

Acute Longitudinal Pain Trajectories in the Traumatically Injured

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Abstract

The purpose of this study was to determine if in-hospital pain trajectories exist and if certain pain trajectories predict the development of pain in 101 participants at four months post-trauma. The growth mixture model analysis suggested the presence of 5 latent classes, with observed and predicted trajectories. It appears that patients in classes 1 (low initial pain) and 3 (high initial pain dropping fast and staying low) tend to have less pain at 4 months, while patients in Class 5 (high initial pain dropping fast, but rebounding) tend to have more pain at 4 months. This study did not provide definitive evidence that the trajectory of in-hospital pain predicts the development of chronic pain. Unfortunately, the latent slope did not predict pain scores at four months. However, it was found that probability of developing chronic pain measured by the numeric pain score (NPS 0-3=no chronic pain, NPS 4-10=chronic pain) with a discharge NPS of 0-2 is 0.06, 2-4 is 0.29, 4-6 is 0.35, 6-8 is 0.50 and 8-10 are 0.80. Pain must be controlled in the hospital to prevent the development of chronic pain out of the hospital. Clinicians can identify those at risk by reviewing their average pain scores on the day of discharge.

Perspective: This manuscript addresses the issues of pain trajectories that have been previously published in the Journal of Pain. However, this study applied the previously published ideas to the longitudinal development of chronic pain. This is a novel attempt at determining pain trajectories and their relationship to the development of chronic pain.

Keywords: Acute Pain, Chronic Pain, Traumatically Injured, Pain Trajectories, Pain Predictors

Introduction

The incidence of chronic pain in traumatically injured patients one year after injury is as high as 79% [1]. Although high initial pain is a predictor of chronic pain in the trauma [2], it is unknown if there is an acute pain trajectory during the hospital stays that predicts the development of chronic pain at four months post-injury.

Initial pain has been identified in the literature as a predictor for the development of chronic pain [3-9,2]. However, the average

pain score in the first twenty-four hours of admission was not predictive of the development of chronic pain [2]. For those with a high initial pain score, there may be more to the in-hospital pain experience that may contribute to the understanding of how and why certain individuals develop chronic pain and others do not.

Pain trajectories have been developed for acute postoperative pain measurement in a variety of elective post-surgical patients in order to improve the precision of assessment and to identify resolution of pain as an important outcome of pain management in postoperative patients [10,11]. Pain trajectories were identified using initial pain as the intercept and six measures of pain in the postoperative period making up a slope, or change in pain over time. Chapman et al. [12] identified three distinct trajectories of acute postoperative pain through simple linear modeling. These trajectories were;

- Pain that resolves over time,
- Pain that remains constant, or
- Pain that worsens over time.

In another example, [13] found that persistent post-surgical pain in living liver transplant donors was associated with both higher pain level initially postoperative and at day three with a positive slope of worsening pain. The concept of pain trajectory suggests that the slope of the trajectory and not one daily score should be the target of pain control intervention [14]. There are no studies on pain trajectories specifically in trauma patients.

Using pain trajectories for acute pain in traumatically injured patients just as it has been done in postsurgical patients may provide more information about how pain changes in the traumatically injured population. It has been hypothesized that poor acute pain management contributes to the development of chronic pain [15,6]. The persistence of severe, inadequately treated acute pain can lead to anatomic and physiologic changes in the nervous system [16]. However, it is not known if there is a timeline in which this process occurs. Having pain trajectory information may provide some understanding about the conversion from acute to chronic pain. Each of the two studies

on pain trajectory took one point in time each day of the study. However, we believe that using average daily pain scores provides a better assessment of the daily pain experience by incorporating all of the pain scores that are obtained in relation to pain medication, activity, and rest and combining them into one score. Therefore, the aim of this study was to determine acute pain trajectories using average daily pain scores and to determine if certain trajectories predicted chronic pain four month post-injury.

Materials and Methods

This study was a secondary exploratory analysis of a prospective longitudinal study evaluating the development of chronic pain from acute traumatic pain.

Purpose

The purpose of this study was to determine if typical in-hospital pain trajectories exist for this population and if certain pain trajectories predict the development of pain at four months post-trauma. The hypotheses for this study were:

- There are pain trajectories in traumatically injured patients similar to those found with postsurgical patients;
- At least one of these pain trajectories predicts the development of chronic pain at 4 months post trauma. In addition, to remove Injury Severity Score (ISS), a score used to compile the severity of each individual injury in a traumatically injured patient, as a possible co-founder in the pain response, it will be identified that
- The relationship ISS does not correlate with initial pain score and the absolute presence of pain or pain score at four months. Chronic pain in this study is defined as a Numeric Pain Scale (NPS) greater than or equal to four.

Sample

Participants were recruited after admission to the Trauma Surgery Inpatient Service of a 500 bed Midwestern level one trauma center. Patients are transported to this center from the surrounding metropolitan area, as well as from over 30 other counties in two states.

All adult patients admitted from the emergency room to the hospital were evaluated to determine their eligibility for this study. Exclusion criteria includes admission less than 48 hours, a Glasgow Coma Scale (GCS) of less than fifteen by 48 hours after admission, age less than 18 years, and preexisting diagnosed chronic pain that was present at the time of the interview. After consent was obtained, the investigator read the questionnaires to the participant and recorded the answers. The remainder of the questions was completed by the researcher from the chart review. The interview took an average of 15 minutes to complete. Follow up contact was initiated approximately one week prior to four months of the initial interview. The participant was contacted first by phone (one to two attempts) to determine if they continued to have pain related to their injury from four months prior. Once, participants were contacted through phone, and asked all the questions from the questionnaires and the answers were recorded by the interviewer in order (Figure 1). If telephone contact was not made, the participant was sent the questionnaires by mail with a postage paid envelope to complete and send back. Of the 225 participants who completed the initial interview, 101 responded to the four-month follow-up interview, a 55% attrition rate. A post hoc power analysis was completed in the original study using the statistical package PASS because of the low response rate. The analysis determined with a sample size of 100 a logistic regression of a binary response variable (presence of pain) on a continuous, normally distributed variable (initial pain score) achieves 43% power at a 0.05 significance level to detect a change in Probability (Y=1) from the value

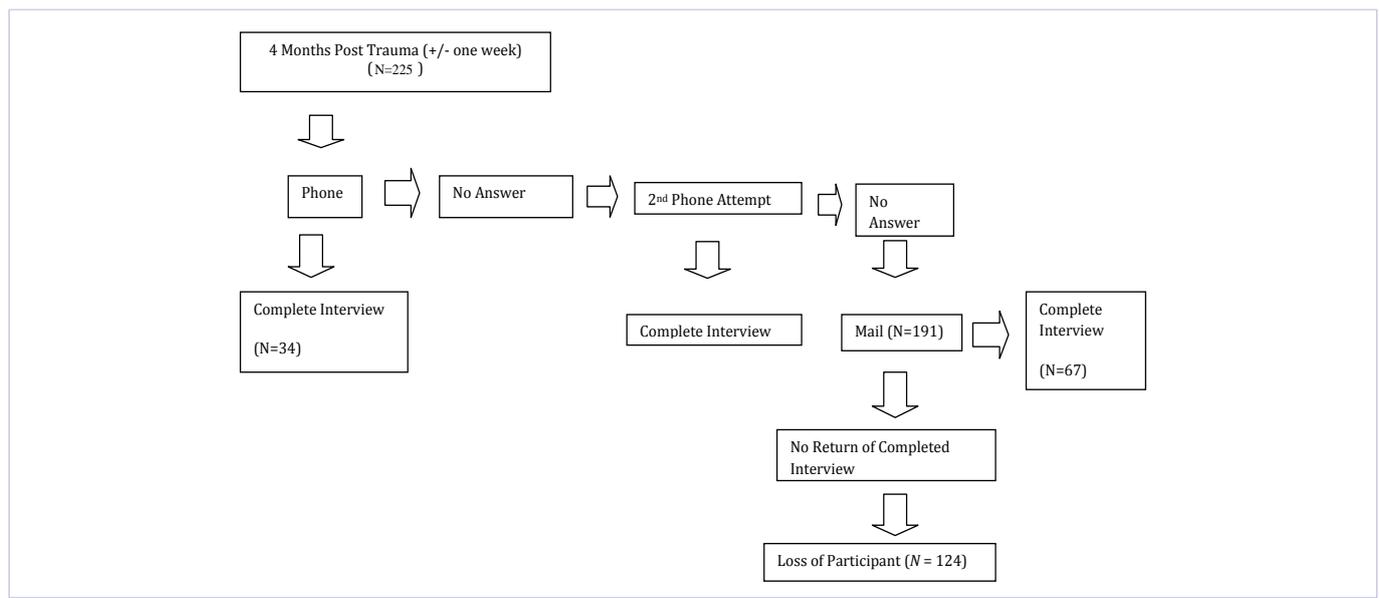


Figure 1: Four Month Interview Timeline.

of 0.500 at the mean of X to 0.412 when X is increased to one standard deviation above the mean. This change corresponds to the odds ratio of 0.700.

Demographic variables were analyzed to determine if there were significant differences between several groups. First, the trauma registry list, the entire population of trauma patients that was evaluated at the Trauma Center during the time of the study and the sample of the initial participants in this study were compared. Next, the study participants were compared between the initial hospitalization and the four months post trauma interviews to determine if those who participated at four months were representative of the initial participant group. Each of these groups was compared based upon age, gender, ethnicity/race, insurance status, and mechanism of injury using independent t-test and chi-square analysis.

Questionnaires

Brief Pain Inventory Short Form (BPI-SF) this questionnaire measures pain intensity through a numeric pain scale (NPS) medication usage, and its interference with daily life. The BPI-SF is a questionnaire that measures pain's intensity and its interference with daily life using an 11 point scale. There are four items measuring pain intensity at the time of the interview and in the previous 24 hours and seven items measuring life interference. The data from this questionnaire was used to describe the chronic pain the patient experienced four months post trauma. Pain interference is typically scored as the mean of the seven interference items when more than 50% of the total items have been completed [17]. Evidence of construct validity using the known group's method was provided by statistically significant chi-square analysis between patient ratings and opioid ($X^2=52.88$) and non-opioid ($X^2=39.40$) medication [18]. Initial validity testing also resulted in significant correlations between worst pain and pain's interference with daily life. For the BPI, Cronbach's alpha reliability ranges from 0.77 to 0.91 and it has been validated in more than 25 different languages for the two-factor structure of severity of pain and impact of pain [19].

Recruitment

Groups:

Trauma Registry: The trauma registry includes all patients admitted to the trauma center.

Trauma surgery inpatient service: This group includes all patients admitted to the trauma center that had a trauma surgery consultation.

Initial interview sample: These were the patients from the trauma surgery inpatient service that met the inclusion criteria for the study (stated under "Sample"), agreed to participate, and completed the initial interview.

Four month sample: These were the patients who completed both the initial interview and the follow-up interview at four months after the initial interview.

For the 101 participants who completed the four month interview, data collected included the ISS from the trauma

registry and the BPI-SF. Also, pain scores for the entire hospital stay were collected and an average was calculated to establish an average daily pain score. The IASP Classification of Chronic Pain, recognizing that a spectrum of time is involved here, opted to distinguish pain as chronic if it persisted for three months or more [20]. Therefore, the timeline of four months was chosen for the determination of the development of chronic pain. The presence of chronic pain at four months was determined to an NPS of greater than four to identify those with moderate or severe pain levels.

The primary pre-planned analysis approach followed the method of Chapman, Donaldson, Davis, & Bradshaw [10] (2011) with simple linear growth curve modeling of the daily pain scores. The average pain scores during the first 4 days of the hospitalization were modeled as a linear function of time, with the latent intercept (at day 1) and latent slope as a predictor of the 4-month pain score. This structural equation model was fitted using the CALIS procedure in SAS 9.3 using the full information maximum likelihood method to incorporate missing observations for the analysis including day 4.

To identify clusters of pain trajectories, in addition to the planned primary analysis, exploratory analysis using growth mixture models was completed using an EM algorithm [21]. The average pain scores during the first 4 days of the hospitalization were classified into latent classes using a quadratic function to model within-class evolution of pain scores. Akaike Information Criterion (AIC) guided the selection of the number of classes. Each patient was classified into the class with the highest posterior probability based on his or her pain trajectory. The 4-month pain scores were then compared between the latent classes as continuous variables using ANOVA, and as binary outcomes of the presence of pain (score>4) using logistic regression. The analyzes were performed using the "flexmix" package in R 2.15.2.

The shape of the discovered latent trajectory classes suggested an additional exploratory analysis investigating the predictive value of pain measured at the day of discharge. Logistic regression was used to evaluate the relationship between this predictor in the presence of pain (score>4) at 4 months as a binary outcome univariately, as well as adjusting for initial pain and day-1 pain as potential alternative predictors.

Analysis of correlation between ISS and initial pain scores, ISS and pain score at 4 months, as well as ISS and the presence of any pain (NPS>0) at 4 months was completed by Pearson's correlation analysis of the 101 patients at the four month interview.

Results

Sample Descriptive Characteristics of Respondent Comparison of groups

The registry and study populations were statistically different in respect to all of the demographics analyzed except ethnicity/race (Table 1). The study participants were younger (mean 43.5 years vs. 47.7 years), more likely to be male (75.4% vs. 69.2%), involved in motor vehicle collisions (27.3% vs. 18.1%), sustained gunshot wounds (12.3% vs. 9.5%), stabbed (10% vs. 4.9%), and

involved in a motorcycle collisions (19.1% vs. 11.9%) than the trauma registry population. The study participants were less likely to be insured (72.9% vs. 78.7%), and to have sustained a fall (17.3% vs. 32.4%) than the trauma registry population.

The initial hospital and 4 months interview groups were statistically different in respect to ethnicity/race and insurance status (Table 2). However, there was no significant difference between the two groups with respect to age, gender and mechanism of injury. The group at four months was more likely to be White (79% vs. 65.2%) and insured (80.2% vs. 72.9%). The four month group was less likely to be Black (17.8% vs. 26.8%) or "other" ethnicities (3% vs. 8%) as compared to the initial interviewees.

Latent linear growth curve analysis of pain scores

Of the 101 participants, 99 had available pain scores on days one through three, and 91 had pain scores on day four. As an increasing number of patients were discharged from the hospital, the number of patients with pain scores dropped off quickly after day four, so those values were not included in the analysis due to concern about informative censoring. Table 3 shows the descriptive statistics of the pain scores at admission, over the first four hospital days, and at 4 months after discharge.

Table 4 shows the results of the latent linear growth curve analysis. The pain scores had an average day 1 latent intercept of 5.65 and decreased an average of 0.37 points per day, with substantial within-patient variability in both parameters. However there is no evidence that the latent slope predicts 4-month pain scores, and only tentative evidence for the latent intercept: patients with 1 point higher value for the projected value on day 1 had 0.44±0.2 point's higher pain score reported at 4 months.

Exploratory growth mixture model of pain scores

The growth mixture model analysis suggested the presence of 5 latent classes, with observed and predicted trajectories shown in figure 2. The description of each component, including the estimated parameters, is shown in table 5. Additionally, the descriptive statistics for the 4-month pain score are also included. It appears that patients in classes 1 (low initial pain) and 3 (high initial pain dropping fast and staying low) tend to have less pain at 4 months, while patients in Class 5 (high initial pain dropping fast, but rebounding) tend to have more pain at 4 months.

Table 1: Comparison of Trauma Population and Study Participants (Registry/Study).

Variable	N		Statistic		df
	Registry	Study	Chi square	F	
Age	1132	225	15.41*		
Gender	1131	224	3.46*		1
Ethnicity/Race	1129	224	5.72		5
Insurance	1131	219	3.50*		1
Mechanism of Injury	1131	221	54.57*		7

*p<.05

Table 2: Comparison of Study Participants: Initial Interview and Four Month Interview.

Variable	N		Statistic		df
	Initial	4 Months	Chi-square	F	
Age	124	101	0.53		
Gender	124	101	1.43		1
Ethnicity/Race	124	101	17.73*		5
Insurance	118	101	4.85*		1
Mechanism of Injury	123	98v	13.89		7

*p<.05

Table 3: Descriptive statistics of the average daily pain scores.

Time	N	Mean (SD)	Range	Percent with score>4
Initial	100	7.05 (3.33)	0 - 10	77%
Day 1	99	5.90 (2.44)	0 - 10	76%
Day 2	99	4.96 (2.21)	0 - 9.7	67%
Day 3	99	4.83 (2.13)	0 - 8.9	66%
Day 4	91	7.74 (2.08)	0 - 8.6	64%
4 months	100	2.99 (2.80)	0 - 10	30%

Table 4: Fitted structural equation coefficients for the linear latent growth curves, estimate (SE).

Outcome		Days 1-4
Pain@4 months	Intercept	0.81 (1.08)
	Latent intercept	0.44 (0.20)*
	Latent slope	0.80 (0.86)
Daily pain scores	Latent intercept	
	Mean	5.65 (0.22)**
	SD	1.78 (0.20)**
	Latent slope	
	Mean	-0.37 (0.09)**
	SD	0.56 (0.11)**
	Latent correlation	
	Slope - intercept	-0.52 (0.13)**

The ANOVA test suggests that the mean 4-month pain scores of the subjects in these classes are different (p=0.035), however, pairwise comparisons using Tukey's HSD identified no statistically different pairs.

Injury Severity Score and Pain

ISS did not correlate with initial pain score in the 101 patients who completed the four month interview (r=-0.031, p=0.757). The average NPS was 7.11 (SD=7.1) and the average ISS was 13.36 (SD=3.3) in this group. The ISS did not correlate with either the absolute presence of pain (yes/no) (r=-0.091, p=0.365) or the NPS at four months post trauma (r= 0.173, p=0.124).

Pain on Discharge

While not an original hypothesis, during the analysis of the trajectory data, it was suggested that an increasing or rebounding

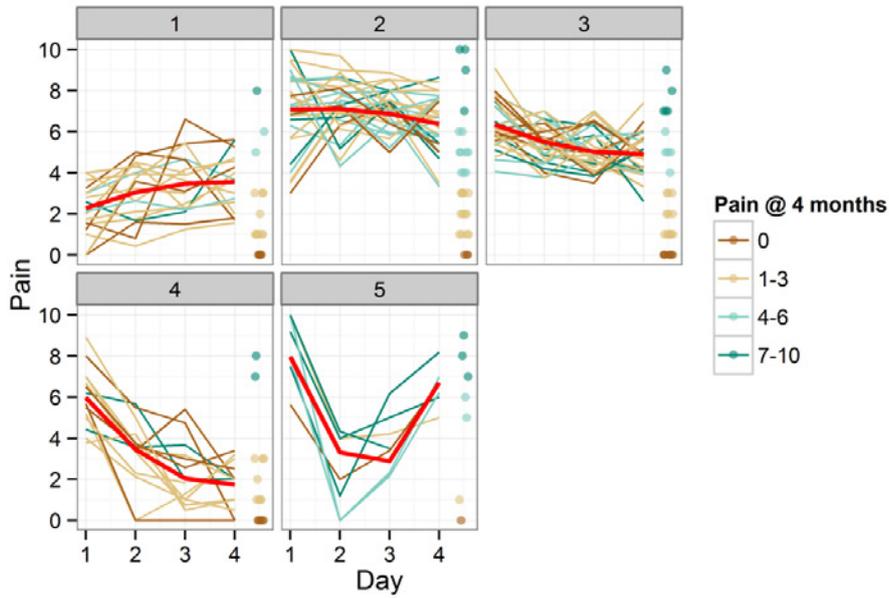


Figure 2: Pain trajectory classes based on Days 1 – 4.

Table 5: Results of the growth mixture model.

Description	Estimated trajectory formula	SD	Pain @ 4 month	
			Mean (SD)	Percent>4
Low pain	$1.19 + 1.27 d - 0.17 d^2$	1.45	2.0 (2.3)	17%
High stable pain	$6.79 + 0.42 d - 0.13 d^2$	1.48	3.7 (2.8)	35%
Slowly decreasing high pain	$7.54 - 1.39 d + 0.18 d^2$	1.07	2.8 (2.8)	30%
Fast decreasing high pain	$9.62 - 4.2 d + 0.56 d^2$	1.51	2.0 (2.5)	13%
Rebounding pain	$16.88 - 11.03 d + 2.12 d^2$	1.72	5.1 (3.4)	71%
	p-value		0.035	0.053

pain trajectory through the hospital stay was associated with pain at four months. Therefore, a full analysis of pain score on the day of discharge was completed to determine if this finding was significant. First, standard multiple regression was used to determine the relationship between initial pain, average pain in the first day of hospitalization, average pain on the day of discharge and pain at four months post-trauma (Figure 3). It is evident that discharge pain score has a more linear correlation. The linear regressions were done with each variable individually and then as multivariate (Table 6). The assumptions of the regression models were evaluated using residual plots. Due to the limited range of the outcome variable in some of the models the tails were less heavy than expected from a normal distribution, but such deviations do not adversely affect the inference.

The probability of developing chronic pain (NPS 0-3=no chronic pain, NPS 4-10=chronic pain) with a discharge NPS of 0-2 is 0.06, NPS 2-4 is 0.29, NPS 4-6 is 0.35, NPS 6-8 is 0.50, and NPS 8-10 are 0.80. It is clear that the discharge score is the strongest predictor by itself ($p=0.00$), or adjusted for the other pain scores ($p=0.00$). In fact, the discharge pain score explains 20% of the

variability in the pain score at four months.

When predicting moderate or severe pain (NPS greater of equal to 4), logistic regression was used. Discharge pain score was the best predictor of the development of chronic pain at four months with an odds ratio of 1.55 ($p=0.00$) (Table 7).

Discussion

Pain trajectories may provide a better assessment of the pain experienced by a traumatically injured patient. It may help to establish a better understanding of who develops chronic pain after a traumatic injury. If it is determined that a certain pain trajectory predicts the development of chronic pain, it will help to identify those at risk in order to provide an aggressive in-hospital treatment plan to try to change that trajectory.

Linear growth curve modeling is appropriate for use in developing postoperative pain trajectories [10-14]. Repeated measures of pain yield better precision. However, in these studies one pain measurement was made per day at a time determined by either the subject or research assistant. No overall pain score or average pain score throughout the day was identified.

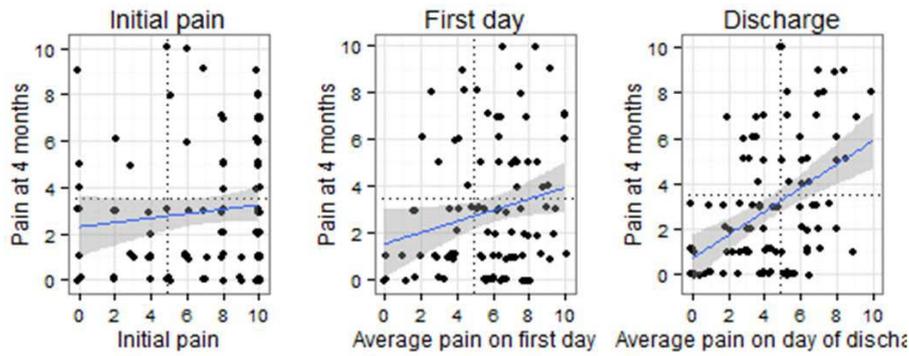


Figure 3: Relationship between initial pain, average day 1 pain, average discharge day pain and pain at four months.

Table 6: The results of individual and multivariate linear regression (The dependent variable was pain at four months).

Predictor	Univariate regression			Multivariable regression		
	Estimate	95% CI	p-value	Estimate	95% CI	p-value
Pain at admission	0.09	-0.07; 0.26	0.272	-0.05	-0.26; 0.15	0.603
Pain on day 1	0.24	0.01; 0.47	0.040	0.15	-0.13; 0.44	0.290
Pain at discharge	0.52	0.31; 0.73	<0.0001	0.50	0.28; 0.72	<0.001

Table 7: Logistic Regression with each predictor individually and then multivariately. (The dependent variable was pain at four months).

Predictor	Univariate regression			Multivariable regression		
	Estimate	95% CI	p-value	Estimate	95% CI	p-value
Pain at admission	0.09	-0.07; 0.26	0.272	-0.05	-0.26; 0.15	0.603
Pain on day 1	0.24	0.01; 0.47	0.040	0.15	-0.13; 0.44	0.290
Pain at discharge	0.52	0.31; 0.73	<0.0001	0.50	0.28; 0.72	<0.001

Therefore, depending on the timing of the pain score, the pain assessment may not give an overall assessment of pain since pain can be affected by activity, the timing of pain medication, and procedural interventions. Using an average pain score for the day can help compensate for these dynamic pain levels. This study attempted to solve some of the issues described in previous studies [10-11] with having one arbitrary pain score described as the “daily pain score”. We averaged the pain scores throughout the day before and after pain medication, and before and after movement and rest. This provided a better score of average pain throughout the day rather than pain at one point in time not controlled for medication administration and movement, two pain altering measures.

This group captured the first four days of the hospital stay to provide a trajectory. This amount of time may have been inadequate to provide a good understanding of how pain changes over time. However, the group was evaluated to ensure that there were no surgeries or procedures that happened within that time period to contribute to a change in the pain trajectory. This group of patients was heterogeneous in their mechanisms and types of injuries. We chose to use this heterogeneous population to determine if there are similarities across all traumatically injured patients. This provides direction and understanding for clinicians who care for patients with varying types of injuries. It focuses on

the pain rather than the injury specifically since the pain score is the focus for treatment. The hospital stay timeframe was chosen because it is a timeframe during recovery that is controlled by the clinicians. Once, the patient is at home, pain management is under full control of the patient and their caregivers. We wanted to understand specifically how our care impacts the pain trajectory.

This study did not provide definitive evidence that the trajectory of in-hospital pain predicts the development of chronic pain. Unfortunately, the latent slope did not predict pain scores at four months. However, the latent intercept showed tentative evidence that increased pain on day one had an association with higher pain at four months with one point higher pain score on day one having 0.44 higher pain score at four months. The presence of 5 latent classes was identified. It appears that patients in classes 1 (low initial pain) and 3 (high initial pain dropping fast and staying low) tended to have less pain at 4 months, while patients in Class 5 (high initial pain dropping fast, but rebounding) tend to have more pain at 4 months. The ANOVA test suggests that the mean 4-month pain scores of the subjects in these classes are different, however pairwise comparisons using Tukey’s HSD showed no statistically different pairs. Despite no prediction of chronic pain, the trend toward high initial and increasing pain in these classes suggest that pain needs to be controlled early and well throughout the hospitalization.

Because increased pain scores were associated with higher pain at four months, the effect of discharge pain scores was evaluated with regression to determine if there was a relationship with those scores and the development of chronic pain. This relationship was not originally identified in the hypotheses because discharge pain has not been identified as a predictor of chronic pain in the literature. However, these conclusions are definitely the most significant and important discoveries from this study. The convincing probabilities that discharge pain scores are possibly more important than both initial and early pain scores. Coupling the predictability of discharge pain scores with the literature supported understanding of the influence of initial pain scores identifies the in-hospital pain experience as a modifiable risk factor for the development of chronic pain post trauma. Pain must be controlled initially and throughout the hospital stay in order to control discharge pain scores. Discharge pain scores can be identified as an outcome for discharge. There are other implications of poor pain control on discharge from the hospital identified such as long-term depression and PTSD [22]. Pain must be controlled in the hospital to prevent the development of chronic pain out of the hospital. Clinicians can identify those at risk by reviewing their average pain scores on the day of discharge.

In future studies, it may be helpful to get more days of pain scores to explore a more longitudinal pain trajectory. There may be more information as time progresses along the recovery period. It may also help to study one mechanism of injury or injury type to provide a more homogeneous study group. With having such a heterogeneous study group, there may have been many co-founders to the pain experience beyond what we were able to identify. One of the major limitations of this study is that, there was 55% loss to follow-up at four months. This could have represented a selection bias.

Disclosures

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