Dronabinol on the Pain Experience (DOPE): a pragmatic randomized- controlled trial

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Protocol Title: Dronabinol on the Pain Experience (DOPE): a pragmatic randomized-controlled trial

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Population: Adult trauma patients admitted to the Surgical Ward (Floor), Surgical Intermediate Unit (SIMU), and Shock Trauma Intensive Care Unit (STICU) at Memorial Hermann Hospital-Texas Medical Center (MHH-TMC).

Number of Sites: Single center, MHH-TMC

Study Duration: 5 to 6 months

Subject Duration: Time while hospitalized

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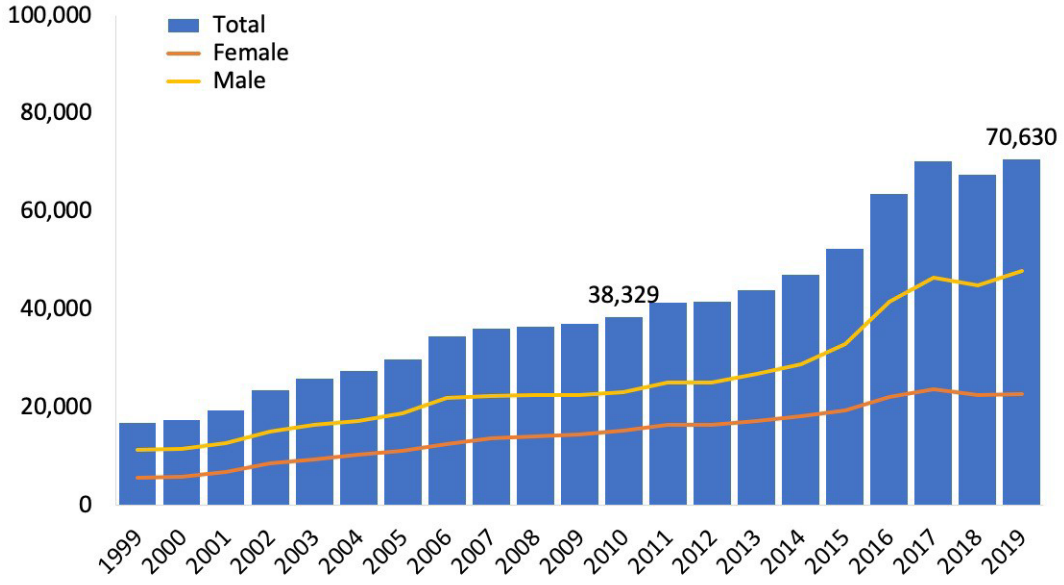
General Information:

The optimal strategy for providing safe and effective pain management after acute traumatic injury is unknown. A recent randomized control trial (MAST) performed at MHH-TMC demonstrated the effectiveness of multi-modal pain regimen (MMPR) in reducing opioid exposure while maintaining pain control.[1] Adjunct analgesic medications are commonly added to MMPRs to diversify the pain management with additional drug classes. One such medication is dronabinol, a synthetic delta-9-tetrahydrocannabinol (delta-9-THC) medication. The proposed project is a randomized comparative effectiveness trial of current pain management strategies in acutely injured trauma patients. A parallel group, randomized trial of our current institutional MMPR with the addition of dronabinol compared to our current institutional MMPR will be performed and analyzed using Bayesian statistics.

Background Information:

Figure 1. National Drug-Involved Overdose Deaths*
Number Among All Ages, by Gender, 1999-2019



*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2019 on CDC WONDER Online Database, released 12/2020.

The opioid epidemic is an ongoing public health crisis that has only intensified during the COVID-19 pandemic.[2-4] Trauma patients are a known group at risk for opioid use disorder.[5,6] Due to the nature of multisystem injuries, need for multiple painful procedures, and lengthy hospitalization, injured patients' acute pain control needs differ from those in other surgical specialties.[7] In an effort to reduce opioid exposure while still providing optimal pain

control, surgeons are increasingly prescribing MMPRs.[8-12] Our current institutional MMPR is derived from the Multi-Modal Analgesic Strategy for Trauma (MAST) trial and was demonstrated to reduce opioid exposure as measured by morphine milligram equivalents (MME) while maintaining pain control.[1] However, this MMPR is just a starting point and many adjunct medications are added to improve pain control. One such adjunct is dronabinol, a synthetic delta-9-tetrahydrocannabinol (delta-9-THC) medication that has FDA approval for anorexia in patients with AIDS and chemotherapy-induced nausea and vomiting. Currently dronabinol is used off-label for its analgesic properties but the data supporting its use for acute pain after traumatic injury is limited.[13]

Objectives:

To perform a randomized comparative effectiveness trial to identify the effect dronabinol has on opioid exposure when used as an adjunct to the current standard MMPR.

Study Design:

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

Study Arms: Treatment Strategies

	Treatment Strategy #1	Treatment Strategy #2
Central Prostaglandin Inhibitor	Acetaminophen	Acetaminophen
NSAID COX Inhibitor	Naproxen	Naproxen
Gabapentinoid	Gabapentin	Gabapentin
Local Anesthetics	Lidocaine Patch	Lidocaine Patch
Cannabinoid	**None**	**Dronabinol 10 mg Q12h**
PRN Medication	Tramadol Other opioids Regional Anesthesia	Tramadol Other opioids Regional Anesthesia

Each patient once randomized will be started on the corresponding treatment strategy. Dosing of other medications will be started based on current standard at our institution unless the patient requires dosing adjustment due to medical comorbidities. Continuing pain management and alteration of the MMPR will be at the discretion of the provider.

A normal dosing strategy will consist of acetaminophen 1000 mg every six hours, naproxen 500 mg every 12 hours, gabapentin 300 mg every eight hours, and Tramadol 50 mg every six hours

as needed for breakthrough pain. Dronabinol 10 mg every 12 hours will be started for the intervention arm. Providers will have the ability to adjust this pain regimen based on clinical judgement. Patients who are NPO for surgery will still be able to take medications with sips of water. Patients who are intubated or are unable to take oral medications will have enteral access placed via small bore nasogastric tube or feeding tube as the discretion of the provider per routine clinical practice. Patients who are strict NPO will not have oral medications until deemed appropriate by the provider.

At discharge patients will be provided a script with the medications they were requiring for pain control prior to discharge at the discretion of the provider. Dronabinol is not commonly given as a prescription at discharge as part of routine clinical practice and will not be prescribed at discharge in this trial.

Setting

This study will be conducted at the Red Duke 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 with approximately 2,000 admissions to the adult Trauma Service per year.

Time Period

IRB submission for the study will occur in January 2023. Using an alpha of 0.05 and a power of 80% to detect a 15% reduction from previously reported MME/d of 34 +/- 23 from the MAST trial to 29 MME/d (equal to 1 x 50 mg Tramadol) a total of 664 patients would need to be enrolled or 332 per arm. Based on admittance patterns this would take approximately 5-6 months.

Outcomes

The primary outcome of the study will be the reduction in opioid exposure measured by MMEs per day, calculated by taking the total of MMEs from all opioids received and dividing by length of stay. MMEs will be measured based on a standard conversion factor listed in the table below:

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

Secondary Outcomes include the following:

- Total MMEs over hospital stay
- Pain Scores calculated by the defense and veterans pain rating scale. Pain scores will be recorded by nursing at timepoints per unit protocol as part of routine practice. An average will be calculated for the entire hospital stay as well for the first 72 hours. Pain scores are already routinely recorded in the electronic medical record (EMR).
- Discharge from the hospital with or without a prescription for an opioid medication
- 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. These are tracked by the institution trauma registry and will be obtained once available from the registry.
- Lengths of stay
    - Hospital length of stay
    - ICU length of stay
    - Ventilator length of stay
    - Hospital free days
    - ICU free days
    - Ventilator free days

Study Population:

Screening

All adult patients (≥16 years) 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 to each treatment arm. Drug regimen dosing will be available for providers placing orders and there is an order set in place for the current MMPR. All patient care aspects other than the randomization to treatment strategy will follow the MHH-TMC policies and guidelines.

Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Adult trauma (≥16 years) patients admitted to the floor, SIMU, STICU at MHH-TMC

Exclusion Criteria:

1. Pediatric patient (<16 years)
2. Age > 80 years old
3.
4. Pregnant

5. Prisoner
6. Patients placed in observation unit
7. Non-acute trauma
8. Admitted with primary burn injury
9. Expired prior to admission
10. Moribund
11. Discharge from emergency department
12. Left against medical advice

Patients will not be excluded if they have a contraindication to a specific drug class to keep with the pragmatic design.

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 Procedure:

Randomization
Allocation will occur through a random number generator via the Redcap system. Research assistants will inform the resident writing admission orders in the Emergency Department of group assignment. Randomization will be stratified by unit of admission (ICU, IMU, or floor).

Data Collection
Data collection will occur by one of two methods: manual entry or automatic capture of data. Data will either be obtained from the National Trauma Database registry, or automatically captured from the electronic medical record.

Follow up
No study-specific follow-up will be required.

Statistics:

Sample Size

Using an alpha of 0.05 and a power of 80% to detect a 15% reduction from previously reported MME/d of 34 +/- 23 from the MAST trial to 29 MME/d (equal to 1 x 50 mg Tramadol) a total of 664 patients would need to be enrolled or 332 per arm. Based on admittance patterns this would take approximately 5-6 months with 75% enrollment of admissions achieved in previous trials.

Data Analysis Plan

A Bayesian statistical model will be the primary model used due to its ability to incorporate previously 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. Using the data gathered from the MAST trial a Bayesian approach will better evaluate the evidence from this trial that there is some probability that an effect of some magnitude exists. 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. 4.2.[14] 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.[15,16] 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).[17] Sensitivity analyses will evaluate robustness of analytic conclusions to missing data. Non-ignorable missing data patterns will be addressed through pattern-mixture modeling methods.[18] 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. Priors will be drawn from the effect size seen in the MAST trial.[1]

Ethics:

Due to the acute clinical status of the trauma patient population (intubation, intoxication, severe pain), it is often not feasible to obtain informed consent from a patient or legally authorized representative prior to administering of pain medications. Therefore, delayed consent will be used and patients will be randomized and enrolled prior to consent. Post-enrollment, a member of the trauma research team will make attempts to contact either the patient or the legally authorized representative to obtain consent for this study. Competency will be assessed by providers and the trained research assistants who will be obtaining consent. Assent will be sought to the extent possible if the subject is unable to give informed consent. 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. If the subject consents to participation, they will sign the consent document. If the subject refuses, data collection will stop at time of refusal. If after 5 days the patient remains unable to self-consent and no legally authorized representative is available, 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. Remaining data will be drawn from the Trauma registry database. 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:

Plan to publish (1) protocol detailing the proposed project and (2) clinical results of the randomized control trial.

References:

1. Harvin JA, Albarado R, Truong VTT, Green C, Tyson JE, Pedroza C, Wade CE, Kao LS; MAST Study Group. Multi-Modal Analgesic Strategy for Trauma: A Pragmatic Randomized Clinical Trial. J Am Coll Surg 2021 -03;232(3):241-251.e3.
2. Nair L, Duggan RP, Moliver CL. The Opioid Epidemic in the Age of the COVID-19 Pandemic. Aesthet Surg J 2021 -10-15.
3. Haley DF, Saitz R. The Opioid Epidemic During the COVID-19 Pandemic. JAMA 2020 -10-27;324(16):1615-1617.
4. Alexander GC, Stoller KB, Haffajee RL, Saloner B. An Epidemic in the Midst of a Pandemic: Opioid Use Disorder and COVID-19. Ann Intern Med 2020 -07-07;173(1):57-58.
5. Yoon JH, Suchting R, Kessler D, Soder HE, Kapoor S, Stotts AL, Heads AM, Harvin JA, Green CE, Lane SD, et al. Utility of a brief assessment of opioid demand among post-discharge trauma care patients. Exp Clin Psychopharmacol 2020 -07-16.
6. Yorkgitis BK, Brat GA. Postoperative opioid prescribing: Getting it RIGHTT. The American Journal of Surgery 2018 April 1,;215(4):707-711.
7. Harvin JA, Truong VTT, Green CE, Allen L, Murry J, Radosevich JJ, Bogert JN, Murphy PB, Padilla-Jones BB, Zarzaur BL, et al. Opioid exposure after injury in United States trauma centers: A prospective, multicenter observational study. J Trauma Acute Care Surg 2020 -06;88(6):816-824.
8. Reagan KML, O'Sullivan DM, Gannon R, Steinberg AC. Decreasing postoperative narcotics in reconstructive pelvic surgery: a randomized controlled trial. Am J Obstet Gynecol 2017 -09;217(3):325.e1-325.e10.

9. Rafiq S, Steinbrüchel DA, Wanscher MJ, Andersen LW, Navne A, Lilleoer NB, Olsen, PS. Multimodal analgesia versus traditional opiate based analgesia after cardiac surgery, a randomized controlled trial. J Cardiothorac Surg 2014 -03-20;9:52.

10. Sim V, Hawkins S, Gave AA, Bulanov A, Elabbasy F, Khoury L, Panzo M, Sim E, Cohn S. How low can you go: Achieving postoperative outpatient pain control without opioids. J Trauma Acute Care Surg 2019 -07;87(1):100-103.

11. Pitchon DN, Dayan AC, Schwenk ES, Baratta JL, Viscusi ER. Updates on Multimodal Analgesia for Orthopedic Surgery. Anesthesiol Clin 2018 -09;36(3):361-373.

12. Wick EC, Grant MC, Wu CL. Postoperative Multimodal Analgesia Pain Management With Nonopioid Analgesics and Techniques: A Review. JAMA Surg 2017 -07-01;152(7):691-697.

13. Schneider-Smith E, Salottolo K, Swartwood C, Melvin C, Madayag RM, Bar-Or D. Matched pilot study examining cannabis-based dronabinol for acute pain following traumatic injury. Trauma Surg Acute Care Open. 2020 Feb 9;5(1):e000391. doi: 10.1136/tsaco-2019-000391.

14. Team, R.C., *R: A Language and Environment for Statistical Computing*. 2017, R Foundation for Statistical Computing: Vienna, Austria.

15. Assmann, S.F., et al., *Subgroup analysis and other (mis)uses of baseline data in clinical trials.* Lancet, 2000. **355**(9209): p. 1064-9.

16. Pocock, S.J., et al., *Subgroup analysis, covariate adjustment and baseline comparisions in clinical trial reporting: Current practice and problems.* Statistics in Medicine, 2002. **21**: p. 2917-2930.

17. Best, N. and A.E.p.-. Thomas, *Bayeisan Graphical Models and Software for GLMs*, in *Generalized Linear Models: A Bayesian Perspective*, D. Dey, S.K. Ghosh, and B.K. Mallick, Editors. 2000, Marcel Dekker, Inc.: New York.

18. Fitzmaurice, G.M. and N.M. Laird, *Generalized linear mixture models for handling nonignorable dropouts in longitudinal studies.* Biostatistics, 2000. **1**: p. 141-156.