

Safety of using iodized oil in chemoembolization for liver tumors in patients with previous adverse reactions to iodinated contrast media

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Abstract

Purpose: To evaluate the safety of using iodized oil in chemoembolization for liver tumors in patients with previous adverse reactions to iodinated contrast media. **Materials and methods:** Records were retrospectively reviewed for all patients with a history of an adverse reaction to iodinated contrast media who underwent angiography using gadolinium-based contrast media and/or carbon dioxide at our institution from January 1998 to September 2006. Patients who underwent chemoembolization or hepatic artery infusion for liver tumors using iodized oil were identified. **Results:** There were 84 procedures with use of iodized oil performed in 36 patients. Mild adverse reactions potentially related to iodized oil were seen in two procedures (2.4%). There were no moderate or severe adverse reactions (0.0%). **Conclusion:** Iodized oil can be safely used in patients with previous adverse reactions to iodinated contrast media.

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1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common lethal malignancies in the world. Although the mainstay of therapy is surgical resection, the majority of patients are not eligible because of tumor extent or underlying liver dysfunction. Transarterial chemoembolization (TACE) is a common technique used to treat unresectable HCC. The rationale for chemoembolization stems from the observation that normal liver tissue receives most of its blood supply from the portal vein, whereas liver tumors receive most of their blood supply from the hepatic artery. Chemoembolization combines hepatic artery embolization with simultaneous infusion of some chemotherapeutic agents followed by embolization particles. In 1983,

Nakakuma et al. [1] reported the selective retention of iodized oil in HCC, following its injection into the hepatic artery. Since then, iodized oil has been widely used as a suspension medium for chemotherapeutic agents [2–4]. This oily medium is a key ingredient to the chemoembolization procedure because it is a drug-carrying, tumor-seeking, and embolic agent [5,6].

Iodinated contrast media are among the most widely used agents of all medications used for diagnosis or treatment. The history of a previous adverse reaction to iodinated contrast media is a strong risk factor for a subsequent adverse reaction [7–10]. Occasionally, patients with a history of an adverse reaction to iodinated contrast media will require a study with iodinated contrast media. In such patients, gadolinium-based contrast media can be used in place of iodinated contrast media [11–13]. Ethiodol (lipiodol) is an iodinated derivative of poppy-seed oil with an iodine content of 37–39% by weight [5]. To our knowledge, there are no reports on the safety of iodized oil in patients with a history of an adverse reaction to iodinated contrast media. The purpose of our study was

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Table 1
Patient characteristics (N=36)

Characteristic	Datum
Age (y) ^a	66.0±11.5 (34.3–85.5)
Sex	
Male	22 (61.1)
Female	14 (38.9)
Liver tumor	
Hepatocellular carcinoma	35 (97.2)
Metastasis, jejunal carcinoid	1 (2.8)
Risk factor	
Asthma	3 (8.3)
Food or drug allergy	6 (16.7)

Unless otherwise specified, data are numbers of patients with the given characteristic, with percentages in parentheses.

^a Data are mean value±S.D., with the range in parentheses.

to evaluate the safety of using iodized oil in chemoembolization for liver tumors in patients with previous adverse reactions to iodinated contrast media.

2. Materials and methods

2.1. Patients

Our retrospective study was approved by the local ethical committee and informed consent was waived. Records were reviewed by one author for all patients with a history of an adverse reaction to iodinated contrast media who underwent angiography using gadolinium-based contrast media and/or carbon dioxide (CO₂) at our institution from January 1998 to September 2006. Patients who underwent chemoembolization or hepatic artery infusion [14] for liver tumors using iodized oil were identified. Information was collected from the medical records by one author and included patient age, sex, disease, history of a previous adverse reaction to iodinated contrast media, risk factors for adverse reactions to contrast media, procedural details, and complications during and after the procedure.

2.2. Angiography procedure

All procedures were performed as part of clinical care at our institution. After a 4- to 5-Fr sheath was placed into the femoral artery, the celiac trunk and superior mesenteric artery were selectively catheterized with use of a 4- to 5-Fr catheter. Depending on the situation, the catheter was positioned in the hepatic artery, or a microcatheter was advanced coaxially through the catheter into the hepatic artery. Contrast material was injected by hand or by power injector.

In all cases, iodized oil (Lipiodol Ultra-Fluid; Guerbet, Villepinte, France) or a mixture of epirubicin (Farmorubicin; Kyowa Hakko Kogyo, Tokyo, Japan) and iodized oil (Lipiodol Ultra-Fluid) was infused into the hepatic artery. In chemoembolization, this was followed by gelatin sponge

particles (Gelfoam; Pharmacia and Upjohn, Kalamazoo, MI, USA) or Spongel (Yamanouchi Pharmaceutical, Tokyo, Japan) or autologous blood clots [15].

2.3. Adverse reactions

Two authors together classified all previous adverse reactions to iodinated contrast media as mild, moderate, or severe. Mild reactions included nausea, mild vomiting, limited urticaria, rhinitis, flush, and fever; moderate reactions included extensive urticaria, facial edema, dyspnea, and decrease in blood pressure; severe reactions included shock and cardiac arrest.

The two authors together classified all procedural complications as procedure-related or non-procedure-related (i.e., potentially related to iodized oil). Postembolization syndrome (nausea, vomiting, abdominal pain, fever) by itself was not considered a complication but rather an expected outcome of embolotherapy [14]. Adverse reactions potentially related to iodized oil were classified as mild, moderate, or severe by the same way.

3. Results

3.1. Patient characteristics

There were 84 procedures with use of iodized oil performed in 36 patients [22 males and 14 females; mean age, 66.0±11.5 years (range, 34.3–85.5)]. Baseline characteristics of the 36 patients are summarized in Table 1. Three patients (8.3%) had asthma and six patients (16.7%) had drug or food allergy. There were no patients with other known risk factors for adverse reactions to iodinated contrast media.

Table 2 shows the severity of previous adverse reactions to iodinated contrast media. Of the 36 patients, 19 patients (52.8%) had mild adverse reactions; nine patients (25.0%) had moderate adverse reactions; three patients (8.3%) had

Table 2
Severity of previous adverse reactions to iodinated contrast media (N=36)

Adverse reaction	Datum
Mild	19 (52.8)
Nausea	8 (22.2)
Limited urticaria	8 (22.2)
Rhinitis	1 (2.8)
Flush	4 (11.1)
Fever	1 (2.8)
Moderate	9 (25.0)
Extensive urticaria	2 (5.6)
Facial edema	2 (5.6)
Dyspnea	2 (5.6)
Decrease in blood pressure	5 (13.9)
Severe	3 (8.3)
Shock	3 (8.3)
Cardiac arrest	0 (0.0)
Unclear	5 (13.9)

Data are numbers of patients, with percentages in parentheses.

Table 3
Complications of 84 procedures

Complication	Datum
Non-procedure-related	2 (2.4)
Mild	2 (2.4)
Limited urticaria	2 (2.4)
Moderate to severe	0 (0.0)
Procedure-related	5 (6.0)
Vasovagal reflex	3 (3.6)
Hyperventilation	2 (2.4)

Data are numbers of complications, with percentages in parentheses.

severe adverse reactions. Details were unclear in the remaining five patients (13.9%).

3.2. Procedural characteristics

Of the total of 84 procedures, 68 (81.0%) were chemoembolization with gelatin sponge particles (Gelfoam or Spongel); 7 (8.3%) were chemoembolization with autologous blood clots, and 9 (10.7%) were hepatic artery infusion (without embolization). The mean volume of iodized oil (Lipiodol Ultra-Fluid) infused into the hepatic artery was 4.6 ± 1.6 ml (range, 2.0–12.0 ml). Epirubicin (Farmorubicin) was used in 75 procedures (89.3%) [mean dose, 19.5 ± 2.9 mg (range, 8.2–30.0)].

All procedures were performed using gadolinium-based contrast media and/or CO₂. Gadodiamide (Omniscan; Daiichi Pharmaceutical, Tokyo, Japan) or gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) was used in 83 procedures (98.8%). In five procedures (6.0%), CO₂ was used alone or in combination with gadodiamide (Omniscan) or gadopentetate dimeglumine (Magnevist).

In all but one procedure (98.8%), H1-antihistamines (hydroxyzine) were used as a premedication for sedation. Corticosteroid premedication (hydrocortisone, methylprednisolone, or prednisolone) was used in only eight procedures (9.5%).

3.3. Adverse reactions

Table 3 shows the complications during and after the procedures. Procedure-related complications were seen in five procedures (6.0%). Non-procedure-related complications (i.e., adverse reactions potentially related to iodized oil) were seen in two procedures (2.4%). Two patients (57-year-old and 75-year-old females) with a history of a mild adverse reaction to iodinated contrast media developed limited urticaria after the procedure. In these two procedures, gadodiamide (Omniscan) was used as contrast media, and corticosteroid premedication was not given. There were no moderate or severe reactions potentially related to iodized oil.

4. Discussion

In our study, we evaluated the safety of using iodized oil in chemoembolization for liver tumors in patients with

previous adverse reactions to iodinated contrast media. Mild adverse reactions potentially related to iodized oil were seen in 2.4% of the total of 84 procedures using iodized oil. There were no moderate or severe adverse reactions. Although these adverse reactions were potentially related to iodized oil, various drugs including antibiotics and gadolinium-based contrast media were used during and after the procedures. Therefore, the true rate of adverse reactions to iodized oil may be less than 2.4%.

TACE is a widely used treatment for unresectable HCC. The effectiveness of systemic chemotherapy for HCC has been minimal [16]. HCC has a tendency to be localized within the liver. The observation that the majority of the blood supply to HCC is derived from the hepatic artery has led to the development of techniques designed to eliminate the tumor's blood supply or to administer chemotherapy directly to the tumor. In TACE, doxorubicin, mitomycin, and cisplatin are the commonly used chemotherapeutic agents [16]. Chemotherapeutic agents are usually emulsified with iodized oil, which promotes intratumoral retention of chemotherapeutic agents. Iodized oil is retained in HCC for periods ranging from several weeks to over a year, while it is quickly cleared from normal liver parenchyma [5]. Recent meta-analyses of randomized controlled trials [17,18] have demonstrated that chemoembolization improves survival of patients with unresectable HCC. The meta-analysis by Llovet and Bruix [18] also showed that embolization alone does not improve survival of patients with unresectable HCC.

The introduction of nonionic low-osmolar contrast media has caused an overall reduction in the number of contrast adverse reactions [7–10]. Although severe adverse reactions to nonionic low-osmolar contrast media are rare, patients with a history of an adverse reaction to iodinated contrast media are at high risk for recurrent reactions [7–10]. There are no reports on the safety of iodized oil in patients with a history of an adverse reaction to iodinated contrast media.

Several limitations of our study should be mentioned. First, it was a retrospective review and had limitations owing to the retrospective nature of the data collection. Second, our sample size was relatively small. Third, various drugs including antibiotics and gadolinium-based contrast media were used during and after angiography. Although non-procedure-related complications were potentially related to iodized oil, other drugs might be the cause of the reactions. Therefore, the true rate of adverse reactions to iodized oil in patients with previous adverse reactions to iodinated contrast media may be less than 2.4%.

In conclusion, the results of our study suggest that iodized oil can be safely used in patients with previous adverse reactions to iodinated contrast media.

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