Pregabalin vs. Gabapentin on Reducing Opioid Usage in Trauma Patients

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Protocol

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Abstract

The pain following trauma can be difficult to manage because it can have more than one cause and differ from patient to patient. It is not uncommon for trauma patients to have localized pain related to their injuries coupled with a component of nerve pain. Pregabalin and gabapentin have both been effectively used in many studies to reduce opioid pain medication usage in patient care. Gabapentinoids (pregabalin and gabapentin) have historically been used to treat seizures, nerve pain, and anxiety. Current research, however, has successfully shown their effectiveness as pre- and post-operative pain medications. However, these studies have examined single-dose use of pregabalin/gabapentin in the management of postoperative pain and opioid consumption. As of yet, studies have not investigated the efficacy of multiple-dose administrations of these drugs on opioid consumption. The purpose of this study is to test the effectiveness of using multiple doses of pregabalin or gabapentin in combination with traditional opioid pain medications in order to decrease the amount of opioid pain medication usage in trauma patients. The primary outcome is to compare those receiving multiple doses of pregabalin vs. gabapentin vs. those receiving neither, and to determine daily average opioid requirement at 24 hour increments up to 7 days following initiation of study medication.

Word Count-163

Aims/Objectives

Primary Objective:

To determine if adding multiple doses of pregabalin or gabapentin upon admission will reduce opioid usage in trauma patients in the first 7 days of hospitalization or until discharge, if discharge < 7 days post-enrollment.

Secondary Objectives:

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I. To compare the change in documented incentive spirometry values from morning physical assessment among patients in each of the study groups who have at least 1 rib fracture. Decreased pain scores may correlate with improved incentive spirometry values, which may facilitate recovery from lung-related injury.

II. To compare the proportion of patients requiring intubation among the study groups. Worsened pain is associated with respiratory distress which increases likelihood of intubation.

III. To assess effectiveness of pain control in each arm based on the average Numeric Pain Rating Scale score per 24 hours following randomization. This scale is a 10 point numeric scale that ranges from 0 that represents "no pain" to 10 which indicates the "worst pain imaginable."

IV. To evaluate the differences among the study arms with respect to hospital length of stay and unplanned ICU admissions.

Background

According to the Centers for Disease Control and Prevention, trauma is the fourth leading cause of death in the United States.[1] It is a major cause of mortality throughout the world. There are many factors that can affect morbidity and mortality in trauma patients including pain. Trauma introduces acute as well as chronic pain into the lives of its victims.[2] In a study by Gross and Amsler, severity of pain before and at least 2 years after poly-trauma, which was defined as patients with a well-defined injury of at least two body regions, was evaluated. After 2.7±0.9 years following injury, only 54% of poly-trauma patients were fully rehabilitated. An astonishing 59% had to undergo a change in their occupation due to their injury(s). In addition, 2 years post-trauma 85% of these patients continued to experience pain.[3] Literature suggest that 22% of the population experience chronic pain and more than one third of those cases are the result of trauma. Forty-six percent of long-term survivors of high energy trauma report daily pain after their trauma as compared to only 5% before the accident.[2]

Improved pain management in trauma patients leads to increased comfort as well as reduced morbidity and improved long-term outcomes.[4] Successful approaches for achieving adequate pain control can vary greatly from patient to patient resulting in difficulty with the routine provision on analgesia. Pain in trauma patients can be a complicated process. Injury severity is often related to the level of pain experienced by trauma patients; however, pain alone can complicate a patient's condition and potentially lead to further clinical deterioration of the patient. Baseline physiology of trauma patients can widely vary from young athletes to elderly frail adults. Presenting with multiple injuries, substance use disorder, delayed care, as well as psychological and emotional issues can further complicate the care process. Understanding pain in trauma patients and how to manage it is crucial to their care.

The opioid crisis in the United States is a public health epidemic. Opioid overdose is a leading cause of injury-related death in the US and costs $78.5 billion a year.[5,6] West Virginia has been cited as having the highest rate of death due to drug overdoses (51.5 deaths per 100,000) by the CDC in 2018.[7] Opioid tolerance occurs in individuals who consume opioids for long-term management of chronic pain, those who are or have been illicit users, or those who are enrolled in opioid substitution programs.[9] Effective management of acute pain in opioid tolerant patients is more difficult. Analgesics may be required for a longer period of time and may deviate from the standard treatment protocols. In an article by Mehta and Lanford, it is discussed that if a patient presents with an opioid tolerance an alternative strategy may be needed to properly manage a patient's acute pain needs. When choosing pain medications, it is best to attempt the use of less addicting medications for the shortest period of time needed. Successful pain management in recovering addicts also poses unique challenges to providers as they struggle to decide if the patient is drug seeking or relapsing, which can be misinterpreted from tolerance.[10]

Pregabalin and gabapentin are controlled substances in the state of West Virginia, but they both are considered adjuvant analgesics which have analgesic properties.[11] By using multi-modal analgesia that targets different pathways of pain in the central and peripheral nervous system, individualized targeted patient therapy is provided.[12] In a trauma patient, whose pain is already difficult to control, this can be an alternative to typical opioid medications or used in conjunction to provide optimal patient centered pain control. Pregabalin and gabapentin are comparable in their mechanism of action, but the drugs differ in their pharmacokinetic and pharmacodynamic characteristics. Both drugs are absorbed by the gastrointestinal tract and are distributed across the blood brain barrier.[13] Gabapentin is slowly absorbed with maximal plasma concentrations in 3-4 hours with oral administration. Pregabalin is absorbed much more rapidly with maximal plasma concentrations within 1 hour after oral administration. Both drugs decrease the release of neurotransmitters from brain tissues though the mechanism of action is not fully understood. Both are approved for treatment of neuropathic pain as well as partial seizures. With gabapentin, 50-75% of the dose (between 1800mg - 4800mg) are not absorbed. The bioavailability is enhanced by any agent that slows down transit time in the small intestines. Pregabalin, however, has greater than or equal to 90% systemic absorption and is not affected by agents which decrease gastrointestinal motility.[14]

There are several studies that support the efficacy of pregabalin and gabapentin in reducing pain when used alone or in conjunction with opioid pain medications. These studies have included evaluations of these agents for pre and postoperative pain management as well as post-traumatic pain.[12, 15, 16-18] Mishra et all conducted a study comparing pregabalin with gabapentin in chronic post thoracotomy pain. Pregabalin was given to patients one hour prior to their surgery and could be administered at lower doses because it has a higher bioavailability (90% vs 33-66%) and it is rapidly absorbed with its peak in 1 hour. The study concluded that pregabalin was an effective and safe adjuvant for reducing chronic post-thoracotomy pain in all age groups and gender without side effects.

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Pain relief was statistically significant after three weeks of treatment and it continued till about six months.[15] In another study, Arumugam, Lau, and Chamberlain examined postoperative opioid consumption in patients undergoing different abdominal and thoracic surgeries. They observed a significant decrease in opioid consumption when using gabapentin.[12] Eidy and colleagues designed a three arm study looking at gabapentin, pregabalin, or placebo effects on pain control in patients undergoing a laparoscopic cholecystectomy. A single pre-operative dose of gabapentin (800mg), pregabalin (150mg) and placebo were given. The study included 108 patients, with 36 in each group and concluded that gabapentin and pregabalin had significantly lower postoperative pain intensity scores than placebo. When compared to each other, pregabalin had significantly lower pain intensity scores than gabapentin. The placebo arm required significantly more postoperative analgesic therapy.[16]

Likewise, pregabalin and gabapentin has been used in management of post-traumatic pain. Gordh and associates looked at the use of gabapentin in traumatic nerve injury pain. When looking at the pain relief between the two treatment periods, more patients reported the pain had subsided by half during the gabapentin treatment (n=22) than during the placebo treatment (n=8). Gabapentin was more efficacious to placebo in providing pain relief by reducing the pain at least by half and improving the overall status of the patient reported by both clinician and the patient.[17] Singh et al looked at the effectiveness of pregabalin in management of post-traumatic peripheral nerve injury not responding to other analgesics. The conclusions of both the case studies reviewed showed improved results.[18]

In conclusion, it is felt that trauma patients may benefit from the use of gabapentin or pregabalin in their pain control regimen. Pain management is a complicated process as patient's needs are individualized and so is their pain control requirements. Current studies have examined the effectiveness of preoperative single-dose or perioperative use of pregabalin/gabapentin in the management of postoperative pain and opioid consumption. As of yet, studies have not investigated the efficacy of extended administrations of these drugs on opioid consumption. Moreover, the majority of

the existing literature focuses on studies that have been conducted with patients having scheduled surgery and therefore administration of these drugs were standardized. Management of trauma patients on the other hand varies as patients present with varying injuries and requires individualized care plans. Accordingly, this study aims to reduce patients' consumption of narcotics in the hospital by utilizing multiple doses of adjunctive non-opioid analgesia for pain management in trauma patients.

Significance

The incidence of prescription opioid analgesic use has continued to increase and unfortunately the death rate from drug overdoses has shown a similar increase over the last several years. With alarming rates of drug-related deaths in West Virginia and the U.S. overall based on CDC data, it is crucial for clinicians to understand the impact that medical use of opioids may have on patients' mental and physical health. Especially, in the trauma patient population where opioid-based analgesia is commonly used to manage acute pain, it is important to treat the patient's pain without adding to the already growing problem. It is important for practitioners to be mindful and try to prescribe the lowest most effective dose needed to optimally control pain. Use of adjunctive analgesics may help lessen the amount of opioids prescribed and help the patient on their path of healing not just physically, but also emotionally and mentally.

Methodology

Study design

This will be a prospective, randomized trial with patients admitted to Charleston Area Medical Center's (CAMC) Trauma Services under the care of Nurse Practitioners (NPs) with attending supervision. Patients included in this study will be separated in three groups: Group A: Patients will be started on gabapentin upon admission after consented. They will receive 300 mg PO every 8 hours without dose titration. Group B: Patients will be started on pregabalin upon consent. They will receive 50 mg every 8 hours without dose titration. Group C: Patients in this group will be neither on gabapentin

nor pregabalin upon consent. In Groups A and B, patients with CrCl < 60mL/min will receive same dose given q12 hours. The q12 hour regimen may be increased to q8 hours if CrCl increases above 60mL/min during the 7 days study period or until discharge (if < 7 days post-enrollment).

Inclusion Criteria

1. NP service admissions
2. 18 year of age and older
3. Patients enrolled within 36 hours of admission
4. Anticipated duration of hospitalization $\geq$ 24 hours from time of consent
5. Active order(s) for opioids in place at the time of enrollment

Exclusion Criteria

1. Clinician discretion based on patient care management
2. Intubated patients
3. Patients with epidural or peripheral nerve block
4. Patients with pregabalin/gabapentin as home medications
5. Patients receiving pregabalin/gabapentin upon admission
6. Traumatic brain injury patients
7. CrCl<30ml/min or on HD
8. Unable to take enteral medications
9. On Patient Controlled Analgesia (PCA)
10. Patients with complicated wound closure
11. History of epilepsy
12. Documented history of substance use disorder (this exclusion criterion was chosen to provide consistency among the study population as pain management may differ among these patients)

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Setting

Charleston Area Medical Center's General Hospital, a Level 1 Trauma Center.

Sample Size

A sample size of 70 patient per study group which includes 10% attrition will be targeted (a total of 210 patients). This is based on Cohen's d formula with a significance of 0.05, 80% power and a medium effect size. Previous studies have evaluated the impact of single dose administration of pregabalin and gabapentin on pain and opioid consumption and were mostly conducted with patients having scheduled surgery. The current study, however, is designed to examine the effectiveness of multiple doses of these drugs in acutely injured trauma patients. Therefore, past reliable data could not be used for the power calculation for this study and Cohen's *d* coefficient was used for effect size. A medium effect size, which indicates a 69% difference between treatment and control groups was set by clinicians. For sample size estimation, instead of using effect size for the overall ANOVA which tests a general hypothesis we utilized effect sizes for the planned comparisons [(pregabalin vs. gabapentin); (pregabalin vs. neither pregabalin nor gabapentin); (gabapentin vs. neither pregabalin nor gabapentin)] using t-statistic.

Procedure/Protocols

Pre-intervention

- The clinical research coordinator will review the investigator's census on a daily basis in order to identify new admissions who may be study candidates.
- All patients who are eligible will be informed about the study. Patients with capacity who agree to participate will be consented using the consent form as written within 24 hours of admission. A note will be made in the patient's chart detailing the consent.

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- A randomization schedule will be generated using a SPSS algorithm. Patients will be assigned a study number and allocated to a respective study arm in order as they are consented.
- Both pregabalin and gabapentin are frequently used as adjunct analgesia in this patient population at CAMC. Thus, there will be no additional cost for participating in the study. However, blinding would not be in the best interest of the study because the design of these medications are identifiable to the trauma providers and it will be costly to get them blinded for this study. The patient will sign and date the consent and the HIPAA authorization form (which will be attached to the consent). Each patient will be assigned a patient study number and randomized accordingly to a pre-determined study arm.
- Original signed consent will be kept and stored in a binder at the CAMC Trauma Research Office. A copy of the consent form will be placed in the patient's chart and another will be given to the participant.

Intervention

- Patients in the pregabalin group will receive 50 mg q8 without dose titration. Patients in the gabapentin group will receive 300 mg q8 without dose titration. Patients enrolled with CrCl < 60mL/min will receive same dose given q12 hours.
- Adjunctive non-opioid analgesia, i.e. non-steroidal anti-inflammatory agents, may also be added at the managing service's discretion. Non-narcotic analgesia as adjunctive therapy may be added at the managing service's discretion. Total daily acetaminophen dose is not to exceed 3 gm.
- Following enrollment, the patients' opioid analgesia regimen may be increased or decreased at the managing service's discretion. Narcotic analgesic can be increased or decreased by 2.5 mgs of oxycodone or equivalent (i.e. oxycodone 5 mg q4 hrs as needed

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to 7.5 mg oxycodone q4 hrs as needed) or increasing the dose of intravenous morphine by 2 mgs or equivalent.

- Decreasing dose of the opioids is at the discretion of the managing service.
- Patients with pre-existing narcotic use will be placed on their home regimens or an intravenous equivalent using a standardized dosing conversion table and adjustments can be made at the discretion of the managing service.

Data Collection

Data will be collected via patient chart review and institution's trauma registry. Data will be collected in an Excel spreadsheet. The following data will be collected for each patient:

- Demographics
  - Gender
  - Age
  - Height
  - Weight
  - Date & time of hospital admission and discharge
  - Comorbidities
- Urine and drug screen
- Admitting injury list
- Length of Stay
- Pre-existing (home) analgesic regimens
- Prior exposure of pregabalin or gabapentin
- Surgery dates and surgeries performed
- Inpatient analgesic exposure prior to enrollment (medications, dose, # of doses) and 7 days post-enrollment or until discharge (if < 7 days post-enrollment)

- Initial Incentive Spirometry value and 7 days post enrollment or until discharge (if < 7 days post-enrollment)
- Documented pain scores for each 24-hour period post-enrollment for 7 days or until discharge (if < 7 days post-enrollment)
    - Additional notation will be made to indicate the first pain score that coincides with the initiation of study medication
- Post-enrollment complications (unplanned intubation, unplanned ICU admission, incidence of VTE, infection, pneumothorax requiring chest tube placement, other)
- Post enrollment daily creatinine value from Basic Metabolic Panel
- Side effects including somnolence, dizziness, fatigue, ataxia, tremor, amnesia and others

Data Analysis

Descriptive analysis will be conducted for each variable in this study. Means and standard deviations or medians and interquartile ranges for continuous variables will be reported. For categorical variables, proportions and frequencies will be computed. To assess statistically significant difference between two cohorts, t-tests or Mann-Whitney U will be conducted for continuous variables. Categorical variables will be compared using chi-square or Fisher's Exact test. Outcome variables will be analyzed with ANCOVA or binary logistic regression controlling for differences in patient characteristics. A sub-analysis will be conducted by examining outcomes based on the number of days patients stay in the hospital post-enrollment. All comparisons will be performed at a level of significance of $p \leq 0.05$. Analysis will be done using 22.0SPSS version.

Subject Population

There are no known vulnerable participants to be included (specifically those under 18, prisoners, or those with pre-existing cognitive defects).

Benefits

Our study might show that pregabalin and gabapentin as adjunctive non-opioid analgesia may significantly reduce opioid usage in trauma patients, which will perhaps lessen complications related to use of opioids in trauma patients.

Risks and Discomfort

Both pregabalin and gabapentin are routinely used as adjunctive non-opioid analgesia by NPs in trauma patient care; and therefore, there is no added risk to their standard care regimen.

Consent Process

All patients who are eligible will be informed about the study. Patients will be informed that their participation is completely voluntary and whether they decide to participate or not will in no way affect their current or future relationship with their attending physicians, residents, or staff at Charleston Area Medical Center (CAMC). Furthermore, they will be also informed that they have the right to withdraw from the research at any time without penalty.

Patients with capacity who agree to participate will be consented using the consent form as written within 36 hours of admission. A note will be made in the patient's chart detailing the consent. The patient will sign and date the consent and the HIPAA authorization form (which will be attached to the consent). Each patient will be assigned a patient study number and randomized accordingly to a pre-determined study arm. Original signed consent will be kept and stored in a binder at the CAMC Trauma Research Office. A copy of the consent form will be placed in the patient's chart and another will be given to the participant.

Confidentiality

Any documents with study information will be kept in a locked office. Patient FIN will be linked to the study number so that we can ensure full data extraction without compromising the patients' privacy. Any electronic data will contain minimal PHI or no PHI. All electronic data will be password protected and can only be accessed by study personnel.

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Costs/Payments

The patient will be responsible for all co-pays and deductibles associated with routine care billable to insurance and/or them. There will be no additional financial burden to the patient for participating in the study.

Payment to Subjects

None

Investigators

Primary Investigator: Nancy Payne APRN, CNP

Co-Investigators: Wes Kafka, PharmD, BCCCP, MBA

Other Participants/Research Support

- Nancy Duvall, RN-BC, MS
- Damayanti Samanta, MS

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