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INTERVENTIONAL RADIOLOGY

ORIGINAL ARTICLE

Liver regeneration after portal vein embolization: comparison between absolute ethanol and *N*-butyl-cyanoacrylate in an *in vivo* rat model

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PURPOSE

To compare the effects of absolute ethanol (ethanol) and *N*-butyl-cyanoacrylate (NBCA) on non-embolized liver lobe regeneration in a rat model.

METHODS

Twenty-seven Sprague–Dawley rats underwent portal vein embolization (PVE) using ethanol:lipiodol, 1:1 (ethanol group, n = 11, 40.74%), NBCA:lipiodol, 1:1 (NBCA group, n = 11, 40.74%), or sham treatment (sham group, n = 5, 18.52%). The non-embolized and embolized lobe-to-whole liver weight ratios 14 days after PVE were compared among the groups (n = 5, 18.52%). The expressions of CD68 and Ki-67 and embolized-lobe necrotic area percentages one day after PVE were compared between the ethanol (n = 3, 11.11%) and NBCA (n = 3, 11.11%) groups.

RESULTS

The non-embolized lobe-to-whole liver weight ratio after PVE was significantly higher in the NBCA group (n = 5, 33.33%) than in the ethanol group (n = 5, 33.33%) (84.28% ± 1.53% vs. 76.88% ± 4.12%, $P = 0.029$). The embolized lobe-to-whole liver weight ratio after PVE was significantly lower in the NBCA group than in the ethanol group (15.72% ± 1.53% vs. 23.12% ± 4.12%, $P = 0.029$). The proportions of CD68- and Ki-67-positive cells in the non-embolized lobe after PVE were significantly higher in the NBCA group (n = 30, 50%) than in the ethanol group (n = 30, 50%) [60 (48–79) vs. 55 (37–70), $P = 0.003$; 1 (0–2) vs. 1 (0–2), $P = 0.004$]. The embolized-lobe necrotic area percentage after PVE was significantly larger in the NBCA group (n = 30, 50%) than in the ethanol group (n = 30, 50%) [29.46 (12.56–83.90%) vs. 16.34 (3.22–32.0%), $P < 0.001$].

CONCLUSION

PVE with NBCA induced a larger necrotic area in the embolized lobe and promoted greater non-embolized liver lobe regeneration compared with PVE with ethanol.

KEYWORDS

Absolute ethanol, *in vivo* rat model, liver regeneration, *N*-butyl-cyanoacrylate, portal vein embolization

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Portal vein embolization (PVE) can be performed to induce compensatory hypertrophy of the remnant liver, thereby increasing the safety of major hepatectomy.[1,2]

Different embolic materials, including absolute ethanol, *N*-butyl-cyanoacrylate (NBCA), gelatin sponge, polyvinyl-alcohol particles, tris-acryl microspheres, vascular plugs, coils, fibrin glue, and polidocanol foam, have been used in PVE on the basis of previous studies.[3] A recent randomized controlled trial (RCT) revealed that NBCA plus iodized oil induced more rapid and robust hypertrophy of the future liver remnant than polyvinyl-alcohol particles plus coils.[4] Compared with the use of NBCA, the use of absolute ethanol by Japanese teams led to a larger future liver remnant after PVE.[5] Moreover, some systematic reviews have shown that absolute ethanol and NBCA induce greater hypertrophy of the future liver rem-

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nant.[6-8] However, to date, a head-to-head comparison between NBCA and ethanol has not been made in an RCT model.

The current study aims to compare the effects of absolute ethanol and NBCA, the embolic materials used in PVE, on non-embolized lobe regeneration in a rat model.

Methods

Animal model

All applicable National Institutes of Health guidelines and/or institutional guidelines for the care and use of animals were followed. All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted (study number: 19-033). Moreover, the study was conducted according to the Fundamental Guidelines for Proper Conduct of Animal Experiments and Related Activities in Academic Research Institutions in Japan.

In total, 27 male Sprague–Dawley rats, weighing 400–450 g, (Oriental Yeast Co., Ltd., Tokyo, Japan) were included in this study. All rats were provided with unlimited access to food and water before and after the operative procedure. The rats were divided into the sham [5 (18.52%)], ethanol [5 (18.52%)], and NBCA [5 (18.52%)] groups. Then, changes in liver weight were evaluated. The remaining rats [12 (44.44%)] underwent histopathological analysis (the study flow is shown in Figure 1).

Portal vein embolization

The PVE process is demonstrated in Figure 2a. Rats were anesthetized via inhalation of isoflurane [Isoflurane Inhalation Solution (Pfizer)®, Mylan Inc., Tokyo, Japan). Then, an anesthetic mixture of 0.15 mg/kg body weight (BW) medetomidine (Domitor®, Nippon Zenyaku Kogyo Co., Ltd., Tokyo, Japan), 2.0 mg/kg BW midazolam (Dormicum®, Astellas Pharma Inc., Tokyo, Japan), and 2.5 mg/kg BW butorphanol (Vetorphale®, Meiji Seika Pharma Co., Ltd., Tokyo, Japan) was administered intraperitoneally.

After performing a midline laparotomy, the portal vein branch was exposed. A 22-gauge intravenous catheter (BD Insyte™ Autoguard™ BC®; Nippon Becton Dickinson Co., Ltd., Tokyo, Japan) was inserted from the portal vein branch (Figure 2a, left image, black arrow). Next, the catheter was advanced to the left-main portal branch under fluoroscopic guidance (Figure 2a, left image, black arrowhead). A 1:1 mixture of lipiodol (lipiodol 480 inj. 10 mL®; Guerbet Japan K.K., Tokyo, Japan) with either absolute ethanol (anhydrous absolute ethanol; Mylan Inc., Tokyo, Japan) [ethanol group, 5 (18.52%)] or NBCA (Histoacryl®, B. Braun Aesculap Japan Co., Ltd., Tokyo, Japan) [NBCA group, 5 (18.52%)] was used to embolize the left-main portal branch. The ethanol and NBCA groups received 0.10 mL of the embolic materials. In the ethanol group, to mimic the balloon occluded absolute ethanol injection, a vascular clip (cat. no. AS-1 KN353, Natsume Seisakusho, Tokyo, Japan) was used to clamp the left-main portal branch for 10 min during embolization (Figure 2a, middle image, curved black arrow). Moreover, to prevent non-targeted embolization, the right-main portal branch was clamped with a vascular clip during the administration of absolute ethanol and NBCA (Figure 2a, middle image, curved white arrow). In the sham group, the catheter was inserted into the left-main portal branches. However, PVE was not performed. At the end of PVE or the sham treatment, the vascular clips were removed, and a 4-0 nylon double-layer running suture was used to close the abdomen. The PVE was performed by an interventional radiologist with 11 years of experience.

Liver weight

The rats in the sham, ethanol, and NBCA groups were euthanized 14 days after the PVE or sham treatment (Figure 1). Then, the whole livers were harvested and divided into the non-embolized and embolized lobes (the left-lateral lobe and left portion of the medial lobe). Next, a laboratory microscale (AW120, SHIMADZU Co., Ltd., Kyoto, Japan) was used to weigh both lobes. In addition, the non-embolized or embolized lobe-to-whole liver weight ratios were calculated, as follows:

Non-embolized or embolized lobe-to-whole liver weight ratio (%) = non-embolized or embolized lobe (g) / whole liver weight (g) × 100.

Histological examination

The rats in the ethanol [3 (11.11%)] and NBCA [3 (11.11%)] groups were euthanized,

Main points

- This study compared the differences in non-embolized lobe regeneration after portal vein embolization (PVE) using absolute ethanol (ethanol) and *N*-butyl-cyanoacrylate (NBCA) in a rat model.
- The NBCA group [5 (33.33%)] had a significantly higher non-embolized lobe-to-whole liver weight ratio than the ethanol group [5 (33.33%)] (84.28% ± 1.53% vs. 76.88% ± 4.12%, $P = 0.029$). However, the NBCA group had a significantly lower embolized lobe-to-whole liver weight ratio than the ethanol group (15.72% ± 1.53% vs. 23.12% ± 4.12%, $P = 0.029$).
- NBCA for PVE induced a larger necrotic area in the embolized lobe and promoted greater non-embolized lobe regeneration compared with ethanol.

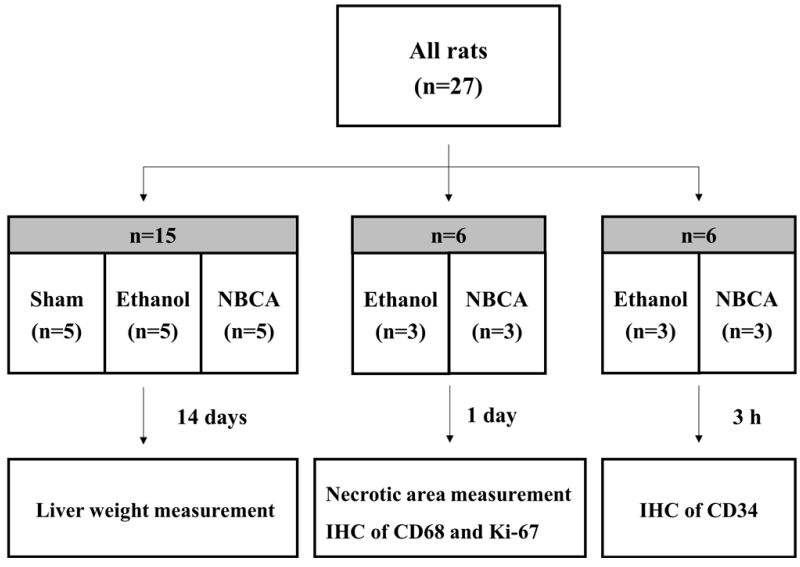

Figure 1. Summary of animal experiments. In total, 27 rats were included in this study. The rats received either sham treatment [5 (18.52%)] or PVE using absolute ethanol [5 (18.52%)] or NBCA [5 (18.52%)]. Then, 14 days after PVE, the liver weights were assessed. Six (22.22%) rats were used to analyze the necrotic area and IHC for CD68 and Ki-67 one day after PVE. The remaining six (22.22%) rats were used to evaluate portal endothelial injury 3 h after PVE via IHC for CD34. PVE, portal vein embolization; NBCA, *N*-butyl-2-cyanoacrylate; IHC, immunohistochemistry.

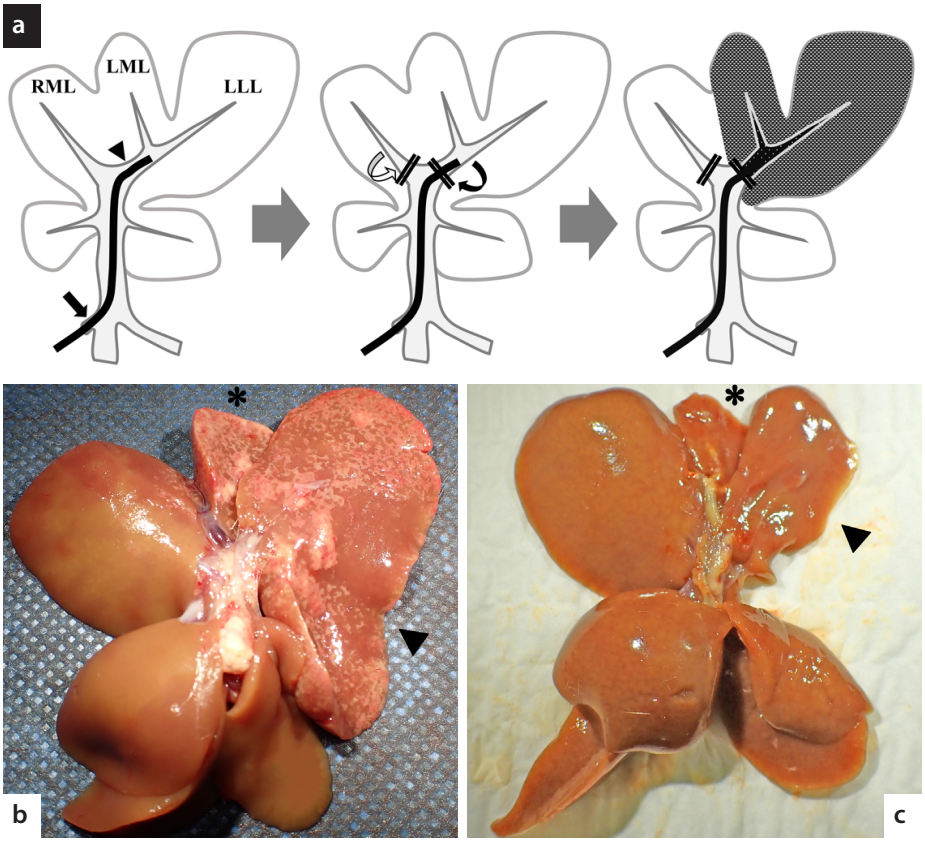

Figure 2. Portal vein embolization. (a) A 22-gauge intravenous catheter (thick black line) is inserted from the portal vein branch (left image, black arrow). Then, the catheter is advanced to the left-main portal branch under fluoroscopic guidance (left image, black arrowhead). The left-main portal branch is clamped with a vascular clip for 10 min during embolization in the ethanol group to mimic the balloon-occluded absolute ethanol injection (middle image, curved black arrow). The right-main portal branch is clamped with a vascular clip during the administration of absolute ethanol and NBCA to prevent the non-targeted embolization of the RML (middle image, curved white arrow). The PVE of the LLL and LML is performed (right image). (b) The liver was harvested one day after PVE using absolute ethanol. The black arrowhead shows the LLL, and the asterisk shows the LML. The color of the embolized lobes changed. (c) The livers were harvested 14 days after PVE. Atrophy of the embolized lobes (black arrowhead, LLL; asterisk, LML) is observed 14 days after PVE. PVE, portal vein embolization; RML, right portion of the medial lobe; NBCA, *N*-butyl-2-cyanoacrylate; LLL, left lateral lobe; LML, left portion of the medial lobe.

and lobe samples were harvested one day after each procedure (Figures 1 and 2b). The samples were used in the analysis of necrotic areas in the embolized lobe and the expression of molecular markers indicating non-embolized lobe regeneration (CD68 and Ki-67). In this study, CD68 and Ki-67 were used as markers for the proliferation of Kupffer and other cells, respectively. The rats in the ethanol [3 (11.11%)] and NBCA [3 (11.11%)] groups were euthanized 3 h after embolization (Figure 1) to evaluate portal endothelial damage via CD34 staining.

The harvested lobe samples were immersed and fixed in 4% formaldehyde and paraffin. A microtome was used to cut the embedded samples into 5-µm-thick sections, and contiguous sections were prepared. One section was stained with hematoxylin and eosin (H&E) to analyze the necrotic area in the embolized lobes. The other contiguous sections were used for immunohistochemical staining for Ki-67 (diluted at 1:100; ab 16667; abcam plc, Cambridge, UK), CD68 (diluted at 1:100; MCA341GA; Serotec Co., Ltd., Sapporo, Japan), and CD34 (diluted at 1:100; AF4117; R&D Systems, Inc., Minneapolis, MN, US).

Quantitative analysis of histopathological samples

OLYMPUS cellSens standard 1.17 (Olympus Corp., Tokyo, Japan) and ImageJ version 1.51 (National Institutes of Health, Bethesda, MD, US) were used to perform quantitative analyses of the histopathological samples. An H&E-stained maximum cut surface specimen obtained from the embolized lobes was used to quantify the necrotic areas in which the nucleus disappeared due to ischemia after PVE. The necrotic areas in the embolized lobes were measured manually in 10 visual fields (original magnification, 100×). Then, the percentage of the necrotic area was calculated.

The proportions of Ki-67- and CD68-positive cells in the non-embolized lobes were assessed in 10 random visual fields per rat at magnifications of 200× and 400×, respectively. The maximum cut surface of the non-embolized lobes was used to perform the evaluations. To evaluate cell count, ImageJ software was used.

Portal vein endothelial injury in the embolized lobe was evaluated 3 h after PVE. Ten CD34-stained specimens per rat were used. The specimens were evaluated at a 100× field of view. Then, the numbers and diameters of the portal veins were recorded. Desquamation of portal endothelial cells was defined as portal vein endothelial injury. The percentages of portal veins with endothelial injury were calculated. The analysis of the histopathological samples was performed by a pathologist with 23 years of experience.

Assessment

The embolized (or sham treatment) and non-embolized lobe-to-whole liver weight ratios 14 days after PVE among the sham, ethanol, and NBCA groups were compared. The percentage of necrotic area in the embolized lobes, expressions of CD68 and Ki-67 in the non-embolized lobes, and the presence of portal endothelium damage were compared between the ethanol and NBCA groups.

Statistical analysis

Descriptive statistics of the data are presented with n (%). Non-normalized variables are shown as the median (min–max), and normal distributions are shown as the mean ± standard deviation. The Shapiro–Wilk test was used to assess the normality of data distribution. If variables were not normally distributed, the Mann–Whitney U test was used. The independent samples t-test was used to analyze data with a normal distribution. The Welch's One-Way analysis of variance was used for three-group comparisons, and then the Games–Howell test was used for a post-hoc comparison if there was a statistical significance. Pearson's chi-squared test and Fisher's exact test were used to evaluate the percentages of portal veins with endothelial injury. All statistical analyses were performed in GraphPad Prism 9 (GraphPad Software Inc., San Diego, CA, US). A P value of <0.050 was considered to be indicative of statistical significance.

Table 1. Liver weight and weight ratios of non-embolized and embolized lobe-to-whole liver

	Sham	Ethanol	NBCA	*P* value			
n (%)	5 (33.33)	5 (33.33)	5 (33.33)	Welch's ANOVA	Games–Howell test		
Liver weight (g)					Sham - ethanol	Sham - NBCA	Ethanol - NBCA
Whole liver, mean ± SD	17.0 ± 1.4	15.6 ± 2.9	14.5 ± 1.0	0.046	0.607	0.031	0.720
Non-embolized lobe, mean ± SD	9.2 ± 0.8	12.0 ± 2.4	12.2 ± 0.8	0.002	0.119	0.001	0.979
Embolized lobe, mean ± SD	7.8 ± 0.9	3.6 ± 0.9	2.3 ± 0.3	<0.001	<0.001	<0.001	0.057
Weight ratio to whole liver (%)							
Non-embolized lobe, mean ± SD	54.03 ± 2.64	76.88 ± 4.12	84.28 ± 1.53	<0.001	<0.001	<0.001	0.029
Embolized lobe, mean ± SD	45.97 ± 2.64	23.12 ± 4.12	15.72 ± 1.53	<0.001	<0.001	<0.001	0.029

Ethanol = absolute ethanol; NBCA, *N*-butyl-2-cyanoacrylate; ANOVA = One-Way analysis of variance; SD, standard deviation.

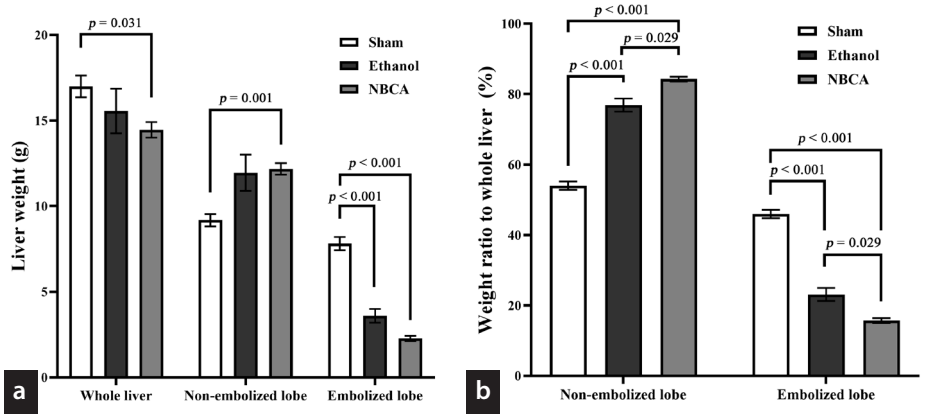

Figure 3. Liver weight and non-embolized and embolized lobe-to-whole liver weight ratio 14 days after PVE. **(a)** Liver weight 14 days after PVE. There are significant differences in all variables of the liver weight between the sham and NBCA groups, and there is a significant difference in the embolized lobe between the sham and ethanol groups (Table 1). The bars represent the SEM. **(b)** Non-embolized and embolized lobe-to-whole liver weight ratios. The non-embolized lobe-to-whole liver weight ratio is significantly higher in the NBCA group [5 (33.33%)] than in the ethanol group [5 (33.33%)] 14 days after PVE (84.28% ± 1.53% vs. 76.88% ± 4.12%, $P = 0.029$, Table 1). The embolized lobe-to-whole liver weight ratio is significantly lower in the NBCA group than in the ethanol group 14 days after PVE (15.72% ± 1.53% vs. 23.12% ± 4.12%, $P = 0.029$, Table 1). The bars represent the SEM. PVE, portal vein embolization; NBCA, *N*-butyl-2-cyanoacrylate; SEM, standard error of the mean.

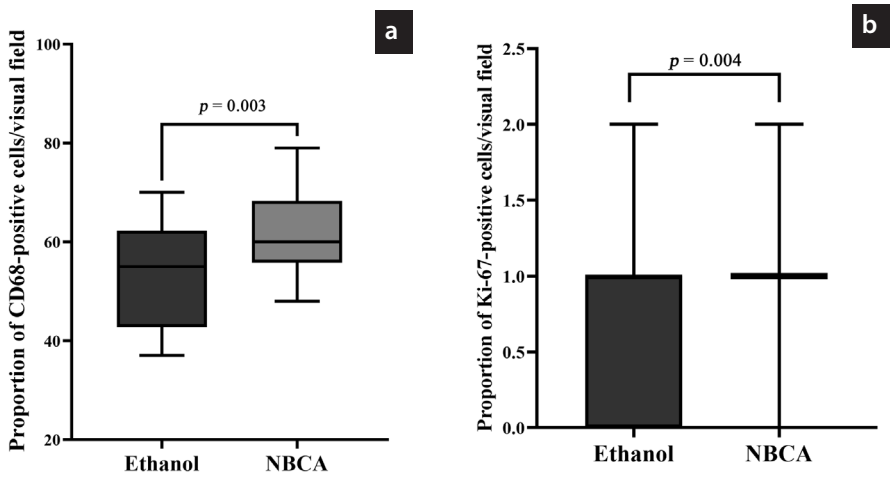

Figure 4. Proportions of CD68- and Ki-67-positive cells in the non-embolized lobe. **(a, b)** The proportions of CD68- and Ki-67-positive cells/visual field are significantly higher in the NBCA group [30 (50%)] than in the ethanol group [30 (50%)] [60 (48–79) vs. 55 (37–70), $P = 0.003$; 1 (0–2) vs. 1 (0–2), $P = 0.004$]. The proportions of CD68- and Ki-67-positive cells are determined in 10 random visual fields at magnifications of 400× and 200×, respectively. NBCA, *N*-butyl-2-cyanoacrylate.

Results

Non-embolized lobe and embolized lobe-to-whole liver weight ratios

The weights of the non-embolized and embolized lobes 14 days after PVE were 9.2 ± 0.8 and 7.8 ± 0.9 g in the sham group [5 (33.33%)], 12.0 ± 2.4 and 3.6 ± 0.9 g in the ethanol group [5 (33.33%)], and 12.2 ± 0.8 and 2.3 ± 0.3 g in the NBCA group [5 (33.33%)], respectively (Table 1, Figure 3a). The non-embolized lobe-to-whole liver weight ratio was significantly higher in the NBCA group than in the sham (84.28% ± 1.53% vs. 54.03% ± 2.64%, $P < 0.001$) and ethanol (84.28% ± 1.53% vs. 76.88% ± 4.12%, $P = 0.029$) groups (Table 1, Figure 3b). By contrast, the NBCA group had a significantly lower embolized lobe-to-whole liver weight ratio than the sham (15.72% ± 1.53% vs. 45.97% ± 2.64%, $P < 0.001$) and ethanol (15.72% ± 1.53% vs. 23.12% ± 4.12%, $P = 0.029$) groups (Table 1, Figure 3b).

CD68 and Ki-67 positive cells in the non-embolized lobe after PVE

The proportion of CD68-positive cells in the non-embolized lobe one day after PVE was significantly higher in the NBCA group [30 (50%)] than in the ethanol group [30 (50%)] [60 (48–79) vs. 55 (37–70), $P = 0.003$] (Table 2, Figure 4a). In addition, the proportions of Ki-67-positive cells in the non-embolized lobe were significantly higher in the NBCA group than in the ethanol group [1 (0–2) vs. 1 (0–2), $P = 0.004$] (Table 2, Figure 4b).

Percentage of necrotic area in the embolized lobe

The percentage of necrotic area in the embolized lobe one day after PVE was significantly larger in the NBCA group [30 (50%)] than in the ethanol group [30 (50%)] [29.46 (12.56–83.90%) vs. 16.34 (3.22–32.0%), $P < 0.001$] (Table 2, Figure 5c).

Table 2. Proportion of CD68- and Ki-67-positive cells, percentage of necrotic area (%)

	Ethanol	NBCA	*P* value
n (%)	30 (50)	30 (50)	
Proportion of CD68-positive cells/visual field, median (min–max)	55 (37–70)	60 (48–79)	0.003
Proportion of Ki-67-positive cells/visual field, median (min–max)	1 (0–2)	1 (0–2)	0.004
Percentage of necrotic area (%), median (min–max)	16.34 (3.22–32.0)	29.46 (12.56–83.90)	<0.001

Ethanol = absolute ethanol; NBCA, *N*-butyl-2-cyanoacrylate.

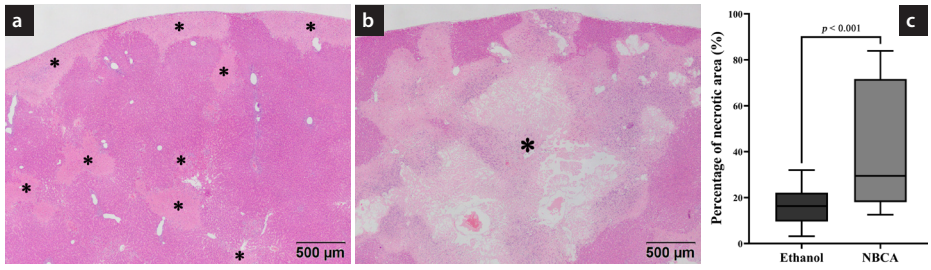

Figure 5. Necrosis in the embolized lobe. **(a, b)** Representative H&E staining of the necrotic area in the embolized lobe after PVE using **(a)** absolute ethanol and **(b)** NBCA (original magnification, 40×). Both groups show a patchy area of lobe necrosis (asterisk). **(c)** The percentage of the necrotic area in the embolized lobe one day after PVE is significantly larger in the NBCA group [30 (50%)] than in the ethanol group [30 (50%)] [29.46 (12.56–83.90%) vs. 16.34 (3.22–32.0%), $P < 0.001$]. The percentage of the necrotic area is evaluated by manually measuring the necrotic area in the embolized lobes in 10 random visual fields (original magnification, 100×). H&E, hematoxylin and eosin; PVE, portal vein embolization; NBCA, *N*-butyl-2-cyanoacrylate.

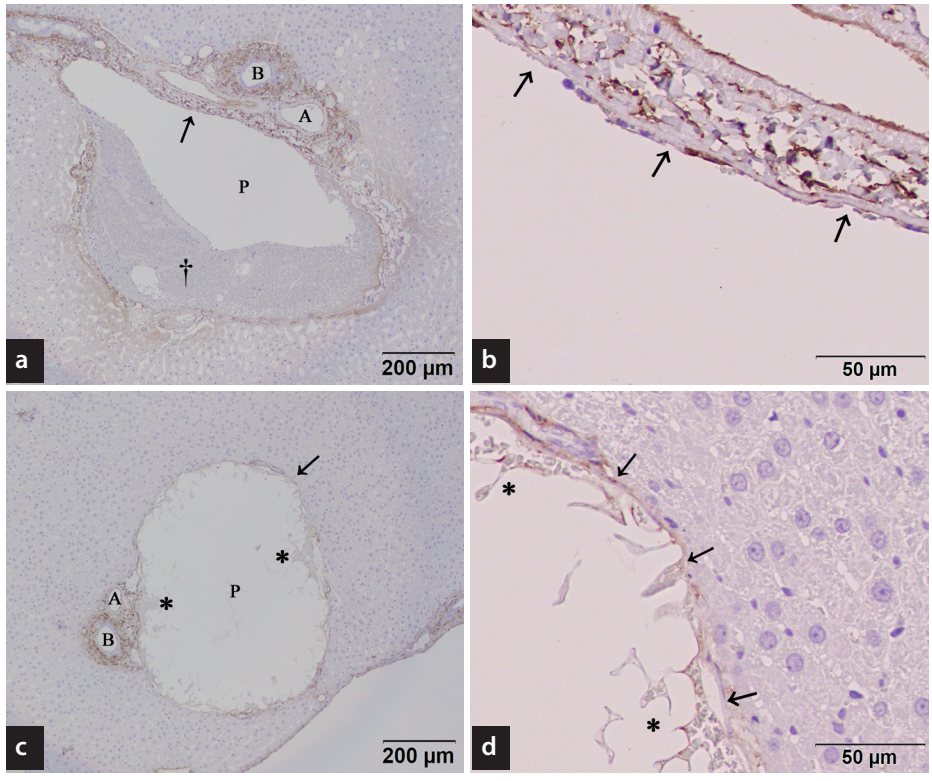

Figure 6. Immunohistochemistry for CD34 in the embolized lobe. **(a, b)** Embolized lobe after PVE using absolute ethanol (original magnification: 100×, 400×). **(c, d)** Embolized lobe after PVE using NBCA (original magnification: 100×, 400×). Injured endothelial cells embolized with absolute ethanol and NBCA after PVE are indicated (arrow). A thrombus is observed along the inner lumen of the portal vein (dagger). An NBCA cast adhesion is noted at the inner lumen of the portal vein (asterisk). PVE, portal vein embolization; NBCA, *N*-butyl-2-cyanoacrylate; P, portal vein; A, hepatic artery; B, bile duct.

Portal vein endothelial injury

Desquamation of portal endothelial cells was observed 3 h after embolization in the ethanol and NBCA groups (Figure 6). The percentage of portal veins with endothelial injury was significantly higher in the ethanol group [30 (32.26%)] than in the NBCA group [8 (6.84%)] ($P < 0.001$) if the portal vein diameter was ≤500 μm (Table 3). The percentages of portal veins with endothelial injury were similar between the ethanol and NBCA groups if the portal vein diameter was >500 μm (Table 3) ($P = 0.621$). In the NBCA group, a deposition of NBCA at the portal endothelium was observed in 9 (56.25%) of 16 portal veins with diameters >500 μm.

Discussion

The non-embolized lobe-to-whole liver weight ratio was significantly higher in the NBCA group than in the ethanol group 14 days after PVE, which showed that NBCA was more effective in promoting non-embolized lobe regeneration than absolute ethanol. The expressions of CD68- and Ki-67-positive cells in the non-embolized lobes were higher in the NBCA group than in the ethanol group. Kupffer cells and monocyte-derived macrophages, as well as CD68-positive cells, have important roles in liver regeneration by releasing growth factors, including hepatocyte growth factor.[9-11] The higher proportions of CD68- and Ki-67-positive cells in the NBCA group might explain the greater regenerative response to this embolic material than to absolute ethanol. However, the mechanisms by which NBCA for PVE promotes non-embolized lobe regeneration were not assessed in this study. One possible explanation is the difference in the degree of liver necrosis between the ethanol and NBCA groups. The percentage of necrotic area in the embolized lobe one day after PVE was larger in the NBCA group than in the ethanol group. Moreover, atrophy of the embolized lobe 14 days after PVE was more severe in the NBCA group than in the ethanol group. These differences might have led to the varying degrees of liver regeneration between the ethanol and NBCA groups. The weights of the non-embolized lobes 14 days after PVE were actually similar between the ethanol and NBCA groups (12.0 ± 2.4 vs. 12.2 ± 0.8 g), but the weights of the non-embolized lobes 14 days after PVE might have been affected by the *body* weights of the ethanol and NBCA groups 14 days after PVE (480 ± 40 vs. 464 ± 16 g).

de Baere et al.[3] showed that the rate of liver hypertrophy increased if necrosis-induced fibrosis in the embolized lobe was

Table 3. Percentage of portal veins with endothelial injury

Diameter of portal vein	Ethanol (n = 93)	NBCA (n = 117)	*P* value
All, n (%)	38 (40.86%)	20 (17.09%)	<0.001
≤500 μm, n (%)	30 (32.26%)	8 (6.84%)	<0.001
>500 μm, n (%)	8 (8.6%)	12 (10.26%)	0.621

The number of portal veins with endothelial injury in relation to the total number of portal veins in the visual field is enclosed in parentheses. Ethanol = absolute ethanol; NBCA, *N*-butyl-2-cyanoacrylate.

larger. Similarly, Furrer et al.[12] revealed that the rate of liver hypertrophy increased with a larger necrotic area in the embolized or ligated lobe. Another possible explanation is the difference in the degrees of foreign body reaction between ethanol and NBCA. In this study, a higher proportion of Kupffer cells was observed in the non-embolized lobe in the NBCA group. Therefore, a stronger foreign body reaction in the NBCA group might promote Kupffer cell recruitment in the non-embolized lobe, leading to greater liver regeneration.[13]

Notably, there was a higher incidence of endothelial injury after PVE using absolute ethanol, particularly in the small (≤500 μm) portal vein. However, the NBCA group had a larger percentage of necrotic areas in the embolized lobe. This discrepancy might be attributed to the different mechanisms of embolization between absolute ethanol and NBCA. Absolute ethanol causes tissue necrosis, and thrombus can form secondary to stagnant blood flow.[14] By contrast, NBCA polymerizes and forms a cast in the blood vessel.[15-18] This cast fills and adheres to the inner lumen of the blood vessel, thereby preventing blood flow and resulting in thrombus formation.[17] In this study, NBCA cast adhesion was observed in nine (56.25%) of the large (>500 μm) portal veins. Therefore, compared with ethanol, NBCA might induce thrombus formation in larger portal veins and a larger necrotic area.

This study had several limitations. First, this was a small-scale animal study. Therefore, the results cannot be immediately applied to humans, so further studies involving a large-scale animal model should be performed. Second, because of the lack of cross-sectional imaging modalities, such as computed tomography and magnetic resonance imaging, the actual lobe volume, including the non-embolized or embolized lobe before PVE, could not be evaluated in these small animals. Third, although various factors such as cytokine and micro-RNA levels can affect liver regeneration,[9,10] they were not investigated in this study. Fourth, the volume ratio of lipiodol and embolic materials was fixed at 1:1, and other ratios were not evaluated. Despite these limitations, this study's results provide useful information for determining the optimal embolic material for PVE that can efficiently promote liver regeneration.

In conclusion, compared with absolute ethanol, NBCA for PVE induced a larger necrotic area in the embolized lobe and promoted greater non-embolized lobe regeneration.

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Conflict of interest disclosure

The authors declared no conflicts of interest.

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