Preoperative Angiotensin-converting Enzyme Inhibitor Use is Not Associated With Increased Postoperative Pain and Opioid Use

Alparslan Turan, MD, Abdulkadir Atim, MD,*† Jarrod E. Dalton, MA,‡ Worasak Keeyapaj, MD,§ Weihan Chu, MS,‖ Ethan Bernstein, MS,¶ Alexander Fu, BSc,‖ Lee Jae Ho, MA,* Leif Saager, MD,* and Daniel I. Sessler, MD**

Aim/Objectives/Background: Angiotensin-converting enzyme inhibitors (ACEIs) increase potent proinflammatory and pain mediators in local tissues. Consistent with these observations, animal and human studies demonstrate that ACEIs have hyperalgesic and proinflammatory properties. However, there is no information in literature whether or not the use of ACEIs is associated with increased postoperative pain. Specifically, we tested the primary hypothesis that use of ACEIs is independently associated with increased opioid requirements and pain scores during the initial 72 hours after surgery.

Methods: Data from 9993 patients undergoing colorectal resection, hysterectomy, nephrectomy, or open prostatectomy were obtained from the Cleveland Clinic Perioperative Health Documentation System. A propensity-matching procedure was used to pair ACEI users to similar nonusers. Corresponding estimates and Bonferroni-adjusted 95% confidence intervals for the effect of ACEIs on each outcome were also estimated. The exact matching procedure, based on type of surgery and propensity score, identified 1038 matched pairs. The final analyzed subsample size was 212.

Results and Conclusions: The adjusted difference in mean 72-hour postoperative using a time-weighted average pain score was estimated at +0.17 [−0.40, +0.74] units on the verbal response scale. This was not statistically significant ($P = 0.50$). Opioid use was estimated by the percent difference in mean 72-hour total postoperative intravenous morphine equivalent dose at −8.1% [−46%, +56%], which was not statistically significant ($P = 0.72$). In conclusion, after controlling for all available factors, we found no significant difference that postoperative pain—as defined by either pain scores or opioid requirements—differed between patients taking ACEIs and patients not taking ACEIs.

Key Words: angiotensin-converting enzyme inhibitors, postoperative pain, postoperative

(*Clin J Pain* 2013;29:1050–1056)

Surgery causes pain by directly activating nociceptors, provoking inflammation, and injuring nerves. The inflammatory response to surgical incisions—including release of inflammatory mediators such as bradykinin, substance P, and histamine—sensitizes local afferent nociceptors which is known as peripheral sensitization.[1,2] Peripheral pain also enhances excitability of neurons in the spinal cord and brain, which is known as central sensitization.[3,4] Inflammation thus plays a crucial role in maintaining postoperative pain until healing,[5,6] and even longer in patients who develop persistent incisional pain.[5,7]

Angiotensin-converting enzyme inhibitors (ACEIs) are commonly prescribed to treat hypertension and heart failure. It is estimated that as many as 149 million prescriptions for ACE Inhibitors are filled in the United States each year, making ACE inhibitors one of the most popular drug groups.[8] A consequence of frequent use of ACE inhibitors is that an increasing fraction of surgical patients take these drugs.

The rennin-angiotensin system modulates nociception both centrally and peripherally. ACEIs prevent conversion of angiotensin I to II, thus decreasing angiotensin II concentrations.[9] Angiotensin II has central analgesic effects.[10] Furthermore, angiotensin-converting enzyme is identical to kininase II, an enzyme involved in the degradation of bradykinin and substance P. Thus, ACEIs increase concentrations of potent proinflammatory and pain mediators such as bradykinin and substance P in local tissues.[9,11,12] Consistent with these observations, animal models demonstrate that ACEIs are both hyperalgesic and proinflammatory.[13,14] Furthermore, ACEIs enhance pain perception and are associated with complex regional pain syndrome in humans.[13,14,15]

Surgical incision releases inflammatory mediators, reducing the pain threshold at the site of injury and in surrounding uninjured tissue. The combination of ACEIs and surgical incision may thus be especially deleterious. However,

TABLE 1. Opioid Conversions

Drugs	Route	Dose
Morphine	IV	10 mg
Fentanyl	IV	100 mcg
Fentanyl	100 mcg patch	100 mcg
Hydrocodone	PO	30 mg
Hydromorphone	IV	1.5 mg
Hydromorphone	PO	7 mg
Meperidine	IV	75 mg
Oxycodone	PO	20 mg
Oxycodone/Acetaminophen 5/325	PO	6 tabs
Hydrocodone/Acetaminophen 5/500	PO	6 tabs
Tramadol	PO	150 mg
Propoxyphene/Acetaminophen 130	PO	1 tab

IV indicates intravenous, PO, per oral.

Received for publication June 19, 2012; revised December 3, 2012; accepted December 27, 2012.

From the Departments of *Outcomes Research; ‡Quantitative Health Sciences and Outcomes Research; §Anesthesiology Institute, Cleveland Clinic; ‖Case Western Reserve University, Cleveland, OH; †Gulhane Military Medical Academy, Ankara, Turkey; and ¶School of Public Health, Rochester University, Rochester, NY.

The authors declare no conflict of interest. Support received from the Departments of Outcomes Research and Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH.

Reprints: Alparslan Turan, MD, Department of Outcomes Research, Cleveland Clinic, 9500 Euclid Avenue, P-77, Cleveland, OH 44195 (e-mail: alparslanturan@yahoo.com), www.OR.org.

available literature does not address the relationship between perioperative ACE inhibitor use and postoperative pain. Our major goal was to determine whether or not the use of ACEIs is independently associated with increased postoperative pain. Specifically, we tested the primary hypothesis that use of ACEIs is independently associated with increased opioid requirements and pain scores during the initial 72 hours after moderate-major surgery.

METHODS

With Cleveland Clinic Institutional Review Board approval, informed consent was waived in this retrospective cohort analysis of 9993 patients undergoing colorectal resection, hysterectomy (abdominal or vaginal), nephrectomy (partial or complete), or open prostatectomy between January 6, 2005 and November 11, 2009. Data were obtained from the Cleveland Clinic Perioperative Health Documentation System that includes the electronic anesthesia record, along with much preoperative and postoperative information. Clinical routine is to record pain scores every 15 minutes in postanesthesia recovery unit and every 4 hours in ward, and we have included all available pain scores.

Available records include chronic medication use, including ACEIs. Initially, baseline ACE inhibitor use was

TABLE 2. Descriptive Statistics for All Patients Meeting Inclusion/exclusion Criteria, All Matched Patients, and the Subsample of Matched Patients Included in the Final Analysis

		All Patients		Matched Patients		Final Subsample	
		ACE Inhibitor Use		ACE Inhibitor Use		ACE Inhibitor Use	
Factors	Level	No (N = 8314)	No (N = 1241)	No (N = 1038)	No (N = 1038)	No (N = 106)	Yes (N = 106)
Type of surgery (%)							
	Colorectal resection	30.3	25.9	26.5	26.5	27.4	27.4
	Hysterectomy	19.7	16.2	15.8	15.8	15.8	17.9
	Nephrectomy	25.0	31.3	31.9	31.9	26.4	26.4
	Open prostatectomy	24.9	26.7	25.8	25.8	28.3	28.3
	Age (y)	56 ± 14	63 ± 12	62 ± 12	63 ± 12	60 ± 12	64 ± 12
	Sex (%)	53.5	60.6	59.4	60.4	50.0	57.5
Race (%)							
	White	86.5	87.7	85.5	88.2	83.5	88.6
	African American	9.5	9.6	11.7	9.2	12.6	9.5
	Other	4.0	2.7	2.9	2.5	3.9	3.9
Year of surgery (mean ± SD)		2007.2 ± 1.2	2006.9 ± 1.2	2006.9 ± 1.1	2007.0 ± 1.2	2007.0 ± 1.2	2007.1 ± 1.1
Body mass index (kg/m^2, median [quartiles])		27 [24, 31]	28 [25, 33]	29 [25, 33]	28 [25, 33]	30 ± 6	29 ± 6
ASA	I	4.5	0.2	0.2	0.2	0.0	0.0
Physical	II	55.8	37.1	38.1	39.6	45.3	28.3
Status	III	37.8	57.5	57.1	56.0	53.8	70.8
	IV	1.9	5.2	4.6	4.2	0.9	0.9
Systolic blood pressure (mm Hg, mean ± SD)		132 ± 20	137 ± 21	137 ± 22	137 ± 21	137 ± 22	135 ± 19
Diastolic blood pressure (mm Hg, mean ± SD)		73 ± 11	74 ± 12	74 ± 12	74 ± 12	74 ± 12	74 ± 13
Serum hematocrit (%, mean ± SD)		42 ± 5	41 ± 5	41 ± 5	41 ± 5	41 ± 5	41 ± 5
Serum creatinine (mg/dL, median [quartiles])		0.9 [0.8, 1.0]	0.9 [0.8, 1.0]	1.0 [0.8, 1.2]	0.9 [0.8, 1.1]	0.9 [0.8, 1.1]	1.0 [0.8, 1.1]
Hypertension (%)		39.6	84.8	83.3	82.8	86.8	83.0
Coronary artery disease (%)		8.0	20.0	17.9	18.0	13.2	16.0
Valve disease (%)		2.6	4.0	3.5	3.9	4.7	3.8
Myocardial infarction (%)		3.3	8.8	8.5	7.9	4.7	4.7
Congestive heart failure (%)		2.0	7.0	5.8	6.0	1.9	4.7
COPD (%)		7.8	10.7	8.3	10.6	13.2	10.4
Liver disease (%)		0.9	0.7	0.7	0.6	0.0	0.0
Ventricular arrhythmia (%)		1.0	1.5	1.4	1.8	1.9	1.9
Supraventricular arrhythmia (%)		2.4	3.0	2.6	3.2	0.9	0.9
S/P CABG (%)		2.7	6.1	6.0	6.0	6.0	2.8
S/P PCI (%)		3.3	8.4	6.7	7.9	6.6	6.6
S/P Dialysis (%)		0.4	1.3	1.5	1.2	6.6	0.9
Use of Steroids (%)		7.2	12.8	12.7	12.1	13.2	12.3
Use of β-blockers (%)		12.7	39.8	37.6	37.1	35.8	34.9
Use of ARBs (%)		6.4	5.2	7.6	5.9	6.6	7.5
Use of calcium-channel blockers (%)		6.2	20.9	20.4	18.3	21.7	21.7
Use of statins (%)		11.1	40.8	33.3	34.4	34.0	40.6

ACE, angiotensin-converting enzyme; ASA, American Society of Anesthesiologists; ARB, angiotensin receptor blockers; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention.

determined by a text search of the patients' medication history. The medication history data are not always accurate or up-to-date; thus, ACE inhibitor use was later validated by a clinical review of electronic medical records. It is our routine, although, to instruct patients who normally take ACEIs to continue until the day before surgery, but not to take them the morning of surgery. Patients with unavailable medication history and emergent patients were excluded from the study population, as were patients receiving regional anesthesia or epidural analgesia.

A propensity-matching procedure was used to pair ACE inhibitor users to presumed nonusers. Propensity scores were estimated using multivariable logistic regression with backward stepwise variable selection. All the variables listed in Table 2 were considered for the propensity score model. We used an exact matching algorithm to perform the matching, restricting successful matches to those with common type of surgery and common propensity scores (to within 2 decimal places). Observations were randomly ordered before the matching to minimize any time biases.

After successfully matching 1038/1189 patients with ACE inhibitors listed in their medication history to controls with no such records, we proceeded to perform a manual review of the matched patients' electronic medical records to confirm ACE inhibitor use and anesthetic modality. Also, while postoperative pain scores are generally available in our registry, postoperative opioid consumption data are not available in adequate detail. These data were therefore recorded during the manual review. Pairs for which at least one of the patients had an incorrect classification of ACE inhibitor use or received regional anesthesia were removed.

A prior power analysis was performed to estimate the number of conforming pairs we needed to obtain from the manual electronic medical record review process. Assuming clinically relevant effects of at least ± 0.5 units for the difference in mean verbal rating scale pain score and at least $\pm 30\%$ for the percent difference in mean total intravenous (IV) morphine equivalent dose, a subsample of 101 pairs was adequate to supply at least 90% power. This power calculation was performed a priori and incorporated Bonferroni-adjusted nominal significance levels of 0.025, a SD of mean verbal rating scale pain score of 1.0 and a coefficient of variation for total IV morphine equivalent dose equal to 0.5, or 50% of the mean. Thus, our manual review proceeded until we had at least 101 pairs that conformed to the study inclusion/exclusion criteria. At the end of our search, however, we actually had 106 conforming pairs (Fig. 1).

For the analysis among the final subsample of 106 pairs, we first assessed balance between the ACE inhibitor group and the non-ACE inhibitor group. This was done graphically using absolute standardized differences (ASDs). The ASD, equal to the absolute value of the difference in means, mean rankings, or proportions divided by the pooled SD, is a measure of statistical distance between 2 groups on a covariable; values >0.2 are considered to be indicative of at least small imbalance between the 2 groups[16] that might thus potentially confound the relationship of interest. We thus adjusted for any potential confounding variables with an ASD > 0.2 in all subsequent analyses.

Two simultaneous hypotheses were evaluated. The first was that matched ACE inhibitor users and nonusers differed on mean 72-hour postoperative pain scores

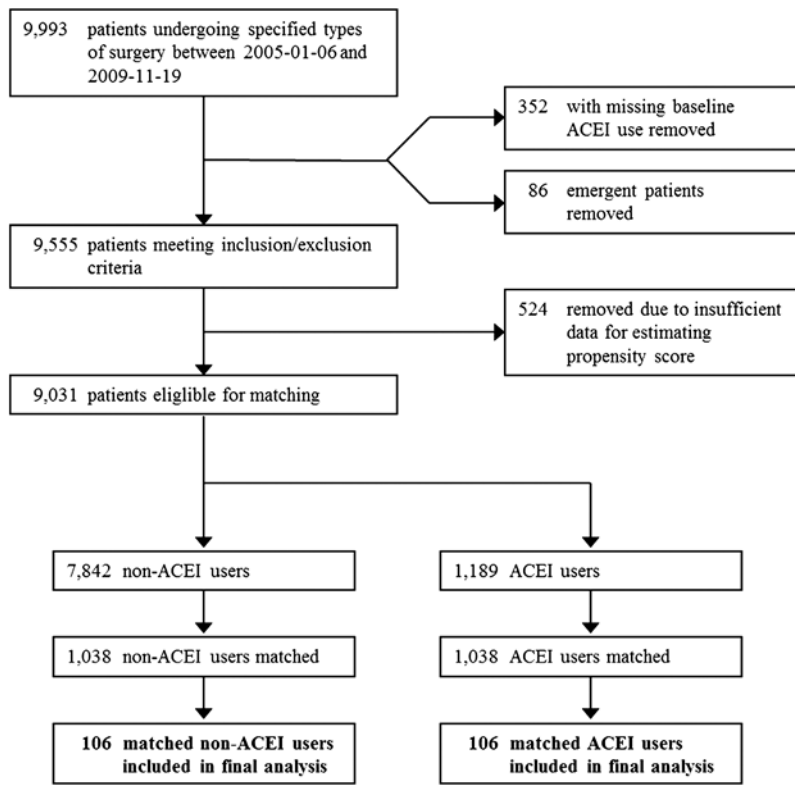

FIGURE 1. Summary of patients included in the study. Selection of the final 101 matched pairs for analysis from the 1038 matched pairs was based on type of surgery and propensity score.

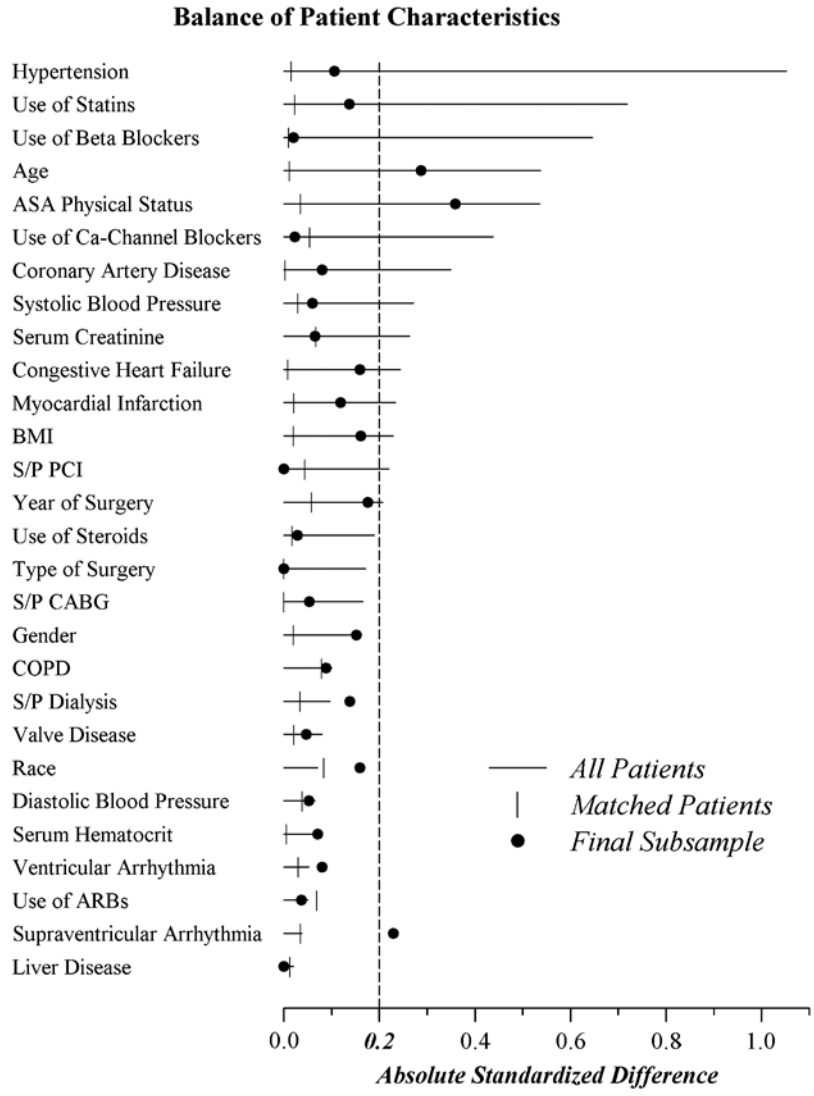

FIGURE 2. Balance of patient characteristics before and after exact matching on propensity score (rounded to the nearest percentage) and type of surgery, as well as among the 100 matched pairs included in the final analysis, as characterized by absolute standardized differences (ASDs). The ASD, equal to the difference in means, mean rankings, or proportions divided by the pooled SD, is a measure of statistical distance between 2 groups on a characteristic; values >0.2 are indicative of imbalance between the 2 groups (and thus potential confounding on the relationship of interest). Age, American Society of Anesthesiologists Physical Status, and supraventricular arrhythmia displayed marginal imbalance among the 212 patients included in the final analysis and were hence, adjusted for within the multivariable linear regression models. ASA indicates American Society of Anesthesiologists; BMI, body mass index; Ca, calcium; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; S/P, status/post.

summarized using a time-weighted average (TWA) algorithm. The second was that matched ACE inhibitor users and nonusers differed on mean 72-hour postoperative opioid requirements as characterized by milligrams IV morphine equivalent dose (Table 1).

To accomplish this testing, outcome-specific multivariable linear regression models were developed. These regression models included all imbalanced potential confounding variables as described by the ASD criterion above. A logarithmic transformation of IV morphine equivalent dose was performed before analysis to meet modeling assumptions. To avoid taking the logarithm of 0 which is undefined, we added 0.1 mg morphine equivalent to those receiving no opioids. Standard t tests for linear regression model coefficients were used for this testing.

An outcome-specific significance criterion of $P < 0.025$ was used for each of the tests to ensure an overall type I (false positive) error rate of 5% for the entire study (Bonferroni correction). Corresponding estimates and Bonferroni-adjusted 95% confidence intervals for the effect of ACE inhibitors on each outcome were also estimated. R Statistical software version 2.11.1 for Windows (The R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analysis.

RESULTS

There were 9555 patients who met our inclusion/exclusion criteria, of whom 1241 (13.0%) were taking ACE inhibitors before their surgery (Fig. 1). Patients taking ACE

TABLE 3. Types of ACEIs Used by Patients

ACEI	No. Patients (N [%])
Lisinopril	61 (59.8)
Enalapril	12 (11.8)
Ramipril	10 (9.8)
Benazepril	8 (7.8)
Quinapril	5 (4.9)
Fosinopril	3 (2.9)
Accupril	1 (1)
Captopril	1 (1)
Monopril	1 (1)

ACEIs indicates angiotensin-converting enzyme inhibitors.

inhibitors were more likely to be hypertensive, to be using statins, β-blockers, and calcium channel blockers, more likely to have coronary artery disease, to have had congestive heart failure, myocardial infarction, and/or percutaneous coronary intervention, more likely to be older, and have a higher American Society of Anesthesiologists (ASA) Physical Status (Table 2).

The stepwise multivariable logistic regression model developed for the estimation of propensity scores identified the following factors as predictive of ACE inhibitors being listed in the medication history: sex, year of surgery, ASA Physical Status, systolic blood pressure, hypertension, history of congestive heart failure, previous coronary artery bypass grafting, steroid use, β-blocker use, angiotensin II receptor blocker use, calcium channel blocker use, and statin use. Estimation of the propensity scores was not possible for 524 patients (5.5%) because of missing data on these factors.

The exact matching procedure, based on type of surgery and propensity score (rounded to the nearest percentage), identified 1038 matched pairs. ASD scores for the factors identified as displaying imbalance (as defined by ASD >0.2) between ACE inhibitor users and nonusers before matching were much smaller after matching (Fig. 2). Postoperative opioid data were ascertained from electronic medical records for a total of 106 matched pairs (see above); this required the review of 199 matched pairs as 93 pairs contained at least 1 patient who did not meet the inclusion/exclusion criteria or whose medication history did not accurately reflect their actual ACE inhibitor usage. ACEI drug distribution in propensity-matched patients is given in Table 3. Thus, our final analyzed subsample was of size N = 212. A graphical summary of pain scores and opioid consumption is given in Figure 3.

Within this final subsample, covariables were generally well-balanced, except for age (ASD = 0.29), ASA physical status (ASD = 0.36), and supraventricular arrhythmia (ASD = 0.23, Fig. 2). We adjusted for these 3 factors within our linear regression models assessing the relationship between ACE inhibitor use and, respectively, mean TWA pain score and total postoperative opioid consumption; ASA physical statuses III and IV were combined during modeling because of small cell sizes.

We found no differences in pain scores or opioid requirements after adjusting for these factors. The adjusted difference (Bonferroni-adjusted 95% confidence interval) in mean 72-hour postoperative TWA pain score (ACE inhibitor users, relative to nonusers) was estimated at $+0.17$ [-0.40, $+0.74$] units on the verbal response scale, which was not statistically significant ($P = 0.50$, linear model t test).

For opioid use, we estimated the percent difference in mean 72-hour total postoperative IV morphine equivalent dose at -8.1% [-46%, $+56\%$], which was also not statistically significant ($P = 0.72$). Adjusted mean TWA pain score was 3.2 [2.8, 3.6] for the ACE inhibitor users and 3.1 [2.7, 3.5] for the nonusers, whereas adjusted mean total opioid consumption was 12.2 [8.5, 17.6] and 13.3 [9.2, 19.1] mg IV morphine equivalent, respectively.

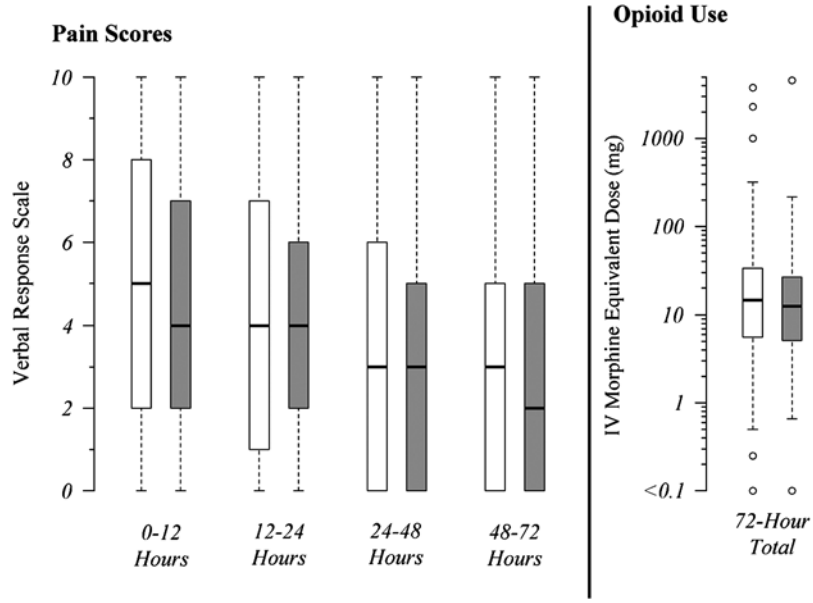

FIGURE 3. Box plots of verbal response pain scores obtained in 4 discrete postoperative intervals and of total 72-hour postoperative opioid consumption (in mg IV morphine equivalent dose), for 212 matched ace inhibitor users (blue) and nonusers (white). The first quartile, median, and third quartiles comprise the boxes. Whiskers extend to the most extreme observations within 1.5 times the interquartile range of the first and third quartiles, respectively; points outside these whiskers are displayed individually.

DISCUSSION

ACEIs potentially augment pain perception by either decreasing plasma angiotensin II and/or increasing tissue bradykinin and substance *P* levels, effects that are manifested clinically as regional pain in patients who take ACEIs.[17,18] Bradykinin is an important mediator of inflammation and pain, acting on nerve terminals to contribute to peripheral sensitization. Bradykinin also produces central sensitization which may augment acute pain.[19] This theory is supported by the observation that pain intensity in human volunteers after muscle contraction correlates with the concentration of tissue bradykinin; and that administration of ACEIs further augments bradykinin concentrations and pain intensity.[20] Angiotensin II has central and peripheral antinociceptive effects with role in regulation of pain and inflammation. The effects of angiotensin II are through presynaptic AT1 inhibition of GABAergic inputs in midbrain periaqueductal gray.[21,22] The antinociceptive role has been demonstrated in the incisional pain model[23] and trigeminal neuralgia.[22] Furthermore, ACEIs prevent migraines by preventing formation of angiotensin II, independent of their effect on blood pressure.[24,25] There were thus well-established reasons to expect patients given ACEIs to experience more postoperative pain. Surprisingly, although, we did not find a significant difference in postoperative pain scores or opioid requirements in patients taking ACEIs.

Our study appears to be the first specifically evaluating the relationship between ACEI use and postoperative pain—and contrast with nonoperative pain studies. For example, Schrader et al[26] demonstrated that ACEIs cause dose-dependent hyperalgesia after thermal injury. Furthermore, a single dose of ACEI in normotensive volunteers decreases the pain perception threshold and increases maximum tolerated pain, indicated that ACEIs cause algesia.[27] And finally, ACEI use is associated with complex regional pain syndrome, possibly by an ACEI-induced increase in substance P and bradykinin.[14] The difference of our results from previous nonsurgical studies suggests the possibility that ACEI effect is relatively small and overwhelmed by intense surgical pain.

Interactions between pain sensitivity and the cardiovascular system are well established. Hypertension in animal and human models is associated with reduced sensitivity to pain.[28] And as might thus be expected, antihypertensive medications reverse reduced pain perception.[29–31] Consistent with this, treatment with ACEIs (enalapril) in hypertensive humans was found to decrease blood pressure but increase sensitivity to pain.[31–33] Increase in pain sensitivity with different ACEIs seems to vary; enalapril, captopril, ramipril, and lisinopril seems to be the most effective.[32] These were the ACEIs that most of our patients took.

Any retrospective analysis, including ours, potentially suffers from selection bias and confounding that are normally largely prevented by randomization. However, we used propensity matching to assemble groups that were comparable on available baseline and surgical factors, even matching exactly on the type of surgery. We also excluded patients with chronic pain whose pain scores and opioid requirements might have been difficult to interpret. It nonetheless remains possible that the treatment groups differed substantially on important factors that are not included in our registry or otherwise available to us. For example, we do not know how well patients complied with their ACEI prescriptions, nor what doses they took.

Perhaps the most serious limitation of our analysis is that while we routinely ask patients not to take ACEIs the morning of surgery, we do not know whether they actually did. Most of the putative mechanisms by which ACEIs are likely to increase surgical pain would seem insensitive to short interruptions of therapy, but the time course of any hyperalgesic efficacy remains unknown. To the extent that continuous ACEI treatment is necessary for hyperalgesia, our patients may not have been a good test. We note, although, that ACEIs usually are held the morning of surgery because of hypotensive concerns. The same concern is not valid for postoperative day 2 and 3, when patients reinitiate their ACEIs. Our results are thus generally applicable.

This is the first clinical study evaluating the role of ACEIs on postoperative pain and opioid consumption. After controlling for all available factors, we found no significant evidence that postoperative pain—as defined by either pain scores or opioid requirements—differed between patients taking ACE inhibitors and patients not taking ACE inhibitors. Perioperative ACEI management should thus be guided by hemodynamic considerations rather than the drugs' putative hyperalgesic effects.

REFERENCES

1. Dahl JB, Moniniche S. Pre-emptive analgesia. *Br Med Bull*. 2004;71:13–27.
2. Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia I: physiological pathways and pharmacological modalities. *Can J Anaesth*. 2001;48:1000–1010.
3. Ji RR, Kohno T, Moore KA, et al. Central sensitization and LTP: do pain and memory share similar mechanisms. *Trends Neurosci*. 2003;26:696–705.
4. Bhave G, Gereau RW. Posttranslational mechanisms of peripheral sensitization. *J Neurobiol*. 2004;61:88–106.
5. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet*. 2006;367:1618–1625.
6. Samad TA, Moore KA, Sapirstein A, et al. Interleukin-1beta-mediated induction of COX-2 in the CNS contributes to inflammatory pain hypersensitivity. *Nature*. 2001;410:471–475.
7. Woolf CJ. Pain: moving from symptom control toward mechanism- specific pharmacologic management. *Ann Intern Med*. 2004;140:441–451.
8. IMS Health. Top therapeutic classes by U.S. dispensed prescriptions. April 6, 2010. Available at: http://www.imshealth.com/deployedfiles/imshealth/Global/Content/StaticFile/Top_Line_Data/Top%20Therapy%20Classes%20by%20U.S.RXs.pdf. Accessed November 15, 2010.
9. Unger T, Azizi M, Belz GG. Blocking the tissue renin-angiotensin system: the future cornerstone of therapy. *J Hum Hypertens*. 2000;14(suppl 2):S23–S31.
10. Gales BJ, Bailey EK, Reed AN, et al. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for the prevention of migraines. *Ann Pharmacother*. 2010;44:360–366.
11. Grafe M, Bossaller C, Graf K, et al. Effect of angiotensin-converting-enzyme inhibition on bradykinin metabolism by vascular endothelial cells. *Am J Physiol*. 1993;264:1493–1497.
12. Erdos EG, Deddish PA, Marcic BM. Potentiation of bradykinin actions by ACE inhibitors. *Trends Endocrinol Metab*. 1999;10:223–229.
13. Irvine RJ, White JM, Head RJ. The renin angiotensin system and nociception in spontaneously hypertensive rats. *Life Sci*. 1995;56:1073–1078.
14. Ercan S, Ilhan M, Turker KR. Alterations by captopril of pain reactions due to thermal stimulation of the mouse foot: interactions with morphine, naloxone and aprotinin. *Eur J Pharmacol*. 1980;63:167–177.
15. de Mos M, Huygen FJ, Stricker BH, et al. The association between ACE inhibitors and the complex regional pain

syndrome: suggestions for a neuro-inflammatory pathogenesis of CRPS. *Pain*. 2009;142:218–224.
16. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd edition. Hillsdale, NJ: Lawrence Erlbaum Associates Inc.; 1988.
17. Kaneko S, Mori A, Tamura S, et al. Intracerebroventricular administration of angiotensin II attenuates morphine-induced analgesia in mice. *Neuropharmacology*. 1985;24:1131–1134.
18. Guasti L, Grimoldi P, Diolisi A, et al. Treatment with enalapril modifies the pain perception pattern in hypertensive patients. *Hypertension*. 1998;31:1146–1150.
19. Brown DA, Passmore GM. Some new insights into the molecular mechanisms of pain perception. *J Clin Invest*. 2010;120:1380–1383.
20. Boix F, Roe C, Rosenborg L, et al. Kinin peptides in human trapezius muscle during sustained isometric contraction and their relation to pain. *J Appl Physiol*. 2005;98:534 –540.
21. Li D-P, Pan H-L. Angiotensin II attenuates synaptic GABA release and excites paraventricular-rostral ventrolateral medulla output neurons. *J Pharmacol Exp Ther*. 2005;313:1035–1045.
22. Xing J, Kong J, Lu J, et al. Angiotensin-(1-7) inhibits neuronal activity of dorsolateral periaqueductal gray via a nitric oxide pathway. *Neurosci Lett*. 2012;522:156–161.
23. Pelegrini-da-Silva A, Rosa E, Guethe LM, et al. Angiotensin III modulates the nociceptive control mediated by the periaqueductal gray matter. *Neuroscience*. 2009;164:1263–1273.
24. Imboden H, Patil J, Nussberger J, et al. Endogenous angiotensinergic system in neurons of rat and human trigeminal ganglia. *Regul Pept*. 2009;154:23–31.
25. Charles JA, Jotkowitz S, Byrd LH. Prevention of migraine with olmesartan in patients with hypertension/prehypertension. *Headache*. 2006;46:503–507.
26. Schrader H, Stovner LJ, Helde G, et al. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomized, placebo controlled, crossover study. *Br Med J*. 2001;322:19–22.
27. Gautam CS, Bhanwra S, Goel NK. Effect of captopril on pain perception in rats. *Indian J Pharmacol*. 2003;35:59–60.
28. Kalra J, Chaturvedi A, Kalra S, et al. Modulation of pain perception by ramipril and losartan in human volunteers. *Indian J Physiol Pharmacol*. 2008;52:91–96.
29. Ghione S. Hypertension-associated hypalgesia. Evidence in experimental animals and humans, pathophysiological mechanisms, and potential clinical consequences. *Hypertension*. 1996;28:494–504.
30. Guasti L, Zanotta D, Diolisi A, et al. Changes in pain perception during treatment with angiotensin converting enzyme inhibitors and angiotensin II type 1 receptor blockade. *J Hypertens*. 2002;20:485–491.
31. Rosa C, Ghione S. Effect of ketanserin on pain perception in arterial hypertension. *Cardiovasc Drug Ther*. 1990;4: 131–133.
32. Guasti L, Grimoldi P, Diolisi A, et al. Treatment with enalapril modifies the pain perception pattern in hypertensive patients. *Hypertension*. 1998;31:1146–1150.
33. Irvine RJ, White JM. The effects of central and peripheral angiotensin on hypertension and nociception in rats. *Pharmacol Biochem Behav*. 1997;57:37–41.

