MAST Trial: Multi-modal Analgesic Strategies in Trauma

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Protocol Title:	MAST Trial: Multi-modal Analgesic Strategies in Trauma
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Population:	Adult trauma patients admitted to the Trauma Service at Memorial Hermann Hospital-Texas Medical Center (MHH-TMC)
Number of Sites:	Single center, MHH-TMC
Study Duration:	One year
Subject Duration:	Time while hospitalized

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General Information

The optimal strategy for providing effective and safe pain management after traumatic injury remains unknown. Although opioids have been a mainstay for pain management for decades, they have been increasingly recognized to be related to increased adverse events, increased costs and resource utilization, long-term dependence or addiction, and death. While opioid-minimizing, multi-modal analgesic strategies are promising, there is no high-quality evidence to guide their use or implementation. The proposed project is a randomized comparative effectiveness study of current pain management strategies in acutely injured trauma patients. A parallel group, randomized trial of two different multi-modal, opioid minimizing analgesic strategies will be performed and analyzed using Bayesian statistics.

Background Information

Opioid prescribing practices after traumatic injuries and surgeries are a significant driver of the current opioid epidemic. Over the last two decades, 75% of patients seeking treatment for heroin addiction were introduced to opioids via prescription drugs.[1]

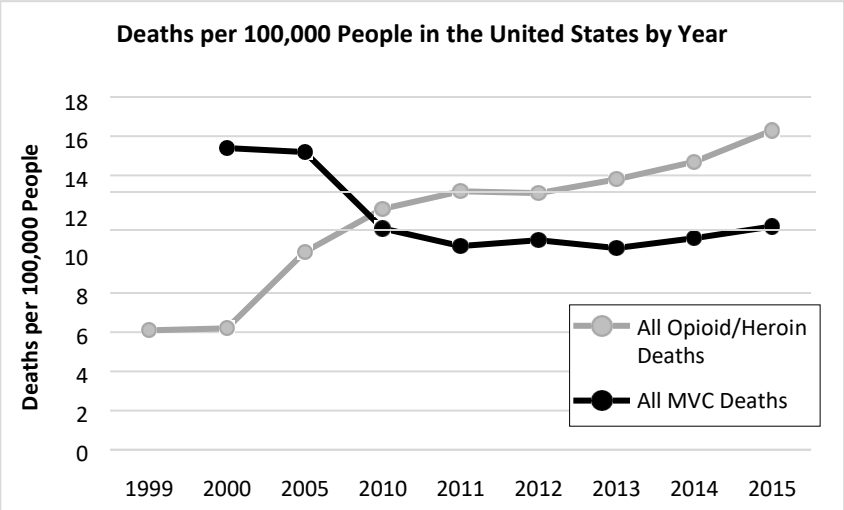


Figure 1: Opioid and heroin-related deaths exceed those due to motor vehicle collisions (MVC). From the Centers for Disease Control and Prevention and Insurance Institute for Highway Safety

In particular, surgeons have a high rate of opioid prescribing (36.5%), second only to pain medicine specialists.[2] The incidence of persistent opioid use in opioid-naïve patients after minor and major surgery is 6%, although rates can range as high as 24% in surgical sub-specialties such as orthopedics.[3, 4] Furthermore, the link between prescription opioids and transition to heroin has resulted in a significant rise in opioid-related deaths, which are now more common than deaths due to motor vehicle-related injuries (**Figure 1**).[5]

Pain control after trauma must be timely and effective in order to allow patients earlier mobilization and improved functional status. Due to their injuries, 59% of trauma patients experience moderate to severe pain and, in 73% of patients, this pain interferes with activity during their acute hospitalization.[6] Pain control after traumatic injury must also be safe. Traditionally, pain regimens have relied on the administration of narcotics; however opioid-based analgesic strategies are associated with significant short- and long-term adverse consequences. In the short-term, opioid-related adverse events include respiratory failure, urinary

retention, ileus, and constipation.[7] In the long-term, opioid addiction and opioid-related deaths may result. In addition, adequacy of pain control as measured by pain scores is increasingly being used as a patient-centered outcome and evidence suggests that there is a lack of equity in pain management based on socioeconomic status, race, age, and gender.[8-10] While multi-modal analgesia is a promising strategy to reduce opioid use, it is unknown if this is the most efficient and cost-effective strategy for post-trauma pain control.

Preliminary Data

Multi-modal analgesic regimens have sought to minimize reliance on opioids for pain control by utilizing combinations of medications from different drug classes including non-steroidal anti-inflammatory drugs (NSAIDs), gabapentinoids, weak mu agonists, and central prostaglandin inhibitors. In 2013, our trauma service introduced a multi-modal analgesic regimen. Traumatically injured patients were immediately started on scheduled pain medications from each of the different drug classes. While this idea of a multi-modal strategy decreased mean opioid use in morphine milligram equivalents (MME) per patient per day (**Table 1**), there was and continues to be significant heterogeneity in the actual regimens prescribed by surgeons.

Trauma Service Line Use of Pain Medications per Fiscal Year of Various Classes of Pain Medication					
	FY 13	FY 14	FY 15	FY 16	FY 17
Morphine milligram equivalents (oral opioids only)	1,936,955	1,566,248	1,155,619	948,088	850,678
Morphine milligram equivalents/patient day (oral opioids only)	**63**	**49**	**38**	**29**	**28**
NSAID mg/patient day	**92**	**160**	**181**	**186**	**271**
Gabapentinoids mg/patient day	**146**	**293**	**464**	**550**	**665**
Tramadol mg/patient day	**43**	**121**	**168**	**159**	**162**
Acetaminophen mg/patient day	**684**	**1,048**	**1,455**	**2,144**	**2,438**

Table 1: Implementation of a multi-modal analgesic strategy has resulted in halving of the use of oral opioids accompanied by a concomitant increase in the use of acetaminophen, NSAIDs, gabapentinoids, and tramadol.

Objectives

Aim 1: To perform a parallel group, randomized controlled trial comparing two multimodal pain strategies on clinical outcomes, patient-reported outcomes, and resource utilization

Aim 2: To better understand the effect of the different multi-modal strategies by evaluating heterogeneity of treatment effect by performing hypothesis-testing and hypothesis-generating subgroup analyses to identify characteristics associated with the need for one strategy over the other

Study Design

This pragmatic, single-blind, randomized trial will be conducted at the Red Duke Trauma Institute at MHH-TMC.

Study Arms: Treatment Strategies

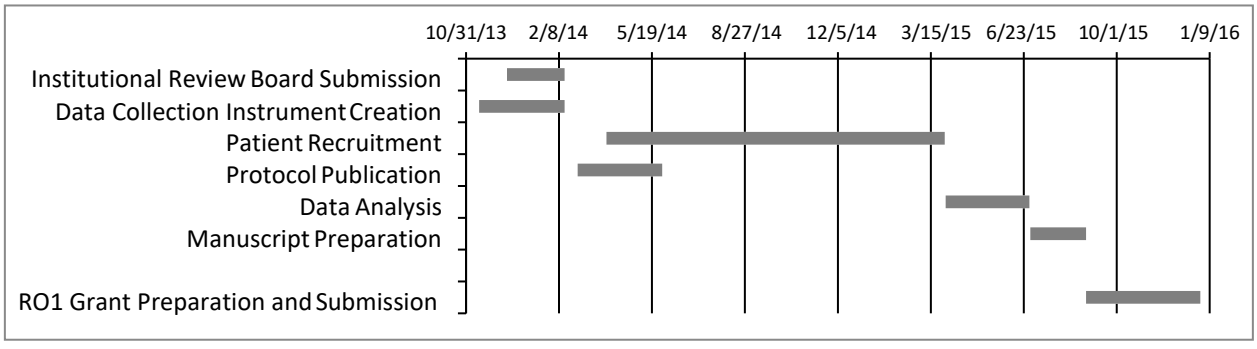
	Treatment Strategy #1		Treatment Strategy #2
	First 48 hours	Thereafter	Admission and thereafter
Central Prostaglandin Inhibitor	Acetaminophen 1g IV/PO q6 hours	Acetaminophen 1g PO q6 hours	Acetaminophen 1g PO q6 hours
NSAID COX Inhibitor	Ketorolac 30mg IV once Celebrex 200mg PO q12 hours	Naproxen 500mg PO q12 hours	Ketorolac 30mg IV once Naproxen 500mg PO q12 hours
Weak Mu Opioid Agonist	Tramadol 100mg PO q6 hours	Tramadol 100mg PO q6 hours	None
Gabapentinoid	Pregabalin 100mg PO q8 hours	Gabapentin 300mg PO q8 hours	Gabapentin 300mg PO q8 hours
Local anesthetics	Lidocaine patch q12 hours	Lidocaine patch q12 hours	Lidocaine patch q12 hours
PRN medications	Opioids Regional anesthesia	Opioids Regional anesthesia	Tramadol Opioids Regional anesthesia
Dosing, dose adjustments, and contra-indications used are available at: https://med.uth.edu/surgery/acute-trauma-pain-multimodal-therapy/			

Setting

This study will be conducted at the Texas Trauma Institute at Memorial Hermann Hospital-Texas Medical Center (MHH-TMC). It is one of two Level 1 trauma centers in the Houston metropolitan area, an area in which over 6 million people reside, and is the busiest trauma center in the country, with approximately 2,000 admissions to the adult Trauma Service per year.

Time Period

IRB submission for the study will occur in December 2017. Enrollment of eligible patient will begin in April 2018 and continue for 12 months.



Outcomes

The primary outcome of the study is opioid use per day until discharge or 30 days post admission (whichever is sooner), calculated by tallying the MME of all opioids received and dividing by the number of days hospitalized. This outcome captures the effectiveness of the combined non-opioid medications in not only achieving pain control but also in reducing opioid administration.

Opioid	Conversion Factor
Oral Opioids	
Codeine (mg)	0.15
Tramadol (mg)	0.1
Hydrocodone (mg)	1
Oxycodone (mg)	1.5
Methadone 1-20 mg/day 21-40 mg/day 41-60 mg/day ≥61-80mg/day	 4 8 10 12
Morphine (mg)	1
Hydromorphone (mg)	4
Transdermal Opioids	
Fentanyl (mcg/hr)	2.4
Intravenous Opioids	
Morphine (mg)	3
Hydromorphone (mg)	15
Fentanyl (mcg)	0.2

The secondary outcomes of the study include:

- Pain scores until discharge or 30 days post admission (whichever is sooner): an average will be calculated of the average daily numeric rating scale of pain (0=no pain, 10=worst pain).
  - Pain scores are currently recorded by nursing staff at standard intervals based upon the patient's level of care.
  - The numeric rating scale of pain is already assessed by nurses multiple times per day at hospitals across the United States, including Memorial Hermann Hospital-Texas Medical Center, and will not require additional training or man power to collect.
- Discharge from the hospital with an opioid prescription
- Incidence of opioid-related complications, such as ileus, aspiration, unplanned intubation, unplanned admission to an intensive care unit, and use of an opioid-reversal agent.
  - Until discharge or 30 days post admission (whichever is sooner)
  - Measures of safety
  - Some of these complications are already recorded by the Trauma Quality Improvement Project (TQIP) and the hospital as a core measure.
- Costs: overall and pharmacy costs
- Lengths of stay: ventilator-/hospital-/ICU-free days
- Measures of function that may be limited by pain, such as percent of predicted daily incentive spirometry volumes (which is based on ideal body weight) and failure to work with physical therapy due to pain (until discharge or 30 days post admission [whichever is sooner])

Study Population

Screening

All adult patients (≥16 years) arriving to the trauma center and admitted to the trauma service will be screened for eligibility in the study. Clinical research staff are available on a 24/7 basis to conduct screening and collect data on those patients meeting inclusion criteria. Research

staff will inform the physicians of randomization allocation and drug regimen/dosages. All patient care aspects other than the randomization to multimodal treatment strategy will follow the MHH-TMC policies and guidelines.

Inclusion/Exclusion Criteria

Patients will be excluded if they are a pediatric patient (<16 years), pregnant, or a prisoner. Additionally, patients placed in observation (i.e. not admitted to the hospital) will be excluded. While certain patients may have contraindications for select drug classes (e.g. NSAID contraindicated in acute kidney injury, tramadol contraindicated in patients with seizures, acetaminophen contraindicated in Child's C cirrhosis), patients will not be excluded based on these individual drug contraindications. Randomization should balance these patients in both treatment strategies.

If a patient meets inclusion criteria without any exclusion criteria, they will be randomized in the Emergency Department so that medications can be ordered and administered as quickly as possible.

Study Procedures

Randomization

Allocation will occur through sequentially numbered, opaque envelopes kept in the research assistants' office in the emergency department. Envelopes will be opened upon trauma resident writing admission orders in the Emergency Department An independent statistician will determine the randomization sequence and oversee the labeling of cards and envelopes. Randomization will be stratified by unit of admission (ICU, IMU, floor).

Data Collection

Data collection will occur by one of two methods: manual entry or automatic capture of data. Data points to be collected are detailed in Supplement One.

Supplement One also indicates the manner by which data points will be collected – manually, from National Trauma Data Base registry, or automatic capture from the electronic medical record.

Follow up

No study-specific follow-up will be required.

Statistics

Sample Size

The function of this preliminary study is to provide the most precise, unbiased estimate of treatment effect possible. The precision of this estimate is largely a function of sample size. As such our goal is to conduct the largest feasible study in a 12 month period upon which to base these estimates. We believe we will be able to enroll 75% of admissions to the trauma service, which would be approximately 1,506 patients in the 12 month period.

% Enrollment	Total Accrual
50%	1,004

The trauma center is one of the busiest in the United States. Of patients who come to the trauma center, the number of patients admitted to the adult trauma surgery service are: 1,974 (FY 2015), 2,022 (FY 2016), and 2,026 (FY 2017). This equates to 167 patients admitted per month.

60%	1,204
70%	1,405
75%	1.506
80%	1.606
90%	1.807
100%	2,007

The table to the right estimates total patient accrual in a 12 month period assuming multiple rates of enrollment.

Data Analysis Plan

We plan a Bayesian statistical approach for three reasons:

1) At an early stage in the development and implementation of an intervention, investigators must decide whether to invest further time and resources on a specific approach given the data they have thus far observed. Fundamentally, this requires evaluation of the probability that the alternative hypothesis is true (i.e. the probability that an effect of some magnitude exists). Frequentist approaches to statistical reasoning do not directly estimate the probability of the alternative hypothesis, focusing instead on the rejection of the null;
2) Bayesian approaches combine any salient prior information with the observed data to form a posterior distribution which then captures the current state of the evidence for the probability that an effect of some magnitude exists. This posterior distribution may then function as an empirically derived, informative prior that provides information in the evaluation of subsequent samples. This permits the analyses from the current project to inform the design and analysis of subsequent studies;
3) the process of updating a prior with data provides a mechanism for continued monitoring of an established program for quality control purposes.

The following data analytic approach applies to evaluation Aims 1 and 2, though we present it only once to conserve space. Broadly, the data analytic strategy will use generalized linear multilevel modeling with level-two random effects to account for clustering of participants within site and, where applicable, observations within participants. Modeling will use R v. 3.4 and Stan v. 1.10.[11, 12]. Initial analyses examining group differences for baseline variables will use cross-tabulation, ANOVA's, and examination of correlations between baseline variables and specified outcomes. For the purposes of evaluating the comparability of groups, a posterior probability of $\geq$ 95% will constitute evidence for statistically reliable differences. Baseline or demographic variables on which group differences are detected and which are correlated with outcomes meet the definition of confounders and will result in two sets of analyses: one in which the relevant variable is included as a covariate and one in which it is not.[13, 14] This will permit determination of the degree to which any group differences might confound conclusions regarding treatment.

All analyses will be conducted on an intention-to-treat basis. Bayesian approaches will implement joint modeling of observed outcomes and the missing data which is robust to ignorable missingness (i.e., MCAR and MAR).[15] Sensitivity analyses will evaluate robustness of analytic conclusions to missing data. Non-ignorable missing data patterns will be addressed through pattern-mixture modeling methods.[16] Convergence of Bayesian analyses on the posterior distributions via Monte-Carlo Markov chain (MCMC) will be assessed via graphical

(Gelman-Rubin Plots) and quantitative (Gelman-Rubin Diagnostics and Effective Sample Size) evidence. Evaluation of posterior distributions will permit statements regarding the probability that effects of varying magnitudes exist, given the data. Specification of diffuse, neutral priors will reflect the initial uncertainty regarding effect sizes. For all generalized linear multilevel models, priors for regression coefficients will be specified as ~Normal (μ=0, σ^2=10) on the identity or log-scale depending upon the model, level one error variances will be specified as ~Half-T (df = 3, mean = 0, standard deviation = 100). Prior distribution for level two variances will use ~Half-T (df = 3, mean = 0, standard deviation = 10). Priors for the comparison of proportions will be specified as ~Beta (α=0.5, β=0.5). For all subgroup analyses using multilevel models the approach will follow that used in Tyson, et al.[17]

Ethics

Due to the acute clinical status of the trauma patient population (intubation, intoxication, severe pain), it is often not feasible to obtain *truly informed* consent from a patient or legally authorized representative (LAR) before pain medications are prescribed. Therefore, we will use delayed consent. The patient will be randomized and enrolled prior to consent.

Once the patient is enrolled, a member of the trauma research team will make attempts to contact either the patient or LAR to obtain consent for this study. Consents will be obtained by trained research personnel Monday through Friday during the day. If a consent needs to be obtained on the weeknight or weekend, research personnel will be available. Once appropriate to approach the patient for consent, a study team member will explain the study, its implications for the patient, and give the patient written study information. Additionally, an educational pamphlet on safe opioid use will be given to the patient.

If the subject consents to participation, they will sign the consent document. If the subject refuses, data collection will stop at time of refusal.

Due to the high enrollment rate, the study team will attempt to inform and consent the patients/LARs for at least five days. If, after 5 days, the patient remains unable to self-consent and no LAR is available to consent, the consent will be waived and data included. Additionally, if the subject does not survive following the traumatic injury or is discharged from the hospital before the study team is able to obtain consent, their information will be included in the data analysis.

Data Handling and Record Keeping

If data is to be extracted by hand, it will be entered into a standardized case report form and entered into a RedCap™ database. Each subject will be assigned a study-specific number. Data will be collected until hospital discharge.

All hard copy source documentation will be kept in a secured, locked cabinet in the research coordinator's office. All study documents will be maintained in a secure location for two years following study completion.

Quality Control and Assurance

Each item on the web forms will have validity checks performed to ensure that the data entered are accurate and that items are not skipped during entry by mistake. Bi-weekly audits of data will be performed by both clinical investigators and research assistants.

Publication Plan

Planned publications include the following:

(1) Protocol paper detailing the proposed project;
(2) Clinical results paper of randomized controlled study

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Supplement One: Data

Variable	RedCap	From Registry/NTDB	Electronic Data Withdrawal
Demographics	• Age • Sex • Race • Prior opioid use		
Injury Information	• Mechanism of injury • Specific injuries: - Total number ribs with a fracture (0-24) (two or more fractures in a single rib counts as 1) - Flail chest - Long bone fracture (radius, ulna, humerus, femur, tibia, fibula) - Vertebral body fracture - Laparotomy - Thoracotomy - Amputation - Any pelvis/acetabular fracture	• AIS values • ISS	
Opioid Specific	• Discharge opioid status • Regional anesthetic used		• Daily morphine milligram equivalents • Pain scores
Complications	• Ileus	• Cardiac arrest • Unplanned admission to ICU • Unplanned intubation	
Hospital Stay		• Hospital length of stay • ICU length of stay • Ventilator days • Mortality	