Multi-Modal Analgesic Strategy for Trauma: A Pragmatic Randomized Clinical Trial

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BACKGROUND: An effective strategy to manage acute pain and minimize opioid exposure is needed for injured patients. In this trial, we aimed to compare 2 multimodal pain regimens (MMPRs) for minimizing opioid exposure and relieving acute pain in a busy, urban trauma center.

METHODS: This was an unblinded, pragmatic, randomized, comparative effectiveness trial of all adult trauma admissions except vulnerable patient populations and readmissions. The original MMPR (IV administration, followed by oral, acetaminophen, 48 hours of celecoxib and pregabalin, followed by naproxen and gabapentin, scheduled tramadol, and as-needed oxycodone) was compared with an MMPR of generic medications, termed the *Multi-Modal Analgesic Strategies for Trauma* (*MAST*) *MMPR* (ie oral acetaminophen, naproxen, gabapentin, lidocaine patches, and as-needed opioids). The primary endpoint was oral morphine milligram equivalents (MMEs) per day and secondary outcomes included total MMEs during hospitalization, opioid prescribing at discharge, and pain scores.

RESULTS: During the trial, 1,561 patients were randomized, 787 to receive the original MMPR and 774 to receive the MAST MMPR. There were no differences in demographic characteristics, injury characteristics, or operations performed. Patients randomized to receive the MAST MMPR had lower MMEs per day (34 MMEs/d; interquartile range 15 to 61 MMEs/d vs 48 MMEs/d; interquartile range 22 to 74 MMEs/d; $p < 0.001$) and fewer were prescribed opioids at discharge (62% vs 67%; $p = 0.029$; relative risk 0.92; 95% credible interval, 0.86 to 0.99; posterior probability relative risk $<1 = 0.99$). No clinically significant difference in pain scores were seen.

CONCLUSIONS: The MAST MMPR was a generalizable and widely available approach that reduced opioid exposure after trauma and achieved adequate acute pain control. (J Am Coll Surg 2021; 232:241–252. © 2020 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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Abbreviations and Acronyms

ACDiT = adapted Clavien-Dindo in trauma scale
BPS = Behavioral Pain Scale
CrI = credible interval
IMU = intermediate care unit
IQR = interquartile range
MAST = Multi-Modal Analgesic Strategies for Trauma trial
MMPR = multimodal pain regimen
NRS = Numeric Rating Scale

Trauma patients are particularly vulnerable to opioid use disorder.[1] They often have multisystem injuries and require multiple procedures, resulting in acute pain that cannot be adequately managed by regional anesthesia or alternative nonsystemic pain control strategies.[2] Multimodal pain regimens (MMPRs) are being used increasingly to reduce opioid exposure, address acute pain effectively, and enhance recovery after operations.[3-7] However, the optimal MMPR for trauma patients is unknown. The ideal MMPR for trauma patients must allow individualized treatment, achieve adequate acute pain control while minimizing opioid use, and be implemented easily. It must also be widely available, cost-conscious, and safe for different populations and locales.

In 2013, our trauma center implemented a pill-based MMPR to decrease opioid exposure. This strategy used a fixed schedule of acetaminophen, gabapentinoids, NSAIDs, lidocaine patches, and tramadol, with stronger opioids available for breakthrough pain. This MMPR reduced opioid exposure by 31%, with a small but substantial reduction in patient-reported Numeric Rating Scale (NRS) pain scores.[8] However, this strategy was not opioid-minimizing (with tramadol administered on a fixed dosing schedule) and involved drugs that were more costly (eg IV acetaminophen) and not widely available in hospital formularies or widely covered by insurance at discharge (eg celecoxib and pregabalin).

Partly for these reasons, we conducted the Multi-Modal Analgesic Strategies in Trauma (MAST) trial and hypothesized that the original MMPR would result in lower opioid exposure compared with the widely available generic MAST MMPR.

METHODS

The MAST trial was a pragmatic, randomized, comparative effectiveness trial comparing the original MMPR with the MAST MMPR. Its rationale and design have been detailed previously.[9] IRB approval was obtained on March 2, 2018. Enrollment took place between April 2, 2018 and March 31, 2019.

Trial design

The trial was conducted at the Red Duke Trauma Institute at Memorial Hermann Hospital-Texas Medical Center, the primary teaching hospital for the McGovern Medical School at UT Health. All eligible patients admitted to the adult trauma service were randomized in a 1:1 allocation ratio stratified by unit of admission (trauma ward, intermediate care unit [IMU], or ICU) to receive the original MMPR or MAST MMPR.

Randomization

Eligible patients were randomized in the emergency department by trauma surgery residents on determination of the unit to which they would be admitted. Residents received the computer-generated randomization allocation from research personnel, available 24 hours per day, 7 days per week, and ordered the MMPR using a standardized electronic order set.

Participants

Every patient (16 years or older) admitted to the adult trauma service was screened for enrollment. Pregnant women, prisoners, and re-admissions were excluded. Waiver of consent for randomization was approved as allowed under 45 CFR §46.116[10] for this minimal risk, comparative effectiveness trial that otherwise would not have been practicable to avoid major selection biases. However, the consent of patients was required to use protected health information and include their data in the analysis.

Interventions

The original MMPR consisted of 5 classes of medication administered on a fixed dosing schedule (Table 1). Acetaminophen was provided intravenously on admission. Once a patient was able to take pills by mouth (or at 24 hours, whichever was earlier), IV acetaminophen was changed to oral acetaminophen. If not contraindicated, a single dose of ketorolac was administered in the emergency department. Celecoxib was scheduled for the next 48 hours and then transitioned to scheduled naproxen. Pregabalin was administered for the first 48 hours, after which the patient was transitioned to gabapentin, titrated as needed. Oral tramadol and lidocaine patches were also components of the fixed dosing schedule. Pure opioid formulations (eg oxycodone, hydromorphone, and fentanyl) were used as needed for breakthrough pain.

The MAST MMPR included a single dose of ketorolac (if not contraindicated) and a fixed dosing schedule of oral

Table 1. Treatment Strategy

Group, medication schedule
Original MMPR
Acetaminophen 1 g IV q6h × 24 h, followed by acetaminophen 1 g po q6h thereafter
Celecoxib 200 mg po q6h × 48 h, followed by naproxen 500 mg po q12h thereafter
Pregabalin 100 mg po q8h × 48 h, followed by gabapentin 300 mg po q8h thereafter
Lidocaine patch q12h
Tramadol 100 mg po q6h
Opioid as needed
MAST MMPR
Acetaminophen 1 g po q6h
Naproxen 500 mg po q12h
Gabapentin 300 mg po q8h
Lidocaine patch q12h
Opioid as needed

The original MMPR and the MAST MMPR were given according to the schedule of medication listed above. In addition to this medication, pure formulations of opioids were prescribed as needed for breakthrough pain or per bedside physician discretion.
MAST, Multi-Modal Analgesic Strategies in Trauma trial; MMPR, multimodal pain regimen.

acetaminophen, naproxen, gabapentin, and lidocaine patches. Pure opioid formulations were used as needed for breakthrough pain. The responsible physicians in this pragmatic trial were free to alter pain management as needed, without limitation to both avoid overtreatment of acute pain when minimal and ensure adequate acute pain control when not. Both MMPRs were part of an acute pain protocol that determines dose modifications and contraindications for conditions such as liver disease (acetaminophen), seizures (tramadol), and acute kidney injury (gabapentinoids and NSAIDs). More information about the acute pain protocol can be found at https://med.uth.edu/surgery/acute-trauma-pain-multimodal-therapy/.

Outcomes

The primary outcome was opioid exposure defined as oral morphine milligram equivalents (MMEs) per day. MMEs per day was calculated by converting all sources of opioids during the hospital stay, including emergency department and operating room, to a single MME value using a standardized conversion chart and dividing by length of hospital stay.[9] MMEs per day was chosen because the value can be easily calculated by other centers with which to compare their patients' opioid exposure and the value accounts for length of stay. Two secondary opioid exposure outcomes included total MMEs and discharge from the hospital with an opioid prescription.

Another secondary endpoint was the mean pain score reported. The NRS reflects the patient's self-reported level of pain (0 = no pain, 10 = worst pain). The Behavioral Pain Scale (BPS) is a 3-dimensional scale (from 3 to 12, with higher scores indicating worse pain) used in nonverbal patients. The scores were recorded by nursing staff during usual clinical care and abstracted directly from the electronic medical record.

Additional secondary outcomes included the incidence of opioid-related complications (eg ileus, unplanned intubation, unplanned admission to an ICU, and use of an opioid-reversal agent), complications graded using the adapted Clavien-Dindo in trauma (ACDiT) scale, and lengths of stay (ie hospital, ICU, and ventilator days).[11] The ACDiT is a standardized method to grade the severity of complications after injury. It evaluates complications on a scale ranging from 0 to 5, with 0 indicating no complications and 5 indicating death.

Sample Size

The mean (SD) for opioid exposure for patients eligible for this trial could not be estimated accurately when the trial was designed. Partly for this reason, a predetermined study period (1 year) rather than a predetermined sample size was used to avoid bias in discontinuing enrollment. We estimated 167 admissions to the adult trauma surgery service each month and aimed to enroll 75% of those patients or 1,506 patients in the 12-month period. In addition to conducting the largest trial feasible in the 1-year recruitment period, we used Bayesian statistical inference to estimate of the probability that the hypothesis was true (ie that the original MMPR confers benefit over MAST MMPR). This probability cannot be estimated using conventional frequentist analyses.

Blinding

Providers could not be blinded to treatment allocation. However, medication regimens were ordered by clinicians, captured in the electronic medical record as part of regular clinical practice, and queried by research personnel after discharge. Pain scores were collected by nurses in usual clinical practice and similarly queried by research personnel after discharge. The majority of the outcomes were obtained from our institutional trauma registry maintained by independent, trained data entry professionals using definitions standardized by the National Trauma Data Bank.[12] Complications were identified and assigned ACDiT scores by trained research personnel.

Statistical Methods

Analyses used an intention-to-treat approach for all eligible randomized patients. Presentation of baseline variables and outcomes used median (interquartile range [IQR]) for continuous data and number (percentage) for categorical data.

Bayesian analyses were used to assess the probability of benefit for the primary and secondary outcomes.[13,14] Bayesian posterior probabilities are statements about the probability that the alternative hypothesis was true, given the observed data.[15] This focus on the probability that the alternative hypothesis was true, which is simply not available in conventional frequentist analyses, maps more directly onto the question clinical decision-makers have, which is, "Given what we know, what are the chances this approach will confer benefit or harm?"[16-18] Bayesian generalized linear models with extremely vague priors and robustness to prior assumptions was checked by examining alternative priors (extremely vague neutral priors ~normal [mean {SD} 0 {1,000}]) for coefficients within the respective model's link function). Additional statistical details are provided in eDocument 1.

We planned to use Bayesian modeling for MMEs per day to provide a treatment effect after covarying for the stratification variable; however, no parametric model fit the MMEs per day data and therefore none could be provided. For this reason, MMEs per day outcomes were compared using a stratified Wilcoxon rank-sum test applying the Hodges and Lehmann alignment method.[19-21] All other analyses remained Bayesian as planned. Total MME data required zero-inflated negative binominal modeling with results presented as estimated marginal means for ease of interpretation. Estimated marginal means are the mean total MME controlling for unit of admission based on the Bayesian models.

Analyses used SAS, version 9.4 (SAS Institute) for nonparametric approaches and R, version 3.6.3 (The R Project) with Stan, version 2.17 (Stan Development Team) for Bayesian models.

RESULTS

During the 12-month period, 3,385 patients were screened for eligibility; 34 eligible patients were not included; 1,634 were randomized; 73 were excluded after randomization (almost all because they refused consent or were ineligible for the trial); and 1,561 were included in the final analysis (Fig. 1). Median age of patients was 45 years (IQR 29 to 63 years), 68% were male, 29% were smokers, 12% reported a history of opioid use, and 24% had a positive urine drug screen on admission (Table 2). The populations of the original and MAST MMPRs were similar in demographic characteristics, medical history, and injury characteristics.

Opioid exposure

The overlaid histograms of observed MMEs per day for both groups are provided in Figure 2 to show the relative distribution of the primary endpoint. Patients randomized to the MAST MMPR had lower daily opioid exposure (34 MMEs/d; IQR 15 to 61 MMEs/d vs original MMPR: 48 MMEs/d; IQR 22 to 74 MMEs/d; $p < 0.001$) (Table 3). No interaction between MMEs per day and unit of admission was seen ($p = 0.77$). Again, no parametric model fit the MMEs per day data and therefore nonparametric results were presented.

Patients randomized to receive the MAST MMPR also had lower total MMEs (164 MMEs; IQR 59 to 450 MMEs vs 218 MMEs; IQR 43 to 490 MMEs; $p < 0.001$) (Table 3). On zero-inflated negative binomial modeling, the estimated marginal mean of the MAST MMPR was lower than that of the original MMPR (262 MMEs; 95% credible interval [CrI], 233 to 296 MMEs vs 274 MMEs; 95% CrI, 246 to 307 MMEs; posterior probability 0.77).

Conducting a priori analyses for subgroup differences, an interaction was found between treatment group and unit of admission for total MMEs (eTables 1 and 2). For patients admitted to the floor, IMU, or ICU, there were higher odds of having zero total MMEs in the MAST MMPR (Table 4). Despite this, patients admitted to the IMU and ICU had a 12% and 8% increase in total MMEs, respectively. Taken together, MAST MMPR patients had increased estimated marginal means of total MMEs when admitted to both the ICU and IMU. Alternatively, the MAST MMPR reduced the estimated marginal mean of total MMEs by 23% in patients admitted to the floor.

The MAST MMPR had a lower rate of opioid prescribing at discharge than the original MMPR (62% vs 67%; $p = 0.029$; relative risk 0.92; 95% CrI, 0.86 to 0.99; posterior probability relative risk $< 1 = 0.99$) (Table 3). In both groups, tramadol was the most commonly prescribed opioid at discharge (89%), followed by oxycodone (11%) and hydrocodone (9%).

Similar to total MMEs, a priori subgroup analyses revealed an interaction between treatment group and unit of admission for the endpoint opioid at discharge (Table 4). The MAST MMPR reduced opioid prescribing at discharge in patients admitted to the ICU and to the floor by 27% and 9%, respectively. The MAST MMPR had minimal effect on opioid prescribing at discharge in patients admitted to the IMU.

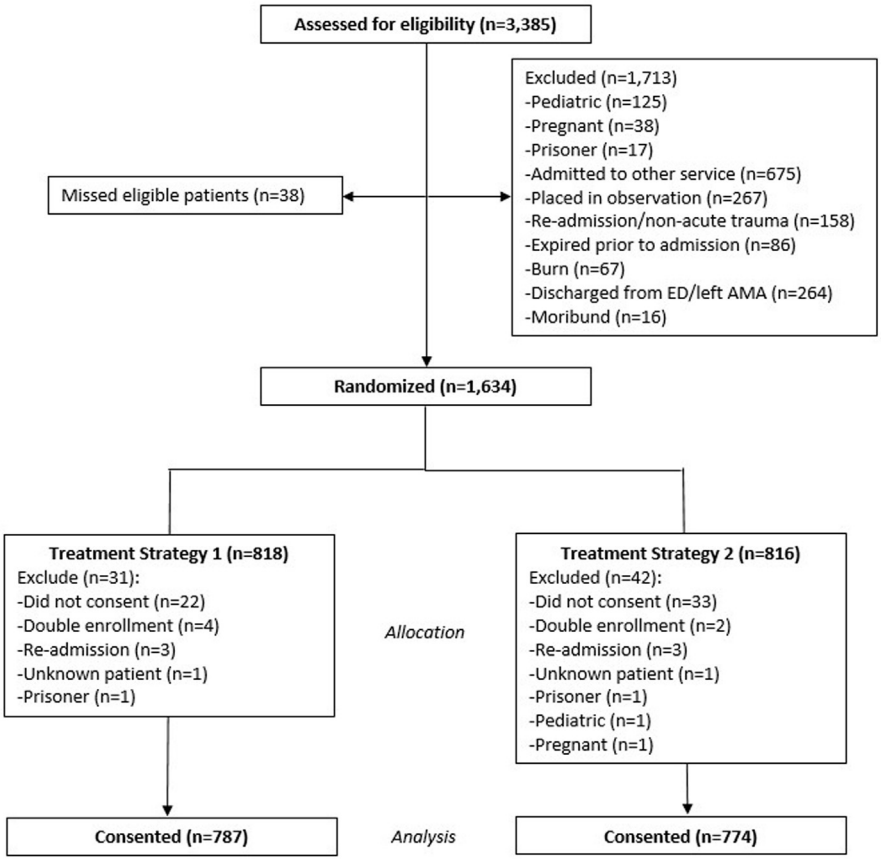

Figure 1. Consolidated Standards of Reporting Trials diagram for the Multi-Modal Analgesic Strategies in Trauma trial. Of 3,385 screened patients, 1,634 were randomized. The primary reason for exclusion after randomization was refusal of consent to the use of protected health information (n = 55 [3%]). An additional 18 patients (1%) were excluded for double enrollment, readmission, incorrect patient identifier resulting in unknown enrolled patient, or identification of a vulnerable patient status. AMA, against medical advice; ED, emergency department.

Pain scales

Mean NRS scores in the 2 treatment groups were similar for patients who could report pain scores (Table 3). eFigure 2 depicts the estimated marginal means for each group. A small increase in mean daily NRS scores occurred in MMPR MAST (marginal mean difference 0.06; 95% CrI, −0.14 to 0.26; posterior probability = 0.71). That is, the MAST MMPR increased the mean daily NRS score by a trivial amount (0.06 on a scale of 0 to 10).

Among the nonverbal patients, the MAST MMPR had a lower average BPS score. The marginal means of each group are shown in eFigure 3. Posterior estimates suggest a small decrease in average daily BPS (marginal mean difference −0.08; 95% CrI, −0.14 to 0.02; posterior probability = 0.99). After exponentiation, this indicates an 8% reduction in mean daily BPS for MMPR MAST relative to original MAST.

Other secondary outcomes

The 2 treatment groups were similar with respect to unplanned intubation, unplanned admission to the ICU, cardiac arrest with resuscitation, ileus, or complications graded by ACDiT scores (eTables 3 and 4). In addition, no differences were noted in the use of naloxone. There was no difference in hospital length of stay (estimate marginal mean of MAST MMPR 5.1 days; 95% CrI, 4.7 to 5.6 days vs original MMPR: 5.0 days; 95% CrI, 4.6 to 5.4 days; posterior probability = 0.76).

DISCUSSION

In this large, pragmatic randomized trial of adult injured patients, the use of the widely available MAST MMPR reduced inpatient opioid exposure and opioid prescribing at discharge with similar pain scores compared with our original MMPR. This finding was contrary to our hypothesis.

Table 2. Patient Demographic and Injury Characteristics

Characteristic	Original MMPR (n = 787)	MAST MMPR (n = 774)
Demographic		
Age, y, median (IQR)	44 (29–63)	45 (28–62)
Sex, n (%)		
Female	248 (32)	252 (33)
Male	539 (68)	522 (67)
Race/ethnicity, n (%)		
Black	140 (18)	167 (22)
Hispanic	264 (34)	223 (29)
Other	20 (3)	21 (3)
White	363 (46)	363 (47)
Previous opioid use, n (%)		
No	690 (88)	685 (89)
Yes	65 (8)	52 (7)
Unknown	32 (4)	37 (5)
Smoking history, n (%)		
No	520 (66)	524 (68)
Yes	243 (31)	217 (28)
Unknown	24 (3)	33 (4)
Positive alcohol screen, n (%)		
No	459 (58)	474 (61)
Yes	118 (15)	130 (17)
Not performed	210 (27)	170 (22)
Positive urine drug screen, n (%)		
No	319 (41)	316 (41)
Yes	175 (22)	202 (26)
Not performed	293 (37)	256 (33)
Injury scoring, median (IQR)		
AIS head	0 (0–2)	0 (0–2)
AIS chest	2 (0–3)	2 (0–3)
AIS abdomen	0 (0–2)	0 (0–2)
ISS	14 (9–22)	14 (9–22)
Injury characteristic		
Rib fracture, n (%)	364 (46)	356 (46)
Rib fracture, median (IQR)		
All patients	0 (0–4)	0 (0–4)
Patient with 1 or more	4 (2–7)	4 (2–7)
Flail segment, n (%)	47 (6)	57 (7)
Long bone fracture, n (%)	252 (32)	249 (32)
Vertebral body fracture, n (%)	136 (17)	144 (19)
Pelvis or acetabulum fracture, n (%)	142 (18)	143 (18)
Traumatic brain injury, n (%)	158 (20)	147 (19)
Unit of admission, n (%)		
Floor	305 (39)	280 (36)
Intermediate unit	186 (24)	194 (25)
ICU	273 (35)	279 (36)
Other	23 (3)	21 (3)
Procedure, n (%)		
Laparotomy	96 (12)	86 (11)

(Continued)

Table 2. Continued

Characteristic	Original MMPR (n = 787)	MAST MMPR (n = 774)
Thoracotomy	35 (4)	29 (4)
Amputation	9 (1)	12 (2)

AIS, Abbreviated Injury Scale; IQR, interquartile range; ISS, Injury Severity Score; MAST, Multi-Modal Analgesic Strategies in Trauma trial; MMPR, multimodal pain regimen.

Overall, the MAST trial demonstrates that an opioid-minimizing acute pain strategy is effective and feasible in such injured patients. We enrolled patients admitted to the adult trauma service only. Because a large proportion of patients with isolated extremity injuries were admitted to a medical service, the enrolled patients were a selectively more-injured cohort. The median Injury Severity Score of the entire cohort was 14 (IQR 9 to 22) and 44% had an Injury Severity Score higher than 15 (definition of severe trauma).

Overall, the MAST MMPR not only reduced opioid exposure during hospitalization (MMEs per day and total MMEs), but also decreased opioid prescribing at discharge. In the MAST trial, 64% of patients were discharged with an opioid, of which only 25% received a schedule II drug such as oxycodone or hydrocodone. Seventy-five percent of patients discharged with an opioid prescription were discharged with tramadol only. In contrast, in a recent multicenter prospective observational study at 7 trauma centers, 73% of patients were prescribed opioids at discharge; 86% of those patients (63% of all patients) received schedule II drugs.[2] Similarly, Chaudhary and colleagues[22] reported that 54% of trauma patients were discharged with a schedule II or III opioid prescription. However, they targeted a less severely injured population (median Injury Severity Score 5; IQR 4 to 10) and did not count tramadol (schedule IV) as a discharge opioid. There is substantial opportunity for MAST to inform hospital opioid-prescribing practices.

Although the generalizability of this strategy is likely to be high, more research is needed to responsibly and effectively address and understand the acute pain needs of our patients. The MAST trial has highlighted many gaps in the current understanding of MMPRs after injury.

First, although MMEs per day were reduced at all levels of care, the interpretation of the outcomes of total MMEs and opioid prescribing at discharge was challenging, as there was an interaction between treatment group and unit of admission for these outcomes. Given the lower MMEs per day, lower overall total MMEs, and lower opioid prescribing at discharge, the MAST MMPR was superior to the original MMPR in patients admitted to the floor. In patients admitted to the IMU, the MAST MMPR decreased MMEs per day and increased the odds of having zero total MMEs, but increased total MMEs for patients likely to receive opioids and had minimal effect on opioid prescribing at discharge. For patients admitted to the ICU, the MAST MMPR decreased MMEs per day, increased the odds of having zero total MMEs, and decreased opioid prescribing at discharge,

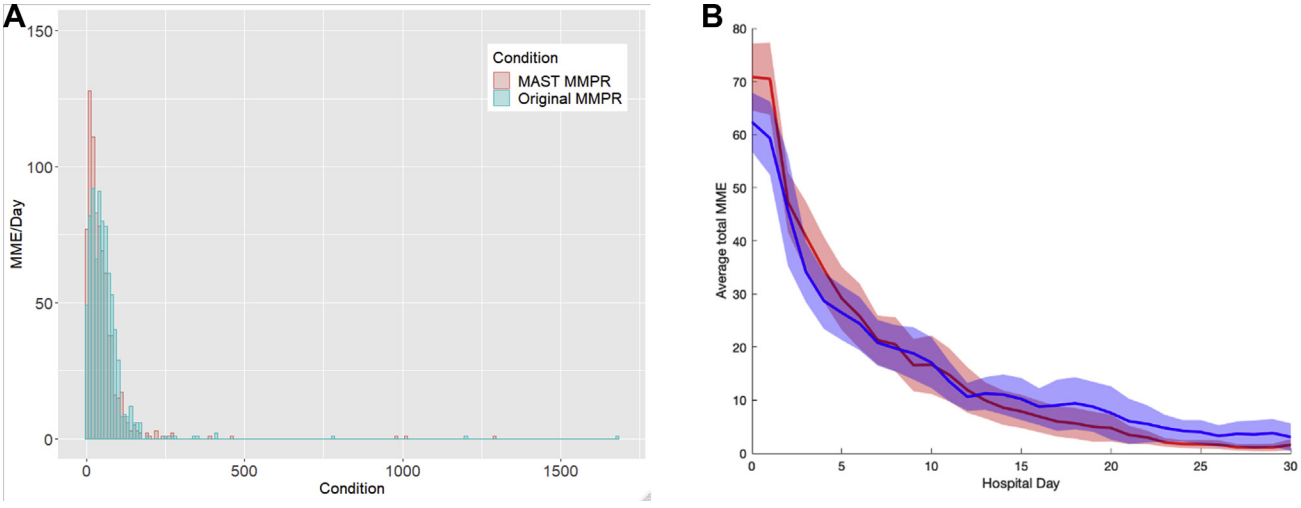

Figure 2. Morphine milligram equivalents (MMEs) per day by treatment group and by hospital day. (A) Histogram of MMEs per day by multimodal pain regimen (MMPR) treatment group. (B) Mean MMEs per day of patients per hospital day by MMPR treatment group. MAST, Multi-Modal Analgesic Strategies in Trauma trial.

Table 3. Opioid Exposure, Pain Score, and Discharge Opioid Prescribing

Opioid outcomes	Original MMPR (n = 787)	MAST MMPR (n = 774)	p Value
Opioid exposure and prescribing			
MMEs/d, median (IQR)	48 (22–74)	34 (15–61)	<0.001
Total MMEs, median (IQR)	218 (93–490)	164 (59–450)	<0.001
Opioid at discharge, n (%)	527 (67)	476 (62)	0.039
Opioid, n (%)			
Tramadol	466 (88)	427 (90)	0.499
Hydrocodone	45 (9)	48 (10)	0.418
Oxycodone	55 (10)	55 (12)	0.590
Codeine	29 (6)	16 (3)	0.115
Methadone	4 (1)	6 (1)	0.447
Fentanyl patch	0 (0)	1 (0)	—
Hydromorphone	2 (0)	1 (0)	0.651
Morphine	3 (1)	1 (0)	0.387
Pain score, median (IQR)			
Mean NRS score	3.3 (1.8–4.8)	3.3 (1.8–4.7)	0.740
Mean BPS score	2.5 (2.1–3.0)	2.3 (1.8–3.0)	0.028

BPS, Behavioral Pain Score; IQR, interquartile range; MAST, Multi-Modal Analgesic Strategies in Trauma trial; MME, morphine milligram equivalent; MMPR, multimodal pain regimen; NRS, Numeric Rating Scale.

but increased the total MMEs for patients likely to receive opioids. In summary, the MAST MMPR seems more appealing for patients admitted to the floor and ICU. The results for patients admitted to the IMU seem neutral comparing the MAST and original MMPRs. Clinically, having one MMPR for a unit of admission (IMU) and another for the other 2 (ICU and floor) would complicate adherence to an acute pain protocol and our group intends to implement the MAST MMPR as our usual practice for all levels of care.

Second, conclusions cannot be made about the effectiveness of the individual components of the 2 MMPRs. More evidence is accumulating that acetaminophen and NSAIDs provide equivalent acute pain control as opioids.[23,24] The evidence for gabapentin and lidocaine patches, however, remains mixed.[25-28] Although lidocaine patches are innocuous and do not imbue a risk for long-term abuse, the abuse of gabapentin is being reported increasingly and the incremental effect of gabapentin in our current regimen is currently unknown.[29,30] Future trials should evaluate the effectiveness of gabapentin in MMPRs. Other promising interventions described in the literature for reducing opioid exposure after injury and opioid prescribing after operations were also not evaluated. These can include expectation-setting or nonpharmacologic interventions, such as virtual reality.[31] Strategies such as development and implementation of a protocol and/or guidelines,[32] use of order sets via the electronic health record,[33,34] and education on opioid prescribing for trainees[35] were all performed in this trial, but for both groups. The relative effectiveness of each is unknown in this patient population.

Lastly, the measurement of acute pain longitudinally from arrival in the emergency department through multiple operations, critical illness, and during recovery continues to be exceedingly difficult. More objective measures of pain, such as sensory testing, are available but not feasible in such a large-scale and dynamic setting as trauma units. Although we relied on the ubiquitous NRS and BPS collected in everyday patient care to help us identify any signal of undertreated acute pain in a standard fashion, feasible and scalable measurements of acute pain for clinical trials powered to change practice are needed. Although the MAST MMPR had a lower average BPS score and no clinically significant difference in mean NRS pain scores, we cannot state that acute pain control was better, given the limitations to estimating acute pain. At most, there was no evidence that acute pain was increased due to the MAST MMPR, despite the overall lower opioid exposure.

This study's limitations were linked to the pragmatic design needed to enroll a large number of patients in a relatively short trial under real-world conditions. The majority of the data were collected electronically and adherence to the regimen was not tracked. Reasons why the bedside physicians adjusted pain medications were not collected so we cannot speculate which, if any, individual classes of drugs confer the most benefit. However, this was beyond the scope or intent of this study. Also, this trial was performed in a center with a

Table 4. A Priori Subgroup Analysis of Total Morphine Milligram Equivalents and Opioid at Discharge by Unit of Admission

	Total MMEs estimate mean and zero-inflated negative binomial model						Opioid at discharge			
			Zero-inflated component		Negative binomial component					
Admission unit	Original MMPR, mean (95% CrI)	MAST MMPR, mean (95% CrI)	OR (95% CrI)	Posterior probability*	IRR (95% CrI)	Posterior probability*	Original MMPR, n (%)	MAST MMPR, n (%)	RR (95% CrI)	Posterior probability*
Floor	304 (266–348)	232 (203–267)	1.20 (0.02–73.88)	0.57	0.77 (0.64–0.92)	0.98	239 (77)	207 (70)	0.91 (0.88–1.18)	0.97
IMU	285 (244–336)	312 (265–371)	19.93 (1.55 –9,273.44)	0.99	1.12 (0.89–1.41)	0.17	134 (62)	135 (64)	1.02 (0.88–1.18)	0.59
ICU	930 (804–1,082)	1,004 (868–1,169)	2.15 (0.03–601.05)	0.71	1.08 (0.87–1.35)	0.24	154 (59)	134 (51)	0.73 (0.86–1.00)	0.97

*The probability that the MAST MMPR reduced the outcomes compared with the original MMPR.
CrI, credible interval; IMU, intermediate unit; IRR, incidence risk ratio; MAST, Multi-Modal Analgesic Strategies in Trauma trial; MME, morphine milligram equivalent; MMPR, multimodal pain regimen; OR, odds ratio; RR, relative risk.

history of adopting MMPRs. The original MMPR was adopted in 2013 and was, at first, resisted by many providers. To normalize the fact that acute pain due to trauma could be controlled with opioid-minimizing MMPRs took many years. This trial was performed in a trauma center where the culture of treating acute pain in an opioid-minimizing manner was established. Implementing the MAST MMPR in centers without such an established background could either limit or increase the MMPR's effectiveness. Lastly, although total MMEs provided better model fit compared with MMEs per day, opioid prescribing at discharge is more compelling as a surrogate for persistent opioid use. Future studies should consider opioid prescribing at discharge as the primary endpoint.

CONCLUSIONS

The MAST MMPR reduced opioid exposure and discharge from the hospital with an opioid prescription while achieving similar pain control after trauma. These findings underscore the efficacy of opioid-minimizing strategies after trauma and the MAST MMPR has become usual practice for injured patients admitted to our trauma center.

Appendix

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Invited Commentary

Pain Management in Trauma: Maximizing Multimodals to Minimize Opioids

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The US has been challenged with an opioid crisis, as these medications account for a substantial number of fatal and nonfatal overdoses. Surgeons are on the front lines of this epidemic, balancing the treatment of pain, while confronting the risks of opioids, such as gastrointestinal effects, respiratory distress, delirium, increased hospital length of stay, and potential misuse or diversion.[1,2] Recently, progress has been made in this battle, as opioid-related deaths fell in 2018 for the first time in decades.[3] The decrease in opioid-related deaths mirrors opioid prescribing rates, as they have been declining over the recent years.[4]

Various systemic initiatives can be attributed to the decrease in opioid prescribing, including use of prescription drug monitoring programs, opioid prescribing limits, and rescheduling of hydrocodone by the Drug Enforcement Agency.[5] At the bedside, nonpharmacologic measures, as well as nonopioid medications, can be a used to decrease opioid use while providing pain relief.[1] Recently, the American College of Surgeons Trauma Quality Improvement Program (TQIP) released pain management guidelines, in which emphasis is placed on the importance of the role of multimodal pain management in trauma patients. Multimodal pain control often encompasses pharmacologic therapy such as "around the clock" acetaminophen and nonsteroidal anti-inflammatory drugs along with muscle relaxants, other nonopioid medications, regional anesthesia, and when needed, opioid medications. Nonpharmacologic therapies can be helpful in the pain management armamentarium and can include positioning, splinting, heat/cold therapy, and cognitive modalities. Education about expectations for management of pain is a powerful tool to inform patients that pain is normal after sustaining a trauma, and the goal is not to remove pain entirely, but to alleviate pain to allow function.[2]

To help improve opioid prescribing, Harvin and colleagues[6] examined a multimodal prescribing approach to trauma patients. Of the 1,561 patients who were randomized into either the original multimodal pain regimen (MMPR) group or the multimodal analgesic strategies for trauma (MAST MMPR), the 774 patients in the latter group had lower morphine milligram equivalents (MME) per day, and fewer patients were prescribed opioids at discharge. This study demonstrated that patients admitted to an adult trauma service can reach a successful level of pain control with a single dose of ketorolac, and fixed dosing of oral acetaminophen, naproxen, gabapentin, and lidocaine patches, therefore reserving opioids for breakthrough pain as needed.[6]

While the authors focused on pharmacologic protocols, further work can include nonpharmacologic therapies, as noted above. Not only is the management of a patient's pain important for patient satisfaction and a quicker road to recovery, but it is also essential for the patient's mental health. Including cognitive modalities and education about pain can address important facets of pain. Patients who are involved in trauma can often develop mental health symptoms, such as depressive mood, post-traumatic stress disorder (PTSD), or pain interference with their daily functioning. Pain interference can be described as how pain affects both a patient's physical and psychological function, in addition to the patient's perception of the extent to which pain limits daily activities. The coexistence of pain and mental health problems after a trauma can lead to more complex management of psychiatric care and higher healthcare costs.[7] While there was no statistically significant difference in pain scores between the 2 groups in the article, the authors have added to the evidence that a multimodal pain approach can reduce the amount of opioids used.[6] It would be interesting to use a more objective means of measuring pain, such as a functional pain score as outlined in the TQIP Acute Pain Management in Trauma Patients Guidelines, while simultaneously evaluating a patient's mental health to see if they coincide.[2]

This study can assist trauma teams to implement an MMPR and work toward reducing prescribing opioids

APPENDIX

ADDITIONAL STATISTICAL DETAILS

With the exception of the nonparametric approach used for MMEs per day, the current project reports Bayesian posterior probabilities. Briefly, a traditional, frequentist p value provides the probability of observing the data, or data more extreme if the null hypothesis is true. Note that such a value only addresses the question of interest indirectly, which is the probability that the alternative hypothesis is true. Bayesian posterior probabilities are statements about the probability that the alternative hypothesis is true given the observed data. This focus on the probability that the alternative hypothesis is true, which is simply not available in conventional frequentist analyses, maps more directly onto the question clinical decision-makers have, which is, "given what we know, what are the chances this approach will confer benefit or harm?"

A priori analyses specified Bayesian generalized linear models with extremely vague priors (ie ~normal ($\mu = 0$, $\sigma = 1 \times 10^{-3}$) for intercepts and coefficients within each model's respective link function. Specification of error terms used a ~folded Student's *t*-test distribution (degrees of freedom = 3, $\mu = 0$, $\sigma = 10$).[1] Robustness of prior assumptions used weak priors for the intercept and coefficients (ie ~normal ($\mu = 0$, $\sigma = 10$)) with error terms continuing to use ~folded Student's *t*-test distribution (degrees of freedom = 3, $\mu = 0$, $\sigma = 10$). Practically speaking, this weak prior has the effect of shrinking estimates towards the null hypothesis of no effect, producing a more conservative estimate than the extremely vague prior. Comparison of the resulting posterior estimates based on different prior distributions permits evaluation of the degree to which the results are robust to the assumptions of the prior distributions.[2] As might be expected, given the large sample size, posterior estimates did not differ in any substantive way across these prior distributions. Model fitting and selection used the Leave-One-Out-Cross-Validation Information Criterion and posterior predictive checking.[3,4] Inability to fit an adequate parametric model to the primary endpoint (ie MMEs per day) required that we apply nonparametric analyses to this endpoint. This latter analysis used a stratified Wilcoxon rank sum test, applying the Hodges and Lehmann alignment method.[5-7] All other models fit parametric assumption.

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eTable 1. Opioid Exposure and Discharge Opioid Prescribing by Unit of Admission

	Unit of admission					
	ICU		IMU		Floor	
Opioid exposure and pain	Original MMPR (n = 260)	MAST MMPR (n = 265)	Original MMPR (n = 215)	MAST MMPR (n = 213)	Original MMPR (n = 312)	MAST MMPR (n = 296)
MMEs/d	47 (21–75)	38 (15–69)	39 (16–62)	25 (12–55)	57 (32–80)	36 (18–60)
Total MMEs	498 (210–928)	385 (110–941)	146 (60–290)	127 (54–348)	174 (87–320)	123 (50–250)

Data are presented as median (interquartile range).
IMU, intermediate unit; MAST, Multi-Modal Analgesic Strategies in Trauma trial; MME, morphine milligram equivalent; MMPR, multimodal pain regimen.

eTable 2. Interaction Between Treatment Group and Unit of Admission for Outcomes of Total Morphine Milligram Equivalents and Opioid at Discharge

Outcomes, interaction	Interaction on RR scale	Posterior probability
Total MMEs, IRR (95% CrI)		
MAST MMPR:IMU	1.46 (1.08−1.97)	0.99
MAST MMPR:ICU	1.42 (1.07−1.89)	0.99
Total MMEs: zero inflation, OR (95% CrI)		
MAST MMPR:IMU	1.90×10^{3} (7.86×10^{-5}−1.60×10^{14})	0.84
MAST MMPR:ICU	4.71 (5.29×10^{-7}−3.02×10^{9})	0.61
Opioid at discharge, RR (95% CrI)		
MAST MMPR:IMU	1.11 (0.93−1.33)	0.89
MAST MMPR:ICU	0.93 (0.78−1.12)	0.77

CrI, credible interval; IMU, intermediate unit; IRR, incidence risk ratio; MAST, Multi-Modal Analgesic Strategies in Trauma trial; MME, morphine milligram equivalent; MMPR, multimodal pain regimen; OR, odds ratio; RR, relative risk.

eTable 3. Secondary Outcomes by Group

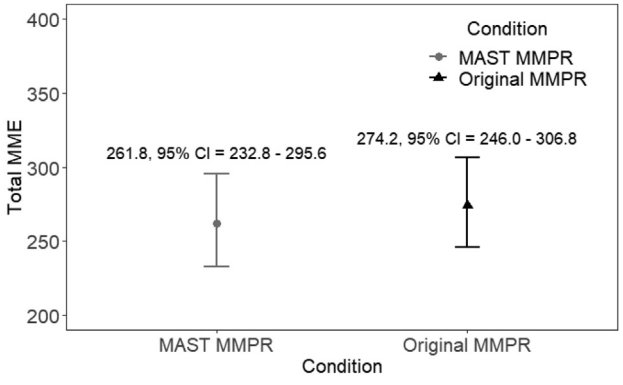
Outcomes	Original MMPR* (n = 787)	MAST MMPR* (n = 774)	Posterior probability†
Hospital stay	4.97 (4.59−5.38)	5.12 (4.72−5.55)	0.76
ICU days	0.21 (0.12−0.34)	0.21 (0.13−0.35)	0.54
Ventilator days	0.08 (0.03−0.18)	0.06 (0.03−0.14)	0.27
ACDiT	0.66 (0.56−0.78)	0.70 (0.59−0.82)	0.73

*For simplification, zero-inflated models are presented as estimated marginal mean (95% credible interval).
†Posterior probability that the MAST MMPR had a higher estimated marginal mean than the original MMPR.
ACDiT, adapted Clavien-Dindo in trauma scale; MAST, Multi-Modal Analgesic Strategies in Trauma trial; MMPR, multimodal pain regimen.

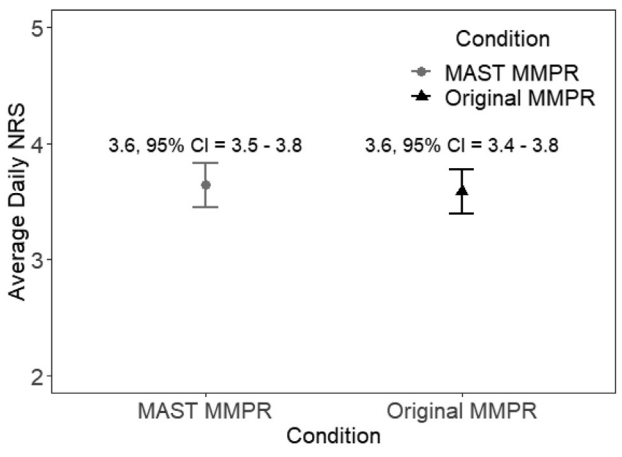
eTable 4. Additional Secondary Outcomes

	Original MMPR (n = 787)		MAST MMPR (n = 774)				
Outcomes	**n**	**%**	**n**	**%**	**Relative risk**	**95% credible interval**	**Posterior probability***
Unplanned intubation	16	2	16	2	1.01	0.50−2.00	0.51
Unplanned admission to ICU	30	4	31	4	1.03	0.63−1.69	0.56
Cardiac arrest with CPR	18	2	13	2	0.71	0.34−1.43	0.17
Ileus	41	5	45	6	1.08	0.72−1.62	0.35
Naloxone reversal	7	1	6	1	0.85	0.27−2.63	0.39

*The posterior probability is the probability that the relative risk is greater than 1, indicating that the original MMPR had increased events compared with the MAST MMPR.
MAST, Multi-Modal Analgesic Strategies in Trauma trial; MMPR, multimodal pain regimen.



eFigure 1. Estimated total morphine milligram equivalents (MMEs) as a function of group. MAST, Multi-Modal Analgesic Strategies in Trauma trial; MMPR, multimodal pain regimen.



eFigure 2. Estimated mean daily Numeric Rating Scale (NRS) pain score as a function of group. MAST, Multi-Modal Analgesic Strategies in Trauma trial; MMPR, multimodal pain regimen.