Test file: Variations in Pre-injury Anticoagulant Use Among Traumatic Brain Injury Patients Across Different Trauma Center Levels

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Abstract

Background: Pre-injury use of anticoagulant and antiplatelet medications is a significant risk factor for worse outcomes in patients with traumatic brain injury (TBI). These medications are commonly prescribed for conditions such as atrial fibrillation and venous thromboembolism. However, the prevalence and patterns of their use among TBI patients presenting to different levels of trauma centers remain inadequately characterized. Understanding these variations is crucial for risk stratification, protocol development, and resource allocation. Objective: This study aimed to determine the prevalence of pre-injury anticoagulant (AC) and antiplatelet (AP) medication use in adult TBI patients and to analyze how this prevalence varies across Level I, Level II, and Level III/IV trauma centers. Methods: A retrospective, multi-center cohort study was conducted using data from a statewide trauma registry over a three-year period. All adult patients (≥18 years) with a diagnosis of TBI (Abbreviated Injury Scale head region score ≥2) were included. Patients were categorized based on the level of the treating trauma center (Level I, II, or III/IV). The primary outcome was the documented use of any pre-injury AC (warfarin, direct oral anticoagulants - DOACs, heparinoids) or AP (aspirin, P2Y12 inhibitors) medication. Secondary analyses examined the specific types of medications, patient demographics, injury severity, and clinical outcomes (in-hospital mortality, neurosurgical intervention) across center levels. Results: Among 12,547 TBI patients analyzed, 2,831 (22.6%) were on pre-injury AC/AP therapy. Prevalence varied significantly by trauma center level: Level I centers had the highest prevalence at 25.8% (1,250/4,850), followed by Level II at 20.1% (1,020/5,075), and Level III/IV at 21.4% (561/2,622) ($p < 0.001$). Level I centers treated a significantly higher proportion of patients on DOACs (9.2% vs. 6.5% in Level II and 5.8% in Level III/IV, $p<0.001$) and had a higher mean patient age. While unadjusted mortality was higher in Level I centers (12.5% vs. 10.8% in Level II and 9.1% in Level III/IV), after adjusting for age, injury severity, and anticoagulant use, the risk-adjusted mortality odds were comparable. Patients on AC/AP therapy across all levels had higher mortality and rates of neurosurgical intervention compared to those not on such medications. Conclusion: The prevalence of pre-injury anticoagulant and antiplatelet use among TBI patients is substantial and varies systematically across trauma center levels. Level I centers manage a significantly higher burden of patients on these medications, particularly newer DOACs, reflecting patient complexity and referral patterns. These findings underscore the need for all trauma centers, regardless of level, to have protocols for rapid reversal of anticoagulation in TBI, while highlighting that Level I centers require enhanced readiness and resources to manage this

high-risk population.

Keywords: Traumatic Brain Injury; Anticoagulants; Antiplatelet Agents; Trauma Center Levels; Direct Oral Anticoagulants (DOACs); Epidemiology; Outcomes.

1.Introduction

Traumatic brain injury (TBI) represents a major cause of mortality and long-term disability worldwide [1]. The management of TBI is further complicated when patients are taking anticoagulant (AC) or antiplatelet (AP) medications prior to their injury. These agents, including warfarin, direct oral anticoagulants (DOACs), aspirin, and clopidogrel, are widely prescribed for the prevention of stroke in atrial fibrillation, treatment of venous thromboembolism, and management of cardiovascular disease [2]. Pre-injury use of these medications is associated with an increased risk of intracranial hemorrhage expansion, worse neurological outcomes, and higher mortality in TBI patients [3, 4].

In the United States and many other countries, trauma care is organized in a tiered system, with Level I centers providing the highest level of comprehensive care, including 24/7 availability of neurosurgery and immediate access to advanced resources like emergency reversal agents and neurocritical care [5]. Level II centers provide significant trauma care but may have more variable resources, while Level III and IV centers stabilize and transfer severely injured patients [6]. This system inherently leads to differential case mixes, with more complex and severely injured patients often triaged or transferred to higher-level centers.

It is plausible that the prevalence of patients on AC/AP therapy—who are often older and have more comorbidities—may differ across these trauma center levels due to geographic referral patterns, differences in the surrounding population's age and health status, and triage protocols [7]. Understanding these variations is not merely an epidemiological exercise; it has direct implications for clinical preparedness, protocol standardization, and resource allocation. For instance, a center with a high prevalence of patients on DOACs must ensure the availability of specific reversal agents like idarucizumab or andexanet alfa [8]. This study hypothesizes that Level I trauma centers treat a significantly higher proportion of TBI patients on pre-injury AC/AP medications compared to lower-level centers, reflecting a more complex and comorbid patient population.

2. Methods

2.1 Study Design and Setting

A retrospective, observational cohort study was conducted using data from a statewide trauma registry spanning January 2019 to December 2021. The registry includes all patients meeting trauma activation criteria treated at over 50 accredited trauma centers, categorized as Level I, II, or III/IV.

2.2 Study Population

Included patients were adults (≥18 years) with a primary or secondary diagnosis of traumatic brain injury, defined as an Abbreviated Injury Scale (AIS) score of 2 or greater in the head region.

Patients with isolated facial fractures (AIS face) without brain injury and those dead on arrival were excluded.

2.3 Variables and Outcomes

The primary exposure variable was the level of the treating trauma center (Level I, II, or III/IV). The primary outcome was the documented use of any pre-injury anticoagulant or antiplatelet medication, as recorded in the trauma registry's pre-hospital or admission medication history field. Medications were categorized as: Vitamin K antagonists (VKA, e.g., warfarin), Direct Oral Anticoagulants (DOACs: dabigatran, rivaroxaban, apixaban, edoxaban), therapeutic heparin/low molecular weight heparin (LMWH), aspirin, and P2Y12 inhibitors (clopidogrel, ticagrelor, prasugrel).

Covariates included patient demographics (age, sex), injury characteristics (mechanism, Injury Severity Score - ISS, Glasgow Coma Scale - GCS on admission), and key clinical outcomes (in-hospital mortality, need for neurosurgical intervention [craniotomy/craniectomy or intracranial pressure monitor placement]).

2.4 Statistical Analysis

Descriptive statistics were presented as means (±SD), medians (IQR), or frequencies (%). Group comparisons across trauma center levels were performed using ANOVA or Kruskal-Wallis tests for continuous variables and chi-square tests for categorical variables. The primary analysis compared the prevalence of AC/AP use across center levels. A multivariable logistic regression model was then constructed to assess the independent association between trauma center level and the odds of AC/AP use, adjusting for age, sex, and injury mechanism. A separate model assessed risk-adjusted mortality, adjusting for age, ISS, GCS, and AC/AP use. A p-value <0.05 was considered statistically significant. Analyses were performed using SAS v9.4.

3. Results

The final cohort consisted of 12,547 TBI patients: 4,850 (38.6%) treated at Level I centers, 5,075 (40.4%) at Level II, and 2,622 (20.9%) at Level III/IV centers.

3.1 Prevalence of Pre-injury AC/AP Use

Overall, 2,831 patients (22.6%) were on pre-injury AC/AP therapy. Prevalence varied significantly: 25.8% (1,250/4,850) in Level I, 20.1% (1,020/5,075) in Level II, and 21.4% (561/2,622) in Level III/IV centers ($p < 0.001$). After adjusting for age, sex, and injury mechanism in multivariable analysis, treatment at a Level I center remained independently associated with higher odds of AC/AP use compared to Level II (aOR 1.38, 95% CI 1.25-1.53) and Level III/IV centers (aOR 1.29, 95% CI 1.14-1.46).

3.2 Patterns of Medication Use

The pattern of specific medications also varied. Level I centers had the highest proportion of patients on DOACs (9.2% of all TBI patients), compared to 6.5% in Level II and 5.8% in Level III/IV ($p<0.001$). The use of warfarin and antiplatelet agents was also highest in Level I centers, though the differences were less pronounced.

3.3 Patient Characteristics and Outcomes

Patients at Level I centers were older (mean age 68.2 vs. 64.5 in Level II and 62.1 in Level III/IV, $p<0.001$) and had higher median ISS (17 vs. 15 vs. 14, $p<0.001$). Unadjusted in-hospital mortality was 12.5% in Level I, 10.8% in Level II, and 9.1% in Level III/IV ($p<0.001$). However, in the risk-adjusted model accounting for age, ISS, GCS, and AC/AP use, trauma center level was not an independent predictor of mortality (Level I vs. Level II: aOR 1.08, 95% CI 0.94-1.25; Level I vs. Level III/IV: aOR 1.12, 95% CI 0.95-1.32). As expected, AC/AP use was a strong independent predictor of mortality (aOR 1.65, 95% CI 1.45-1.87) and neurosurgical intervention (aOR 1.40, 95% CI 1.22-1.61) across all center levels.

4. Discussion

This statewide analysis confirms significant variation in the prevalence of pre-injury anticoagulant and antiplatelet use among TBI patients across different trauma center levels, with Level I centers managing the highest burden. The nearly 6-percentage-point absolute difference between Level I and Level II centers is clinically meaningful and supports our primary hypothesis.

The higher prevalence in Level I centers likely stems from multiple factors. First, these centers often serve as regional referral hubs for the most complex cases, including elderly fall patients with multiple comorbidities who are more likely to be prescribed AC/AP therapy [9]. Second, emergency medical services triage protocols may direct patients on anticoagulants with head trauma to the highest level of care due to perceived higher risk [10]. The notably higher use of DOACs in Level I centers is particularly relevant, as the management of DOAC-related bleeding requires specific knowledge and access to costly reversal agents that may not be routinely available at all facilities [11, 12]. This finding suggests that formulary planning and staff education regarding DOAC reversal should be prioritized at Level I centers.

The comparable risk-adjusted mortality across center levels is reassuring and speaks to the effectiveness of the tiered trauma system, where appropriate triage and transfer protocols ensure patients ultimately receive care commensurate with their injury severity and complexity [13]. However, the persistent, strong independent association between AC/AP use and worse outcomes across all levels reinforces that the presence of these medications, rather than where care is initially received, is a key driver of mortality and morbidity in TBI [14]. This universal risk underscores the necessity for all trauma centers, regardless of designation, to have clear, evidence-based protocols for the rapid identification and reversal of anticoagulation in head-injured patients [15].

5. Limitations

This study has limitations inherent to retrospective registry data. Pre-injury medication use is subject to reporting inaccuracies and may be under-documented, especially in altered patients. The registry does not capture details like medication adherence, timing of last dose, or laboratory values of coagulation (e.g., INR for warfarin). We also could not analyze transfer patterns in detail; some patients initially seen at Level III/IV centers and later transferred to Level I/II centers would only be represented in the data of the final treating center.

6. Conclusion

Pre-injury use of anticoagulant and antiplatelet medications is common in TBI patients and varies significantly by trauma center level, with Level I centers treating the largest and most complex cohort of such patients. These variations highlight differential preparedness needs across the trauma system. While Level I centers must be equipped to manage a high volume of patients on novel agents, all trauma centers require robust systems to identify and address anticoagulation in TBI. Future efforts should focus on standardizing reversal protocols across the care continuum and ensuring equitable access to necessary pharmacological agents to improve outcomes for this vulnerable population.

7. References

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