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Impact Of Opioid Dose Administered During Anesthesia On Mortality Associated With Severe Trauma: Secondary Analysis From The Proppr Study

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Background& Rationale: Currently, there is a lack of clinical evidence supporting the beneficial effect of opioids in acute trauma patients undergoing anesthesia. We analyzed data from the PROPPR (Pragmatic, Randomized, Optimal Platelet and Plasma Ratios) study to examine the impact of opioid dose on mortality in severely injured patients. We hypothesized that an anesthetic with a higher opioid dose would be associated with a lower likelihood of death in severely injured trauma patients.
Methods: This study was a planned secondary analysis from the PROPPR trial which examined the ratio of blood components in 680 actively bleeding trauma patients during damage control resuscitation at 12 participating level 1 trauma centers in North America. Of the 680 subjects, 526 had an emergent procedure requiring anesthesia. Opioid dose was calculated as morphine milligram equivalents (mme) per hour using anesthesia start and end times. Quartiles were used to divide opioid dose into 4 levels. 128 subjects of the 526 were missing anesthesia time variables and had opioid dose calculated using either OR or IR procedure time in hours. Mortality is the main dependent variable, and the outcomes were compared between the 4 dose quartiles at 6 hours post-op, 24 hours post-op, and 30 days post-op**.** Association with opioid dose was evaluated by using the Kruskal-Wallis test for continuous variables, and the Fisher[ENTamp;#8217;s exact test for categorical variables. The generalized linear mixed model (GLMM) was used to assess the impact of opioid dose on mortality outcome, controlling for demographics, PROPPR treatment and disease severity. The fixed effect factors included treatment arm, age, gender, race, ethnicity, ISS, and opioid dose. Site was included in the GLMM as the random effect factor. We used quartiles to categorize all continuous variables.
Results: The patient demographics for each quartile are listed in table 1. The lowest quartile opioid dose group were older, more severely injured, more frequently female, and white. In the generalized linear mixed model, mortality outcomes comparing quartiles 2, 3, and 4 to quartile 1, are noted in table 2. The decreased odds of mortality in opioid dose quartiles 2, 3, and 4, compared to the low dose quartile 1 was statistically significant for all 3 time points.
Conclusion: Adjusted for age, gender, injury severity score, PROPPR treatment arm, race, ethnicity, and site, these findings suggest that higher dose opioids may be protective for mortality in a severely injured trauma population. However, because this was a post-hoc analysis and opioid dose was not a randomized therapeutic intervention, uncontrolled confounding will only be resolved with future studies focusing on opioids as the exposure in prospective analyses. Nevertheless, this finding in a large, multi-institutional study may be relevant to clinical practice at level 1 trauma centers.

References: Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma: The PROPPR Randomized Clinical Trial. JAMA. 2015;313(5):471-482. doi:10.1001/jama.2015.12
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Figure 1

Patient Characteristics by Opioid Dose (mme) (N=526)					
	Dose Quartile 1 (0-2.54)	Dose Quartile 2 (2.55-7.39)	Dose Quartile 3 (7.4-14.0)	Dose Quartile 4 (14-103)	p-values
N	132	132	130	132	
Age, median (IQR)	40 (27 to 55.5)	32 (24 to 46)	30.5 (23 to 46)	32 (23 to 43)	0.003
Male sex, No. (%)	100 (76)	103 (78)	106 (82)	117 (89)	0.043
Race, No. (%)					0.021
White	91 (68.9)	80 (60.6)	73 (56.2)	76 (57.6)	
Black	35 (26.5)	35 (26.5)	43 (33.1)	50 (37.9)	
Other	6 (4.6)	17 (12.9)	14 (10.8)	6 (4.6)	
Hispanic ethnicity, No. (%)	25 (18.9)	25 (18.9)	28 (21.5)	16 (12.1)	0.22
Treatment group, No. (%)					0.26
1:1:1	61 (46.2)	76 (57.6)	63 (48.5)	70 (53.0)	
1:1:2	71 (53.8)	56 (42.4)	67 (51.5)	62 (47.0)	
Injury Severity Score, median (IQR)	33 (22 to 43)	26 (17.5 to 41)	25 (16 to 34)	25 (16 to 36)	<0.001
Status at 6 hours, No. (%)					<0.001
Alive	94 (71.2)	131 (99.2)	124 (95.4)	129 (97.7)	
Deceased	38 (28.8)	1 (0.8)	6 (4.6)	3 (2.3)	
Status at 24 hours, No. (%)					<0.001
Alive	88 (66.7)	130 (98.5)	124 (95.4)	127 (96.2)	
Deceased	44 (33.3)	2 (1.5)	6 (4.6)	5 (3.8)	
Status at 30 days, No. (%)					<0.001
Alive	71 (53.8)	116 (87.8)	116 (89.2)	120 (90.9)	
Deceased	61 (46.2)	16 (12.1)	14 (10.8)	12 (9.1)	

Table 1. Demographics

Figure 2

	6-hour mortality		24-hour mortality		30-day mortality	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Dose quartile 2 vs. 1	0.02 (0.01 – 0.13)	<0.001	0.02 (0.01 – 0.10)	<0.001	0.13 (0.06 – 0.27)	<0.001
Dose quartile 3 vs. 1	0.12 (0.05 – 0.31)	<0.001	0.09 (0.03 – 0.22)	<0.001	0.14 (0.07 – 0.29)	<0.001
Dose quartile 4 vs. 1	0.05 (0.01 – 0.17)	<0.001	0.06 (0.02 – 0.18)	<0.001	0.11 (0.05 – 0.23)	<0.001

Table 2. Adjusted odds ratios of mortality