Review Article

ACE Inhibitor Use Does Not Significantly Affect Occurrence of Manipulation Under Anesthesia Following Total Knee Arthroplasty

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Conflicts of Interest Statement for Dr. Frederick

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Introduction

Common medications may attenuate fibroblast proliferation and scar tissue formation. This study aims to evaluate the association between angiotensin converting enzyme inhibitor (ACEI) use and post-operative stiffness assessed by rate of manipulation under anesthesia (MUA) and change in range of motion (ROM) following total knee arthroplasty (TKA).

Methods

Patients undergoing primary TKA January 2014 - September 2019 were identified. Demographic information, use of ACEI medications, occurrence of MUA in the 6 months following surgery, and ROM was determined by chart review. MUA was indicated upon failure to achieve 90° ROM at 1-month follow-up. Demographics were analyzed using Student's t-test and Chi-Squared tests. SPSS (version 24, IBM) multivariate regression calculated odds ratios for MUA controlling for age, BMI, American Society of Anesthesiologist's class, and gender.

Results

1590 primary TKA's were identified. 274 patients (17.3%) were taking ACEI medications. 46 patients required MUA (2.9%). Five patients (1.8%) taking an ACEI required MUA, versus 41 of the 1316 control patients (3.1%). No significant difference in MUA rates between the ACEI and control cohorts (odds ratio 0.670, 95% CI: 0.259 – 1.735, p=0.410) was identified. Change in ROM was not significantly different between cohorts at 1 and 3 month intervals. At 1-year, improvement in ROM was significantly less in patients taking ACEIs (+6.54° vs. +9.90°, p=0.035) and significantly fewer ACEI cohort patients achieved 118° flexion (56.9% vs. 68.4%, p=0.013).

Conclusions

This study supplies evidence that ACEIs do not reduce post-operative stiffness following TKA. Additionally, patients taking ACEI medications have significantly less improvement in ROM 1 year post-operatively.

INTRODUCTION

Total Knee Arthroplasty (TKA) is recognized as an effective treatment of end-stage knee osteoarthritis in patients who have failed conservative measures. The reliable improvements in functional mobility, pain, and quality of life offered by TKA are well-documented (Meding et al. 2012; Kane et al. 2005; Aujla and Esler 2017; Feng et al. 2018; Kurtz et al. 2007; Kurtz 2005). The procedure is one of the most frequently performed throughout the country and is increasingly being done in patients under the age of 55 (Aujla and Esler 2017; Fingar, Stocks, Weiss, et al. 2014). In 2010, the prevalence of TKA in the total United States population was 1.52%, and 10.38% among individuals over

age 80 (Maradit Kremers et al. 2015). At that time, approximately 620,000 per year were performed (Steiner et al. 2012), and this number has been projected to increase to 3.48 million by the year 2030 (Kurtz et al. 2007).

Despite the general success of TKA, as many as 1 in 5 patients report dissatisfaction with the procedure. This is most significantly attributed to pain and decreased range of motion due to stiffness (T. K. Kim et al. 2009; Bourne et al. 2010; Ali et al. 2014). Arthrofibrosis, a pathologic stiffening of the joint resulting from an exaggerated inflammatory response and hyperplasia of connective tissue, is a common cause of postoperative stiffness (Thompson et al. 2019a; Cheuy et al. 2017; Ritter et al. 2008a; Nelson, Kim, and Lotke 2005; Yercan et al. 2006). Early postop-

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erative stiffness can significantly contribute to poor long-term outcomes as concomitant postoperative pain may prevent adequate physical therapy and subsequently result in poor range of motion (ROM). Patients with ROM of 128° to 132° demonstrate the best functional results following TKA while those with less than 118° show markedly compromised outcomes (Ritter et al. 2008a). Stiffness resulting in decreased ability to perform activities of daily living (ADL) may require surgical management, which includes manipulation under anesthesia (MUA), lysis of adhesions, or revision arthroplasty (Thompson et al. 2019a). These procedures can provide satisfactory results but are costly and delay the rehabilitation process (Nelson, Kim, and Lotke 2005; Yercan et al. 2006), and as such the goal of management for arthrofibrosis is prevention.

Recently, the renin-angiotensin-system (RAS) has become a target for the prevention of arthrofibrosis. Angiotensin II, the end product of RAS, serves to upregulate transforming growth factor Beta-1 (TGF-β1), which in turn promotes fibrous tissue formation via collagen gene expression (K. K. Kim, Sheppard, and Chapman 2018). Medications that target angiotensin II therefore may theoretically limit TGF- β1 and thus scar formation. Indeed, ACE Inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been demonstrated to limit skeletal and cardiac muscle fibrosis (Kakutani et al. 2020a; Russo et al. 2018a; Demir et al. 2018a; Tan et al. 2018a). In their 2020 publication, Langston et al. report for the first time the use of these drugs in regard to arthrofibrosis. Their study demonstrates that 6-month postoperative ROM greater than 118° is not correlated with concomitant use of ACEIs or ARBs.

Similarly, this study seeks to examine the effects of RAS blockade on arthrofibrosis following TKA. As MUA is the procedure of choice for patients with unacceptable stiffness and diminished ability to complete ADLs, we will here describe the relationship between ACEI use and MUA.

METHODOLOGY

Approval from the institutional review board was obtained prior to the start of this study (Protocol IRB-AAAS7478). This retrospective study comprises all TKAs performed for osteoarthritis by three senior arthroplasty surgeons at a large academic medical center between January 2014 and September 2019 as identified in an institutional arthroplasty database.

The electronic medical records (EMR) of these patients was reviewed in order to collect basic demographical information, use of an ACEI, arc of motion of the operative knee preoperatively and at one, three and twelve month intervals following surgery, and occurrence of a manipulation under anesthesia up to six months following surgery. Basic demographic information included age, gender, American Society of Anesthesiologist's (ASA) class, and body mass index (BMI). Arc of motion data and occurrence of a MUA was collected from the documentation obtained during post-operative follow-up visits with the arthroplasty surgeon. Indications for MUA were patient specific but generally the procedure was indicated if the patient failed to achieve 90 degrees arc of motion at the one-month post-operative follow-up interval. ACE-inhibitor use was identified and confirmed by review of the patient's discharge summary from the TKA hospitalization and a medicine reconciliation tool within the EMR.

STATISTICAL ANALYSIS

Pearson's Chi-Square test was used to analyze categorical variables including gender, ASA class, and the proportion of patients that achieved an arc of motion of 118 degrees or greater at three and twelve months. Student's T-test was used to analyze continuous variables such as age, BMI, and the average difference between preoperative ROM and ROM at each follow up interval. Multinomial logistic regression for MUA rate was performed controlling for age, gender, BMI, and ASA class. Analysis of covariance (ANCOVA) was performed to determine the difference in arc of motion attributable to ACEI use at one, three and twelve months compared to the pre-operative arc of motion while controlling for age, BMI, ASA class, and gender. All preliminary analyses were performed utilizing the Excel data analysis tool version 16.0 (Microsoft, Inc Redmond, WA). Multinomial logistic regression and ANCOVA was performed using SPSS version 24 (IBM Corp., Armonk, NY).

Table 1. Patient demographics

	ACE Inhibitor Cohort	Control Cohort	p- value
n =	274	1316	
Age (yrs)	70.2 ± 8.0	70.0 ± 9.5	0.051
BMI	31.3 ± 5.3	30.2 ± 5.8	**0.005***
Female, n (%)	180 (65.7)	920 (69.9)	0.169
ASA Score			0.149
I	0 (0)	37 (2.8)	
II	181 (66.1)	865 (65.7)	
III	93 (33.9)	409 (31.1)	
IV	0 (0)	5 (0.4)	

ACE, Angiotensin Converting Enzyme; ASA, American Society of Anesthesiologists; BMI, body mass index.

* Denotes significance at p < 0.05

RESULTS

Query of our institutional arthroplasty database identified 1590 primary TKA procedures for inclusion in this study. 274 (17.3%) TKA procedures were associated with patient records indicating sustained postoperative use of an ACEI medication and were stratified into the ACEI study cohort. The remaining 1316 TKA procedures formed the control cohort. Patient demographics are summarized in Table 1. BMI was significantly higher in the ACEI cohort (31.1 vs. 30.2, p = 0.005). This demographical difference was controlled for in the multivariate logistic regression examining MUA rate.

Five (1.8%) TKA procedures in the ACEI cohort required MUA. Forty one (3.1%) TKA procedures in the control cohort required MUA. Multivariate logistic regression analysis found no significant difference in the odds of MUA when comparing the ACEI cohort to the control cohort (odds ratio 0.670, p = 0.410) (Table 2). Table 3 summarizes arc of motion (ROM) characteristics for each cohort. ROM data was retrievable for 90.9% of procedures pre-op, 89.3% at 4 weeks follow-up, 78.9% at 3 months follow-up, and 43.0% at 1 year follow-up. Both cohorts had similar retrieval rates. No significant difference existed between the average preoperative ROM between the ACEI and control cohorts (108.61° vs. 108.63° respectively, p = 0.989). No significant differences existed between the ACEI and control cohorts in the change from preoperative ROM at 4 weeks (-7.81° vs. -7.78°, p = 0.987) and 3 month (+5.50° vs. +5.66°, p = 0.889) follow-up intervals. At the 1 year follow-up interval, the ACEI cohort had a significantly lower gain in ROM than the control cohort (+6.54° vs. +9.90°, p = 0.035). ANCOVA analysis identified ACEI use as associated with a decreased change in ROM by 1.01° at 4 weeks and 1.22° at 3 months though neither attained significance (p = 0.471 and 0.347 respectively). At 1 year, ACEI use was associated with a significant decrease in change in ROM by 4.27° (p = 0.012) (Table 4). Additionally, there was no significant difference between the cohorts in the percent of patients achieving 118° total ROM at the 3 month follow-up interval (49.5% vs. 55.1%, p = 0.130), however, by the 1 year follow-up in-terval, significantly more control cohort patients achieved 118° ROM (56.9% vs. 68.4%, p = 0.013).

DISCUSSION

Our single institution study of 1590 TKA patients found no significant difference in odds of undergoing MUA between a cohort of patients who received ACEI medications and patients who did not receive ACEI medications (Odds ratio = 0.670, p = 0.410). Though not significant, the proportion of patients requiring MUAs was lower in the ACEI cohort (1.8% vs. 3.1%). This suggests that ACEI medications may play a small role in the prevention of short-term post-operative joint stiffness, however, it has yet to be determined if this effect is clinically meaningful within a single surgeon's typical patient volume.

The reduction in MUA rates may in part be explained by a reduction in arthrofibrosis secondary to ACEI use. These medications inhibit an enzyme in the renin angiotensin aldosterone system, which has been linked to fibrotic processes in pulmonary, cardiac and renal disease. Studies have demonstrated that these medications can reduce fibrosis of striated muscle (Kakutani et al. 2020b; Russo et al. 2018b) and scar tissue formation in soft tissues (Demir et al. 2018b; Tan et al. 2018b; Zheng et al. 2019).

Stiffness following TKA was further assessed by range of motion. Charting ROM data for the two cohorts provides insight into the flexibility of the knee joint throughout recovery following TKA in patients taking ACEI medications. Measures of the preoperative total range of motion, the change in ROM at the 1-month follow up interval, and the change in ROM at the 3-month follow up interval were near equivalent between the two cohorts (p = 0.989, 0.471, and 0.347 respectively). Notably, the gain in ROM at the 1-year follow up interval is significantly less in patients in the ACEI cohort (+6.54° vs. +9.90°, p = 0.012). In addition, we investigated the number of patients achieving 118° total ROM as this is an important milestone for patients to be able to independently engage in various activities of daily living and below this range, function is significantly reduced (Langston et al. 2020; Ritter et al. 2008b). Similar

Table 2. Multivariate logistic regression for MUA rate

Comparison	Odds Ratio (95% CI)	p - value
ACE-inhibitor cohort compared to Control cohort	0.670 (0.259 – 1.735)	0.410

	ACE Inhibitor Cohort	Control Cohort
Number of MUAs Required n (%)	5 (1.8%)	41 (3.1%)

MUA, manipulation under anesthesia; ACE, Angiotensin Converting Enzyme; CI, Confidence Interval.
Denotes significance at p < 0.05

Table 3. Arc of motion characteristics

	ACE Inhibitor Cohort	Control Cohort	p - value
Pre-op AOM (degrees)	108.61° ± 16.32°	108.63° ± 17.39°	0.989
Change in AOM at 4 weeks post-op (degrees)	-7.81°	-7.78°	0.987
Change in AOM at 3 months post-op (degrees)	+5.50°	+5.66°	0.889
Change in AOM at 1 year post-op (degrees)	+6.54°	+9.90°	**0.035***
Proportion of patients achieving 118° 3 months post-op	49.5%	55.1%	0.130
Proportion of patients achieving 118° 1 year post-op	56.9%	68.4%	**0.013***

ACE, Angiotensin Converting Enzyme; ASA, American Society of Anesthesiologists; BMI, body mass index.
Denotes significance at p < 0.05

Table 4. ANCOVA Analysis of Change in Arc of Motion

	Change in AOM Attributable to ACE-I Use	p - value
4 weeks post-op (degrees)	-1.01°	0.471
3 months post-op (degrees)	-1.21°	0.347
1 year post-op (degrees)	-4.27°	**0.012***

Denotes significance at p < 0.05

to the other ROM findings, the differences between the cohorts is not significant at the 3-month follow up interval. However, at the 1-year follow up interval, the proportion of the ACEI cohort meeting this goal is significantly lower (56.9% vs. 68.4%, p = 0.013) than in the control cohort.

The observed difference in achieved ROM may not be directly caused by use of ACEI medications. Post-operative knee stiffness and MUA risk increase with various pre, peri and post-operative factors (Newman et al. 2018; Thompson et al. 2019b). While our analysis accounted for some of the known risk factors of MUA, such as age, and differences between the cohorts such as BMI, we hypothesize that the factors inherently contributory to a population necessitating ACEIs, namely hypertension, lack of physical activity, and obesity, likely play a significant role in long-term recovery of joint range following arthroplasty and thus explain the results observed here. In support of this hypothesis, the ACEI cohort did have a significantly higher average BMI than the control cohort (31.3 vs. 30.2, p = 0.005). Additionally, a 4° difference at 1-year follow-up may not be clinically significant.

To our knowledge, there has only been one other investigation on the effects of ACEI medications and rate of MUA following surgery. Langston et al retrospectively reviewed 141 patients taking either an ACEI, angiotensin receptor blocker, or neither and found no significant difference in achievement of 118° total ROM at six months (Langston et al. 2020). Our investigation of a large patient cohort was able to analyze both achieved ROM as well as MUA rate. In addition to the limitations inherent to any retrospective study, we acknowledge that our investigation does not account for the dosage and formulation of ACEI medications a patient is taking and does not use patient reported outcomes and functional scores as end metrics. This field would benefit from future randomized control trials taking into account these differences and outcomes. Furthermore, oral administration of these medications may produce different results following TKA than topical or intraarticular administration. In several animal models, local administration of ACEI medications has been shown to reduce scar tissue formation (Tan et al. 2018b; Zheng et al. 2019).

CONCLUSIONS

In conclusion, ACEI use was not associated with a statistically significant decreased rate of MUA following total knee arthroplasty but it was associated with a decrease in proportion of patients achieving 118 degrees ROM at 1 year. Patients in the ACEI cohort also had decreased mean ROM at 1-year follow up compared to patients in the control cohort though the difference is unlikely to reach clinical significance.

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