

Selenium for the Prevention of Contrast-Induced Nephropathy in Patients Undergoing Coronary Angiography and Percutaneous Interventions: A Double-Blinded Randomized Controlled Trial

Hamid Reza Sanati¹, Behdad Bahadorian^{2*}, Ali Zahedmehr¹, Farshad Shakerian¹, Ata Firouzi¹, Reza Kiani¹, Sakineh Pedarpour², Hossein Fathi², Ali Reza Tatina² and Nasrin Azizian²

¹Cardiovascular Intervention Research Center, Rajaie Cardiovascular, Medical and Research Center, Tehran University of Medical Sciences, Tehran, Iran

²Department of Cardiology, Rajaie Cardiovascular, Medical and Research Center, Tehran University of Medical Sciences, Tehran, Iran

*Corresponding author: Behdad Bahadorian, Cardiovascular Intervention Research Centre, Rajaie Cardiovascular, Medical & Research Center, Tehran University of Medical Science, Tehran, 1413814587, Iran, Tel: + 98 21 23922178; Mobile: +98 9121874093; Fax: + 982122055594; E-mail: behdadbahadorian@gmail.com

Rec date: Jul 23, 2014, Acc date: Sept 03, 2014, Pub date: Sept 13, 2014

Copyright: © 2014 Bahadorian B, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited

Abstract

Background: Contrast-induced nephropathy (CIN) is a common cause of acute kidney injury and is associated with significant morbidity and mortality even if transient or successfully treated. The preventive measures currently available have failed to show significant efficacy. Selenium, which is involved in anti-oxidative reactions, might have protective effects against CIN.

Methods: 237 patients undergoing coronary angiography or intervention were randomly assigned to receive placebo (n=120) or selenium (200 mcg daily on the pre-procedural day, procedural day, and the first post-procedural day) (n=117). Serum creatinine was measured before and two days after the procedure. The primary endpoint was the occurrence of CIN within forty-eight hours.

Results: Baseline characteristics were not different between the groups. CIN occurred in 13 (11.1%) patients in the selenium group and in 23 (19.2%) in the placebo group (odds ratio (or) 95% confidence interval (CI): 1.72 (0.92-3.24), p value=0.084). Selenium intake was significantly associated with lower rates of CIN in the males (or (95% CI): 2.33 (1.10-5.48), p value=0.04), hypertensive patients (or (95% CI): 2.69 (1.12-7.53), p value=0.04), those with a left ventricular ejection fraction <50% (or (95% CI): 5.38 (1.26-22.9), p value=0.008), and those who underwent percutaneous coronary interventions (or (95% CI): 1.98 (1.01-3.99), p value=0.04).

Conclusion: Selenium, as an antioxidant, might decrease the occurrence of CIN, especially in high-risk patients undergoing coronary angiography or percutaneous coronary intervention. Nevertheless, routine recommendation of selenium to these patients needs further investigations.

Keywords: Contrast-induced nephropathy; Coronary angiography; Percutaneous coronary intervention; Selenium

Introduction

Nowadays, contrast agents are increasingly employed in various diagnostic and therapeutic techniques. Contrast-induced nephropathy (CIN) is one of the most important complications of contrast agents and ranges in severity from mild to severe and even life-threatening [1,2]. Core elements that are intertwined in the pathophysiology of CIN include direct toxicity of iodinated contrast to nephrons, micro showers of athero-emboli to the kidneys, and contrast- and athero-emboli induced intra-renal vasoconstriction [3,4]. Recently, a causative role for antioxidants in the pathophysiology of CIN has been proposed [5].

Unfortunately, CIN is increasing in rate due to performing complex procedures requiring large doses of contrast agents in elder population with a high prevalence of comorbid diseases. The widespread use of coronary angiography and percutaneous coronary interventions (PCI) probably has played a major role in bringing CIN into the headlines. CIN occurrence, even if transient and self-limited or successfully

treated, is allied with poor outcomes in patients scheduled for coronary angiography and PCI [6-10]. The occurrence of CIN might be expected in high-risk patients based on history, baseline renal function, clinical status and risk scores [7,11]. Optimal hydration and administration of the least possible amount of contrast media are the cornerstone of CIN prophylaxis, but the current paucity of data and lack of randomized controlled trials should be paid sufficient heed to [12].

There are many studies targeting pharmacological therapies in CIN prevention, but no specific agent has shown any clear and consistent evidence of reduced kidney injury. Of those are N-acetyl cysteine, Theophylline, Pentoxifylline, Ascorbic acid, Prostaglandin E1 (alprostadil), calcium channel blockers, Fenoldopam, and Dopamine; neither has demonstrated promising results regarding CIN, nor is currently approved for routine use to prevent CIN [13-23]. Selenium, a trace element in the structure of antioxidant enzymes [24]. We sought to evaluate the possible protective role of this element against CIN in angiography and PCI patients.

Materials and Methods

Study design

This randomized controlled trial was a single-center study on coronary angiography and PCI patients, who were randomized to double-blind treatment with placebo or selenium, with parallel design and allocation ratio of 1:1. The local Ethics Committee of Rajaie Cardiovascular, Medical and Research Center, Tehran University of Medical Sciences, approved the trial design.

Patient population and randomization: 550 patients were initially evaluated between September 2010 and October 2011. Patients were considered eligible for enrolment if they were over 18 years of age with chronic stable angina or acute coronary syndrome with classic indications for coronary angiography or PCI. Exclusion criteria were history of non-coronary cardiac procedures, acute ST-elevation myocardial infarction and primary PCI patients, hemodynamic instability or cardiogenic shock at presentation or during hospital course, untreated major complications during the procedure, hemodialysis and pregnancy. In addition, patients with contraindication for administration of contrast media such as history of severe allergic reactions, chronic renal failure patients not on hemodialysis or untreated hyperthyroidism did not undergo angiographic procedure.

Randomization was performed based on the computerized balanced block randomization method in blocks of 4:117 patients to the selenium treatment group and 120 to the placebo. Randomization concealment was performed via the sealed envelope technique.

Procedural protocol and follow-up: The study patients in both groups received the same routine preparation protocol for coronary angiography and PCI, including hydration with normal saline before and after the procedure. Normal saline (1 cc/kg) was administered from twelve hours before to six hours after the procedure. The patients in the treatment group received daily oral 200 mcg selenium for three consecutive days before, during and after the procedure. Placebo pills, similar in shape and color, were given to the placebo group to achieve treatment concealment. Coronary angiography and PCI were performed according to the current guidelines. The procedures were conducted using the iso-osmolar non-ionic contrast media Iodixanol (Visipaque 320, GE Healthcare, Cork, Ireland). Laboratory data were obtained from a single hospital laboratory, with the staff blinded to the study protocol. Serum creatinine was measured before and 48 hours after the procedure.

The primary end point of the study was the occurrence of CIN, defined as a minimum 0.5 mg/dl or 25% increase in serum creatinine above baseline.

Statistical analysis

The continuous quantitative variables are presented as mean \pm standard deviation and the qualitative variables as percentage and frequency. Comparison of the means was done using the t-test, and the chi-square test was employed to compare the ratios. Additionally, the relations between the quantitative variables were investigated via the Pearson correlation test.

The independent relationships between the variables and CIN were investigated using the multivariable logistic regression analysis. A p-

value < 0.05 was considered statistically significant, and the analyses were conducted with SPSS 15 software.

Results

Of the 550 patients, who were initially evaluated, 240 patients were subjected to random assignment: 120 to each group; and finally, 117 patients were analysed in the selenium, and 120, in the placebo arms. The study patients were fairly comparable in terms of baseline demographic, laboratory, and procedural characteristics, although there was a significantly larger number of male patients in the selenium group (Table 1). The mean age of the patients was 59.1 years (range=35-79 years) and 60% were male. Renal function tests were not significantly different at baseline. The mean serum creatinine was 0.98 ± 0.25 mg/dl in the selenium group and 1.01 ± 0.3 mg/dl in the placebo group before the procedure (p-value=0.57). The mean contrast volume injected was 185 ± 110 cc in the selenium group and 175 ± 115 cc in the control group (p value=0.35). Type of the procedure, including coronary angiography versus PCI, was also comparable between the two arms (p value=0.24). Of the patients who underwent PCI, 21.3% in the selenium group and 27.5% in the placebo arm received a minimum of 2 stents (p value=0.46).

	Placebo (n=120)	Selenium (n=117)	P value*
Age (Mean)	59.4 \pm 11.3 years	58.9 \pm 11.2 years	0.70
Sex			0.01
Male	63 (52.5%)	79 (68.7%)	
Female	57 (47.5%)	36 (31.3%)	
Risk Factors			
Smoking	72 (60%)	83(71%)	0.30
Hypertension	60 (50%)	43 (36.8%)	0.05
Dyslipidemia	35 (29.2%)	32 (27.4%)	0.75
Diabetes	36 (30%)	35 (29.9%)	0.99
Family history	11 (9.2%)	13 (11.1%)	0.62
Body mass index (mean)	26.5 \pm 3.7	26.9 \pm 4.5	0.50
Left ventricular function			0.90
Ejection fraction \geq 50%	75 (62.5%)	73 (62.4%)	
Ejection fraction <50%	45 (37.5%)	44 (37.6%)	
Anemia	32 (26.7%)	22 (18.8%)	0.16
Hyperglycemia on admission	30 (25%)	17 (14.5%)	0.07
Baseline creatinine (mg/dl)	1.01 \pm 0.3	0.98 \pm 0.25	0.42
Contrast volume (cc)	175 \pm 115	185 \pm 110	0.35
Type of procedure	CAG: 52 (43.3%) PCI: 69 (56.7%)	CAG: 42 (35.9%) PCI: 75 (64.1%)	0.24

Table 1: Background and procedural data of the study participants. *P-value < 0.05 was considered statistically significant.

	CIN* (%) in the placebo group (n=120)	CIN(%) in the selenium group (n=117)	Odds ratio (95% CI)	P value**
Age				
>60 years	15 (26.8%)	8 (17%)	1.57 (0.73-3.38)	0.23
≤60 years	8 (12.5%)	5 (7.2%)	1.72 (0.59-5.01)	0.30
Sex				
Male	13 (20.6%)	7 (8.9%)	2.33 (1.10-5.48)	0.04
Female	10 (17.5%)	6 (16.7%)	0.94 (0.31-2.85)	0.91
Smoking	19 (16.8%)	13 (12.3%)	1.37 (0.71-2.63)	0.34
Hypertension	15 (25%)	4 (9.3%)	2.69 (1.12-7.53)	0.04
Diabetes	10 (27.8%)	4 (11.4%)	2.43 (0.84-7.03)	0.08
Obesity (BMI >30)	2 (12.5%)	0	3.62 (0.89-6.92)	0.10
Anaemia	8 (25%)	3 (13.6%)	1.83 (0.55-6.15)	0.30
Hyperglycemia	7 (17.9%)	4 (12.9%)	1.39 (0.45-4.32)	0.56
LV dysfunction (Ejection fraction <50%)	11 (24.4%)	2 (4.5%)	5.38 (1.26-22.9)	0.008
Contrast volume				
≥300 cc	6 (28.6%)	3 (12%)	1.38 (0.68-8.38)	0.15
<300 cc	17 (17.2%)	10 (10.9%)	1.58 (0.76-3.27)	0.21
Type of procedure				
Coronary angiography	5 (9.6%)	3 (7.1%)	1.35 (0.34-5.31)	0.66
PCI	18 (26.5%)	10 (13.3%)	1.98 (1.01-3.99)	0.04

Table 2: Multivariate logistic regression model

*CIN is defined as a minimum 0.5 mg/dl or 25% increase in serum creatinine above baseline 48 hours after contrast media administration. **P value <0.05 was considered statistically significant. LV: Left Ventricle; PCI: Percutaneous Coronary Intervention

Based on 48 hour post-procedural creatinine, 13 (11.1%) patients in the selenium and 23 (19.2%) patients in the placebo group experienced CIN, which was, albeit not significantly, marginally different between the two groups (odds ratio (or) 95% confidence interval (CI): 1.72 (0.92-3.24), p value=0.084). Moreover, there was no significant difference in post-procedural serum creatinine level between the groups (1 ± 0.32 mg/dl vs 1.04 ± 0.36 mg/dl, p value=0.42). Multivariate analysis using logistic regression model did not show a strong and independent association between the selenium intake and the occurrence of CIN. However, selenium administration was associated with a lower frequency of CIN in the males (or (95% CI): 2.33 (1.10-5.48), p value=0.04), hypertensive patients (or (95% CI): 2.69 (1.12-7.53), p value=0.04), left ventricular ejection fraction <50% (or (95% CI): 5.38 (1.26-22.9), p value=0.008), and those who underwent PCI (or (95% CI): 1.98 (1.01-3.99), p value=0.04) (Table 2).

Discussion

CIN is an increasing important cause of acute renal failure [25]. CIN is currently described as one of the most common causes of

hospital-acquired renal failure, accounting for approximately 11% of cases [26]. Accordingly, many prophylactic strategies have been proposed and tested in numerous studies; none of them, however, has shown constant positive results and there is currently no approved agent for the prevention of CIN.

Selenium, a trace element needed in the structure of antioxidant enzymes such as glutathione peroxidase, can protect cells against damage due to free radicals (oxidative damage) caused by inflammation, malignancies, or toxic materials. Selenium also has a role in the proper functioning of the thyroid gland and adjusting the responses of the immune system [27].

The fact that free radicals play a part in the occurrence of CIN has raised the theory of protective role of Selenium against CIN. Though still in small trials, the available data on this protective role are promising [28-30]. To our knowledge, this study is the first randomized trial to evaluate the role of selenium in CIN prevention. The results obtained from the data collected in this study indicate that selenium intake was not significantly associated with lower rates of

CIN in overall patients. CIN was occurred in 11.1% of the patients in the selenium group and 19.2% patients in the control group; although not statistically significant; the difference shows a trend toward less nephropathy in the Selenium arm (or (95% CI): 1.72 (0.92-3.24), p value=0.084).

Selenium intake was shown to be significantly associated with lower rates of CIN in the male patients (8.9% vs 20.6%, p value=0.04). However, the gender ratio was not the same, there were more male patients in the selenium group than in the control group. In an attempt to avoid the effects of this issue, we separately analysed the results in the two gender groups.

Our study also revealed that selenium might be associated with lower frequencies of CIN in hypertensive patients and those with left ventricular dysfunction. These high-risk patients are classically more prone to CIN and seem to benefit the most from the antioxidant effects of selenium supplementation. Our PCI patients experienced significantly less CIN with selenium supplementation than those in the placebo arm or those who underwent coronary angiography. According to Thiele, balloon angioplasty and stenting are associated with a reduction in selenium levels in serum and whole blood, which is due to an increase in the formation of free radicals following reperfusion or by the procedure itself [31]. These alterations might have some roles in the development of CIN and could be preventable with selenium supplementation.

Study limitations

First and foremost among the limitations of the present study is that it is not sufficiently powered because of the small number of participants. Considering the marginal trend toward a reduction in CIN occurrence with selenium, we may assume that, with a larger sample size, the reduction could have been significant. In addition, selection of patients with higher risk of CIN development might reveal higher efficacy of selenium. It is noteworthy to mention that serum levels of selenium were not measured in the study population. Patients who have selenium deficiency are likely to benefit the most from supplementation.

Conclusion

Our findings indicate that selenium might have a preventive effect against CIN. Nonetheless, this effect is most probably observed in certain high-risk subgroups such as patients with hypertension and left ventricular dysfunction or those who undergo PCI. Lower levels of serum selenium or higher concentrations of free radicals in these patients might be associated with CIN, which could be prevented by selenium supplementation.

Acknowledgement

The authors wish to thank Farshad Amouzadeh, Sara Sasani for editorial assistance and Dr Faraz Ranjpoor for statistical and methodological supervision.

References

1. Solomon R, Werner C, Mann D, D'Elia J, Silva P (1994) Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. *N Engl J Med* 331: 1416-1420.
2. Margulies K, Schirger J, Burnett J Jr (1992) Radiocontrast-induced nephropathy: current status and future prospects. *Int Angiol* 11: 20-25.
3. Keeley EC, Grines CL (1998) Scraping of aortic debris by coronary guiding catheters: a prospective evaluation of 1,000 cases. *J Am Coll Cardiol* 32: 1861-1865.
4. Denton KM, Shweta A, Anderson WP (2002) Preglomerular and postglomerular resistance responses to different levels of sympathetic activation by hypoxia. *J Am Soc Nephrol* 13: 27-34.

5. Andersen KJ, Christensen EI, Vik H (1994) Effects of iodinated x-ray contrast media on renal epithelial cells in culture. *Invest Radiol* 29: 955-962.
6. McCullough PA, Sandberg KR (2003) Epidemiology of contrast-induced nephropathy. *Rev Cardiovasc Med* 4: 1-5.
7. Mehran R, Aymony ED, Nikolsky E, Lasic Z, Iakovou I, et al. (2004) A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol* 44: 1393-1399.
8. Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, et al. (1998) Renal dysfunction after myocardial revascularization: risk factors, adverse outcomes, and hospital resource utilization. The Multicenter Study of Perioperative Ischemia Research Group. *Ann Intern Med* 128: 194-203.
9. Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, et al. (2002) Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 105: 2259-2264.
10. McCullough PA (2002) Cardiorenal risk: an important clinical intersection. *Rev Cardiovasc Med* 3: 71-76.
11. Li WH, Li DY, Han F, Xu TD, Zhang YB, et al. (2013) Impact of anemia on contrast-induced nephropathy (CIN) in patients undergoing percutaneous coronary interventions. *Int Urol Nephrol* 45: 1065-1070.
12. Liu Y, Tan N, Zhou YL, He PC, Luo JF, et al. (2012) The contrast medium volume to estimated glomerular filtration rate ratio as a predictor of contrast-induced nephropathy after primary percutaneous coronary intervention. *Int Urol Nephrol* 44: 221-229.
13. Miao Y, Zhong Y, Yan H, Li W, Wang BY, et al. (2013) Alprostadil plays a protective role in contrast-induced nephropathy in the elderly. *Int Urol Nephrol* 45: 1179-1185.
14. Yavari V, Ostovan MA, Kojuri J, Afsharian R, Hamidian A, et al. (2014) The preventive effect of pentoxifylline on contrast-induced nephropathy: a randomized clinical trial. *Int Urol Nephrol* 46: 41-46.
15. Wu MY, Hsiang HF, Wong CS, Yao MS, Li YW, et al. (2013) The effectiveness of N-acetylcysteine in preventing contrast-induced nephropathy in patients undergoing contrast-enhanced computed tomography: a meta-analysis of randomized controlled trials. *Int Urol Nephrol*.
16. Firouzi A, Eshraghi A, Shakerian F, Sanati HR, Salehi N, et al. (2012) Efficacy of pentoxifylline in prevention of contrast-induced nephropathy in angioplasty patients. *Int Urol Nephrol* 44: 1145-1149.
17. Nallamothu BK, Shojania KG, Saint S, Hofer TP, Humes HD, et al. (2004) Is acetylcysteine effective in preventing contrast-related nephropathy? A meta-analysis. *Am J Med* 117: 938-947.
18. Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, et al. (2000) Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med* 343: 180-184.
19. Madyoon H, Croushore L, Weaver D, Mathur V (2001) Use of fenoldopam to prevent radiocontrast nephropathy in high-risk patients. *Catheter Cardiovasc Interv* 53: 341-345.
20. Kini AS, Mitre CA, Kamran M, Suleman J, Kim M, et al. (2002) Changing trends in incidence and predictors of radiographic contrast nephropathy after percutaneous coronary intervention with use of fenoldopam. *Am J Cardiol* 89: 999-1002.
21. Jo SH, Koo BK, Park JS, Kang HJ, Cho YS, et al. (2008) Prevention of radiocontrast medium-induced nephropathy using short-term high-dose simvastatin in patients with renal insufficiency undergoing coronary angiography (PROMISS) trial- a randomized controlled study. *Am Heart J* 155: 499 e1-e8.
22. Spargias K, Alexopoulos R, Kyrzopolous S, Iokovis P, Greenwood DC, et al. (2004) Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *Circulation* 110: 2837-2842.
23. Bagshaw SM, Ghali WA (2005) Theophylline for prevention of contrast-induced nephropathy: a systematic review and meta-analysis. *Arch Intern Med* 165: 1087-1093.

24. Boucher FR, Jouan MG, Moro C, Rakotovo AN, Tanguy S, et al. (2008) Does selenium exert cardioprotective effects against oxidative stress in myocardial ischemia? *Acta Physiol Hung* 95: 187-194.
25. Nash K, Hafeez A, Hou S (2002) Hospital-acquired renal insufficiency. *Am J Kidney Dis* 39: 930-936.
26. Taylor AJ, Hotchkiss D, Morse RW, McCabe J (1998) PREPARED: Preparation for Angiography in Renal Dysfunction: a randomized trial of inpatient vs outpatient hydration protocols for cardiac catheterization in mild-to-moderate renal dysfunction. *Chest* 114: 1570-1574.
27. McKenzie RC, Rafferty TS, Beckett GJ (1998) Selenium: an essential element for immune function. *Immunol Today* 19: 342-345.
28. Eaton CB, Abdul Baki AR, Waring ME, Roberts MB, Lu B (2010) The association of low selenium and renal insufficiency with coronary heart disease and all-cause mortality: NHANES III follow-up study. *Atherosclerosis* 212: 689-694.
29. Block CA, Manning HL (2002) Prevention of acute renal failure in the critically ill. *Am J Respir Crit Care Med* 165: 320-324.
30. Saint-Georges MD1, Bonnefont DJ, Bourelly BA, Jaudon MC, Cereze P, et al. (1989) [Correction of selenium deficiency in patients with renal failure undergoing hemodialysis]. *Presse Med* 18: 1195-1198.
31. Thiele R, Winnefeld K, Lotze U, Fischer HJ, Haas J, et al. (1999) [Coronary angiography and change in antioxidative status]. *Med Klin (Munich)* 94 Suppl 3: 74-77.