MEDICAL PRACTICE

Transcatheter embolisation of intrahepatic arteriovenous shunts in patients with hepatocellular carcinoma

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This paper assesses the feasibility of transcatheter embolisation of arteriovenous shunts in patients with hepatocellular carcinoma, and reviews available embolic agents, based on our experience and a literature review. From 2001 to 2007, 11 patients with unresectable hepatocellular carcinoma and significant arteriovenous shunts underwent transcatheter embolisation of liver arteriovenous shunts. The age range was 36 to 80 years. A total of 17 embolisations were performed using different embolic agents including absolute ethanol (n=11), histoacryl (n=1), coils (n=2), and polyvinyl alcohol particles (n=1). We reviewed the degree of shunt occlusion and the clinical outcomes. There were 15 arteriovenous shunts. Nine (60%) were arterioportal venous shunts and six were arteriohepatic venous shunts. Two were classified as 'simple' types, according to our protocol, and 13 were 'complex' types. More than 80% occlusion was achieved in 80% of the shunts. In the simple shunts, coil embolisation achieved complete occlusion. In complex shunts with multiple feeders and draining veins, liquid or particulate agents were required to achieve satisfactory occlusion. Managing arteriovenous shunts with embolisation was feasible. The choice of embolic agent should be based on good understanding of the underlying mechanism of the shunts and their angio-architecture.

Introduction

In most patients with hepatocellular carcinoma (HCC), the tumours are not resectable at the time of initial presentation. The reported rate of non-resectability is between 76% and 84%.[1] Transarterial chemoembolisation (TACE) has been proven an effective means of managing unresectable HCC[2-10] and improves the survival rate in both European and Asian patients. Nevertheless, the presence of an arteriovenous shunt is one of the main impediments and relative contra-indications to TACE. Arteriovenous shunts have been seen in 1.3 to 63% of hepatic angiograms done in patients with HCC.[11,12] In Chinese patients its prevalence has been reported as 31.2%.[13] The two major types of shunts are categorised according to their venous outflow: arteriohepatic venous shunts (AHVS) and arterioportal venous shunts (APVS). Apart from posing the risk of hepatic infarcts and pulmonary embolisms during TACE, shunts have a haemodynamic effect on the portal and systemic systems. An APVS can cause portal hypertension and portal regurgitation leading to bleeding varices, refractory ascites, refractory diarrhoea, and hepatic encephalopathy. Therefore, effective management of arteriovenous shunts is necessary.

A number of previous reports describe use of a variety of embolic agents, including coils, gelatin sponges, a combination of coils and gelatin sponges, ethanol, and polyvinyl alcohol (PVA).[14-19] Different embolic agents were reported to achieve shunt embolisation with different degrees of occlusion. Nevertheless, the reason for choosing particular embolic agents is seldom mentioned. We reviewed our cases of shunt embolisation in patients with HCC and evaluated their radiological and clinical outcomes. We postulate a management strategy for choosing particular embolic agents, based on our experience and a literature review.

Methods

Between 2001 and 2007, patients with significant arteriovenous shunts during performance of pre-TACE hepatic angiogram for HCC were reviewed. The diagnosis of HCC was based on contrast-enhanced computed tomographic (CT) scans, biochemical markers (alpha-fetoprotein), and histological results based on the current therapeutic recommendations from the Barcelona Clinic Liver Cancer system.[2]

We graded the arteriovenous shunts as significant when we found the degree of

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shunting seen on angiograms rendered subsequent TACE unsafe. Three radiologists with 6 to 15 years of experience in interventional radiology performed the assessment and embolisations. Computed tomographic imaging and angiograms indicated that all the patients had no thrombi in their main portal veins and no tumour thrombi in both the right and left portal veins.

為肝癌患者進行經導管栓塞肝內動靜脈分流

本文是按我們的經驗及文獻回顧，探討經導管栓塞動靜脈分流術治療肝癌患者的可行性，並找出可以使用的栓塞劑。研究對象包括2001年至2007年期間，11位介乎36至80歲患有末期肝癌及嚴重動靜脈分流，並接受經導管栓塞治療肝內動靜脈分流的病人。共進行了17次栓塞術，使用不同的栓塞劑包括：純乙醇（n=11）、組織黏膠（n=1）、螺旋綫圈（n=2）和聚乙稀醇（n=1）。我們分析了分流閉塞及臨床結果：共有15例動靜脈分流，其中9例動脈門靜脈分流，6例肝動靜脈分流；據我們的分類，2例屬「單純型」、13例屬「複雜型」。八成分流有超過80%的閉塞。單純型分流中，螺旋線圈栓塞術成功達至完全閉塞。有多個動靜脈分流或門脈的複雜型分流須用液體或顆粒劑達至令人滿意的閉塞。本研究顯示栓塞治療動靜脈分流是可行的。要選擇適當的栓塞劑，必須對分流的隱藏機制及栓塞劑對血管結構的影響有相當認識。

Shunt embolisation

All patients gave their written consents after discussion about the details and risks of the procedure. A femoral artery approach was adopted, using the Seldinger technique under local anaesthesia. Baseline digital subtraction angiography of the coeliac trunk and the superior mesenteric artery was performed to visualise the liver vasculature and evaluate the portal vein patency. The common hepatic artery, right and left hepatic arteries were cannulated, and more superselective cannulation of the feeders to the arteriovenous shunts was performed, if indicated, with or without the use of microcatheters.

Different types of embolic agents were available and the choice of embolic agent depended on angio-architecture of the shunt and operator's experience. This will be further elaborated on in the Discussion section. The embolic agents available included coils, PVA particles (PVA, Ivalon Contour 350-500 emboli; Boston Scientific, Mississauga [ON], Canada), histoacryl (NBCA, N-butyl cyanoacrylate; B Braun, Melsungen, Germany) mixed with lipiodol (Laboratoire Guerbet, Roissy, France) at a ratio of 1:2, and absolute alcohol (dehydrated alcohol BP, DBL; Mayne Pharma Pty, Melbourne, Australia).

Shunt classification

We reviewed the angiograms and classified the shunts according to their angio-architecture. Simple shunts were defined as those with a single feeding artery and a single draining vein, essentially arteriovenous fistulae. Complex shunts were defined as those with multiple arterial feeders and/or multiple venous outflows.

Assessment of feasibility

We reviewed the degree of shunt reduction based on the pre- and post-embolisation digital subtraction angiograms. The degree of shunt occlusion was divided into two categories: complete and partial occlusion. Complete occlusion was defined as absence of residual opacification of the shunt and the draining veins. Partial occlusion was defined as visible evidence of a residual shunt and these were semi-quantitatively divided into two groups: those with less than 80% reduction and those with 80% or more reduction. We set the criteria at 80% occlusion because the chance of sequential complete occlusion during follow-up would be high as small shunts can spontaneously resolve with conservative treatment.[18] Immediate technical success was defined as occlusion of 80% or more of the shunt.

Safety and complications

Complications were defined as major when they caused admission to hospital for therapy, an unplanned increase in the level of care, prolonged hospitalisation, permanent adverse sequelae, or death. Minor complications were those that led to no sequelae but required nominal therapy or a short hospital stay for observation.[20]

Follow-up evaluation

Patients were clinically and biologically monitored with measurement of their serum alpha-fetoprotein levels and liver functions. They had follow-up non-contrast CT scans (single-detector CT scanner for studies done before April 2005 and 16-slice multi-detector CT [Brilliance 16; Philips Medical Systems, Best, The Netherlands] for studies done afterwards) 2 weeks after embolisation and TACE. Subsequent hepatic angiography and TACE were arranged 6 to 8 weeks afterwards.

We reviewed the follow-up angiograms to detect any shunt recurrence, new shunts, and repeated shunt embolisation. We reviewed the patients' clinical outcomes, the number of patients able to proceed to TACE, and the total number of TACE sessions performed. The follow-up period ended once TACE and hepatic angiograms were no longer indicated because we could no longer monitor any shunt recanalisation with angiograms.

TABLE 1. Demographic features of patients with hepatocellular carcinoma (HCC) and arteriovenous shunts*

Patient No.	Sex/age (years)	Hepatitis status	Previous management on HCC	Tumour status	Maximal tumour size (cm)
1	M/50	HBsAg	Rt lobe wedge excision, Rt segmentectomy, Lt lateral segmentectomy, RFA, PEI	Bilobed	2
2	F/75	Non-HBsAg and non-HCVAb	RFA	Bilobed	3
3	M/51	HCVAb	Nil	Bilobed	3
4	M/53	HBsAg	Nil	Rt lobe	7
5	M/56	HBsAg	Lt hepatectomy, PEI	Rt lobe	5
6	M/55	HBsAg	Nil	Rt lobe	10
7	M/50	HBsAg	Nil	Rt lobe	10
8	M/60	HBsAg	Nil	Bilobed	3
9	M/80	HBsAg	Nil	Bilobed, Lt portal vein invasion and thrombosis	7
10	M/72	HBsAg	PEI	Bilobed	2
11	M/36	HBsAg	Rt segmentectomy	Rt lobe, tumour thrombus within IVC	5

* HBsAg denotes hepatitis B surface antibody–positive, HCVAb hepatitis C antibody–positive, PEI percutaneous ethanol injection, RFA radiofrequency ablation, IVC inferior vena cava, Rt right, and Lt left

Results

There were 15 arteriovenous shunts in 11 patients. Seventeen shunt embolisations were performed. There were 10 men and one woman ranging from 36 to 80 (mean, 58) years. Most of them were hepatitis B surface antigen–positive. Some of them had had previous surgery or interventions such as radiofrequency ablation (RFA) and percutaneous ethanol injections. Most of them presented with multifocal HCC, and the size of their maximal individual tumours ranged from 2 to 10 cm (Table 1).

Among the 15 arteriovenous shunts, nine were APVS (60%) and the other six were AHVS. Using our classification, 13 of the shunts were complex, with multiple feeders and draining veins. Two were simple shunts related to previous RFA and needle biopsies. The embolic agents used include absolute ethanol (n=11), PVA particles (n=1), histoacryl (n=1), and coils (n=2). The amount of absolute ethanol injected ranged from 2.5 to 17.5 mL per embolisation.

The two simple shunts were completely occluded by coils as demonstrated by immediate post-embolisation angiograms. Each shunt required two coils for embolisation. In patient 1, two coils (VortX-10 diamond-shaped fibred platinum coil [2 mm/4 mm, 41 mm long]; Boston Scientific, Cork, Ireland) were used. In patient 7, two liquid coils (2.5 mm x 20 cm; 5 mm x 15 mm; Berenstein; Target Therapeutics/Boston Scientific, Fremont [CA], US) were used. Of the 13 complex shunts, 10 were partially occluded by 80% or more as demonstrated by immediate angiograms. The other three complex shunts were occluded by less than 80%. These shunts occurred in two patients (patients 5 and 9). Therefore, the immediate technical success rate was 80.0% (Table 2).

Subsequent TACEs were successfully performed in eight patients without complications. The number of TACE sessions each received ranged from 1 to 20 (Table 3). One shunt (patient 5) could not be optimally controlled and was complicated by mild acute pancreatitis. Therefore, TACE was not given. One patient (patient 11) proceeded to external radiotherapy of his liver because he was found to have tumour thrombus in his inferior vena cava, and one patient (patient 8) proceeded to left hepatectomy, a procedure planned during his initial assessment, after satisfactory shunt control by embolisation. The patients were followed up for 2 to 39 months (mean, 15.5 months) after their first embolisation. Six had tumour progression and deteriorating liver function or general condition rendering them unsuitable for TACE. Six patients had died by the time this article was written.

Complications

There was one minor complication. One of our patients (patient 5) suffered from mild acute pancreatitis diagnosed by detection of a raised amylase level (6332 IU/L) 6 weeks after TACE, during routine follow-up in the out-patient clinic. He had mild intermittent abdominal pain and required no hospitalisation. A CT scan of his abdomen showed an oedematous pancreas. His amylase level returned to normal 4 months after embolisation. There were no major complications during this study.

TABLE 2. Embolisation of arteriovenous shunt and occlusion results*

Patient No.	Shunt				Embolic agent	No. of sessions of embolisation	Immediate angiogram occlusion	Shunt in follow-up angiogram
	Nature/type (simple [S] or complex [C])	Related mechanism	Site (lobe)	Major feeding artery				
1	APVS/S	Post-RFA	Right	RHA	Coils	1	Completed	Absent
2	APVS/C	Post-RFA	Right	RHA	Histoacryl	1	>80%, near complete	Absent
3	APVS/C	HCC	Left	LHA	PVA particles	1	>80%, near complete	Absent
4	AHVS/C	HCC	Right	RHA	Histoacryl	1	>80%, near complete	Minimal residual shunt
5	APVS/C	HCC	Right	CHA	Ethanol	1	<80%	NA†; significant shunt in follow-up CT
	APVS/C	Post-resection (left hepatectomy)	At resection margin	LGA	Ethanol	1	<80%	NA†; significant shunt in follow-up CT
6	APVS/C	Post-biopsy	Right	RHA	Ethanol	3	>80%, near complete	Minimal residual shunt
7	AHVS/C	HCC	Right	RHA	Histoacryl	1	>80%, near complete	Minimal residual shunt
	AHVS/S	Post-biopsy	Right	RIPA	Coils	1	Completed	Absent
8	APVS/C	HCC	Left	LHA	Ethanol	1	>80%, near complete	Minimal residual shunt
9	AHVS/C	HCC	Right	RHA	Ethanol	1	>80%, near complete	Minimal residual shunt
	AHVS/C	HCC	Left	LHA	Ethanol	1	>80%, near complete	Minimal residual shunt
	APVS/C	HCC	Left	LHA	Ethanol	1	<80%	Extensive shunt, more severe than initial presentation
10	APVS/C	HCC	Right	RHA	Ethanol	1	>80%, near complete	Absent
11	AHVS/C	HCC	Right	RHA	Ethanol	1	>80%, near complete	NA†; minimal residual shunt in follow-up CT

* AHVS denotes arteriohepatic venous shunt, APVS arterioportal venous shunt, CHA common hepatic artery, CT computed tomography, HCC hepatocellular carcinoma, LGA left gastric artery, LHA left hepatic artery, PVA polyvinyl alcohol (Ivalon 350-500 contour emboli; Boston Scientific), RFA radiofrequency ablation, RHA right hepatic artery, and RIPA right inferior phrenic artery

† Not available as a follow-up angiogram was not performed; follow-up computed tomography of the liver was performed

TABLE 3. Follow-up and clinical outcomes

Patient No.	Follow-up interval (months)	Post-embolisation transarterial chemoembolisation (No. of sessions)	Outcome (death or still alive)	Current condition details
1	39	20	Death	-
2	13	3	Alive	No viable tumour in follow-up computed tomography
3	14	1	Death	-
4	9	1	Death	-
5	14	0	Alive	Persistent shunt detected in follow-up computed tomography
6	24	16	Death	-
7	31	3	Death	-
8	11	0	Alive	Proceeded to left hepatectomy after shunt embolisation; no viable tumour in follow-up computed tomography
9	5	2	Death	-
10	8	4	Alive	Repeated episodes of tumour recurrence
11	2	0	Alive	Proceeded to external radiotherapy of liver

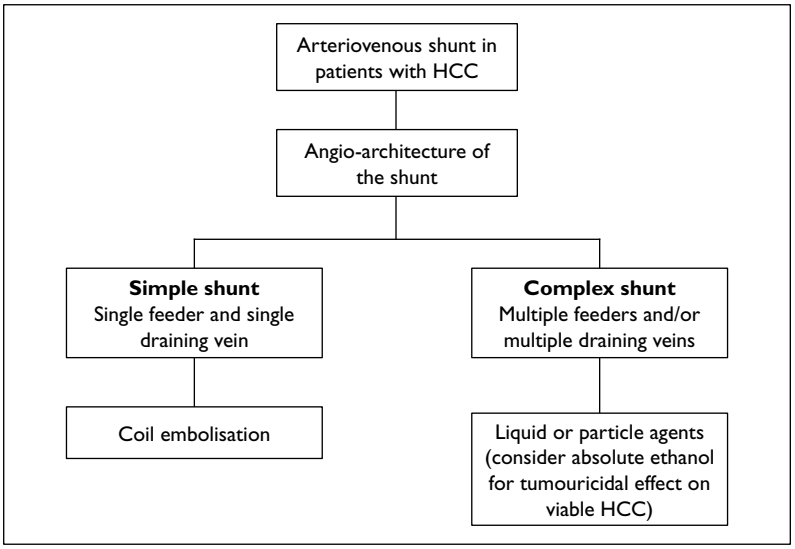

FIG 1. Management of arteriovenous shunts in patients with hepatocellular carcinoma (HCC)—flowchart showing strategy used for the choice of embolic agent

Discussion

Arteriovenous shunts have been reported in HCC, haemangiomas,[21,22] chronic liver disease,[23] metastases, hepatic trauma, after liver biopsies,[24] RFA, and after hepatic surgery. Shunt embolisation was first used to control haemobilia.[15] With wider use of TACE to manage patients with HCC, arteriovenous shunts pose risks during TACE. Furthermore, the presence of an arteriovenous shunt is a poor prognostic factor in patients with HCC.[16,19]

A wide variety of agents have been used for shunt embolisation in patients with HCC and arteriovenous shunts, in particular gelatin sponges and coils or a combination of both agents.[16-19] The effectiveness of the embolic agent, the shunt recanalisation rates, patient tolerance, and the potential risks have varied. We believe the choice of embolic agent should be based on its embolisation properties. We also believe that angio-architecture of the shunt and its underlying mechanism should be taken into account when choosing an embolic agent (Fig 1).

We could find no quantitative system for assessing the degree of occlusion of an arteriovenous liver shunt after embolisation in the literature. In this study, we tried to categorise the occlusion in a semi-quantitative way. We designated 80% occlusion as technical success for several reasons. First, complete occlusion may not be possible immediately after embolisation, depending on the action of the embolic agent. Second, differentiating between complete occlusion and a high level of occlusion may not be practicable if based on angiographic images. Third, experience with embolisation of extrahepatic arteriovenous shunts indicates that a shunt that appears highly occluded in the immediate post-embolisation angiogram is likely to proceed to complete occlusion due to progressive formation of thrombus in a markedly narrowed blood vessel with sluggish blood flow. Therefore, shunts that were categorised as 80% occluded were likely to progress to complete occlusion.

Gelatin sponge can be resorbed within 2 to 4 weeks, the recanalisation rate should be high. Use of gelfoam to occlude arterioportal shunts achieved a reported 64% occlusion rate after initial treatment, with a recanalisation rate 1 month after embolisation of 83%, and a complete occlusion rate of 18%.[16] We did not use gelfoam for shunt embolisation because of its relatively temporary effect.

Coils have been used to embolise arterioportal shunts in patients with HCC and portal vein thrombosis. One study showed complete resolution of the arterioportal shunts in 10 patients by using steel coils; 10 or more coils were used in two patients.[17] We did not know what type of shunts the patients in this study had, but one would argue that it may not be feasible to embolise a shunt with coils if the shunt has multiple minute feeders. First, it may not be possible to reach each feeder because of the small size, difficult access and distal location. This leads inadvertently more proximal embolisation. Second, shunts with multiple feeders are prone to recanalisation, either by other feeders or by developing collaterals. Therefore, we suggest using coils in simple shunts but not in complex shunts.

Simple shunts may be caused by a previous liver biopsy or RFA. The needle punctures cause direct communication between the arterial and venous circulations. A simple shunt has a single arterial feeder and single draining vein, and is essentially an arteriovenous fistula. Superselective cannulation of the single corresponding feeder and permanent occlusion with coils is feasible. In this circumstance, coils are easier to use and less likely to cause inadvertent embolisation than liquid agents. We suggest using coils in simple shunts (Fig 2).

However, most shunts are of the complex type with multiple arterial feeders and/or draining veins. They are related to tumour, cirrhosis or previous surgery. In HCC, there are several mechanisms that lead to the formation of shunts. One is the trans-sinusoidal route, which is thought to occur in cirrhosis.[13,25] In this route, there is flow from the hepatic artery to the hepatic sinusoids and then retrograde flow into branches of the portal vein because of high flow resistance in hepatic venules. Another route is the transvasal route particularly where there is portal vein thrombosis. Tumour thrombi are hypervascular and are supplied by vasa vasorum of the portal vein wall, thus blood may pass through the thrombi to the portal vein and form APVS. Alternatively, a tumour

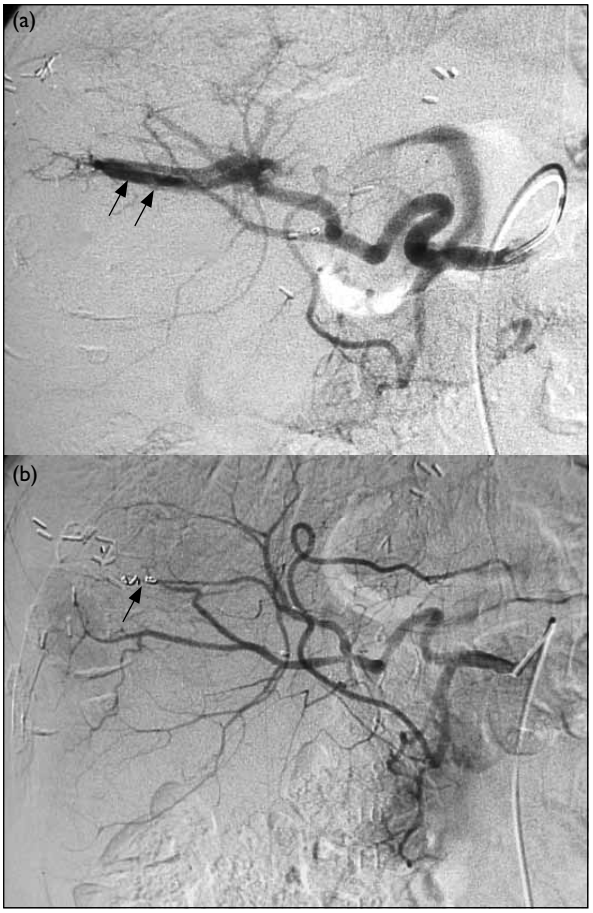

FIG 2. (a) Right hepatic artery angiogram shows simple-type arterioportal venous shunt (arrows) with the right hepatic artery being the single feeding artery. (b) Post-embolisation angiogram shows complete occlusion of the shunt by multiple coils (arrow)

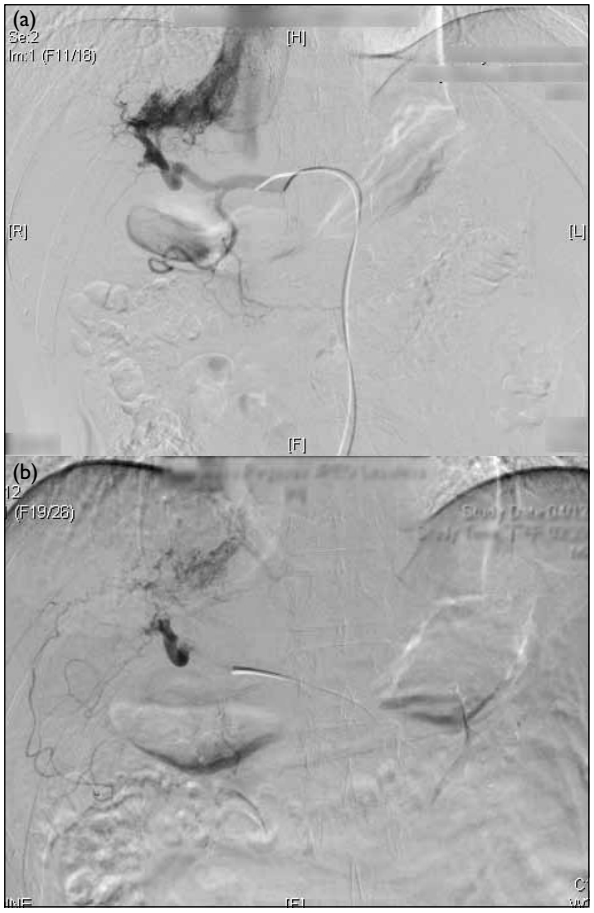

FIG 3. (a) Right hepatic artery angiogram shows a complex-type arteriohepatic venous shunt between the right hepatic artery and the right hepatic vein. (b) Post-embolisation angiogram shows that most of the shunt has been occluded after embolisation with absolute ethanol

may directly invade the portal venous system early and form a shunt.

In complex shunts, obliterating one of the feeders without managing the others will alter the haemodynamic flow, eventually leading to early recurrence of the shunt and further recruitment of new collaterals. Therefore, we suggest using liquid or particle agents to occlude all the feeders, in order to abolish the shunts (Fig 3).

In this study, PVA particles were used in one patient and histoacryl in one other. These cases were among the earliest in our study period. Therefore, we cannot use our experience to draw any conclusions on the value of PVA particles and histoacryl. Nonetheless, other authors have reported on the use of PVA particles for shunt embolisation and one study described improvement in 60% of arterioportal shunts.[19] Polyvinyl alcohol is not absorbable and thus is potentially able to produce more permanent occlusion because recanalisation is more difficult when compared with gelatin sponge. Different sizes of PVA particles are available in commercial package and the size of 355 to 500 μm and 500 to 710 μm PVA particles were more commonly used. Larger particles may be used in extensive shunts.[19] Histoacryl was used in one of our patients based on our experience in embolisation of intracranial arteriovenous fistulae. Histoacryl has the unfavourable property of rapid polymerisation upon contact with ionic fluid such as blood or vascular endothelium. This poses difficulties in preparation of the appropriate proportion of the mixture, restricted injection time, and necessity of rapid withdrawal of the catheter after injection. Therefore, we do not favour its use than other embolic agents but it was reported to be effective in embolisation of arterial venous fistula in HCC.[26]

Ethanol is a liquid agent that denudes the endothelium by denaturing proteins to cause immediate embolisation. It is a potent sclerosing agent with long-term effects. Development of collaterals after embolisation with ethanol is uncommon and the rate of shunt recanalisation is

much lower than that seen with gelatin sponges.[16] It achieved a complete occlusion rate of 83% in one study.[16] Apart from its embolisation effect, it has a tumouricidal effect thus in patients with viable HCC, absolute ethanol injection may help to reduce the tumour load.[27]

Intra-arterial injection of absolute ethanol, however, carries some risks. First, patients may experience abdominal pain during ethanol injection. Second, ethanol is a liquid agent and its flow and action depend on the blood flow and the rate and amount of ethanol injected. Ideally, absolute ethanol acts at the level of the shunt without damaging adjacent arteries and veins, but if the injection volume or rate is too high or the blood flow is too slow, a high concentration of ethanol may act too proximal or distal to the shunt. Therefore, it is necessary to inject an incremental, small volume of ethanol each time. In our study, we gave multiple intermittent ethanol injections slowly and gently at the rate of about 1 mL/min. A repeated angiogram was performed to evaluate the extent of shunt occlusion. If significant persistence of the shunt was seen, additional ethanol was injected, repeatedly, in the same way. Therefore, absolute ethanol embolisation may be more technically demanding and has its potential risks.

After effective shunt embolisation, TACE can be performed. However, if embolisation at the shunt level has not been achieved or a shunt arises from a dominant tumour-supplying artery, inadvertent embolisation of the tumour-supplying artery or embolisation distal to the level of the shunt is possible. Embolisation that is too proximal might occlude the tumour-supplying artery and thus may abolish the only arterial access for TACE. If the embolisation is distal to the shunt level, it may enter the portal venous system in APVS and cause portal vein thrombosis. Both conditions are devastating and could impair the patient's hepatic function. Since shunt embolisation is a dynamic event depending on shunt size, velocity, location, angio-architecture and the actions of each particular embolic agent, thorough knowledge and experience are needed when using each type for shunt embolisation.

Use of external radiotherapy for shunt obliteration after gelfoam embolisation has recently been reported. The total response rate, including partial and complete obliteration, was 25%.[28] The response was delayed and it may take 2 to 3 months for complete shunt obliteration to occur after radiotherapy. The low response rate and delayed effects suggest that TACE may be further delayed in these patients. Therefore, endovascular embolisation remains the treatment of choice for arteriovenous shunts in patients with HCC. Endovascular embolisation of arteriovenous shunts is feasible. We hope the introduction of our management flowchart will help other practitioners perform the procedure safely and practically in a clinical setting.

Conclusion

Different embolic agents proved to be feasible for embolising arteriovenous liver shunts. The choice of embolic agent should be based on the underlying mechanism of the shunts and their angio-architecture.

Declaration

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