Comparing the use of IV anxiolytics plus standard analgesic care versus standard analgesic care alone in controlling severe, acute pain in the Emergency Department

Uriel Manzo, MD; Andrew Fischer, MD; Jing Liu, MD; Wafa Ahmed; Laura Celene Castro; Rick McPheeters, DO

Affiliations: UCLA – Kern Medical Department of Emergency Medicine

Introduction

Controlling acute pain remains a common and challenging problem in the emergency department (ED). Undertreating pain can lead to poor patient satisfaction and unnecessary suffering. However, excessive analgesic treatment can be dangerous and still does not guarantee that the patient will have satisfactory pain control. In the pediatric, dental, and anesthesia literature combining anxiolytics and opioid analgesics has been shown to control acute pain better than single agent opiates.

Objectives

Our study seeks to determine whether a combined, anxiolytic plus opioid analgesic, treatment offers a clinically significant improvement over the standard of care, analgesic only, treatment for acute pain in the ED.

Methods

Study Design: This is a small sample analysis of an ongoing prospective, single-blinded randomized clinical trial.

Study Setting: Kern Medical Emergency Department from September 2016 to January 2018; Sample size was 28 individuals.

Study Protocol: We enrolled opioid naïve patients complaining of severe acute pain 7/10 or higher and then surveyed their pain levels with a 0-10 cm visual analogue scale (VAS) at 30 minutes, 1 hour, 2 hour, and 4 hours after administration of pain medication. A pain level of 4 cm or below represented successful control of pain. The intervention group received both IV standard 2 mg dosage of the anxiolytic midazolam and a standard analgesic dosage of 0.1 mg per kg of IV morphine while the control group only received morphine per standard of care. The number of patient requests for additional morphine and the total amount of morphine administered were also tracked for both groups.

Measurements: Medication administered (morphine, or midazolam and morphine), time (initial and intervals in hours), pain scores (Visual Analog Scale; **Figure 1**) at each time interval, and conscious state (Ramsay Sedation Assessment Scale; **Figure 2**).

Data Analysis: Time to pain control and total morphine dosage as means with standard deviations and medians with interquartile ranges. Logistic regression for each time to pain control treatment group as well as total morphine dosage. Analyses included Kaplan-Meier curves.

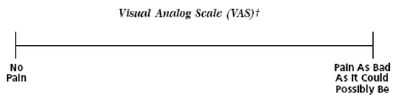

Figure 1. An illustration of the Visual Analog Scale (VAS) used to survey patient pain level at different time intervals. It is not drawn to scale.

Ramsay Sedation Assessment Scale

Awake Levels:	Patient anxious or agitated or both	1
	Patient cooperative, oriented and tranquil	2
	Patient responds to commands only	3
Asleep Levels:	A brisk response to a light glabellar tap	4
	A sluggish response to a light glabellar tap	5
	No response	6

Figure 2. The Ramsay Sedation Assessment Scale survey used to determine level of consciousness while the patient is taking the VAS survey.

Results

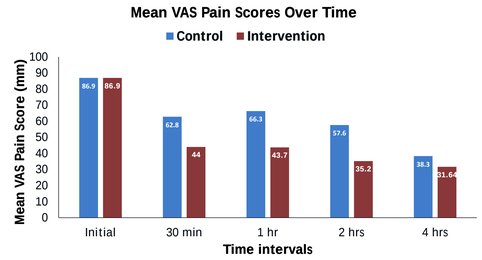

Figure 1. The mean pain level according to the visual analog pain scale per control and intervention treatment groups at each time interval (P < 0.05 at the 30 minute interval, 1 hour interval, 2 hour interval and overall).

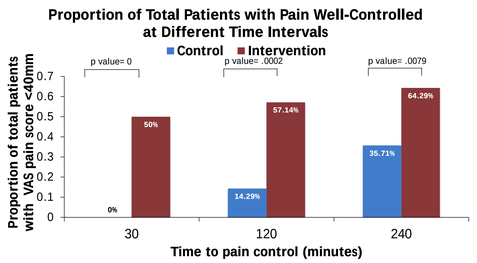

Figure 2. Proportion of total patients with pain well-controlled (VAS pain scores <40mm) for control and intervention groups at times 30 minutes, two hours, and four hours.

Table 1. Descriptive statistics for Total Morphine administered that include the means, standard errors (SE), and 95% confidence intervals (CI). X indicates total morphine administered (mg) and Y indicates time to pain control (min). n=28

Treatment	Mean X	Mean Y	SE (X)	SE (Y)	95% C.I. (X)	95% C.I. (Y)
Control	10.43	188.57	0.82	16.47	1.76	35.58
Intervention	6.29	109.29	0.83	24.88	1.8	53.76

Table 2. Regression statistics of total morphine (mg) administered that includes t-values, P values, and coefficient of determination (r^2).

Treatment	t value (X)	t value (Y)	P Value	r^2
Control	12.767	11.449	0.812	0.005
Intervention	7.529	4.392	0.041	0.303

Table 3. Descriptive statistics for Time to Pain Control that include the means, standard errors (SE), and 95% confidence intervals (CI). X indicates time intervals to pain control and Y indicates pain level per patient. n=28

Treatment	Mean X	Mean Y	SE (X)	SE (Y)	95% C.I. (X)	95% C.I. (Y)
Control	192	37.95	19.6	5.86	44.33	13.27
Intervention	76.67	31.56	30.87	7.65	71.18	17.65

Table 4. Time to Pain Control regression analysis that includes t-values, P values, and coefficient of determination (r^2.)

Treatment	t value (X)	t value (Y)	P value	r^2
Control	9.798	6.471	0.481	0.064
Intervention	2.484	4.124	0.003	0.745

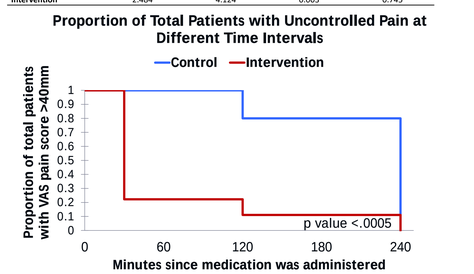

Figure 3. Kaplan-Meier curve showing the proportion of total patients with pain not well controlled (VAS pain scores >40mm) for control and intervention groups at times 30 minutes, two hours, and four hours.

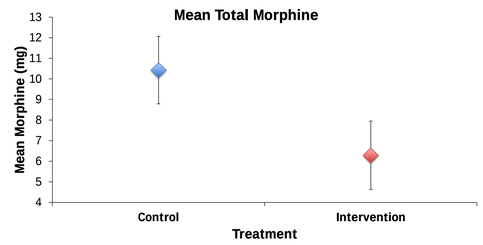

Figure 4. The mean total morphine (mg) to pain control for both control and intervention treatment groups. The means are represented by the markers and the error bars represent the 95% confidence interval (n=28).

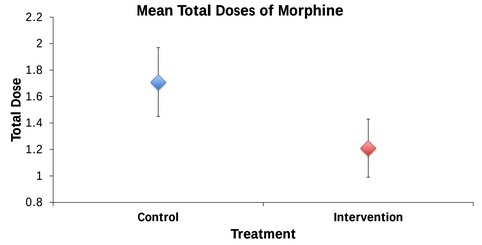

Figure 5. Mean total doses of morphine administered per patient in each treatment group. The means are represented by the markers and the error bars represent the 95% confidence interval (n=28).

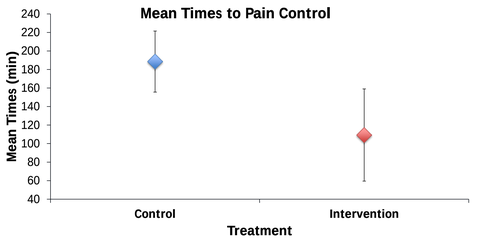

Figure 6. Mean time to pain controlled equal to or less than 4/10 for both control and intervention treatment groups. The means are represented by the markers and the error bars represent the 95% confidence interval (n=28).

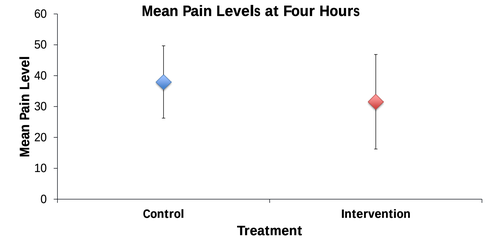

Figure 7. The mean pain level according to the visual pain scale per control and intervention treatment groups at 4 hours. The means are represented by the markers and the error bars represent the 95% confidence interval (n=28).

Simple multivariate analyses was performed to analyze the data. The intervention group had significant improvement in their pain scores compared to the control group at the 30 minute interval, 1 hour interval, 2 hour interval and overall (P < 0.05, n=28; **Figure 1**). Additionally, the control group required more total IV morphine during their ED course and more frequent morphine re-dosing than the intervention group (P < 0.05; **Figure 4** and **Figure 5**). Furthermore, the intervention group had their pain successfully well controlled faster (**Figure 6**) and had a higher proportion of patients with well-controlled pain compared to the control group (**Figure 2** and **Figure 3**). Importantly, there were no adverse events with the concomitant administration of midazolam and morphine.

Discussion

- Our data corroborates findings in the dental, pediatric and anesthesia literature that combining an anxiolytic with an analgesic provides better pain control than an analgesic alone. The intervention group had their pain well controlled faster and required less morphine.
- However, more research will be needed to identify safe monitoring parameters in the ED given recent FDA warning on the combine use of benzodiazepines and opiates. Also, the use of non-benzodiazepine anxiolytics and non-opiate analgesics should be explored to see whether combination treatments with these agents also produce superior effect than single agent analgesics.
- Limitations: Small study, small sample size, study not powered

Conclusions

Incorporating anxiolytics to the standard of care with IV opiates in the management of acute pain in the ED may lead to better and faster pain control than opiates alone.

References

- Bird SB, Dickson EW. Clinically significant changes in pain analog the visual analog scale. *Annals of Emergency Medicine*. 2001;38:6.
- Castillo RC, Wegener ST, Heins SE, Haythornthwaite JA, Macjenzie EJ, Bosse MJ. Longitudinal relationships between anxiety, depression, and pain: Results from a two-year cohort study of lower extremity trauma patients. Paino. 2013;154:2860-2866.
- Craven P, Cinar O, Madsen T. Patient anxiety may influence the efficacy of ED pain management. *American Journal of Emergency Medicine*. 2013.
- Fein JA, Zempsky WT, Cravero JP. Relief of pain and anxiety in pediatric patients in emergency medical systems. *Pediatrics*. 2012;130:1391.
- Klossika I, Flor H, Kamping S, Bleichhardt G, Trautmann N, Treede RD, et al. Topical review emotional modulation of pain: A clinical perspective. *Pain*. 2006;124: 264-268.
- Kroenke K, Spitzer RL, Williams JBW, Lowe B. An ultra-brief screening scale for anxiety and depression: The PHQ. *Psychosomatics*. 2009;50:6.
- Neighbor ML, Dance TR, Hawk M, Kohn MA. Heightened pain perception in illicit substance—using patients in the ED: Implications for management. *American Journal of Emergency Medicine*. 2011; 29:50-56.
- Spiitzer RL, Kroenke K, Williams JBW. Validation and utility of a self-report version of PRIME-MD the PHQ primary care study. *JAMA*. 1999;282(18).
- Thompson T, Keogh E, French CC, Davis R. Anxiety sensitivity and pain: Generalizability across noxious stimuli. Pain. 2008; 134:187-196.
- Tsze DS, Hirschfield G, von Baeyer CL, Bulloch B, Dayan PS. Clinically significant differences in acute pain measured on self-report pain scales in children. *Society for Academic Emergency Medicine*. 2015;doi:10.1111/acem.12620.

** For the rest of references, see printed appendix.*

Acknowledgements

-- We would like to thank the Kern Medical Emergency Department, including attendings, residents, and research assistants.

--Additionally, thank you Joan Buddecke for all of your help and support.