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Transcatheter Arterial Embolization in Hepatocellular Carcinoma

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INTISARI

Arif Faisal – *Embolisasi intraarteriel melalui kateter pada hepatoma.*

Terapi embolisasi intraarteriel melalui kateter *(transcatheter arterial embolization)* merupakan terapi alternatif pada hepatoma stadium lanjut. Tindakan ini dapat dilakukan di rumah sakit dengan fasilitas peralatan angiografi. Teknik embolisasi intraarteriel tidak terlalu sukar, tetapi diperlukan pengalaman dalam bidang angiografi untuk jangka waktu tertentu.

Indikasi yang tepat sangat penting diperhatikan untuk melakukan terapi embolisasi intraarteriel, oleh karena beberapa komplikasi dan efek samping dapat terjadi setelah tindakan. Mengenai *embolic agents* dapat dipilih dari beberapa bentuk yang tersedia dan biasanya disesuaikan dengan kebutuhan.

Meskipun hasil yang dicapai belum sepenuhnya memuaskan, tetapi kombinasi terapi embolisasi dengan sitostatika menunjukkan hasil yang lebih baik.

Key Words: anticancer drugs – embolization – hepatocellular carcinoma – hepatoma – lipiodol

INTRODUCTION

Hepatocellular carcinoma (HCC) or hepatoma is a relatively common malignant tumor in Indonesia and Asian countries, and patients with this neoplasm have a poor prognosis. The first choice of treatment is hepatectomy, but most cases are considered inoperable due to extreme tumor extention at the time of diagnosis.

According to the report of The Liver Cancer Study Group of Japan (1979), only 9% of hepatoma patients underwent hepatectomy. The one-year survival rate after surgery was only 28%. Chemotherapy produced the one-year survival rate 7% and the mean length of survival was 3–6 months.

Many hospitals in Japan have performed transcatheter arterial embolization (TAE) in cases of unresectable hepatoma which demonstrated far more satisfactory results than other existing treatment. According to Yamada *et al.* (1983) the cu-

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mulative one-year survival rate was 44% by TAE. Charnsangavej *et al.* (1983) demonstrated the results of TAE in their cases of which median survival rate was 17,4 months in cases of hepatoma. In the development of TAE combined with anticancer drugs and iodized oil showed the results of treatment was better (Kobayashi *et al.*, 1986; Yodono *et al.*, 1989).

Equipments

1. Angiographic unit of X-ray machine for fluoroscopy and radiography.
2. Film changer (AOT, PUCK).
3. Automatic injector.
4. Life saving equipment in the angiographic room.

Materials for TAE

1. *Catheters*
   a. 5–6 F, 80 cm length, radiopaque
   b. Many types of catheter:
      - Cobra head
      - Modified Shepard Hook (*e. g.* SHK)
      - RH type and modified RH (*e. g.* Takekawa No. 2)
      - Loop the loop
      - etc.

2. *Guide wires*
   a. Size is the same to each catheter (size of lumen)
   b. Straight tip, curved tip, and deflecting type tip
   c. Stainless steel and heparin-coated
   d. Special coating (Radifocus, Terumo).

3. *Introducer*

   Introducer, used for exchanging the catheter and guide wire, will be located at the puncture site of the femoral artery, usually on the right side. The introducers usually have a checkvalve mechanism (leak-proof).

4. *Contrast media*
   a. Non-ionic contrast media: Omnipaque, Iopamiron.
   b. Ionic contrast media: Angiografin, Urografin, Hexabrix.

   Non-ionic contrast media is still expensive, but the side-effect is much milder and the diagnostic quality is superior to the ionic (Uchida *et al.*, 1987).

5. *Embolic agents*
   a. Gelfoam (Upjohn Company, Kalamazoo, Michigan, USA). Non-irritating and non-antigenic gelatine sponge. This agent is used very commonly. There are two types: block and powder. Spongel is quite similar to gelfoam.
   b. Lipiodol (Laboratoires André Guerbet, Aulnay-sous-bois, France). Iodinated ethyl esters of the fatty acids of poppy seed oil. Lipiodol is very popular recently as a vehicle of anticancer drugs.

c. Ivalon (Unipoint Industries, High Point, NC 27260, USA). Polyvinyl alcohol foam particles. Ivalon can be used in combination with some other material in the treatment of hepatic neoplasms. According to Miller (1987) Ivalon may have only a temporary occlusive effect in hepatic artery. Tadavarthy *et al.* (1974) injected Ivalon to stop bleeding in iliac artery and preventing fatal hemorrhage.

d. Cotton tail and wool coil (Gianturco). Stainless steel with cotton or wool. This mechanical devices was developed by Gianturco *et al.* in 1975. Cotton tails were used in smaller arteries and wool coils for larger Vessels (Giantruco *et al.*, 1975). Combination of steel coil with other embolic material was used by Chuang & Wallace (1981) for proximal occlusion of hepatic artery in treatment of hepatic neoplasms. Tisnado *et al.* (1979) reported displacement of stainless steel coil from left renal artery to common femoral artery.

e. Ethibloc (Ethicon GmbH, Norderstedt, West Germany). Viscous emulsion containing the protein zein, oleum papaveris, contrast medium and alcohol. Ethibloc is a radiopaque liquid with a honey-like viscosity. Once in contact with water, the protein component of Ethibloc precipitates and forms a chewing gum-like material. The alcohol component of Ethibloc acts only as a solvent, and is therefore not responsible for its vascular occlusive effects. For TAE, Ethibloc should be warmed to body temperature and should be injected in small quantities (0.5 – 1.5 ml) (Jaschke & Hoevels, 1988).

f. Ethiodol (Savage Laboratories, Melville, N. Y.). Ethyl esters of fatty acids of poppy seed oil and contains 37% iodine. Ethiodol was used combine with anticancer drugs by Yumoto *et al.* (1985) and Ohishi *et al.* (1985).

g. Oxycel (Parke-Davis & Co). Absorbable cellulose. There are two types: Oxycel clot and Oxycel fibre.

h. Autologous clot and subcutaneous tissue. Effective in the control of various form of benign bleeding, it has relatively short life span (hours and days) (Goldstein *et al.*, 1976).

i. Absolute alcohol. Intraarterial injection of alcohol produces sludging of blood corpuscles, coagulation of protein, arterial spasm and intimal damage, which results in thrombosis and arterial occlusion, perivascular leucocyte infiltration and perisinuidal and periportal fibrosis. The optimal indications for the use of alcohol for TAE are still to be established (Wallace *et al.*, 1984), but alcohol has been used for treating other tumors or bleeding. Jaschke & Hoevels (1988) did not recommend the alcohol for hepatic arterial occlusion because alcohol produced many complications.

j. Bucrylate. Isobutyl 2–cyanoacrylate. Mostly experimental, but some used it clinically.

6. *Anticancer drugs*

Combination of TAE and anticancer drugs injection namely chemo-embolization. Anticancer drug is mixed with Lipiodol suspension or Gelfoam before injecting. Adriamycin and Mitomycin C are used very commonly in

the procedure. Other drugs may be administrated. The dosage of anticancer drugs is as follows:

Adriamycin	10 – 40 mg
Mitomycin C	10 – 20 mg
Cisplatin (CDDP)	100 mg
5–Fluorouracil	300 mg
Cytosine arabinoside	25 mg
Ethoposid	under investigation.

Transcatheter arterial embolization technique

1. Transfemoral approach for inserting the catheter and guide wire. Local anesthesia.
2. Selective arteriography in celiac trunk or hepatic artery.
3. Arterial portography via superior mesenteric artery (SMA). Inject Prostaglandin E 1 (PGE 1) into SMA before injecting contrast medium. Prostaglandin F 2 can be used, but slightly more stimulating the bowel movement (peristalsis).
4. Preparation of embolic agent and anticancer drugs (Lipiodol, Adriamycin, Mitomycin C or Cisplatin).
5. Embolic agent and anticancer drugs is injected slowly under control of fluoroscopy, into feeder arteries or proper hepatic artery.
6. The mixture of Gelfoam pieces immersed in the contrast medium is injected into feeder arteries after Lipiodol. Amount of Lipiodol: smaller amount than 10–15 ml would be safer, because injection of a larger amount than 15 ml or so may cause embolization of portal vein branches.
7. If the patient feels pain in the right upper quadrant, morphin or analgesic agent such as Sosegon (Pentazocin) 15 mg i. m. may be given.

Photographic technique

Position : supine
Projection: anteroposterior (AP)

1. Celiac trunk or hepatic artery
   a. Contrast medium:
      – rate : 6 – 8.5 ml/s
      – total : 25 – 35 ml.
   b. Film:
      – 2 film/s for 3 s
      – 1 film/s for 3 s
      – 1 film/2 s for 12 s.
2. Arterial portography
   Injection of PGE 1 20–40 mg i. a. or PGF 2 à 100 mg i. a.
   a. Contrast medium:
      – rate : 8 – 9 ml/s
      – total : 40 ml.

b. Film:

- 1 film/ s for 7 s
- 1 film/2 s for 16 s.

3. Plain film after completing embolization.
4. Intra-Arterial Digital Subtraction Angiography (IADSA) would be a nice set up to check the degree of occlusion of the artery.

Indications

Indications of TAE in hepatoma are:

1. Inoperable hepatoma (Yamada *et al.*, 1983).
2. Preoperative resectable hepatoma (Nakamura *et al.*, 1983).
3. Hepatoma with abdominal bleeding (Takekawa *et al.*, 1979).
4. Recurrent hepatoma (Takekawa *et al.*, 1985).
5. To inhibit tumor growth, relieve pain and perhaps to stimulate an immune response to ischemic neoplasm (Chuang & Wallace, 1980).

Criteria of patients

The criteria for patients who will be treated by TAE and anticancer drugs (Yang *et al.*, 1989; Takekawa, 1989):

1. Histology proven either by cytology or biopsy, or with strong proof by AFP.
2. Clinical performance status of Child's A and B patients.
3. No main portal vein invasion causing obstruction, as seen on an angiogram and/or CT.
4. No distant metastasis.
5. No severely elevated total bilirubin.
6. No severe renal damage.
7. No remarkable esophageal varices.

Contraindications

1. Hepatic cirrhosis with severe hepatic dysfunction.
2. Tumor thrombus in main portal vein and or its branches.
3. Very large tumor with many feeder arteries.

Complications

1. Pain, usually in the right hypochondriac region or right upper abdomen, has been reported by many authors. Pain in the epigastrium or left hypochondrium may indicate acute pancreatitis from regurgitation of embolic materials.

2. Fever, due to necrosis of tumor or liver tissue.
3. Nausea and vomiting.
4. Increase in ascites (Yamada *et al.*, 1983).
5. Necrosis of gallbladder, due to migration of embolic agent into the cystic artery (Miller & Mineau, 1983; Kuroda *et al.*, 1983; Onodera *et al.*, 1984; Takayasu *et al.*, 1985).
6. Emphysematous cholecystitis (Nakamura & Kondoh, 1986).
7. Splenic infarction (Takayasu *et al.*, 1984).
8. Acalculous cholecystitis (Yeung *et al.*, 1989).
9. Acute pancreatitis and pseudocyst of pancreas.
10. Progression of cirrhosis of the liver.

Post–embolization management

1. Pain: a. High dose meperidine or morphine during the first 48 hours.
   b. Scopolamine during the first 3 days.
   c. Analgesic suppository (Diazepam, Cercin).
2. Nausea and vomiting: Prochlorperazine.
3. Fever: a. Aspirin or acetaminophen within a few days.
   b. Steroid 1–2 days, suppository is easier to use.

This management of post-embolization syndrome was modified from Clouse & Lee (1984) and Takekawa (1989).

DISCUSSION

Transcatheter arterial embolization (TAE) was first reported by Goldstein *et al.* (1976), and then reported by many authors as an effective therapy for liver malignancy (Chuang & Wallace, 1981; Charnsangavej *et al.*, 1983; Yamada *et al.*, 1983). The principal of TAE technique is to obliterate the feeder arteries for tumor tissue, and cause necrosis of the tumor.

The normal hepatic parenchyma has a dual blood supply, with 25–30% deriving from the hepatic artery and 70–75% from the portal vein. Primary and secondary hepatic neoplasma receive 90% of their blood supply from the hepatic artery. Portal vein blood supply protects the normal hepatic tissue from necrosis in embolization of hepatic artery. Fujisawa *et al.* (1986) reported a case of hepatoma with main blood supply from the portal vein. In this case, celiac arteriography showed a poor arterial supply but a rich portal supply as observed at percutaneous transhepatic portography.

Devascularization of a hepatic neoplasm could be achieved percutaneously by combined peripheral embolization of particulate material (Gelfoam/Spongel/ etc.) and central occlusion with a stainless steel coil (Chuang & Wallace, 1980). Hepatic artery collaterals (intrahepatic and extrahepatic) could be demonstrated following embolization and occlusion (Charnsangavej *et al.*, 1983), and the presence of these collaterals was significant in the management of hepatic neoplasms.

In hypervascular hepatic tumor the inferior phrenic arteries represent a source of collateral blood flow for neoplasm, and these arteries should be embolized with minimal complications. There was no evidence of diaphragmatic necrosis except possibly in the patient who developed pleural effusion after embolization (Duprat *et al.*, 1988).

In performing TAE for hepatoma, it is important to obtain information as detailed as possible about the invasion of the tumor into the portal vein, and for this purpose it is necessary to visualize the intrahepatic portal vein as clearly as possible. Intraarterial portography is done via superior mesenteric artery (SMA). Bolus injection of Prostaglandin E 1 (PGE 1) into SMA produces slight dilatation of the artery and blood flow is markedly increased. The portal vein is first seen 3 to 10 seconds (mean 5 seconds) after the beginning of contrast medium injection, with optimal opacification after 6 to 13 seconds (mean 10 seconds). The quality of the portal vein opacification is greatly improved after using PCE 1 (Jonsson *et al.*, 1977). According to investigation of Nakamura *et al.* (1987), visualisation of intrahepatic portal vein was improved by injection of PGE 1 and balloon occluding superior mesenteric arteriography. By this method there was neither a rebound of the catheter into the aorta nor a backflow of contrast medium into the aorta. The sharpest image of the intrahepatic portal vein was obtained from 8 to 12 seconds after initiation of filming. Prostaglandin F 2 α had the same effect with PGE 1 and the price was cheaper, but slightly more stimulating to the peristalsis of the bowel (Takekawa, 1989).

The results of treatment of hepatoma had been reported by many authors, which can be seen in TABLE 1 as a summary of those results. The methods of therapy and evaluation were different by different authors. Combination of TAE and anticancer drugs showed higher survival rate than TAE or anticancer drug alone. Adriamycin and Mitomycin C were used very commonly, but Cisplatin (CDDP), 5–Fluorouracil derivative and Fluxidine were occasionally used.

To improve and intensify the anticancer drugs in the tumor tissue iodized oil (Lipiodol) is used as a vehicle. Anticancer drugs were suspended in iodized oil with a dispersing stabilizer aluminium monostearate (Nakakuma *et al.*, 1983; Kobayashi *et al.*, 1986; Yodono *et al.*, 1989), and injected into hepatic artery or its branches. Lipiodol particles filled all branches of hepatic artery of a diameter over 25 um and Lipiodol retention in the tumor tissue could be detected more than one year by abdomen plain film or CT examination. Level of biologic anticancer drugs activity in tumor tissue was higher compared to normal hepatic tissue (Nakakuma *et al.*, 1983).

In the normal hepatic tissue Lipiodol disappears very early. The washed-out Lipiodol in normal hepatic tissue probably passed into the sinusoidal spaces and slowly permeated into the liver cells, or it might be caught by the reticuloendothelial system or the liver (Nakakuma *et al.* 1983), and the hepatic lymphatics (Yumoto *et al.* 1985). According to the study by Miller *et al.* (1987) it was shown that early clearence of iodized oil into bile might possibly be caused by localized hepatic ischemia from oil microemboli or by direct phagocytosis by Kupfer cells and there was no evidence that iodized oil was cleared by hepatic lymphatics.

TABLE 1.– The results of treatment in hepatoma

Authors	Cases	TAE	Anticancer	Survival
Charnsangavej *et al.* (1983)	11	Gelfoam Ivalon Steel coil	–	17.4 mos. (median)
	14	–	FAM Cisplatin	12.3 mos. (median)
Yamada *et al.* (1983)	120	Gelfoam	MMC 10 mg Adr. 20 mg	44% 1 yr.
Ohishi *et al.* (1985)	97	Ethiodol Gelfoam	MMC. Adr.	89% 6 mos. 69% 1 yr.
Kobayashi *et al.* (1986)	41	Lipiodol (ADMOS)	MMC. 8–32 mg Adr. 10–40 mg	55% 1 yr.
Yang *et al.* (1989)	129	Lipiodol Gelfoam	MMC. 10 mg Adr. 20–30 mg	49% 1 yr. 22% 2 yrs.
Hirai *et al.* (1989)	191	–	MFC/AFC	22% 1 yr. 8.9% 2 yrs.
	187	Lipiodol Gelfoam	MMC. 10–20 mg Adr. 20–40 mg	66.2% 1 yr. 36.5% 2 yrs.
Takayasu *et al.* (1989)	69	Lipiodol Gelfoam	MMC. 10 mg Adr. 20 mg	53% 1 yr. 24% 2 yrs.

Note: FAM = Fluxuridine, Adriamycin, Mitomycin. MMC = Mitomycin C.
Adr. = Adriamycin. MFC = Mitomycin C, 5–fluorouracil, Cytosine arbinoside.
AFC = Adriamycin, 5–fluorouracil, Cytosine arbinoside.
ADMOS = Adriamycin and/or Mitomycin C suspended in iodized oil (Lipiodol).

The washed-out Lipiodol in tumor tissue disappears very slowly. The vessels in tumor tissue does not have sufficient blood flow to clear away the adhesive Lipiodol, the blood flow is slow through the tortuous and irregular neoplastic vessels, which often lack both a muscular and elastic lamellae (Nakakuma *et al.*, 1983). The disappearance of Lipiodol from the injected artery seems to depend on washout by flowing blood in a nontumorous tissue.

The other advantage of the long period of selective retention of an oily contrast medium or Lipiodol in hepatic tumor is to aid in the diagnosis of these tumors. This method is considered to be effective not only for treatment of hepatic tumor but also useful for evaluation of post-TAE changes in the tumor and diagnosis of small daughter nodules (which could not be diagnosed by angiography and/or CT prior to TAE) due to the long-term accumulation of iodized oil in tumor tissue (Nakakuma *et al.*, 1985; Ohishi *et al.*, 1985; Yumoto *et al.*, 1985). But uptake and retention of Lipiodol are not characteristic of the hepatic malignant tumors, because uptake and retention up to 3 months was demonstrated in hepatic cavernous hemangioma also (Uflacker *et al.*, 1989). It is not recommended to use intraarterial injection of Lipiodol in differentiating hepatocellular carcinoma from cavernous hemangioma of the liver.

Prognosis of hepatoma after TAE is still not completely satisfactory, and 5-year survival rate is hardly attained. The prognosis is influenced by many factors. According to Takayasu *et al.* (1989), the size of the main tumor significantly

influenced the prognosis following TAE, whereas the frequency of TAE, intrahepatic metastasis and degree of liver dysfunction showed a slight correlation.

CONCLUSION

Vascular catheterization technique has been used not only for diagnostic purposes but also in treating certain diseases. Current uses of the procedure include transcatheter arterial embolization (TAE) in unresectable hepatoma due to the advanced stage of the tumor and/on hepatic cirrhosis.

The materials for TAE and angiographic facilities in a hospital are needed for performing TAE. Selection of patients to be a candidate for TAE is very important because detection of contraindications prior to TAE should be done very carefully and we have to be aware of complications that may occur. Application of TAE technique to the patient sometimes is not very easy but this problem can be solved by obtaining experience in angiography that require a certain period.

The better result of treatment is obtained by combination of TAE and anticancer drugs. Prognosis after TAE is still not completely satisfactory, but the patient has a longer survival time. Therefore, TAE should be seriously considered in the treatment of patients with advanced or inoperable hepatocellular carcinoma to prolong their life with good quality.

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