RESEARCH

Oral curcumin in elective abdominal aortic aneurysm repair: a multicentre randomized controlled trial

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ABSTRACT

BACKGROUND: Curcumin, a popular herbal supplement from the plant turmeric, has prevented ischemic reperfusion and toxin-induced injury in many animal studies and a single-centre randomized human trial. We sought to test whether perioperative oral curcumin (compared with placebo) affects the inflammatory response and risk of postrepair complications after elective abdominal aortic aneurysm repair in humans.

METHODS: We conducted a parallel-group, randomized, placebo-controlled trial of patients from 10 hospitals in Canada who were scheduled to undergo elective repair of an unruptured abdominal aortic aneurysm (November 2011 to November 2014). Patients in the treat-ment group received perioperative oral curcumin (2000-mg doses 8 times over 4 d). Patients, health care providers and local research staff were unaware of the treatment assignment. The primary outcomes were median concentrations of 4 biomarkers indicating injury and inflammation (postoperative urine interleukin-18 and perioperative rise in serum creatinine, plasma *N*-terminal pro–B-type natriuretic peptide and plasma high-sensitivity C-reactive protein).

RESULTS: Baseline characteristics were similar in the 2 groups (606 patients overall; median age 76 yr). More than 85% of patients in each group took more than 80% of their scheduled capsules. Neither curcumin nor placebo significantly affected any of the 4 biomarkers (*p* > 0.05 for all comparisons). Regarding the second-ary outcomes, there was a higher risk of acute kidney injury with curcumin than with placebo (17% v. 10%, *p* = 0.01), but no between-group difference in the median length of hospital stay (5 v. 5 days, *p* > 0.9) or the risk of clin-ical events (9% v. 9%, *p* = 0.9).

INTERPRETATION: Curcumin had no beneficial effects when used in elective abdominal aortic aneurysm repair. These findings emphasize the importance of testing turmeric and curcumin before espousing their health benefits, as is cur-rently done in the popular media. **Trial registration:** ClinicalTrials.gov, no. NCT01225094.

Many modern medicines come from plants.[1,2] Turmeric, a plant in the ginger family that is native to South Asia, has been used for centuries as a spice and traditional medicine. The active medicinal ingredient, curcumin, is a poly-phenol that constitutes about 3% of turmeric by weight. Sales of oral curcumin as a natural health product continue to rise worldwide,[3] supported by many biological studies that show its antioxidant and anti-inflammatory properties.[4–6] For example,

more than 35 animal studies have shown that curcumin reduces the risk of ischemic reperfusion and toxin-induced injury to the kidney (see section 1 of Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.180510/-/DC1, which includes animal models of abdominal aorta cross-clamping and contrast-induced injury).[7,8] Curcumin has the potential to prevent organ injury from surgery by preserving endothelial function, reducing inflammation and limiting oxidative stress (see section 2 of

Appendix 1).[9] In a randomized controlled trial of 121 consecutive patients undergoing coronary artery bypass graft surgery at a single centre in Thailand, oral curcumin, relative to placebo, reduced the risk of postoperative myocardial infarction and lowered concentrations of plasma biomarkers for inflammation, oxidation and injury. Specifically, it attenuated the perioperative rise in the plasma concentration of *N*-terminal pro–B-type natriuretic peptide (NT-pro-BNP), C-reactive protein and malondialdehyde).[10]

Elective abdominal aortic aneurysm repair, a common operation worldwide, can injure the kidneys and other organs through ischemia from aortic cross-clamping (open procedure) or an intravascular contrast agent (endovascular repair). We conducted this multicentre randomized, placebo-controlled trial to test whether perioperative oral curcumin alters a biomarker panel assessing injury and the inflammatory response or the risk of postrepair complications after elective abdominal aortic aneurysm repair.

Methods

We conducted a randomized, parallel-group, placebo-controlled trial with blinding of patients, providers and assessors. Participants were recruited at 10 academic hospitals in 4 provinces (listed in section 3 of Appendix 1).

Participants
The complete eligibility criteria are reported in section 3 of Appendix 1. In brief, eligible patents were scheduled for elective repair of an abdominal aortic aneurysm, planned as either an open or an endovascular procedure. Patients scheduled for an endovascular procedure had to have at least 1 preoperative risk factor for surgical complications (diabetes mellitus, older than 70 years of age or elevated serum creatinine concentration, defined by value > 177 μmol/L in men or > 146 μmol/L in women). All participants provided written informed consent before randomization.

Randomization
Research personnel at the participating sites entered demographic and baseline clinical characteristics into a secure web-based database system that also provided randomization. Baseline data were checked to confirm each patient's eligibility, and the system then assigned the participant to curcumin or placebo therapy, with assignments in a 1:1 ratio stratified by centre. The sequence of assignment was determined by the web-based, computer-generated blocked random number table.

Blinding
Participants, their health care providers and the data collectors were unaware of the group assignment. The placebo capsules looked, smelled and tasted the same as the curcumin capsules, and were made of yellow food colouring, gelatin and cellulose.

Interventions
Patients were assigned to take curcumin or placebo according to the trial regimen, which is described and justified in section 4 of Appendix 1. All specifications for the curcumin and placebo capsules, including tests confirming stability of the capsules, were submitted to Health Canada. The curcumin capsules contained 95% curcumin extracted from the rhizome of *Curcuma longa* (turmeric) and were free of impurities. Participants randomly assigned to the intervention group were scheduled to receive a total of 4000 mg of curcumin per day in 2 divided doses for 2 days before the repair, followed by 2000 mg the morning of the repair, 2000 mg on call to the operating room, 2000 mg 6 hours after surgery and 2000 mg the next morning. We did not impose any dietary restrictions, as foods spiced with turmeric provide exceedingly small amounts of curcumin.[11,12] We did not monitor participants' use of over-the-counter curcumin or turmeric supplements, but we did ask all participants to refrain from taking such supplements.

Outcome measures
Full definitions of the trial outcomes are provided in section 5 of Appendix 1. Preoperative blood samples were collected a median of 9 (interquartile range [IQR] 5 to 17) days before the repair. Postoperative urine and blood samples for biomarkers other than serum creatinine were collected a median of 1 (IQR 1 to 1) hour after the end of the repair and were used for postoperative biomarker measurement. Serum creatinine concentrations were measured for the first 2 days after surgery; any postoperative value greater than 9 μmol/L (0.1 mg/dL) above the preoperative value resulted in at least 2 more days of measurements, even if the patient was discharged from hospital. The postoperative serum creatinine used in the primary outcome was the highest value in the 7 days after surgery. Patients were contacted 30 days after surgery to determine whether clinical events had occurred after hospital discharge, and again 90 days after surgery to obtain a serum creatinine value and to record vital status.

The primary outcomes were 4 biomarkers to assess different aspects of injury and the inflammatory response in the kidney and other organs: postoperative concentration of urine interleukin-18 and perioperative (postoperative minus preoperative) rise in the concentration of serum creatinine, plasma NT-pro-BNP and plasma high-sensitivity C-reactive protein.

Interleukin-18, which mediates kidney ischemic reperfusion injury in animals, is synthesized by several tissues, including proximal kidney tubular epithelial cells.[13,14] The preoperative concentration of urine interleukin-18 is constitutively low and has no prognostic significance. A high concentration of urine interleukin-18 in the hours after cardiac surgery is associated with higher risks of clinical acute kidney injury and death and also with a longer hospital length of stay.[15] Rising serum creatinine concentrations in the days after an insult are used in clinical practice to diagnose acute kidney injury. The biomarker NT-pro-BNP is released from the myocardium when it is stretched, inflamed or ischemic; higher postoperative plasma concentrations after noncardiac surgery are associated with a greater 30-day risk of mortality and nonfatal myocardial infarction.[16] Plasma high-sensitivity C-reactive protein is a common measure of systemic inflammation, where a higher

postoperative concentration is associated with a greater magnitude of surgical injury.[17]

The secondary outcomes were acute kidney injury (based on, relative to the preoperative value, either an increase ≥ 26.5 μmol/L [≥ 0.3 mg/dL] in the concentration of serum creatinine in the 48 h after surgery or an increase of ≥ 50% in the concentration of serum creatinine in the 7 days after surgery),[18] hospital length of stay and a composite of 14 adjudicated clinical events within 30 days of surgery (described in section 5 of Appendix 1 and including outcomes of death, myocardial infarction and stroke). Outcomes to assess curcumin safety included diarrhea, bleeding and hypoglycemia.[19]

Statistical analysis

As presented in section 6 of Appendix 1, we determined that enrolling 600 patients would give the trial 80% power to detect meaningful differences in our primary biomarker outcomes. Thus, the target recruitment for this trial was 600 patients for analysis. The external data and safety monitoring committee reviewed the safety data 4 times during the trial and recommended that the trial be completed as planned. We evaluated all patients who did not withdraw their consent from trial participation according to the group to which they were assigned, consistent with a slight modification of the intention-to-treat principle (see Results section; most withdrawals occurred before the first day on which study capsules were scheduled to be taken).

We used standard statistics to describe baseline characteristics. We compared continuous variables between the 2 groups using an independent-samples t test or Wilcoxon rank-sum test, and compared dichotomous variables using a χ^2 or Fisher exact test.

To compare curcumin and placebo outcome measures, we used linear regression for continuous variables and logistic regression for binary variables. A 2-sided p value of less than 0.05 indicated statistical significance, without adjustment for multiple comparisons. We decided that if curcumin was associated with significant improvement in at least 2 of our 4 primary biomarker outcomes, with no evidence of harm in the remaining outcomes, we would conclude that curcumin exerts a positive biological effect. The chance of observing statistical significance (in any direction) on at least 2 of the 4 biomarker outcomes was 1.4% if, in truth, there was no biological effect of curcumin. We imputed missing continuous variables using multiple imputations with monotone linear regression, and did the same for missing binary variables using monotone logistic regression.

We completed 3 additional analyses. We adjusted for the following relevant clinical baseline characteristics in the regression models: age; sex; body mass index; estimated glomerular filtration rate; presence of congestive heart failure, coronary artery disease or a previous cerebrovascular event; history of smoking; type of repair planned; and baseline medication use (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, diuretics, nonsteroidal anti-inflammatory drugs and statins). We also performed a complete case analysis

using the same outcome definitions and covariable adjustments as the imputed models. Finally, we explored the effect of surgery type (open v. endovascular) by including an interaction term with treatment assignment in the models.

All analyses were performed with the use of SAS software, version 9.3 (SAS Institute Inc.).

Ethics approval

Ethics approval was granted by the institutional review board at each participating site, with the initial granting body being Western University Health Sciences Research Ethics Board. An independent data safety and monitoring board oversaw the trial's safety and ethical conduct.

Results

Patient enrollment and baseline characteristics

Between November 2011 and November 2014, we randomly assigned 624 participants to receive curcumin (n = 313) or placebo (n = 311) (Figure 1; section 7 of Appendix 1). A total of 16 patients (7 in the curcumin group, 9 in the placebo group) were withdrawn before the scheduled first day of study capsule intake, and 2 patients (both in the curcumin group) had their data withdrawn for other reasons, which left 606 patients in the modified intention-to-treat population of curcumin (n = 304) versus placebo (n = 302). The last 30-day follow-up visit after surgery occurred on Jan. 2, 2015, after which time clinical outcomes were adjudicated and biosamples were sent to a reference laboratory at Yale University, New Haven, Conn., for analysis.

A total of 10 (2%) of the 606 patients died within 30 days of surgery (5 curcumin, 5 placebo), and all but 1 of the remaining patients completed their 30-day follow-up after surgery to determine whether any clinical events had occurred after hospital discharge. Missing data were minimal among the 606 patients; completeness of the 4 primary biomarker measures ranged from 96.5% to 99.8%.

The 2 study groups were well balanced on all baseline characteristics (Table 1). The median age was 76 years, 501 (83%) of the patients were men, 591 (98%) were of white race, 145 (24%) had diabetes, 194 (32%) had an estimated glomerular filtration rate less than 60 mL/min per 1.73 m², and 286 (47%) of the patients underwent an open procedure.

More than 85% of patients in the curcumin and placebo groups took more than 80% of their scheduled trial capsules, as determined by patient self-report combined with pill counts performed by the research coordinators (for use at each time point, see section 8 of Appendix 1). In the curcumin group, curcumin metabolites were detected in the urine using high-performance liquid chromatography and mass spectrometry, as described in section 9 of Appendix 1, at a concentration significantly higher than detected in the placebo group.

Other than the trial capsules, co-interventions (procedures and treatments) in the perioperative period were similar between the 2 groups (Table 2). These similarities included the

use of prophylactic antibiotics, the volume of intravenous fluid administered, the type of anesthesia, the use of intravenous contrast agent and whether certain blood pressure medications or diuretics were used in the 24 hours before surgery.

Primary outcomes

Primary outcomes are presented in Table 3, and the preoperative and postoperative values for serum and plasma biomarkers are presented in section 10 of Appendix 1. Except for serum
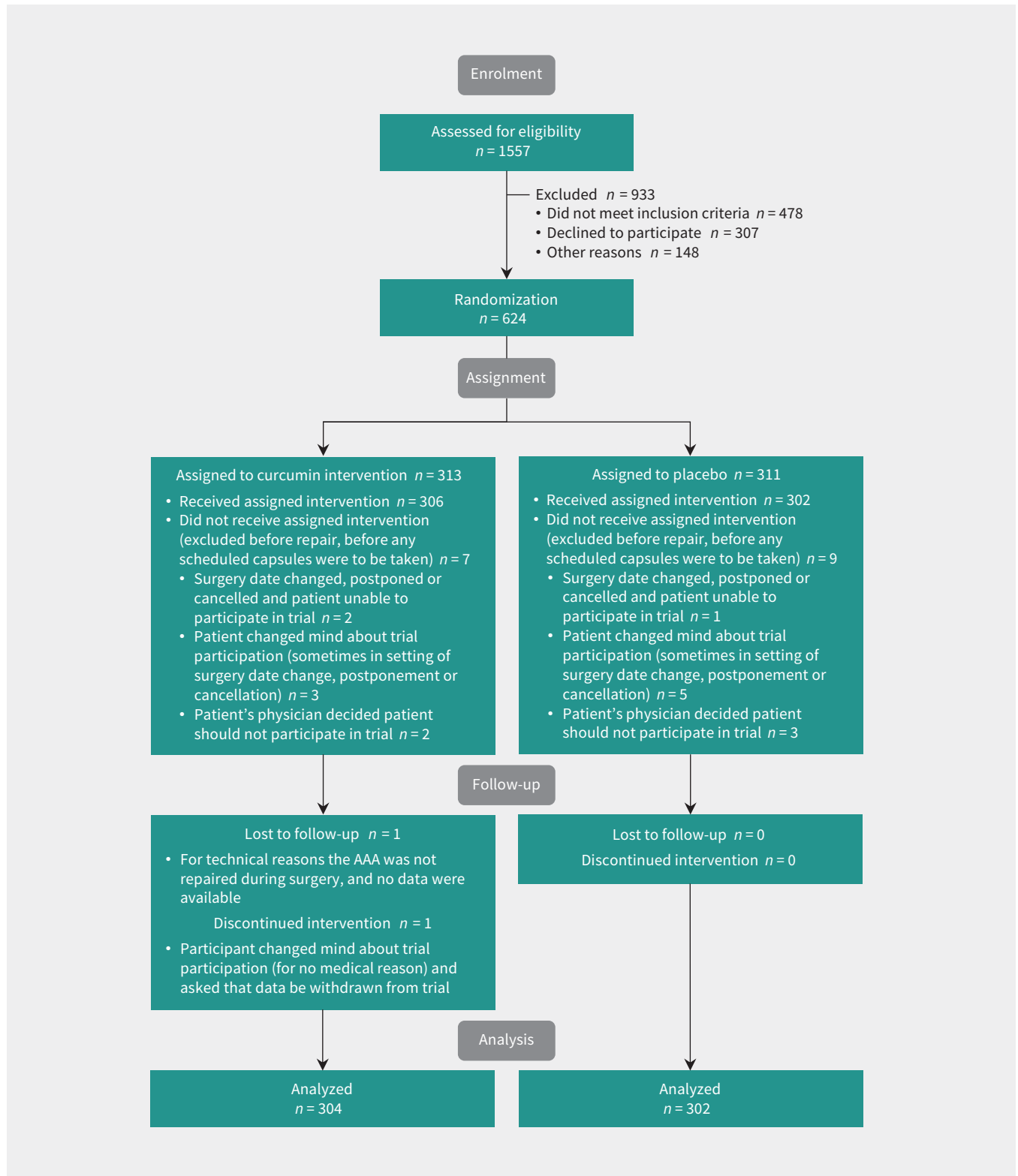

Figure 1: Patient enrolment, allocation and follow-up. Note: AAA = abdominal aortic aneurysm.

Table 1: Characteristics of the patients at baseline

Characteristic	Study group; no. (%) of patients*†	
	Curcumin n = 304	Placebo n = 302
Demographic		
Age, yr, median (IQR)	76 (71 to 80)	76 (70 to 81)
Sex, women	58 (19)	47 (16)
Ethnicity, white	298 (98)	293 (97)
Comorbidities		
Abdominal aortic aneurysm, mm diameter, median (IQR)	57 (54 to 61)	57 (55 to 60)
Current smoker	94 (31)	92 (30)
Diabetes mellitus	73 (24)	72 (24)
Congestive heart failure	14 (5)	13 (4)
Hypertension	238 (78)	224 (74)
Chronic obstructive pulmonary disease	81 (27)	86 (28)
Coronary artery disease, including angina	184 (61)	182 (60)
Prior stroke or transient ischemic attack	42 (14)	35 (12)
Gastroesophageal reflux disease	74 (24)	73 (24)
Medications		
ACE-I or ARB	178 (59)	184 (61)
Diuretic	101 (33)	90 (30)
Calcium channel blocker	94 (31)	83 (27)
β-Blocker	118 (39)	128 (42)
Antiplatelet drug, including ASA	211 (69)	191 (63)
Anticoagulant	18 (6)	20 (7)
Oral hypoglycemic	61 (20)	58 (19)
Insulin	6 (2)	7 (2)
Statin	212 (70)	209 (69)
Physical examination		
Weight, kg, median (IQR)	83 (71 to 94)	86 (74 to 98)
Body mass index > 35 kg/m^2	25 (8)	34 (11)
Systolic blood pressure, mm Hg	134 (122 to 146)	134 (122 to 146)
Diastolic blood pressure, mm Hg	79 (70 to 85)	78 (70 to 83)
Laboratory investigations: eGFR, mL/min per 1.73 m^2		
45 to < 60	61 (20)	55 (18)
30 to < 45	34 (11)	24 (8)
< 30	12 (4)	8 (3)

Note: ACE-I = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, ASA = acetylsalicylic acid, eGFR = estimated glomerular filtration rate assessed with the Chronic Kidney Disease Epidemiology (CKD Epi) equation, IQR = interquartile range.
*Except where indicated otherwise.
†There were no significant differences between the 2 groups for any of the characteristics.

Table 2: Non-study drug procedures and treatments used in the perioperative period

Procedure or treatment	Study group; no. (%) of patients*†	
	Curcumin n = 304	Placebo n = 302
IV fluids and antibiotics		
Before repair		
Volume of fluids given		
None	102 (34)	100 (33)
< 100 mL	16 (5)	18 (6)
100 to 500 mL	139 (46)	138 (46)
> 500 mL	47 (15)	46 (15)
Sodium bicarbonate	12 (4)	9 (3)
Prophylactic antibiotics	254 (84)	258 (85)
Vancomycin	16 (6)	18 (6)
Aminoglycoside	13 (4)	14 (5)
During repair		
Volume of fluids given, L, median (IQR)	2.7 (2.0 to 4.0)	2.5 (1.9 to 4.0)
Colloids	64 (21)	57 (19)
Mannitol	19 (6)	16 (5)
Furosemide	5 (2)	5 (2)
Inotrope or vasopressor	175 (58)	190 (63)
Medications received in 24 h before repair		
ACE-I or ARB	84 (28)	91 (30)
Oral diuretic	39 (13)	40 (13)
Antiplatelet drug, including ASA	127 (42)	120 (40)
Type of anesthesia		
General	265 (87)	275 (91)
Neuraxial	166 (55)	140 (46)
Surgical procedure performed		
Endovascular	153 (50)	167 (55)
Open, or endovascular and open	151 (50)	135 (45)
Use of suprarenal clamp	27 (9)	19 (6)
Use of IV contrast	153 (50)	166 (55)
Renal artery revascularization	29 (10)	22 (7)
Lower limb revascularization	35 (12)	31 (10)
Medications received in 24 h after repair		
ACE-I or ARB	90 (30)	84 (28)
Oral diuretic	58 (19)	53 (18)
Antiplatelet drug, including ASA	205 (67)	214 (71)

Note: ACE-I = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, ASA = acetylsalicylic acid, IQR = interquartile range, IV = intravenous.
*Except where indicated otherwise.
†There were no significant differences between the 2 groups for any of the characteristics.

Table 3: Primary, secondary and safety outcomes

Outcome	Study group; no. (%) of patients*		p value
	Curcumin n = 304	Placebo n = 302	
Primary†			
Postoperative urine IL-18, pg/mL, median (IQR)	13 (6 to 27)	16 (7 to 30)	0.2
Perioperative rise (postoperative minus preoperative)			
Serum creatinine, µmol/L , median (IQR)	1 (–7 to 19)	1 (–6 to 12)	0.2
Plasma NT-pro-BNP, mesoscale pg/mL , median (IQR)	221 (67 to 511)	184 (48 to 431)	0.1
Plasma high-sensitivity C-reactive protein, µg/mL , median (IQR)	58 (28 to 95)	58 (30 to 90)	0.9
Secondary‡			
Acute kidney injury	51 (17)	30 (10)	0.01
Hospital length of stay, d , median (IQR)	5 (2 to 8)	5 (2 to 7)	> 0.9
Composite of clinical events	28 (9)	27 (9)	0.9
Outcomes to assess curcumin safety‡			
Change in hemoglobin (postoperative minus preoperative), g/L , median (IQR)	–33 (–46 to –23)	–32 (–43 to –24)	0.6
Clinically important bleeding	7 (2)	10 (3)	0.4
Peptic ulcer	2 (1)	1 (< 1)	0.6
Glucose 0–3 h after repair, mmol/L, median (IQR)	7 (6 to 9)	7 (6 to 9)	0.3
Hypoglycemic event	9 (3)	3 (1)	0.1
Diarrhea	16 (5)	20 (7)	0.5
Any nausea	31 (10)	25 (8)	0.4

Note: IL-18 = interleukin-18, IQR = interquartile range, NT-pro-BNP = N-terminal pro–B-type natriuretic peptide.
*Except where indicated otherwise.
†Preoperative and postoperative values for serum creatinine, plasma NT-pro-BNP and plasma high-sensitivity C-reactive protein are presented in the table in section 10 of Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.180510/-/DC1). See Methods section for a description of the measurement schedule.
‡Outcomes are defined in section 5 of Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.180510/-/DC1).

creatinine, the postoperative biomarkers were measured at a median (IQR) of 1 (1 to 1) hour after the end of the repair. For both curcumin and placebo groups combined, there was a 202% rise in the mean perioperative concentration of plasma NT-pro-BNP ([postoperative minus preoperative value]/ preoperative value) and a 1846% rise in the mean perioperative concentration of plasma high-sensitivity C-reactive protein. Relative to placebo, curcumin did not significantly affect any of the 4 biomarker concentrations (curcumin v. placebo, median postoperative urine interleukin-18 13 v. 16 pg/mL, p = 0.2; median perioperative [postoperative minus preoperative] rise in serum creatinine, 1 v. 1 µmol/L, p = 0.2; median perioperative rise in plasma NT-pro-BNP, 221 v. 184 pg/mL, p = 0.1; and median perioperative rise in plasma high-sensitivity C-reactive protein, 58 v. 58 µg/mL, p = 0.9).

Secondary outcomes
Secondary outcomes are also presented in Table 3. There was a higher risk of acute kidney injury with curcumin than with placebo (51/304 [17%] v. 30/302 [10%], p = 0.01), and no difference between the 2 groups in the median length of hospital stay (5 v. 5 days, p > 0.9) or the risk of a composite of

clinical events ([including death, myocardial infarction and stroke, as described in section 5 of Appendix 1], 28/304 [9%] v. 27/302 [9%], p = 0.9).

Safety outcomes
Outcomes used to assess curcumin safety are also presented in Table 3. There were no statistically significant differences in the likelihood of these outcomes between the curcumin and placebo groups, including the risk of clinically important bleeding (7/304 [2%] v. 10/302 [3%], p = 0.4), hypoglycemia (9/304 [3%] v. 3/302 [1%], p = 0.1) or diarrhea (16/304 [5%] v. 20/302 [7%], p = 0.5).

Additional analyses
No effect of curcumin versus placebo on study outcomes was consistent in our 3 additional analyses, as described in section 11 of Appendix 1, including the adjusted analysis, analysis restricted to patients with complete data and analysis with both subgroups defined by type of repair (open or endovascular). Furthermore, there was no meaningful between-group difference in kidney function at 90 days, as described in section 12 of Appendix 1.

Interpretation

In this study, perioperative oral curcumin in patients undergoing elective abdominal aortic aneurysm repair had no beneficial effect on a biomarker panel assessing injury and inflammatory response, hospital length of stay or a composite of clinical events.

Our findings are discordant from a prior single-centre trial, in which curcumin (compared with placebo) attenuated the rise in concentrations of 3 biomarkers after coronary artery bypass graft surgery.[10] We measured 2 of these 3 biomarkers in our trial, and our trial enrolled 5 times the number of patients across 10 centres in the setting of a different surgical procedure. Both trials used a total daily dose of 4 g for the studied treatment; however, unlike the capsules in our trial, those in the prior trial were given for a period of 8 days, were ingested 4 times a day, and included demethoxycurcumin and bisdemethoxycurcumin in addition to curcumin. It is unknown whether differences in the trial capsules or their dosing schedule explains the discordant findings between the 2 trials.

We found no statistically significant between-group difference in the perioperative rise in serum creatinine concentration; however, we did find a higher risk of clinical acute kidney injury among patients who received curcumin than among those who received placebo. It is possible that the latter was simply a chance finding in the context of multiple statistical comparisons. However, this risk should be carefully assessed in future trials of curcumin, given that adverse events with natural health products often go unrecognized.[20]

Limitations

Our methods to conduct, analyze and report this randomized controlled trial resulted in a low risk of bias.[21] In this trial, we observed no benefit of curcumin on 4 biomarkers assessing different aspects of perioperative injury and the inflammatory response, but these biomarkers have all the limitations of surrogate outcomes. For reasons of cost, we initially measured postoperative biomarkers (except serum creatinine) right after the abdominal aortic aneurysm repair; upon observing the results of these measurements, we elected to not pursue further biomarker measurements in the samples collected in the days after the repair. Although the concentration of some markers at this first postoperative time point were very different from the preoperative values, our finding of no beneficial effect of curcumin might have differed if we had measured these markers multiple times in the days after repair. Nonetheless, given the primary and secondary outcome findings of this study, it would be difficult to justify the substantial resources needed to conduct a larger trial to determine more precisely the effects of our curcumin regimen on the perioperative outcomes that matter most to patients and their health care providers.

Our curcumin regimen of 4000 mg a day is the average dose used in many published and registered clinical trials. We hypothesized that this dose would exert a pharmacodynamic effect. However, it remains possible that a different formulation of curcumin could have achieved a higher concentration in blood and a different trial result. Curcumin is notorious for being poorly absorbed from the gastrointestinal tract;[22] however, in our study we detected metabolites of curcumin in the urine.

Conclusion

Turmeric has been used for thousands of years in Indian and Chinese medicine, and curcumin continues to gain popularity today as a natural health supplement. In this randomized trial, the largest to date, perioperative oral curcumin did not ameliorate the complications of elective abdominal aortic aneurysm repair. Our findings emphasize the importance of testing turmeric and curcumin in rigorous human clinical trials before espousing any health benefits, as is currently done in the popular media.

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