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Short Communication

Protective Effects of Angiotensin-Converting Enzyme Inhibitors on Developing Ankylosis of the Knee Following Knee Injury

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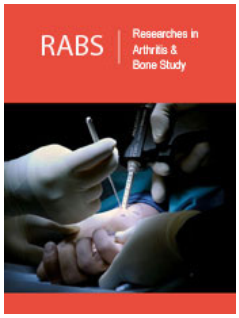
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Abstract

Purpose: Anterior cruciate ligament (ACL) injuries may lead to complications such as knee stiffness and ankylosis, resulting in functional impairment. Hypertension contributes to endothelial dysfunction and chronic inflammation, which may impair tissue healing and promote fibrosis. Angiotensin-converting enzyme (ACE) inhibitors possess anti-inflammatory and anti-fibrotic properties, whereas beta blockers do not demonstrate similar effects on fibrotic pathways. However, the impact of antihypertensive medication selection on musculoskeletal outcomes remains unclear. This study aimed to compare the risk of knee ankylosis in hypertensive patients with ACL injury treated with ACE inhibitors versus beta blockers.

Methods: A retrospective cohort study was conducted using the TriNetX Global Health Research Network, including over 134 million patients from 49 healthcare organizations. Patients with ACL injury and hypertension treated with either ACE inhibitors or beta blockers were identified. Cohorts were matched 1:1 based on age, sex, race, and obesity, yielding 3,666 patients per group. The primary outcome was knee ankylosis (ICD-10 M24.66). Risk differences, risk ratios, and Kaplan-Meier survival analyses were performed, with hazard ratios estimated using Cox proportional hazards models.

Results: Ankylosis occurred in 1.1% of the ACE inhibitor group and 1.7% of the beta blocker group. The risk difference was -0.7% (95% CI: -1.2% to -0.1%; p=0.017), with a risk ratio of 0.62, indicating a 38% relative risk reduction. Kaplan-Meier analysis demonstrated improved ankylosis-free survival in the ACE inhibitor cohort (p = 0.007), with a hazard ratio of 0.58 (95% CI: 0.39–0.87). Differences in recurrent episodes were not statistically significant (p = 0.272).

Conclusion: In hypertensive patients with ACL injury, ACE inhibitor use was associated with a significantly lower risk of knee ankylosis compared to beta blocker use. These findings suggest a potential musculoskeletal benefit of ACE inhibitors and highlight the role of systemic medication selection in orthopaedic outcomes. Prospective studies are warranted to confirm these findings.

Introduction

The anterior cruciate ligament (ACL) is one out of two ligaments that are responsible for providing stabilization of the knee joint [1]. The ACL is made of connective tissue and collagenous Fibers. This ligament is the most commonly injured ligament in the knee mostly due to sport injuries. The annual reported ACL injury incidence in the United States is 1 in 3,500 people most commonly affecting the younger and active population [2]. The prevalence of hypertension in the United States affects 49.4% of adults over the age of 20 years [3].

Hypertension has been increasingly observed amongst patients sustaining orthopaedic injuries as the active population ages.

Hypertension is associated with endothelial dysfunction which leads to impaired blood flow and a reduction of oxygen delivery to tissues. Hypertension exacerbates systemic inflammation through the sustained release of pro-inflammatory cytokines including Interleukin-6, Interleukin-17 and Tumor Necrosis Factor-alpha [4]. This dysfunction can lead to delay and impaired wound healing, and an increase in fibrotic changes following ACL injury. Angiotensin-converting enzyme (ACE) inhibitors are known to possess anti-fibrotic and anti-inflammatory properties and are used to treat hypertension. Several preclinical studies have shown that ACE inhibitors decrease scar formation through the downregulation of several genes leading to a decrease in fibroblast proliferation and collagen deposition in animal models [5,6]. Beta blockers are also used to manage hypertension and have been shown to provide cardiovascular protection. In literature, limited information is known about their activity on the pathways leading to fibrosis compared to ACE inhibitors [7].

Ankylosis of the knee is the pathological fusion of the knee involving the bones of the patella, tibia, and femur. According to the American Academy of Orthopaedic Surgeons (AAOS), an ankylosed knee is defined as a knee with an arc movement of less than 30 degrees. Knee ankylosis is a complication following acute cruciate ligament injury leading to knee stiffness and flexion contracture [8]. Although the literature lacks clear data on the incidence of knee ankylosis, knee stiffness, a known precursor has been reported to occur in 5–12% of patients six months after anterior cruciate ligament reconstruction [8]. Stiffness of the knee can significantly impair a person's function, leading to a reduction in the ability to perform daily life activities [8,9].

The biological processes underlying knee ankylosis following ACL injury involve a post-surgical inflammatory response, changes to cartilage metabolism, and mechanical factors. Studies have shown that post ACL injury inflammatory response is characterized by elevated levels of cytokines such as Interleukin-1β and Intyerleukin-6 [9,10]. Sustained inflammation contributes to cartilage degradation and promotes the formation of fibrotic tissue around the joint capsule, ultimately leading to restricted knee mobility and joint stiffness [9,10]. Studies have shown following ACL injury, alterations in knee joint kinematics and loading patterns can trigger increased inflammation, which may in turn promote fibrotic tissue formation within the joint.

The association between hypertension and ACL injury is an underexplored topic that influences musculoskeletal recovery. As the prevalence of hypertension continues to rise, its systemic effects, particularly endothelial dysfunction and chronic inflammation, disrupt the biological environment necessary for healing, increasing the risk of fibrotic complications such as ankylosis. Pharmacologic modulation with ACE inhibitors through the use of their anti-fibrotic and anti-inflammatory properties may confer protection in the development of fibrosis. Our studies aim to examine whether the choice of antihypertensive therapy influences the risk of a patient developing ankylosis following ACL injury.

Methods

This retrospective cohort study utilized data from the TriNet X Research Network, US Collaborative Network, an electronic health record repository of United States healthcare organizations aggregating de-identified electronic health records from 49 healthcare organizations.

Patients met the inclusion factor if they had a documented diagnosis of anterior cruciate ligament injury (International Classification of Disease (ICD)-10-CM code S83.51 – Sprain of ACL) and a concurrent diagnosis of hypertension (ICD-10-CM codes I10–I16). Patients were also required to have an active prescription for either an angiotensin-converting enzyme inhibitor or a beta blocker. Patients prescribed both medication classes concurrently were excluded to minimize confounding.

The outcome of interest was the development of knee ankylosis, defined by diagnostic coding using ICD-10-CM code M24.66 (Ankylosis of knee joint). Propensity score matching (1:1 nearest-neighbour matching without replacement) was performed based on age, sex, race, and obesity status to control for baseline differences. After matching, two balanced cohorts were established: 3,666 patients receiving ACE inhibitors and 3,666 patients receiving beta blockers, for a total of 7,332 patients.

Primary analyses assessed the incidence of knee ankylosis between groups using risk difference, risk ratio, and odds ratio calculations, with 95% confidence intervals reported. Statistical significance was defined as $p < 0.05$. Kaplan-Meier survival analysis was conducted to evaluate time to ankylosis, with differences assessed using the log-rank test. Hazard ratios and 95% confidence intervals were estimated using Cox proportional hazards models. The proportional hazards assumption was evaluated, and violations were noted. All data analyses were conducted using the TriNet X Analytics platform.

Results

In our study analysis, we have a total of 49 healthcare organizations from the TriNet X network contributing to a matched cohort of 7,332 patients. After propensity score matching for age, sex, race and obesity, two treatment groups were established: 3,666 patients receiving ACE inhibitors and 3,666 patients receiving beta blockers. All patients had a documented history of ACL injury and a diagnosis of hypertension.

We found that the incidence of knee ankylosis was significantly lower in the ACE inhibitor group compared to the beta blocker group (Figure 1). The absolute risk difference was -0.7%, indicating a lower occurrence of ankylosis among ACE inhibitor users. The risk ratio was 0.619, demonstrating that patients on ACE inhibitors had a 38% reduced risk of developing knee ankylosis compared to those on beta blockers. The odds ratio for developing ankylosis in the ACE inhibitor group was 0.615 (95% CI: 0.41–0.92, $p = 0.017$), suggesting a statistically significant reduction in risk.

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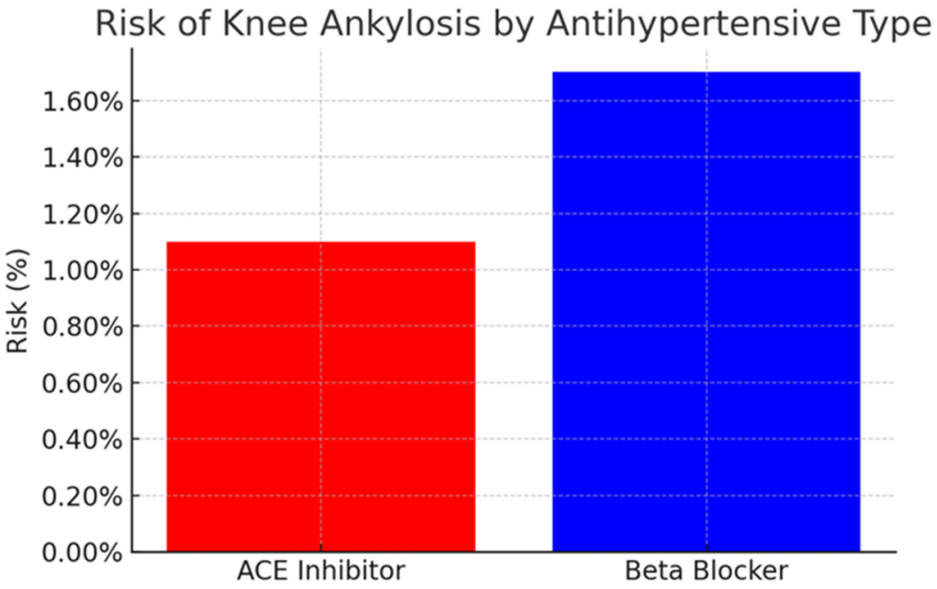


Figure 1: Risk of knee ankylosis by antihypertensive type.

Kaplan-Meier survival analysis revealed a significant difference in time to ankylosis between the two treatment groups. The log-rank test yielded a p-value of 0.007, indicating a statistically significant difference in the timing of ankylosis onset. The hazard ratio was 0.580 (95% CI: 0.389–0.865), suggesting that ACE inhibitor use was associated with a 42% reduction in the instantaneous risk of developing ankylosis over time. However, the p-value associated with the test for proportional hazards (p = 0.271) suggested that the proportional hazards assumption may not have been fully met. While patients in the ACE inhibitor group experienced fewer repeat episodes of knee ankylosis compared to those in the beta blocker group, this difference was not statistically significant.

Discussion

In this matched cohort study of patients with ACL injury and hypertension, those treated with ACE inhibitors had a significantly lower risk of developing knee ankylosis compared to those on beta blockers. The absolute risk of ankylosis was 1.1% in the ACE inhibitor group versus 1.7% in the beta blocker group, corresponding to a 38% relative risk reduction. Kaplan-Meier analysis confirmed a higher probability of remaining free from ankylosis over time in the ACE inhibitor group (Figure 2), and although the difference in the number of repeated ankylosis episodes did not reach statistical significance, the trend favoured ACE inhibitor use.

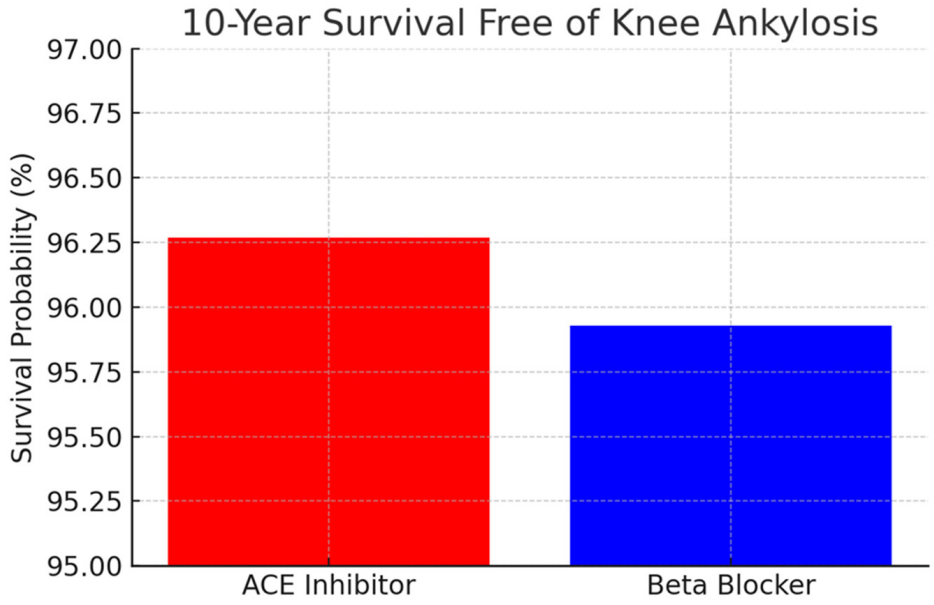


Figure 2: 10-Year survival free of knee ankylosis.

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The use of ACE inhibitors may offer protective effects in musculoskeletal health through their known anti-fibrotic and anti-inflammatory properties. Angiotensin-converting enzyme activity has been implicated in tissue remodelling and development of fibrosis, and its inhibition has been shown in preclinical studies to reduce joint stiffness and collagen deposition [6,11]. In this context, the use of ACE inhibitors may help mitigate fibrotic processes following ACL injury or surgery leading to a reduction of the risk of joint contractures and ankylosis. Additionally, ACE inhibitors have been associated with improved endothelial function and tissue perfusion, which may contribute to optimal healing environments post-injury through a decrease in oxidative stress [5].

In contrast, beta blockers, while effective for blood pressure control and cardiac protection, do not appear to confer similar benefits in joint health. In this cohort, beta blocker users had a higher incidence of ankylosis and slightly more repeat episodes. Beta blockers have limited effects on fibrotic pathways and have been shown in studies to reduce peripheral circulation, potentially impairing tissue repair [12]. While their use is necessary in specific cardiovascular contexts, this finding raises the possibility that in patients with orthopaedic injuries, beta blockers may lack the tissue-protective effects seen with ACE inhibitors.

Conclusion

Overall, the findings in this study highlight the importance of considering comorbid conditions and medication profiles in musculoskeletal injury recovery following ACL surgery. For hypertensive patients with ACL injury, ACE inhibitors may offer the dual benefits of effective blood pressure control and reduced risk of joint complications such as ankylosis. Further prospective studies are needed to confirm these associations and exploration of the mechanisms underlying the observed protective effects.

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