N	Study ID	Site	Intervention 1 (n)	Intervention 2/ Control (n)	Dose of intervention 1	Dose of intervention 2	Rescue analgesia for intervention 1 (type/n)	Rescue analgesia for intervention 2 (type/n)	Male n (%)	Age mean (SD)	Indication for analgesia	Inclusion Criteria	Time of Pain assessment after analgesia	Scales for Pain Assessment	VAS mean (SD)	Face pain scale mean (SD)	Assessed Adverse events	Adverse events (n)	Conclusion
1	**Frey 2018**	Tertiary care Children's Hospital ED	Ketamine (43)	Fentanyl (42)	1.5 mg/kg	2 microgram/kg	Ibuprofen, Fentanyl, Morphine Ketamine, Toradol (type-not reported separately/11)	Morphine, Fentanyl, Ibuprofen (type-not reported/9)	57 (66.27%)	11.8 (2.6) - Intervention 1 12.2 (2.3) - Intervention 2	Acute extremity injury	(1) age 8 to 17 years, (2) presence of acute extremity injury, (3) visual analog scale (VAS) score higher than 35 mm (moderate to severe pain), (4) legal guardian presence	15 minutes, 30 minutes, 60 minutes	Visual analog Scale	31 mm for Intervention 1 32 mm for Intervention 2	N/A	Dizziness, dysphoria. Dissociation, unpleasant taste, drowsiness, nausea/vomiting, itchiness, vision changes, headache, rash, light headedness, nystagmus	63 adverse events in 47 of 86 total patients	Intranasal ketamine noninferior to intranasal fentanyl, risk of AE greater in IN ketamine
2	**Graudins 2014**	EDs of 2 Monash Health hospitals: Monash Clayton and Monash Dandenong	Fentanyl (40)	Ketamine (40)	50 microgram/mL	200 mg/2 mL	Fentanyl (IN), Morphine (IV) (n=12)	Fentanyl (IN), Morphine (IV) (n=5)	46 (57.5%)	Median: 9 - Intervention 1 7 - Intervention 2	Isolated limb injury	1. children aged 3 to 13 years, 2. weight less than 50 kg, 3. isolated limb injury, 4. moderate to severe pain evidenced by 6 or more on a 11-point verbal rating scale at triage, 5. Intranasal Fentanyl as norm for analgesia	15 minutes, 30 minutes, 60 minutes	Facial Pain Scale-Revised (for children 3 - 6 years old) Visual analog scale (for children 7 years or older)	40 mm for Intervention 1 45 mm for Intervention 2	40 mm for Intervention 1 45 mm for Intervention 2	Bad taste in mouth, drowsiness, dizziness, itchy nose, nausea, dysphoria, hallucinations	24 Adverse Events in Intervention 1 67 Adverse Events in Intervention 2	Similar reductions in pain ratings, significant analgesic effect in both groups, increased number of adverse effects in IN ketamine group, no unwanted sedation
3	**Fein 2016**	Pediatric Emergency Department	Fentanyl (24)	Normal (0.9%) Saline (25)	2 microgram/kg	Equivalent volume as Intervention 1	Morphine (IV/1), Ketorolac (IV/2)	Morphine (IV/5), Ketorolac (IV/0)	30 (61.2%)	10.6 (5.3) - Intervention 1 12.5 (5.1) - Intervention 2	Vaso-occlusive sickle cell crisis	(1) age between 3 and 20 years and (2) having any SCD genotype and (3) willingness to receive the study drug.	10 minutes, 20 minutes, 30 minutes	Modified Wong–Baker FACES Pain Rating Scale	NA	Median scores: At 10 minutes: INF: 8; Placebo:8 At 20 minutes: INF: 6.5; Placebo: 8 At 30 minutes: INF:8; Placebo: 8	Hypertension, hypoxia, respiratory distress, bradycardia, sleepiness, headaches, itching, nausea, vomiting, nasal pain, prolonged cough, prolonged gagging	53 Adverse events in Intervention 1 35 Adverse events in Intervention 2	INF reduced VOC pain more than placebo at 20 minutes, no significant difference in AEs, lower hospitalization and higher PED return in IN fentanyl group, 24 hr. return rates about the same
4	**Quinn 2018**	Pediatric Emergency Department	Ketamine (11)	Fentanyl (11)	1 mg/kg	1.5 microgram/kg	Morphine (IV/0)	Morphine (IV/0)	18 (81.81%)	9.77 - Intervention 1 9.58 - Intervention 2	Acute moderate to severe pain	Patients aged 3 to 17 years, of weight less than 64 kg, presenting to the ED with acute moderate to severe pain, defined as at least 6 on a total 11-point Numeric Rating Scale (NRS) or equivalent Wong-Baker FACES Pain Scale, and being of sufficient intensity to require opioid analgesia as determined by the treating ED attending physician.	10 minutes, 20 minutes, 30 minutes, 60 minutes	Numeric Rating Scale and Wong-Baker FACES Pain Scale	NA	Median scores: At 20 minutes: Intranasal Ketamine: 4 Intranasal fentanyl: 2	sedation, dizziness	73% adverse effect rate in Intervention 1 9% adverse effect rate in Intervention 2	IN ketamine provides similar analgesia at 20 minutes after administration, IN ketamine is associated with greater rates of sedation and dizziness
5	**Borland 2011**	Pediatric Emergency Department	Fentanyl (91)	Fentanyl (98)	300 micrograms/mL	50 micrograms/mL	Morphine (IV/1), Paracetamol (oral/4), Ibuprofen (oral/20), Paracetamol/codeine (oral/11), Codeine (oral/1)	Morphine (IV/0), Paracetamol (oral/13), Ibuprofen (oral/34), Paracetamol/codeine (oral/14), Codeine (oral/0)	119 (62.96%)	8.8 - Intervention 1 9.1 - Intervention 2	Closed deformed long bone fractures	Children aged 3–15 years, presenting to the ED, clinically deformed closed long bone fractures	10 minutes, 20 minutes, 30 minutes	VAS and Faces Pain Scale - Revised	Median decrease after 30 minutes: 40mm (in both groups)	Incorporated in VAS	Nausea, sedation, vomiting, rash, itch, other (dizziness)	31 adverse effects in intervention 1 23 adverse effects in intervention 2	Two concentrations of INF equivalent in reducing pain
6	**Ruffin 2022**	Pediatric Emergency Department	Fentanyl (17)	Acetaminophen/hydrocodone (17)	1.5 micrograms/Kg	0.15 mg/kg	Not specified	Not specified	41% in Intervention 1 59% in intervention 2	3.1 - Intervention 1 1.8 - Intervention 2	Painful infectious mouth lesions	Children between 6 mo. and 18 y of age Diagnosed by the treating physician with a painful infectious mouth condition (herpangina, hand-foot-and-mouth disease, and herpetic gingivostomatitis) Parental complain of poor oral intake Require analgesic medication per the treating physician Does not require intravenous rehydration per the treating physician All races, sex, genders Guardian must be able to consent to study in English	15 minutes and 30 minutes	VAS, FLACC, FACES	Intervention 1: At 15 minutes: 1.7 At 30 minutes: 0.6 (p = 0.088) Intervention 2: At 15 minutes: 2.9 At 30 minutes: 1.6 (p = 0.059)	Intervention 1: At 15 minutes: 1.7 At 30 minutes: 0.6 (p = 0.088) Intervention 2: At 15 minutes: 2.9 At 30 minutes: 1.6 (p = 0.059)	Nasal irritation, crying, sleepiness	12 adverse effects in Intervention 1	IN Fentanyl safe and effective alternative to acetaminophen with hydrocodone in reducing pain and improving hydration status in children with painful infectious mouth lesions and poor oral intake
7	**Reynolds 2017**	Children's Hospital Emergency Department	Ketamine (43)	Fentanyl (44)	1 mg/kg	1.5 microgram/kg	Ketamine (IN/10), Opioid (NI/7)	Ibuprofen (oral/20), Paracetamol/codeine (oral/11),	54 (62%)	Median: 8	Pain from suspected isolated extremity fractures	Verbal children ages 4–17 years with a suspected, single extremity fracture requiring analgesia evidenced by deformity or pain to palpation in a single extremity in a patient with an initial Wong-Baker FACES Pain Scale Score of 4 or greater (for patients 4–10 years) or an Adult Pain Rating Scale score of at least 3 (for patients ages 11–17	10 minutes, 20 minutes, 30 minutes, 60 minutes, 90 minutes, 120 minutes	Faces Pain Scale - Revised (FPS-R) for children ages 4–10 years and the Visual Analog Scale (VAS) for children ages 11–17 years	Score reduction at 20 minutes: 44 (36) - Intervention 1 35 (29) - Intervention 2 Score reduction at 60 minutes: 42 (32) - Intervention 1 44 (28) - Intervention 2	Score reduction at 20 minutes: 44 (36) - Intervention 1 35 (29) - Intervention 2 Score reduction at 60 minutes: 42 (32) - Intervention 1 44 (28) - Intervention 2	Bad Taste in Mouth/Throat, Dizziness, Sleepiness, Itchy Nose , Visual Disturbance, Mood change, Dysphoria , Talkativeness, Nausea , Trouble Concentrating , Funny Dreams, and Transient hypotension	41 adverse effects in intervention 1 25 adverse effects in Intervention 2	Pain reduction similar with both groups at 20 minutes, cumulative number of side effects 2.2x higher in IN ketamine group, no serious adverse events, IN ketamine associated with more minor side effects

8	**Kenedy 1998**	St Louis Children's Hospital ED	Fentanyl (130)	Ketamine (130)	fentanyl, 10 mg/mL	ketamine, 10 mg/mL	Midazolam	Midazolam	Fentanyl 94 (72.3%), Ketamine 88 (67.7%)	Fentanyl: 9.7±3.01, Ketamine: 9.7±3.27		patients between 5 and 15 years of age requiring FR and meeting American Society of Anesthesiologists (ASA) class I or II criteria33 were invited to participate in the study between June 1, 1993, and December 31, 1994.	15-20 minutes	Observational Score of behavioral Distress-Revised,VAS, FAS	NA	NA	Dry mouth. Sleepy, Pleasant dreams, Crying , Dizziness, Balance, Headache, Nausea, Nightmares , Vomiting , and Hallucinations	……	We conclude that during emergency orthopedic FR, intravenous ketamine/midazolam is more effective than fentanyl/midazolam for relief of pain and anxiety in children. Respiratory complications occur less frequently with ketamine/midazolam than with fentanyl/midazolam, but respiratory support may be needed with either regimen. Both regimens are effective in facilitating fracture reduction and both produce amnesia in nearly all children, but average time required for recovery is longer for ketamine/midazolam than for fentanyl/ midazolam. Vomiting occurs more frequently with ketamine/midazolam than with fentanyl/midazolam and emergence reactions occur in small and statistically equivalent numbers with both regimens