European Review for Medical and Pharmacological Sciences 2022; 26: 1543-1548

Embolization with more diluted glue-lipiodol in patients with massive hemoptysis: single center experience results

M. KOLU[1], Ş. KURTULUŞ[2], O. DERE, N. YURTTUTAN[4], İ.O. YILDIRIM[5]

[1]Diyarbakır Memorial Hospital, Department of Radiology, Diyarbakır, Turkey
[2]Harran University, Faculty of Medicine, Department of Chest, Şanlıurfa, Turkey
[3]Harran University, Faculty of Medicine, Department of Radiology, Şanlıurfa, Turkey
[4]Sutcu Imam University, Faculty of Medicine, Departmant of Radiology, Kahramanmaraş, Turkey
[5]Inonu University, Faculty of Medicine, Department of Radiology, Malatya, Turkey

Abstract. – OBJECTIVE: The aim of the study was to demonstrate the efficacy and safety of bronchial artery embolization (BAE) with more diluted N-butyl-2- cyanoacrylate (NBCA) in patients with massive hemoptysis.

PATIENTS AND METHODS: In this retrospective study, there are 48 patients who underwent NBCA and BAE for massive hemoptysis between March 2018 and September 2021. Demographic data, technical and clinical results, immediate hemoptysis control, recurrent hemoptysis and complications were evaluated.

RESULTS: The technical success rate and immediate hemoptysis control were achieved in 97.9% and 93.7%, respectively. The 3 patients who were exitus within the first 10 days were removed from the follow-up range. During the follow-up period (range, 5 months-42 months; median, 27.5 months), recurrent hemoptysis was found in 3 of the 45 patients (6.6 %). Since 1 patient refused and one patient died within the first 24 hours, repeated BAE procedures were performed in 4 patients. A total of 55 sessions of BAE with NBCA was performed to 48 patients. The underlying diseases causing hemoptysis were determined to be bronchiectasis (n=16), tuberculosis (n=8), neoplasm (n=7), aspergilloma (n=3), and arteriovenous malformation (n=2). In 4 patients, bronchiectasis and tuberculosis were present together and in 8 patients, the cause could not be specified.

CONCLUSIONS: In conclusion, BAE with more diluted NBCA is a safe and effective embolization method. In addition, the use of more diluted NBCA reduces the recurrence rates in patients with hemoptysis.

Key Words:
Bladder rupture, Interventional treatment, Embolization.

Introduction

Bronchial artery embolization (BAE) is a minimally invasive treatment method, which is accepted as an alternative to surgery for patients with massive and recurrent hemoptysis. In the traditional approach, particles, such as polyvinyl alcohol (PVA) are preferred in BAE. However, embolisation with PVA has limitations, such as a long procedural time required for complete embolisation, non-optimal visualisation of the embolic agent, and embolisation outside the target area as a result of reflux of the agent. There are also reports in literature stating that recurrent bleeding is seen more as a result of early recanalization[1].

Although successful results have been reported some treatments with new embolic agents in BAE, the optimum embolic agent in BAE has not been defined as yet[2,3].

N-butyl-2-cyanoacrylate (NBCA) (Histoacryl, B. Braun, Melsungen AG) is a permanent liquid embolizing agent, which was first approved in central nervous system arteriovenous malformation (AVM) embolisation. It is used in the treatment of aneurysms in various vascular beds and in acute arterial bleeding in the peripheral circulation[4,5].

In studies of the use of NBCA in BAE, the main reasons include that in comparison with iodised oil it is highly visible under fluoroscopy, a short procedural time is required for complete embolisation, the polymerisation time and level can be controlled because the NBCA to iodised oil ratio can be adjusted, and it has long-term efficacy as the rate of small vessel recanalization is low[1-6].

Corresponding Author: Mehmet Kolu, MD; e-mail: drrdylg@gmail.com

Some studies have previously been published which have used NBCA in BAE[1,6-8]. Unlike the literature, the aim of the current study was to present our experience and the results of the use of a more diluted concentration of NBCA in BAE in a very broad population.

Patients and Methods

Approval for the study was granted by the Local Ethics Committee of Harran University, Şanliurfa, Turkey, and the need for informed consent was waived. This retrospective study included 48 patients who underwent BAE with NBCA because of massive hemoptysis between March 2018 and September 2021. The technical and clinical results were defined as immediate control of hemoptysis, recurrent hemoptysis, or procedural complications. Demographic data were obtained from the electronic medical records. The patients comprised 33 males and 15 females with a mean age of 52 years (range, 18-78 years). Pulmonary radiographs, thorax computed tomography (CT), and flexible bronchoscopy findings were retrieved from the hospital information system and PACS for all patients, and from these the causes of hemoptysis were lateralised and potential etiologies were determined.

Statistical Analysis

SPSS v2 program (Armonk, NY, USA) was used in the statistical analysis of the data. Kaplan-Meier test was used for survival analysis. Pearson chi-square test was used in the analysis of qualitative data. A value of p=0.05 and below was accepted as significant in all statistical analyses. In the analysis of quantitative data, *t*-test and Mann-Whitney u-test were used in independent groups. Mean and percentage values were used to describe the data. When we look at the distribution of the data, the standard deviation was calculated.

NBCA Embolization Technique

All the angiography procedures were performed by a single interventional radiologist (MK: 5 years of experience). All the procedures were made under local anaesthesia with entry from the right femoral artery. First aortography was performed with a 5F pigtail catheter to encompass the thoracic aorta and upper abdominal aorta. The orifices of the bronchial artery or pathological systemic arteries were determined according to the aortography and CT angio findings. Diagnostic angiographs were then obtained with a 5F diagnostic catheter (Cobra, Simmons 1; Cordis). Abnormal expansion, parenchymal hypervascularity, the presence of bronchopulmonary shunt, or extravasion of contrast material were evaluated as pathological[9] (Figure 1A, 2A).

After the diagnostic angiography, the catheter was left at the point of origin of the pathological artery. A 2F microcatheter (Progreate; Terumo) and a 0.014 microguidewire (Transend; Boston Scientific, Marlborough, MA, USA) were entered coaxially into the pathological bronchial artery

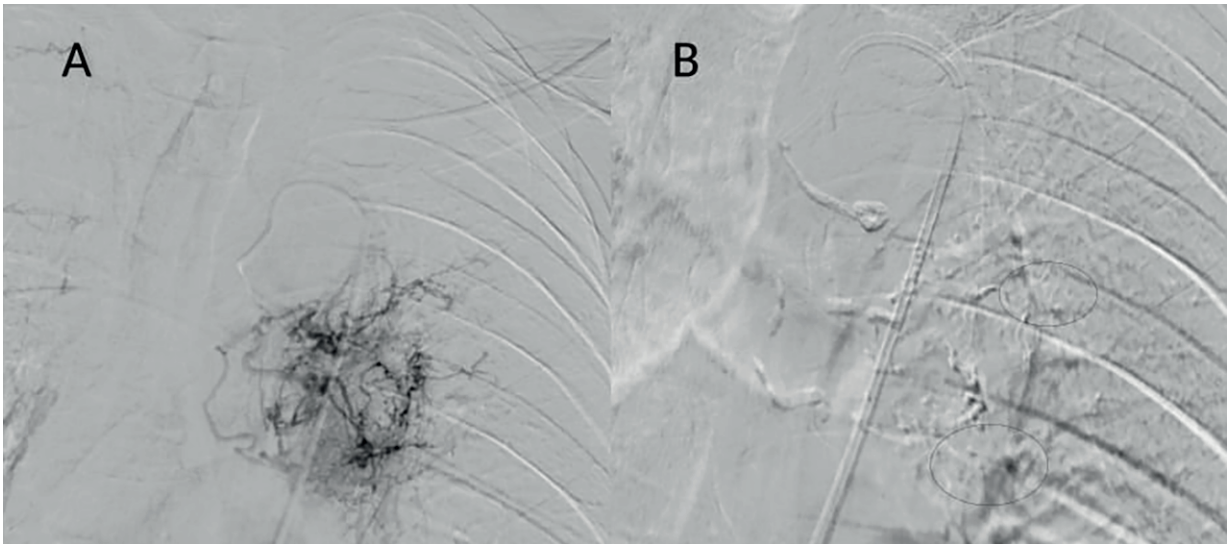

Figure 1. A, DSA image showing anarchic blood supply of a malignant mass lesion in the paramediastinal region of the upper lobe of the left lung. **B,** Diluted glue embolization, we see glue cast even in the most distal areas (*black circles*).

or systemic arteries. To avoid reflux to the aorta of the embolising agent, the microcatheter was placed as distal as possible from the spinal feeders. NBCA (Histoacryl, Braun) was mixed with Lipiodol (Lipiodol Ultra Fluide, Guerbet, France) at the ratio of 1:14 (0.5 ml NBCA-7 ml Lipiodol). The microcatheter lumen and hub were washed with a 5% dextrose solution to prevent polymerisation before the arterial segment was reached. The 0.1 ml NBCA-Lipiodol mixture within the microcatheter was injected for 2 seconds. Then, under fluoroscopy, the NBCA-Lipiodol mixture within the catheter was immediately advanced slowly with 5% dextrose to the distal bed. Injections of the NBCA-Lipiodol mixture followed by 5% dextrose were made with the same technique until the distal bed was filled (Figure 1B, 2B). A total of 0.5-4 ml mixture was injected according to the dimensions of the pathological vessel and distal bed. When there was reflux up to 1 cm from the end of the catheter, it was rapidly withdrawn, and the injection was terminated. The inside of the diagnostic catheter was then washed with 5% dextrose and control angiograms were taken.

Follow-Up and Analysis

The medical records of all the patients were retrospectively scanned. The technical and clinical results were recorded as immediate sucess, recurrence rate, and procedure-related complications. Technical success was defined as complete embolisation of bronchial and non-bronchial collaterals[10]. Immediate clinical success was defined as the absence of hemoptysis in the first 24 hours after BAE[11]. Minor and major complications were recorded. Procedure-related complications which required additional treatment or prolonged hospitalisation, and procedure-related mortality were evaluated as major complications and other complications as minor[12].

All patients underwent follow-up examinations at intervals of 1-3 months after discharge. All patients underwent CT every 3-6 months for assessment of evaluation for progression of underlying disease. Patients with recurrence of hemoptysis who presented at the emergency department underwent CT angiography. The follow-up period was defined as the last date for which follow-up information was obtained for patients who lost follow-up or died. The decision for repeat BAE to be applied to the patient was made by the pulmonologist and interventional radiologist together.

Results

The baseline characteristics of the patients are presented in Table I. Considering the age distribution of the recurrence groups, no significant difference was found between the groups (p=0.760). Considering the distribution of recurrence groups by gender, there was no statistical difference between the groups (p=0.662). Considering the recurrence rates according to the etiological groups, no statistically significant difference was found between the groups (p=0.836). When mortality rates were compared according to the recurrence groups, a statistically significant difference was found (p<0.001).

The underlying diseases causing hemoptysis were determined to be bronchiectasis (n=16),

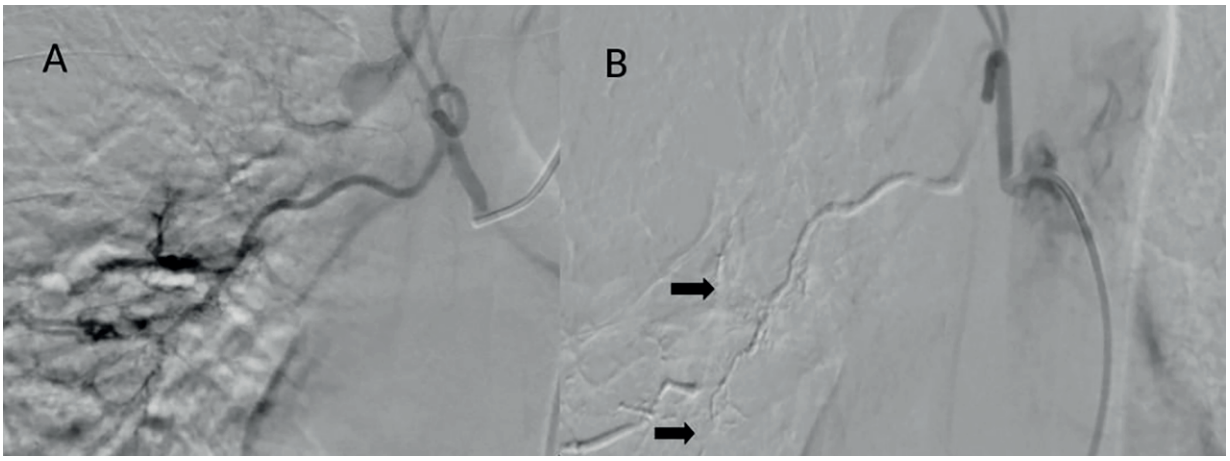

Figure 2. A, DSA image of hypervascularization secondary to bronchiectasis in the lower lobe of the right lung. **B,** We see that the diluted glue cast fills the distal bed.

Table I. Baseline characteristics of the 48 patients who underwent BAE using NBCA.

Age (years)	55 (18-78)
M/F ratio	33/15
Etiology	
Bronchiectasis	16
Tuberculosis	8
Lung cancer	7
Aspergilloma	3
Arteriovenous malformation	2
Bronchiectasis and tuberculosis	4
Other	8
Follow-up duration (months)	5-42 (mean 27.5)
Technical success	47/48 (97.9)
Immediate clinical success	45/48 (93.8 %)
Recurrence	4/45 (8.9 %)
Exitus	3/48
Repeat BAE	5/48
Total NBCA BAE sessions	55/48

tuberculosis (n=8), neoplasm (n=7), aspergilloma (n=3), and arteriovenous malformation (n=2). In 4 patients, bronchiectasis and tuberculosis were present together and in 8 patients, the cause could not be specified.

With the exception of 1 patient, immediate control of hemoptysis was obtained in all the other 47 patients, giving a technical success rate of 47/48. No bleeding was observed in the first 24 hours in 45 patients, giving an immediate clinical success rate of 45/48.

One patient with end-stage lung carcinoma had not immediate hemoptysis and was exitus on the same day. In 2 patients, immediate hemostasis was obtained, but bleeding started again within 24 hours in the Intensive Care Unit. One of these patients did not accept a repeat intervention and was exitus on the 3rd day. The other patient had bronchiectasis with widespread bronchial-systemic-pulmonary artery fistula and developed recurrent hemoptysis within 24 hours, then again on the 5th and 8th days. Repeat BAE was performed twice but the patient was exitus on the 10th day. None of the causes of death were procedure-related, as these 3 patients were exitus because of recurrent hemoptysis which could not be stopped because of the primary disease.

The 3 patients who were exitus within the first 10 days were removed from the follow-up range. The mean follow-up time of the remaining 45 patients was 27.5 months (range 5-42 months). Recurrent hemoptysis developed in 3 of these patients. Repeat BAE with NBCA was applied to these patients. In 1 patient who developed recurrent hemoptysis twice on days 10 and 85, 2 sessions of repeat BAE were performed. Two patients with recurrent hemoptysis who were applied with 2 sessions of BAE were patients with chronic tuberculosis ongoing for approximately 20 years. On the digital subtraction angiography (DSA) images in repeat BAE procedures, there were seen to be widespread bronchiopulmonary artery fistula.

Recurrent hemoptysis developed in 6 patients. Since one patient did not accept re-BAE and one patient died within the first 24 hours, 4 patients underwent repeated BAE embolization. A total of 55 sessions of BAE with NBCA was performed to 48 patients. The underlying pulmonary diseases of the 6 patients who developed recurrence were neoplasm (2), tuberculosis (2), aspergilloma (1), and bronchiectasis (1).

On the repeat embolization DSA images of the patients who developed recurrent hemoptysis, the recurrence was seen to be from intercostal arteries. Recanalisation was not observed in vessels embolised with NBCA in any patient.

No spinal or vascular complications related to the procedure developedin any patient after BAE. Temporary chest pain and shortness of breath developed during the NBCA-Lipiodol injection during the procedure in all the patients, and in the majority, this spontaneously recovered within a few minutes. In 5 patients, these complaints were prolonged, requiring painkillers and oxygen treatment support in the first 6-24 hours. Complaints of nausea and vomiting which required anti-emetic treatment developed in 12 patients.

Discussion

In this retrospective study, the results were analyzed of patients who underwent BAE with more diluted NBCA because of massive hemoptysis. Technical success was obtained in the vast majority of the patients (47/48). With the exception of 3 patients, immediate clinical success was obtained. These results were obtained due to being able to fill the distal bed more with a more diluted BAE mixture and are supported by the results of previously published studies thereby demonstrating that NBCA is a promising embolic agent for BAE[1,6,7].

As the proximal part of the vessel is embolised in coil embolisation, it does not allow repeat embolisation when there is recurrence[9]. In the traditional approach, PVA is the agent, with which there has been the most experience in BAE. The clustering of PVA particles within the catheter

can cause incomplete embolisation. Other limitations of the use of PVA particles are the long procedure time required for complete embolisation and that the fluoroscopic visualisation of the embolising agent is not optimal[7]. The water-soluble contrast materials used for PVA to acquire radio-opacity are more viscous than the NBCA mixture used. This can cause uncontrolled reflux when the pressure in the distal bed is increased during embolisation. It has been reported in some studies that recanalisation can develop after embolization with PVA particles[1,13].

Ravazi and Murphy[1] compared PVA and NBCA in BAE and reported that while recurrent hemoptysis developed in 33% of the patient group where embolisation was applied with PVA because of massive hemoptysis, the recurrence rate in the NBCA group was 16.6%. In that study, embolisation was performed with PVA in 36 patients and with NBCA in 12 patients, whereas in the current study of a larger patient group, the recurrence rate was found to be lower (8.9%). In the previous study by Ravazi and Murphy[1] the NBCA dilution ratios were 1:2, 1:3, and 1:4, whereas in the current study, NBCA-Lipiodol was used in the ratio of 1:14.

High rates of recurrent hemoptysis, such as 20%-30% have been reported in literature[14-16]. Recurrent hemoptysis can originate from incomplete initial embolization, disease progression, or the recanalization of vessels previously embolized. One of the significant causes of suboptimal embolization is that tissue and arteries are covered by the culprit vessel without affecting the level. PVA particles usually form large tortuosity more proximal than the targeted level. These tortuous progresses more distally within minutes or hours and at this time blood flow also progresses distally. This can cause early recanalisation[1].

In another retrospective study by Baltacioglu et al[6] which used NBCA in BAE, immediate hemostasis was obtained in all 25 patients, and in a mean follow-up period of mean 14 months, recurrent hemoptysis developed in 16% of the patients. A mixture of 0.5 ml NBCA:3.5 ml Lipiodol (12.5% concentration) was used in that study. Together with the lower recurrence rate of 8.9 %, the NBCA mixture used in the current study was more diluted and the mean follow-up time was longer (27.5 months).

As a result of a study of a much larger series examining BAE applied using NBCA at ratios of 1.2-1:4, Yoo et al[7] reported an immediate clinical success rate of 97.2 %. This was consistent with the current study (93.8 %). Similar to the current study, Yoo et al[7] reported recurrent hemoptysis in 20 % of the patients remaining in the follow-up range. The recurrence rate of 8.9 % in the current study can be attributed to the use of a more diluted concentration of NBCA.

The most important arguments stated against BAE with NBCA are in respect of complications such as tissue necrosis and that embolisations are often outside the target area as a result of uncontrolled reflux[9]. However, these factors can be controlled in the hands of well-trained and experienced endovascular therapists. The adjustment of the glue concentration and the speed and timing of the injection are under the control of the operator, and thus controlled embolisation can be performed preventing reflux. In the long follow-up period of the current study, no tissue necrosis developed in any patient.

In a previous *in vivo* study[17], an NBCA-Lipiodol mixture at ratios of 1:1, 1:3, and 1:9 was injected to the renal arteries of dogs, and the cortical distal bed of the kidney was evaluated pathologically. It was reported that as the ratio increased, a broader peripheral bed area was seen to have been filled by the mixture. According to our experience, it was seen that as the NBCA concentration was reduced, the distal bed was filled better with the embolising agent. Therefore, by avoiding more the proximal embolisation expected in PVA in the initial embolisation, more distal filling was obtained, and this was seen to be the most important factorin the low recanalisation rates. As demonstrated in the current study, NBCA: Lipiodol concentration of 1:14 protected against premature reflux by providing early polymerisation.

To the best of our knowledge, the current study is the BAE series in literature to have used the lowest concentration of NBCA. The experience gained from the mean 27.5 months follow-up period of this extensive series of 48 patients can be considered to contribute to the literature.

Chest and shoulder pain are the most common complications reported following BAE[9]. In the current study group, temporary chest pain and shortness of breath developed in all the patients and the majority of these resolved spontaneously within a few minutes. In 5/48 patients, these complaints were prolonged, requiring painkillers and oxygen treatment support in the first 6-24 hours. Complaints of nausea and vomiting which required anti-emetic treatment developed in 12 patients. No major complications were observed in any patient.

There were some limitations to this study. As the results were presented only of patients applied with BAE with NBCA, comparisons with other agents could only be made according to literature. As different dilution rates were not used, comparisons could not be made. There is a need for further randomised studies with larger patient groups to compare different concentrations of NBCA.

Conclusions

NBCA is a liquid embolizing agent, which is reliable and low cost, with very high success rates and low complication rates, which can be preferred in BAE performed for massive hemoptysis. It can be considered that recurrent hemoptysis rates can be reduced by avoiding proximal embolization through the use of more dilute concentrations thereby filling the distal bed more.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Funding
None.

References

1) Razavi MK, Murphy K. Embolization of bronchial arteries with N-butyl cyanoacrylate for management of massive hemoptysis: a technical review. Tech Vasc Interv Radiol 2007; 10: 276-282.
2) Corr PD. Bronchial artery embolization for life-threatening hemoptysis using tris-acryl microspheres: short-term result. Cardiovasc Intervent Radiol 2005; 28: 439-441.
3) Vrachliotis T, Sheiman RG. Treatment of massive hemoptysis with intraarterial thrombin injection of a bronchial artery. AJR Am J Roentgenol 2002; 179: 113-114.
4) Kish JW, Katz MD, Marx MV, Harrell DS, Hanks SE. N-butyl cyanoacrylate embolization for control of acute arterial hemorrhage. J Vasc Interv Radiol 2004; 15: 689-695.
5) Kim BS, Do HM, Razavi M. N-butyl cyanoacrylate glue embolization of splenic artery aneurysms. J Vasc Interv Radiol 2004; 15: 91-94.
6) Baltacioğlu F, Cimşit NC, Bostanci K, Yüksel M, Kodalli N. Transarterial microcatheter glue embolization of the bronchial artery for life-threatening hemoptysis: technical and clinical results. Eur J Radiol 2010; 73: 380-384.
7) Yoo DH, Yoon CJ, Kang SG, Burke CT, Lee JH, Lee CT. Bronchial and nonbronchial systemic artery embolization in patients with major hemoptysis: safety and efficacy of N-butyl cyanoacrylate. AJR Am J Roentgenol 2011; 196: W199-204.
8) Woo S, Yoon CJ, Chung JW, Kang SG, Jae HJ, Kim HC, Seong NJ, Kim YJ, Woo YN. Bronchial artery embolization to control hemoptysis: comparison of N-butyl-2-cyanoacrylate and polyvinyl alcohol particles. Radiology 2013; 269: 594-602.
9) Yoon W, Kim JK, Kim YH, Chung TW, Kang HK. Bronchial and nonbronchial systemic artery embolization for life-threatening hemoptysis: a comprehensive review. Radiographics 2002; 22: 1395-1409.
10) Kalva SP. Bronchial artery embolization. Tech Vasc Interv Radiol 2009; 12: 130-138.
11) Barben J, Robertson D, Olinsky A, Ditchfield M. Bronchial artery embolization for hemoptysis in young patients with cystic fibrosis. Radiology 2002; 224: 124-130.
12) Sacks D, McClenny TE, Cardella JF, Lewis CA. Society of Interventional Radiology clinical practice guidelines. J Vasc Interv Radiol 2003; 14: S199-202.
13) Tomashefski JF Jr, Cohen AM, Doershuk CF. Longterm histopathologic follow-up of bronchial arteries after therapeutic embolization with polyvinyl alcohol (Ivalon) in patients with cystic fibrosis. Hum Pathol 1988; 19: 555-561.
14) Barben J, Robertson D, Olinsky A, Ditchfield M. Bronchial artery embolization for hemoptysis in young patients with cystic fibrosis. Radiology 2002; 224: 124-130.
15) Vidal V, Therasse E, Berthiaume Y, Bommart S, Giroux MF, Oliva VL, Abrahamowicz M, du Berger R, Jeanneret A, Soulez G. Bronchial artery embolization in adults with cystic fibrosis: impact on the clinical course and survival. J Vasc Interv Radiol 2006; 17: 953-958.
16) Fartoukh M, Khalil A, Louis L, Carette MF, Bazelly B, Cadranel J, Mayaud C, Parrot A. An integrated approach to diagnosis and management of severe haemoptysis in patients admitted to the intensive care unit: a case series from a referral centre. Respir Res 2007; 158: 11.
17) Takasawa C, Seiji K, Matsunaga K, Matsuhashi T, Ohta M, Shida S, Takase K and Takahashi S. Properties of N-Butyl Cyanoacrylate–iodized Oil Mixtures for Arterial Embolization: In Vitro and In Vivo Experiments. J Vasc Interv Radiol 2012; 23: 1215-1221.