Comparison of the efficacy of IV Ketamine vs Fentanyl for treatment of acute pain.

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2nd Party Appraiser:

Clinical Scenario: You're called for a compound ankle fracture for an adult who was playing soccer. There is an obvious deformity with bone visible and the patient is in significant pain. You are wondering what medication will best manage this patient's pain.

PICO (Population – Intervention – Comparison – Outcome) Question:

In adult patients with moderate to severe acute pain is ketamine more effective at reducing pain scores compared to Fentanyl?

Search Strategy: (Pubmed)

Prehospital OR adults OR out of hospital OR emergency AND trauma OR acute pain OR injury OR MSK OR fracture OR dislocation AND ketamine OR anaket OR ketalar OR esketamin OR norketamine AND fentanyl OR fentanil

Filter: results by year of 2010-2021

Search Outcome:

971

Relevant Papers:

AUTHOR, DATE	POPULATION: SAMPLE CHARACTERISTICS	DESIGN (LOE)	OUTCOMES	RESULTS	STRENGTHS/ WEAKNESSES
Bronsky et al. 2019	200 adults - propensity matched analysis yielded 79 per treatment group	Retrospective observational review LOE II	Change in pain score	Patients receiving Ketamine IV demonstrated significantly larger decrease in pain (9.6 to 4.2 numerical scale) after treatment compared to Fentanyl IV. (9.6 to 7.2 numerical scale)	**Strength:** Matching analysis created comparable tx groups - Pt only received one form of analgesia **Weakness:** Not a RCT, no injury severity score
Majidinejad et al, 2014	126 Patients included (Age 18-55) with long bone fractures	Retrospective Double Blind RCT LOE I	Effect of Ketamine on pain relief	Patients receiving Ketamine IV demonstrated significant decrease in pain after treatment (2.7 + 1.8; P<0.0001)	**Strengths:** Double blind Randomized control trial **Weaknesses:** Short follow up period of patients. Absence of placebo group due to ethical considerations. Different administration routes should be evaluated for further study.
Friesgaard, K. 2015	Pre-hospital medical charts from 2348 adults treated with intravenous fentanyl by ambulance personnel during a 6-month	Retrospective chart review LOE II	Analgesia (Reduction in Pain Score) NRS Reduction of >2	NRS Before Tx: 8 NRS After Tx: 4 NRS Reduction: (Average) 3 79.3% of patients had	**Strengths:**Chart Review allows for lots of data to quickly be found Shorter and cheaper than RCT

	period were reviewed.			over 2 point reduction in NRS	All patients received the same dose of fentanyl /kg **Weaknesses:**Undocumented Tx or demographics can skew generalizability.Study lacked variables such as injury severity score or injury region that would have otherwise been available from a trauma registry and allowed for a more in-depth and complete analysis. Future research should focus on employing blinded, truly randomized designs with in-depth collection of adverse event data encompassing a greater number of prehospital systems to better generalize our results for prehospital pain management. Some patients may only have received one dose of fentanyl due to short transport times.

Comments: There were surprisingly few studies comparing Ketamine and Fentanyl for analgesia. For this reason, search parameters had to be broadened. Due to this, studies comparing Ketamine and morphine for analgesia were also examined.

Consider: Studies show that there is lower risk of complications (ie respiratory depression) when using Ketamine as a first line analgesic. Also that Ketamine is comparable in reducing pain scale in comparison to opioids such as Morphine. For these reasons, we would consider advocating for a change in practice to consider Ketamine as a first line analgesic for pain.

Clinical Bottom Line: Both ketamine and fentanyl have been shown to be highly effective in reducing moderate to severe pain from acute injuries. Ketamine has significantly less risk of cardiovascular and respiratory compromise. Not only this but sub-dissociative dose ketamine has relatively minor adverse effects compared to a dissociative dose (emergence phenomenon) and should therefore be implemented in more patients requiring analgesia for moderate to severe pain.

References:

Majidinejad, S., Esmailian, M., & Emadi, M. (2014). Comparison of Intravenous Ketamine with Morphine in Pain Relief of Long Bones Fractures: a Double Blind Randomized Clinical Trial. Emergency (Tehran, Iran), 2(2), 77–80.

Bronsky, E. S., Koola, C., Orlando, A., Redmond, D., D'Huyvetter, C., Sieracki, H., Tanner, A., 2nd, Fowler, R., Mains, C., & Bar-Or, D. (2019). Intravenous Low-Dose Ketamine Provides Greater Pain Control Compared to Fentanyl in a Civilian Prehospital Trauma System: A Propensity Matched Analysis. Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors, 23(1), 1–8. https://doi.org/10.1080/10903127.2018.1469704

Friesgaard, K. D., Nikolajsen, L., Giebner, M., Rasmussen, C. H., Riddervold, I. S., Kirkegaard, H., & Christensen, E. F. (2016). Efficacy and safety of intravenous fentanyl administered by ambulance personnel. *Acta anaesthesiologica Scandinavica*, *60*(4), 537–543. https://doi.org/10.1111/aas.12662

Paramedic – Evidence Based Medicine (P-EBP) Program

1. Article Summary Table:

Article: (first author last name, year) **Bronsky et al, 2019**
P (# pooled subjects, characteristics) **200 Patients in the initial study sample (Adults >18) Presenting with severe pain (Pain scale 7-10)**
I (intervention details) **Low dose IV Ketamine (0.3mg/kg q. 20 min as needed) maximum 3 doses**
C (comparison details) ***Fentanyl IV (2mcg/kg bolus over 1-2 mins) additional dose every 10 minutes as needed***
O (outcome measures) Primary Outcome: Change in Pain score, Secondary Outcome: Change in vital signs and GCS after treatment

2.Study design used?

PROSPECTIVE STUDY (looking *forward* in time)	NO
RETROSPECTIVE STUDY (looking *back* in time)	YES
HAS A CONTROL GROUP? (study compares 2 or more groups of subjects)	Yes

3. Was the article ***VALID***? Key questions for therapy articles:.

QUESTION	*NOTES*
1. Were patients randomized?	No
2. Were patients in the treatment & control groups similar? (*Look for a Table of Characteristics usually called "Table 1")*	Yes - Matching Analysis

4. Outcomes & Results Table" Each outcome in the article's PICO should have results reported

OUTCOMES (What the author was looking for)	**RESULTS** (What the author found, numbers/data)
Analgesia (Reduction in Pain Score)	Patients receiving Ketamine IV demonstrated a significantly larger decrease in pain (9.6 to 4.2 numerical scale) after treatment compared to Fentanyl IV. (9.6 to 7.2 numerical scale). 25% of Fentanyl IV patients experienced zero change in pain score. P-value <0.001
Changes to vital signs and GCS	No significant changes to vital signs in either group

5. Weaknesses & Strengths

STRENGTHS	**WEAKNESSES**
Matching Analysis increases comparability between Tx groups. Gets rid of outliers that skew results.	Propensity matched analysis within a retrospective cohort does not provide as strong empirical evidence as an RCT
Secondary Outcomes like vital signs increase knowledge	Study lacked variables such as injury severity score or injury region that would have otherwise been available from a trauma registry and allowed for a more in-depth and complete analysis.

Pt's only received fentanyl or ketamine as an analgesic. Many other analgesic comparison studies have mixed analgesics per patient and this can confound results. (Ex. tylenol + hydromorphone, or morphine and later fentanyl)	Future research should focus on employing blinded, truly randomized designs with in-depth collection of adverse event data encompassing a greater number of prehospital systems to better generalize our results for prehospital pain management. Some patients may only have received one dose of fentanyl due to short transport times.

6. Assign a **Level of Evidence** to the article. Check One:

Level I	Evidence obtained from adequately powered properly designed randomized controlled trials (RCTs) on live human participants, or systematic reviews or meta-analysis with only RCTs. No pilot studies are to be included here.
Level II	Evidence obtained from adequately powered non-randomized studies with a comparison group of live human participants, or systematic reviews/meta-analyses of non-randomized studies with a comparison group. Prospective or retrospective registry-type studies in which comparisons are made; cohort and case control studies are included her
Level III	Evidence from studies with no randomization and no comparison group, simulation/manikin studies and animal studies. Pilot studies are listed here.

7. Assign a **Direction of Evidence** to the article. Check One:

Green	The results of this study are supportive for the use of this intervention
Yellow	The results of this study are neutral for the use of this intervention
Red	The results of this study oppose the use of this intervention. The results demonstrate harm or caused a negative impact.

Comparison of Intravenous Ketamine with Morphine in Pain Relief of Long Bones Fractures: a Double Bline Randomized Clinical Trial

1. Article Summary Table:

Article: (first author last name, year) Majidinejad et al, 2014
P (# pooled subjects, characteristics) **126 Patients included (Age 18-55) with fractures of long bones and randomly divided into two groups**
I (intervention details) **IV Ketamine (0.5mg/kg)**
C (comparison details) IV Morphine (0.1mg/kg)
O (outcome measures) Primary Outcome: Effect of Ketamine in relieving pain

2.Study design used?

PROSPECTIVE STUDY (looking *forward* in time)	NO
RETROSPECTIVE STUDY (looking *back* in time)	YES
HAS A CONTROL GROUP? (study compares 2 or more groups of subjects)	Yes

3. Was the article ***VALID***? Key questions for therapy articles:.

QUESTION	*NOTES*
1. Were patients randomized?	YES
2. Were patients in the treatment & control groups similar? (*Look for a Table of Characteristics usually called "Table 1")*	YES

4. Outcomes & Results Table" Each outcome in the article's PICO should have results reported

OUTCOMES (What the author was looking for)	**RESULTS** (What the author found, numbers/data)
After therapeutic intervention, the pain severity significantly decreased in ketamine (2.7±1.8; P<0.0001)	Significant decreases in pain for both Ketamine (8.8 to 2.7 numerical scale) and Morphine (8.9 to 2.4 numerical scale).
The success rate of the treatment at 10-minute interval in those receiving ketamine was 93.65%	No statistically significant difference between the two interventions (P=0.28).
	No complications with Morphine, but 9.5% of Ketamine patients experienced emergency phenomenon. 6.3% of ketamine patients also required a rescue dose due to short period of ketamine drug effect.

5. Weaknesses & Strengths

STRENGTHS	**WEAKNESSES**
Randomized control trial. Double blind.	Short follow up period for patients. All patients were only evaluated for 10 minutes. Longer follow up periods recommended for future studies.
Ketamine used as sole intervention. Previous studies have primarily used Ketamine in conjunction with other drugs.	Absence of placebo group. Not possible to withhold medical intervention due to ethical considerations.

	Single route of administration. Continuous use or infusions should be considered for further studies.

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Efficacy and safety of intravenous fentanyl administered by ambulance personnel

1. Article Summary Table:

Article: (first author last name, year) **Friesgaard, K., et al. 2015.**
P (# pooled subjects, characteristics) **Pre-hospital medical charts from 2348 adults treated with intravenous fentanyl by ambulance personnel during a 6-month period were reviewed.**
I (intervention details) **EMTs and PMs were allowed to administer a total of 2 lg/kg per transport, with each administration not exceeding 1 lg/kg and given with at least 5-min intervals.**
C (comparison details) **No direct comparison group as this is a retrospective chart review. The comparison is previous pain scale before analgesia vs after analgesia.**
O (outcome measures) Primary Outcome: Decrease in NRS Pain scale after analgesia. **Secondary: proportion of patients with clinically meaningful reduction in pain intensity, defined as NRS ≥ 2, from before fentanyl administration to hospital arrival.**

2.Study design used?

PROSPECTIVE STUDY (looking *forward* in time)	NO
RETROSPECTIVE STUDY (looking *back* in time)	YES. Chart Review over last 6 months
HAS A CONTROL GROUP? (study compares 2 or more groups of subjects)	No.

3. Was the article ***VALID***? Key questions for therapy articles:.

QUESTION:	*NOTES*
1. Were patients randomized?	No
2. Were patients in the treatment & control groups similar? (*Look for a Table of Characteristics usually called "Table 1")*	N/A

4. Outcomes & Results Table" Each outcome in the article's PICO should have results reported

OUTCOMES (What the author was looking for)	**RESULTS** (What the author found, numbers/data)
Analgesia (Reduction in Pain Score)	NRS Before Tx: 8 NRS After Tx: 4 NRS Reduction: (Average) 3
NRS Reduction of >2	79.3% of patients had over 2 point reduction in NRS.

5. Weaknesses & Strengths

STRENGTHS	WEAKNESSES
Chart Review allows for lots of data to quickly be found	Undocumented Tx or demographics can skew generalizability.
Shorter and cheaper than RCT	Study lacked variables such as injury severity score or injury region that would have otherwise been available from a trauma registry and allowed for a more in-depth and complete analysis.
All patients received the same dose of fentanyl /kg	Future research should focus on employing blinded, truly randomized designs with in-depth collection of adverse event data encompassing a greater number of prehospital systems to better generalize our results for prehospital pain management. Some patients may only have received one dose of fentanyl due to short transport times.

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