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Effect of Melatonin Administration on Prevention of Contrast-Induced Nephropathy following Coronary Angiography

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Abstract

Introduction. Contrast-induced-nephropathy (CIN) is a common complication during angiography that may lead to long-term complications. This study was conducted to investigate the effect of melatonin administration on prevention of CIN in patients who underwent coronary angiography with intra-arterial contrast agents.
Method. This is single-blind randomized clinical trial that was performed over 100 patients with indication for coronary angiography. Patients are randomly assigned to two equal groups. All patients in the 12 hours before and 12 hours after the procedure, were received adequate intravenous hydration with normal saline and for the intervention group in addition to hydration, the day before angiography and immediately after angiography 3 mg melatonin was administered. For all patients, serum level of creatinine (Cr), blood urea nitrogen (BUN) and glomerular filtration rate (GFR) before and 48 hours after the procedure were measured. Data were analyzed using SPSS 18 software.
Results. Totally 100 participants with the mean age of 64.0±8.2 years were enrolled (63% male). There was no significant difference between intervention and control groups in baseline and demographic characteristics (P> 0.05). Although the mean serum Cr and BUN level increased in both groups, but the mean Cr, BUN and GFR before and after coronary angiography was not statistically significant. Based on the definition of CIN in the current study, 3(6%) patients from intervention group and 2(4%) patients from control group were affected by CIN (P = 0.243).
Conclusion. It is likely that, melatonin administration has no significant effect on prevention of CIN following coronary angiography.

Keywords: acute kidney injury, contrast media, coronary angiography, melatonin, prevention and control

Introduction

Contrast induced nephropathy (CIN) is the third most common cause of in-hospital acute kidney injury, after hypotension and surgical intervention [1,2]. In other words, CIN is responsible for 5-30% of acute kidney injuries in inpatient setting, and after aminoglycoside agents, it is the second most common cause of nephrotoxicity [3-5]. CIN is defined as increased creatinine of at least 0.5 mg/dL or 25% increase in serum creatinine level after contrast administration. Elevation of serum creatinine occurs within 48-72 hours after the contrast imaging performance and usually returns to normal levels within 7-10 days [6-8]. Based on the evidence from previous studies, the prevalence of CIN varies from 0.6 to 2.3% in the general population to 20% in some patients with underlying cardiovascular disease [9]. Although the probability of kidney function recovery from CIN is high, in 10-25% of the cases dialysis was required. It could increase duration of hospital stay and mortality by 5 times that may lead to higher risk of complications such as respiratory failure, sepsis and hemorrhage [9-12]. According to the prior studies, patients with a history of kidney injury, especially those with underlying diabetes mellitus, congestive heart failure, hypotension, concomitant use of nephrotoxic agents or administration of high volume contrast agents are at higher risk of kidney injury [13]. The mechanism of kidney injury caused by contrast agents is unclear, may be it is related to the toxic effects on renal epithelial cells and oxidative stress [14,15]. Due to the devastating effects of intravenous contrast agents on kidney function in some patients, various materials have been used to prevent this destruction [9]. Nowadays, use of low osmolality contrast agents, adequate hydration before and after contrast administration, discontinuation of diuretics and metformin, reducing the dosage of contrast agent and administration of vasodilator drugs are applied to prevent CIN [16]. In several studies in order to prevent harmful effects of contrast agents on kid-

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ney, other substances such as theophylline contrast agents, sodium bicarbonate, HMG-COA reductase inhibitors, ascorbic acid, dopamine and N-acetyl cysteine (NAC) were used in various clinical trials [17]. Melatonin (N-acetyl-5-methoxytryptamine) is a hormone that is secreted from the pineal gland, which has effects besides adjusting sleep-wake cycles such as blood pressure mediator, sedation and analgesic effects [18,19]. According to the previous studies, one of the important effects of melatonin is its antioxidant effect that removes free radicals [20,21]. Previous studies also addressed about minimal side effects of melatonin and also it is rapidly absorbed after oral administration and its performance begins immediately [20,21]. Considering the assumption of melatonin's antioxidant effect and its impact on the process of kidney injury and also due to the high availability and the role of oxidative stress in contrast induced nephropathy, some animal studies support prophylactic and therapeutic effects of melatonin in CIN [20-25]. This study was conducted to investigate the effect of melatonin administration on prevention of contrast induced nephropathy in patients who underwent coronary angiography with contrast agents.

Materials and methods

This is a single blind randomized clinical trial conducted in Arak, Iran. The research protocol was approved by the ethical committee of Arak University of Medical Sciences. The researchers followed the tenets of the Declaration of Helsinki throughout the study. Informed consent was obtained from the participants.

All patients with more than 18 years old that candidate for performing coronary artery angiography were enrolled to the study using convenience sampling method. The patients were excluded if any known history of allergy to melatonin or contrast agents, pregnancy and lactation, gastrointestinal malabsorption problem, recent infectious diseases, history of chronic systemic disease, recent melatonin administration at any dose, and concomitant use of medications that may have an impact on renal function such as theophylline, dopamine, mannitol, furosemide.

The sample size was calculated to be 50 persons for each group with respect to the prevalence of CIN in similar studies (α=0.05). Participants in two groups were matched in terms of age, sex, history of diabetes mellitus and hypertension, serum level of creatinine (Cr), blood urine nitrogen (BUN) and glomerular filtration rate (GFR). Levels of serum Cr and BUN were measured and GFR were calculated using Cockraft-Gault Formula. This formula was selected following an expert consult with a nephrologist.

Baseline and demographic information including age, gender, history of diabetes mellitus and hypertension, serum Cr and BUN and the level of GFR were recorded in pre-prepared checklist.

Participants were randomized at a ratio of 1:1 to either intervention group (50 patients) or control group (50 patients). Both groups of patients were hydrated with 1 ml/kg/hour normal saline 9%, from 12 hours before angiography through to 12 hours after that. In the intervention group melatonin was also administered; 1 tablet (3 mg) a day before angiography and 1 tablet (3 mg) immediately after angiography. Since melatonin has not been used for CIN in human studies before, and based on expert opinion, minimum dose of melatonin was used.

Patients were followed by the clinical information checklist before angiography, and 48 hours after that. Their serum Cr and BUN and GFR was measured as well. According to the prior studies, CIN was defined as 25% increase in serum creatinine level or increased creatinine of at least 0.5 mg/dL, 48 hours after angiography.

There is no reported side effect due to melatonin administration, still due to the effects of sleep regulation by melatonin, patients were recommended not to drive or carry on work that requires full mental concentration within 12-24 hours after taking melatonin.

Evaluation and recording the clinical response (based on laboratory measurements) of patients was done by another doctor who had no knowledge of prescription drugs and patients' group.

Data were analyzed using SPSS version 18 (version 18, SPSS Inc, Chicago, IL) and statistical methods to determine the frequency of variables. In order to analyze the quantitative variables, Student t-test was used and X2 test was used for qualitative variables. The p-value < 0.05 was considered as significant level.

Results

The mean age of the participants was 64±8.2 years and 63% were male. Demographic and baseline characteristics of patients are presented in Table 1. Based on the findings, 74(74%) and 81(81%) patients had diabetes mellitus and hypertension respectively. The baseline mean creatinine, BUN and GFR level was 0.83±0.92

Table 1. Demographic and baseline characteristics of studied patients

Variable	Case group	Control group	p
Age (year)	63.6±7.7	66±7.3	0.451
Sex			
Male	44	39	0.343
Female	26	32	0.462
Past medical history			
Diabetes mellitus	46	48	0.246
Hypertension	52	49	0.091
Bassline renal function tests			
Creatinine (mg/dl)	0.19±0.4	0.49±0.4	0.29
Blood urine nitrogen (mg/dl)	18.7±6.8	19.03±9.6	0.64
Glomerular filtration rate (ml/min)	84.04±25.2	86.4±30.1	0.64

mg/dl, 18.86±8.7 mg/dl, and 85.32±27.9 ml/min respectively. There was no significant difference between intervention and control groups in baseline clinical and demographic characteristics (P>0.05).
Table 2 shows mean Cr, BUN and GFR before and 48 hours after angiography in both studied groups. The mean serum Cr and BUN level raised in both groups, and the mean GFR decreased in result. But the difference between the two groups was not statistically significant.

Table 2. The mean creatinine, blood urea nitrogen and glomerular infiltration rate before and 48 hours after angiography in two studied groups

Variable	Case group	Control group	p
Creatinine (mg/dl)			
Pre Angiography	0.19±0.4	0.49±0.4	0.29
48 hours Later	0.39±0.4	0.89±0.3	0.18
p	0.25	0.08	
Blood urine nitrogen (mg/dl)			
Pre Angiography	18.7±6.8	19.03±9.6	0.64
48 hours Later	20.3±3	22.2±6.2	0.57
p	0.24	0.16	
Glomerular filtration rate (ml/min)			
Pre Angiography	84.04±25.2	86.4±30.1	0.64
48 hours Later	80.2±30.1	81.7±32.3	0.57
p	0.1	0.07	

Based on the definition of CIN in the current study, 3(6%) patients from intervention group and 2(4%) patients from control group were affected by CIN. This difference was not statistically significant (P=0.243).

Discussion

This study showed that melatonin as an adjunct therapy for inhibiting CIN does not have greater advantage over use of rehydration alone. According to the current evidence regarding the benefits of anti-oxidative agents in prevention of kidney injury process, it was assumed that the melatonin may be effective in this regard [14, 20-22]. However, based on the results of current study, the melatonin was not significantly effective on CIN prevention. Nasri *et al*. showed that melatonin can significantly prevent and treat CIN in rat [22]. In a study by Gazi *et al*. it was reported that both preventive and treatment administration of melatonin were lead to significant improvement of kidney function in rats [26]. In the study of Kilic *et al*. serum Cr and BUN level in the mice that had been using combination of melatonin and cisplatin, were significantly lower than that those who were only using cisplatin [27]. The study of Zararsiz *et al*. showed that melatonin can significantly prevent the oxidative damage in the kidney that arises from formaldehyde [28]. Lee *et al*. addressed that melatonin can significantly prevent the gentamycin induced oxidative injury based on histopathologic analysis [29]. According to the results of previous animal studies, it seemed that melatonin could be beneficial in prevention of CIN. Nevertheless, the results of our survey was not consistent with the result of these studies [22,24,25,30].
The limitations of our study included small sample size and lack of long-term evaluation in patients that may suffered from CIN. To the best we know, no clinical human study has been conducted regarding assessing the role of melatonin administration on prevention of CIN and also there is few animal model, further studies with larger sample size and further fallow up is recommended. There are some other formulas such as Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) in terms of GFR measurement that could be used instead of Cockcroft-Gault [31]. Considering these formulas in future research would be valuable.

Conclusion

It is likely that, melatonin administration has no significant effect on prevention of CIN following coronary angiography.

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Authors' Contribution:

All the authors have contributed to drafting/revising the manuscript, study concept. All of the authors declared their accountability for all parts of the article.

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References

1. Tepel M. Acetylcysteine for the prevention of radiocontrast-induced nephropathy. *Minerva cardioangiologica* 2003; 51(5): 525-530.
2. O'sullivan S, Healy D, Moloney MC, *et al*. The Role of N-Acetylcysteine in the Prevention of Contrast-Induced Nephropathy in Patients Undergoing Peripheral Angiography A Structured Review and Meta-Analysis. *Angiology* 2013; 64(8): 576-582.
3. Barrett BJ, Parfrey PS. Preventing nephropathy induced by contrast medium. *New England Journal of Medicine* 2006; 354(4): 379-386.
4. Abushouk AI, Taheri MS, Pooransari P, *et al*. Pregnancy Screening before Diagnostic Radiography in Emergency Department; an Educational Review. *Emergency* 2017; 5(1): 60.

5. Hashemi B, Safari S, Hosseini M, *et al*. A Systematic Review of Iranian Experiences in Seismo-Nephrology. *Archives of trauma research* 2016; 5(2): e28796.
6. Stacul F, van der Molen AJ, Reimer P, *et al*. Contrast induced nephropathy: updated ESUR contrast media safety committee guidelines. *European radiology* 2011; 21(12): 2527-2541.
7. Thomsen H, Morcos S. Contrast media and the kidney: European Society of Urogenital Radiology (ESUR) guidelines. *The British journal of radiology* 2003; 76(908): 513-518.
8. Persson PB, Hansell P, Liss P. Pathophysiology of contrast medium-induced nephropathy. *Kidney international* 2005; 68(1): 14-22.
9. Mehran R, Nikolsky E. Contrast-induced nephropathy: definition, epidemiology, and patients at risk. *Kidney international Supplement* 2006; (100): S11-S15.
10. Saitoh T, Satoh H, Nobuhara M, *et al*. Intravenous glutathione prevents renal oxidative stress after coronary angiography more effectively than oral N-acetylcysteine. *Heart and vessels* 2011; 26(5): 465-472.
11. Safari S, Yousefifard M, Hashemi B, *et al*. The value of serum creatine kinase in predicting the risk of rhabdomyolysis-induced acute kidney injury: a systematic review and meta-analysis. *Clinical and experimental nephrology* 2016; 20(2): 153-161.
12. Safari S, Yousefifard M, Hashemi B, *et al*. The Role of Scoring Systems and Urine Dipstick in Prediction of Rhabdomyolysis-induced Acute Kidney Injury: a Systematic Review. *Iranian journal of kidney diseases* 2016; 10(3): 101-106.
13. Goldenberg I, Shechter M, Matetzky S, *et al*. Oral acetylcysteine as an adjunct to saline hydration for the prevention of contrast-induced nephropathy following coronary angiography. A randomized controlled trial and review of the current literature, 2004.
14. Weisbord SD, Palevsky PM. Radiocontrast-induced acute renal failure. *Journal of Intensive Care Medicine* 2005; 20(2): 63-75.
15. McCullough PA. Contrast-induced acute kidney injury. *Journal of the American College of Cardiology* 2008; 51(15): 1419-1428.
16. Stevens M, McCullough P, Tobin K, *et al*. A prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy: results of the PRINCE Study. Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation. *Journal of the American College of Cardiology* 1999; 33(2): 403-411.
17. Allaqaband S, Tumuluri R, Malik A, *et al*. Prospective randomized study of N-acetylcysteine, fenoldopam, and saline for prevention of radiocontrast-induced nephropathy. Catheterization and cardiovascular interventions. *Official journal of the Society for Cardiac Angiography & Interventions* 2002; 57(3): 279-283.
18. Wilhelmsen M, Amirian I, Reiter R, *et al*. Analgesic effects of melatonin: a review of current evidence from experimental and clinical studies. *Journal of pineal research* 2011; 51(3): 270-277.
19. Peres M. Melatonin, the pineal gland and their implications for headache disorders. *Cephalalgia: an international journal of headache* 2005; 25(6): 403-411.
20. Sezgin G, Ozturk G, Guney S, *et al*. Protective effect of melatonin and 1, 25-dihydroxyvitamin D3 on renal ischemia-reperfusion injury in rats. *Renal failure* 2012; 35(3): 374-379.
21. Hara M, Yoshida M, Nishijima H, *et al*. Melatonin, a pineal secretory product with antioxidant properties, protects against cisplatin-induced nephrotoxicity in rats. *Journal of pineal research* 2001; 30(3): 129-138.
22. Nasri H, Tavakoli M, Ahmadi A, *et al*. Ameliorative effect of melatonin against contrast media induced renal tubular cell injury. *Pakistan journal of medical sciences* 2014; 30(2): 261-265.
23. Murphy SW, BARRETT BJ, Parfrey PS. Contrast nephropathy. *Journal of the American Society of Nephrology* 2000; 11(1): 177-182.
24. Bailey SR. Past and present attempts to prevent radiocontrast nephropathy. *Reviews in cardiovascular Medicine* 2000; 2: S14- S18.
25. Bagshaw S, Ghali W. Theophylline for prevention of contrast-induced nephropathy: a systematic review and meta-analysis, 2005.
26. Gazi S, Altun A, Erdogan O. Contrast-induced nephropathy: preventive and protective effects of melatonin. *Journal of pineal research* 2006; 41(1): 53-57.
27. Kilic U, Kilic E, Tuzcu Z, *et al*. Melatonin suppresses cisplatin-induced nephrotoxicity via activation of Nrf-2/HO-1 pathway. *Nutrition & metabolism* 2012; 10(1): 7-.
28. Zararsiz I, Sarsilmaz M, Tas U, *et al*. Protective effect of melatonin against formaldehyde-induced kidney damage in rats. *Toxicology and industrial health* 2007; 23(10): 573-579.
29. Lee I, Kim S, Lee S, *et al*. Melatonin attenuates gentamicin-induced nephrotoxicity and oxidative stress in rats. *Archives of toxicology* 2012; 86(10): 1527-1536.
30. Millea P. N-acetylcysteine: multiple clinical applications. *American family physician* 2009; 80(3): 265-269.
31. Michels WM, Grootendorst DC, Verduijn M, *et al*. Performance of the Cockcroft-Gault, MDRD, and New CKD-EPI Formulas in Relation to GFR, Age, and Body Size. Clinical Journal of the American Society of Nephrology. *CJASN* 2010; 5(6): 1003-1009.