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Multimodal analgesia is superior to opiates alone after tibial fracture in patients with substance abuse history

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Abstract

Objectives: To evaluate the effectiveness of multimodal analgesia in patients with a tibial shaft fracture.

Design: Retrospective review.

Setting: Large, urban, academic center.

Patients: One hundred thirty-eight patients were evaluated before implementation of multimodal analgesia. Thirty-four patients were evaluated after implementation. All patients were treated operatively with internal fixation for their tibial shaft fracture. Patients with polytrauma were excluded.

Intervention: Multimodal analgesia.

Main Outcome Measures: Pain levels at rest and with movement were assessed. Morphine milligram equivalents (MMEs) dosed per patient were calculated each day. Length of stay was also documented.

Results: After implementation of a multimodal analgesic program, there was a statistically significant decrease in pain score at rest (4.7–4.0, $P = 0.034$) and with movement (5.8–4.8, $P = 0.007$). MMEs dosed in the multimodal analgesic program correlated with pain score ($R^2 = 0.5$), whereas before implementation of the program, MMEs dosed were not dependent on pain score ($R^2 = 0.007$). Patients with a history of substance abuse had the most profound effect from this paradigm change. For those with a history of substance abuse, treatment of pain using a multimodal approach reduces MMEs dosed and length of stay (5.7–3.1 days, $P = 0.016$).

Conclusions: Multimodal analgesia improves patient pain scores both at rest and during movement. In patients with a history of substance abuse, multimodal analgesia not only decreases pain but also decreases length of stay and MMEs dosed to levels consistent with someone who does not have a substance abuse history.

Level of Evidence: Therapeutic Level III.

Keywords: multimodal analgesia, substance abuse, tibial fracture, pain management

1. Introduction

There are approximately 70,000 hospitalizations because of tibial shaft fractures in the United States, with close to 500,000 fractures occurring each year, predominantly in a younger population.[1] Although these fractures can sometimes be managed in the outpatient setting through casting, a significant portion of these fractures require operative repair. Without operative treatment, these fractures can be slow to heal and can cause permanent disability.[2] Operative treatment is dependent on the severity of the fracture and can include internal and/or external fixation and staged treatment plans in fractures where there is significant deformity.[3] The preferred operative treatment is intramedullary nailing[4] where osseous union, length, and alignment are reproducibly able to be achieved.[5]

Tibial fractures are quite painful, but ineffective coping strategies and pain medication regimens can make the pain much more severe for the patient. Patients with tibial fractures require postoperative pain management. While postoperative pain is expected, it can be variable in patient experience. Opioids are the primary medication given to patients to treat their pain, but these drugs are not always effective alone and carry a high risk of dependence. Patients who take opioids often report greater pain intensity and less satisfaction regarding pain relief compared with those on a multimodal regimen.[6] There is also very little evidence that opiates are more

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beneficial than other analgesics.[7] In addition, over 50% of patients on single drug regimens report that they are dissatisfied with their pain management postinjury, with this dissatisfaction not dependent on the type of analgesia received.[7,8]

A multimodal approach to both increase pain control and decrease opioid use is often required. Multimodal analgesia combines medications from two or more drug classes to achieve a synergistic effect at lower doses than individual medications alone.[9,10] These plans are personalized to include supplemental nonpharmaceutical interventions, such as massage, dimming the lights, and music therapy, with the goal to not only lower opioid dosing but also to produce fewer adverse events.[9,11]

The purpose of this study was to compare patient pain scores and the amount of opiates used by patients with tibial fractures enrolled in a multimodal pain control program with patients receiving opiates as needed. We hypothesize that patients with tibial fractures on a multimodal pain control regimen will have less opiate consumption per day and a reduction in pain at rest and with movement compared with those receiving opiates. Patients with a history of alcohol or substance abuse are often excluded from pain studies because they can confound the results. We analyzed this group of patients separately, hypothesizing that multimodal pain control can improve their responses after tibial fracture as well.

2. Methods

Approval was obtained from our institutional review board to perform this study (HHC-2020-0117). The author discloses in the methods section of the manuscript that any investigation involving human subjects or the use of patient data for research purposes was approved by the committee on research ethics at the institution in which the research was conducted in accordance with the Declaration of the World Medical Association (www.wma.net) and that any informed consent from human subjects was obtained as required. This study was a retrospective, nonrandomized, single-center observational study comparing morphine milligram equivalents (MMEs), length of stay, and pain scores (Numeric Rating Scale [NRS]) before the implementation of multimodal analgesia and after the hospital-wide adoption of multimodal analgesia on September 1, 2019.

Patients were included in the study if they were between the ages of 18 and 80 years and were admitted with a tibial fracture between August 1, 2016, and May 15, 2020. The following diagnosis codes were used to include all tibial fractures, S82.1-9. Patients were excluded from the study if their data set was incomplete; if they had polytrauma or injuries in addition to an isolated tibial fracture; if they had a contraindication for any of the standard multimodal regimen, including any allergies to methocarbamol, acetaminophen, or gabapentin; if their length of stay was less than 1 day because this was due to the patient having an ancillary procedure such as a manipulation under anesthesia or an external fixator removal; or if they had undergone a previous surgery for the tibial injury.

A patient was determined to have a history of substance abuse if their chart indicated "ethanol abuse," "opiate abuse," or "substance abuse." Patients currently taking buprenorphine/naloxone with a documented substance abuse history were also included in this cohort. Patient charts were assessed to determine whether substance abuse was an active problem. For patients where alcohol or illicit drugs played a role in their injury, the chart was individually evaluated to determine whether the patient likely had a history of substance abuse, that is, multiple emergency department (ED) visits for alcohol intoxication.

The multimodal analgesic program at our institution combines 975 mg acetaminophen by mouth every 6 hours, 300 mg gabapentin 3 times daily, and 750 mg methocarbamol 4 times daily, with opioids given only for breakthrough pain.[11] Before the implementation of multimodal analgesia, patients received 975 mg acetaminophen by mouth as needed and 5–10 mg of oxycodone by mouth every 3 hours, also as needed. All patients with a tibial fracture receive a peripheral nerve block. Nonsteroidal anti-inflammatory drugs are not prescribed because of a minimal risk of nonunion.[12,13]

A power analysis was completed for MMEs using a clinically meaningful significant difference in MMEs of 15%. The power analysis for MMEs showed that each group would need 28 patients for a total patient pool of 56. With 56 patients, the probability is 80% that the study will detect a treatment difference at a 2-sided 0.05 significance level if the true difference between treatments is 15 MME.

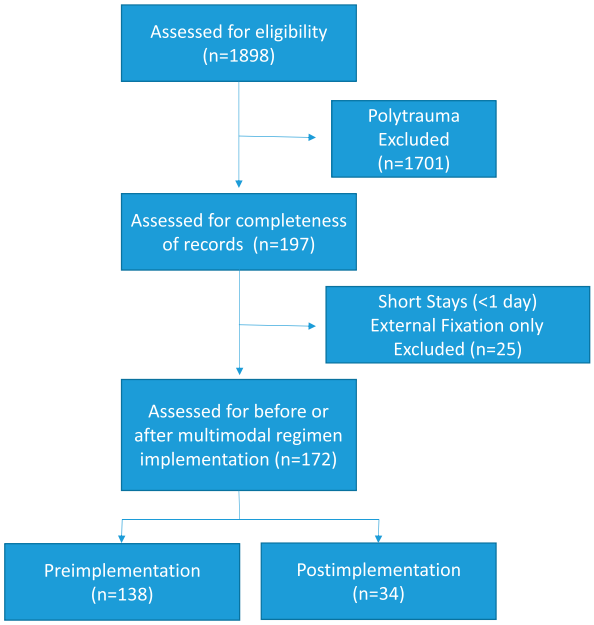
Analyses compared the preimplementation with postimplementation pain scores and MMEs used per day between patients receiving opiate-based pain control postoperatively and patients receiving multimodal pain control postoperatively. Because the data were normally distributed, parametric statistical tests were conducted. A 2-tailed Student t test was used to compare the multimodal pain group with the opiate pain group for both variables: pain score change and MMEs received per day. All analyses were conducted using Microsoft Excel 2016. All results yielding $P < 0.05$ are deemed statistically significant.

3. Results

A total of 1628 patients in the preimplementation group and 270 patients in the postimplementation group were assessed for eligibility (Fig. 1). Once patients with polytrauma were manually assessed and excluded, there were 157 patients in the preimplementation group and 40 patients in the postimplementation group. For this patient group, polytrauma was defined as injuries in addition to an isolated tibial fracture. After further excluding patients with incomplete data sets, short stays, and external fixation only, there were 138 cases before implementation of the multimodal regimen available for analysis and 34 cases after implementation.

Before implementation, the patient pool ranged from age 18 to 80 years, with 50% of the population being male. After implementation, the patient pool ranged from age 24 to 80 years, with 55% of the population being male. Patients with a substance abuse history in both groups were more likely to be older and male. For those with a history of substance abuse, before implementation, the age range was 35–73 years, with 60% of the patients being male. After implementation, the age range was 34–69 years. All patients were male. All patients in the preimplementation and postimplementation groups received general anesthesia during their procedure.

For all patients, length of stay, ED return rate, and cumulative MMEs dosed were comparable (Figs. 2A–C). A statistically significant difference was seen in pain levels, both at rest and with movement in patients who received multimodal analgesia (Fig. 2D). Pain at rest showed a drop of 0.7 units ($P = 0.034$), and pain with movement showed a drop of 1 unit ($P = 0.007$). MMEs dosed after implementation are highly correlative with pain score ($R^2 = 0.499$), whereas before this implementation, MMEs dosed were not as dependent on pain score ($R^2 = 0.161$).



	Age Range	% Male	Anesthesia Type
Preimplementation (All)	18-80	50%	General
Postimplementation (All)	24-80	55%	General
Preimplementation (substance use)	35-73	60%	General
Postimplementation (substance use)	34-69	100%	General

Figure 1. Selection process for inclusion, including patient demographics.

When patients were striated by sex, male patients tended to experience greater pain levels than female patients and require additional MMEs ($P = 0.002$) but also responded more favorably to the implementation of multimodal analgesia ($P = 0.007$) (Fig. 3A). Despite this difference in perceived pain level, there was no significant difference seen in daily MMEs when striated by sex

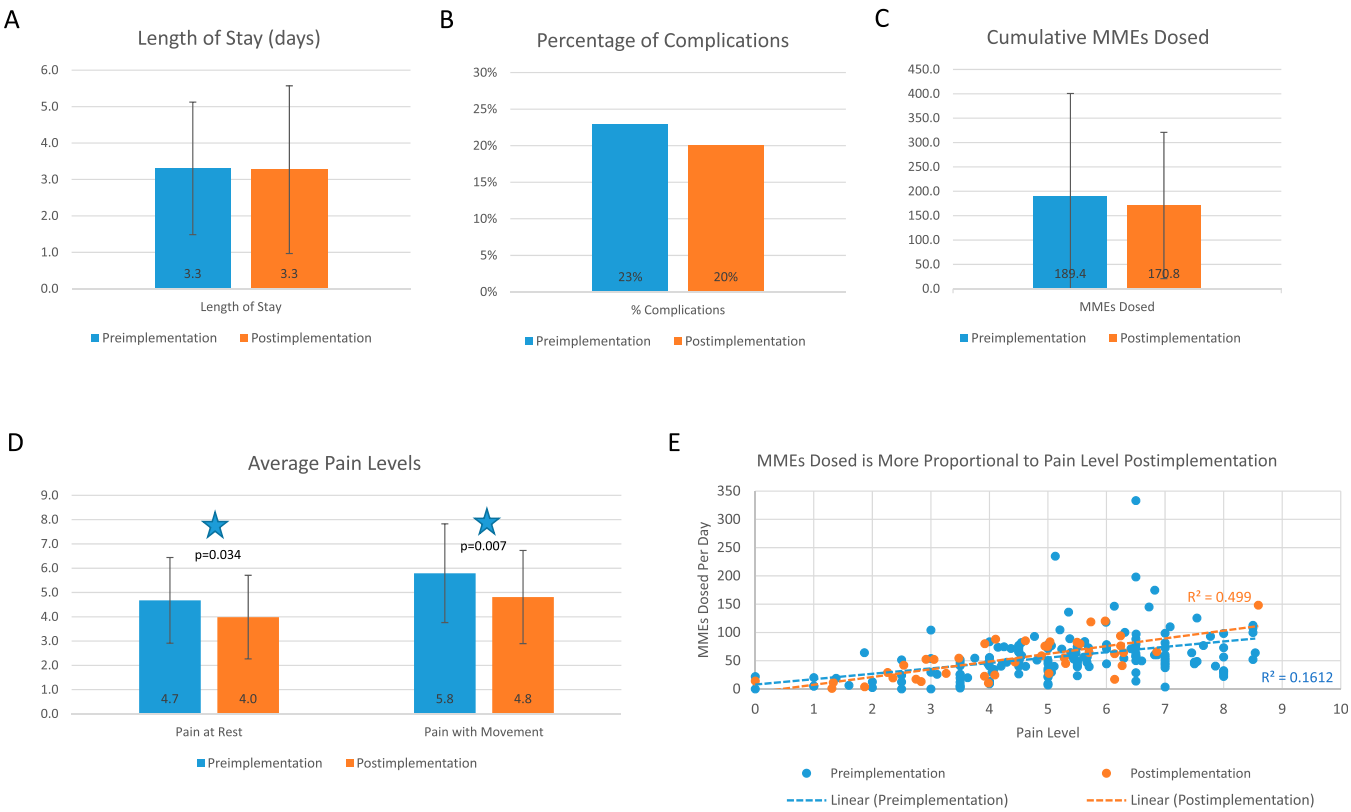


Figure 2. Multimodal analgesia reduces pain levels and allows for more precise opiate dosing. Blue bars indicate preimplementation of multimodal analgesia. Orange bars indicate postimplementation of multimodal analgesia. A, Length of stay for the population in days. B, Percentage of patients with postoperative complications, before implementation and after implementation. C, Cumulative MMEs dosed for these populations. D, Average pain levels at rest (first set of bars on left) and with movement (second set of bars on right). Pain levels are significantly reduced at rest ($P = 0.034$) and with movement ($P = 0.007$) in the postimplementation group. Statistical significance greater than 0.05, as denoted by the blue star. E, Scatterplot comparing pain levels with MMEs dosed per day, before implementation and after implementation and corresponding linear trend lines and R^2 values, indicating that postimplementation pain scores and MMEs are more correlative.

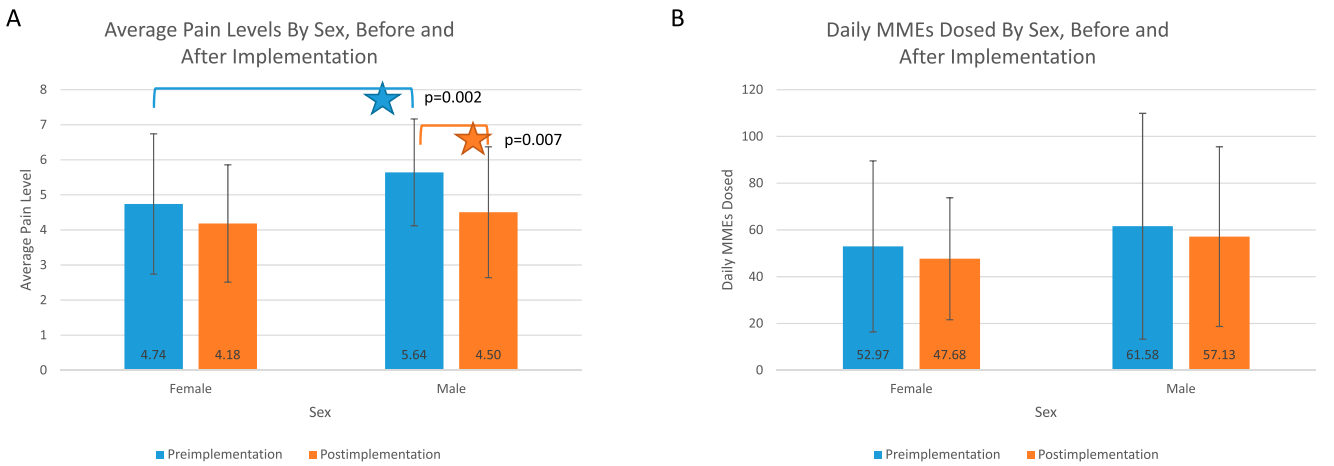


Figure 3. Sex affects pain levels and MME dosing. Blue bars indicate preimplementation of multimodal analgesia. Orange bars indicate postimplementation of multimodal analgesia. A, As a whole, female patients seem to perceive pain less acutely than male patients ($P = 0.002$, blue star). Although both groups showed a reduction in pain after implementation, this was statistically significant only in male patients ($P = 0.007$, orange star). B, Daily MMEs were also higher in male patients as compared with female patients, although this difference was not statistically significant.

(Fig. 3B), although there is a trend toward male patients requiring more MMEs than female patients before implementation ($P = 0.228$).

The substance abuse subgroup was analyzed separately. Before implementation, those with a history of substance abuse had a significantly longer length of stay ($P = 0.009$) than those without any history of substance abuse, which was not because of social factors (Fig. 4A). Once multimodal analgesia was implemented, those with a history of substance abuse had a 3-day decrease in their average length of stay ($P = 0.015$, Fig. 4A), which was similar to the length of stay seen in patients without a substance abuse history. Complication rates, defined as return to the ED for pain management, deep vein thrombosis, or infection, are greater for those with a history of substance abuse; however, multimodal analgesia was able to reduce the complication rate for these patients by 7% (Fig. 4B).

Cumulative MMEs dosed followed the same trend as length of stay (Fig. 4C). Multimodal analgesia caused a reduction in pain score, and this reduction was much more pronounced in patients with a history of substance abuse (NRS 6.6–4.0, $P = 0.086$) compared with those without that history (NRS 5.7–4.8, $P = 0.045$) (Fig. 4D). Before the implementation of multimodal analgesia, those with a history of substance abuse were rating their pain as almost 1 full unit higher than patients without a history of substance abuse (Fig. 4D).

4. Discussion/Conclusion

We have shown that our multimodal analgesia regimen is most beneficial for patients with a history of substance abuse. Although multimodal analgesia does decrease pain for all patients, the decreases in pain, length of stay, and breakthrough opiate use in patients with a history of substance abuse are profound in this understudied patient population.

The Orthopedic Trauma Association's Clinical Practice Guidelines recommend multimodal analgesia as opposed to opioid monotherapy for acute musculoskeletal injury.[14] Patient comfort and safety must be carefully balanced, with the amount of opiates prescribed tailored to the patient's injuries and comorbidities.[14] As a whole, orthopaedic injuries cause a high degree of pain.[15–19] The pain after orthopaedic surgery is complex in nature, and appropriate management is important in allowing for early mobilization, resulting in reduced complications, such as blood clots, and subsequent better function.[17,19] Owing to the painful nature of the procedures that they perform, orthopaedic surgeons account for 7.7% of all opioid prescriptions, making orthopaedics one of the highest prescribing specialties of opiates.[20,21]

The use of multimodal analgesia has been associated with a decrease in opiates, although the decrease is often statistically but not clinically significant. Our data support this conclusion. These results are similar to those seen by Rasmussen et al[22] in their study of multimodal analgesia after total hip arthroplasty. However, not all studies on multimodal analgesia have found the program to be beneficial. Maheshwari et al[23] stopped their trial of multimodal analgesia after spine surgery after finding that pain management and opioid use were not reduced to clinically significant parameters.

Multimodal regimens vary between institutions and departments, making it difficult to compare treatment modalities across subspecialties. A large number of nonopioid medications and combinations have been used in clinical practice, although rarely have these combinations undergone rigorous single factorial trials,[24] and clinicians are dependent on meta-analyses for recommendations.[10,24–27]

Gabapentinoids, in particular, have come under recent scrutiny. These anticonvulsants are also used on-label and off-label to treat chronic neuropathic pain. More recently, gabapentinoids have been used in the management of pain postoperatively to decrease pain and subsequent opiate use.[26] The clinical benefit of these drugs has been mixed. Gabapentinoids seem to decrease pain scores, but not opioids used.[14] Some studies show a significant effect in pain reduction compared with opiates,[18,27–29] but some double-blinded studies, including one sponsored by the manufacturer,[18,22,30] do not show such an effect. A recent meta-analysis by Verret et al[26] evaluated the use of gabapentinoids on postoperative acute pain and did not find large difference in pain scores or MMEs, although both values were trending lower. Despite some of the time points reaching statistical significance, clinical significance was not achieved during this study. The authors concluded that gabapentinoids do not seem to be effective at preventing postoperative pain.[26] Our study found that the addition of gabapentin showed a mild benefit in reducing pain scores and MMEs in the general patient population. However, there

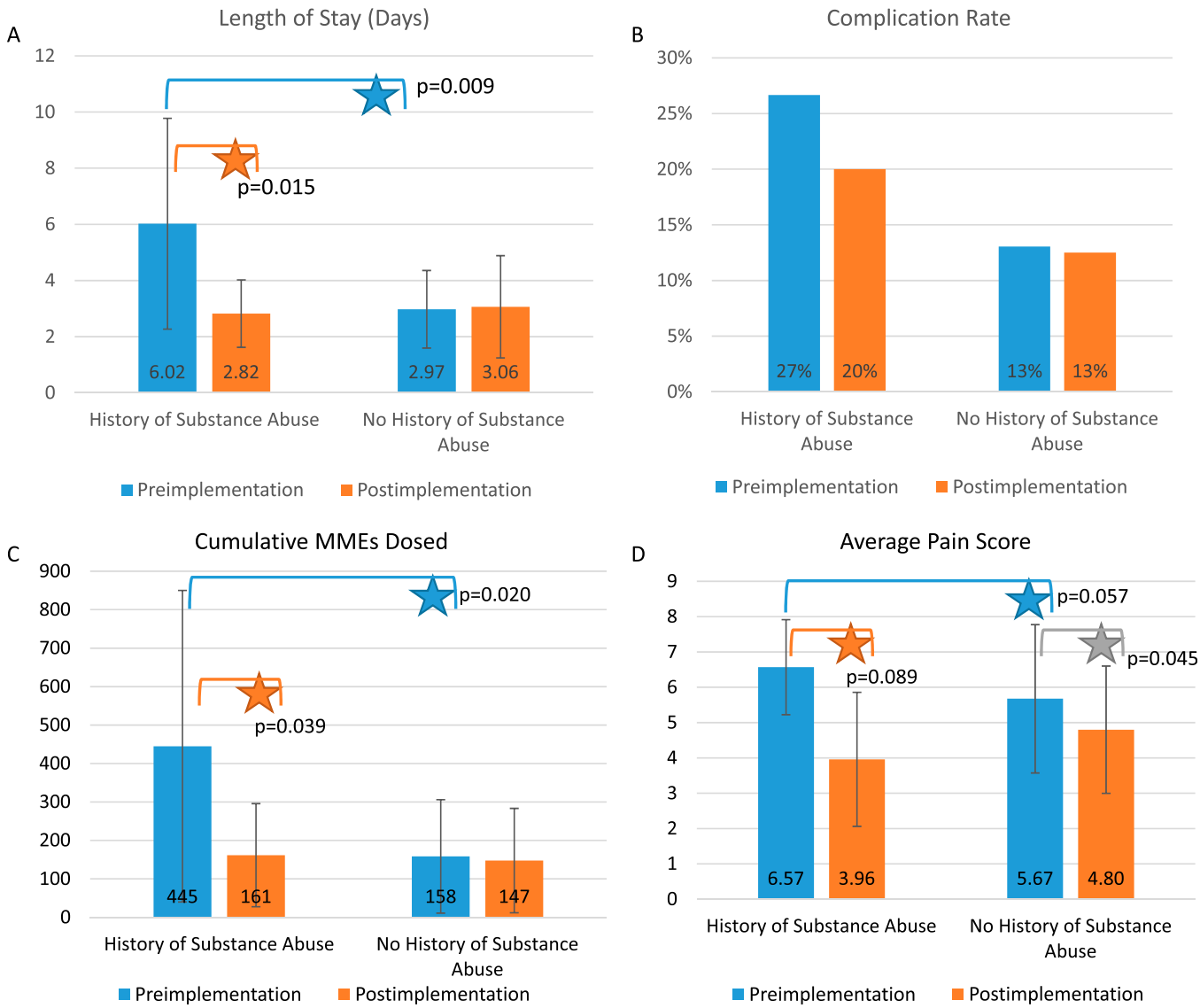


Figure 4. Multimodal analgesia normalizes parameters for patients with a history of substance abuse. Blue bars indicate preimplementation of multimodal analgesia. Orange bars indicate postimplementation of multimodal analgesia. A, Before the implementation of multimodal analgesia, patients with a history of substance abuse stayed on average 6.02 days. This is significantly different than those without a history of substance abuse ($P = 0.009$, blue star). After implementation, patients with this history stayed 2.82 days ($P = 0.015$, orange star). B, Complication rates for patients with a history of substance abuse were reduced after implementation of multimodal analgesia. C, Cumulative MMEs were reduced from 445 to 161 after implementation of multimodal analgesia in patients with a history of substance abuse ($P = 0.039$, orange star). Before the implementation of multimodal analgesia, cumulative MMEs dosed were significantly different between those with a history of substance abuse and those without ($P = 0.020$, blue star). D, Average pain scores were reduced overall after the implementation of multimodal analgesia ($P = 0.045$, gray star). Significant differences were seen in those with a history of substance abuse ($P = 0.089$, orange star). Patients with a history of substance abuse originally perceived their pain to be much greater than those without that history (6.57–5.67, $P = 0.057$, blue star).

was a substantial benefit from the addition of multimodal analgesia when used in patients with a substance abuse history.

In opiate-tolerant individuals, pain management is much more complicated. Patients with a history of substance abuse have a hypersensitivity to pain which persists even after the patient is no longer using opiates.[31] Substance abuse often contributes to trauma as well, with over a third of the trauma population having a positive toxicology screen.[18] For the subgroup of patients with a history of substance abuse, our data tells a much more positive story. Multimodal analgesia reduces length of stay, cumulative MMEs, and pain scores for these patients in a clinically significant fashion. It is clear that with our multimodal protocol,[11] this population benefits the most. Although multimodal analgesia is important for reducing opiate consumption as a whole, its effect on pain seems to be strongest in a population sensitized to the addictive effects of illicit drugs and alcohol. We suggest that studies on the effectiveness of multimodal analgesia should be expanded to include people with current and past substance abuse to determine what group most benefits from this medication regimen after trauma or surgery.

Some limitations for our study include the retrospective nature of this study, the small number of patients after implementation who also have a history of substance abuse, and our lack of long-term follow-up for these patients. Ideally, we would like to see whether patients are still using opiates at 30 or 90 days postfracture and how their pain levels have responded to the multimodal regimen, although this is not possible in this retrospective study because these data points were not collected.

In addition, patients could be more closely matched regarding age, sex, and pre-existing conditions.

In our experience, multimodal analgesia consisting of 975 mg acetaminophen by mouth every 6 hours, 300 mg gabapentin 3 times daily, and 750 mg methocarbamol 4 times daily seems to reduce pain levels and overall reduces the amount of break though opiates given. The effect is small in patients without a history of substance abuse. For patients with a history of substance abuse, the effect of our multimodal protocol is profound and we strongly recommend that patients with any history of substance use disorder be given a multimodal protocol which minimizes opiate use.

In conclusion, this study indicates that multimodal analgesia helps patients with isolated tibial fractures undergoing operative fixation, especially in patients with a history of substance abuse. For these patients, treatment of pain using a multimodal approach decreases MME requirements and reduces length of stay, decreasing the care burden. Future studies will further striate patients by medical condition to look for additional trends within this population.

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