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Akut koroner sendromlu hastalarda iyodiksanol ile iyopamidolün nefrotoksik etkilerinin karşılaştırması

Comparison of the nephrotoxic effects of iodixanol versus iopamidol in patients with acute coronary syndrome

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ÖZET

Amaç: İzo-ozmolar bir kontrast ajan olan iyodiksanol ozmolaritesi düşük kontrast ajanlara göre daha az oranda kontrasta bağlı akut böbrek hasarı ile ilişkili olabilir. Bu çalışmada iyodiksanol ile ozmolaritesi düşük bir kontrast ajan olan iyopamidolün akut koroner sendromlu (AKS) hastalarda nefrotoksik etkilerinin karşılaştırılması amaçlanmıştır.

Çalışma planı: Üçüncü basamak bir kardiyovasküler merkeze ST yükselmesiz miyokart enfaktüsü ile başvuran hastalardan, erken koroner anjiyografi yapılan ardışık 275 hasta (ortalama yaş 58±11 yıl, %79 erkek) çalışmaya alındı. Koroner anjiyografi için kontrast ajan olarak 230 hastada iyopamidol ve 45 hastada iyodiksanol kullanıldı. İşlem sonrası 72 saat içinde en yüksek kreatinin değeri, kreatinin değerinde mutlak değişiklik, kreatinin değerinde değişiklik yüzdesi ve kontrast maddenin indüklediği nefropati gelişimi açısından iki ajan karşılaştırıldı.

Bulgular: Anjiyografi öncesi temel demografik ve klinik özellikler her iki gruptaki hastalarda benzerdi. Gruplar arasında işlem öncesi kreatinin değerleri (iyopamidol 1,10±0,54 mg/dl, iyodiksanol 1,09±0,24 mg/dl, p=0,680), glomerüler filtrasyon hızları (GFH) (iyopamidol 89±35 ml/dk/1,73 m^2, iyodiksanol 89±26 ml/dk/1,73 m^2, p=0,934) ve kullanılan kontrast madde miktarı (iyopamidol 180±80 ml ve iyodiksanol 166±73 ml, p=0,226) açısından fark yoktu. İşlem sonrası kreatinin değerlerinde mutlak (iyopamidol 0,136±0,346 mg/dl, iyodiksanol 0,072±0,070 mg/dl, p=0,118) ve yüzde (iyopamidol %12,1±29.6, iyodiksanol %6,8±6,9, p=0,075) değişimler iyopamidol ve iyodiksanol için istatiksel farklılık göstermedi. Kontrast maddenin indüklediği nefropati iyopamidol grubunda %10 (%95 güven aralığı [GA] %6-14), iyodiksanol grubunda %2,2 (%95 GA %-2-7) bulundu (p=0,144).

ABSTRACT

Objectives: The iso-osmolar contrast agent iodixanol may be associated with fewer contrast-induced acute kidney injuries when compared with low-osmolar contrast agents. The aim of this study was to compare iodixanol and iopamidol in patients with acute coronary syndrome (ACS) who were undergoing coronary angiography.

Study design: Two hundred and seventy five consecutive patients (mean age 58±11 years, males, 79%). who presented to a tertiary cardiovascular center with acute non-ST elevation myocardial infarction and underwent coronary angiography as a part of an early invasive strategy were included in the study Study participants were administered either iodixanol (n=45) or iopamidol (n=230) and the groups were compared for the highest creatinine levels, the absolute and percent change in creatinine levels, and for the development of contrast induced nephropathy within 72 hours of the procedure.

Results: Baseline demographic and clinical characteristics of the patients were similar between the two groups. There were no differences in the preprocedural serum creatinine (iopamidol 1.10±0.54 mg/dl, iodixanol 1.09±0,24 mg/dl, p=0.680), glomerular fltration rate (iopamidol 89±35 ml/dk/1.73 m^2, iodixanol 89±26 ml/dk/1.73 m^2, p=0.934) or contrast volume used during the procedure (iopamidol 180±80 ml vs. iodixanol 166±73 ml, p=0.226) between the groups. The absolute change in serum creatinine levels after the procedure (iopamidol 0.136±0.346 mg/dl, iodixanol 0.072±0.070 mg/dl, p=0.118) and the percent change in serum creatinine levels after the procedure (iopamidol 12.1±29.6%, iodixanol 6.8±6.9%, p=0.075) were not statistically significant between the two groups. Contrast induced nephropathy developed in 10% (95% confidence interval [CI] 6–14%) of the patients in the iopamidol, and 2.2% (95% CI -2-7%) of iodixanol users (p=0.144).

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Sonuç: Akut koroner sendrom ile yatırılan hasta grubunda iyodiksanolün koroner anjiyografi sonrası böbrek fonksiyonları üzerine etki açısından iyopamidole üstünlüğü görülmemiştir.

Conclusion: Iodixanol has not demonstrated more favourable effects relative to iopamidol on renal functions after coronary angiography in a general patient population hospitalized with the diagnosis of ACS.

Abbreviations:

ACS *Acute coronary syndrome*
GFR *Glomerular filtration rate*
CABG *Coronary artery bypass graft*
CIN *Contrast-induced nephropathy*
PCI *Percutaneous coronary intervention*

Contrast-induced kidney injury has been reported at a rate of 11 percent, and ranks third among the most frequently seen causes of in-hospital acute renal failure.[1] It is an important clinical entity in that it prolongs hospital stay, induces permanent renal damage, and it is associated with risk of mortality. [2-4] Though its pathogenesis is not completely known, based on increasing number of evidence, mechanisms as direct toxic effect on renal tubular epithelium, oxidative stress, ischemic damage, and renal tubular obstruction are held responsible. [5] The most effective preventive measures consist of identification of the risk factors, maintenance of adequate hidration before, and after the procedures, and minimization of the volume of the contrast agent used as far as possible. [6] The most frequently reported risk factors are congestive heart failure, hypotension, advanced age (≥ 75 yrs), anemia, diabetes mellitus, volume of the contrast material used, and chronic renal failure [serum creatinine >1.5 mg/dl or glomerular filtration rate (GFR) <60 ml/dk/1.73 m^2]. [7]

Choice of the contrast material has an important impact on the development of nephropathy. Hyperosmolar agents induce renal damage more frequently than low-, and iso-osmolar agents.[8] In meta-analysis of the initial studies comparing low-osmolar contrast agents, an iso-osmolar contrast agent iodixanol, iodixanol was found to be less toxic as for the development of contrast-induced kidney injury.[9] However in randomized studies published more recently, lack of any significant difference between iodixanol, and low-osmolar contrast agent as for incidence of CIN has been reported.[10-13] Among the main reasons for different outcomes obtained in various studies can be attributed to the route of administration (intravenous or intraarterial), volume of the contrast material used, patient selection criteria, and various definitions of nephropathy induced by the preferred low-osmolar contrast agent.

In this study, we aimed to compare the effects of an iso-osmolar contrast agent iodixanol (non-ionic dimer, 320 mg I/ml, 290 mOsm/kg H_2O) with those of a low-osmolar contrast agent, iopamidol (non-ionic monomer, 300 mg I/ml, 616 mOsm/kg H_2O) used during coronary angiography of in-patients with acute coronary syndrome (ACS) on renal functions.

PATIENTS AND METHOD

Patients

Two hundred and seventy five consecutive patients hospitalized with the diagnosis of non-ST elevation acute coronary syndrome (non-ST ACS) in a tertiary cardiovascular center were evaluated. Among these patients, those who had been scheduled for early invasive treatment, and underwent early coronary angiography at the time of hospitalization were included in the study after their written, and undersigned informed consent for participation in the study was obtained. Patients with acute renal failure, those undergoing chronic dialysis because of end-stage renal failure, cases with known alergies against contrast materials, individuals exposed to contrast agents within the previous 7 days, metformin users, patients with labile hemodynamic state or those requiring emergency intervention were not enrolled into the study. Vital signs, and standard electrocardiograms of the patients were recorded, and blood samples were drawn for the measurement of routine biochemical parametres on the first day of their hospital stay. After establishment of their clinical stabilization, each patient underwent transthoracic echocardiographic evaluations. The study was conducted in compliance with Good Clinical Practice Directives of Helsinki Declaration, and approval was obtained from the Local Ethics Committee.

Coronary angiography, and percutaneous coronary intervention

After written, and undersigned approval of the patient, coronary angiography was performed via femoral route. Each patient underwent selective left, and right coronary angiography, and left ventriculography. Angiograms of the left internal thoracic artery, and saphenous graft (if present) were obtained in patients who had previously undergone coronary artery bypass graft (CABG) operation All patients received isotonic saline infusions (1ml/kg/hr) starting 12 hours before coronary angiographic

examination, and continuing 24 hours after the procedure.[14] In case of clinical indication, coronary angiograms were obtained, and then in the same session percutaneous intervention (PCI) was applied for the culprit lesion. For coronary angiographic examinations, as a contrast material, either iopamidol or iodixanol was used. Volume of the contrast material used during the procedure was noted. If not contraindicated, before the procedure. all patients were started on acetylsalicylic, clopidogrel, enoxaparin (at GFR-adjusted doses), statin, and beta-blocker (contraindiced if heart rate < 50 bpm; systolic blood pressure < 100 mm Hg) therapy. In cases of clinical indications (left ventricular systolic dysfunction, hypertension, diabetic nephropathy etc.) an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker was addesd to the therapy in the absence of contraindications (serum creatinine, > 3.5 mg/dl; ABP z 100 mm Hg).

Clinical follow-up

GFR was estimated from prehidration values using Cockcroft-Gault formula [15] During the hospitalization period, cardiac troponin values were monitored, and peak value was recorded. Renal functions of the patients were monitored for at least 72 hours following coronary angiographic procedures. Serum creatinine levels were measured at every 24 hours after coronary angiography, and the peak value determined within the first 72 hours were recorded. Postprocedural increase of 25 % in serum creatinine levels or an absolute increase from its baseline value was defined as CIN.[16] However to refrain from weakening statistical power of estimations because of two separate definitions of CIN, two contrast material were also compared in terms of continuous variables as absolute, and percent increase in serum creatinine values.

Statistical analysis

Nominal variables related to patient characteristics were presented as numbers, and percentages. For the comparison of nominal variables, *chi*-square or Fisher's exact test was used as deemed appropriate. Numerical variables were expressed as mean ± standard deviation. The patients were divided into 2 groups based on the contrast material used as iopamidol, and iodixanol groups. Numerical variables in groups with non-symmetrical distribution were compared with *t*-test after appropriate arithmetic conversions. Two-sided *p* value of <0.05 was accepted as statistically significant. All data were statistically analyzed using "SPSS for Windows 15.0" (SPSS inc, Chicago, Illinois USA) program.

RESULTS

During the study period, 310 patients with the diagnosis of non-ST elevation myocardial infarction who met the study criteria were hospitalized. Thirty five patients in whom early invasive treatment was not contemplated were discharged with medical therapy, and excluded from the study. The remaining 275 patients were enrolled in the study, and underwent coronary angiographic examinations following initial medical therapy according to early invasive treatment strategy. Median age of the patients was 58 years, and study population consisted of male (79 %), hypertensive (60 %) and diabetic (27.4 %) patients. The patients had previously undergone CABG, and PCI procedures.

The patients were divided into 2 groups according to contrast agents used as iopamidol, and iodixanol groups. Mean age, gender, risk factors of coronary artery disease, and clinical characteristics of ACS were not different between both groups (Table 1). Routine biochemical parametres, creatinine and eGFR values at hospital admission were similar in both groups. Patients with mildly (GFR <90 ml/dl/1.73 m^2), and moderately-to-severely (GFR <60 ml/dl/1.73 m^2) impaired renal functions demonstrated similar distribution. Amount of contrast agents used during coronary angiography, severity of coronary artery disease, and rates of PCI performed were also comparable between both groups.

Tablo 1. Demographic, and clinical characteristics of the study group, and two groups determined by the contrast agent used

	All patienta (n=275) n (%) Mean ± SD	Iopamidol (n=230 n (%) Mean ± SD	Iodixanol (n=45) n (%) Mean ± SD	*p*
Age (year)	58±11	58±11	56±10	0.194
Gender (male)	216 (79)	181 (79)	35 (78)	0.891
Body mass index (kg/m^2)	28.5±4.6	28.5±4.7	28.7±3.9	0.802
History				
Hypertension	164 (60)	138 (60)	26 (58)	0.781
Diabetes	76 (28)	65 (28)	11 (24)	0.589
Hyperlipidemia	147 (53)	121 (53)	26 (58)	0.544
Smoking	125 (46)	106 (46)	19 (42)	0.634
Previous CABG	27 (10)	24 (10)	3 (7)	0.588
Previous PCI	38 (14)	29 (13)	9 (20)	0.189
Clinical characteristics				
Troponin I (ng/ml)	3.0±8.2	3.1±8.7	2.3±3.9	0.566
ST-segment elevation	62 (23)	55 (24)	7 (16)	0.215
Systolic blood pressure (mm Hg)	130±19	129±18	131±21	0.467
Diastolic blood pressure (mm Hg)	76±11	77±12	74±14	0.642
Killip class I	7 (3)	7 (3)	0 (0)	0.606
Ejection fraction (%)	53±10	53±9	54±11	0.517
ACEI or ARB therapy	246 (89)	204 (89)	42 (93)	0.795
Statin therapy	271 (99)	227 (99)	43 (96)	0.886
Laboratory test results				
WBC (10^3/ml)	8.9±2.9	8.9±2.9	9.1±2.1	0.655
Hemoglobin (g/dl)	13.3±1.8	13.2±1.8	13.5±1.8	0.294
Platelets (10^3/ml)	246±69	244±69	254±71	0.395
Glucose (mg/dl)	135±66	135±65	135±76	0.992
Total cholesterol (mg/dl)	189±48	187±45	198±60	0.193
LDL-C (mg/dl)	115±38	113±37	122±40	0.121
HDL-C (mg/dl)	40±10	40±10	42±10	0.241
Triglyceride (mg/dl)	187±132	186±129	192±146	0.779
Preprocedural creatinine (mg/dl)	1.10±0.51	1.10±0.54	1.09±0.24	0.680
eGFR (ml/min/1.73 m^2)	89±33	89±35	89±26	0.934
GFR < 90 ml/min/1.73 m^2)	145 (53)	120 (52)	25 (56)	0.715
GFR<60 ml/min/1.73 m^2)	50 (18)	45 (20)	5 (11)	0.150
Coronary angiography				
Volume of the contrast agent used ml)	178±79	180±80	166±73	0.226
1-vessel disease	68 (25)	54 (24)	14 (31)	0.278
2-vessel disease	79 (29)	69 (30)	10 (22)	0.292
3-vessel disease	96 (35)	85 (37)	11 (24)	0.107
PCI	93 (34)	79 (34)	14 (31)	0.745

ACEI, Angiotensin –converting enzyme inhibitor; ARB: Angiotensin receptor blocker: CABG: Coronary artery bypass graft ; GFR: Glomerular filtration rrate; PCI: Percutaneous coronary artery intervention

Postprocedural renal functions were measured using more than one criteria (Figure 1). Among them, postprocedural maximum creatinine value (iopamidol 1.24±0.78 mg/dl, iodixanol 1.16±0.26 mg/dl, p=0.745), and absolute increase in creatinine values (iopamidol 0.136±0.346 mg/dl, iodixanol 0.072±0.070 mg/dl, p=0.118) were not different between groups. Though postprocedural percent change in creatinine values was not statistically significantly different between groups, a trend towards smaller amount of change was found in the iodixanol group (iopamidol 12.1±29.6%, iodixanol 6.8±6.9, p=0.075%). Finally, in 10% [95 % confidence interval (CI: 6-14%] of the patients in the iopamidol group, and in 2.2% (95 % CI -2-7%) of the

iodixanol users CIN developed, but without any statistically significant difference between groups (p=0.144).

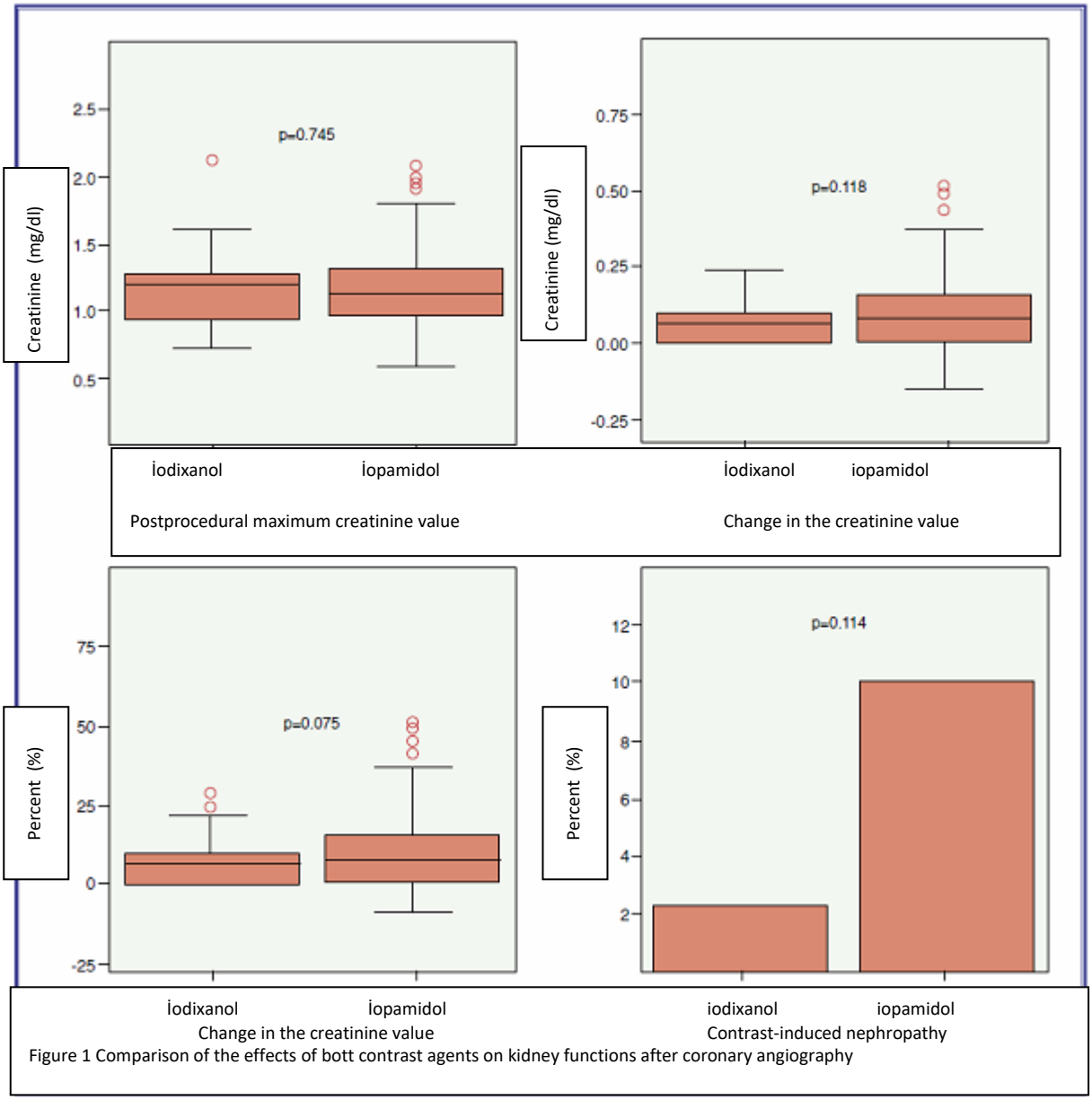

Figure 1 Comparison of the effects of bott contrast agents on kidney functions after coronary angiography

DISCUSSION

In this study, iso- (iodixanol), and low-osmolar (iopamidol) contrast agents were compared as for development of acute kidney injury following coronary procedures. Study group consisted of unselected ACS patients frequently encountered in routine clinical practice. Changes in renal functions following coronary interventions in two groups with similar characteristics were analyzed using more than one criteria. At the end of the study, any superiority of iodixanol over iopamidol was not observed with respect to the postprocedural maximal creatinine value, absolute increase, and percent change in creatinine values, and development of CIN.

In meta-analysis of preliminary studies performed by iso-osmolar contrast agent iodixanol, investigators reported lower rate of development of contrast-induced acute kidney injury with low-osmolar contrast agents.[9] However this meta-analysis was criticized because of comparison between low-osmolar contrast agents, mostly ioxaglate, and iodixanol. Many randomized studies performed more recently could not find significant differences between iodixanol, and low-osmolar contrast agents. CARE (Cardiac Angiography in Renally Impaired Patients) study compared development of CIN following non-urgent coronary angiographic, and PCI procedures in patients with chronic renal failure (GFR <60 ml/min/1.73 m^2) who were given iodixanol or iopamidol.[13] In this study, rates of CIN development which was defined as more than 25 % increase in serum creatinine values relative to baseline values were found to be comparable between both groups. In a randomized study where iodixanol was compared with another low-osmolar

contrast agent, similar rates of development of CIN, and nearly identical increase in median creatinine values were detected.[17]

In a meta-analysis which encompassed recent randomized studies, a significant difference between low-osmolar contrast agents, and iodixanol was not revealed. However in the same meta-analysis, superiority of iodixanol especially over iohexol was mentioned during intraarterial procedures, and in patients with impaired renal functions.[18] In the RECOVER (Renal toxicity Evaluation and Comparison between Visipaque and Hexabrix in Patients with Renal İnsufficiency Undergoing Coronary Angiography) study, iodixanol was compared with low-osmolar contrast agent ioxaglate in patients with chronic renal failure undergoing coronary angiographic procedures . In this study, lower incidence of contrast-induced nephropathy in the iodixanol group relative to ioxagalate users has been demonstrated (7.9 *vs* 17 %) .[19] In the NEPHRIC (Nephrotoxic Effects in High-Risk Patients Undergoing Angiography) study, nephrotoxic effects of iodixanol, and iohexol use during angiographic procedures were compared.[20] In this study which included patients with creatinine values of 1.5-3.5 mg/dl, iodixanol induced minor increases in creatinine values when compared with iohexol.

Among low-osmolar contrast agents, iohexol, and ioxaglate appear to cause CIN relatively more frequently than iodixanol A meta-analysis published by Heinrich et al [16] could not find any superiority of iodixanol over other low-osmolar contrast agents not including iohexol, and ioxaglate. Low-osmolar contrast agents constitute a heterogenous group, and in the development of contrast-induced nephropathy, some molecule-specific characteristics may be thought to play a role apart from osmolarity. In similarly designed PREDICT study (Patients with Renal Impairment and Diabetes Undergoing Computed Tomography) where iopamidol and iodixanol was compared in patients with chronic renal failure and diabetes, the investigators reported comparable incidences of contrast-induced nephropathy, and nearly identical mean change in the creatinine value in both groups after contrast-enhanced computed tomographic examinations.[10] Although their study population comprise of more risky patients than ours, amount of the mean contrast agent they used was much smaller than employed in our study (approximately 104 *vs* 175 ml). In a multicenter randomized trial where iopamidol or iodixanol was used in patients with GFR <60 ml/min/1.73 m^2 and diabetes mellitus, development of CIN, and peak creatinine values after coronary angiography were compared in both groups of patients..[21] CIN was detected in 11.2 % of iodixanol, and 9.8 % of iopamidol users, respectively. The investigators indicated similarities between these two radiocontrast agents regarding incidence of contrast-induced acute kidney injury. Our study differs from the cited one in that it has a patient population with a wider range of GFRs. In our iopamidol group the rate of CIN development (10 %) was in accordance with their results. However in our iodixanol group CIN developed in a fewer patients (2.2 %) but without any statistically significant divergence from the previous investigation. In all of these studies, data retrieved from the patient population in general, and highly risky patients could not demonstrate a significant superiority of iodixanol over iopamidol.

The advantage thought to be possessed by iso-osmolar agents either has not been demonstrated in meta-analyses of large scale randomized studies conducted so far or comparatively smaller differences without any statistical significance have been detected. Lack of any clinical significance between iso-, and low-osmolar agents (excl. some radiocontrast agents) can be said. Application of prophylactic hidration before, and after the procedure, and use of minimal amounts of contrast agents seem to be the most effective preventive measures against development of CIN.[22,23] However, studies investigating the differences between iso-, and low-osmolar contrast agents regarding the development of contrast-induced nephropathy in the most risky patient group (i.e. cases requiring urgent intervention, patients with GFR <30 ml/min/1.73m^2, advanced age, and diabetes) are needed.

Limitations of the study

In the study though not statistically significant, a trend in favour of iodixanol use was observed regarding percent change in postprecedural creatinine levels (p=0.075). Similarly, development of CIN in the iodixanol group was encountered less frequently in comparison with the iopamidol group without a statistically significant difference between groups Both conditions may be related to relatively limited number of patients (type 2 statistical error) in the iodixanol group. These results should be confirmed by the outcomes of larger scale studies.

Conclusion

In general usage, iodixanol is not superior to low-osmolar contrast agent iopamidol as for the development of contrast-induced acute kidney injury. Considering gradually increasing usage of coronary angiographic procedures in routine practice, use of cost-efficient low-osmolar contrast agents with similar efficacy, and safety comparable to iodixanol will be a reasonable approach. Maintenance of the volume of the contrast agent used at a minimum level, and application of prophylactic hidration are

still the most effective methods of decreasing contrast-induced acute kidney injury.

Conflict of Interest: None declared

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Anahtar sözcükler: Böbrek hastalıkları/kan; glomerüler filtrasyon hızı; injeksiyon, intra-arteryel; iyodiksanol; iyopamidol; kalp kateterizasyonu;
kontrast maddesi/yan etki; kreatinin/kan; perkütan koroner girişim; ozmolar konsantrasyon.

Key words: Kidney diseases/blood; glomerular filtration rate; injections, intra-arterial; iodixanol; iopamidol; cardiac catheterization;
contrast media/adverse effects; creatinine/blood; percutaneous coronary intervention.