Percutaneous transcatheter super-selective renal arterial embolization with N-butyl cyanoacrylate for iatrogenic renal hemorrhage

Xishan Li\textsuperscript{a}, Guodong Chen\textsuperscript{a,*}, Dongliang Zhu\textsuperscript{b}

\textsuperscript{a} Department of Interventional Radiology, Guangzhou First People’s Hospital, No.1 Panfu Road, Guangzhou, 510180, PR China
\textsuperscript{b} Department of Interventional Operation Center, Guangzhou First People’s Hospital, No.1 Panfu Road, Guangzhou, 510180, PR China

\section*{ARTICLE INFO}

\textbf{Keywords:}
Iatrogenic Renal hemorrhage N-butyl cyanoacrylate Super-selective Renal arterial embolization

\section*{ABSTRACT}

\textbf{Background:} To evaluate the safety and efficacy of percutaneous transcatheter super-selective renal arterial embolization (SRAE) with N-butyl cyanoacrylate (NBCA) for iatrogenic renal hemorrhage.

\textbf{Methods:} Between January 2014 and December 2019, 45 patients (including 18 patients with coagulopathy), who underwent percutaneous transcatheter SRAE with NBCA for iatrogenic renal hemorrhage at our institution, were retrospectively reviewed. The technical success rate, clinical success rate, and embolization-related complications were analyzed. The values of estimated glomerular filtration rate (eGFR), serum creatinine (sCr), and serum urea (sUr) were analyzed at the time of pre-SRAE, post-SRAE, and last follow-up to evaluate the effects of NBCA-based SRAE on renal function.

\textbf{Results:} Diagnostic renal arteriography revealed contrast extravasation in 18 patients and pseudoaneurysms in 27 patients. NBCA mixed with iodized oil in a 1:2–1:4 ratio was the sole embolic agent. No procedure-related mortality or major complications occurred. The technical and clinical success rates were both 100%. The values of eGFR, sCr, and sUr were not found to be significantly different between pre-SRAE, post-SRAE and last follow-up (eGFR: $91.52 \pm 21.17$ vs. $90.98 \pm 22.11$ vs. $92.14 \pm 23.51$ mL/min/1.73 m$^2$, $p = 0.729$; sCr: $74.73 \pm 11.08$ vs. $75.27 \pm 12.43$ vs. $73.95 \pm 10.14$ μmol/L, $p = 0.543$; sUr: $5.69 \pm 0.84$ vs. $5.71 \pm 0.96$ vs. $5.70 \pm 0.79$, $p = 0.515$, respectively).

\textbf{Conclusions:} Percutaneous transcatheter SRAE with NBCA is a safe and effective treatment modality for iatrogenic renal hemorrhage with no deterioration of renal function.

\section*{1. Introduction}

Iatrogenic renal hemorrhage has increased in clinical settings because of the extensive utilization of urological interventional procedures. Conservative therapies, such as nephrostomy tube clamping, hemostatic drug use, and blood transfusion, are the first-line approaches to hemodynamically stable patients. However, given that arterial hemorrhage may not be self-limiting, massive hemorrhage or continuous hematuria with hemodynamic instability may result from prolonged hemorrhage.

Percutaneous transcatheter super-selective renal arterial embolization (SRAE) has been widely used as a preferred alternative to conservative therapies for hemodynamically unstable renal hemorrhage. It is shown to be associated with a high success rate, low incidence of complications, and minimal impact on renal function.\textsuperscript{1,2} Emergency arteriography is the golden diagnostic method to reveal the injured renal artery or its branches, and performing embolization in the same session is effective in stopping the bleeding.\textsuperscript{1,2} A variety of embolic agents have been used in SRAE for renal hemorrhage, including gelatin sponge pieces, polyvinyl alcohol particles, microcoils, and liquid glue, all with their own pros and cons.\textsuperscript{3–8} A consensus on which embolic agent should be used is lacking. Thus, the choice of embolic agent is usually made on a case-by-case basis, depending on various factors such as vascular anatomy and pathology, coagulation status of the patient, material availability, and personal preference of the interventional radiologist performing the procedure.\textsuperscript{9–10}

N-butyl cyanoacrylate (NBCA), a liquid and permanent glue embolic agent, has been widely used in vascular interventions for bleeding, aneurysm, vascular malformation, and other pathophysiologies.\textsuperscript{11–24} NBCA polymerizes immediately upon contacting blood and occludes the vessel regardless of the patient’s coagulation status, \textsuperscript{9,10} which is effective for patients with coagulopathy. Owing to its low degree of viscosity, NBCA can be delivered far distally to the delivery catheter and offers...
immediate occlusion of small arteries and collateral circulations. This has been considered a huge advantage, given that small arteries and collat- eral circulations are difficult to be embolized with microcoils and other solid embolic agents in a single session in cases of life-threatening bleeding that requires urgent hemostasis. In this article, we analyzed the safety and efficacy of SRAE using NBCA as the sole embolic agent in the treatment of iatrogenic renal hemorrhage.

2. Patients and methods

2.1. Patients

Between January 2014 and December 2019, 45 patients (25 men and 20 women; mean age, 48.46 ± 16.37 years; range, 26–77 years), who underwent transcatheter SRAE with NBCA for iatrogenic renal hemor-

rhage at our institution, were retrospectively reviewed. The indications for angiography and SRAE included clinical hemorrhagic symptoms (persistent gross hematuria lasting ≥72 h, persistent or sudden flank or back pain, or hemodynamic instability requiring blood transfusion) and imaging evidence of vascular injury (perirenal hematoma, active extravasation of contrast medium, pseudoaneurysm formation, etc.). Only those patients in which conservative therapies were not deemed to be effective were included. Patients who were allergic to contrast agents or had thyroid dysfunction and uncontrolled infection were excluded.

Iatrogenic renal hemorrhage was defined as renal hemorrhage after urological interventional procedures. The iatrogenic etiologies consisted of percutaneous renal biopsy (n = 13), nephrolithotomy (n = 11), lith-
thripsy (n = 8), nephrostomy (n = 7), and partial nephrectomy (n = 6). Hemodynamic instability was defined as systolic pressure ‘100 mmHg and/or heart rate ‘100 beats/min. Coagulopathy was defined by platelet count <5 x 10^4/μL and/or international normalized ratio (INR) > 1.5.11

This study was approved by the institutional review board of our institution. Written informed consent for angiography and SRAE was obtained from each patient and/or the patient’s family.

2.2. SRAE procedure

After a common femoral artery puncture under local anesthesia, diagnostic renal arteriography was performed with a 5-F catheter (MIK, Cook, Bloomington, IN; or Cobra, Terumo, Tokyo, Japan) to identify the hemorrhage site according to the iatrogenic operation site. A 2.7-F microcatheter (Microferret; Cook, Bloomington, IN) was then introduced coaxially, and the tip was advanced as close to the site of vascular injuries as possible. NBCA (Histoacryl; B. Braun, Melsungen, Germany) was mixed with lipiodol (Ethiodised Poppysed Oil Injection; Jiangsu Hengrui Medicine Co., Ltd., P.R. China) at a 1:2–1:4 ratio, depending on the distance from the tip of the microcatheter to the target lesion and the rate of blood flow through the vessel. Before the NBCA-lipiodol mixture injection, the microcatheter was flushed with a 5% glucose solution to prevent its polymerization. The NBCA-lipiodol mixture was injected slowly using a 1 mL syringe under continuous digital subtraction angiography monitoring. The adequate volume and injection rate of the NBCA-lipiodol mixture were estimated by a simulated injection with contrast medium, and the endpoint for the injection was extravasation of the NBCA-lipiodol mixture from the bleeding site or filling of the pseu-
doaneurysm with or without the appearance of anastomotic channels. Immediately after the injection, the microcatheter tip was pulled back slowly without flushing until it was no longer in contact with the column of NBCA-lipiodol mixture in the embolized artery, after which the de-
livery microcatheter was removed quickly and washed with 5% dextrose solution for potential reuse. The 5-F angiographic catheter was aspirated and then flushed. Then post-SRAE arteriography was performed to confirm successful occlusion of the target vessel (Figs. 1–5).

All procedures were performed by one or two interventional radiolo-
gists with more than 5 years of clinical experience in SRAE. During the peri-procedure, strategies, including intravenous saline hydration and using iso-osmolar contrast agents (Visipaque 320, GE Healthcare, Cork, Ireland), were performed to prevent contrast-induced nephropathy.15 Antibiotic prophylaxis with a first-generation cephalosporin was initiated

Fig. 1. Case 1. Male, 35 years. After the left renal percutaneous lithotripsy, coil embolization was performed in another hospital for renal hemorrhage, and the left side continued low back pain accompanied by hematuria lasted 1 week. CT scan revealed a slightly high-density area in the left renal parenchyma, which was considered to be an active hemorrhagic hematoma(a1). The selective and super-selective DSA angiography, respectively, identify the rupture of the small artery branch of the left renal artery with contrast agent extravasation (a3–4). The contrast extravasation disappeared after 0.4 mL NBCA glue embolization(a5). 1 month later, CT reexa-
namination of renal low-density area considered hematoma absorption(a2).
at the beginning of SRAE. Patients were followed up with a clinical visit one month after the procedure and once every 3–6 months thereafter. Follow-up imaging, such as ultrasonography and computed tomography (CT) imaging, was performed as appropriate during the follow-up.

2.3. Definitions

The embolization time was defined as the elapsed time from the angiographic detection of hemorrhagic signs to that confirming cessation of bleeding on post-SRAE arteriography.9 Technical success was defined as angiographic evidence of bleeding cessation on post-SRAE arteriography.1,15 Clinical success was defined as no recurrent hemorrhage without the need for further intervention or surgical procedure.1 The values of estimated glomerular filtration rate (eGFR), serum creatinine (sCr), and serum urea (sUr) at diagnosis of iatrogenic renal hemorrhage (pre-SRAE), one month after embolization (post-SRAE), and at last follow-up were recorded and analyzed to evaluate the effects of NBCA-based SRAE on renal function. Patients undergoing hemodialysis were excluded from the analysis. All complications were recorded and classified in accordance with the Committee of Practice Guidelines of the Japanese Society of Interventional Radiology, 2012 edition.11

2.4. Statistical analysis

All analyses were performed using the Statistical Package for the Social Sciences software (version 23.0; SPSS Inc., Chicago, IL). Categorical variables were presented as numbers with percentages, and continuous variables were presented as mean ± standard deviation. The values of eGFR, sCr, and sUr at pre-SRAE, post-SRAE, and the last follow-up were compared using repeated measures analysis of variance. A two-sided \( p < 0.05 \) was statistically significant.

3. Results

The clinical symptoms included hematuria in 20 patients, sudden flank or back pain in 16 patients, and hemodynamic instability in 9 patients. Eighteen patients (40.0%) had a coagulopathy with platelet count <5 × 10^9/μL (n = 8, 17.8%) and/or INR >1.5 (n = 10, 22.2%). The median level of hemoglobin decrease before SRAE was 58.5 ± 21.6 g/L (range, 17–97). Nine patients received transfusion before SRAE, and the mean unit of blood transfusion was 4.7 ± 2.6 units (range, 3.5–7.0 units). Ultrasonography and/or CT were performed in 30 of the patients before angiography, and the other 15 underwent immediate angiography without any diagnostic radiologic examinations. The details of patients and clinical characteristics are presented in Table 1.

3.1. Technical and clinical outcomes

The mean time from iatrogenic operation to hemorrhage and SRAE were 7.3 ± 2.1 days (range, 0–17 days) and 8.6 ± 1.2 days (range, 0–23 days), respectively. Diagnostic renal arteriography revealed contrast extravasation in 20 patients and pseudoaneurysm in 25 patients. The median number of pseudoaneurysms was 1 (range, 1–3) with a median size of 21 mm (range 8–47 mm).

All patients were successfully treated in a single-session NBCA-based SRAE and showed excellent angiographic results and significant
improvement in their clinical courses. NBCA mixed with iodized oil in 1:2–1:4 ratios were the sole embolic agent used for all native patients. The majority of NBCA had a lipiodol ratio of 1:3 (n = 30). The mean volume of the NBCA-lipiodol mixture injected per patient was 0.94 ± 0.43 mL (range, 0.4–0.2 mL), and the mean embolization time was 5.93 ± 2.60 min (range, 3–14 min). The mean duration of hospitalization from embolization to discharge was 5.78 ± 1.38 days (range, 3–10 days). Details of angiographic findings and NBCA-based SRAE procedures are given in Table 2.

The technical and clinical success rates were both 100%. The clinical symptoms were alleviated immediately (n = 14) or 2–4 days (n = 31) after SRAE, and no recurrent hemorrhage occurred during a median follow-up period of 41 months (range, 8–78 months). Six patients were haemodynamic instability prior to the procedure, but all patients recovered immediately after the embolization procedure. None required a post-procedural blood transfusion.

### 3.2. Complications

No procedure-related mortality or major complications occurred. Two patients (4.4%) had minor complications (light or mild back or abdominal pain in the side of the embolized kidney), which were managed conservatively for 1–3 days. Other complications mentioned in reported studies, such as catheter sticking, non-target embolization, peri-renal abscess or renal abscess, arterial hypertension, and others with endovascular procedures (puncture-site hematoma, arterial dissection or rupture, thrombosis, contrast-induced nephropathy, anaphylactic reactions, etc.), were not observed in any of the patients.

### 3.3. Effects of NBCA-based SRAE on renal function

The effects of SRAE on renal function could be analyzed in 39 patients (66%), excluding 6 patients with pre-existing chronic kidney disease who required hemodialysis before iatrogenic renal injury. The values of eGFR,
Table 2
Details of angiographic findings and NBCA-based SRAE procedures.

| Characteristics                        | Results |
|----------------------------------------|---------|
| Angiographic findings                  | 18      |
| Contrast extravasation                 | 27      |
| Pseudoaneurysm                         | 21      |
| Site of vascular lesions               | 11      |
| Upper pole                             | 13      |
| Middle pole                            | 12      |
| Lower pole                             | 9       |
| Anatomical levels of vascular injuries | 5       |
| Segmental artery                       | 8       |
| Interlobar or distal artery            | 31      |
| Capular artery                         | 6       |
| Embolization time (min)                | 5.93 ± 2.60 (3-14) |
| NBCA: Lipiodol ratio                   | 1:2     |
|                                       | 7       |
|                                       | 1:3     |
|                                       | 30      |
|                                       | 1:4     |
|                                       | 8       |
| Volumes of used NBCA-lipiodol mixture (mL) | 0.94 ± 0.43 (0.4-2.2) |

Note-NBCA = N-butyl cyanoacrylate, SRAE = superselective renal arterial embolization.

- Values are presented as number.
- Values are presented as mean ± standard deviation (range).

sCr and sUr were not significantly different at the time of pre-SRAE, post-SRAE, and the last follow-up (eGFR: 91.52 ± 21.17 vs. 90.98 ± 22.11 vs. 92.14 ± 23.51 mL/min/1.73 m², p = 0.729; sCr: 74.73 ± 11.08 vs. 75.27 ± 12.43 vs. 73.95 ± 10.14 μmol/L, p = 0.543; sUr: 5.69 ± 0.84 vs. 5.71 ± 0.96 vs. 5.70 ± 0.79, p = 0.515, respectively). Details about the analysis of renal function are given in Table 3.

4. Discussion

Previous studies have shown that embolization of iatrogenic renal arterial injuries is a safe, effective, and tissue-preserving treatment method that is associated with high technical and clinical success rates.16 The present study, including 45 patients, is one of the largest studies describing the technical and clinical success rates of SRAE with NBCA for iatrogenic renal hemorrhage. The NBCA-lipiodol mixture occludes the injured renal artery definitively with neither recanalization nor recurrent bleeding occurring during the median follow-up period of 41 months. The rate of technical and clinical success was 100%, and the rates of recurrent bleeding, major complications, and in-hospital mortality were 0%. The high success rate of the present study suggests equivalent efficacy to that found in some previous studies.16-17 This study, therefore, reiterated the feasibility and efficacy of NBCA-based SRAE.

NBCA occludes vessels instantly by polymerizing in the blood, and the embolization can be completed quickly in cases of acute arterial hemorrhage, which is vital in saving a patient’s life by preventing them from falling into an irrecoverable condition, especially in cases of life-threatening hemorrhagic shock. A case-control study reported that the operations were completed more quickly in the NBCA group (9 ± 4 min) than in the microcoil group (37 ± 19 min) or in the gelatin sponge particle group (25 ± 10 min).1 In our study, the mean embolization time was 5.93 ± 2.60 min (range, 3–14 min). Timely and effective hemostasis is important to reduce medical disputes in the current medical environment in China.

The most common complication following SRAE with NBCA is a post-embolization syndrome, including flank pain, fever, nausea, and vomiting 1–3 days following embolization. In our series, 2 patients (4.4%) experienced self-limiting back or abdominal pain in the side of the embolized kidney, which complies with the reported incidence of 0.6–7.5%. Prophylactic administration of anti-inflammatory and anti-nausea agents before SRAE can lessen the effects of the post-embolization syndrome and avoid subsequent infection of infarcted areas.18 Non-target embolization might be caused by an overflow of NBCA to proximal vessels, migration of NBCA upon withdrawal of a microcatheter, or unintended inflow of NBCA through a collateral vessel.19 Other reported adverse events specific to NBCA, such as intra-vascular fixation of the microcatheter, secondary vascular rupture after withdrawal of a fixed catheter,20 and disrupted and residual microcatheter,21 were not observed in this study. The super-selective procedure, with the microcatheter tip wedged within the vascular lumen, reduces the pericatheter flow and decreases the risk of reflux of NBCA, thereby facilitating the safe injection of NBCA. The adequate dose and injection rate volume of the NBCA-lipiodol mixture were estimated by a simulated injection with manual injection of contrast medium. The careful injection can avoid the reflux of the mixture into non-target vessels and minimize the risk of distal embolization.

In our series, renal function was preserved in 39 patients, and we did not observe significant impairment of renal function (eGFR, sCr, and sUr) between pre-SRAE, post-SRAE, and the last follow-up. These observations are consistent with previous studies that reported no significant change in renal function after SRAE for renal hemorrhage, which iterates the importance of super-selective embolization.21

A variety of embolic agents, including gelatin sponge pieces, polyvinyl alcohol particles, microcoils, and liquid glue, have been used in SRAE for renal hemorrhage, all with various pros and cons.5,6,8,22,23 The advantages of using a gelatin sponge include cost-effectiveness and a relatively low risk of tissue necrosis, whereas the risk of recanalization is thought to be high. Polyvinyl alcohol particles are associated with an increased risk of renal infarction because they cannot be visualized or precisely deposited and may reflux to non-target arteries. Microcoil embolization is the primary treatment of choice for renal hemorrhage, especially for pseudoaneurysms. However, coil embolization depends on the anatomy, the size of arterial lesions, and the technical ability to super-selective catheterization. The vessels may be too small or too tortuous to achieve stable catheter positioning or have many collateral circulations originating from the pseudoaneurysm, which is time-consuming and technically difficult to achieve ideal and prompt embolization.24

NBCA has several advantages as an embolic agent for iatrogenic hemorrhage compared with other embolic materials. Firstly, with the characteristic of low viscosity and fast polymerization, complete hemostasis using NBCA can be achieved easily by a single session through small or tortuous vessels or all potential collateral channels, which is important, particularly in cases of life-threatening bleeding that requires urgent hemostasis. Secondly, NBCA is useful in patients with coagulopathy because its polymerization is not affected by coagulation.25 Furthermore, Cantasdemir et al.26 reported that NBCA provides a permanent, cost-effective, and accurate embolization.

Acute arterial bleeding is likely to be more deadly for patients with coagulopathy than those without coagulopathy. Coagulopathy is, hence, considered a negative factor in the control of hemorrhage. Moreover, coagulopathy is associated with recurrent bleeding after SRAE for renal hemorrhage. When gelatin sponges, polyvinyl alcohol particles, or microcoils were used in patients with coagulopathy, the successful

Table 3
Effects of NBCA-based SRAE on renal function (N = 39).

| Variables                  | Pre-SRAE       | Post-SRAE      | At the last follow-up |
|----------------------------|----------------|---------------|-----------------------|
| eGFR (mL/min/1.73)         | 91.52 ± 0.729  | 90.98 ± 0.729 | 92.14 ± 23.51         |
| m²                         | 21.17 ± 1.12   | 22.11 ± 1.12  |                       |
| Serum                      | 74.73 ± 0.543  | 75.27 ± 0.543 | 73.95 ± 10.14         |
| creatinine(µmol/L)         | 11.08 ± 0.515  | 12.43 ± 0.515 |                       |
| Serum urea (mmol/L)        | 5.69 ± 0.84    | 5.71 ± 0.96   | 5.70 ± 0.79           |

Note-NBCA = N-butyl cyanoacrylate, SRAE = superselective renal arterial embolization, eGFR = estimated glomerular filtration rates.

Data are given as mean ± standard deviation.

- Six patients with pre-existing chronic kidney disease who required hemodialysis before SRAE was excluded.
- Repeated-measures analysis of variance was performed.
bleeding control rates were between 43% and 46%. Yonemitsu et al. reported that the recurrent bleeding rate was significantly higher in the gelfoam sponge group (23.1%) than in the NBCA group (0%) because gelfoam sponges, polyvinyl alcohol particles, and microcoils rely on the patients’ coagulation status for vessel occlusion. By contrast, NBCA polymerizes immediately upon contacting blood and occludes the vessels, regardless of the patient’s coagulation status. In our series, the presence of coagulopathy did not affect clinical outcomes, even though 18 patients suffered from coagulation disorders.

Liquid embolic agents, such as NBCA and Onyx, present the considerable advantage of low viscosity for easy injection through small or tortuous catheters, which provides faster and better hemostasis than other embolic agents. However, Onyx copolymer vials require being shaken on a mixer for at least 20 min before use to ensure adequate mixing and homogeneous radiopacity, which is time-consuming, especially for urgent life-threatening massive hemorrhage conditions. In addition, the Onyx copolymer is dissolved in dimethyl sulfoxide, a solvent excreted through the lungs, and systemic pulmonary toxicity related to Onyx embolization has been reported.

The application of NBCA is limited compared with other embolic materials, which possibly causes inadvertent embolization of the non-target vessels due to lack of control owing to its liquidity and quicker-than-desired rate of polymerization time. However, recent reports and the present study have shown that SRAE with NBCA is safe and effective, especially in the hands of an experienced interventional radiologist. Achieving a precise and safe embolization and reduced complications has several requirements, including familiarity with the specific vascular anatomy, a simulated injection with contrast media pre-embolization, injection monitoring under digital subtraction angiography guidance or road-mapping, use of a microcatheter without flushing after NBCA injection, and adequate experience and training. The application of NBCA for embolization of varied etiologies involving the renal artery is safe and effective in the hands of an experienced interventional radiologist.

Our study has several limitations. Firstly, the sample size and retrospective nature might have introduced bias in our results; however, a large sample of iatrogenic renal hemorrhage cases is difficult to obtain, and designing a prospective study is not feasible. Secondly, NBCA was used as a sole embolic agent in the present study, and no comparison with other embolic materials was performed. The encouraging outcomes of our study suggest a useful framework for future research to explore the safety and effectiveness of SRAE for non-iatrogenic renal hemorrhage.

5. Conclusions

Percutaneous transcatheter SRAE with NBCA is a safe and effective treatment for iatrogenic renal hemorrhage without deterioration of renal function.

Author contributions

Xishan Li: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision. Guodong Chen: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing - Review & Editing, Visualization, Supervision. Dongliang Zhu: Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing - Review & Editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors acknowledge the colleagues of the Department of Interventional Operative Centre in our hospital for their assistance in the collection of angiographic data.

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