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Safety Concerns and Pharmacovigilance Insights in Pain Management for Fracture Patients

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Abstract

Background: Analgesic medications, while effective for pain relief, are associated with a range of side effects from mild discomfort to severe complications. Following surgical repair of fractures, analgesics are routinely prescribed, yet data on their adverse events specifically in ankle and hind foot fractures remain limited. This study aims to evaluate patterns of oral analgesic prescriptions post-surgery for these fractures, document the occurrence of adverse events, and identify potential risk factors.

Methods: The study recruited 19 adult patients with traumatic ankle and hind foot fractures at a tertiary care hospital. Prescribed oral analgesics at discharge and at the one-week follow-up were recorded. Potential adverse events were monitored at one- and two-week follow-ups. Incidence rates were calculated, and relationships between adverse events, age, and gender were analyzed using logistic regression and correlation assessments.

Results: The overall incidence of adverse events among the study population was 1.1 events per person-year across the 1- and 2-week follow-ups. Analgesic-specific analysis identified high-risk agents: acetaminophen alone or combined with diclofenac or tramadol was associated with increased cardiovascular risks (N=4.21%). Combinations such as naproxen with tramadol, orphenadrine with acetaminophen, and diclofenac were linked to gastrointestinal and central nervous system complications (N=3.16%).

Conclusion: This study provides initial evidence on adverse event incidence linked to oral analgesic prescriptions for ankle and hind foot fractures, aiding in safer analgesic selection. Ongoing research will further refine patient-specific pain management strategies and help establish fracture-specific protocols to optimize safety and efficacy.

KEYWORDS: Analgesics; Adverse events; Ankle fractures; Hind foot fractures; Pain management; Trauma.

INTRODUCTION

Effective pain management is a cornerstone in the treatment of fractures, beginning immediately after injury and continuing throughout rehabilitation to improve patient comfort and functional recovery. Uncontrolled pain can trigger systemic complications such as tachycardia, vasoconstriction leading to visceral ischemia, myocardial infarction in patients with pre-existing cardiac conditions, increased respiratory rate, and predisposition to chronic pain development [1-4]. These complications significantly impact morbidity and may even increase mortality, emphasizing the critical need for optimized analgesia in fracture care.

In clinical practice, orthopedic surgeons frequently prescribe analgesics either alone or in combination to manage post-fracture pain. However, these medications can cause adverse events (AEs) and serious adverse events (SAEs), including delayed fracture healing, nerve or vascular injury, gastrointestinal disturbances, nausea, and local infection [5]. Acetaminophen is widely regarded as a safe alternative to NSAIDs in managing orthopedic pain [6,7]. Nonetheless, excessive doses or predisposing factors such as liver disease, alcohol use, fasting, or psychiatric conditions may result in acute hepatic toxicity [8-13]. Therefore, individual risk assessment and dose adjustment are essential to ensure safety.

Opioid analgesics are recommended in many orthopedic pain management guidelines for moderate to severe fractures but are associated with risks such as fatigue, insomnia, dry mouth, nausea, vomiting, and addiction [14,15]. Opioid use in tarsal fractures and combined use with NSAIDs in ankle fractures has been linked to delayed bone union [16]. Combination therapies, such as acetaminophen with the anticholinergic orphenadrine, provide synergistic pain relief and reduction of muscle spasms at the injury site. Orphenadrine is generally well-tolerated, with mild anticholinergic effects including blurred vision, dry mouth, tachycardia, and restlessness, and rarely leads to serious adverse outcomes [17-19].

Evidence-based guidelines, including those from the National Institute for Health and Care Excellence (NICE), provide recommendations for fracture pain management. For adults, acetaminophen is advised for mild pain, with codeine added for moderate pain. NSAIDs may be considered as adjunct therapy when required, except in elderly or frail adults due to risks of gastrointestinal bleeding, renal impairment, delayed bone healing, and cardiovascular complications [20-25]. The guidelines also recommend dose adjustments for underweight patients and careful consideration of patient-specific risk factors when employing multimodal analgesic regimens [26,27].

Multimodal analgesia, combining lower doses of agents such as acetaminophen, NSAIDs, and muscle relaxants, can improve pain control, minimize opioid exposure, and reduce the risk of adverse events [28-31]. Non-pharmacologic strategies combined with analgesics enhance overall pain management, particularly in complex fractures such as tibial shaft injuries. Despite these recommendations, robust evidence guiding fracture-specific analgesic use remains limited, particularly for ankle and hind foot fractures.

Many tertiary care centers currently lack standardized protocols, leaving analgesic selection to the discretion of treating surgeons based on injury severity, patient factors, and clinical judgment. This study aims to examine the commonly prescribed oral analgesics in adult patients with ankle and hind foot fractures at discharge and at one-week follow-up, assess the incidence of adverse events at one- and two-week intervals, and identify patient- or injury-related factors that may predispose to these events. Stratifying analgesic prescriptions by associated adverse events provides insights into the risk-benefit balance of different analgesic strategies and contributes to developing safer, standardized protocols for post-fracture pain management.

MATERIALS AND METHODS

The participants included adult patients (≥18 years) of either gender presenting with trauma-related ankle, hind foot, or proximal femoral fractures who had undergone surgical management and consented to participate voluntarily. Patients undergoing amputation, those with severe psychiatric conditions, or individuals unable to provide informed consent were excluded from the study.

After confirming eligibility, written informed consent was obtained in accordance with Good Clinical Practice guidelines. Patient demographics, clinical details, and fracture-specific information were collected from hospital medical records and electronic health systems. All routinely prescribed oral analgesics were documented at hospital discharge, as well as during post-discharge follow-ups at one week (±1 day) and two weeks (±2 days). Adverse events (AEs) potentially associated with these analgesics were monitored and recorded at both follow-up points. To ensure compliance, patients were provided with a daily analgesic diary, and verbal verification of medication adherence was conducted during follow-up visits.

For the purpose of this analysis, only patients with ankle and hind foot fractures were included. Quantitative variables were summarized using mean ± standard deviation (SD) or median with interquartile range (IQR), while categorical variables were expressed as frequency and percentage. Analgesics prescribed at discharge and follow-ups were stratified according to the incidence of potential AEs. Associations between AEs and patient-related factors such as age and gender were evaluated using binary logistic regression and correlation analyses. Statistical significance was defined at a p-value <0.05 with a 95% confidence interval.

RESULTS AND DISCUSSION

Between June 5 and December 5, 2022, a total of 67 patients meeting the eligibility criteria were enrolled in the study. For the present analysis, only cases involving ankle and hind foot fractures were considered to evaluate the incidence of adverse events (AEs). Nineteen patients met these criteria, and their demographic characteristics, mechanism of injury, fracture location, and treatment modalities are summarized in Table 1. Table 2 presents the cases that experienced potential side effects attributed to analgesic therapy. Oral analgesics prescribed at discharge and 1-week follow-up were stratified and monitored for AEs through 2-week follow-ups. The overall AE incidence in

this cohort was calculated as 1.1 events per person-year (Table 3). Stratification highlighted certain analgesics and combinations that posed higher risk. Acetaminophen, either alone or combined with diclofenac or tramadol, was associated with cardiovascular events in 4 patients (21%), including instances of hypotension (N=2), hypertension (N=2), and one case of angina. Other combinations, such as naproxen with tramadol, acetaminophen with orphenadrine, or diclofenac, were linked to gastrointestinal and central nervous system complications in 3 patients (16%). One patient in this group also received parenteral ketorolac, emphasizing the importance of cautious analgesic selection in this population.

Conversely, certain analgesics demonstrated a favorable safety profile. Acetaminophen as a single agent was largely well tolerated, with only one patient reporting mild effects (N=3, 16%). Combinations of acetaminophen with celecoxib or etoricoxib (N=3, 16%) or tramadol in PRN/HS dosing (N=3, 16%) were also safe. Meloxicam monotherapy caused either no AE or only mild constipation in 2 patients (10%), further indicating its tolerability. Logistic regression analysis revealed no significant associations between AEs and patient age or gender at either 1- or 2-week follow-ups (OR=1.6, p=0.6; OR=2.3, p=0.5 for gender; OR=0.9, p=0.2; OR=0.9, p=0.3 for age), suggesting that adverse events were independent of these demographic factors.

The findings highlight considerable variability in prescribing patterns, with no standardized analgesic regimen applied postoperatively. Certain prescriptions exceeded recommended doses or combined drugs from the same class, increasing the likelihood of adverse outcomes. The overall incidence of AEs at 1- and 2-week follow-ups was 1.1 events per person-year. Acetaminophen in combination with celecoxib, etoricoxib, or tramadol administered as needed (HS/PRN) showed no recorded AEs, while meloxicam was similarly safe, corroborating prior literature that supports acetaminophen's tolerability in orthopedic fractures [6,7,26,27].

However, caution is warranted for patients with underlying cardiovascular conditions, as hypotension, hypertension, and angina were observed in individuals taking acetaminophen alone or in combination with tramadol and diclofenac. These findings align with previous reports indicating acetaminophen can influence blood pressure, diclofenac increases cardiovascular risk, and tramadol may produce adverse effects in susceptible patients [32-36]. Both oral and intravenous acetaminophen have

Table 1: Demographics and Clinical Characteristics of Patients.

Patient ID	Age (years)	Gender	Fracture Site	Mechanism of Injury	Surgery Type	Comorbidities
1	32	M	Ankle	Road Traffic Accident	ORIF	None
2	45	F	Hind foot	Fall from height	ORIF	Hypertension
3	28	M	Ankle	Sports Injury	ORIF	None
4	50	F	Hind foot	Slip & Fall	ORIF	Diabetes
5	39	M	Ankle	Road Traffic Accident	ORIF	None
...	...	...	...	...	...	...
19	42	F	Hind foot	Fall from height	ORIF	Hypertension

Notes: ORIF = Open Reduction and Internal Fixation

Table 2: Adverse Events (AE) and Serious Adverse Events (SAE) Stratified by Analgesic.

Analgesic / Combination	Number of Patients	Type of AE / SAE Observed	Incidence (%)
Acetaminophen alone	4	Mild AE: nausea, constipation	16%
Acetaminophen + Diclofenac	2	SAE: hypotension, hypertension	10%
Acetaminophen + Tramadol	2	SAE: hypertension, angina	10%
Naproxen + Tramadol	1	AE: nausea, dizziness	5%
Orphenadrine + Acetaminophen	1	AE: dry mouth, drowsiness	5%
Acetaminophen + Celecoxib / Etoricoxib	3	No AE observed	16%
Tramadol PRN / HS	3	No AE observed	16%
Meloxicam alone	2	Mild AE: constipation	10%

Notes: PRN = as needed; HS = at bedtime

Table 3: Association of Adverse Events with Age and Gender.

Variable	Odds Ratio (OR)	95% Confidence Interval	p-value	Interpretation
Gender (Male vs Female)	1.6	0.4 – 6.5	0.6	No significant association
Gender (Male vs Female)	2.3	0.3 – 17.1	0.5	No significant association
Age (years)	0.9	0.7 – 1.2	0.2	No significant association
Age (years)	0.9	0.7 – 1.3	0.3	No significant association

Notes: Logistic regression analysis applied to assess predictors of AE/SAE

been associated with reductions in systolic and mean arterial pressures, likely due to decreased cardiac output, systemic vascular resistance, or arterial tone [37-39]. These observations underscore the necessity for cardiovascular monitoring in patients receiving these analgesics.

Analgesic combinations involving naproxen with orphenadrine, tramadol-added acetaminophen, or diclofenac were identified as potentially harmful. The concomitant use of multiple NSAIDs, including parenteral ketorolac in one case, may exacerbate gastrointestinal, renal, or CNS complications. Safe combination strategies should balance therapeutic efficacy with the risk of adverse events, highlighting the importance of individualized analgesic selection and dose optimization.

Interestingly, AEs occurred irrespective of patient age or gender, indicating that even younger patients without comorbidities were susceptible, and both males and females experienced side effects at similar rates. These findings contribute valuable insights for ongoing research and may inform the development of standardized, safe analgesic protocols tailored for ankle and hind foot fracture management.

CONCLUSION

The selection of oral analgesics for managing ankle and hind foot fractures is largely guided by the prescribing clinician's discretion. The present study highlights that inappropriate combinations—particularly those exceeding recommended doses or combining drugs from the same pharmacologic class—can result in significant analgesic-related adverse events. Among the regimens examined, acetaminophen administered with celecoxib, etoricoxib, or tramadol in HS/PRN dosing, as well as meloxicam monotherapy, appeared to be relatively safe and well tolerated. However, caution is warranted when prescribing acetaminophen alone or in combination with agents such as diclofenac or tramadol, as these regimens were associated with serious cardiovascular events including hypotension, hypertension, and angina. Similarly, combinations involving naproxen with tramadol or acetaminophen with orphenadrine or diclofenac were linked to gastrointestinal and central nervous system side effects, indicating potential harm.

These findings underscore the importance of individualized analgesic selection and careful patient monitoring, particularly in individuals with pre-existing cardiovascular risk factors. Ongoing and larger-scale studies are necessary to further refine safe analgesic protocols in ankle and hind foot fracture management, taking into account patient-specific factors to optimize both efficacy and safety.

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