



RANDOMIZED CONTROLLED TRIAL

Angiotensin-converting Enzyme Inhibitors taken on Day of Total Joint Replacement are associated with Adverse Outcomes: A Randomized Controlled Trial

¹Sawley Wilde, ²Tyler Vovos, ³Kevin McCoy, ⁴Daniel Mangiapani, ⁵Jennifer Friend, ⁶Cynthia L Green
⁷Samuel Wellman, ⁸Michael Bolognesi

ABSTRACT

Introduction: Angiotensin-converting enzyme inhibitors (ACE-Is) are among the most frequently prescribed medications used to treat hypertension and are commonplace among patients undergoing elective total hip and knee arthroplasty. It is the purpose of this study to evaluate the perioperative effects of ACE-Is in an elective total hip and knee arthroplasty patient group.

Materials and methods: A total of 46 patients were randomized to one of two study arms: An ACE-I cessation arm, who were instructed to stop their ACE-I 2 days prior to surgery (last dose >48 hours prior to surgery), and an ACE-I continuation arm, who continued their ACE-I prior to surgery.

Results: Despite being underpowered to detect a significant difference between cessation and continuation arms of the study, the continuation arm had more intraoperative hypotension (61 vs 39%, $p = 0.140$), more intraoperative vasopressors (83 vs 61%, $p = 0.102$), more postoperative hypotension (13 vs 9%, $p = 1.000$), and more acute kidney injury (AKI) (22 vs 14%, $p = 0.700$). Further, a patient in the continuation arm sustained severe intraoperative hypotension and required escalation of care.

Conclusion: The results of this randomized controlled trial did not reach statistical significance, but showed a clear trend toward worse outcomes in total joint arthroplasty patients who continued ACE-Is through the perioperative period.

Keywords: Angiotensin-converting enzyme inhibitors, Postoperative hypotension, Randomized clinical trial, Total joint arthroplasty.

Wilde S, Vovos T, McCoy K, Mangiapani D, Friend J, Green C, Wellman S, Bolognesi M. Angiotensin-converting Enzyme Inhibitors taken on Day of Total Joint Replacement are associated with Adverse Outcomes: A Randomized Controlled Trial. *The Duke Orthop J* 2018;8(1):33-36.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Angiotensin-converting enzyme inhibitors are among the most frequently prescribed medications used to treat hypertension and are commonplace among patients undergoing elective total hip and knee arthroplasty.¹ Perioperative practices regarding cessation of ACE-Is are varied; it is sometimes recommended to have patients stop taking their ACE-I 1 or 2 days prior to the day of surgery.

Total hip and knee arthroplasty can be classified as major elective surgery, and as such, patients undergo fluid shifts within the body around the time of surgery. Frequently, patients are hypotensive both intraoperatively and postoperatively, and up to 18% of patients have been reported to suffer AKI around the time of total joint arthroplasty.²⁻⁵ Postoperatively, hypotensive events may also cause patient discomfort in the form of lightheadedness; dizziness and nausea and can result in the withholding of pain medications, leading to increased pain. Some have postulated that the continued use of an ACE-I preoperatively, specifically on the same day of surgery, predisposes patients to both intraoperative and postoperative hypotensive events.⁵⁻¹¹

Conversely, several authors have reported that in conjunction with general anesthetics, renin-angiotensin system (RAS)-blockading agents either do not effect, or improve, cardiovascular stability in the perioperative period.¹²⁻¹⁴ Stress to the body, including surgery and hypotension, stimulates the generation of angiotensin II.¹⁵ Angiotensin II induces vasoconstriction to maintain blood pressure but simultaneously reduces blood flow to organs including the kidneys and intestine.¹⁵ This angiotensin II-induced reduction in blood flow may contribute to postoperative morbidity in the form of AKI and/or splanchnic ischemia.¹⁶⁻¹⁸ In turn, blockade of

^{1,2}Resident, ^{3,4,7,8}Attending Surgeon, ⁵Research Coordinator
⁶Statistician

¹Department of General Surgery, Duke University Medical Center, Durham, North Carolina, USA

^{2,5,7,8}Department of Orthopedic Surgery, Duke University Medical Center, Durham, North Carolina, USA

³Department of Orthopedic Surgery, University of Maryland, The Orthopaedic Center, Queenstown, Maryland, USA

⁴Department of Orthopedic Surgery, Hofmann Arthritis Institute Salt Lake City, Utah, USA

⁶Department of Biostatistics and Epidemiology, Duke University Medical Center, Durham, North Carolina, USA

Corresponding Author: Tyler Vovos, Resident, Department of Orthopaedic Surgery, Duke University Medical Center, Durham North Carolina, USA, Phone: +6085773701, e-mail: Tyler.Vovos@duke.edu

the RAS with ACE inhibitors may have some protective value with regard to circulation in these regions of the body^{13,19,20} and has led some to recommend uninterrupted continuation of these medications during the preoperative period, particularly in certain high-risk patients.^{1,21} There are also concerns regarding postoperative hypertension when ACE-Is are discontinued preoperatively. In a randomized controlled trial by Pigott et al,²² the effects of continuing *vs* discontinuing ACE-Is in cardiac surgery patients were investigated and they found no difference in intraoperative hypotension, but a higher rate of postoperative hypertension that required vasodilator administration in those who discontinued ACE-Is.

Despite numerous small studies in the general surgery literature investigating the issue, there is no evidence-based consensus regarding the pros and cons of continuing ACE-I and angiotensin receptor blocker (ARB) therapy during the perioperative period. This uncertainty stems from a lack of randomized controlled trials designed to examine differences between outcomes in patients treated with continuation or cessation of ACE-Is, especially in the joint arthroplasty literature. It was the purpose of this study to evaluate the perioperative effects of ACE-Is in an elective total hip and knee patient group. A better understanding of the consequences of withholding or continuing these medications in the perioperative period will enhance the care of patients electing to undergo total joint arthroplasty. We hypothesized that there would be no difference in intraoperative and postoperative outcomes between patients who withheld or continued their prescribed ACE-I preoperatively.

MATERIALS AND METHODS

This study was approved by the appropriate institutional review board. Adult patients aged 18 years and over electing to undergo primary or revision total hip or knee arthroplasty and currently taking an ACE-I were asked to participate in this study. Exclusion criteria for this study included trauma patients, immunosuppressed patients (human immunodeficiency virus/acquired immunodeficiency syndrome, chronic steroid use, on chemotherapy, or history of organ transplant), patients with history of severe hypertension-related illness (such as hypertension-associated stroke or myocardial infarction), and patients in whom continuation of their ACE-I was expressly mandated by their prescribing physician. Informed consent was obtained from all participants. Total hip or knee arthroplasty was performed as per the standard of care as determined by the patient, attending surgeon, and attending anesthesiologist. No alterations of the surgical procedure or anesthesia were performed as a result of the proposed study.

Patients were randomized to one of two study arms, including cessation and continuation. A randomization scheme was generated for a single site using a block size of 4 to balance treatment arms 1:1. At the time of consent, patients were randomized to one of the two study arms. Patients in the cessation arm were instructed to stop their ACE-I 2 days prior to surgery (last dose >48 hours prior to surgery). Patients in the continuation arm continued their ACE-I and took their scheduled dose on the day of surgery. Demographics of each patient, including age, gender, race, type of total joint arthroplasty (hip or knee), and anesthesia type were recorded.

Patients were tracked in the perioperative period. Instances of both mild (systolic <85 mm Hg) and severe hypotension (<65 mm Hg systolic) were recorded. Both intraoperative and postoperative use of vasopressors was also recorded, as well as median hospital length of stay and instance of acute kidney insufficiency, as measured by an increase in creatinine of 0.3 or greater from baseline. In addition, we recorded the requirement of escalation of care requiring transfer to a step-down unit or intensive care unit (ICU), and the use of allogeneic blood.

Continuous data are presented using the mean, standard deviation, median, or range based on distribution of variable, and categorical data are summarized using counts with percentages. Comparisons between treatment arms utilized the t-test or Wilcoxon rank sum test for continuous variables and chi-square or Fisher's exact test for categorical data (expected cell counts <5). Analyses were performed by the Duke Department of Biostatistics (Durham, NC) using SAS version 9.4 (SAS, Inc., Cary, NC). All statistical tests were two-sided superiority tests and a p-value < 0.05 was considered statistically significant.

RESULTS

A total of 59 people met criteria and agreed to participate in the study. Of those, 6 were lost to follow-up, 3 did not undergo total joint surgery, 2 subjects withdrew their participation prior to scheduled surgery, and 2 subjects were withdrawn by the study team due to perioperative deviations from surgery protocol (One patient underwent unicompartmental knee arthroplasty and one patient was randomized to continuation arm but was instructed to stop ACE-I by anesthesia team). Data were analyzed from the remaining 46 participants, of which 23 had been randomized to the continuation arm, and 23 randomized to the cessation arm. Demographics of each group are shown in Table 1.

Despite being underpowered to detect significant differences between cessation and continuation arms of the study, the continuation arm had more intraoperative hypotension (61 *vs* 39%, $p = 0.140$), more intraoperative

Table 1: Comparison of demographics between the randomized groups

Category	Continuation arm	Cessation arm	p-value
N	23	23	
Mean age (years)	63.3 ± 10.8	63.7 ± 8.7	0.893
Male gender	15 (65.2)	12 (52.2)	0.369
Caucasian race	18 (78.3)	17 (73.9)	0.730
Total hip arthroplasty	10 (43.5)	10 (43.5)	1.000
Spinal anesthesia	15 (65.2)	17 (73.9)	0.526

The continuation group continued taking their prescribed dosage of ACE-I up to the day of surgery. The cessation group stopped taking their prescribed ACE-I 2 days prior to surgery. Data are presented as mean ± standard deviation or as count (percentage)

vasopressors (83 vs 61%, $p = 0.102$), more postoperative hypotension (13 vs 9%, $p = 1.000$), and more AKI (22 vs 14%, $p = 0.700$). Further, in the continuation arm, 1 patient sustained severe intraoperative hypotension and required postoperative escalation of care requiring transfer of care to a step-down unit or the ICU. This same patient also required the use of allogeneic blood. In the cessation arm, no patients sustained severe intraoperative hypotension, required transfer of care to a step-down unit or the ICU, or required the use of allogeneic blood. Due to the low number of these rare events occurring, statistical comparative analysis was not performed (Table 2).

DISCUSSION

The results of this randomized controlled trial did not show a statistical difference between treatment groups but did show a trend toward worse outcomes in total joint arthroplasty patients who continued ACE-Is through the perioperative period. Based on intraoperative hypotension rates observed in each arm, we would need at least 82 subjects randomized per arm to have at least 80% statistical power to show a significant difference using a two-sided Z-test with pooled variance and significance level of 0.05. Measured outcomes included intraoperative hypotension, use of vasopressors, postoperative hypotension, hospital stay, and incidence of AKI. Despite being underpowered to detect a significant difference between cessation and continuation arms of the study, the continuation arm had more intraoperative hypotension (61 vs 39%, $p = 0.140$), more intraoperative vasopressors (83 vs 61%, $p = 0.102$), more postoperative hypotension (13 vs 9%, $p = 1.000$), and more AKI (22 vs 14%, $p = 0.700$). Further, a patient in the continuation arm sustained severe intraoperative hypotension, requiring postoperative escalation of care and allogeneic blood transfusion.

Patients undergoing elective total joint procedures often have preoperative appointments with their primary care physicians and anesthesiologists where they are given

Table 2: Comparison of intra- and postoperative outcomes between the cessation and continuation arms

Category	Continuation arm	Cessation arm	p-value
N	23	23	
Intraoperative hypotension	14 (60.9)	9 (39.1)	0.140
Intraoperative vasopressors given	19 (82.6)	14 (60.9)	0.102
Postoperative hypotension	3 (13.0)	2 (8.7)	1.000
AKI	5 (21.7)	3 (13.6)	0.700
LOS, days	2.0 (1–13)	2.0 (1–7)	0.702
*Any adverse event	17 (73.9)	13 (56.5)	0.216

Data are presented as count (percentage) or median (range); *Any adverse event includes intra- or postoperative hypotension, AKI, or LOS > 3 days; Hypotension: Systolic blood pressure <85 mm Hg; LOS: Length of stay

strict instructions regarding us of their home medication on the day of surgery. Antihypertensive medications, including ACE-Is, are sometimes held on the day of elective total hip or knee arthroplasty with the intent of minimizing complications in the perioperative period. However, conflicting data exist for the recommendation of discontinuing antihypertensives prior to surgery,⁵⁻¹¹ and uncertainty remains as to whether or not continuing ACE-Is in the preoperative period leads to intraoperative and postoperative complications. The findings of the current study have prompted the authors to advise caution when continuing ACE-Is in the elective total joint arthroplasty perioperative period.

The cause of perioperative hypotension is no doubt multifactorial with factors including the specific type of anesthesia administered, dehydration from preoperative fasting, and the patient's routine use of antihypertensives. Colson et al⁷ reported on the hemodynamic effects of anesthesia in patients chronically treated with ACE-Is. They found that in these patients with intraoperative hypotension, they were able to attain rapid restoration of arterial BP with IV fluids and occasional vasopressors, and in addition, found that this did not lead to postoperative complications. In the current study, we found that intraoperative hypotensive events associated with the continuation of ACE-Is may not be so benign and may even require escalation of care or blood transfusion.

Again, a limitation of this study is low statistical power, as we assessed a relatively small number of participants. In addition, this study excluded patients with a history of severe hypertension-related illness, such as stroke and myocardial infarction, who may be more prone to significant hypotension after induction of general anesthesia with continuation of ACE-Is or ARBs on the morning of surgery.²³ Further retrospective studies are recommended to determine if a patient's prior medical

history, particularly those of cardiac and cerebrovascular events, or preoperative hydration status, may prove to be a better indicator of possible postoperative hypotensive events. Although this study was limited by its statistical power, we would recommend against other prospective studies comparing continuation *vs* cessation of ACE-Is on the day of elective arthroplasty surgery as the trend toward worse outcomes with continuation of ACE-Is appears to be real and dangerous.

CONCLUSION

When comparing patients in a select population who continued ACE-Is on the day of total hip or knee arthroplasty with those who ceased taking their ACE-I 2 days prior to surgery, there was a trend toward worse outcomes in those that continued ACE-Is. We recommend that caution be taken when continuing ACE-Is in the elective total joint arthroplasty perioperative period.

REFERENCES

- Colson P, Ryckwaert F, Coriat P. Renin angiotensin system antagonists and anesthesia. *Anesth Analg* 1999 Nov;89(5):1143-1155.
- Kimmel LA, Wilson S, Janardan JD, Liew SM, Walker RG. Incidence of acute kidney injury following total joint arthroplasty: a retrospective review by RIFLE criteria. *Clin Kidney J* 2014 Dec;7(6):546-551.
- Goren O, Matot I. Perioperative acute kidney injury. *Br J Anaesth* 2015 Dec;115 (Suppl 2):ii3-14.
- Nielson E, Hennrikus E, Lehman E, Mets B. Angiotensin axis blockade, hypotension, and acute kidney injury in elective major orthopedic surgery. *J Hosp Med* 2014 May;9(5):283-288.
- Vijay A, Grover A, Coulson TG, Myles PS. Perioperative management of patients treated with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers: a quality improvement audit. *Anaesth Intensive Care* 2016 May;44(3):346-352.
- Rosenman DJ, McDonald FS, Ebbert JO, Erwin PJ, LaBella M, Montori VM. Clinical consequences of withholding versus administering renin-angiotensin-aldosterone system antagonists in the preoperative period. *J Hosp Med* 2008 Jul;3(4):319-325.
- Colson P, Saussine M, Seguin JR, Cuchet D, Chaptal PA, Roquefeuil B. Hemodynamic effects of anesthesia in patients chronically treated with angiotensin-converting enzyme inhibitors. *Anesth Analg* 1992 Jun;74(6):805-808.
- Rajgopal R, Rajan S, Sapru K, Paul J. Effect of pre-operative discontinuation of angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists on intra-operative arterial pressures after induction of general anesthesia. *Anesth Essays Res* 2014 Jan-Apr;8(1):32-35.
- Bertrand M, Godet G, Meersschaert K, Brun L, Salcedo E, Coriat P. Should the angiotensin II antagonists be discontinued before surgery? *Anesth Analg* 2001 Jan;92(1):26-30.
- Calloway JJ, Memtsoudis SG, Krauser DG, Ma Y, Russell LA, Goodman SM. Hemodynamic effects of angiotensin inhibitors in elderly hypertensives undergoing total knee arthroplasty under regional anesthesia. *J Am Soc Hypertens* 2014 Sep;8(9):644-651.
- Comfere T, Sprung J, Kumar MM, Draper M, Wilson DP, Williams BA, Danielson DR, Liedl L, Warner DO. Angiotensin system inhibitors in a general surgical population. *Anesth Analg* 2005 Mar;100(3):636-644, table of contents.
- Colson P, Grolleau D, Chaptal PA, Ribstein J, Mimran A, Roquefeuil B. Effect of preoperative renin-angiotensin system blockade on hypertension following coronary surgery. *Chest* 1988 Jun;93(6):1156-1158.
- Colson P, Ribstein J, Mimran A, Grolleau D, Chaptal PA, Roquefeuil B. Effect of angiotensin converting enzyme inhibition on blood pressure and renal function during open heart surgery. *Anesthesiology* 1990 Jan;72(1):23-27.
- Yates AP, Hunter DN. Anaesthesia and angiotensin-converting enzyme inhibitors. The effect of enalapril on peri-operative cardiovascular stability. *Anaesthesia* 1988 Nov;43(11):935-938.
- Herd JA. Cardiovascular response to stress. *Physiol Rev* 1991 Jan;71(1):305-330.
- Moran SM, Myers BD. Pathophysiology of protracted acute renal failure in man. *J Clin Invest* 1985 Oct;76(4):1440-1448.
- Cohen MM, Sitar DS, McNeill JR, Greenway CV. Vasopressin and angiotensin on resistance vessels of spleen, intestine, and liver. *Am J Physiol* 1970 Jun;218(6):1704-1706.
- Bjorck M, Hedberg B. Early detection of major complications after abdominal aortic surgery: predictive value of sigmoid colon and gastric intramucosal pH monitoring. *Br J Surg* 1994 Jan;81(1):25-30.
- Joob AW, Harman PK, Kaiser DL, Kron IL. The effect of renin-angiotensin system blockade on visceral blood flow during and after thoracic aortic cross-clamping. *J Thorac Cardiovasc Surg* 1986 Mar;91(3):411-418.
- Mirenda JV, Grissom TE. Anesthetic implications of the renin-angiotensin system and angiotensin-converting enzyme inhibitors. *Anesth Analg* 1991 May;72(5):667-683.
- Prys-Roberts C. Withdrawal of antihypertensive drugs before anesthesia. *Anesth Analg* 2002 Mar;94(3):767-768.
- Pigott DW, Nagle C, Allman K, Westaby S, Evans RD. Effect of omitting regular ACE inhibitor medication before cardiac surgery on haemodynamic variables and vasoactive drug requirements. *Br J Anaesth* 1999 Nov;83(5):715-720.
- Twersky RS, Goel V, Narayan P, Weedon J. The risk of hypertension after preoperative discontinuation of angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists in ambulatory and same-day admission patients. *Anesth Analg* 2014 May;118(5):938-944.