Clinical efficacy of transcatheter embolization of visceral artery pseudoaneurysms using N-butyl cyanoacrylate (NBCA)

Y. Won, S.L. Lee, Y. Kim, Y.M. Ku*

Department of Radiology, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Abstract
Purpose: Transcatheter endovascular embolization within a reasonable time before rupture or deterioration of a patient’s general condition is an important procedure for managing visceral pseudoaneurysms. N-butyl 2-cyanoacrylate (NBCA, enbucrilate) is an embolic material used in the blockade of visceral pseudoaneurysms. This study evaluated the clinical efficacy of transcatheter embolization of visceral artery pseudoaneurysms using NBCA.

Methods: Between June 2004 and February 2014, 13 patients (9 males and 4 females; age range, 26–80 years; mean, 57.9 years) with 14 pseudoaneurysms were treated by transcatheter embolization using NBCA. NBCA was mixed with iodized oil at a 1:3 ratio to control its polymerization time and to render it radiopaque. Pseudoaneurysms were located on the gastroduodenal artery (n = 1), pancreaticoduodenal artery (n = 2), dorsal pancreatic artery (n = 1), proximal jejunal artery (n = 1), colic artery (n = 1), splenic artery (n = 3), renal artery (n = 4; two in one patient), and hepatic artery (n = 1).

Results: All patients recovered immediately following the embolization procedure, and two patients showed minor complications that required only medical observation.

Conclusions: Transcatheter embolization using NBCA for the treatment of visceral pseudoaneurysms is a safe, effective, and low-cost treatment method with a high success rate.

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KEYWORDS
False aneurysm; Hemorrhage; Therapeutic embolization; Enbucrilate; Interventional radiology
Selective arterial embolization has been accepted as an appropriate therapy for the treatment of visceral pseudoaneurysms with a high success rate (> 80%) and a low complication rate [1]. Pseudoaneurysms, or false aneurysms, usually result from pancreatitis, trauma, surgery, or peptic ulcer disease. Among visceral pseudoaneurysms, frequently noted sites include the splenic artery, pancreaticoduodenal artery, and, less often, the celiac artery [2]. By contrast to true aneurysms, pseudoaneurysms do not contain all three layers of the vascular wall and are thus more fragile. Pseudoaneurysms contain a single loose connective tissue layer and have a tendency to enlarge progressively and rupture, and so must be managed [3,4]. Various embolic materials have been used successfully, including N-butyl 2-cyanoacrylate (NBCA), microcoils, gelatin sponge particles, ethanol, polyvinyl alcohol, and thrombin [5–7].

Although various materials have been used to embolize pseudoaneurysms, coils are used most often while liquid embolic materials such as NBCA are rarely used because of handling difficulty and concerns regarding potentially fatal complications related to ischemic injury. NBCA allows rapid and permanent embolization with rapid polymerization when in contact with blood [8]. Serious complications, including bowel ischemia or innocent vessel embolization, have been reported only rarely and can be minimized by treating patients with appropriate indications and ensuring that the procedures are performed carefully by trained personnel [4,8,9].

In this report, we present our experiences regarding endovascular management using NBCA for visceral pseudoaneurysms in thirteen patients, together with a review of the literature.

Patient and methods

Patients

Between June 2004 and February 2014, 13 patients (9 males and 4 females; age range, 26–80 years; mean, 57.9 years) were referred to our department for angiography. All 13 patients had previously undergone diagnostic imaging studies, and, in particular, contrast-enhanced multi-detector computed tomography (MDCT) or three-dimensional MDCT angiography.

Angiography was performed in cases of hemorrhage within 1–5 days after clinical signs, laboratory data, or relevant imaging findings, and two asymptomatic patients underwent angiography electively. This study was performed retrospectively in compliance with the requirements of our institutional review board, and informed consent for angiography and embolization was obtained from each patient or the patient’s family.

Endovascular technique

After common femoral artery puncture, standard angiography was performed. A 2.4-F microcatheter was introduced coaxially into the 5-F catheter, and the tip of the microcatheter was placed as close as possible to the neck of the pseudoaneurysm. However, if the catheter tip could not be properly positioned at the pseudoaneurysm neck because of the artery’s small caliber or tortuosity, it was wedged into the inlet of the arteries to be embolized so as to limit retrograde pericatheter reflux of the NBCA mixture.

Once the microcatheter was in place, a mixture of NBCA (Histoacryl Blue®; B. Braun, Melungen, Germany) and ethiodized oil (Lipiodol Ultra-Fluide®; Guerbet, Roissy-Charles-de-Gaulle, France, Switzerland) at a ratio of 1:3 was prepared. The iodized oil provided radiopacity to the mixture and delayed the polymerization time. Angiography and embolization were performed by an interventional radiologist. Prior to injection of the NBCA mixture, the lumen of the microcatheter was flushed with 5% dextrose to prevent polymerization before reaching the arterial segments. The NBCA mixture was injected using a 1-mL syringe and under careful fluoroscopic monitoring until it filled the outflow, pseudoaneurysm neck, and parent artery inflow. Immediately after injection, the microcatheter was removed to prevent adherence of the catheter tip to the vessel wall. The inner lumen of the guiding catheter was then cleared, and post-embolic angiography was performed (Figs. 1–3).

The technical and clinical outcomes were followed in terms of the immediate control of bleeding, recurrence of bleeding, and complications. Following embolization, patients were monitored for clinical symptoms and signs of bleeding as well as hemoglobin levels, and they underwent optional imaging studies, as needed. Patients were followed up after discharge on an outpatient basis.

Results

The pseudoaneurysms were located on the gastroduodenal artery (n = 1), pancreaticoduodenal artery (n = 2), dorsal pancreatic artery (n = 1), proximal jejunal artery (n = 1), colic artery (n = 1), splenic artery (n = 3), renal artery (n = 4, two in one patient), and hepatic artery (n = 1) (Table 1). The aneurysms ranged from 4 to 25 mm in diameter, as measured from the angiograms. Active bleeding from an aneurysm presented as contrast extravasation on the angiograms.

The predisposing etiologies were as follows: splenic artery pseudoaneurysms caused by chronic pancreatitis (n = 2) or after total gastrectomy due to gastric cancer (n = 1); iatrogenic pseudoaneurysms occurring after a biopsy or laparoscopic lumpectomy of a 2.5-cm renal cell tumor; a gastroduodenal artery pseudoaneurysm after Whipple’s procedure for ampulla of Vater cancer; a hepatic artery pseudoaneurysm after percutaneous transhepatic biliary drainage for biliary lithiasis; and an anterosuperior pancreaticoduodenal artery pseudoaneurysm because of pancreatic cancer in a patient who had been medicated with warfarin for 40 years because of an arterial flutter.

Transcatheter embolization using the liquid agent NBCA, referred to as ‘glue’, was performed initially during our early clinical experience in two patients, combined with the use of a coil. NBCA embolization was successful in all of our patients, and there was complete occlusion of all pseudoaneurysms. There were only two minor complications related to the embolization procedure. One patient (patient 1) showed persistent, minor hematuria without a significant decrease in the hematocrit reading for 3 days, while
a second patient (patient 5) showed subsegmental haziness at the right lung base, which was suspected of being subsegmental lung embolization, although there was no apparent associated clinical manifestation. Among the patients with active bleeding, one (patient 12) was affected more severely than the others; however, his overall condition, even after the development of an acute hemorrhage, did not deteriorate and was maintained via transfusion. No patient developed hypovolemic shock or disseminated intravascular coagulation. One patient (patient 7) had a history of long-term warfarin use, but his International Normalized Ratio was maintained at 2. Neither recurrent active bleeding nor clinical evidence of end-organ damage after embolization was noted during the follow-up period. Follow-up imaging studies did not show aneurysms or evidence of bleeding. One patient died 3 months later from an existing malignant

disease and poor general condition. Our patients with the longest follow-up times have experienced no adverse events even after 10 years.

Discussion

Pseudoaneurysms are caused by trauma, inflammation, surgery, and cancer; they are characterized by a weakened or disrupted arterial wall with encapsulation by fibrous tissue [4,6]. Therefore, treatment of pseudoaneurysms is highly recommended because bleeding from pseudoaneurysms is associated with high mortality rates [10,11]. Pseudoaneurysms may be distinguished from true aneurysms both clinically and by imaging. Clinically, patients with pseudoaneurysms present with a history of trauma, intra-abdominal or retroperitoneal inflammation or malignancy, or manipulation. Imaging revealed focal, lobulated aneurysmal sac disruption surrounded by inflammation. Patients 10 and 12 had no definite prior traumatic or inflammatory histories. We thus performed various vasculitis- and autoimmune disease-related examinations, but the findings were negative.

Angiographic imaging revealed that patient 10 had an irregularly shaped aneurysm.

Patient 12 had a history of alcohol abuse; thus, we suspected that subclinical pancreatitis was the cause of the pseudoaneurysm. This patient had already presented with a ruptured aneurysm; thus, we performed embolization using NBCA. NBCA may be used to successfully manage a pseudoaneurysm or a false aneurysm, but most of our patients had pseudoaneurysms.

Endovascular embolization has gained widespread acceptance for the optimal, initial treatment of unruptured (or even of ruptured) aneurysms because it is less invasive and more selective than traditional techniques. Compared with endovascular embolization of an aneurysm, the 'traditional' method of surgical clipping may be more invasive and difficult to accomplish in cases involving a large hematoma because the aneurysm itself can be missed during laparotomy [5,12,13].

The use of metallic coils has been reported in several studies, and many interventional radiologists favor them for the treatment of visceral pseudoaneurysms; this is because they are assumed to have no association with any potential risk of arterial rupture due to the high-pressure injection of gelatin sponge particles. Also, coils can be delivered directly into the sac of a pseudoaneurysm without compromising the patency of the parent artery. However, NBCA has more several benefits as an embolic agent to occlude visceral pseudoaneurysms because visceral pseudoaneurysms often have complex shapes with many arteries and collateral vessels. The vessels may also be too small or have too tortuous a course to achieve super-selective catheterization and stable catheter positioning, both of which are essential for achieving ideal coil embolization [14,15]. The bowel ischemia rate is of relatively little concern because collateral vessels develop. For these reasons, the liquid properties and low viscosity of NBCA make it beneficial as an embolic material for visceral pseudoaneurysms versus the use of coils.

NBCA solidifies rapidly; thus, some operators may be hesitant to use it. However, this problem can be overcome by familiarization with the dilution time of the NBCA mixture with iodized oil and fluoroscopic-guided monitoring. In an experimental study, Stoesslein et al. [16] indicated that a mixture of NBCA and iodized oil at a mixing ratio of 1:3–1:4 provided an optimal embolic material with a polymerization time of 7.5–11.5 s and with excellent contrast definition. However, the in vivo polymerization time for NBCA appears to be shorter than the in vitro time due to the higher body temperature and higher anion concentration in the intravascular environment. Pollak and White [9] suggested that the estimated NBCA polymerization time in vivo for iodized oil mixtures prepared at ratios of 1:1 and 1:4 was 1–4 s, and that there was a linear relationship between the polymerization time and mixture ratio.

Theoretically, there are two methods for the endovascular transcatheter embolization of an aneurysm. One is the "packing" technique, which deploys the embolic material into the aneurysm sac and which is preferable and more
<table>
<thead>
<tr>
<th>Number</th>
<th>Sex/age (year)</th>
<th>Symptom</th>
<th>Site of Lesion Size</th>
<th>Etiology</th>
<th>Embolic agent</th>
<th>Immediate outcome</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/35</td>
<td>Rupture</td>
<td>Lt. renal a. (15 mm)</td>
<td>Biopsy</td>
<td>Glue</td>
<td>Success</td>
<td>Hematuria for 3 days</td>
</tr>
<tr>
<td>2</td>
<td>M/75</td>
<td>Rupture</td>
<td>Splenic a. (15 mm)</td>
<td>Pancreatitis</td>
<td>Glue</td>
<td>Success</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>M/56</td>
<td>Rupture</td>
<td>Splenic a. (15 mm)</td>
<td>Surgery for gastric cancer</td>
<td>Glue</td>
<td>Success</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>M/52</td>
<td>Asymptomatic</td>
<td>Splenic a. (20 mm)</td>
<td>Pancreatitis</td>
<td>Glue</td>
<td>Success</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>F/72</td>
<td>Asymptomatic</td>
<td>Lt. renal a. (25 mm, 10 mm)</td>
<td>Surgery for renal cell ca.</td>
<td>Glue</td>
<td>Success</td>
<td>Asymptomatic pulmonary embolization</td>
</tr>
<tr>
<td>6</td>
<td>F/53</td>
<td>Rupture</td>
<td>Gastroduodenal a. (15 mm)</td>
<td>Surgery for ampullar of Vater cancer</td>
<td>Glue and coil</td>
<td>Success</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>M/67</td>
<td>Rupture</td>
<td>Anterior superior PDA (22 mm)</td>
<td>R/O duodenal cancer and arterial flutter</td>
<td>Glue and coil</td>
<td>Success</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>M/70</td>
<td>Rupture</td>
<td>RHA anterior division (6 mm)</td>
<td>Post-PTBD</td>
<td>Glue</td>
<td>Success</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>F/80</td>
<td>Gradual growing</td>
<td>Rt. colic a. (25 mm)</td>
<td>Post. operation</td>
<td>Glue</td>
<td>Success</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>M/26</td>
<td>Rupture</td>
<td>Proximal jejuna a. (6 mm)</td>
<td>Not known</td>
<td>Glue</td>
<td>Success</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>M/40</td>
<td>Rupture</td>
<td>Rt. renal a. (20 mm)</td>
<td>Traffic accident</td>
<td>Glue</td>
<td>Success</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>M/49</td>
<td>Rupture</td>
<td>Inferior posterior PDA(22 mm)</td>
<td>R/O pancreatitis</td>
<td>Glue</td>
<td>Success</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>F/78</td>
<td>Rupture</td>
<td>Dorsal pancreatic a. (4 mm)</td>
<td>Post. Whipple op.</td>
<td>Glue</td>
<td>Success</td>
<td>No</td>
</tr>
</tbody>
</table>

M: male; F: female; PDA: pancreaticoduodenal artery; RHA: right hepatic artery; PTBD: percutaneous transhepatic biliary drainage; Lt.: left; Rt.: right; a.: artery; ca.: cancer; op.: operation.
selective than the "isolation" technique, which excludes the inflow, neck, and outflow of the pseudoaneurysm from the circulation. We planned to differentiate the dilution rate depending on the embolization technique for packing and isolation as follows: when both a stable catheter position and super-selection were feasible, we used the packing technique with a higher mixing ratio of NBCA to lipiodol (1:1 to 1:2) to avoid prolonged polymerization and to prevent migration of embolic materials into the feeding artery. However, when the microcatheter could not readily approach the pseudoaneurysm entrance and a stable catheter position could not be achieved, we used the isolation technique, with a lower NBCA to Lipiodol® Ultra-Fluide mixing ratio (1:3). In fact, the selection of a pseudoaneurysm neck is rarely achieved in cases of visceral pseudoaneurysm, and there is a risk of pseudoaneurysm rupture when deploying the embolic material due to the increase in intra-anEURysmal pressure [10,17]. We treated most cases with the isolation technique and fixed the ratio at 1:3 (i.e., 25% NBCA). The constant polymerization time and viscosity allow the operator to become accustomed to the mixture’s properties as well as the injection speed so that, after adequate training, the operator could modify the force and speed of the injection under careful monitoring with fluoroscopic guidance.

The combined use of a microcoil and NBCA is also a successful strategy because coil embolization decreases blood flow and prevents distal embolization, and the procedure decreases the amount of NBCA injected and the number of coils used.

As NBCA becomes more widely used, instances of its successful employment in the uterine artery and peripheral extremity embolization are appearing in the literature. Notably, NBCA does not seem to be associated with any serious end-organ injury issues [18,19].

None of our patients developed symptomatic, end-organ infarctions, except for a small degree of subsegmental pulmonary infarction, with no related symptoms, and our high success rates correspond with those in previous reports [4,8]. According to our experience, endovascular transcatheter NBCA injection was both safe and relatively easy to perform in the setting of the interventional radiology suite, although NBCA is a risky embolic material that can cause severe complications. A small number of complications have been reported using the technique, including distal embolization, visceral fistula, septic complications, and pancreatitis. Thus, the long-term efficacy and the potential of this technique to become a standard treatment strategy remain to be determined in larger randomized trials. Our study has several limitations. The first is the limited number of patients and the retrospective nature of the study. Second, no comparison with other embolic agents was performed.

Based on our experience and literature review, selective transcatheter embolization using NBCA for the treatment of visceral pseudoaneurysms is an efficient endovascular treatment tool that can be used as a first-attempt treatment to achieve bleeding control of a ruptured pseudoaneurysm and to seal an unruptured pseudoaneurysm in the clinical setting of a well-organized interventional suite. The method is relatively low-cost and affords a high rate of success.

Disclosure of interest
The authors declare that they have no conflicts of interest concerning this article.

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