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Iopaque 300 versus Omnipaque 300: A Randomized Double Blind Clinical Trial for Comparison of Efficacy and Adverse Effects in Peripheral Angiography

Background/Objective: The contrast medium has to be selected with regard to safety and efficacy. Iohexol is produced in Iran as the brand name Iopaque. Currently, there are some concerns about using this brand instead of its traditional more expensive brand—Omnipaque. This study was conducted to compare the safety and radiographic efficacy of 300 mg I/mL of Iopaque and Omnipaque in peripheral angiography.

Patients and Methods: 84 patients were randomly received 300 mg I/mL of one of the two brands of contrast mediums iohexol: Iopaque (Daroopakhsh, Tehran, Iran) or Omnipaque (Nycomed Imaging AS, Oslo, Norway). The radiological efficacy of the drugs was compared according to the distribution of the vascular enhancement and the amount of radiodensity in arterial, capillary, and venous phases of angiography, using visual analogue score (VAS). The adverse events were recorded by a close follow-up by the investigator at baseline, after 1 and 4 hours, and 3 days after angiography.

Results: Baseline characteristics including gender, age, and type of angiography were not statistically different between the two study groups. Both contrast agents produced acceptable visualization of the vascular structures [VAS: 8.2±1.4 in Omnipaque and 8.1±1.5 in Iopaque groups; $p>0.05$]. 23 patients in each group showed early and delayed adverse reactions related to contrast media. Changes in biochemistry parameters were not of clinical importance.

Conclusion: The safety and efficacy of Iopaque and Omnipaque in peripheral angiography are the same.

Keywords: Iohexol, safety, efficacy, angiography, peripheral

Introduction

Despite the advent of newer imaging modalities, contrast-enhanced imaging (e.g. angiography) remains necessary in many patients with cardiovascular and neurologic diseases.[1,2]

The contrast medium has to be selected with regard to safety and efficacy parameters. The introduction of the second-generation iodinated non-ionic monomeric contrast medium iohexol that is used for a wide range of diagnostic procedures, dramatically reduced the adverse events related to contrast-enhanced investigations. This improvement continued by production of non-ionic dimeric contrast media (e.g. iotrolan) which provide the best ratio of radiodensity beside their low osmolality.[3,4]

The mainstay of radiologic efficacy is to provide sufficient information to make an adequate diagnosis rather than the enhancement.[5] However, non-ionic dimeric contrast media may produce a more suitable radiological visualization, cost consideration mean to use mostly available monomeric contrast media during conventional contrast-enhanced investigations.

The data collection method and how one defines "adverse event" are important parameters for comparison of different studies in respect to the reported frequencies of adverse events; these parameters, however are often not explained in detail.

Iohexol has been producing in Iran since several years ago as the brand name of Iopaque. Currently, there are some concerns about using this brand instead of its traditional more expensive brand—Omnipaque.

Whether Iopaque can work similar to Omnipaque with no more adverse effects has not been assessed yet. To answer this question, we aimed to compare the safety and radiographic efficacy of 300 mg I/mL of Iopaque and Omnipaque in peripheral angiography.

Patients and Methods

The study was designed as a randomized, double-blind, comparative study performed on 84 patients. The study was approved by the ethics committee of Radiology Research Center affiliated to Tehran University of Medical Sciences. Oral and written information were presented to all patients before they gave their written consent. Consecutive patients referred for peripheral angiography in the period from July 2005 to March 2006 were included.

The exclusion criteria included pregnancy, lactation, administration of contrast medium within the previous seven days, history of serious reactions to iodinated contrast media, clinically-unstable condition (i.e., patients whose hemodynamic, respiratory, or neurologic status can deteriorate quickly), emergency cases, known cases of hyperthyroidism and end-stage renal disease. Moreover, we excluded patients less than two years of age. No medication was given during or after the examination to any patients.

Hiring block randomization method with six patients in each block (provided before the initiation of the study) was used. The patients were then allocated to receive 300 mg I/mL of one of the two brands, either Iopaque (Daroopakhsh, Tehran, Iran) or Omnipaque (Nycomed Imaging AS, Oslo, Norway). Only one member of the team (SA) was aware of the contrast material used; she did not participate in the evaluation of the data collected. Therefore, the radiologist who performed angiography, the physician who followed the patients and patients themselves were blind to the type of injected contrast media. The volume of the injected contrast medium varied from 120 to 140 mL. The injection rate was 8 mL/s with a total volume of 12 mL/injection for brain angiography and 6 mL/s with a total volume of 9 mL/injection in peripheral angiography.

The radiological efficacy of the drugs was compared based on the distribution of the vascular enhancement and the amount of radiodensity in arterial, capillary, and venous phases of the angiogram, which were separately scored by two experienced radiologists using a visual analogue scale (VAS). VAS is a straight line, scaled from 0 to 10. In this scaling, zero and ten correspond to the worst and best possible radiological efficacy, respectively. For each patient, the total radiological efficacy score for each vascular phase calculated as the mean of scores given by those two radiologists.

If the enhancement was not enough for proper diagnosis, a supplementary dose of drug was administered.

Adverse events were recorded by a close follow-up by the investigator at baseline and one and four hours after angiography. Moreover, patients visited for any adverse effects on the day three of radiological investigation. Patients were observed and questioned regarding adverse events and were instructed to report any symptoms. Serum creatinine, blood urea nitrogen, cell blood count, and thyroid function were measured before examination and three days after the examination.

Data were analyzed using SPSS (v. 11.5.1) software. All parameters were evaluated by descriptive statistical methods. Student's t-test was used to evaluate the technical quality and laboratory data. Bland-Altman plot was used to evaluate the level of agreement between two radiologists.

Results

The mean age of patients was 41.1 (range: 16–65) years. The male/female sex ratio was 1.5. Sixty-eight patients had been scheduled for four-vessel angiography; the remaining 16 patients had been scheduled for either lower or upper extremities angiography.

Table 1. Summary of patient population

	Omnipaque 300	Iopaque 300
Total patients	**42**	**42**
Women		
Number	19	14
Age: mean (SD)	43.2 (11.3)	42.2 (11.9)
4 vessels angiography	18	10
Extremities angiography	1	4
Men		
Number	23	28
Age: mean (SD)	40.8 (14.6)	39.5 (14.6)
4 vessels angiography	14	26
Extremities angiography	9	2

Patients were randomly assigned to receive 300 mg I/mL of either Omnipaque or Iopaque. Table 1 depicts the age, sex, and type of angiography in each group. There were no statistically significant differences between the two groups.

The Bland-Altman plot shows that among 45 observation, only 1 (= 2%) was beyond the ± 2SD line; therefore there was an excellent agreement between two radiologists who reported the results (Figure 1). The quality of overall diagnostic information for both contrast media was not statistically different (Table 2).

The frequency of patients with any adverse effects was equal in both groups (Table 3). Chest pain, hypotension, hypertension, and cardiac or respiratory arrest, did not occur at all.

No changes of clinical importance were occurred in blood biochemistries checked before and three days after angiography. Moreover, changes occurred in both groups were not of clinical importance. Although, the change in platelet count between the two groups studied was statistically significant, case to case analysis revealed a variation of no clinical importance (Table 4).

Discussion

When a previously-approved drug is produced under the license of other companies rather than its original producer, new trials to compare the safety and efficacy of the new brand with the previously-approved brands is necessary, because the production process and the drug vehicles used may differ from those of the original format.

The phenomenon of present-day radiologic imaging would be lacking without contrast media. [1,2] In recent years, the most conventional contrast media being used in Iran is iohexol (Figure 2), a nonionic iodinated monomer. Iohexol is traditionally used to find out the efficacy level and the rate of adverse effects of newly-produced contrasts.[3-6] In Iran, the previously-

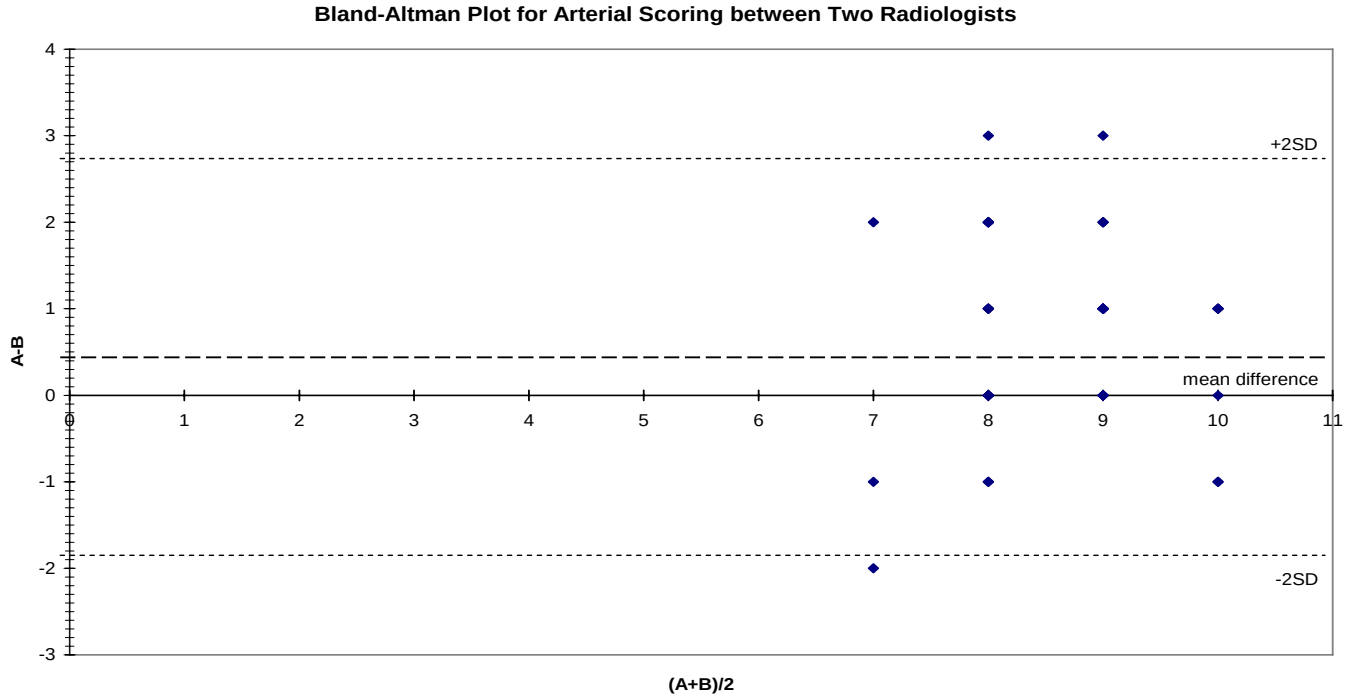

Fig 1. Bland-Altman plot was for evaluation the level of agreement between two radiologists.

Table 2. Quality score according to the visual analogue scale

phase	Omnipaque 300 (n=42)	Iopaque 300 (n=42)	P-value (independent *Student's t*- test)
Arterial	8.4±1.3*	8.1±0.8	0.2
Venous	8.2±1.5	8.1±0.7	0.8
Capillary	8.2±1.3	8.1±0.8	0.8

* VAS: mean±SD

available brand was Omnipaque 300. Due to frequent needs to use contrast media in radiologic studies, and for the high cost of this brand of iohexol, production of the Iranian brand seemed necessary. At present, iohexol 300 is available by the Iranian brand name of Iopaque.

In nonionic monomers, the tri-iodinated benzene ring is made water-soluble by the addition of hydrophilic hydroxyl groups to organic side chains placed at positions 1, 3, and 5. Nonionic monomers do not ionize in solution. Thus, for every 3 iodine atoms, only 1 particle is made in solution. Therefore, nonionic monomers have approximately one half the osmolality of ionic monomers.[2] In addition to their nonionic nature and lower osmolalities, they are potentially less chemotoxic than the ionic monomers .[4-6]

Table 3. Adverse events at any time after peripheral angiography

Adverse effect	Omnipaque 300 (n=42)	Iopaque 300 (n=42)
Heat sensation	3	3
Nausea	3	3
Vomiting	-	1
Pallor	2	4
Rash	1	-
Itching	1	-
Flashing	-	1
Face edema	1	-
Chilling	4	3
Palpitation	2	1
Dyspnea	1	1
Sore throat	-	1
Hoarseness	-	1
Sneezing	1	-
Coughing	1	-
Headache	6	15
Dizziness	3	3
Eye pain	1	4
Back pain	12	6
Abdominal pain	2	2
Muscular pain	1	-
Muscular spasm	1	1
Total number of patients	23	23

A sensation of heat during the injection of contrast medium may be explained to some degree by the osmolality of the contrast medium and by the speed of the injection. The other important factor is the route of injection. For instance, during intravenous injection of monomeric non-ionic contrast media, the frequency of such heat sensation varies from 20% to 90% while during iohexol 300-mediated peripheral angiography, Gorden, et al, reported a frequency of moderate to severe heat sensation of 61%.[7-10] Heat sensation affected only 7% of our patients which was lower than that reported by Gorden et al.[10] Furthermore, Doerfler et al. reported heat sensation in 4% of patients who had received iohexol.[11] the lower rate in our patients may be attributed to the lower speed of injection in our patients, or the fact that we did not register all heat sensations expressed by our patients. Anyway, comparing both drugs revealed that they were similar in producing patient discomfort regarding the rate of heat sensation.

The incidence of any adverse reactions to iodinated contrast media was around 15%. Most of these reactions were mild and required no treatment.[2] In one large series, the overall risk of any adverse reactions was 3.13% with nonionic iodinated contrast media. The risk of developing a severe adverse drug reaction was 0.04% for nonionic contrast media; the risk of developing a very severe adverse drug reaction was 0.004%.[3] A meta-analysis of the published data from 1980-1989 revealed that the risk of severe adverse reaction is 0.157% for high-osmolality contrast media and 0.031% for nonionic contrast media.[12] During a 13-year study, Chocran et al. reported a reaction rate to nonionic agents of 0.2%.[4] Caro et al. found that the risk of death was one in 100,000 patients with either type of agents.[13] According to literature, the majority of adverse events are allergy like reactions.[1,2]

Delayed reactions become apparent at least 30 minutes (though, it may occur within 7 days) after the

Table 4. The mean (SD) of blood biochemistries before and 3 days after peripheral angiography

Parameter	Omnipaque 300		Iopaque 300		P-Value (independent t- test)†
	Before	After ngiography	Before	After angiography	
Hemoglobin(g/dl)	15 (1.7)*	14.6 (1.6)	15.3 (1.7)	14.5 (2.5)	0.1
Red cell count (/µl)	5013 (548)	4930 (560)	5247 (711)	5160 (1072)	0.2
White cell count (/µl)	8375 (3689)	8464 (3753)	8232 (3153)	7463 (2690)	0.2
Platelet count (/µl)	248561 (57493)	266176 (65909)	239744 (74423)	217908 (74891)	0.04
Serum creatinin (mg/dl)	0.8 (0.2)	0.8 (0.2)	1.3 (1.9)	3.1 (0.5)	0.2
Blood urea nitrogen (mg/dl)	28.6 (10.6)	26.6 (10.1)	28.3 (10.7)	24.4 (10.1)	0.5
T3 (ng/ml)	131.7 (35.8)	131.6 (35.7)	123.7 (29.6)	122.1 (30.3)	0.1
Ft4 (ng/dl)	1.4 (0.6)	1.3 (0.5)	1.4 (0.4)	1.4 (0.3)	0.3
Thyroid stimulating hormone(TSH) (ng/ml)	1.9 (1.8)	3.4 (8.1)	1.4 (0.5)	1.6 (1.4)	0.2

*Mean (standard deviation)
†compared mean changes between 2 groups

injection of contrast media.[2,14] These reactions are identified in as many as 8%–10% of patients after the injection of nonionic monomers.[2]

Fifty-six percent of adverse effects observed in our study although distributed equally in both groups, were dramatically higher than previous reports. Even after omitting back pain, which was not commonly reported in literature, the rate of adverse events in our study was higher than previous reports. We do not know the reason, though we think that the high rate of complications, which were mostly subjective, is due to taking the informed consent, as reported elsewhere.[17] Due to the low power of the study, the statistical comparison of the adverse effect rates was not possible.

The results of biochemical tests were in accordance with previous reports suggesting fewer detrimental effects from the use of low osmolality contrast media.[18-20] Contrast agent related nephropathy is defined as an elevation in serum creatinine level of >0.5 mg/dL or >50% of baseline during 1–3 days after the contrast media injection, which has not been observed in our patients.[2]

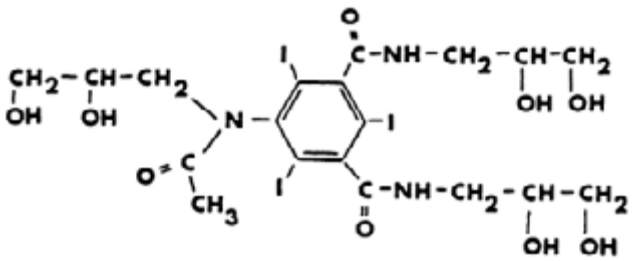

Fig. 1.—Iohexol. Empirical formula: $C_{19}H_{26}I_3N_3O_9$
N,N'-6$_{1s}$(2,3-dihydroxypropyl)
-5-(N-(2,3-dihydroxypropyl) Acetamido)
-2,4,6, triiodoisothalamide.
Molecular weight: 821.14. Iodine content: 300 mg I/ml. Tonicity: 690 mOsm/kg.

Fig 2. Structure of iohexol 300.[10]

In our study, both contrast agents produced good to excellent visualization of the vascular structures, which was in concordance with previous reports about iohexol. The investigators could not detect statistically significant differences between the two groups.[10,21]

The safety and efficacy of Iopaque and Omnipaque in peripheral angiography of Iranian patients is therefore confirmed, however the frequency of mild adverse effects seemed to be high. The contrast quality of Iopaque is at least as good as with Omnipaque in all phases of peripheral angiography. Due to availability and lower price, Iopaque is therefore recommended for conventional contrast mediated radiological studies.

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Conflict of Interests

The study sponsors were not involved in the study design, collection, analysis and interpretation of the data, and in the writing of the report.

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