Clinical Radiology 74 (2019) 975.e11–975.e16

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Transarterial embolisation with bleomycin and N-butyl-2-cyanoacrylate –Lipiodol mixture for symptomatic polycystic liver disease: preliminary experience

J.Y. Yan, J.L. Zhang, K. Yuan, J.X. Fu, Y. Wang, B. Yuan, M.Q. Wang*

Department of Interventional Radiology, The First Medicine Center of Chinese PLA General Hospital, Beijing 100853, China

ARTICLE INFORMATION

Article history:
Received 4 June 2019
Accepted 20 August 2019

AIMS: To evaluate the therapeutic effect and safety of transarterial embolisation using a bleomycin–Lipiodol mixture and N-butyl-2-cyanoacrylate (NBCA)–Lipiodol mixture (BNL) for the treatment of polycystic liver disease (PLD).

MATERIALS AND METHODS: From June 2012 to July 2018, a total of consecutive 14 symptomatic patients (13 women and 1 man; mean age, 49.3±9.9 years) with PLD were referred and underwent transcatheter arterial embolisation (TAE) with BNL.

RESULTS: Technical success was achieved in all cases. PLD-related severe symptoms were improved remarkably in 13 of the treated patients. The mean maximum abdominal circumference decreased significantly from 100.6±9.4 to 94.9±9.1 cm ($p<0.01$). The total liver volume decreased significantly compared with pre-TAE in 13 patients at 6–12 months after TAE. It decreased from 9,776±2,219 to 8,303±2,009 cm^3 ($p<0.01$). There were no major complications associated with the procedure.

CONCLUSION: TAE with the bleomycin–Lipiodol mixture and NBCA–Lipiodol mixture may be an effective method for treating symptomatic PLD patients, with improvement of symptoms and shrinkage of cyst volume.

Introduction

Polycystic liver disease (PLD) occurs in the setting of two distinct hereditary disorders, either as a primary presentation of autosomal dominant PLD (ADPLD), or associated with polycystic kidneys in autosomal dominant polycystic disease (ADPKD).[1] Most PLD patients are asymptomatic and need no treatment; however, approximately 10–20% of PLD patients have moderate to severe symptoms.[2] Symptoms are typically caused by massive hepatomegaly leading to abdominal distension, pain, early satiety, gastroesophageal reflux, malnutrition, ascites, and dyspnoea in some patients. In severe PLD, mass effects can induce hepatic venous outflow obstruction, and compression of the inferior vena cava (IVC) and bile duct.[3] So these patients may need treatment to abrogate symptoms and/or improve quality of life by reducing the liver volume.

The typical therapeutic schedules for symptomatic PLD including medical management, percutaneous

* Guarantor and correspondent: M. Q. Wang. Tel.: +86 13910531926; fax: +86 10 66936327.
E-mail address: wangmq@vip.sina.com (M.Q. Wang).

https://doi.org/10.1016/j.crad.2019.08.009

sclerotherapy, surgical cyst fenestration, partial hepatectomy, as well as liver transplantation[4,5]; however, until now there are no unified criteria for therapeutic schedules, because each has its own advantages and limitations. Transcatheter arterial embolisation (TAE) was first introduced in 2001 by Ubara in Japan,[6] and this technique has been certified to improve both hepatic volume and nutrition.[7] The theoretical basis is that hepatic cysts in PLD patients are mostly supplied by hepatic arteries rather than portal veins, and TAE of the hepatic artery branches supplying major hepatic cysts can shrink the cysts and liver size.[6,8]

Bleomycin is a well-known cytotoxic agent in the systemic treatment of various types of cancer. In addition, it has a sclerosing effect on endothelial cells with a non-specific inflammatory reaction.[9] Bleomycin has been used in the treatment of symptomatic hepatic haemangioma[10] and focal nodular hyperplasia[11] as a vascular endothelial sclerosing agent during TAE. This has been demonstrated to be safe and efficient with good long-term symptomatic control and reduction in lesion size. Inspired by this, the present study was undertaken to investigate embolisation effect of the micro arteries supplying cysts using a bleomycin–Lipiodol mixture and N-butyl-2-cyanoacrylate (NBCA)–Lipiodol mixture (BNL). The present study reports the results of 14 consecutive patients, who underwent embolisation with BNL for symptomatic PLD at a single centre.

Materials and methods

Patient population

This retrospective study was approved by the ethics committee of the hospital. The procedures of TAE were explained, and written informed consent for embolisation was obtained from each patient or their guardians. From June 2012 to July 2018, a total of consecutive 14 symptomatic patients (13 female, 92.9%; one man, 7.1%) with PLD were referred and underwent hepatic TAE. The average patient age at admission was 49.3±9.9 years (range 36–68 years). The diagnosis of PLD was established using computed tomography (CT) or magnetic resonance imaging (MRI) with Ravine's revised unified diagnostic criteria.[12] All patients had concomitant polycystic kidney disease.

Patient inclusion criteria were as follows: (a) patients with severe compression symptoms, such as abdominal distention, pain, early satiety leading to malnutrition, dyspnoea, not relieved with medical treatment; but they must had at least one segment almost intact, maintaining functioning liver parenchyma; (b) not candidates for surgery (or had declined other interventions); (c) patients who had severe psychological stress because of bulging of the abdomen and had a strong desire for therapy were also included.

Patient exclusion criteria were severely decreased liver function (i.e., aspartate aminotransferase [AST] or alanine aminotransferase [ALT] >80 IU/l, total bilirubin > 50 μmol/l), serum creatinine >120 μmol/l, allergic to contrast media, moderate–massive ascites, liver cyst infection, or other systemic infection.

Treatment protocol

All the procedures were performed by two senior interventional radiologists. TAE was performed under sterile conditions. All patients underwent interventions in a therapeutic angiography suite (INNOVA 4100 IQ; GE Healthcare, Milwaukee, WI, USA). Intervention was performed under local anaesthesia via a unilateral femoral approach. A 4 F hepatic artery catheter (Radifocus, Terumo, Japan) was advanced to catheterise the coeliac and superior mesenteric artery. Selective digital subtraction angiography with non-ionic contrast agent (Visipaque 320 mg iodine/ml; GE Healthcare, USA) was performed to visualise the blood supplying to the cysts and assess the patency of the portal vein. Super-selective angiography of the branches feeding the cysts was selectively catheterised by using a 2.6 F microcatheter (Progreat, Terumo).

Subsequently, bleomycin-iodinated oil mixture (including 15 mg bleomycin hydrochloride [Hisun Pfizer, China] mixed with 10 ml iodinated oil [Lipiodol, Laboratoire Guerbet, Roissy, France]) was injected through the microcatheter until the mixture had accumulated thickly at the target peripheral vessels. The dosage of iodinated oil used varied depending on the number and size of the cysts and patient's weight. Then a mixture of NBCA (Histoacryl-Blue; Braun, Melsungen, Germany) and Lipiodol in a ratio of 1:4 was injected to occlude the sub-segmental hepatic arteries supplying the cysts. Before the injection of this mixture, the microcatheter was immediately flushed with a 2–3 ml of 50% dextrose water solution to prevent the contact of NBCA and the blood in the lumen of the microcatheter.[13] The extrahepatic collaterals (i.e., the internal thoracic artery, the inferior phrenic artery, and the omental artery) supplying the hepatic cystic lesions were also embolised using polyvinyl alcohol (PVA) particles (300–500 μm; PVA foam embolisation particles, Cook, Bloomington, IN, USA) if necessary. Embolisation was performed until final arteriography demonstrated no further filling of the lesion.

Post-procedural management

The patients stayed in the hospital for 3–5 days after TAE for observation and then were discharged if with no complications. Appropriate hydration was administered for 2–3 days after TAE. Non-opioid analgesics and anti-emetics were given during and after TAE if needed.

Follow-up protocol and data collection

The subjective symptoms after TAE were recorded. Patients were followed up until loss contact, death, or 30 October 2018. All patients underwent follow-up CT or MRI at every 3 months during the first year and every 6 months thereafter. The abdominal circumferences and laboratory data, including hepatic function (e.g., ALT, AST, alkaline phosphatase [ALP], γ-glutamyl transferase), complete blood

cell count, carbohydrate antigen 19-9 (CA19-9) were recorded before TAE, on day 3 after the procedure, and during the follow-up period. When abdominal imaging was complete, images of the portal vein phase were loaded into a post-processing workstation (AW 4.7, GE Healthcare). The total liver volume, intrahepatic cyst volume, and parenchyma volume (total liver volume minus cyst volume) was depicted and measured using a volume-rendering three-dimensional imaging technique by two senior radiologists (blinded for review).

Outcome parameters

TAE was considered technically successful when the target hepatic arteries were fully embolised, as demonstrated by hepatic arterial angiography performed at completion of the procedure. Clinical assessment was judged by the patient subjective evaluation. Clinical success was defined as resolution of PLD-related symptoms (such as abdominal distention, pain, and dyspnoea) after the interventional procedure and no invasive therapies were required after the procedure.

Statistical analysis

Categorical data were expressed as the number and percentage. Continuous data were expressed as mean ± standard deviation (SD), and compared using Student's *t*-test when appropriate. Statistical analysis was performed using statistical software SPSS 22.0 (SPSS, Chicago, IL, USA). Significance was established as p-values <0.05.

Results

Patients

All patients included were symptomatic. Abdominal distension was the most common symptom in 12 (85.7%) of 14 patients. Before TAE, seven (50%) of 14 patients received percutaneous cyst aspiration, but all of them had symptomatic recurrence and the symptoms became more serious than before. The patients' characteristics are shown in Table 1.

Technical success

Technical success rate was 100% (14/14). TAE was performed only once in all the patients. The mean dose of bleomycin used was 9±2 mg and the mean amount of NBCA used for TAE was 0.5±0.2 ml. During the interventional procedure, the extrahepatic arteries supplying the cystic lesions were observed in 12 patients (85.7%). In total, 17 collateral vessels that feed the cysts were demonstrated on digital subtraction angiography, including the inferior phrenic artery (n=12), internal thoracic artery (n=2), intercostal artery (n=2), left gastric artery (n=1). All the collateral vessels were successfully embolised.

Table 1
Baseline characteristics of the included patients before treatment.

Characteristics	Before treatment
Sex	
Female	13 (92.9)
Male	1 (7.1)
Age	48.6±7.6 (37–68)[a]
Symptoms	
Abdominal distention	14 (100)
Early satiety	5 (35.7)
Pain	4 (28.6)
Dyspnoea	3 (21.4)
Abdominal circumference (cm)	100.6±9.4 (86–121.0)[a]
Proportion of cysts in the liver[b]	0.859±0.060 (0.767–0.927)[a]
Previous treatment: cyst aspiration	7 (50)
Laboratory values	
WBC count, 10^9/l	4.80±1.95 (1.79–8.95)[a]
Platelet count, 10^9/l	177±78 (81–324)[a]
Haemoglobin, g/dl	116±17 (80–142)[a]
Aspartate aminotransferase, IU/l	21.7±5.0 (14–33.1)[a]
Alanine aminotransferase, IU/l	18.5±7.5 (8.9–31.1)[a]
Total bilirubin, μmol/l	15.2±4.9 (8.2–26.4)[a]
Albumin, g/l	41.4±2.8 (35.9–46.1)[a]
Alkaline phosphatase, U/l	89.5±44.9 (41.8–179.1)[a]
γ-Glutamyl transferase, U/l	92.0±70.6 (36.5–249.1)
Creatinine, μmol/l	69.2±12.9 (51.3–88.2)[a]
CA19-9, U/ml	
0.1–37	8 (57.1)
>37	6 (42.9)

Data are shown as n (%).
[a] Data are the mean ± standard deviation, with the range in parentheses.
[b] Data are calculated from CT or MRI. SD: Standard deviation.

Clinical outcome

Mean length of hospital stay was 6.5±2 days (range 5–9 days). After the procedure, all the 14 patients had mild to severe post-embolisation syndrome characterised by abdominal pain, nausea, abdominal distension, loss of appetite, or pyrexia. These symptoms were transient and self-limited. Transient impairment of liver function was found in seven patients, in whom liver transaminase level increased to twice or triple of the normal baseline value on day 3 after the procedure, but the liver function returned to normal within 2 weeks in all patients.

No major complication related to TAE was found. Major complications related to bleomycin, such as sclerosing cholangitis, interstitial pneumonia, or pulmonary fibrosis were not noted in this study. No severe complications associated with the treatment protocol were noted.

Initial follow-up was achieved in all the 14 patients 3–9 months after embolisation. The mean follow up period was 27±17 months (range 6–60 months). No significant improvements were shown immediately after TAE. During the follow-up of 3–7 months, the PLD-related symptoms (i.e., abdominal distention, pain, dyspnoea) notably improved in 13 (92.9%) of the patients. No recurrent symptoms were reported during the follow-up. Of these patients, the mean maximum abdominal circumference decreased significantly from 100.6±9.4 cm (86–121 cm) to 94.9±9.1 cm (81–116 cm; $p<0.01$). TAE failed to benefit one patient: the PLD-related symptoms were the same as before without the symptoms worsening after the procedure.

Total liver volume before TAE was 9,776±2,219 cm^3 (range 4,150–12,900 cm^3), representing marked hepatomegaly. At follow-up CT or MRI, the total liver volume showed no statistically significant differences between baseline and at 3 months ($p>0.1$). At 6–12 month follow-up, the volumes of liver cysts and total liver decreased significantly ($p<0.01$); the volumes of liver parenchyma increased significantly compared to pre-TAE ($p<0.01$; Fig 1, Table 2). Of these patients, eight cases were followed >20 months: three patients had further decrease in the volume of hepatic cysts (Fig 2) and five patients had no significant changes in the total intrahepatic cyst volume compared with those at 12 months after TAE.

One patient presented a poor treatment response. From immediately after TAE to the 12 months follow-up, the total liver volume and total intra-hepatic cyst volume showed no statistically significant change ($p=0.6$), but the patient did not show significantly increased intra-hepatic cyst volume during follow-up.

Discussion

As reported before,[13] hepatic arterial branches supplying the cysts are stiff and stretched, and this may because of the compression and traction by the cysts. Therefore, appropriate embolic material is needed to completely occlude these tiny arteries. Hoshino *et al.*[7] used platinum microcoils as the embolic material. This material has been certified safe, but the mean percentages of liver volume reduction rates compared with pretreatment at 6 and 12 months were 5.3% and 9.2%, respectively. The clinical efficiency rate is not high enough and the cost is high. Park *et al.*[14] used PVA particles and micro-coils as the embolic material; however, immediate post-embolisation syndrome (such as fever, epigastric pain, and nausea) was severe enough to stop them from recruiting more patients. Wang *et al.*[13] reported super-selective hepatic artery embolisation by using a pilot embolic material (a mixture of NBCA and iodised oil), which is different from previous reports for symptomatic PLD

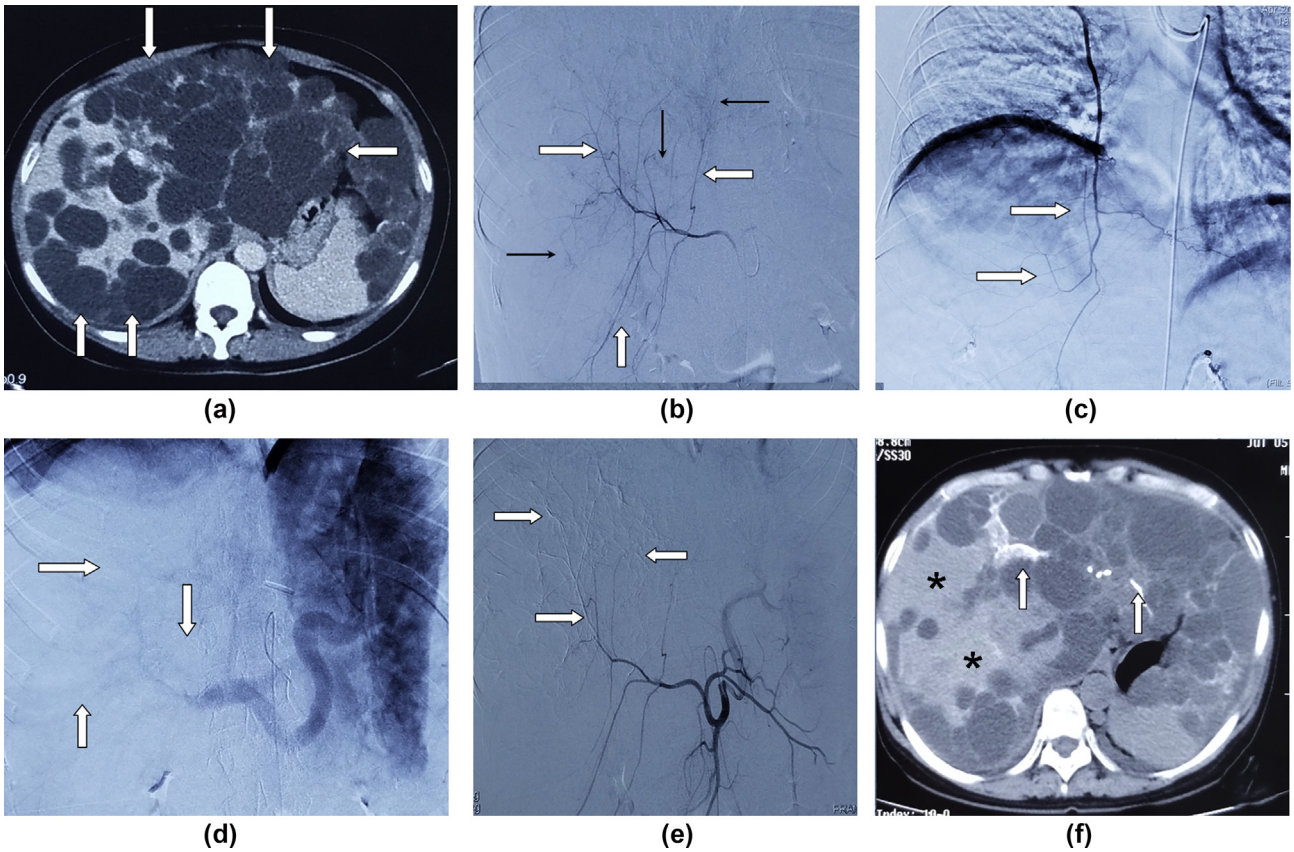

Figure 1 A 36-year-old female PLD patient presented with severe abdominal distention. (a) CT before the procedure demonstrates obviously hepatomegaly and almost the entire liver parenchyma is replaced by multiple cysts (arrows). (b) Coeliac arterial angiography before TAE shows that the right and left hepatic arterial branches are stretched (white arrows), representing cystic regions. The liver lobes were occupied by multiple cysts (black arrows). (c) Selective right internal thoracic artery angiography before TAE shows multiple small branches supplying the cysts in the right liver lobe (arrows). (d) Pre-TAE, portal venography at the late phase of superior mesenteric artery angiography shows that the right portal vein branches are obstructed (arrows), which correspond to the right hepatic region replaced by multiple cysts. (e) Coeliac arteriography post-TAE shows the multiple linear branches obstructed by the mixture of NBL (arrows). (f) CT image at the same level obtained at 6 months after TAE, shows the iodised oil deposited in the cystic regions (arrows) and marked decrease in the intra-hepatic cyst volume and increased hepatic parenchyma volume (asterisks).

Table 2
Changes in the hepatic cysts, liver parenchyma, and liver volumes (cm^3) before and after TAE.

Parameters	Total liver volume (cm^3)	Total intra-hepatic cyst volume (cm^3)	Total parenchymal volume (cm^3)
Pre-TAE	9,776±2,219 (4,150–12,900)	8,486±2,394 (3,270–10,800)	1,290±4,170 (880–2,100)
3 months post-TAE	9,769±2,208[b] (4,130–12,640)	8,426±2,377[a] (3,240–10,520)	1,349±4,027[a] (890–2,120)
6–12 months post-TAE	8,303±2,009[a] (4,080–12,360)	6,846±2,163[a] (3,170–10,230)	1,457±4,155[a] (910–2,130)

Data are the mean ± standard deviation, with the range in parentheses.
TAE, transcatheter arterial embolisation.
[a] Compared to pre-PAE $p<0.01$.
[b] Compared to pre-PAE $p>0.05$.

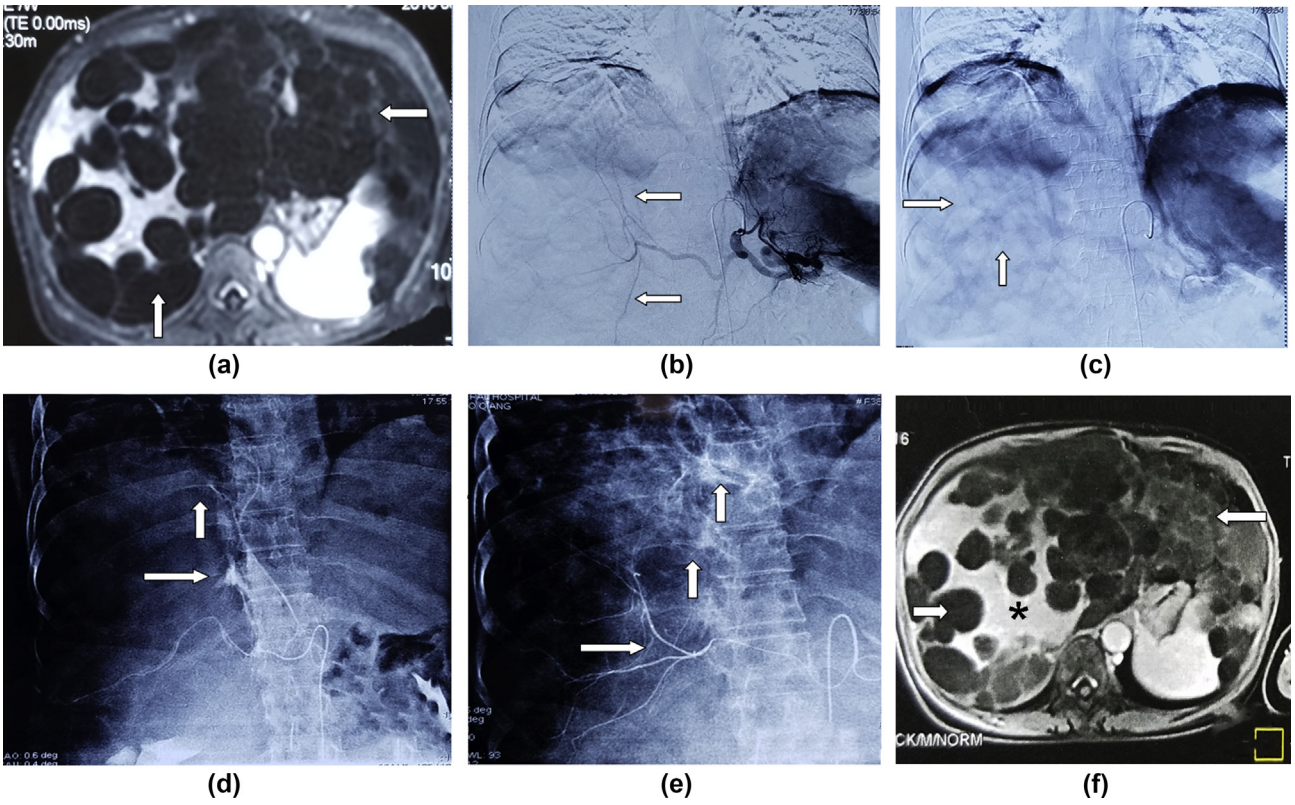

Figure 2 A 55-year-old female PLD patient presented with severe abdominal distention and loss of appetite. (a) Preprocedural portal phase MRI demonstrates obviously hepatomegaly and almost the entire liver lobe is replaced by multiple cysts (arrows). (b) Coeliac arterial angiography before TAE shows that the right hepatic arterial branches are stiff and stretched (arrows). (c) Indirect portal venography obtained at the late phase of superior mesenteric artery angiography shows that the portal vein branches in the cystic regions (arrows) are obstructed. (d,e) Fluoroscopy with spot film shows super-selective injection of the mixture of NBL in the inferior phrenic artery and hepatic artery branches supplying the cystic regions (arrows). (f) MRI image at the same level as in (a), obtained at 36 months after TAE, shows obviously reduction of the cysts (arrows), and the normal hepatic parenchyma is markedly expanded (asterisks).

patients and concluded this is an acceptable embolic agent. More than 2-years follow-up by Zhang *et al.*,[15] certified that the NBCA–Lipiodol mixture (NL) for PLD appears to be a safe and effective embolic material. The mean liver cystic volume reduction rates compared with pre-TAE were 23% at 6 months, 36% at 12 months, 37% at 24 months, and 38% at 36 months after TAE. The clinical outcome is better, but there is one limitation that only the mixture of NBCA and iodised oil was used and they did not use the other embolic materials.

Bleomycin was first used as an anti-tumour agent that inhibits DNA synthesis, but it was soon discovered that this drug also has a sclerosing effect on endothelial cells with a non-specific infiammatory reaction.[9] Now bleomycin has been widely used as a sclerosing agent in the treatment of vascular malformation and haemangiomas. Apart from this, scanning electron microscopy of PLD confirmed that villous change of the cyst epithelium may be closely associated with largest cyst volume via the proliferation of cyst lining cells in PLD.[16] Inspired by this, the embolic materials were improved by using BNL. In PLD treatment, bleomycin is acting as a local sclerosing effect on the vascular endothelium inducing secondary formation of intraluminal microthrombi and resulting in the destruction of the feeding arteries of the cysts.[9,11] The combination of bleomycin may be more conducive to occlude the smaller branches of the

hepatic artery. In the present study, the total intra-hepatic cyst volume decreased from 8,486±2,394 to 6,846±2,163 cm^3 and the total parenchymal volume increased from 1,290±4,170 to 1,457±4,155 cm^3 6–12 months after TAE. The results seem to be better than previous reports.

TAE using the mixture of BNL for patients with symptomatic PLD is also a safe treatment option. At 6–60 months follow-up, PLD-related symptoms were improved remarkably in 92.9% of the patients. The most concerning complications related to bleomycin are pulmonary fibrosis, sclerosing cholangitis, or interstitial pneumonia, but these occur more commonly with total doses >450 mg via intravenous usage.[17] The dose of bleomycin used in the present study was 9±2 mg, which was much lower than the toxicity level. The potential side effects of bleomycin were not noted in the present study. Other side effects, such as transient impairment of liver function, were found in all patients, in whom the liver transaminase level increased to twice or triple the normal baseline value on day 3 after the procedure, but levels returned to normal in 2 weeks in all patients.

Another phenomenon worth attention is that 45% of patients might have elevated serum tumour marker CA19-9 without proof of malignancy.[18] In the present study, a high level of CA19-9 was seen in 42.9% of patients, and the numerus even up to 421.8 U/ml. This is due to the production and secretion of the compound by local cyst epithelia and its leakage into the circulation,[19] so unnecessary tests should be dismissed in the PLD patients.

There are three limitations in the present study. First, few patients were enrolled and this may due to the strict inclusion criteria and this is only a single centre study. A larger sample of patients is needed. Second, only the mixture of BNL was used and other embolic materials were not used (i.e., NL only, microcoils, particles) as a control. Third, the number of patients followed and the duration of follow-up were not uniform or standardised.

In conclusion, TAE with the bleomycin–Lipiodol mixture and NBCA–Lipiodol mixture may be considered as an effective and minimally invasive method for the treatment of symptomatic PLD patients, with improvement of symptoms and shrinkage of cysts volume.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (grant number 81801801), the Miao Pu Scientific Foundation of Chinese PLA General Hospital (grant number 16KMM11), and the Chinese PLA Scientific Foundation of the Twelve-Five Program (grant number BWS11J028).

References

1. Gevers TJ, Drenth JP. Diagnosis and management of polycystic liver disease. *Nat Rev Gastroenterol Hepatol* 2013;**10**(2):101–8.
2. Bistritz L, Tamboli C, Bigam D, *et al*. Polycystic liver disease: experience at a teaching hospital. *Am J Gastroenterol* 2005;**100**:2212–7.
3. Yang J, Ryu H, Han M, *et al*. Comparison of volume-reductive therapies for massive polycystic liver disease in autosomal dominant polycystic kidney disease. *Hepatol Res* 2016;**46**:183–91.
4. van Aerts RMM, van de Laarschot LFM, Banales JM, *et al*. Clinical management of polycystic liver disease. *J Hepatol* 2018;**68**:827–37.
5. Bernts LHP, Echternach SG, Kievit W, *et al*. Clinical response after laparoscopic fenestration of symptomatic hepatic cysts: a systematic review and meta-analysis. *Surg Endosc* 2019;**33**:691–704.
6. Ubara Y, Takei R, Hoshino J, *et al*. Intravascular embolization therapy in a patient with an enlarged polycystic liver. *Am J Kidney Dis* 2004;**43**:733–8.
7. Hoshino J, Ubara Y, Suwabe T, *et al*. Intravascular embolization therapy in patients with enlarged polycystic liver. *Am J Kidney Dis* 2014;**63**:937–44.
8. Hoshino J, Suwabe T, Hayami N, *et al*. Survival after arterial embolization therapy in patients with polycystic kidney and liver disease. *J Nephrol* 2015;**28**:369–77.
9. Zeng Q, Li Y, Chen Y, *et al*. Gigantic cavernous hemangioma of the liver treated by intra-arterial embolization with pingyangmycin–Lipiodol emulsion: a multi-center study. *Cardiovasc Intervent Radiol* 2004;**27**:481–5.
10. Akhlaghpoor S, Torkian P, Golzarian J. Transarterial bleomycin–lipiodol embolization (B/LE) for symptomatic giant hepatic hemangioma. *Cardiovasc Intervent Radiol* 2018;**41**:1674–82.
11. Zhang G, Wang M, Duan F, *et al*. Transarterial embolization with bleomycin for symptomatic hepatic focal nodular hyperplasia. *Diagn Interv Radiol* 2017;**23**:66–70.
12. Pei Y, Obaji J, Dupuis A, *et al*. Unified criteria for ultrasonographic diagnosis of ADPKD. *J Am Soc Nephrol* 2009;**20**:205–12.
13. Wang MQ, Duan F, Liu FY, *et al*. Treatment of symptomatic polycystic liver disease: transcatheter super-selective hepatic arterial embolization using a mixture of NBCA and iodized oil. *Abdom Imaging* 2013;**38**:465–73.
14. Park HC, Kim CW, Ro H, *et al*. Transcatheter arterial embolization therapy for a massive polycystic liver in autosomal dominant polycystic kidney disease patients. *J Korean Med Sci* 2009;**24**:57–61.
15. Zhang JL, Yuan K, Wang MQ, *et al*. Transarterial embolization for treatment of symptomatic polycystic liver disease: more than 2-year follow-up. *Chin Med J (Engl)* 2017;**130**:1938–44.
16. Kojima K, Hashimoto M, Ubara Y. Scanning electron microscopy of polycystic liver disease. *Clin Exp Nephrol* 2018;**22**:1226–7.
17. Yang Y, Sun M, Ma Q, *et al*. Bleomycin A5 sclerotherapy for cervicofacial lymphatic malformations. *J Vasc Surg* 2011;**53**:150–5.
18. Waanders E, van Keimpema L, Brouwer JT, *et al*. Carbohydrate antigen 19-9 is extremely elevated in polycystic liver disease. *Liver Int* 2009;**29**:1389–95.
19. Yilmaz B, Roach EC, Koklu S. An unusual cause of a high carbohydrate antigen 19-9 level in an elderly individual: polycystic liver disease. *J Am Geriatr Soc* 2015;**63**:1487–8.