, it is an ideal alternative analgesic.

Lastly, ultrasound-guided regional anesthesia provides complete pain relief for pain associated with traumatic limb pain in a way opioids cannot. Regional anesthesia can be used in lieu of opioids for acute extremity fracture pain or procedural sedation for joint reduction in the pediatric, adult, and geriatric ED populations. The use of sub-dissociative dose ketamine, administered either alone or in combination with opioids, is safe and effective for the treatment of acute pain in the ED and might result in opioid-sparing. Its use has been associated with relatively high rates of minor and short-lived adverse side effects that might be reduced by utilizing a short- infusion of ketamine via intravenous and subcutaneous routes and smaller initial dosing with frequent titration for intranasal route. Despite the limited evidence, the role of intravenous lidocaine given as a single agent or as an adjunct for acute pain management in the ED appears promising. In properly selected patients, this analgesic modality provides effective and safe pain control. However, before this therapy can be broadly used in the ED, it needs to be studied in larger populations with underlying cardiac disease. Knowledge of alternative therapies empowers emergency physicians to choose from a host of a pain-specific interventions, leaving opioids as a rescue or second-line agent. Continued research and education regarding alternative modalities for pain management will hopefully shift the paradigm of acute pain management away from reliance on opioids by decreasing exposure and, ultimately, the potential for addiction.

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CME/CE Questions

1. What is the best strategy to prevent side effects associated with low-dose ketamine administration?
   a. Intravenous midazolam
   b. Small doses of propofol
   c. Ketamine infusion over 10 minutes*
   d. Intranasal ketamine
2. Which of the following is *not* a common side effect of sub-dissociative dose ketamine?
   a. Feeling of unreality
   b. Headache*
   c. Nausea
   d. Dizziness
3. Which of the following is true regarding ultrasound-guided regional anesthesia (USRA) in the ED?
   a. Opioids are superior to USRA for the relief of pain associated with extremity fracture.
   b. The majority of evidence is against the use of USRA when there is a concern for compartment syndrome.
   c. The incidence of permanent nerve injury after USRA is high.
   d. Ultrasound-guided regional anesthesia can be performed in lieu of procedural sedation for joint dislocation.*
4. A 95-year-old patient with mild dementia presents with a fractured hip. Which of the following is the best treatment for her pain, assuming all are available?
   a. Morphine 10 mg IV
   b. Hydromorphone 2 mg IV
   c. Ultrasound-guided regional nerve block*
   d. Lidocaine IV infusion
5. Symptoms of lidocaine toxicity include all of the following *except*:
   a. Cardiopulmonary collapse
   b. Tinnitus
   c. Seizures
   d. Emergence reactions*
6. The maximum dose of lidocaine in a 50 kg patient is:
   a. 250 mg*
   b. 25 mg
   c. 15 mg
   d. 150 mg
7. Which of the following statements is *false*?
   a. Early relief of pain may prevent chronic pain syndromes.
   b. Early analgesia may decrease delirium or confusion in the elderly.
   c. Early pain medications reduce the ability to diagnose patients with abdominal pain.*
   d. Use of non-opioid pain treatments in the ED can reduce length of stay.
8. Severe lidocaine toxicity can be treated with:
   a. Ketamine
   b. Lipid infusion*
   c. Flumazinel
   d. Glucagon

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