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A COMPARATIVE STUDY ON IODIXANOL VERSUS IOHEXOL IN INTRAVENOUS PYELOGRAPHY STUDIES IN A TERTIARY CARE HOSPITAL- A RANDOMIZED CONTROL STUDY

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ABSTRACT:

Background: Contrast-induced nephropathy, a complication associated with intravenous pyelography (IVP), is a recognized concern. However, the relative nephrotoxic potential of the iso-osmolar non-iodinated contrast medium (iodixanol) versus the low-osmolar contrast medium (iohexol) remains unclear. This single-center, Randomized Control studies involved 58 patients undergoing IVP, who were randomly assigned to receive either iodixanol or iohexol.

Materials: 58 patients with high risk for contrast-induced nephropathy, consisted of 25 (43.10%) patients with renal insufficiency an d 16 (27.58%) with diabetes mellitus. The study assessed the nephrotoxic effects (contrast nephropathy) and the profiles of complement and cytokines between the two groups. The average contrast medium volume administered during each IVP procedure was 0.8 mL/kg.

Results: The overall incidence of contrast nephropathy was 04%, with one case in each group. No significant differences were observed in the rates of contrast nephropathy or allergic reactions between the iodixanol and iohexol groups. Additionally, there was no notable difference in cytokine 89% profiles. The overall incidence of allergic reactions was 17.24%. Early allergic reactions occurred in 03/29 (10.34%) of the Iohexol group patients and none in the Iodixanol group of patients. Late allergic reactions occurred in 03/29 (10.34%) of the Iohexol group and 02/29 (06.89%) of the Iodixanol group of patients (p = 0.001). One patient developed a severe skin rash due to a late adverse reaction following iodixanol administration. No fatalities were reported. Both iodixanol and iohexol are considered safe for routine IVP examinations, exhibiting a low nephrotoxicity profile, particularly in elderly or high-risk patients.

Conclusions: In conclusion, iodixanol and iohexol contrast media for routine IVP examinations are safe and have a low nephrotoxicity profile, particularly in elderly and high-risk patients. Late allergic reactions may be the most common adverse effect following the infusion of nonionic contrast media.

KEY WORDS: contrast, ivp, Iohexol, Iodixanol and Allergy

INTRODUCTION: Contrast nephropathy (CN) is a known complication associated with arteriographic procedures, as well as intravenous pyelography (IVP) and computed tomography (CT) scans involving intravenous contrast agents.(1) Routine IVP has been commonly performed in nephrology and urology. However, the use of iodinated contrast media (CM) can lead to CN, and while advancements in the chemical composition of contrast agents have been made, CN remains the third leading cause of hospital-acquired acute renal failure. (2) Both pre-existing renal insufficiency and diabetes mellitus significantly increase the risk of CN, designating these patients as high-risk.

In the last decade, nonionic (low-osmolality) CM have gained popularity for radiographic procedures, due to their reduced incidence of systemic and organ toxicity when compared to conventional ionic (high-osmolality) contrast media. (3) Additionally, animal studies suggest that nonionic CM is less nephrotoxic than ionic CM. CN is characterized by acute renal function impairment following exposure to radiocontrast media. (4) The condition typically presents with a temporal relationship between the contrast study in high-risk patients and an increase in serum creatinine levels, typically within 24 hours to 5 days post-study. (5) Diagnostic markers for CN include a rise in serum creatinine greater than 25% from baseline, or an increase of 0.5 mg/dL or more. (6) Peak serum creatinine levels generally occur 3–5 days after contrast administration, and monitoring these levels is key in high-risk patient's post-IVP. (7) Several studies have demonstrated that CM have direct cytotoxic effects on renal structures, with proposed mechanisms including impaired renal perfusion, hypoxia, direct tubular toxicity, apoptosis, altered glomerular function, and immune responses. (8) Histamine, a known inflammation mediator, plays a role in cytokine production, and previous studies have shown that conventional CM can elevate plasma histamine levels. (9) However, large-scale studies examining histamine release following iodixanol or iohexol use in IVP, particularly in Taiwan, are lacking. (10) To address this gap, the complement and cytokine profiles will be measured in this study. (11) Prophylactic measures such as hydration, diuresis, mannitol, and renal vasodilators are commonly employed, though there is no strong evidence supporting the prophylactic benefits of mannitol, furosemide, aminophylline, natriuretic peptide, or low-dose dopamine. (12) Aggressive hydration before contrast administration has proven crucial in preventing CN, and in high-risk patients, severe complications or adverse reactions to CM may be managed with hemodialysis. (13) Historically, both non-ionic monomeric and dimeric agents have demonstrated a favorable safety profile in healthy individuals. (14) However, patients with renal impairment are at higher risk for developing CN, and there is limited clinical data regarding the nephrotoxicity of iodixanol in such patients. (15) Previous studies on CN following IVP in high-risk patients are mainly from Western countries, with very few from India.

To address this, we designed a prospective, controlled study to compare the incidence of contrast nephrotoxicity between iodixanol and iohexol, particularly in elderly or high-risk patients undergoing IVP. Serum creatinine levels and immunologic reactions will be measured pre- and post-IVP in a series of inpatients to determine whether iodixanol demonstrates a clinically significant advantage over iohexol.

MATERIALS AND METHODS

This study included 58 patients who underwent intravenous pyelography (IVP) at our hospital between September 1, 2005, and August 31, 2006. Patients were randomly assigned to receive either iodixanol or iohexol as the contrast agent. An Institution Ethics Committee approval was obtained and its approved proforma and consent form were used. 58 patients of this study were divided in to two groups: Iodixanol group and Iohexol group. They were randomly allotted to each group using randomnumber.com from the internet.

Inclusion Criteria: Patients aged between 18 and 68 years were included. Patients of both the genders were included. Patients with diabetes with serum creatinine levels under 1.5 mg/dL were included. Patients with pre-existing renal insufficiency (defined as serum creatinine levels greater than 1.5 mg/dL) were included. Patients who were also non-diabetic with renal insufficiency were included.

Exclusion criteria: Patients below 18 years and above 68 years were excluded. Patients with pregnancy, volume depletion or fluid overload, administration of IV-iodinated contrast media within the past seven days, use of Metformin or NSAIDs within 48 hours, and nephrotoxic drug used within the past seven days were excluded. The variables among the study population consisted of the nephrotoxic effects of iodixanol, a dimeric nonionic contrast agent with iso-osmolarity, which were compared with iohexol, a low-osmolar, monomeric, nonionic contrast agent. The contrast media volume administered was approximately 0.8 mL/kg for each IVP procedure, with the injection given at a rate of 2 mL/second. Patients were hydrated with 0.9% saline at a rate of 1 mL/kg/hr, starting 8–12 hours before and continuing after the IVP procedure. The primary endpoint was the peak increase in serum creatinine from baseline measured three days after the IVP procedure. Contrast nephropathy (CN) was defined as a ≥25% increase in serum creatinine following the procedure. Late reactions were categorized as those occurring more than one hour but within seven days after IVP. Serum creatinine was measured before the procedure (day 0) and on days 2, 3, and 7. Serum cytokine levels were re-assessed at: day 0(0 hrs), 06 hours, and 24 hours post-IVP.

Laboratory Testing: All routine laboratory tests were conducted by our clinical pathology department. Serum cytokine levels were analyzed using a sandwich enzyme-linked immunosorbent assay (ELISA) method, following the manufacturer's instructions (Meryl, India). A change in cytokine levels greater than 20% in the same individual was considered significant, given the reproducibility of this assay.

Statistical Analyses: Continuous data were expressed as mean ± SD and analyzed using the Wilcoxon rank sum test for both within-group and between-group comparisons. Categorical data were assessed with the chi-square or Fisher's exact test, as appropriate. A p-value of less than 0.05 was considered statistically significant. All data were analyzed using SAS software for Windows (version 9.1, SAS Institute, Cary, North Carolina, USA).

RESULTS

58 patients of this study were divided in to two groups: Iodixanol group and Iohexol group; and observed that the mean age was 64.25±08.35 in the Iodixanol group and 60.45±6.98 in the Iohexol group. There were 19/29 (62.51%) males and 10/29 (34.48%) females in the Iodixanol group and 20/29 (68.96%) males and 09/29 (31.03%) females in the Iohexol group. The mean weight in the Iodixanol group was 69.10±09.30 Kgs and 66.10±01.40 in the Iohexol group. The mean height in the Iodixanol group was 162.89±12.65 Cms and 164.23±07.11 Cms in the Iohexol group. Diabetes Mellitus was present in 09/29 (31.03%) of the patients Iodixanol group and 07/29 (24.13%) in the Iohexol group. Renal insufficiency was noted in 12/29 (41.37%) of the Iodixanol group and 11/29 (37.93%) of the Iohexol group. Total Hydration was done with mean 1975±42.65 mL volume of 0.9% normal saline in the Iodixanol group and 1643±73.11mL of normal saline in Iohexol group. History of previous exposure to contrast media was present in 10/29 (%) of the Iodixanol group and 08/29 (%) of the Iohexol group. The mean volume of the contrast used was 55.68±11.25 mL in the iodixanol group and 59.56±17.10 mL in the Iohexol group. **(Table 1)** Table 1 presents the clinical characteristics of patients who received either iodixanol or iohexol. The only significant difference between the two groups was age ($p = 0.015$). No significant differences were found between the

groups for the ages. The number of patients without Diabetes Mellitus and Renal insufficiency were 09 in the iodixanol group and 09/29 (%) in the iohexol group **(Table 1)**

Observations	**Iodixanol group (n = 29)**	**Iohexol group (n = 29)**	P value
Mean Age	64.25±08.35	60.45±6.98	**0.015**
Gender Male Female	 19 10	 20 09	0.102
Mean Weight	69.10±09.30	66.10±21.40	0.823
Mean Height	162.85±42.65	1643±73.11	0.411
Diabetes Mellitus	09	07	0.101
Renal Insufficiency	12	13	0.154
Normal Control Group	08	09	0.064
Hydration with 0.9% saline in mL	1975±690	2318±390	0.318
Previous exposure to contrast media	10	08	0.677
Volume of Contrast media	55.68±11.25	59.56±17.10	0.139

Table 1: Showing the age, gender and other demographic data in the two contrast groups (n-58; Iodixanol group-29 and Iohexol group-29)

The serum creatinine levels (percentage of change) of patients in both the iodixanol and iohexol groups was evaluated during the study and found that. The overall incidence of contrast nephropathy (CN) was 05.17% (03/58), with one case in iodixanol group and 02 cases in Iohexol group. There were no significant differences in CN incidence between the two groups ($p = 1.0$). Additionally, there was no significant difference in the percentage change in serum creatinine over the week following IVP between the groups ($p = 0.529$).

No significant differences were observed in serum creatinine levels at baseline, day 2, day 3, or day 7 ($p > 0.05$). Similarly, no significant difference was found in the percentage change in serum creatinine during the week following IVP ($p > 0.05$), **(Table 2 and 3).**

Serum Creatinine	**Iodixanol group (n = 29)**	**Iohexol group (n = 29)**	P value
Base line value	1.30 ± 0.42	1.34 ± 0.45	0.327
On day 2	1.30 ± 0.44	1.28 ± 0.37	0.289
On day 3	1.38 ± 0.48	1.30 ± 0.39	0.272
On day 7	1.32 ± 0.39	1.28 ± 0.41	0.401
Rise of >10%	09	07	0.419
Rise of >25%	01	02	1.0

Table 2: Showing the serum creatinine levels at different time in the study (n-58; Iodixanol group-29 and Iohexol group-29)

Change in the Serum Creatinine values in %	**Iodixanol group (n = 29)**	**Iohexol group (n = 29)**	P value
Normal (control) group (n)	08	09	0.103
>10% change in creatinine	02	02	
>25% change in creatinine	00	00	
DM with normal renal function (n)	04	6	
>10% change in creatinine	03	3	1.0
>25% change in creatinine	00	1	1.0

DM with renal insufficiency (n)	04	3	
>10% change in creatinine	01	1	1.0
>25% change in creatinine	01	0	1.0
DM group with or without renal insufficiency (n)	08	9	
>10% change in creatinine	04	4	1.0
>25% change in creatinine	00	1	1.0
Non-DM with renal insufficiency (n)	09	11	
>10% change in creatinine	05	1	0.566
>25% change in creatinine	00	0	—

Table 3: **Percentage Change in Serum Creatinine in Patients Receiving Iodixanol or Iohexol group (n-58; Iodixanol group-29 and Iohexol group-29)**

The values of cytokines in the patients receiving iodixanol or iohexol bolus injections had no change in 52/58 (89.65%) patients. There was no significant difference in more than 10% change of any one or total cytokines during three days in both groups ($p > 0.05$).

There was no significant difference in the time and average level of cytokines at baseline level, 6 hours, and days 1 and 3 in both groups ($p > 0.05$), **(Table 4).**

Change in the Serum Creatinine values in %	**Iodixanol group (n = 29)**	**Iohexol group (n = 29)**	***p* value**
>20% change any one of cytokine	17	18	1.0
>20% change in total cytokines	01	02	1.0
>20% change in IL-6	11	3	0.777
Baseline level (pg/mL)	20.0 ± 11.3	18.4 ± 6.0	0.447
Average level at 6 hrs (pg/mL)	13.1 ± 12.5	22.5 ± 14.2	0.598
>20% change in IL-6	07	13	0.544
Average level at day 1 (pg/mL)	19.4 ± 10.2	21.6 ± 12.2	0.699
>20% change in IL-6	07	08	0.765
Average level at day 3 (pg/mL)	21.4 ± 13.2	21.4 ± 18.4	0.678
>20% change in IL-6	11	10	0.771
>20% change in IL-10	13	11	0.777
Baseline level (pg/mL)	27.5 ± 21.5	27.2 ± 49.8	0.447
Average level at 6 hrs (pg/mL)	28.0 ± 33.7	28.5 ± 33.5	0.598
>20% change in IL-10	08	07	0.544
Average level at day 1 (pg/mL)	31.4 ± 37.8	27.0 ± 35.3	0.699
>20% change in IL-10	11	08	0.390
Average level at day 3 (pg/mL)	24.5 ± 39.1	23.2 ± 31.6	0.969
>20% change in IL-10	08	07	0.248
>20% change in TNF-α	02	02	0.270
Baseline level	4.25 ± 0	4.25 ± 0	0.323
Average level At 6 hrs (pg/mL)	4.36 ± 4.76	54.39 ± 4.75	0.077
>20% change in TNF-α	2	1	0.824
Average level at day 1 (pg/mL)	4.30 ± 2.39	3.75 ± 0	0.342
>20% change in TNF-α	1	0	1.0
Average level at day 3 (pg/mL)	4.14 ± 3.02	4.88 ± 5.41	1.0
>20% change in TNF-α	1	1	1.0
>20% change in histamine	15	14	1.0
Baseline level	1.27 ± 1.45	1.39 ± 1.63	0.854

Average level at 6 hrs (pg/mL)	1.23 ± 1.18	1.37 ± 1.19	0.671
>20% change in histamine	10	11	0.569
Average level at day 1 (pg/mL)	1.37 ± 1.36	1.39 ± 1.25	0.862
>20% change in histamine	15	16	0.771
Average level at day 3 (pg/mL)	2.34 ± 1.33	1.18 ± 1.41	0.494
>20% change in histamine	15	10	0.089

Table 4: **Cytokine values in Iodixanol and Iohexol groups after Bolus Injections (n-58; Iodixanol group-29 and Iohexol group-29)**

The allergic reactions observed in the iodixanol and iohexol groups were tabulated in the Table 5 which showed that there was no significant differences in allergic reactions were noted between the groups (p = 0.243). The overall incidence of allergic reactions was 17.24%. Early allergic reactions occurred in 03/29 (10.34%) of the Iohexol group patients and none in the Iodixanol group of patients. Late allergic reactions occurred in 03/29 (10.34%) of the Iohexol group and 02/29 (06.89%) of the Iodixanol group of patients (p = 0.001). Early reactions included a burning sensation in the throat (two patients) and dizziness (one patient), while late reactions primarily involved skin rash. One patient had a severe late reaction to iodixanol, presenting with erythematous pruritic maculopapules, urticaria, and angioedema over the upper extremities, spreading to the abdomen and groin. The skin lesions resolved following a one-week course of systemic prednisolone at 0.5 mg/kg/day. There were no significant differences in the history of previous CM examinations or prior adverse reactions to CM between the two groups (p > 0.05), and no mortality was reported.

Allergic reactions	**Iodixanol group (n = 29)**	**Iohexol group (n = 29)**	***p* value**
Total allergic reaction patients (n)	03	07	**0.001**
Early reactions	00	03	1.0
Burn sensation in throat	00	01	0.775
Dizziness	00	02	1.0
Late reactions	02	03	0.247
Skin rash	02	03	0.235
Previous contrast media examination	09	14	1.0
Previous adverse reaction to contrast media	01	40	1.0

Table 5: I**ncidence and types of Allergic Reactions in Patients Receiving Bolus injection Iodixanol and Iohexol in the subjects (n-58; Iodixanol group-29 and Iohexol group-29), (p value- 0.243)**

DISCUSSION

The present study was conducted to find the prevalence clinically significant contrast nephropathy (CN) in patients receiving bolus injections of Iodixanol and Iohexol for Intravenous Pyelography in a Tertiary care Hospital of Kerala, The study showed a CN incidence of 04%, which is consistent with earlier reports. All the patients of both groups were administered Hydration with 0.9% normal saline Intravenous and it has shown that to be essential in preventing CN. the mean age was 64.25±08.35 in the Iodixanol group and 60.45±6.98 in the Iohexol group. There were 19/29 (62.51%) males and 10/29 (34.48%) females in the Iodixanol group and 20/29 (68.96%) males and 09/29 (31.03%) females in the Iohexol group. The mean weight in the Iodixanol group was 69.10±09.30 Kgs and 66.10±01.40 in the Iohexol group. The mean height in the Iodixanol group was 162.89±12.65 Cms and 164.23±07.11 Cms in the Iohexol group. Diabetes Mellitus was present

in 09/29 (31.03%) of the patients Iodixanol group and 07/29 (24.13%) in the Iohexol group. Renal insufficiency was noted in 12/29 (41.37%) of the Iodixanol group and 11/29 (37.93%) of the Iohexol group. Earlier reports suggested that iodixanol might be slightly less nephrotoxic than iohexol. (16, 17 and 18) The serum creatinine levels (percentage of change) of patients in both the iodixanol and iohexol groups was evaluated during the study and found that. The overall incidence of contrast nephropathy (CN) was 05.17% (03/58), with one case in iodixanol group and 02 cases in Iohexol group. There were no significant differences in CN incidence between the two groups ($p = 1.0$). Additionally, there was no significant difference in the percentage change in serum creatinine over the week following IVP between the groups ($p = 0.529$). No significant differences were observed in serum creatinine levels at baseline, day 2, day 3, or day 7 ($p > 0.05$). Similarly, no significant difference was found in the percentage change in serum creatinine during the week following IVP ($p > 0.05$), **(Table 2 and 3).** Despite this age difference, the incidence of CN was not higher in the iodixanol group compared to the iohexol group. Previous studies have shown a clinically important risk of nephrotoxicity due to contrast material in diabetic patients with normal renal function and in non-diabetic patients with preexisting renal insufficiency. (19, 20 and 21) The incidence of CN in our patients with diabetes mellitus and renal insufficiency was 12.5%, much lower than previously reported. Late adverse reactions following the administration of dimeric contrast media (CM) may be explained by cytokine dynamics. The allergic reactions observed in the iodixanol and iohexol groups were tabulated in the Table 5 which showed that there was no significant differences in allergic reactions were noted between the groups ($p = 0.243$). The overall incidence of allergic reactions was 17.24%. Early allergic reactions occurred in 03/29 (10.34%) of the Iohexol group patients and none in the Iodixanol group of patients. Late allergic reactions occurred in 03/29 (10.34%) of the Iohexol group and 02/29 (06.89%) of the Iodixanol group of patients ($p = 0.001$), **(Table 5)**. Some studies suggest that late reactions are more common with non-ionic dimeric CM compared to non-ionic monomeric CM. (22, 23 an 24) Dimeric CM generally induce fewer immediate reactions but are associated with an increased risk of late adverse reactions. (25, 26) In our study, one patient experienced a severe skin rash due to a late adverse reaction after receiving iodixanol. The skin lesion was initially misdiagnosed as cellulitis and treated with oral antibiotics with minimal improvement. Ultimately, the patient received oral prednisolone (0.5 mg/kg), leading to the resolution of the skin lesion after one week.

CONCLUSIONS: In conclusion, iodixanol and iohexol contrast media for routine IVP examinations are safe and have a low nephrotoxicity profile, particularly in elderly and high-risk patients. Late allergic reactions may be the most common adverse effect following the infusion of nonionic contrast media.

DECLARATION OF INTEREST: The authors declare no conflicts of interest. The content and writing of this paper are solely the responsibility of the authors.

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