Multimodal Analgesia and Opioid Use in Critically Ill Trauma Patients

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BACKGROUND: Opioids are the mainstay of pain management in critically ill trauma patients. However, the risks of opioid use mandate a different approach. Multimodal analgesia employs a combination of opioid and nonopioid agents using different mechanisms that have synergistic effects in treating pain. This study examines the effects of multimodal analgesia on the opioid requirements of critically ill trauma patients.

STUDY DESIGN: This was a pre-post cohort study of adult trauma ICU patients before and after implementation of a multimodal pain management order set. Patients were excluded if their hospital stay was less than 5 days, head Abbreviated Injury Scale score was greater than 1, or pre-injury medications included methadone or buprenorphine. The total oral morphine equivalent (OME) dose was calculated for each 24-hour period on days 2 through 5 of admission and the last 24 hours before discharge using standardized ratios. The primary endpoint was cumulative OME doses over the second through fifth days of admission.

RESULTS: There were 65 patients in the pre-group and 62 in the post-group. Median cumulative OME dose was significantly lower in the post-group (125.6 mg, interquartile range [IQR] 45.0 to 415.0 mg) compared with the pre-group (481.5 mg, IQR 174.8 to 881.3 mg), $p < 0.001$. Patients who received 3 or more multimodal agents had a lower cumulative OME dose (116.3 mg, IQR 52.5 to 496.5 mg) compared with those who were on 1 to 2 multimodal agents (363 mg, IQR 115.5 to 743 mg) or 0 multimodal agents (479 mg, IQR 185 to 736.5 mg), $p = 0.024$. There were no differences between pre-group and post-group mean pain scores on hospital day 5 (4.48 ± 0.34 vs 3.50 ± 0.38, $p = 0.058$) or at hospital discharge (3.43 ± 0.34 vs 3.56 ± 0.32, $p = 0.789$).

CONCLUSIONS: Implementation of a multimodal pain management strategy significantly reduced opioid use in critically ill trauma patients without compromising patient comfort. (J Am Coll Surg 2019;228:769–775. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Critically ill trauma patients commonly experience acute pain from their injuries, procedures, and routine care performed while in the ICU. Recent guidelines recommend that intravenous opioids be considered as first-line treatment for non-neuropathic pain in critically ill patients.[1] However, there are both short-term and long-term risks associated with opioid therapy. In-hospital risks of opioid use include nausea, constipation, sedation, urinary retention, and potentially life-threatening respiratory depression.[2] Additionally, patients may develop opioid tolerance and chronic dependence.[3] Opioid-related death rates have more than tripled over the past 20 years, with a

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Abbreviations and Acronyms
IQR = interquartile range
ISS = Injury Severity Scale
LOS = length of stay
OME = oral morphine equivalent
SOFA = sequential organ failure assessment

large proportion of these deaths related to prescribed opioids.[4,5] Collectively, these risks mandate a different approach for pain management in critically ill trauma patients.

Multimodal analgesia uses a combination of opioid and nonopioid agents with different mechanisms that have synergistic effects in treating pain.[6] This approach aims to limit opioid exposure and the subsequent risks, without sacrificing patient comfort or impeding rehabilitation. Recent literature suggests that multimodal pain management is effective in other patient populations, but this strategy has not been studied in critically ill trauma patients.[7-9] This study examines the effects of implementing a multimodal pain management order set on the opioid requirements of critically ill trauma patients. We hypothesized that a multimodal approach to pain control in these patients would decrease overall opioid use, measured as daily oral morphine equivalent (OME) doses.

METHODS

This investigation was designed as a retrospective pre-post cohort study of critically injured trauma patients admitted to the ICU at an academic level 1 trauma center before and after implementation of a multimodal pain management order set. The pre- and post-groups included all consecutively admitted trauma service patients from September to December in 2015 and 2017, respectively. Patients from 2016 were not included because the order set was under development, and multimodal analgesia use was variable among trauma surgeons during this period. Patients were excluded if their hospital stay was less than 5 days, head Abbreviated Injury Scale score was greater than 1, or pre-injury home medications included methadone or buprenorphine. Patients were identified by querying our institution's prospectively collected trauma registry (TraumaOne, Lancet Technology Incorporated). We designed this study in reference to the standards described in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies.[10] The Institutional Review Board approved this study.

Data for each patient were extracted from the trauma registry and manual chart review in the electronic medical record (Epic, Epic Systems Corporation). Demographic data included age, sex, injury type and mechanism, Injury Severity Score (ISS), sequential organ failure assessment (SOFA) score, and opioid use before admission. All opioid doses were recorded for each 24-hour period on the second through fifth days of admission and the last 24 hours before discharge. For comparison purposes, opioids were converted to equianalgesic OME doses using standardized ratios from the opioid conversion table used at our institution (eTable 1).

Multimodal analgesic medications were recorded as given or not given on the second through fifth days of admission and the last 24 hours before discharge, but specific doses were not documented. Multimodal analgesic medications were defined as the agents included in our institution's multimodal pain management order set, with scheduled acetaminophen as the default selected agent. The order set also incorporates various other pharmacologic modalities including nonsteroidal anti-inflammatory drugs (ketorolac, ibuprofen, celecoxib), drugs targeting neuropathic pain (gabapentin), muscle relaxant agents (methocarbamol, baclofen, diazepam, cyclobenzaprine), topical anesthetics (lidocaine patches), and local anesthetics (ropivacaine nerve blocks). For each of the modalities, standardized dosing and agent selection recommendations for age and special populations are included in the order set (eAppendix 1, online only).

Data regarding pain control were extracted for day 5 of admission and the 24 hours before discharge as snapshots to gauge overall pain control during the study period. Pain scores were recorded on the Behavioral Pain Scale.[11] Scores were documented every 4 hours and were averaged for each of the extracted 24-hour periods. Discharge prescription OME doses were recorded as the maximum possible daily dose a patient could receive based on his or her discharge prescription.

The primary endpoint was cumulative OME doses over the second through fifth days of admission. Secondary endpoints included OME doses stratified by number of multimodal analgesic medications used, pain scores, ICU length of stay (LOS), hospital LOS, and coma- and delirium-free days. Coma- and delirium-free days were defined as the number of days with a Richmond Agitation Sedation Scale (RASS) score between -1 and +4 and a negative Confusion Assessment Method for the ICU (CAM-ICU) score within the first 7 days of hospital admission. Those who died were automatically given a score of 0. Naloxone use was considered a safety endpoint.

In an a priori power calculation, it was determined that 60 patients per group were necessary to detect a 25% change in the primary outcome with 80% power. Data

were evaluated for normality using tests for skewness and kurtosis. If normally distributed, continuous data were compared using a 2-tailed *t*-test and were reported as mean ± standard error of the mean. If not normally distributed, continuous data were compared using a Wilcoxon rank-sum test and were reported as the median and interquartile range. Categorical data were compared using a chi-square test. A value of $p < 0.05$ was considered significant. Analysis with a linear mixed effects model was performed to control for repeated measures and differences in baseline characteristics between groups. All statistical analysis was performed using commercially available statistics software (Stata 14.2, StataCorp LLC).

RESULTS

During the study period, 2,043 patients were admitted to the ICU on the trauma service and screened for exclusion criteria (Fig. 1). There were 65 patients in the pre-group and 62 patients in the post-group included for analysis. There were no differences between groups in sex, mortality, ISS, SOFA score, pre-admission opioid status, or number of operations within the initial 5 days of hospitalization (Table 1). The mean age of patients in the post-group was older compared with those in the pre-group (59.6 ± 23.1 years vs 48.4 ± 22.5 years, $p = 0.006$). A higher proportion of patients in the post-group suffered blunt trauma compared with the pre-group (90% vs 65%, $p < 0.001$). The 3 most common mechanisms of injury included gunshot wounds, motor vehicle collisions, and falls (eTable 2).

The cumulative OME dose was significantly lower in the post-group (125.6 mg, IQR 45.0 to 415.0 mg) compared with the pre-group (481.5 mg, IQR 174.8 to 881.3 mg), $p < 0.001$. For each day on days 2 through 5, median daily OME doses were significantly lower in the post-group compared with the pre-group (Fig. 2). In the 24 hours before discharge, there was no difference between the OME dose in the post-group compared with that in the pre-group (30.0 mg, IQR 0 to 82.5 mg vs 46.9 mg, IQR 11.3 to 105.0 mg, respectively, $p = 0.067$). Patients who received 3 or more multimodal agents had a lower cumulative OME dose (116.3 mg, IQR 52.5 to 496.5 mg) compared with those who were on 1 to 2 multimodal agents (363 mg, IQR115.5 to 743 mg) or 0 multimodal agents (479 mg, IQR 185 to 736.5 mg), $p = 0.024$ (Fig. 3). In the linear mixed effects model that included age and injury type, the reduction of opioid exposure in the post-group remained significant ($p < 0.001$).

There were no differences between pre-group and post-group mean pain scores on hospital day 5 (4.48 ± 0.34 vs 3.50 ± 0.38, $p = 0.058$) or at hospital discharge (3.43 ± 0.34 vs 3.56 ± 0.32, $p = 0.789$). Other secondary outcomes including ICU LOS, hospital LOS, and coma- and delirium-free days did not differ between groups (Table 2). One patient in the pre-group and 2 patients in the post-group received a dose of naloxone.

All patients in the post-group received at least 1 multimodal analgesic medication, with 84% receiving 2 or more agents; whereas, only 30% of patients in the pre-group received 2 or more agents. More patients in the

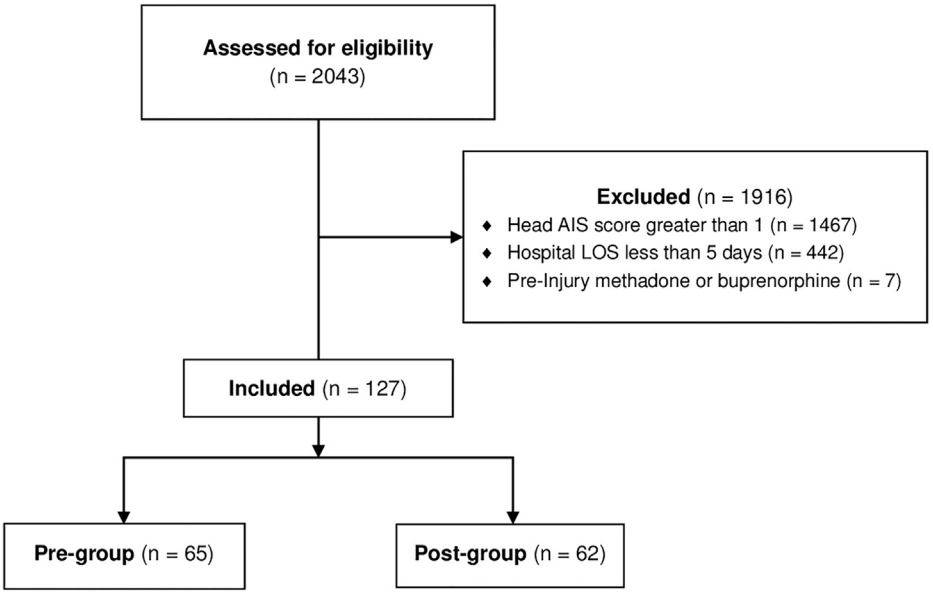

Figure 1. Study design. AIS, Abbreviated Injury Scale; LOS, length of stay.

Table 1. Baseline Demographic and Clinical Characteristics of Critically Ill Trauma Patients

Characteristic	Pre-group (n = 65)	Post-group (n = 62)	p Value
Age, y, mean ± SD	48.4 ± 22.5	59.6 ± 23.1	0.006
Male sex, n (%)	44 (68)	41 (66)	0.85
Injury type, n (%)			<0.001
Blunt	42 (65)	56 (90)	
Penetrating	23 (35)	6 (10)	
Injury Severity Score, mean ± SD	14.3 ± 9.9	13.3 ± 10.0	0.58
SOFA Score, mean ± SD	4.2 ± 0.4	4.8 ± 0.4	0.29
Died, n (%)	3 (5)	1 (2)	0.33
Opioid status before admission, n (%)			0.55
None	46 (71)	47 (76)	
Yes	6 (9)	7 (11)	
Unknown	13 (20)	8 (13)	
Operation during initial 120 h of admission, n, mean ± SD	1.0 ± 1.0	1.0 ± 1.2	0.74

SOFA, sequential organ failure assessment.

post-group received scheduled acetaminophen (95% vs 32%, p < 0.001), gabapentin (61% vs 18%, p < 0.001), lidocaine patches (55% vs 9%, p < 0.001), and methocarbamol (13% vs 0%, p = 0.003) compared with patients in the pre-group. There were no differences between groups in the use of nonsteroidal anti-inflammatory drugs, diazepam, cyclobenzaprine, baclofen, or ropivacaine nerve blocks (Table 3).

Of the 127 patients included in the study, 77 patients (60%) were prescribed a higher daily dose of opioids on discharge than they required in the preceding 24 hours (Fig. 4.). Similarly, of the 29 patients in the study who received no opioids in the 24 hours before discharge, 12 of these patients received an outpatient prescription for an opioid.

DISCUSSION

In critically ill trauma patients at our institution, implementation of a multimodal pain management order set reduced the cumulative opioid dose received. This relationship remained significant even after adjusting for differences in age and type of injury. Furthermore, the reduction in opioid dose did not compromise patient comfort; pain scores were not different after implementation of the multimodal pain management strategy. Multimodal analgesia is a potential tool for reducing opioid exposure in this patient population.

The OME dose reduction with multimodal analgesia we observed is similar to those in previous studies in other patient populations. A recent, randomized controlled trial demonstrated a reduction of total OME dose from 157.7 mg to 67.6 mg with a multimodal analgesic approach after elective orthopaedic surgery.[8] Dorr and colleagues[12] further showed that a multimodal oral pain medication protocol could effectively control postoperative pain and minimize complications associated with parenteral

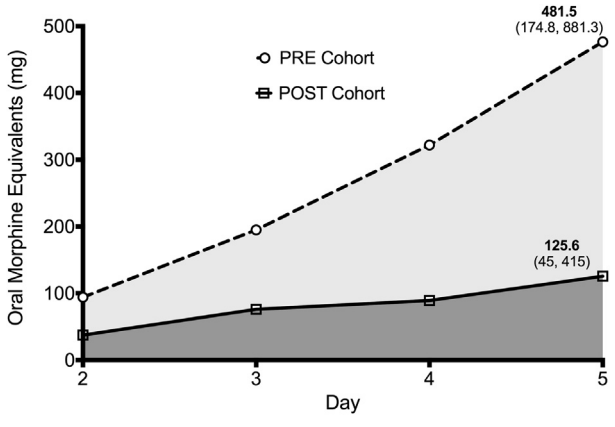

Figure 2. Cumulative opioid exposure.

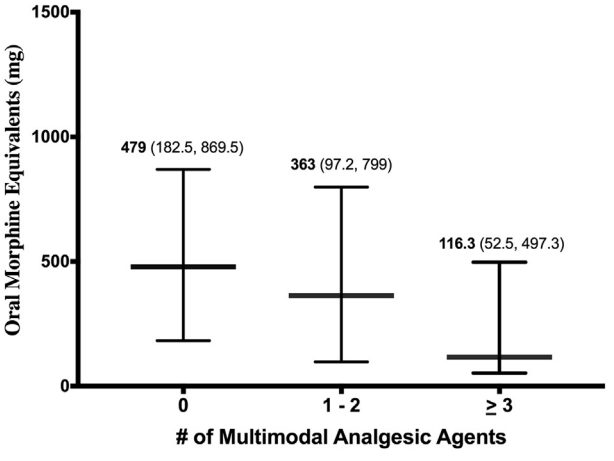

Figure 3. Cumulative opioid exposure vs number of multimodal agents.

Table 2. Secondary Outcomes of Critically Ill Trauma Patients Before and After Implementation of a Multimodal Pain Management Order Set

Outcome	Pre-group (n = 65), mean ± SD	Post-group (n = 62), mean ± SD	p Value
Pain score at day 5	4.5 ± 0.3	3.5 ± 0.4	0.06
Pain score at hospital discharge	3.4 ± 0.3	3.6 ± 0.3	0.79
ICU LOS, h	103.6 ± 88.7	98.5 ± 79.6	0.75
Hospital LOS, h	346.6 ± 55.0	271.1 ± 29.3	0.21
Coma- and delirium-free days	5.4 ± 0.3	5.9 ± 0.2	0.17

LOS, length of stay.

narcotics after total knee arthroplasty. Although data in trauma patients are limited, Koehler and associates[7] showed that a multimodal soft tissue injection of ropivicaine, epinephrine, and morphine decreased opioid use after surgery for traumatic femur fractures, although that study was limited to the immediate postoperative period. Our study shows that the principle of multimodal analgesia is also applicable to the population of severely injured trauma patients, supporting recent updates to guidelines that emphasize a multimodal approach to pain management in ICU patients.[13] Future research should focus on determining what components of this approach are best suited to different patient populations and injury patterns.

Opioid use during the first day of admission was omitted to allow the multimodal analgesic agents time to reach steady state and achieve therapeutic effects. We compared the cumulative OME dose over days 2 through 5 of the patient's hospital stay because this is the period of maximal tissue injury, inflammation, and pain after traumatic injury.[14,15] The use of multimodal analgesia early in the patient's hospital course allows for maximal benefit. In our study, the reduction in OME dose in the 24 hours before discharge did not reach statistical significance. This could reflect a decrease in the favorable effects of multimodal analgesia over the course of treatment. However, this may also just be due to the overall reduction in opioid dose required as patients approach hospital discharge and the small sample size of this study.

Adequate pain control promotes faster rehabilitation, reduces the risk of postoperative complications, and increases patient satisfaction and quality of life.[16-20] Importantly, the reduction in opioid requirements in our study was not accompanied by a compromise in pain control. Pain scores were not different between the 2 groups on hospital day 5 or at discharge. Furthermore, there was a trend toward better pain control in the post-group on hospital day 5, indicating that the synergistic approach offered by a multimodal pain regimen may even improve pain control for trauma patients.

We also observed that many patients were discharged home on higher OME doses than they required within their last 24 hours of hospital stay. Similarly, some patients were discharged with an opioid prescription despite not requiring any opioids in the day before discharge. A recent, large retrospective review observed comparable overprescribing in postoperative patients across a range of surgical specialties, although trauma patients were not included.[21] Our findings suggest that there should be more diligence when prescribing opioids for trauma patients on hospital discharge, just as in other patient populations. Development of a protocol or algorithm may be a useful tool to help provide guidance on appropriate discharge opioid prescriptions. Future research

Table 3. Proportion of Patients Receiving Specific Multimodal Analgesic Medications Before and After Implementation of a Multimodal Pain Management Order Set

Outcome	Pre-group (n = 65), n (%)	Post-group (n = 62), n (%)	p Value
Scheduled acetaminophen	21 (32)	59 (95)	< 0.001
NSAID	10 (15)	14 (23)	0.30
Methocarbamol	0 (0)	8 (13)	0.003
Baclofen	1 (2)	1 (2)	0.97
Diazepam	10 (15)	6 (10)	0.33
Cyclobenzaprine	2 (3)	5 (8)	0.22
Gabapentin	12 (18)	38 (61)	< 0.001
Lidocaine patch	6 (9)	34 (55)	< 0.001
Ropivacaine block	7 (11)	3 (5)	0.21

NSAID, nonsteroidal anti-inflammatory drug.

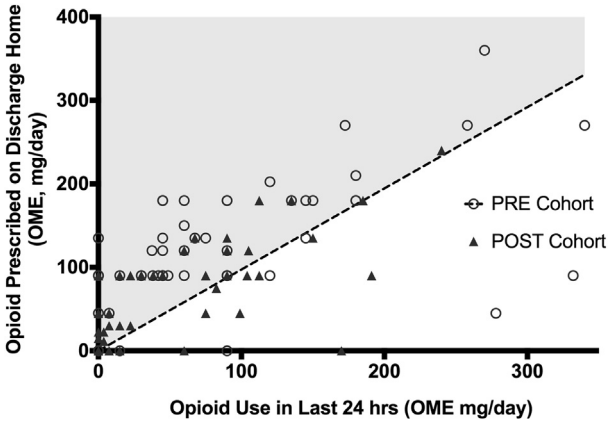

Figure 4. Oral morphine equivalent (OME) required during final 24 hours before discharge compared with prescribed daily OME dose on discharge.

should investigate the ideal pain management strategies for trauma patients at the time of hospital discharge and during subsequent follow-up and rehabilitation.

The opioid epidemic has greatly affected current practice, and opioid abuse awareness has increased between the time periods in this study. This may have affected opioid ordering practices during the study. It is also important to note that the post-group in our study did not overlap with the national intravenous opioid shortage, which began affecting our institution in January 2018. Although the purpose of the order set was to expedite a cultural change of judicious opioid use within our institution, we realize that the order set alone did not institute this change in opioid use. The success of this initiative required close collaboration between the physicians, pharmacists, and nurses at our institution. Expedient and wide implementation relied on education for all ICU providers and staff, support from the critical care attending physicians, buy-in from the critical care nursing team, and continual guidance from the clinical pharmacist.

Scheduled acetaminophen was the workhorse of our multimodal order set because it was the default selection, and this likely explains why nearly all patients in the post-group were on this agent. The order set provides a framework for agent selection, but therapy must be individualized to each patient, with consideration for patient-specific factors. These factors include age, underlying organ dysfunction, injuries, allergies, and medication interactions, which explains the variability in the use of multimodal agents. Careful daily assessments of the type of pain the patient may be experiencing and appropriateness of continued therapy beyond the acute pain period must be considered. Additional research is warranted to determine if there is a point at which multimodal analgesic agents may have a diminished benefit and are no longer indicated after the acute phase of an injury.

As with any single center, observational cohort study, generalizability to other patient populations and hospital systems is limited. The impact of this intervention on opioid use may be especially limited for centers that already widely use multimodal pain management strategies. The decrease in opioid use seen in this study was limited to the patient's hospital stay and does not include data on long-term opioid use. The study did not include children and pregnant women, and therefore, it may be inappropriate to apply these findings to these patient populations. This study did not evaluate the negative effects attributed to opioids, such as nausea, constipation, or urinary retention, due to their inconsistency in reporting in the medical record; however, there was no difference in the use of naloxone for opioid reversal between the 2 groups.

There were significant differences in age and proportion of injury types between the groups, despite including consecutively admitted patients to limit selection bias. Although these baseline differences may have affected opioid requirements, it is unlikely to be the sole explanation for the significant decrease in the post-group. Furthermore, the observed difference in opioid use persisted in a mixed effects model that included age and injury type. We did not specifically perform a subgroup analysis of the penetrating and blunt trauma patients because of the small sample size.

To the best of our knowledge, this is the first study to assess the use of multimodal analgesia in the critically ill trauma population. Additionally, the pre-post study design is a pragmatic approach to evaluate implementation of this intervention. Although small, the study achieved the targeted sample size. We attempted to control for outliers by excluding patients with head injury and patients with a history of methadone or buprenorphine use as pre-injury medication.

CONCLUSIONS

Implementation of an order set was an effective tool to transition practice to a multimodal pain management strategy. As a consequence, the use of multimodal pain management significantly reduced opioid use in critically ill trauma patients without compromising patient comfort.

Author Contributions

Study conception and design: Lee, Cocanour, Duby
Acquisition of data: Hamrick, Lee

Analysis and interpretation of data: Hamrick, Beyer, Lee, Cocanour, Duby
Drafting of manuscript: Hamrick, Beyer, Lee, Cocanour, Duby
Critical revision: Hamrick, Beyer, Lee, Cocanour, Duby

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eTable 1. Equianalgesic Table

Oral	Analgesic	Intravenous
30	Morphine (mg)	10
20	Hydrocodone (mg)	—
20	Oxycodone (mg)	—
10	Oxymorphone (mg)	1
4	Hydromorphone (mg)	1.5
—	Fentanyl (mcg)	0.1
200	Codeine (mg)	—
300	Meperidine (mg)	75

eTable 2. Mechanisms of Injury in the Study Cohort

	Pre-group (n = 65)		Post-group (n = 62)	
Mechanism of injury	**n**	**%**	**n**	**%**
Gunshot wound	14	22	3	5
Motor vehicle collision	9	14	17	27
Fall	19	29	25	40
Stabbing	4	6	2	3
Self-inflicted	5	8	1	2
Bicycle crash	2	3	2	3
Found down	3	5	0	0
Assault	2	3	3	5
Pedestrian hit by car	3	5	2	3
Animal bite	1	2	0	0
Motorcycle crash	1	2	3	5
Other	2	3	4	6