Risk of Delirium and Use of Regional Analgesia in Geriatric Trauma Patients with Multiple Rib Fractures

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Abstract

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Objective: To examine the risk of delirium in geriatric trauma patients with rib fractures treated with systemic opioids alone compared to those treated with regional analgesia (RA). **Methods**: Cohort study of patients ≥ 65 years with ≥ 3 rib fractures admitted to Harborview Medical Center from 2011-2016. The primary outcome was delirium positive ICU days. Risk of delirium was estimated using generalized linear mixed models with Poisson distribution and robust standard errors. **Results**: The incidence of delirium in the No RA group was 26% compared to 59% in the RA group. Risk of delirium was 19% higher on ICU day #1 compared to the No RA group (IRR 1.19, 95% CI 0.01, 3.94), and remained higher on ICU day #7 (IRR 1.14, 95% CI 1.02, 1.27). **Conclusions**: Limitations of this study prevent clear interpretation of the results, and further studies are needed to assess the association of delirium and RA in geriatric patients with multiple rib fractures.

DELIRIUM AND USE OF REGIONAL ANALGESIA IN GERIATRIC TRAUMA PATIENTS WITH MULTIPLE RIB FRACTURES

INTRODUCTION

With advances in medical technology, in many parts of the world adults are living longer and enjoying more active lifestyles than their predecessors. People 65 years and older will comprise 20% of the U.S. population by 2030, portending substantial growth of geriatric patients within the trauma population.[1] Blunt thoracic injury is common in older adults, resulting in rib fractures in at least 10% of patients.[2,3] Elderly patients with rib fractures have been shown to have a high incidence of pulmonary complications, longer ICU and hospital length of stay, and in-patient mortality up to 19%.[4-7] This increasingly prevalent and high-risk patient population can benefit from a multidisciplinary, geriatric-centric approach to optimize outcomes after traumatic injury.[8-12]

The cornerstone of rib fracture management at any age is adequate analgesia in order to facilitate participation in respiratory physiotherapy and early mobilization.[13] However, the ideal approach to pain management for rib fractures has been debated in recent years. Thoracic regional analgesia (RA) provides targeted pain relief with continuous infusion of local anesthetic into the epidural space (epidural catheters), or paravertebral space (paravertebral catheters), by blocking the spinal nerves and preganglionic/postganglionic sympathetic nerves. Alternatively, systemic opioid therapy is readily available, less resource intensive, and has fewer contraindications. The Eastern Association for the Surgery of Trauma and the Trauma Anesthesiology Society recently published guidelines for pain management in blunt thoracic trauma, in which the authors conditionally recommend epidural analgesia over non-regional modalities of pain control.[13] In

light of the paucity of data specific to older adults, the authors noted that older age may in fact presage greater benefit in regards to certain outcomes with use of RA.

Delirium, the clinical manifestation of acute brain failure, is an outcome especially relevant in geriatric trauma patients. Delirium is present in thirty percent of older hospitalized adults, and is associated with poor short and long-term outcomes including functional decline, sustained cognitive impairment, increased hospital length of stay, and higher mortality.[14-17] Delirium has been identified as a modifiable factor that is associated with precipitating risks including, but not limited to, uncontrolled pain, systemic opioid administration, and benzodiazepine use.[18-21] Although it is speculated that RA use decreases the incidence of delirium by controlling pain, decreasing need for systemic opioid and benzodiazepine use, the relationship between RA and delirium has not been examined.[22,23]

The purpose of this study was to evaluate the association between RA use and risk of delirium in geriatric trauma patients with multiple rib fractures. We hypothesized that RA use in older adults with three or more rib fractures would be associated with lower risk of delirium and reduced pulmonary complications.

METHODS

Study Design and Patient Population

This was a retrospective cohort study of patients admitted to Harborview Medical Center (HMC), a regional Level I trauma center in Seattle, WA from 1/1/2011-6/30/2016. Inclusion criteria were patients sixty-five years and older with three or more rib fractures, blunt trauma

mechanism, and admission to the trauma Intensive Care Unit (ICU). Exclusion criteria included significant head injury, as defined by abbreviated injury scale (AIS) ≥3, significant spine injury (AIS ≥3), history of dementia, and death within 24-hours of admission. Because three or more rib fractures in patients sixty-five years and older is a known risk factor for increased mortality, these patients meet criteria for automatic trauma ICU admission per institutional policy.[24]

Patient demographics, trauma-specific data, and hospital outcomes were collected from the HMC trauma registry. ICU-specific data, including nursing assessments and medication administration records, were extracted from the electronic health record using the commercially available Amalga Unified Intelligence System™ (Amalga).[25] Chart review was performed to collect data from the Acute Pain Service consultation documentation, as well as from operative reports. Data collection was limited to the days the patient was treated in the ICU, up until ICU day number thirty.

Patients were divided into two groups based on their administered pain regimen. Patients who received Acute Pain Service consultation with thoracic RA, either epidural or paravertebral catheters, were defined as the "RA" group. Patients within the RA group also may have received systemic opioids and non-opioid pain medications in addition to RA. Patients who received pain management exclusively with systemic opioids and non-opioid pain medications were categorized as the "No RA" group. Date of admission to the ICU was considered No RA ICU day #1, and date of RA placement was considered Post-Catheter ICU day #1. All patients admitted to HMC were initiated on a rib fracture protocol, which includes multimodal systemic analgesia, aggressive pulmonary therapy with serial monitoring of PIC scores (pain, incentive

capacity, cough), and early mobilization.[26] Clinical criteria for early consultation to the Acute Pain Service (within the first eight hours of admission) included the following criteria: 1) Total PIC score of <4 or 1 in any of the three categories, 2) Pain that was limiting the patient's recovery, 3) Trial of multimodal systemic therapy with suboptimal pain control.

Outcomes

The primary outcome was risk of delirium during ICU stay, assessed using the Confusion Assessment Method for the ICU (CAM-ICU).[27] Routine documentation of CAM-ICU assessments performed by nursing staff each shift was mandatory in the trauma ICU starting in 2011. For each assessment, the patient was identified as either: 1) delirious (CAM+), 2) not delirious (CAM-), or 3) unable to assess. For the purposes of this study, an ICU day was considered "delirium positive" if at least one of the CAM-ICU assessments performed during a 24-hour period (12:00am – 11:59pm) was positive for delirium (CAM+). CAM assessments were not routinely performed by nursing staff outside of the ICU, thus limiting the scope of the study to the ICU admission.

Secondary outcomes included respiratory complications (pneumonia, empyema, unexpected intubation, duration of mechanical ventilation), thrombotic complications (deep venous thrombosis, pulmonary embolism), and hospital outcomes (ICU and hospital length of stay, inpatient mortality, discharge disposition). Additional comparisons were made for ICU outcomes including agitation/sedation assessed using the Richmond Agitation-Sedation Scale (RASS), maximum daily pain scores using a Verbal Descriptor Scale (none-mild, moderate-severe), and

daily Morphine Equivalent Dose (MED).[28] A RASS other than zero was considered abnormal in this study.

Statistical Analysis

The Washington Agency of Medical Directors' Group web-based opioid dose calculator was used to convert all opioids into MEDs.[29] Dates in which patients received continuous opioid infusions as a component of comfort-focused care at the end-of-life were excluded from the MED calculation. Medication administration data for Acetaminophen, Ketorolac, Ibuprofen, Tramadol, Gabapentin, Lorazepam, Midazolam, Haloperidol, and Quetiapine was compared between the study groups. IV Midazolam doses were converted into oral Lorazepam doses to assess daily benzodiazepine usage.

Univariate statistics were used to compare patient demographics, trauma-specific data, and hospital outcomes for the two study groups. Differences between treatment groups were determined with the chi-square test for dichotomous variables, and the Student-t test for continuous variables. Delirium, agitation/sedation, and pain incident rate ratios (IRR), and MED mean differences (MD) with 95% confidence intervals (95% CI) were estimated using generalized linear mixed models with Poisson distribution and robust standard errors. This model was used to examine the risk of these outcomes in the Post-Catheter group compared to the No RA group because it takes into account change over time in the ICU. Multivariable models included covariates that were determined a priori for age, sex, race, ethnicity, maximum chest AIS, complications, and comorbidities. Primary and secondary outcomes were examined in

multivariate models. All statistical analyses were performed using Stata software v 13.0 (StataCorp, College Station, TX).

RESULTS

Patient Characteristics

There were 6,350 geriatric trauma patients admitted to HMC from 2011 through July 2016, 3,514 of whom were admitted to the trauma ICU. The study cohort consisted of 144 patients who were identified as potential candidates for RA based on study inclusion and exclusion criteria. The Acute Pain Service provided consultation on 54 (38%) patients. Their services included an attempt to optimize the current pain regimen, determination of eligibility for RA, placement of RA catheter, and ongoing management of the entire pain regimen (including systemic opioids, non-opioid pain medications, and RA). Out of the entire patient cohort, 27 (19%) received thoracic RA while 117 (81%) received a systemic opioid-based pain regimen. Of the patients who received RA, 14 (52%) received epidural catheters and 13 (48%) received paravertebral catheters (Figure 1). The median time from hospital admission to RA placement and initiation was 2 days (IQR 2, 4). Within the group of 27 patients who were evaluated by the Acute Pain Service and did not receive RA, 17 (63%) were determined to have adequate pain control without RA, 4 (15%) had a coagulopathy, 4 (15%) had other peripheral nerve catheters, 1 (4%) was not near extubation, and 1 (4%) had a failed attempt at RA placement.

The RA and No RA groups were comparable for age, sex, race, mechanism of injury, body mass index, and comorbidities (Table 1). Injury characteristics, including Injury Severity Score (ISS) and chest AIS, were similar between the groups. In general, patients who received RA had more

complicated chest trauma with more hemopneumothoraces (33% vs. 15%, p= 0.031), thoracostomy tube placement (33% vs. 14%, p=0.015), flail segment (26% vs. 9%, p=0.019), and need for mechanical ventilation (67% vs. 24%, $p < 0.001$).

Unadjusted Outcomes

Table 2 demonstrates the unadjusted primary and secondary outcomes for the two cohorts. The overall incidence of delirium in this study was 32%, with a higher proportion of the RA group having at least one CAM positive assessment compared to the No RA group (59% vs. 26%, p=0.020). The unadjusted rate of complications including pneumonia, empyema, aspiration, pulmonary embolism, and deep venous thrombosis were not statistically different between the RA and the No RA groups. Unexpected intubation at any point during the hospitalization was more common in the RA group (11% vs. 3%, p=0.045). ICU and hospital length of stay were longer for the RA group (10 vs. 3 days, $p < 0.001$ and 14 vs. 7 days, $p < 0.001$). Discharge disposition, including to the hospital morgue, was not different between the groups. Overall in-hospital mortality in this study was 7%.

Table 3 shows the average daily dosage of analgesic and sedative medications for the two groups. Median daily MED (15 vs. 10, p=0.024), Acetaminophen doses (3g vs. 2g, $p < 0.001$), and Ketorolac doses (45mg vs. 26mg, p=0.014) were higher for the RA group. Median daily LED (1mg vs. 2mg, $p < 0.001$), and Quetiapine doses (50mg vs. 63mg, p=0.001) were lower for the RA group. Median daily doses of Ibuprofen, Tramadol, Gabapentin, and Haloperidol were not appreciably different between the study groups.

Multivariable Analysis of Outcome Parameters

Table 4 demonstrates the risk of unadjusted and adjusted outcomes over time in the Post-Catheter group compared to the No RA group. The risk of delirium in the Post-Catheter group was higher compared to the No RA group on ICU day #1 (IRR 1.19, 95% CI 0.01, 3.94) and decreased slightly by ICU day #7 (IRR 1.14, 95% CI 1.02, 1.27). Similarly, the risk of agitation /sedation in the Post-Catheter group is higher compared to the No RA group on ICU day #1 (IRR 1.12, 95% CI 0.94, 1.31) and decreased over time to a lower risk than the No RA group on ICU day #7 (IRR 1.02 , 95% CI 0.87, 1.19). The risk of moderate-severe pain was lower in the Post-Catheter group on ICU day #1 (IRR 0.87, 95% CI 0.73, 1.02) and increased over time to a higher risk than the No RA group on ICU day #7 (IRR 1.01, 95% CI 0.84, 1.21). Morphine equivalent doses were higher in the Post-Catheter group compared to the No RA group on ICU day #1 (MD 4.23 (95% CI -4.58, 13.36)) and remained higher over time. There were too few complications within this group to include in the multivariate analysis.

DISCUSSION

This study is the first to examine the association between delirium and RA utilization in patients with rib fractures. The results suggest an increase in the risk of delirium in geriatric patients with severe chest trauma and rib fractures after initiation of RA compared to patients who did not receive RA.

The overall cumulative incidence of delirium in this study was 32%, which is lower than previously reported among trauma patients (35-61%).[18,30,31] This is likely attributable to the exclusion of patients with severe traumatic brain injury and exclusion of history of dementia in

the current study. Before initiation of RA, delirium was more common in the RA group compared to the No RA group. Patients who received RA were more severely injured as evidenced by more frequent flail segment, hemopneumothoraces, chest tube placement, and need for mechanical ventilation, thus predisposing them to delirium. Previous studies of epidural analgesia in patients with rib fractures have demonstrated a similar tendency toward more frequent use of RA in more severely injured patients with longer ICU length of stay.[22,32] Analysis of the unadjusted data in this study suggests a higher incidence of complications in the RA group. However, due to the low number of complications overall, adjustment for other predictors of these outcomes was not performed, and so we are unable to make a conclusion regarding which group suffered more complications.

It is uncertain whether the benefits of RA outweigh the risks associated with the procedure, the added labor intensity (physician and nursing resource utilization for placement, monitoring, and maintenance of RA), and longer length of stay in patients with rib fractures. Duch and Møller performed a systematic review with meta-analysis which included six randomized controlled trials comparing continuous epidural analgesia with other analgesic interventions in patients with rib fractures.[33] The review concluded that there was poor quality and quantity of evidence to support use of epidural analgesia over alternative analgesic interventions. Of note, none of the studies included delirium in the observed outcomes. Cognizant of these limitations, The American College of Critical Care Medicine published guidelines for the management of pain, agitation, and delirium in adult ICU patients in which they make the following two recommendations: “1) We suggest that non-opioid analgesics be considered to decrease the amount of opioids administered (or to eliminate the need for IV opioids altogether) and to

decrease opioid-related side effects (+2C), and 2) We suggest that thoracic epidural analgesia be considered for patients with traumatic rib fractures (+2B)."[17]

Trauma patients pose several limitations to ubiquitous use of thoracic RA including hemodynamic instability, coagulopathy (physiologic and pharmacologic), spinal fractures, and restrictions for optimal positioning for RA placement. Side effects of thoracic epidurals (hypotension, motor nerve blockade), and challenges concerning timing of RA placement (DVT prophylaxis administration, anesthesia provider availability) create barriers to obtaining timely and consistent RA placement at many institutions. Intercostal nerve blocks (ICNB) are used as an alternative non-opioid pain intervention, which can be administered by non-anesthesia providers and carry a lower risk profile compared to epidural and paravertebral catheters.[34] Intermittent ICNB, although effective, requires multiple injections at each rib fracture level (plus one intercostal level above and below) every 4-6 hours with short-acting local anesthetic. Need for repeat injections, risk of pneumothorax, and difficulty of administration for more cephalad fractures (due to obstruction of landmarks by thick musculature and the scapula) limit the utility of this approach in busy trauma centers. Intercostal nerve block catheters have been used to facilitate intermittent dosing without repeated injections.[35,36] Use of long-acting liposomal bupivacaine (extended release formula of bupivacaine designed to allow drug diffusion to occur up to 96 hours after a single administration) has been used for post-surgical pain control by injection into the surgical incision at completion of the operation, and was recently FDA approved for regional anesthesia use via interscalene brachial plexus block.[37] Injection of liposomal bupivacaine into the intercostal space has been described for patients undergoing

thoracic surgery, however, safety and efficacy of use in trauma patients with multiple rib fractures is yet to be reported.[38,39]

It is believed that delirium is preventable in 30-40% of cases, and so the occurrence of delirium is increasingly being used as a quality indicator for hospitalized elderly patients.[40,41] Delirium is also expensive for health care systems, adding an estimated $16,000-$64,000 in additional costs per patient.[42] Consequently, physicians and hospital administrators have a vested interest in preventing delirium beyond avoiding adverse outcomes for their patients. Several groups have taken a systematic approach to risk reduction by implementing delirium protocols.[41,43] These protocols are designed to target the multifactorial etiologies of delirium with a multi-component and interdisciplinary approach. Similarly, Todd et al. reported increased epidural analgesia use, decreased duration of mechanical ventilation, length of stay, and infectious morbidity and mortality after implementation of a multidisciplinary clinical pathway for patients with rib fractures.[11]

The major limitations of this study are the small sample size and the very small number of patients who received RA. Ideally, the analysis would have excluded patients who developed the outcome (delirium) prior to the exposure (RA) in order to assess the association between the two. Additionally, the analysis did not account for confounding by accumulated time spent in the ICU, censoring after discharge from the ICU, or the effect of Acute Pain Service consultation independent of RA utilization. A matched cohort study design would lessen concerns of confounding and censoring by ICU length of stay; however, the current study was unable to employ this approach. Another limitation of the study design was that temporal changes in

baseline pain and delirium risk could not be completely addressed. Comparison of outcomes in the No RA group and the Post-Catheter group using generalized linear mixed models was intended to account for correlation between unbalanced and longitudinal observations.[44] Furthermore, the accuracy of CAM-ICU assessments was lower at the beginning compared to the end of the study, with the proportion of assessments coded as "unable to assess" decreasing steadily each year as CAM-ICU was integrated into the ICU culture. Lastly, although there was an established set of clinical criteria that triggered a consultation to the Acute Pain Service, there was variability in consultation practices depending on the ICU attending physician. There was not an established institutional guideline for patient selection for RA use during the study, resulting in variability in RA utilization based on the Acute Pain Service attending physician.

The limitations of this preliminary study prevent any clear interpretation of its results. Larger studies with a better ability to remove inherent differences between treatment groups will be needed before any firm conclusions can be drawn.

FIGURES / TABLES

FIGURE 1. Regional Analgesia Distribution

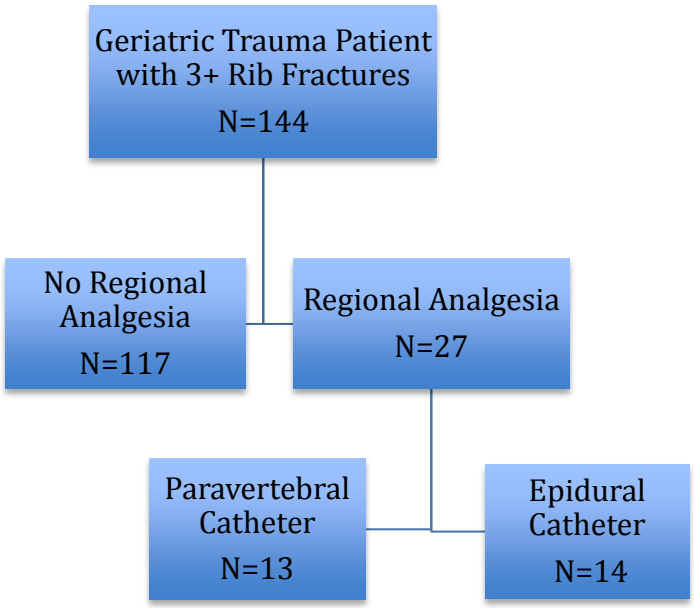

TABLE 1. Patient Demographics and Injury Data

	No Regional Analgesia	Regional Analgesia	
	N=117 (81%)	N=27 (19%)	*p*-value
Age, years*	75 (8)	74 (8)	0.424
Female	43 (37)	7 (26)	0.287
Comorbidities*	2 (1)	2 (1)	0.274
Hypertension	70 (60)	17 (63)	0.764
Stroke	7 (6)	2 (7)	0.783
CHF	13 (11)	2 (7)	0.570
Diabetes	33 (28)	8 (30)	0.882
COPD	13 (11)	5 (19)	0.294
Mechanism of injury			
Fall	39 (33)	8 (29)	
MVC	48 (41)	14 (52)	
Pedestrian struck / bicycle	15 (13)	1 (4)	0.662
Motorcycle	11 (10)	3 (11)	
Other	4 (3)	1 (4)	
ISS**	17 (14, 22)	17 (14, 27)	0.371
<15	35 (30)	7 (26)	
15-24	62 (53)	13 (48)	0.568
>24	20 (17)	7 (26)	
Chest AIS			
2	5 (4)	1 (4)	
3	95 (81)	19 (70)	0.551
4	14 (12)	6 (22)	
5	3 (3)	1 (4)	
Flail segment	11 (9)	7 (26)	0.019
Sternal fracture	18 (15)	6 (22)	0.390
Hemopneumothorax	18 (15)	9 (33)	0.031
Chest tube placement	16 (14)	9 (33)	0.015
Mechanical ventilation	28 (24)	18 (67)	<0.001
Ventilator days**	3 (1, 10)	4 (2, 10)	0.435
Operations			
VATS****	3 (3)	2 (7)	0.215
Thoracotomy	0 (0)	0 (0)	N/A
Rib stabilization	4 (3)	3 (11)	0.094
Laparotomy	3 (3)	1 (4)	0.745

*Mean (SD)

**Median, IQR

***AIS = Abbreviated Injury Score

****VATS = Video-assisted thoracoscopic surgery

TABLE 2. Unadjusted Univariate Analysis of Outcomes

	No Regional Analgesia	Regional Analgesia	
	N=117 (81%)	N=27 (19%)	*p*-value
Delirium	30 (26)	16 (59)	0.020
Complications*	0.6 (1)	1 (1)	0.007
Pneumonia	10 (9)	3 (11)	0.675
Empyema	1 (1)	0 (0)	0.630
Aspiration	2 (2)	2 (7)	0.104
Unexpected intubation	3 (3)	3 (11)	0.045
Pulmonary embolism	1 (1)	0 (0)	NA
Deep venous thrombosis	2 (2)	2 (7)	0.104
ICU LOS**	3 (2, 6)	10 (6, 14)	<0.001
Hospital LOS**	7 (4, 11)	14 (8, 21)	<0.001
Discharge disposition			0.894
Home	49 (42)	9 (33)	
Skilled nursing facility	53 (45)	15 (56)	
Morgue	7 (6)	3 (11)	

Regional Analgesia group includes observations *before and after* regional analgesia initiation
Delirium incidence measured as the number of patients with at least one CAM+ assessment while in the ICU
Discharge disposition sites were collectively compared between the study groups
*Mean (SD)
**Median, IQR

TABLE 3. Average Daily Dosage of Pain and Sedation Medications

	No Regional Analgesia		Regional Analgesia		
	N=117 (81%)		N=27 (19%)		
	ICU Days	Median (IQR)	ICU Days	Median (IQR)	*p*- value
Pain Medications					
Morphine*	463	10 (3, 24)	188	15 (2, 47)	0.024
Acetaminophen (g)	371	2 (1, 3)	169	3 (2, 3)	<0.001
Ketorolac (mg)	20	26 (15, 30)	16	45 (30, 60)	0.014
Ibuprofen (mg)	3	400 (400, 600)	4	500 (400, 600)	0.683
Tramadol (mg)	5	100 (50, 100)	5	75 (75, 100)	0.910
Gabapentin (mg)	100	600 (300, 900)	53	300 (300, 1200)	0.567
Benzodiazepines					
Lorazepam**	43	2 (1, 5)	23	1 (0.5, 1.5)	<0.001
Antipsychotics					
Haloperidol (mg)	33	4 (2, 5)	21	5 (2, 13)	0.205
Quetiapine (mg)	60	63 (50, 100)	37	50 (25, 75)	0.001

*Daily Morphine equivalent dose (oral Morphine)
**Daily Lorazepam equivalent dose (oral Lorazepam)

TABLE 4. Change in Risk of Unadjusted and Adjusted Outcomes in the Post-Catheter Group Compared to the No RA Group

	Time at risk (person days)	Number of events	ICU Day #1 IRR (95% CI)	ICU Day #3 IRR (95% CI)	ICU Day #7 IRR (95% CI)
Delirium					
No RA	596	165	Ref	Ref	Ref
Post-Cath Unadjusted	158	54	1.13 (1.00, 1.29)	1.10 (0.99, 1.25)	1.05 (0.94, 1.19)
Post-Cath Adjusted			1.19 (0.01, 3.94)	1.17 (1.04, 1.34)	1.14 (1.02, 1.27)
Agitation / Sedation					
No RA	596	355	Ref	Ref	Ref
Post-Cath Unadjusted	158	102	1.13 (0.97, 1.35)	1.10 (0.95, 1.28)	1.05 (0.90, 1.22)
Post-Cath Adjusted			1.12 (0.94, 1.31)	1.07 (0.92, 1.24)	1.02 (0.87, 1.19)
Pain					
No RA	596	309	Ref	Ref	Ref
Post-Cath Unadjusted	158	93	0.89 (0.75, 1.01)	0.98 (0.83, 1.15)	1.09 (0.82, 1.48)
Post-Cath Adjusted			0.87 (0.73, 1.02)	0.93 (0.83, 1.05)	1.01 (0.84, 1.21)
Morphine Equivalent Dose			**ICU Day #1 MD (95% CI)**	**ICU Day #3 MD (95% CI)**	**ICU Day #7 MD (95% CI)**
No RA	596	NA	Ref	Ref	Ref
Post-Cath Unadjusted	158	NA	4.39 (-6.18, 14.95)	7.76 (-3.06, 18.58)	12.2 (-7.93, 32.46)
Post-Cath Adjusted			4.23 (-4.58, 13.36)	7.43 (-4.73, 13.18)	11.70 (-8.55, 31.96)

IRR = incident rate ratio

MD = mean difference

Post-Catheter group contains observations starting on the ICU day when regional analgesia was initiated (ICU day#1). Observations that occurred prior to regional analgesia initiation are not included in this analysis.

Delirium assessed with Confusion Assessment Method for the ICU (dichotomized as CAM-ICU positive vs. CAM-ICU negative)

Pain assessed as maximum daily pain score (dichotomized as none-low vs. moderate-severe)

Agitation assessed with RASS = Richmond Agitation Sedation Scale (dichotomized as RASS=0 vs. RASS≠0)

Daily Morphine Equivalent Dose (oral morphine)

Adjustment for age, sex, race/ethnicity, severity of chest injury, comorbidities, complications

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