N-Butyl Cyanoacrylate Embolization for Control of Nonvariceal Gastric Bleeding: A 4.5-Year Retrospective study of Treatment and Outcome

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To retrospectively evaluate the clinical efficacy and safety of transcatheter arterial embolization (TAE) with N-Butyl Cyanoacrylate (NBCA) for gastric arterial bleeding.

Between July 2004 and February 2009, TAE for nonvariceal gastric bleeding was performed in 20 patients using NBCA as the primary embolic material at our institution (13 men, 7 women; mean age, 62.8 years). The endoscopic approach failed to control bleeding in all studied patients. TAE was performed using 1:1-1:3 mixtures of NBCA and iodized oil. Outcomes, including technical and clinical success rate, recurrent bleeding, 30-day mortality rate, and complications, were recorded.

The technical and clinical success rates were 100% and 85% (17/20), respectively. Recurrent bleeding occurred in three patients (15%) and the overall mortality rate within 30 days was 45%. Follow up endoscopic evaluations were performed in 11 patients (55%) after the embolization. Multiple shallow gastric ulcers were seen in three of the 11 patients (27%) who underwent embolization of a large area, and conservative treatment was sufficient. No symptomatic gastrointestinal ischemia, stenosis, or obstruction was observed in any of the patients.

Despite the more complex arterial network and angulation of the gastric arterial supply, TAE with NBCA is feasible, rapid and safe in the management of gastric arterial bleeding.

Transcatheter arterial embolization (TAE) has been widely used to control nonvariceal upper gastrointestinal hemorrhage, especially when prior therapeutic endoscopy has failed to stop bleeding [1-3]. A variety of embolic materials have been used for embolization and the more commonly used agents are gelatin sponge pieces and coils [4]. Embolization with these materials may be ineffective in some cases as a result of inability to adequately reach the bleeding site, collateral blood flow to the bleeding site, or recanalization of the embolized vessels [5]. N-Butyl Cyanoacrylate (NBCA) as a liquid embolic material has been rarely used, because of concerns about complicated ischemic injury and the difficulty of handling the materials. However, NBCA is considered able to achieve hemostasis more rapidly; this is very important, particularly in cases of life-threatening massive bleeding [6]. Besides, permanent hemostasis can be achieved by a single injection with simultaneous embolization of collateral vessels connected to the bleeding focus, which can cause back bleeding or rebleeding if not treated.

Embolization of the upper gastrointestinal tract is generally safe owing to the rich collateral arterial supply of the stomach and duodenum. The more complex arterial network and angulation of the gastric arterial supply makes localized embolization of
arterial bleeding from the stomach more difficult and complicated [7]; consequently the efficacy of angiographic therapy for gastric and duodenal arterial bleeding should be studied separately. However, there has been little published information focusing on massive arterial bleeding from the stomach [8, 9]. The studies reported by Lang et al and Rosch et al demonstrated that the patients were treated with embolotherapy using only pledges of gelfoam or steel coils. The purpose of this retrospective study was to evaluate the clinical efficacy and safety of TAE with NBCA for nonvariceal gastric bleeding that could not be controlled by conventional endoscopic procedures at our institution over a 4.5-year period.

MATERIALS AND METHODS

Between July 2004 and February 2009, TAE for nonvariceal gastric bleeding was performed in 20 patients using N-Butyl Cyanoacrylate (Histoacryl, Braun, Melsungen, Germany) as the primary embolic material at our institution and these patients were included in this study. There were 13 men and 7 women, with an age range of 36-80 years (mean age, 62.8 years). The endoscopic approach had failed because of its inability to control the bleeding in all patients before angiographic therapy. Retrospective collection of data about clinical records and medical imagings was carried out for all patients. Pertinent patient information including comorbid conditions, shock status, coagulopathy and transfusion of packed red blood cells prior to TAE was summarized in the Table. The causes of bleeding included benign gastric ulcers (n = 16) and gastric cancers (n = 4).

The embolized arteries were the left gastric arteries (n = 8), right gastric arteries (n = 5), left gastroepiploic artery (n = 1), right gastroepiploic arteries (n = 3), short gastric artery (n = 1), left inferior phrenic artery (n = 1) and collateral vessel from superior mesenteric artery (n = 1). The angiographic findings were extravasation of contrast media in 18 patients (two mixed with pseudoaneurysm formation), abnormal mucosal blush and no imaging evidence of contrast extravasation in 1 patient, each.

Approval for this retrospective review of imaging and medical records was obtained from the institutional review board at our hospital. Written informed consent for transcatheter embolization was obtained from each patient or a family member. After common femoral artery puncture, a standard 4-F angiographic catheter was used to access suspected bleeding sites and it was also used as an introducing catheter. Diagnostic angiograms of the celiac, the left gastric and gastroduodenal arteries were performed routinely to identify the bleeding source. If no obvious bleeding site could have been identified, further selective angiography, based on previous endoscopic findings, such as right gastric, gastroepiploic, splenic or inferior phrenic arteriogram, was necessary. Then a 2.7-F microcatheter (Progreat, Terumo Co., Tokyo, Japan) was advanced as close as possible to the bleeding point for the embolotherapy. The mixing rate, administered dose and endpoint of the mixture of NBCA and iodized-oil (Lipiodol, Andre Guerbet, Aulnay-Sous-Bois, France) were basically determined by manual test injection of contrast medium under fluoroscopic guidance. We determined the appropriate dilution and amount of NBCA depending on the flow rate, the distance between microcatheter tip and the target of embolization, and the injection time required for extravasation of the contrast medium from the bleeding site or filling of the pseudoaneurysm with or without the presence of anastomotic channels after test injection. We mixed NBCA with iodized-oil in ratios varying from 1:1 to 1:3. Extravasation of the NBCA mixture from the bleeding site, filling of the afferent and efferent arteries and/or the pseudoaneurysm, and unexpected overflow or backflow into other vessels were considered as the endpoint of embolization (Fig. 1).

Prior to injection of the NBCA mixture, the microcatheter was flushed with 5% dextrose solution to prevent premature polymerization of the mixture from contacting with residual blood or saline. The NBCA mixture was injected using a 3mL syringe under careful fluoroscopic monitoring. Only a small amount of NBCA mixture, approximately 0.2-0.6 mL (excluding intraluminal volume of about 0.3mL of progreat), was necessary to reach target embolization. Immediately after the injection, the microcatheter was removed to prevent adherence of the mixture to the bleeding point and being discarded without flushing. Then the inner lumen of the guiding catheter was aspirated and post-embolization angiography was performed.

The outcomes, including technical and clinical success rates, recurrent bleeding, 30-day mortality rate, and complications, were evaluated. Technical success was defined as when post-embolization angiography demonstrated cessation of extravasation with no back-bleeding from collateral flow, no opacification of the pseudoaneurysm on celiac or
NBCA for control of nonvariceal gastric bleeding

no superior mesenteric involvement on angiograms at the end of the procedure. Clinical success was defined as clinical improvement with complete cessation of bleeding after embolization without the need for emergent surgery or other interventional procedures. Cessation of bleeding was defined by a clear nasogastric aspirate by 24 hours after embolization or absence of bleeding on endoscopic examination as well as stabilization of the hemoglobin level within 48 hours of the embolization procedure. Patients who met one of the following criteria were considered to have a coagulopathy: prothrombin ratio greater than 1.5, partial thromboplastin time greater than 45 seconds, or platelet count of less than 80,000/\( \text{L} \) [2, 10, 11]. Hypovolemic shock was defined by a systolic pressure < 100 mmHg and heart rate > 100 beats per minute.

**RESULTS**

Characteristics of clinical data and procedures in all 20 patients are summarized in Table 1. It was possible for the delivery of the NBCA mixture to the bleeding site in 19 study patients. Empirical embolization of the left gastric artery using NBCA was performed in one patient according to the endoscopic finding of a deep gastric ulcer at the lesser curvature side of the middle body. The technical success rate was 100% (20/20). The NBCA mixture was the only embolic material used to achieve angiographic success in 18 patients; other embolic agents were used in combination with NBCA mixture in two patients, microcoil in one case and gelatin sponge pieces in one case.

Clinical success was achieved in 17 patients...
<table>
<thead>
<tr>
<th>Patient No./Age/Sex</th>
<th>Underlying disease</th>
<th>Shock</th>
<th>Coagulopathy</th>
<th>PRBC prior to TAE</th>
<th>Angiographic finding</th>
<th>Vessel embolized using NBCA</th>
<th>Follow up endoscopy</th>
<th>Clinical success</th>
<th>Survival within 30 days</th>
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</thead>
<tbody>
<tr>
<td>1/66/m</td>
<td>GU, DM, ESRD, LC</td>
<td>Yes</td>
<td>Yes</td>
<td>8</td>
<td>Extravasation</td>
<td>LGA</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<td>2/67/f</td>
<td>GU, breast cancer, pneumonia with respiratory failure, congestive heart failure</td>
<td>No</td>
<td>Yes</td>
<td>2</td>
<td>Extravasation</td>
<td>LGA</td>
<td>Yes*</td>
<td>Yes</td>
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<tr>
<td>3/73/f</td>
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<td>Yes</td>
<td>No</td>
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<td>Extravasation</td>
<td>LGA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4/76/f</td>
<td>GU, lung cancer</td>
<td>No</td>
<td>Yes</td>
<td>6</td>
<td>Extravasation</td>
<td>RGA</td>
<td>No</td>
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<td>5/36/m</td>
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<td>Yes</td>
<td>6</td>
<td>Extravasation and pseudoaneurysm</td>
<td>LGA</td>
<td>No</td>
<td>Yes</td>
<td>No, sepsis</td>
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<td>6/46/m</td>
<td>GU, lung cancer, pneumonia with respiratory failure</td>
<td>No</td>
<td>Yes</td>
<td>2</td>
<td>Abnormal mucosal blush</td>
<td>RGA</td>
<td>No</td>
<td>Yes</td>
<td>No, respiratory failure</td>
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<td>7/77/m</td>
<td>Marginal ulcer, HCC, LC, subtotal gastrectomy due to GU</td>
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<td>Yes</td>
<td>6</td>
<td>Extravasation</td>
<td>LGEA</td>
<td>Yes</td>
<td>No</td>
<td>No, rebleeding</td>
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<tr>
<td>8/72/m</td>
<td>Gastric cancer bleeding, pneumonia</td>
<td>Yes</td>
<td>No</td>
<td>2</td>
<td>Extravasation</td>
<td>LIPA</td>
<td>Yes</td>
<td>Yes</td>
<td>No, MOF</td>
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<td>9/71/m</td>
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<td>No</td>
<td>No</td>
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<td>LGA</td>
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<td>No</td>
<td>4</td>
<td>Extravasation</td>
<td>RGA</td>
<td>No</td>
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<td>11/54/m</td>
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<td>No</td>
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<td>12/49/f</td>
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<td>Yes</td>
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<td>SGA</td>
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<td>Extravasation</td>
<td>RGA</td>
<td>Yes*</td>
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<td>LGA</td>
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<td>No</td>
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<td>Extravasation</td>
<td>LGA</td>
<td>Yes*</td>
<td>Yes</td>
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<td>17/50/f</td>
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<td>Yes</td>
<td>No</td>
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<td>Negative</td>
<td>LGA</td>
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<td>No</td>
<td>No, rebleeding</td>
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<td>Collateral from SMA</td>
<td>No</td>
<td>Yes</td>
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<td>RGEA</td>
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<td>Yes</td>
<td>18</td>
<td>Extravasation</td>
<td>RGEA</td>
<td>No</td>
<td>Yes</td>
<td>No, MOF</td>
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* Follow up endoscopy revealed multiple shallow gastric ulcers, which could be related to the proximal or segmental embolization performed in the parent arteries.
occlusion and are available in a wide variety of sizes. Precise. They provide controlled delivery with rapid control of gastrointestinal hemorrhage [5]. Coils with metallic coils and/or particulate agents for the occlusion of normal tissue. TAE is typically performed in 1 to 3 seconds estimated after the test injection. The test injection is strongly recommended for optimal control of its embolic distribution. After a short learning curve, NBCA can opacify the agent and polymerization time can be tempered with an increased ratio of iodized oil to NBCA. Pollak et al suggested that the estimated in vivo was 1-3 seconds, to achieve embolization far peripheral to the delivery. Microcatheter tip or directly at the tip by controlling the speed of polymerization and the injection rate [12, 13]. The addition of iodized oil to NBCA can opacify the agent and polymerization time can be tempered with an increased ratio of iodized oil to NBCA. Combination of iodized oil and NBCA can be used as a technique to achieve slow, controlled delivery.

There was no evidence of symptomatic infarction of the bowel or other major complications directly related to NBCA embolization in any of the patients. Follow up endoscopic evaluations were performed in 11 patients (55%) between 1 and 1122 days (mean 184 days) after the embolization. In three of the 11 patients (27%) (patient 2, 13 and 16), multiple shallow gastric ulcers, which could be related to embolization of a large area, were found. However, none of these patients presented with symptoms or signs of gastroduodenal ischemia or clinically significant gastroduodenal stenosis or obstruction.

DISCUSSION

Acute upper gastrointestinal haemorrhage is a common and potentially life-threatening problem. Despite the prominence of endoscopy, therapeutic radiological procedures play an important role in the management of upper gastrointestinal haemorrhage resistant to endoscopic therapy in recent years [1-3]. A variety of embolic agents have been used and major considerations for choosing an embolic occluding agent are speed and reliability of delivery, duration of occlusive effect, and preservation of normal tissue. TAE is typically performed with metallic coils and/or particulate agents for the control of gastrointestinal hemorrhage [5]. Coils are ideal for single vessel injuries, larger vessels, or cases in which the site of vessel occlusion must be precise. They provide controlled delivery with rapid occlusion and are available in a wide variety of sizes. However, embolization with coils requires placement of a catheter or microcatheter at the bleeding site. This is not always possible as a result of small vessel size or tortuous vessel anatomy. In cases in which lesions are multiple, distal in location, or supplied by numerous collateral pathways, the use of particulate agents is indicated. However, particulate agents may clump and occlude the delivery catheter and can be difficult to deliver through small microcatheter or through tortuous anatomy.

NBCA is an alternative permanent liquid embolic material and tissue adhesive that was approved by the US Food and Drug Administration for use in cerebral arteriovenous malformations in 2000. NBCA as a liquid embolizer requires experience for optimal control of its embolic distribution. After a short learning curve, NBCA can be injected to achieve occlusion far peripheral to the delivery microcatheter tip or directly at the tip by controlling the speed of polymerization and the injection rate [12, 13]. The addition of iodized oil to NBCA can opacify the agent and polymerization time can be tempered with an increased ratio of iodized oil to NBCA. Combination of iodized oil and NBCA can be used as a technique to achieve slow, controlled delivery.
any of the patients after NBCA embolization during follow-up period. These results correlate well with the experience of Yamakado et al and Kish et al [5, 16], who similarly had no cases of organ infarction. Although further study is necessary to determine the safety margin of this agent more definitively, NBCA embolization is feasible when performed with an understanding of the regional arterial anatomy and collateral blood supply. Occasionally, previous surgery may result in precarious collateral supply and in these patients embolization should be performed with caution. The gastroduodenal ischemia can be avoided with careful attention to the vascular anatomy and to the injection of embolic agent as selective as possible into the bleeding vessel.

Other reported complications of NBCA embolization include abscess formation and entrapment of the delivery catheter within the embolized artery [17-19]. In our 20 patients, no catheter entrapment occurred but sepsis developed in one patient (patient 5) two days after embolization. Although bacteremia was reported once after injection of NBCA [7], it could be difficult to determine the true cause of bacteremia or sepsis because both the patient reported by Lee et al and the case in our series had undergone other invasive procedures, including injection of epinephrine at panendoscopy and insertion of a central venous catheter.

The stomach has abundant submucosal plexuses supplied by the left and right gastric, gastroepiploic, gastroduodenal, splenic, and inferior phrenic arteries. Despite the plethora of vessels supplying the stomach, however, most cases of gastric bleeding with angiographically demonstrated contrast extravasation are found to be originated from branches of the left gastric artery [20]. Prophylactic embolization of the left gastric artery has been reported as a safe and successful procedure to control the presumed intermittent bleeding in patients with endoscopically documented recurrent gastric bleeding but with no active extravasation angiographically [21, 22]. In our series, we had successfully controlled the bleeding (patient 17) after prophylactic embolization of the left gastric artery, although she still died of multi-organ failure thereafter. In one case (patient 2), microcoils were used in combination with NBCA for blockade of high flow rates through parent artery distal to the orifice of the bleeding vessel and, then, the microcatheter was withdrawn to the proximal portion of the parent artery for NBCA injection. Lee et al [7] performed similar segmental embolization by injecting a higher concentration (40%) of NBCA at a very slow rate into parent artery distal to the orifice of the bleeding branch and then withdrawing the microcatheter to proximal portion for continuous NBCA injection. In our opinion, when the flow rate of the parent artery is very high, microcoil in combination with NBCA may provide segmental embolization with a more precise and safe advantage. Gelatin sponge pieces were used in combination with NBCA for empirical blockade of left and right gastric arteries in addition to embolization of the bleeding left inferior phrenic artery using NBCA in one case (patient 9) with massive bleeding from gastric cardiac cancer. Clinical success was achieved without rebleeding from cancer but the patient died within 30 days because of multi-organ failure.

The study reported by Lang et al focused on massive arterial bleeding in the stomach showed that the mortality rate of patients treated with embolotherapy using pledgets of Gelfoam or steel coils was 46% [8]. While the overall mortality of all patients with nonvariceal upper gastrointestinal bleeding remains 6–10%, the mortality rate of patients who required urgent surgery was 17–43% and that of patients who required transcatheter embolization was 10–45% [10, 11, 23]. Encarnacion et al [10] demonstrated that three patients in their series treated with embolotherapy using gelatin sponge plugs died of causes unrelated to bleeding (preexisting meningitis or aspiration pneumonia related to achalasia and sepsis) and the mortality rate in this group was 10%. However, other ten patients continued to bleed and subsequently died after embolization and the overall mortality rate in their study was 45%. Their patient population had a high incidence of underlying medical conditions, and coagulopathy had a significant impact on the mortality rate. Clinical factors that predicted poor outcomes except coagulopathy were multi-organ failure, cirrhosis, older age, cancer, and the recurrence of bleeding [2]. Walsh et al found longer time to angiography (P=.01), more total units of packed red blood cells (P=.003), and prior surgery for bleeding (P=.02) to be predictors of embolization failure by multivariate analysis [24]. However, the clinical results of previous studies varied considerably and most studies have included a mixed population of all upper gastrointestinal bleeding. In our experience, focusing on nonvariceal gastric bleeding using NBCA for embolization, the mortality rate (45%) within 30 days was relatively high. Advanced age, coagulopathy, more transfusion of packed red blood cells prior to procedure, and more comorbidities in our patient population probably contributed
to the high mortality rate, which simultaneously reflects the high surgical risk in this population.

In conclusion, although a more complex arterial network and angulation of the gastric artery makes localized embolization for arterial bleeding from the stomach more difficult and complicated, NBCA can be an alternative embolic material which is effective, rapid and safe for use in transcatheter arterial embolization for gastric bleeding and it may possibly be life-saving in very emergent situations. Modern endovascular devices with better maneuverability enable more precise assessment of target vessels with delivery of NBCA to a limited area. Therefore, serious complications, such as bowel ischemia and innocent vessel embolization, can be minimized by adequately trained interventionists. The limitation of this study lies mainly in the small number of patients. Further studies should be undertaken to fully document these findings and long-term complications should be carefully observed. ▶

REFERENCES

利用氰基丙烯酸正丁酯（NBCA）治疗非静脉瘤之胃出血：回顾四年半之治疗成效

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陈炯毓3 方瑞隆1

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本篇回溯性收集2004年7月至2009年2月间，利用氰基丙烯酸正丁酯（NBCA）经导管动脉栓塞术，治疗非静脉瘤胃出血之病例计20例。所有病例先以内镜治疗胃出血，失败后才进行经导管动脉栓塞术，NBCA和碘化油（iodized oil）以1:1至1:3的比例混合，藉以控制其黏稠度及凝固时间，来进行胃出血栓塞。栓塞技术之成功率100%，临床治疗成功率为85%，三位病患栓塞后发生再出血（15%），其中两人在一个月内死亡，而整体之30天内死亡率为45%，11位病人（55%）在栓塞后接受追踪性内镜检查，其中三人产生数个细小而浅的胃溃疡并接受保守性治疗，所有病人皆无肠梗阻或狭窄发生。因此，虽然胃动静脉血管较为复杂，但利用NBCA 经导管动脉栓塞术治疗非静脉瘤胃出血，仍为一有效、快速、而安全的治疗方式。