

Gadolinium-based Contrast Agents: Evaluation of Effect On Renal Function Parameters

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A B S T R A C T

Introduction: Earlier studies have been carried out to examine the clinical safety of gadolinium-based contrast agents currently available. The primary objective of the study was to study the effect of gadolinium-based contrast agents (Gadodiamide) on renal function based on and creatinine clearance and serum creatinine in patients without any preexisting renal disease. We also aimed to evaluate the effect of gadolinium-based contrast agents on renal functions in patients with diabetes and hypertension who were well controlled with oral medications.

Materials and Methods: A prospective cross sectional was study on a total of 47 patients who underwent Contrast-enhanced magnetic resonance imaging(CEMR). Renal function analysis was done based on serum creatinine and creatinine clearance levels which were performed 24 hours prior to CEMR and between 24- 48 hours after CEMR. The effect of contrast media on the renal system was observed with statistical comparison of pre and post CEMR values of serum creatinine and creatinine clearance.

Results: Out of 47 patients, We found that there was minimal dip in the serum creatinine values of post CEMR (0.72mg/dL) as compared to that of pre CEMR (0.75mg/dL) We did not find any significant increase in creatinine clearance values post CEMR and in patients with Diabetes mellitus and hypertension.

Conclusion: Renal functions are better evaluated with a combination of serum creatinine and creatinine clearance than serum creatinine alone. The administration of GBCA in patients undergoing CEMRI has shown to be safe in patients with normal renal function, but consideration should be given to the potential benefit of the examination and the expected low risk of developing Contrast-induced nephropathy.

Key words: Gadolinium-Based Contrast Agents, Renal, Creatinine Clearance, Serum Creatinine

INTRODUCTION

Of all the imaging modalities, MRI might most reasonably be thought to be the one least in need of pharmacological contrast enhancement. A considerable investment is being made by a significant number of pharmaceutical companies, large and small, in the development of new ones.¹ Since the introduction of the first gadolinium-based contrast agent in 1988, Millions of doses of gadolinium-based contrast agents (GBCAs) are now administered every year. Most of the approved contrast agents incorporate one atom of the rare earth metal gadolinium into a chelate complex to improve the safety of the ordinarily toxic free gadolinium.² Till date there have been few studies that have published information on the renal changes in patients with normal renal function hence we intended to do the same given the importance of CEMRI(Contrast Enhanced Magnetic resonance imaging) in the present day setting. In the interest of the patient, there is an absolute indication for us to study the effects of gadolinium-based contrast media on the renal system and to justify the use of contrast media in patients. This understanding will surely help us predict the possibility

of patients who may go into nephrotoxicity due to contrast media.

Few studies have studied the effect of gadolinium on the serum creatinine concentration and estimated GFR as surrogate markers of renal function.³ This study was performed to evaluate the effect of Gadodiamide in a dose sufficient for diagnostic purposes. We in our study would like to predict the effect of contrast-enhanced MRI on the renal system in patients with normal renal function.

Study aims and objectives were to study the effect of gadolinium-based contrast agents (GBCAs) on renal function based on serum creatinine and creatinine clearance in patients without preexisting renal disease, to evaluate the effect of contrast agents on renal functions based on creatinine clearance and serum creatinine and in patients with hypertension and diabetes who are on well-controlled medications and to predict the possibility of reduced renal function in patients undergoing contrast-enhanced studies.

MATERIAL AND METHODS

This study was conducted in Vydehi Institute of Medical Sciences and Research Centre institution in Bengaluru,

India at the department of radio-diagnosis and the central diagnostic laboratory.

Our institutional ethical clearance committee approved this investigation, and all patients provided written informed consent and release of their medical information for the purpose of this research. It was a cross-sectional study done on a total of 45 patients.

Inclusion criteria

- All patients without a pre- existing renal disease
- Diabetic patients well controlled with oral medications
- Hypertensive patients well controlled with oral medications.

Exclusion criteria

- Un co-operative patients
- Severely debilitated patients
- Patients with pre- existing renal disease
- Patients allergic to contrast media

All the patients who were included in this study were provided with the use of a clean, leak-proof, 10liter disposable container and instructed to collect a 24-hour urine sample after voiding the first stream of urine after the patient's arising from a night's sleep collecting from 7 am on day one to 7am on day two. The Blood samples were then collected for serum creatinine under aseptic precautions using a standard phlebotomy technique 3 – 6 hours prior to CEMR. The height in centimeters and weight in kilograms of every patient was then recorded to calculate the BMI. Following which the patients proceeded for their CEMR examinations after which the patients were asked to come back anytime between a period of 24 – 72 hours after the CEMR examination and were asked to follow instructions similar as that of pre CEMR.

Contrast media:

In our study we used standard contrast media that was being used by our department, which is Gadodiamide (0.5 mmol/ml).

The dosage was:

Contrast was injected at the rate of 2.5- 3ml/ second by a pressure injector.

A total quantity of 8- 10 ml was injected on average for all CEMR studies.

The contrast used was Gadodiamide (0.5 mmol/ml).

Biochemical evaluation of plasma creatinine was done by collecting fresh samples of blood prior to CEMR and between 48 – 72 hours after CEMR.

We had a code sharing with the central diagnostic lab where they named our tests as

- Pre CEMR Serum creatinine(BCE 667)
- Pre CEMR creatinine clearance (BCE 668)
- Post CEMR serum creatinine(BCE 669)
- Post CEMR creatinine clearance (BCE 670)

These tests were given codes mentioned in brackets, which differentiated general patients from our study patients.

Biochemical evaluation of creatinine clearance

Creatinine clearance was calculated using the formula

$$U \times V \div P \times 1.73$$

$$\text{Where; } \frac{A}{A}$$

U- urinary creatinine in mg/dl

P- Plasma creatinine in mg/dl

V- Volume of urine excreted per minute

Total volume = volume/ minute

24 x 60

Absolute surface area

1.73- standard body surface area.

We used an automated machine to calculate the creatinine and creatinine clearance values.

The normal range considered was

Type	Conventional units	S.I. Units
Serum or Plasma (Male)	0.9 to 1.3 mg/dL	80 to 115umol/L
Serum or Plasma (Female)	0.6 to 1.1mg/dL	53 to 97 umol/L
Reference range Serum creatinine. ¹		

STATISTICAL SOFTWARE

The Statistical software used for the analysis of the data was SPSS version 19.0 Microsoft word and Excel have been used to generate tables.

RESULTS

An Evaluation prospective clinical study with 47 patients was undertaken to study the effect of contrast agent on renal functions, based on serum creatinine, creatinine clearance We had 4 patients in the age group of 11 to 10 (8.5%), 17 patients in the age group of 21 to 30 (29.8%), 4 patients in the age group of 31 to 40 (8.5%), 13 patients in the age group of 41 to 50(14.9%), 7 patients in the age group of 51 to 60 (14.9%), and five patients in the age group above 60(10.6%). There were 29 (61.7%) male patients and 18 (38.3%) female patients.

Out of the 47 patients 11 (23.4%) patients had associated conditions like diabetes and hypertension and 21 (44.7%) patients were not associated with these conditions. 14.9 (7%) patients had diabetes, 8 (17%) patients had hypertension and 11 (23.4%) patients were suffering from both the conditions. All these patients were well controlled with oral medications.

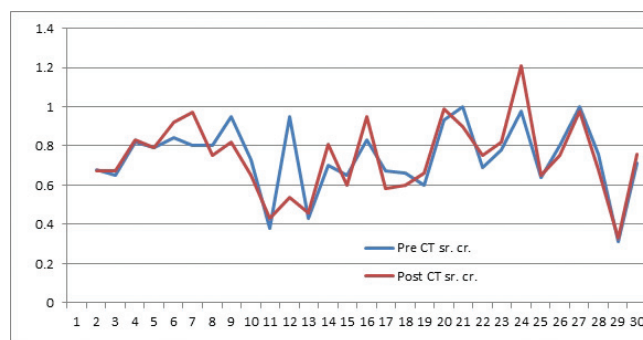


Figure-1: Trend of mean pre and post serum creatinine value in patients with no associated conditions.

Study variables	Min-Max	Mean ± SD
Serum creatinine	0.31 -1.10mg/dL	.752±.17
Creatinine clearance	24.00-151.00mL/min	.753 ±.18

Table-1: Descriptive statistics of study variables studied

Study variables	Pre MR	Post MR	P value
Serum creatinine	0.75±0.22mg/dL	0.72±0.20mg/dL	0.944
Creatinine clearance	84.01 ±27.00mL/min	86.05 ±23.92	0.546

Table-2: Effect of Contrast agents on renal functions test

HTN	Difference of Pre-MR and Post MR	
	Serum creatinine	Creatinine clearance
No	.09	16.88
Yes	.04	22.27
Total	.018	19.06
P value	.062	.155

Table-3: Difference of pre-MR and Post MR of Renal Functions parameters according to Incidence of Hypertension

The minimum and maximum values of serum creatinine were 0.31mg/dL and 1.1mg/dL value respectively. Similarly the minimum and maximum values of creatinine clearance were 24mg/dL and 151 mg/dL respectively (table 1).

The difference between the Pre and post MR renal function parameters according to age distribution, gender distribution and body mass index were calculated. Difference of pre-MR and Post MR of Renal Functions parameters according to Incidence of DM, Hypertension were not statistically significant. Pre and post contrast values of serum creatinine and creatinine clearance in patients with no associated conditions were not statistically significant. Figure 1 show the trend of Pre and post contrast values of serum creatinine and creatinine clearance of all patients.

DISCUSSION

We screened a total of 47 patients (n=47) all of who were scheduled to undergo contrast enhanced magnetic resonance imaging. All the patients met our inclusion criteria. We had obtained written and informed consent forms from all the patients who underwent the study. All patients were administered Gadodiamide (0.5 mmol/ml) contrast media, the dosage depending on the type of examination and the weight of the patient, approximately 8 to 10ml was injected intravenously.

As already mentioned we did a base line screening of serum creatinine and 24hour creatinine clearance before contrast enhanced magnetic resonance imaging for all patients which was followed by The same tests repeated between 48 – 72 hours after contrast enhanced magnetic resonance imaging. Earlier studies have been carried out to examine the clinical safety of gadolinium-based contrast agents currently available. These studies focused on allergic adverse reactions of gadolinium without investigation of a potential change in renal function after its administration, quite a few of the studies done until now have used only serum creatinine to estimate the renal functions⁴ but we in our study went a step ahead a decided to use creatinine clearance which is a far superior predictor of renal functions along with serum creatinine. These figures of serum creatinine and creatinine clearance also helped us compare and contrast between creatinine clearance and serum creatinine and decide which a better indicator of renal functions was.

In our study we interestingly found that there was minimal

dip in the serum creatinine values of post contrast enhanced magnetic resonance imaging (0.72mg/dL) as compared to that of pre contrast enhanced magnetic resonance imaging (0.75mg/dL) which was statistically insignificant (P value = 0.944), this fact goes against the definition of contrast induced nephropathy where in which there is an increase in the serum creatinine post contrast enhanced magnetic resonance imaging from the base line value of pre contrast enhanced magnetic resonance imaging. Our study observations were similar to the results of the studies conducted by Harb TS, Laird JR, Whitman D et al, Sam et al, U.Hoffmann et al, Lundby B, Lien HH, et al and Elena Ledneva, et al, who found that the glomerular filtration rate, as reflected by serum creatinine and creatinine clearance, was generally unaffected in patients in normal renal function.⁵⁻⁷

However when the collective values of creatinine clearance pre (84.01mL/min) and post (86.05mL/min) CEMR were compared it showed a minimal increase in creatinine clearance values in post CEMR (table 2) with a P value of less than 0.5 which was statistically insignificant but had a noticeable effect. Again our study observations were similar to the results of the study conducted by Sam et al, U.Hoffmann et al, Lundby B, Lien HH, et al and Prince, Arnolduset al who, found that the Glomerular filtration rate, as reflected by creatinine clearance, which was generally unaffected in patients in normal renal function.^{4,6-7}

The study of age wise differentiation of pre and post CEMR serum creatinine and creatinine clearance did not show any significance. Similarly, the gender wise differentiation also did not yield any significant values. These observations were similar to the results of a study which was conducted by U.Hoffmann et al.³

We did a comparison of the difference between the pre CEMR and post CEMR values of serum creatinine and creatinine clearance based on the presence and absence of diabetes mellitus. Here again, the serum creatinine did not show much of change as evidenced by a P value of > 0.05. However, the creatinine clearance was decreased noticeably but was not statistically significant (P value= .125). These observations were similar to the results of the study conducted by U.Hoffmann et al(4), however, a study by Elena Ledneva et al showed that diabetic patients with a baseline serum creatinine value less than 2.0 mg/dL were at higher risk for CIN than were non diabetic patients, whereas all patients with a serum creatinine greater than 2.0 mg/dL were at high risk for CIN.⁸ With a small sample size of 18 patients, it was a major limitation in determining or commenting on the effects of contrast media on the renal system in patients with diabetes mellitus.

Our next objective was to evaluate the risk of nephrotoxicity in hypertensive patients who underwent CEMR. We had a very small group of 19 patients representing this category. The comparison of pre CEMR and post CEMR serum creatinine

and creatinine values (table 3) did show a noticeable change. However the difference was not statistically significant (P value = .155). Probably in this category with the sample size being small, it was again a major limitation in determining or commenting on the effects of contrast media on the renal system in patients with hypertension. The last comparison between body mass index and renal function did not show any statistically significant results.

CONCLUSION

Gadolinium was given at a mean dose of 10ml (0.5mmol/ml). Before the administration of gadolinium, mean serum creatinine concentration was 0.75 ± 0.22 mg/dl and 0.72 ± 0.20 mg/dl after gadolinium. The study demonstrated that the little trend for decrease in serum creatinine concentration in all these groups was not statistically significant.

There no significant depletion in renal functions post CEMR in general however we did not come across any case of absolute CIN going by the definition as increase in the serum creatinine of 0.5 mg/dL (44.2 micromol/L) or a 25% increase from the baseline value 48 hours after an intravenous injection of contrast media (in the absence of alternative etiology).

Conclusion - It was difficult to predict the effect of contrast media on the renal system based on other variables in patients other than those with risk factors. In a patient with normal renal function, gadolinium-based contrast material can probably be administered without the consideration of NSF since the use of gadolinium based contrast agents have shown to be safe in patients with normal renal function parameters. Our study also showed a minimal decrease in creatinine clearance and mild rise in serum creatinine which however being statistically insignificant, could possibly be an indicator for increased risk to contrast induced nephropathy in the older age group.

REFERENCES

1. Dawson P. Contrast agents in magnetic resonance imaging. *European journal of radiology* 1996;23(3):201-204.
2. Kuo PH. Gadolinium-containing mri contrast agents: Important variations on a theme for nsf. *Journal of the American College of Radiology: JACR* 2008;5(2):29-35.
3. Hoffmann U, Fischereider M, Reil A, Fischer M, Link J, Kramer BK. Renal effects of gadopentetate dimeglumine in patients with normal and impaired renal function. *European journal of medical research* 2005;10(3):149-154.
4. Bongartz G. Imaging in the time of nfd/nsf: Do we have to change our routines concerning renal insufficiency? *Magma (New York, N.y.)* 2007;20(5):57-62.
5. Barrett KE, Ganong WF. *Ganong's review of medical physiology*. In. New York: McGraw-Hill Medical, 2010.
6. Lundby B, Berg KJ, Lien HH, Aamdal S. A double blind study to evaluate the tolerability of gadodiamide injection and its effect on renal function in patients undergoing cerebral magnetic resonance imaging. *The British Journal of Radiology* 1993;66(2):871-876.
7. Nyman U, Elmstahl B, Leander P, Nilsson M, Golman

K, Almen T. Are gadolinium-based contrast media really safer than iodinated media for digital subtraction angiography in patients with azotemia? *Radiology* 2002;223(3):311-319.

8. Ledneva E, Karie S, Launay-Vacher V, Janus N, Deray G. Renal safety of gadolinium-based contrast media in patients with chronic renal insufficiency. *Radiology* 2009;250(1):618-628.

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