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ORIGINAL RESEARCH

Effects of allopurinol and vitamin E on renal function in patients with cardiac coronary artery bypass grafts

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Background: Acute renal failure is a common complication of cardiac surgery, with oxidants found to play an important role in renal injury. We therefore assessed whether the supplemental antioxidant vitamin E and the inhibitor of xanthine oxidase allopurinol could prevent renal dysfunction after coronary artery bypass graft (CABG) surgery.

Methods: Of 60 patients with glomerular filtration rate (GFR) < 60 mL/min scheduled to undergo CABG surgery, 30 were randomized to treatment with vitamin E and allopurinol for 3–5 days before surgery and 30 to no treatment. Serum creatinine levels and potassium and creatinine clearances were measured preoperatively and daily until day 5 after surgery.

Results: The patients consisted of 31 males and 29 females, with a mean age of 63 ± 9 years. After surgery, there were no significant differences in mean serum creatinine (1.2 ± 0.33 vs 1.2 ± 0.4 mg/dL; $p = 0.43$) concentrations, or creatinine clearance (52 ± 12.8 vs 52 ± 12.8 mL/min; $p = 0.9$). The frequency of acute renal failure did not differ in treatment group compared with control (16% vs 13%; $p = 0.5$). Length of stay in the intensive care unit (ICU) was significantly longer in the control than in the treated group (3.9 ± 1.5 vs 2.6 ± 0.7 days; $p < 0.001$).

Conclusion: Prophylactic treatment with vitamin E and allopurinol had no renoprotective effects in patients with pre-existing renal failure undergoing CABG surgery. Treatment with these agents, however, reduces the duration of ICU stay.

Keywords: antioxidants, coronary artery bypass, prevention and control, renal function

Introduction

Acute renal failure (ARF) is a common and dangerous complication of cardiac surgery, especially after surgery for cardiac coronary artery bypass graft (CABG),[1] obstructive jaundice,[2] and aortic aneurysm.[3] ARF frequently arises because of decreased tissue perfusion, ischemia, adverse effects of free radicals,[4] and blood vessel constriction stimulating the release of angiotensins such as endothelins.[5] ARF following CABG has been found to increase mortality, morbidity, and intensive care unit (ICU) stay, with some patients requiring dialysis.[6,7] To date, no effective prophylaxis has been found to prevent ARF. Among the agents that have been tested are calcium channel blockers,[8,9] anti-endothelin,[10–12] theophylline,[13,14] prostaglandin E1,[15] low-dose dopamine,[16–19] intercellular adhesion molecule 1 (ICAM 1),[20–22] platelet-activating factor (PAF),[23,24] and alpha melanocyte-stimulating hormone (αMSH),[25,26] but results have not been satisfactory. As ischemia is involved in ARF after CABG, we assessed the effects of the supplemental antioxidant vitamin E and the inhibitor of xanthine oxidase allopurinol in the prophylaxis of ARF.

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Materials and methods

The study involved patients with AFR undergoing CABG between March 2006 and March 2008. Inclusion criteria included age >18 years, glomerular filtration rate (GFR) < 60 mL/min, and no prior use of allopurinol or vitamin E. Exclusion criteria included nonelective emergency surgery, history of dialysis, allergy to vitamin E or allopurinol, and use of radio contrast media within three months prior to surgery. Patients were randomized to receive 100 units vitamin E four times per day and 100 mg allopurinol twice daily for three to five days prior to elective surgery, or to no treatment. None of patients were treated with these drugs before they were enrolled in the study. Patients in both groups were in the surgical ward and ICU of a cardiac super-specialization center and were treated under similar conditions. To prevent bias, the surgeons, nurses, and laboratory technicians were blinded to patient assignment. All patients received 1–2 L of normal saline before surgery to prevent dehydration. The study protocol was approved by our Institutional Ethics Committee, and all patients provided informed consent.

We assessed baseline demographic characteristics, including age, gender, body mass index (BMI), blood pressure, and history of cigarette smoking, history of diabetes, and any previous myocardial infarction (MI). Serum creatinine and potassium concentrations were measured one day before surgery and daily for five days after surgery using standard laboratory methods. Creatinine clearance (CCr) was calculated using the Cockcroft–Gault equation [CCr (mL/min) = (140 – age) × lean body weight (kg)/Cr (mg/dL) × 72] for men, with multiplication by 0.85 required for women. ARF was defined as a fall in GFR by 25%. Other surgery-related parameters included the presence of arrhythmia during and after surgery, length of surgery, left ventricular ejection fraction (EF) before and after surgery, duration of time on-pump, use of a defibrillator, duration of aortic clamp (in minutes), episodes of hypotension (systolic blood pressure <90 mm Hg) during surgery, and need for dopamine and dobutamine infusion during and after operation. We also assessed the duration (in days) of ICU stay, mortality rate, and any adverse effects of allopurinol and Vitamin E.

Statistical analysis

Data are expressed as means ± standard deviations (SDs). Student's *t*-test and the Mann–Whitney *U* test for unpaired data, or chi-square analysis, were used as appropriate to assess between-group differences. The SPSS 15 software program (SPSS Inc., Chicago, IL) was used for all analyses.

Results

During the study period, from March 13, 2006 until March 21, 2008, a total of 70 patients met our initial inclusion criteria. Of these, 10 were excluded, two because of a history of dialysis, three because of a history of injection with radio contrast media during the previous month, and five because of a history of allopurinol usage. Of the remaining 60 patients (31 males, 29 females), 30 were randomized to treatment with vitamin E and allopurinol and 30 to no treatment. The baseline demographic and clinical characteristics of the two groups were similar (Table 1).

After surgery, renal function, hemodynamic condition, ICU stay, and other parameters were compared between the two groups (Table 2). We found that GFR, serum creatinine concentration and the frequency of ARF did not differ significantly in the two groups. In contrast, length of stay in the ICU was significantly lower in the treatment group. For six months following surgery, no patient in either group died

Table 1 Baseline clinical and demographic characteristics of patients in the control and treatment groups

Variable[a]	Treatment group	Control group	p value[b]
Age	65 ± 9.5 years	61 ± 7.90 years	0.103
Sex (M/F)	17/13	14/16	0.4
BMI	24.4 ± 3.22	24.1 ± 2.53	0.77
DM (no.)	11	18	0.71
HTN (no.)	14	18	0.59
History of MI (no.)	17	11	0.108
Smoking (no.)	11	4	0.016
Duration of operation (h)	3.6 ± 0.56	3.2 ± 0.83	0.169
Duration of aortic clamp (min)	32.5 ± 13.33	24.3 ± 9.76	0.185
Pump on (no.)	25	18	0.31
Preoperation EF	44.7 ± 12.29	49.4 ± 12.6	0.354
Preoperation serum Cr (mg/dL)	1.3 ± 0.45	1.3 ± 0.53	0.918
Preoperation serum potassium (meq/L)	4.6 ± 0.48	4.2 ± 0.66	0.019
Preoperation CCr (mL/min)	48 ± 10	50 ± 10.3	0.412
Urine volume (mL)	1689.1 ± 921.20	1530.0 ± 554.43	0.518

Notes: [a]Normal distribution of continuous variables was proven by Kolmogorov–Smirnov; [b]By a Bonferroni correction, a p value < 0.00333 was considered significant.
Abbreviations: BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; MI, myocardial infarction; EF, ejection fraction; Cr, creatinine; CCr, creatinine clearance; h, hour; min, minute.

Table 2 Clinical and paraclinical state of patients during and after surgery in the treatment and control groups

Variable[a]	Treatment group	Control group	P value[b]
Postoperation serum potassium (meq/L)	4.4 ± 0.30	4.3 ± 0.36	0.784
Postoperation serum Creatinine (mg/dL)	1.2 ± 0.33	1.2 ± 0.40	0.435
Postoperation CCr (mL/min)	52.5 ± 12.84	52.3 ± 12.89	0.952
Postoperation ARF (no.)	5	4	0.5
Postoperation EF	44 ± 10.9	45 ± 10.4	0.74
Received dopamine infusion[c] (no.)	8	5	0.65
Hypotension (systolic BP ≤ 90 mm Hg)[c] (no.)	1	6	0.034
Arrhythmia[c] (no.)	12	18	0.56
ICU stay (day)	2.6 ± 0.75	3.9 ± 1.54	0.000[d]

Notes: [a]Normal distribution of continuous variables was proven by Kolmogorov–Smirnov; [b]By a Bonferroni correction, a p value < 0.00555 was considered significant; [c]During surgery; [d]A parametrical test (Student's *t*-test) was performed. However, a nonparametrical test (Mann–Whitney *U* test) was also performed and a P value of 0.004 was obtained.

Abbreviations: EF, ejection fraction; CCr, creatinine clearance; min, minute; ARF, acute renal failure; ICU, intensive care unit.

or required dialysis. Only one patient receiving allopurinol had skin lesions, on the last day of treatment.

Discussion

We found that the combination of allopurinol and vitamin E did not have a significant effect after CABG on the renal function of patients with chronic renal failure. Among the possible causes of ARF after CABG are decreased tissue perfusion, ischemia, and free radical generation.[4] To our knowledge, this study is the first to assess the effect of simultaneous treatment with allopurinol and vitamin E on kidney function in patients with pre-existing renal failure.

Allopurinol was selected as the choice of xanthine oxidase inhibitor because of the effects of this chemical on the ischemic process. For example, the blood concentrations of xanthine and hypoxanthine in CABG patients treated with either pump-on or pump-off procedures were shown to be significantly higher after than before surgery.[4] Although these levels were higher in pump-on than in pump-off patients, the highest concentrations were observed in cases admitted to the ICU. In addition, Allopurinol inhibition of xanthine oxidase may have an impact on lesions of ischemia-reperfusion, a potential occurrence in CABG surgery, and a condition in which xanthine oxidase has clearly been implicated.[27] The potential effect of decreasing urate levels of allopurinol could have the therapeutic effect. However, we did not measure urate level and it is a limitation of the study.

Although no prior studies have evaluated whether allopurinol might prevent ARF in humans, the xanthine oxidase inhibitor oxypurinol did not prevent decreased renal function in rats, which may be because of the effect of oxypurinol to prevent the proliferation of nephron tubular cells.[28] Similarly, in our study, the lack of effect of allopurinol on renal function may be related to drug antiproliferative effects on tubular cells.[28]

Patients receiving allopurinol were also treated with the antioxidant vitamin E to determine if these two agents might show an additive effect in preventing renal dysfunction in patients with ischemia. In rats, the lipid-soluble antioxidant α-tocopherol was shown to reduce oxidative stress, thus decreasing chronic renal failure.[29] Vitamin E may prevent acute decreases in renal function induced by ischemia, contrast media, or drugs.[30] In pigs, the combination of vitamins E and C after cisplatin caused significant increases in renal total superoxide scavenger activity; this, in turn, strengthens the renal antioxidant system, eliminates oxidation reactions, and prevents cisplatin-induced kidney failure.[31] Vitamin E has also been found to prevent acute tubular necrosis following glycerol administration in rats,[32] and to prevent damage following renal ischemia.[33] Roberts and colleagues[34] have shown that a vitamin E treatment period of at least 16 weeks and 800 units/day was necessary for the significant increase in plasma concentrations of vitamin E. However we only used 3–5 days and 400 units of vitamin E. Therefore, it may be that the lack of effects seen here is due to insufficient antioxidants.

We did not administer vitamin E and allopurinol after surgery due to their possible lack of effect on renal function. Therefore, we suggest postsurgical administration of these drugs in further studies.

Various clinical trials have assessed the ability of different interventions to prevent ARF after CABG. The antioxidant N-acetylcysteine was found to have no effect in preventing ARF in cardiac patients,[35] or in reducing the rate

of renal failure in patients undergoing heart and/or aortic surgery.[36–38] The renal function of on-pump CABG patients was improved by leukodepletion, which prevented tubule destruction,[39] and infusion of sodium nitroprusside resulted in improved renal function in cardiac patients.[40] As hydration prior to surgery has been found to prevent renal damage,[41] our patients were infused with 1–2 L of normal saline to prevent confounding the effects of dehydration with those of allopurinol and vitamin E. Calcium channel blockers, such as diltiazem[42] and verapamil,[43] have been shown to increase urine output and to maintain tubular integrity after cardiac surgery, without significantly affecting the GFR. The selective dopamine receptor fenoldopam has been found to maintain creatinine clearance in the 0–4 h and 4–8 h intervals after CABG.[44] Although dopamine has been used to prevent ARF, this drug has not been shown to have any effect.[19,45,46] The ability of the α2-adrenergic receptor clonidine to prevent renal dysfunction in cardiac surgery patients may result from a reduction in the sympathetic nervous system response to CABG surgery.[47] In a randomized study, simultaneous infusion of nifedipine and maintenance of the hemodynamic state resulted in preservation of GFR and creatinine clearance after cardiac surgery.[48]

We found that duration of ICU stay was significantly shorter in the treatment group than in the control patients. In addition to a renoprotective effect, fenoldopam reduced the duration of ICU stay compared with placebo,[49] a finding similar to ours. Another randomized study showed that N-acetylcysteine had no effect on renal function, duration of mechanical ventilation, postsurgical mortality, or required dose of dopamine.[50]

Although the mechanism of action by which the combination of allopurinol and vitamin E reduces ICU stay is not known, the antioxidant and xanthine oxidase inhibition effects of these drugs may decrease the amount of free radicals after surgery. In a finding similar to our study, Bartels and colleagues[51] showed that length of ICU stay was significantly shorter in the vitamin E treatment group than in the placebo group. Their explanation was that vitamin E could reduce the impact of ischemia and reperfusion injury in liver surgery. Goode and colleagues[52] also found that decreased tocopherol (vitamin E) plasma concentrations in patients admitted to the ICU resulted in enhanced free radical activity.

Although the benefit effects of antioxidant and xanthine oxidase inhibitor were mentioned above, the adverse effects of radical scavenger on immune system have been reported. Remer and colleagues[53] showed that nitric oxide played an important role in the control of brain infection with listeria and administration of radical scavenger resulted in rapid death of the treated animals. We did not compare the frequency of the infectious diseases in two groups. This subject should be considered in further studies.

We reported skin lesion in one patient receiving allopurinol. However, several other potentially severe adverse reactions associated with allopurinol administration such as Stevens–Johnson syndrome and toxic epidermal necrolysis.[54] On the other hand, large doses of vitamin E increase mortality.[55] Therefore, the risk and benefit ratio of this treatment should be considered.

Conclusion

We found that the combination of vitamin E and allopurinol at the selected dose had no effect on renal function. Future studies, including patients with lower GFRs or higher creatinine levels, may show that antioxidants have significant effects on renal function. Allopurinol and vitamin E have a significant positive role in reducing the duration of ICU stay in CABG patients.

Disclosure

The authors report no conflicts of interest in this work.

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