

EFFECTS OF CONTRAST MEDIA ON ENDOTHELIN AND NITRIC OXIDE SYSTEM AFTER COMPUTED TOMOGRAPHY

BİLGİSAYARLI TOMOGRAFİ SONRASI KONTRAST MADDENİN ENDOTELİN VE NİTRİK OKSİD SİSTEMİ ÜZERİNE ETKİSİ

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ABSTRACT

Purpose : Among the mechanisms of contrast media induced renal dysfunction, renal ischemic injury is the main reason and some of the vasoactive substances may mediate the renal haemodynamic effects of contrast media (CM). The present study was designed to determine the role of nitric oxide and endothelin on occurrence of contrast media nephrotoxicity. **Methods :** A total of 20 patients were given one of the following low osmolar CM; iopamidol, iopromid or iohexol for abdominal computed tomography scanning. Blood samples for endothelin and nitric oxide metabolites (NOx; nitrate, nitrite) were drawn just prior to and 10 minutes after the contrast media administration. Serum creatinine levels were determined prior to the administration of contrast media and on the first and third postscanning days. Radioimmunoassay for endothelin was performed while NOx was measured by using Sievers Instruments Model 280 A Nitric Oxide Analyser. **Results:** Intravascular administration of CM appeared to elicit a rise in plasma endothelin but this was not statistically significant ($p=0.154$). Contrast media also did not affect the nitrate ($p=0.709$) and nitrite ($p=0.699$) levels significantly. Mean serum creatinine levels increased significantly from 0.62 ± 0.13 mg/dl to 0.72 ± 0.22 mg/dl ($p=0.049$). There was a weak correlation between baseline endothelin levels and the change in serum creatinine over the three days ($r=0.39$, $p=0.088$). **Conclusion :** In this study, we have demonstrated that CM did not interfere with serum NOx and endothelin levels. It is feasible to suggest that nitric oxide is unlikely play a major role in the haemodynamic effects induced by CM. However the role of ET in the pathophysiology of contrast media nephrotoxicity cannot be eliminated in this study because of the study protocol which excluded the patients with predisposing factors.

Key Words : Contrast Media, Kidney, Endothelin, Nitric Oxide.

ÖZET

Amaç: Renal iskemik zedelenme kontrast maddeye bağlı gelişen renal yetmezlik mekanizmaları arasında başlıca nedendir ve gelişen bu hemodinamik değişikliklere bir takım vazoaaktif maddeler aracı olmaktadır. Bu çalışma, KM nefrotoksite oluşumunda nitrik oksit (NO) ve endotelinin (ET) rolünü tespit etmeye yöneliktir. Toplam 20 hastaya abdominal tomografi çekimi esnasında şu 3 düşük osmolariteli KM den biri kullanılmıştır: iopamidol, iopromid veya iohexol. İşlemden hemen önce ile KM uygulamasından 10 dakika sonra ET ve NO metabolitleri (Nox: nitrat, nitrit) için kan örnekleri alınmıştır. Serum kreatinin seviyeleri KM uygulanmasından önce ve uygulamanın 1. ve 3. günlerinde kontrol edilmiştir. Endotelin ölçümü radyoimmünoassayla, NOx ölçümü ise Sievers Instrument Model 280A NO Analyser ile yapılmıştır. İntravenöz KM uygulaması ile plazma ET seviyesinde bir artış izlenmesine karşın, bu istatistik olarak önemli değildi ($p=0.154$). Ayrıca KM, nitrat (0.709) ve nitrit ($p=0.699$) seviyelerini de anlamlı olarak etkilemedi. Bazal ET seviyesi ile 3 gün içindeki serum kreatinin değişimi arasında zayıf bir korelasyon bulunmaktaydı ($r=0.39$, $p=0.088$). Bu çalışmada sonuç olarak, kontrast maddenin serum NOx ve endotelin seviyelerini etkilemediğini tespit ettik. Kontrast maddenin başlattığı hemodinamik etkilerde NO in bariz bir rolünün olmadığını bu sonuçlarla önerebiliriz. Ancak çalışma protokolüne bağlı olarak predispozan faktöre sahip hastaların çalışma dışı bırakılması nedeniyle endotelinin KM nefrotoksitesinde rolünü ekarte etmemiz mümkün olmamaktadır.

Anahtar Kelimeler: Kontrast Madde, Böbrek, Endotelin, Nitrik Oksit.

INTRODUCTION

Contrast media nephropathy (CMN) is characterised by an abrupt decline of renal function that follows the intravascular administration of contrast media (CM) (1). Commonly used criteria for diagnosis of CMN include an increase in serum creatinine (Scre) of ≥ 0.5 mg/dl over the baseline value or a reduction in the calculated creatinine clearance of 50 percent per day (2). CMN is the third most common cause of hospital acquired acute renal failure (3). It appears that renal failure increases the risk of death from pre-existing nonrenal conditions, as well as contribute to major nonrenal morbidity (4). However, the use of CM remains essential for many diagnostic imaging examinations. Thus every effort should be made to understand the pathophysiological mechanisms of the renal dysfunction and thereby prevent kidney injury. Intrarenal vasoconstriction caused by an imbalance between vasoconstrictive and vasodilative factors may result from systemic or local vasoactive agents that act on the small vessels of the kidney and have an important role in the development of this renal dysfunction (5).

The present study was designed to determine whether low osmolar CM interferes with nitric oxide (NO) and endothelin (ET) system components.

PATIENTS AND METHODS

Patients aged 18 and over, who were referred for non emergency abdominal computed tomography to the Gazi University Hospital Radiology Department were eligible for the study. The reasons for referral included hepatic hemangiomas, cystic diseases of liver disease, polyp in the gallbladder, splenomegaly and splenic calcification. None of the patients had a previous history of renal disease and all patients had normal baseline serum creatinine (less than 1.5 mg/dl). Patients with known risk factors for CMN including diabetes mellitus, hypertension, cardiovascular events due to atherosclerosis, multiple myeloma, hypercalcemia and patients on ACE inhibitors, diuretics, calcium antagonists, theophylline, nitrates, cyclooxygenase inhibitors and IV 0.9% NaCl infusion were excluded. A total of 20 patients were included in the study; 11 men, 9 women, aged 27-71 years (mean age 42 ± 10 years). Blood

pressures were in the normal range before the procedure.

Radiological Procedure: The abdominal computed tomography scanning was carried out after at least 8 hours of fasting. All patients received one of the three lower osmolality CM, iopamidol (iopamiro, Santa Farma), iopromid (ultravist, Shering) or iohexol (omnipaque, Erkim).

Laboratory Methods: A venous blood specimen value was drawn 24 hours prior to and 24 and 72 hours following the administration of CM for the Scre. Creatinine was measured by Jaffe Chromotogen reaction (Beckman Creatinine Analyzer 2) utilizing fresh specimens.

Ten millilitres of blood were drawn just prior and 10 minutes after the CM administration for ET and NO metabolites (NOx ; nitrate, nitrite). Prechilled test tubes containing sodium EDTA (1.5 mg per millilitre) were used for ET determination, the specimen centrifuged immediately at 4 °C and extracted plasma was stored at -7 C° until assayed. Radioimmunoassay for ET was performed using a standard double antibody precipitation technique (reagents obtained from Wychem, Netherlands). The amount of total NOx was determined using the purge system of a Sievers Instruments Model 280A Nitric Oxide Analyser.

Urine samples were collected for 24 hours prior to and 24 hours after the CM injection. Urine creatinine was measured in each urine sample and creatinine clearance (Ccr) was calculated from the following formulae;

$$Ccr = \frac{U \times V}{(Scre \times 1440)}$$
 where U=creatinine in urine, V=urinary volume.

Statistics : Paired Student's t test was used to assess significant differences among the baseline and 10th minutes' values for ET, nitrate and nitrite. The Spearman correlation test was used to test the correlations between plasma ET, nitrate and nitrite levels and Scre levels within three days. P value <0.05 was taken as significant.

RESULTS

Baseline and postcontrast media exposure laboratory values are demonstrated in table 1:

Renal Function Parameters : Mean Scre levels increased significantly from

Table -1: Results of measurements before and after contrast media.

	Before contrast media	After contrast media	p
Creatinine (mg/dl)	0.62±0.13	0.72±0.22	0.049
Creatinine clearance (ml/min)	95.5±15.01	93.45±19.17	0.638
Endothelin (pmol/L)	5.09±4.12	6.84±8.46	0.154
Nitrate (ppb)	6.22±3.21	6.75±6.54	0.709
Nitrite (ppb)	0.83±0.29	0.86±0.41	0.699

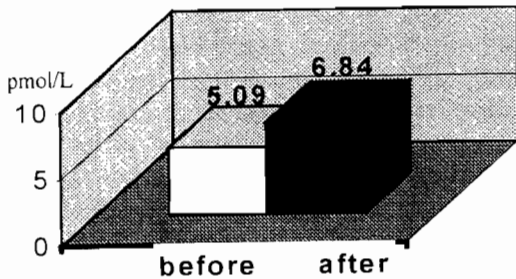


Fig. 1: Plasma endothelin levels before and after contrast media administration.

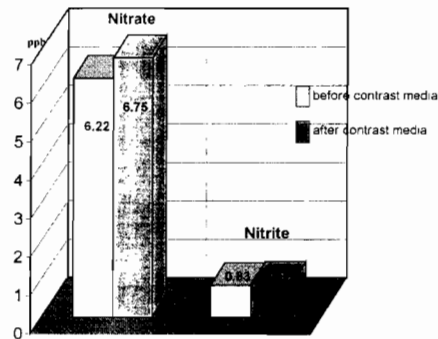


Fig. 2: The changes of plasma nitrate and nitrite levels with contrast media administration.

0.62±0.13mg/dl to 0.72±0.22 mg/dl (p=0.049). However, the postcontrast media exposure mean Scre level remained within the normal range. The mean change in Scre levels from baseline to three days postcontrast media was 0.1 mg/dl (19%). In one patient, the increase in Scre level, which was 0.8 mg/dl per day, fell to the diagnostic criteria of CMN. Ccr values did not change significantly after CM exposure (p=0.638).

Endothelin, Nitrate, Nitrite : ET increased from 5.09±4.12 pmol/L to 6.84±8.46 pmol/L. after CM exposure, however this was not statistically significant (p=0.154, t=1.48) (Fig. 1). Plasma nitrate increased from 6.22±3.21 ppb to 6.75±6.54 ppb and plasma nitrite increased from 0.83±0.29 to 0.86±0.41 ppb (Fig. 2). These parameters were also not statistically significant (p=0.709, p=0.699 respectively). There was only a weak correlation between the change in Scre within three days and baseline ET levels (r=0.39, p=0.088) (Fig. 3). No correlation was found between the changes of Scre levels and the

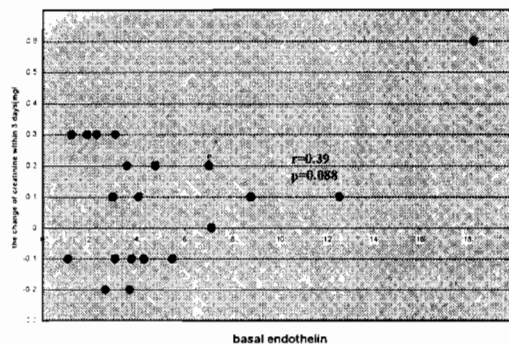


Fig. 3: The weak positive correlation between basal endothelin levels and the change of serum creatinine levels.

changes of plasma nitrate and nitrite levels (r=-0.318 p=0.17, r=-0.120 p=0.61 respectively). The changes of serum ET and NOx levels after CM administration did not correlate with each other (r=-0.126 p=0.59 for nitrate, r=0.093 p=0.69 for

nitrite).

DISCUSSION

Iodinated contrast medium is a well known cause of nephrotoxic acute renal failure especially in patients presenting with one or more pre-existing risk factors (6). The major risk factors are renal failure and diabetes mellitus. In the current study, although mean S_{cre} levels increased significantly after CM exposure, they remained within the normal ranges, except for one patient. The percentage of patients at particular risk for CMN lies between 12 and 27 % (7). In prospective studies, the reported incidence for patients without risk factors is 0-7%(8). The prevalence in the presented study detected is 5% (1/20), with only one patient who had a S_{cre} level which rose from 0.8 mg/dl to 1.6 mg/dl. This patient's clinical course was consistent with the typical findings of CMN, characterised by nonoliguric benign renal failure. Renal function tests returned to normal levels in a few days with appropriate hydration.

Changes in tubular function, structure and renal haemodynamics are the primary factors believed to be responsible for CMN (9). The renal haemodynamic alterations induced by CM are characterized by an initial transient renal vasodilation followed by a sustained vasoconstriction. An imbalance between the vasodilator NO and the vasoconstrictor ET may impair renal medullary perfusion resulting in kidney injury. The endogenous production of NO, which is released continuously under physiologic conditions keeping the vasculature in a dilated state, is considered to be an important protective mechanism against ischemic insult induced by CM (10). In the presented study, injection of CM resulted in an immediate but not significant increase in NOx. One possible explanation for this should be that vasoconstrictive stimulants by the non-ionic CM was insufficient. Therefore there was no need to counter this hemodynamic effect by NO response. Alternatively, the interactions of multiple vasodilatory influences including prostaglandin and adenosine, together with NO might preserve renal function without a need to increase NOx (11,12). The production of NO may be important especially in situations in which there is a decrease in the synthesis of NO in kidney, including diabetes mellitus and

hypertension. In these conditions, the ischemic insults of CM are accentuated (13). As we eliminated such a NO deficient state by the study protocol, we had an opportunity to observe NOx response in a population without obvious risk factors. However, it is also reasonable to think that the haemodynamic response induced by CM is not dependent on endogenous production of NO. Recent experimental data have also shown that NO does not seem to play a major role in vasodilation caused by diatrizoate in the isolated perfused rat kidney (14). It is now becoming clear that CM induce vasodilation via adenosine more effectively (15).

The role of ET in mediating the renal haemodynamic effects of CM has recently been identified (16). In the presented study, circulating ET increased, however this was not significant. A link between prostaglandin and ET should be considered prior to interpretation of the present data. Based on our present knowledge, nephrotoxicity is enhanced when the contrast agent is combined with other renal insults mimicking the predisposing factors for CMN, including inhibition of prostaglandin synthesis (17). In other words when prostaglandin synthesis is inhibited, the vasoconstrictive effects of ET predominate, and there is prolonged renal hypoperfusion. In the present study, excluding the patients on cyclooxygenase inhibitors might explain why the rise of ET levels remained insignificant.

An interesting observation was made regarding the patient whose renal function declined. He had the highest baseline ET level and the magnitude of the increase in his plasma ET was the greatest. These observations support the role of ET in the pathogenesis of CMN. Similar observations were also made by Clark et al in patients with risk factors for CMN (18). Increased baseline ET levels may relate endothelial dysfunction and/or decreased clearance, but we could find no reason for the high ET level in our patient. It seems to correlate that some of these disturbances are known as risk factors for CMN for a prevailing increase in the production of ET even under baseline conditions (19).

In conclusion, we studied a population without obvious risk factors for CMN and found no significant change in serum NOx and ET

levels. It is feasible to suggest that NO is unlikely play a major role in the haemodynamic effects induced by contrast media. However the role of ET in the pathophysiology of CMN cannot be eliminated in this study because the study protocol excluded the patients with predisposing factors. Moreover, the results have suggested that a high baseline ET level seems to be a poor indicator for the development of CMN. Unfortunately, ET receptor antagonists were found to prevent renal vasoconstriction in animal models of CMN, and did not reduce the risk in patients with significant pre-existing renal dysfunction but rather increased the incidence of CMN (20, 21). A better understanding of the interactions of multiple vasodilatory and vasoconstrictor influences is required for a better approach to the prevention of CMN.

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