Université de Bourgogne

UFR des Sciences de Santé

Circonscription Médecine

ANNEE 2017

N°

EFFICACITE ET SURETE DE L'EMBOLISATION D'HEMOSTASE AU CYANOACRYLATE GLUBRAN®2 : UNE ETUDE MONOCENTRIQUE DE 104 PATIENTS.

THESE

présentée

à l'UFR des Sciences de Santé de Dijon
Circonscription Médecine

et soutenue publiquement le 30 juin 2017

pour obtenir le grade de Docteur en Médecine

par GILLES ABDUL MALAK

Né(e) le 12 novembre 1988

à Sisteron

Université de Bourgogne

UFR des Sciences de Santé

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Remerciements

A mon jury de thèse,

A mon président de jury, Monsieur le Professeur Denis KRAUSE,
Je vous remercie pour votre enseignement spécialement en imagerie osteo-articulaire, ainsi que pour votre appui qui m'a permis de partir poursuivre ma formation dans ce domaine. Vous me faites l'honneur de présider ce jury. Trouvez ici l'expression de mon respect et de ma gratitude.

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SERMENT D'HIPPOCRATE

"Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions.

J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité.

Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera.

Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque."

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Liste des abréviations

TAE : Transcatheter arterial embolization

NBCA-MS : N-Butyl Cyanoacrylate Metacryloxylsulfolane

RBC :Red Blood Cells

INR : International Normalized Ratio

PTT : Thromboplastin Time

SIR : Society of Interventional Radiology

Safety and efficacy of transcatheter embolization with Glubran®2 cyanoacrylate glue for acute arterial bleeding: a single-center experience with 104 patients

Abstract

Purpose: To assess the efficacy and the safety of Glubran®2 n-butyl cyanoacrylate metacryloxysulfolane (NBCA-MS) transcatheter arterial embolization (TAE) for acute arterial bleeding from varied anatomic sites and to evaluate the predictive factors associated with clinical success and 30-day mortality.

Methods: Retrospective review of consecutive patients who underwent emergent NBCA-MS Glubran®2 TAE between July 2014 and August 2016. Variables including age, sex, underlying malignancy, cardiovascular comorbidities, coagulation data, systolic blood pressure and number of red blood cells units (RBC) transfused before TAE were collected. Clinical success, 30-day mortality and complication rates were evaluated. Prognostic factors were evaluated by uni- and multivariate logistic regression analyses for clinical success, and by uni- and bivariate analyses after adjustment by bleeding sites for 30-day mortality.

Results: 104 patients underwent technically successful embolization with bleeding located in muscles (*n*=34, 32.7%), digestive tract (*n*=28, 26.9%) and visceras (*n*=42, 40.4%). Clinical success rate was 76% (*n*=79) and 30-day mortality rate was 21.2% (*n*=22). Clinical failure was significantly associated with mortality ($p<0.0001$). A number of RBC units transfused greater than or equal to 3 was associated with poorer clinical success ($p=0.025$) and higher mortality ($p=0.03$). Complications (*n*=4, 3.8%) requiring surgery occurred only at puncture site. No ischemic complications requiring further invasive treatment occurred. Mean TAE treatment time was 4.55 minutes.

Conclusions: NBCA-MS Glubran®2 TAE is a fast, effective and safe treatment for acute arterial bleeding whatever the bleeding site.

Keywords

Arterial bleeding, gastrointestinal bleeding, rectus sheath hematoma, cyanoacrylate glue, embolization, outcomes.

Introduction

L' embolisation artérielle radiologique est un traitement d'hémostase efficace, apparaissant dans des recommandations de sociétés savantes concernant la prise en charge des hémorragies digestives et du polytraumatisé [1-5]. Plusieurs agents d'embolisation peuvent être utilisés comme les coils, les éponges de gelatine, les particules et le N-Butyl Cyanoacrylate (NBCA) qui est une colle. Le NBCA est un agent d'embolisation liquide polymérisant au contact d'ions comme ceux contenus dans le sang. Il présente de multiples avantages, tout d'abord celui d'être efficace malgré la presence d'une coagulopathie, qui peut être induite par une prise médicamenteuse, ou être secondaire au choc hémorragique [6-8]. Par ailleurs le temps d'injection du produit est court en comparaison à celui des microcoils, ce qui permet de réduire les temps de procedure, dans une population des patients présentant parfois, une instabilité hémodynamique justifiant une prise en charge rapide [7]. Du fait de sa nature liquide il permet également d'effectuer des embolisations de vaisseaux de petit calibre ou à la morphologie sinueuse rendant difficile un catheterisme. Pour autant le NBCA reste peu utilisé en radiologie interventionnelle, souvent associé à l'image d'un produit difficile à maitriser, et à risque de complications ischémiques à distance, dues à un reflux au cours de son injection. Quelques études ont montré l'efficacité et la sureté des embolisations d'hemostase au NBCA, essentiellement chez des patients présentant des hémorragies digestives ou rénales, mais elles présentaient pour la majorité une faible puissance[9-26] . Par ailleurs peu d'études ont inclus des patients présentant des saignements hépatiques, musculaires ou encore spléniques [27-33]. Enfin, la majorité des études réalisées sur les embolisations au NBCA utilisaient l'Histoacryl® ou le Trufill® et rarement le Glubran®2. Glubran®2 est historiquement une colle chirurgicale au sein de laquelle le NBCA est combiné avec un co-monomère le metacryloxysulpholane (MS) aboutissant à un processus de polymerisation plus stable engendrant une reaction exothermique moins importante (45°C). Ce gain de température générée permet de diminuer l'histotoxicité ainsi que l'inflammation induite. Glubran®2 est ainsi un agent d'embolisation couramment utilisé dans notre service. Les objectifs de notre étude étaient d'étudier l'efficacité et la sureté des embolisations artérielles d'hémostase au NBCA-MS dans une large

population de patients présentant des sites de saignement variés. Dans un deuxième temps il s'agissait de déterminer les facteurs pronostiques liés à l'efficacité clinique et la mortalité à 30 jours.

Introduction

Transcatheter arterial embolization (TAE) has become over the years an important treatment of arterial bleeding, appearing in guidelines for digestive tract and posttraumatic hemorrhage [1-5]. Several embolic agents may be used for vascular occlusion like coils, gelatine sponge, particles and n-butyl-cyanoacrylate (NBCA) glue. NBCA is a liquid embolic agent which polymerizes in contact with any fluids rich in ions like blood. It has major advantages like being effective despite coagulopathy which is often present in bleeding because of anticoagulant medication or induced by hemorrhagic shock itself [6-8]. Glue has therefore the benefit of being quickly administered in comparison of microcoils, which is important especially in a setting of hemodynamic instability [7]. Furthermore, it allows embolization of small or tortuous vessels thanks to its liquid nature. However, glue is still not popular and underutilized in interventional radiology field, probably because considered as a hard product to handle, with fear of ischemic complications and nontarget vessel occlusion due to potential uncontrolled reflux during the injection. Some reports have attested the effectiveness and safety of NBCA TAE in acute arterial bleeding embolization, especially for digestive tract and renal bleedings but they were mostly limited by the small number of patients included [9-26]. Therefore, few studies have included patients with liver, spleen or intramuscular hemorrhages [27-33]. Lastly, no large study has reported the use of Glubran®2 as the main liquid embolic agent, the majority of authors using other NBCA glues like Histoacryl® or Trufill®. Glubran®2 is a well-known surgical glue in which NBCA is combined with another comonomer, metacryloxysulpholane (MS), to produce a more pliable and stable polymer whose milder exothermic reaction (45°C) results in less inflammation and histotoxicity. Glubran®2 has been recently introduced as first embolic agent in our institution for the treatment of arterial bleeding patients. The goal of our study was to report our experience with the use of glue and to evaluate the efficacy and safety of NBCA-MS Glubran®2 TAE for acute arterial

bleeding, in a large population of patients with various bleeding sites, and to determine predictive factors of clinical outcomes and 30-day mortality.

Materials and Methods

Patients Selection

We retrospectively reviewed the medical records of all patients who underwent technically successful TAE with NBCA-MS Glubran®2 for acute arterial bleeding from all visceral and peripheral territories from July 2014 to August 2016 at our institution. Patients were identified using the database maintained prospectively by our Interventional Radiology Department. Patients with head or neck embolizations were excluded from the study.

Embolization Technique

All angiographic procedures were performed by 1 of 3 experienced interventional radiologists with standard percutaneous transfemoral catheterization using a 5-Fr or 6-Fr sheath. Selective opacification of the suspected bleeding artery was performed using standard 4-Fr or 5-Fr catheters, followed by superselective arteriography using a 2.7-Fr co-axial microcatheter (Progreat; Terumo, Leuven, Belgium). All pathologic arteries were embolized using NBCA-MS (Glubran®2; GEM Srl, Viareggio, Italy). When there is no vascular abnormality on angiography, the feeding artery was embolized based on endoscopic or computed tomography (CT) findings. The microcatheter was introduced coaxially into the angiographic catheter and advanced as distal as possible to avoid reflux of the embolic material into nontarget vessels. NBCA-MS was mixed with iodized oil (Lipiodol Ultra Fluide; Guerbet, Roissy, France) at a ratio ranging from 1:3 to 1:6 depending on territory and operator preference. After the microcatheter was flushed with 5% dextrose solution to avoid gluing and occlusion of the lumen during injection of NBCA-MS, 0.5 to 2mL of the mixture was carefully injected under fluoroscopic monitoring. The ratio, volume, and injection rate of the mixture were based on the size and flow of the embolized vessels. To avoid adhesion of the catheter tip to the vessel

wall, the microcatheter was quickly removed after injection. After completion of embolization, arteriogram was performed to confirm the absence of any other residual bleeding arteries.
For bleeding from viscera, embolization was performed as distal as possible (*Figure 2*). For gastrointestinal bleedings, embolization was performed as previously described according to the bleeding site, after failure of endoscopic treatment (*Figure 3*). For rectus sheath hematoma, the targeted vessel for embolization was the homolateral inferior epigastric artery (*Figure 4*). For psoas hematoma, three homolateral lumbar arteries were systematically embolized, the bleeding one based on angiographic findings and the upper and lower ones on both sides, empirically, to avoid revascularization. Embolization was usually achieved at the discretion of the interventional radiologist using glue alone or in combination with other embolic agents (*Table 2*). All agents were released near the bleeding site until cessation of angiographic extravasation and/or occlusion of the targeted vessel as shown by fluoroscopic monitoring.

Definitions and Analytic Items

All radiological and electronic medical records were reviewed to collect data on patients. The following variables were collected: patients demographics, comorbidities, treatments, laboratory data on coagulation parameters (international normalized ratio, partial thromboplastin time, platelet count), hemoglobin level, systolic blood pressure and number of red blood cells (RBC) units transfused before TAE, bleeding sites, computed tomography scan and angiographic findings, vessel(s) embolized, embolic material used, technical and clinical outcomes, complications and 30 day-mortality.
Cardiovascular comorbidities were defined as any medical history of ischemic stroke and/or coronary heart disease and/or cardiac arrhythmia and/or heart failure and/or peripheral occlusive arterial disease.
Patients who met one of the following criteria were classified in the coagulopathy group: international normalized ratio (INR) greater than 1.5, partial thromboplastin time (PTT) longer than 45 seconds, or platelet count less than 80,000/mm3.
Arteriography was considered positive in case of extravasation of contrast medium or presence of a false aneurysm-like lesion. Duration of treatment was defined as the elapsed time between the last

angiography with a microcatheter in place before glue injection and the first angiography after glue injection which confirmed occlusion of the target vessel.

Technical success was defined as the cessation of the complete occlusion of the target vessel or the cessation of extravasation on the postembolization arteriography [34]. Clinical success was defined as the absence of persistent bleeding or rebleeding within 30 days after a technically successful single embolization procedure. Persistent bleeding was defined as a failure of cessation of bleeding after TAE, bleeding with a greater than 2.0 g/dL decrease in the hemoglobin level and/or a lack of effectiveness of conservative medical treatment. Rebleeding was defined as a novel episode of bleeding at the same site more than 48 hours and less than 30 days after initial TAE, based on the same criteria.

Complications were classified according to the standards of the Society of Interventional Radiology (SIR), as major complications if they required surgery and/or prolonged hospitalization and as minor complications otherwise [34].

Statistical Analysis

Qualitative variables were described using numbers (percentages). Continuous data were expressed as means (with standard deviations, SD) and medians (with ranges). Determinants of treatment efficacy were estimated using uni- and multivariate logistic regression. All variables with a p value of 0.15 or less were included in the multivariate model. Odds ratios are given with their 95% confidence intervals (CI). Correlations between dependent variables were tested. When 2 variables were correlated with a coefficient higher than 0.5, only one was entered in the multivariate model, according to the clinical relevance. Factors associated with 30-day mortality were determined by univariate analysis. Regarding the small number of events only bivariate analysis was performed including two dependent variables, the clinical success and the number of red blood cells units after adjustment by bleeding site, chosen because of their clinical relevance. All p values less than 0.05

were considered statistically significant. All *p* values were two-sided. Analyses were performed using SAS 9.3.

Results

Patient Characteristics

A total of 104 patients underwent technically successful NBCA-MS Glubran®2 TAE for acute arterial bleeding during the study period and were included for statistical analysis as shown in the study flow shart (*Figure 1*).

Patients were mostly males (*n*=66, 63.5%) with a mean age of 64.8±18 years (range, 18-94 years) (*Table 1*). Underlying malignancy was found in 25 patients (24%) as cardiovascular comorbidities (*n*=25, 24%). A treatment promoting bleeding was taken in 61.5% of patients (*n*=64) as antiplatelets alone (*n*=10, 9.6%), anticoagulants alone (*n*=39, 37.5%) or a combination of both (*n*=15, 14.4%). Furthermore, 54 (51.9%) patients had a coagulopathy as previously described: PTT > 45 seconds (*n*=38, 36.5%) and/or INR (*n*=37, 35.6%) and/or platelet count < 80,000/mm^3 (*n*=11, 10.6%).

Regarding parameters that reflected the severity of initial hemorrhage, a median of 3 RBC units were transfused during the 24 hours before TAE (range, 0-17). Moreover, median level of hemoglobin before TAE was 7.8 g/dL (range, 2.6-14) and median systolic blood pressure was 96.5 mmHg (range, 62-180).

Bleeding sites were divided into 3 main territories: viscera (*n*=42, 40.4%), muscles (*n*=34, 32.7%) and digestive tract (*n*=28, 26.9%). Sites of visceral bleeding were kidney (*n*=13), liver (*n*=9) and spleen (*n*=6). Other visceral locations (*n*=14) were prostate (*n*=4), lung (*n*=3), adrenal gland (*n*=2), cervix (*n*=2), mesentery (*n*=1), pancreas (*n*=1) and mediastinum (*n*=1). Muscular bleedings were located mostly in ilio-psoas (*n*=26) then rectus sheath (*n*=8). Digestive hemorrhages were mainly encountered in the upper digestive tract (*n*=24) (*Table 2*).

Bleeding causes according to the location are detailed in *Table 3*. Among the 34 muscular bleedings, anticoagulant overdose was the cause of bleeding in 10 patients (29.4%). Few occurred after trauma

(*n*=4, 11.8%) and the majority occurred spontaneously without any etiology (*n*=20, 58.8%). Most of the 28 bleedings from the gastrointestinal tract were due to gastric or duodenal ulcers (*n*=17, 60.7%) far ahead diverticulum (*n*=3, 10.7%), postoperative bleeding (*n*=3, 10.7%) and malignancy (*n*=2, 7.2%). Other causes of gastrointestinal bleeding (*n*=3, 10.7%) were oesophagitis (*n*=1) and spontaneous duodenal wall hematoma (*n*=2). Visceral bleedings occurred mainly after trauma (*n*=10), malignancy (*n*=5), benign tumor (*n*=5), as a complication of surgery (*n*=7) or biopsy (*n*=4) and after pancreatitis (*n*=2). Other etiologies of visceral hemorrhages (*n*=9) were spontaneous renal hematoma (*n*=3), mesenteric mycotic pseudoaneurysm (*n*=1), splenic pseudoaneurysm (*n*=1), post-partum pseudoaneurysm (*n*=1), cholecystis (*n*=1), and after lung radiotherapy (*n*=2).

In total, 7 patients had a cancer related bleeding (6.7%): two from adrenal gland (1 patient with cortical carcinoma and 1 with metastasis), two from the liver (1 patient with hepatocellular carcinoma and 1 with sarcoma), two from the digestive tract (1 patient with gastric metastasis of hepatocellular carcinoma and 1 with gastric cancer) and one from lung.

Imaging and Angiographic Features

CT scan was performed in 83 patients (79.8%) with an extravasation of contrast medium seen in 61 patients (58.6%), a pseudoaneurysm in 11 patients (10.6%) and none of them in 11 patients (10.6%) (*Table 1*). Angiography was positive in 74 patients (71.1%) showing an extravasation in 54 patients (51.9%) and a pseudoaneurysm in 20 patients (19.2%). Among the 30 patients with negative angiography, bleeding sites were essentially located in the upper digestive tract, muscles and lung. Mismatch between CT scan and arteriography was encountered in 17 patients (20.5%). Especially, 10 patients had an extravasation on CT scan and a negative angiography, mainly related to muscular bleeding (*n*=7). On the other hand, 3 patients had a negative CT scan and a positive angiography with bleeding located in kidney (*n*=1), spleen (*n*=1) or digestive tract (*n*=1). Lastly, arteriography showed a pseudoaneurysm in 4 patients corresponding to an extravasation on CT scan. Other embolic agents were used in combination with glue in 24 patients (23.1%), mainly microcoils (*n*=18) in order to prevent nontarget vessel embolization or to occlude another target vessel. Finally, in 3 patients, NBCA

was used after another embolic agent failed. Mean treatment time or duration of treatment, corresponding to glue injection with microcatheter in place and was available in 94 patients, was 4.5±1.7 minutes (range, 2-9). Regarding the embolized vessels, overall 158 vessels were embolized in 104 patients (*Table 4*).

Clinical Outcomes

Clinical Success

The overall clinical success rate was 76% (*n*=79) (*Table 5*). It varied according to the bleeding site with a higher success rate for viscera (*n*=42, 90.4%) than for the digestive tract (*n*=17, 60.7%) and muscles (*n*=24, 70.6%). Clinical failure (*n*=25, 24%) was related to persistent bleeding (n=17, 16.3%) more than rebleeding (*n*=8, 7.7%). Among the 25 patients with clinical failure, 7 were treated by surgery, 3 by re-endoscopy, 3 by re-embolization with NBCA-MS and the remaining 12 patients had conservative medical treatment due to limitation of care (*n*=10) or low severity of bleeding (*n*=2). Two patients who underwent surgery for ilio-psoas hematoma continued to bleed and died within one week. Re-endoscopic treatment failed in 2 patients: one of them died from rebleeding and the other one was successfully treated with a third endoscopy. All three patients managed with re-embolization had revascularization and extravasation from a collateral vessel of the superior mesenteric artery, successfully treated with glue. Secondary treatment after initial failure was successful in 100% of bleedings from viscera (4/4), in 63.6% of bleedings from the digestive tract (7/11) and in 0% of bleedings from muscles (0/10), respectively.

30-Day Mortality

The 30-day mortality rate was 21.2% (*n*=22) and varied according to the bleeding site with a higher rate for muscles (*n*=13, 38.2%) than for digestive tract (*n*=5, 17.9%) or viscera (*n*=4, 9.5%) (*Table 5*). Among deaths, 16 were due to multi-organ failure: 15 secondary to hemorrhagic shock and one due to pulmonary infection. Two patients died from peritonitis which occurred after ischemic colitis in 1 patient and colonoscopy in the other one. Two patients had heart attack within 30 days. Other

etiologies of death were as follows: respiratory distress in 1 patient and posttraumatic intra-cranial hypertension in the other one. The 30-day mortality rate directly related to rebleeding was 15.4% (*n*=16).

Complications

Overall complication rate was 17.3% (*n*=18). No technical complications as catheter sticking or nontarget occlusion occurred. Minor complications were noted in 10.6% of the study population (*n*=11), mainly postembolization syndrome (*n*=9, 8.7%), then local complications at the puncture site (*n*=2, 1.9%) with two hematomas, all managed conservatively with medical treatment. Major complications were observed in 7 patients (6.7%). Five of them were due to the procedure: splenic abscess after splenic artery embolization in 1 patient treated by percutaneous drainage, hematoma at puncture site in 3 patients and arterial dissection of the femoral artery in 1 patient which all 4 required surgical treatment. Two other major complications not related with the procedure were also noted in two patients who developed an abscess of retroperitoneal hematoma treated with percutaneous drainage. No bowel ischemia requiring surgery occurred.

Predictors of Outcomes

Statistical analyses showed that a number of RBC units transfused greater than or equal to 3 was statistically associated with a lower clinical success rate in both uni- (p=0.003) and multivariate (p=0.025) analysis, and a higher 30-day mortality rate in uni- and bivariate analysis (p=0.03, OR=4.8). Otherwise, patients who underwent clinically successful embolization were more likely to survive in uni- and bivariate analysis (p<0.0001). The presence of a coagulopathy did not impact the clinical success in the univariate analysis (p=0.169) but was significantly associated with mortality (p=0.011). Other variables as underlying malignancy, cardiovascular comorbidities, angiographic features, the use of another embolic agent and cancer related bleeding were not associated with clinical success and 30-day mortality rate. Systolic blood pressure and the number of RBC units transfused were correlated (rho=-0.58). Data are summarized in *Table 6*.

Discussion

The current study, presently the largest series focused on patients with acute arterial bleeding at varied abdominal sites treated with Glubran®2 NBCA-MS TAE, demonstrated the safety and efficacy of TAE with NBCA. Approximately 24% of the patients experienced either continued bleeding or rebleeding after embolization and required additional intervention. Despite agressive treatments, 21.2% of the patients died within 30 days after TAE. The ischemic complications were minimal. The technical success rate was 100% and the overall clinical success rate was 76%. Clinical success was strongly associated with lower mortality. A high rate of mortality (38.2%) was noted for muscular bleeding, meaning that rectus sheath or ilio-psoas hematomas are life-threatening condition with poorer outcomes despite prompt TAE. Indeed, large muscle hematoma can maintain muscle tears and bleeding and favor growth of hematoma like some kind of vicious circle. It is then less likely to respond to TAE. A number of RBC units transfused greater than or equal to 3 was associated with poorer clinical outcomes and higher mortality. This tends to prove that the severity of the initial hemorrhage increases the risk of clinical failure and then mortality. Few NBCA TAE studies assessed predictive factors of clinical failure.

Transcatheter embolization of the visceral arteries is now considered the gold standard treatment in a variety of situations because it is feasible and minimally invasive, while offering effective hemostasis [9-13, 21-23, 27, 35, 36]. Numerous embolic materials are commercially available and each possesses its advantages and disadvantages [37]. The choice of embolic material is usually made on a case-by-case basis, depending on various factors such as vascular anatomy and pathology, as well as personal preference of the interventional radiologist performing the procedure. Compared to the more commonly advocated metallic coils and particulates there has been limited use of NBCA in peripheral endovascular intervention. Recently, however, an increasing number of articles have focused on the use of NBCA for TAE of various vascular pathologies ranging from post-traumatic bleeding to tumors

and its range of application continues to expand [9-13, 28, 30, 33]. Kish *et al* reported a successful hemostasis rate of 87.5% for transcatheter NBCA embolization of acute arterial bleeding [38]. Liquid adhesive embolic agents offer the advantages of low viscosity for easy injection through small or tortuous catheters [37]. Cyanoacrylates are glues with a high adhesive strength. Their polymerization triggers an exothermic reaction that contributes to the destruction of the vascular endothelium. Few glues are available on the market worldwide for endovascular use. NBCA glues, Trufill® (Cordis, Miami Lakes, FL) and Histoacryl® (B/Braun, Tuttlingen, Germany), have quite similar properties [39]. Trufill® is has FDA approval but is available only in the United States. Histoacryl® has been used for decades, especially in Europe, although normally not allowed for endovascular purpose because of the absence of CE marking. The cyanoacrylate variant used in our case series, NBCA-MS, has advantages over classic cyanoacrylate. Classic Histoacryl® NBCA has a polymerization temperature of 90°C and a polymerization rate < 30 seconds. Glubran®2 (GEM, Viareggio, Italy) is a specific surgical glue in which NBCA is combined with another monomer, metacryloxysulpholane, to produce a more pliable and stable polymer whose milder exothermic reaction (45°C) results in less inflammation and histotoxicity than Histoacryl® or Trufill® [37]. With Glubran®2 the polymerization rate is slower, making the handling and release easier. Because the exothermic reaction is weaker, it is therefore less painful at the time of injection [40, 41]. The final polymer is more flexible and, unlike conventional cyanoacrylate, does not fragment. Glubran®2 has a CE certificate for intravascular use. NBCA should be released under a fluoroscopic control mixed with Lipiodol. The mixture with lipiodol also modulates the polymerization rate. Lipiodol is used for two reasons: first, to make the NBCA mixture radio-opaque and, second, to dilute the NBCA to the desired concentration depending on how much the interventional radiologist wants to prolong the time to polymerization. A higher NBCA/Lipiodol ratio, by adding less amount of Lipiodol, offers quicker occlusion time while restricting time to inject the NBCA mixture through the catheter before it has to be removed. On the other hand, a lower NBCA/Lipiodol ratio will allow more time for injection while increasing the risk of distal embolization. This allows the operator to control the degree of distal vessel penetration, allowing for occlusion at or significantly beyond the catheter tip [16, 19, 23]. Another important point to consider is the injection rate of NBCA mixture. Careless injection at a high rate will

cause reflux of the mixture into non-target vessels exposing the end-organ to potential risk of infarction. 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. Embolization with Glubran®2 is cost-effective. One mL is comparable in cost to a single conventional pushing coil and is sufficient for successful treatment in the majority of cases [37, 40]. NBCA has a cosmetic advantage, as cyanoacrylate is absorbed over time by hydrolysis. The coils will appear in imaging tests throughout the patient's lifetime.

Two major advantages of NBCA were confirmed in our study. First, it enabled to shorten the procedure with a mean treatment time of 4.55 minutes corresponding to the elapsed time for the dilution of NBCA with Lipiodol, its injection and the microcatheter withdrawal. Yonemitsu *et al* previously found that the use of NBCA reduces procedure times compared to microcoils and gelatin sponge, with a mean time of 9 minutes [6]. This discrepancy may be explained by different treatment time definitions, which started just after detection of an extravasation for them and only after positioning of the microcatheter in the target vessel for us. Secondly, the presence of a coagulopathy didn't affect clinical outcomes in the present study whereas 51.9% of the population suffered from coagulation disorders. Polymerization of NBCA in contact with blood does not depend on coagulation parameters providing better hemostasis than other embolic agents, especially in patients with coagulopathy [37]. Further comparative studies are warranted.

Regarding complications, such as inadvertent distal embolization, undesired embolization of non-target vessels due to backflow, or catheter entrapment, we experienced none. This was most probably because the interventional radiologists who performed the procedures were familiar with the characteristics of NBCA through past experience. In this series, no patients developed bowel infarction or mesenteric ischemia after NBCA embolization. These results correlate well with the experience of Yamakado *et al*, who similarly had no cases of organ infarction [42]. This result can be explained by the lack of glue penetration into distal capillary or arteriolar beds thanks to its viscosity. Other reported complications of NBCA embolization include abscess formation after end-organ ischemia [28, 31]. We experienced this complication in 3 of 104 patients, managed with percutaneous drainage.

There are some limitations to this study, such as its retrospective nature from a single center. In addition, three different radiologists performed the procedures in this case series and, therefore, we cannot exclude the possibility that there may have been minor differences in the technique of embolization. It would be beneficial to conduct a comparative study with the standard treatment using other embolic agents as coils or gelatin sponge. Also, the groups included for analysis were heterogeneous with respect to underlying disease or bleeding site. Lastly, the goal of this study was to assess the efficacy of emergent hemostatic procedures, then no long-term follow-up was available.

In conclusion, the use of Glubran2 NBCA-MS as an embolic agent for endovascular treatment of acute arterial bleeding at varied abdominal sites is a therapeutic alternative that is effective, safe and inexpensive. NBCA may be specifically useful in the setting of hemodynamic instability, coagulopathy, and narrowed vessels that are not amenable to distal embolization by microcoils. Interventional radiologists should be aware of the clinical factors associated with rebleeding because these could influence the clinical outcome. Further investigations are warranted to define the ideal indications and achieve successful hemostasis.

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THESE SOUTENUE PAR Mr ABDUL MALAK GILLES

CONCLUSIONS

L'utilisation de N-Butyl Cyanoacrylate-Metacryloxyl Sulfolane (Glubran®2) comme matériel d'embolisation d'hémostase est efficace et sure.

Ce produit a présenté dans notre étude l'avantage de permettre des embolisations rapides, utiles dans les situations d'urgence que représentent les instabilités hémodynamiques. Par ailleurs l'occlusion vasculaire obtenue était indépendante des paramètres de coagulation. Il peut ainsi s'avérer utile dans les contextes de coagulopathies qui sont fréquentes dans ces populations traitées, liées à la prise d'un traitement ou à l'état de choc lui même. Son faible cout apparait enfin être un critère non négligeable au vu des objectifs de maitrise des dépenses de santé.

La crainte de complications ischémiques explique essentiellement sa faible utilisation. Celles-ci n'ont pas été retrouvées dans notre étude, en particulier sur le plan digestif. L'équipe de radiologues opérateurs ayant réalisée la procédure étant expérimentée, un apprentissage rigoureux de la technique d'embolisation semble pouvoir prévenir ces risques.

L'efficacité des embolisations d'hémostase est dépendante du degré de gravité du saignement initial. Les échecs cliniques étaient en effet plus fréquents au sein des populations ayant les transfusions en culots globulaires les plus importantes avant la procédure.
Les résultats cliniques apparaissent également influencés par le site embolisé avec une efficacité supérieure pour les viscères en comparaison aux muscles et au tube digestif.
L'importante collatéralité de la vascularisation digestive et les lésions vasculaires induites par les volumineux hématomes semblent pouvoir expliquer les échecs plus fréquents dans ces populations.

Une étude comparative avec d'autres matériels d'embolisation apparait ainsi nécessaire pour confirmer ces résultats prometteurs.

Le Président du jury,

Pr D. Vinault

Vu et permis d'imprimer

Dijon, le 16 JUIN 2017

Le Doyen

Pr. F.HUET

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Table 1. Demographic data and procedural characteristics in 104 patients.

Characteristics	Number (%) of patients
Age (years)	
Mean±SD	64.8±18
Median (range)	67 (18-94)
Gender	
Male	66 (63.5)
Female	38 (36.5)
Underlying malignancy	25 (24)
Cardiovascular comorbidities	25 (24)
Prior promoting bleeding treatment	
Yes	64 (61.5)
Antiplatelets alone	10 (9.6)
Anticoagulants alone	39 (37.5)
Both	15 (14.4)
No	40 (38.5)
Prior coagulopathy	
Yes*	54 (51.9)
Partial thromboplastin time > 45 seconds	38 (36.5)
Platelet count < 80,000/mm^3	11 (10.6)
International normalized ratio > 1.5	37 (35.6)
No	50 (48.1)
Hemoglobin level before TAE (g/dL)	
Mean±SD	8±2
Median (range)	7.8 (2.6-14)
Systolic blood pressure before TAE (mmHg)	
Mean±SD	102±24
Median (range)	97 (62-180)
RBC units before TAE	
Mean±SD	4.1±3.7
Median (range)	3 (0-17)
CT findings	
CT scan	83 (79.8)
Extravasation	61 (58.6)
False aneurysm-like lesion	11 (10.6)
None	11 (10.6)
No CT scan	21 (20.2)
Angiography findings	
Extravasation	54 (51.9)
False aneurysm-like lesion	20 (19.2)
None	30 (28.9)
Duration of treatment (min)**	
Mean±SD	4.5±1.7
Median (range)	5 (2-9)
NBCA-MS glue used	
Alone	80 (76.9)
In combination	24 (23.1)
Microcoils	18 (17.3)

Gelatin sponge particles	4 (3.8)
Microspheres	1 (1)
Onyx	1 (1)

Footnote:

* Partial thromboplastin time > 45 seconds and/or platelet count < 80,000/mm^3 and/or international normalized ratio > 1.5; ** Corresponding to glue injection microcatheter in place; SD, standard deviation; RBC, red blood cell; CT, computed tomography; TAE, transcatheter arterial embolization; NBCA-MS, n-butyl cyanoacrylate-metacryloxysulfolane

Table 2. Sites of bleeding in 104 patients.

Site of bleeding	Number (%) of patients
Viscera	42 (40.4)
Kidney	13
Liver	9
Spleen	6
Other	14
Muscle	34 (32.7)
Ilio-psoas	26
Rectus sheath	8
Digestive tract	28 (26.9)
Upper GI tract	24
Lower GI tract	4

Footnote: GI, gastrointestinal

Table 3. Etiology of bleeding according to anatomic site.

Etiology of bleeding	Number (%) of patients
Viscera	42
Traumatic	10 (23.8)
Postoperative	7 (16.7)
Malignancy	5 (11.9)
Benign tumor	5 (11.9)
Post-biopsy	4 (9.5)
Pancreatitis	2 (4.8)
Other	9 (21.4)
Muscle	34
Anticoagulant overdose	10 (29.4)
Traumatic	4 (11.8)
Spontaneous	20 (58.8)
Digestive tract	28
Gastric or duodenal ulcer	17 (60.7)
Diverticulum	3 (10.7)
Postoperative	3 (10.7)
Malignancy	2 (7.2)
Other	3 (10.7)

Table 4. Embolized arteries in the study population.

Artery	Number
Viscera	
Renal artery	13
Hepatic artery	11
Splenic artery	6
Prostatic artery	4
Bronchial artery	3
Adrenal artery	2
Vaginal artery	2
Pancreatic artery	2
Internal thoracic artery	1
Muscle	
Lumbar artery	75
Inferior epigastric artery	9
Circumflex iliac artery	1
Digestive tract	
Gastroduodenal artery	16
Left gastric artery	6
Inferior mesenteric artery	4
Superior mesenteric artery	3

Footnote: 158 vessels were embolized in 104 patients

Table 5. Outcomes after embolization

	All (*n*=104)	**Viscera (*n*=42)**	**Muscle (*n*=34)**	**Digestive tract (*n*=28)**
Technical success (%)	104 (100)	42 (100)	34 (100)	28 (100)
Clinical success (%)	79 (76)	38 (90.4)	24 (70.6)	17 (60.7)
Clinical failure (%)	25 (24)	4 (9.6)	10 (29.4)	11 (39.3)
Persistent bleeding	17 (16.3)	2 (4.8)	8 (23.5)	7 (25)
Re-bleeding < 30 days	8 (7.7)	2 (4.8)	2 (5.9)	4 (14.3)
Complications (%)	18 (17.3)	14 (33.3)	2 (5.9)	2 (7.2)
Technical complications	0 (0)	0 (0)	0 (0)	0 (0)
Catheter sticking[*]	0 (0)	0 (0)	0 (0)	0 (0)
Nontarget occlusion[**]	0 (0)	0 (0)	0 (0)	0 (0)
Clinical complications	18 (17.3)	14 (33.3)	2 (5.9)	2 (7.2)
Minor[***]	11 (10.6)	8 (19.1)	2 (5.9)	1 (3.6)
Postembolization syndrome	9 (8.7)	8 (19.1)	0 (0)	1 (3.6)
Puncture-site related	2 (1.9)	0 (0)	2 (5.9)	0 (0)
Major[****]	7 (6.7)	6 (14.2)	0 (0)	1 (3.6)
Abscess	3 (2.9)	3 (7.1)	0 (0)	0 (0)
Puncture-site related	4 (3.8)	3 (7.1)	0 (0)	1 (3.6)
Bowel ischemia	0 (0)	0 (0)	0 (0)	0 (0)
30-day mortality (%)	22 (21.2)	4 (9.5)	13 (38.2)	5 (17.9)

Footnote:

* Necessitating to leave the catheter into the body; ** By reflux of glue; *** Managed conservatively; **** Requiring drainage or surgery

Table 6. Predictors of clinical success and 30-day mortality.

Variables	Clinical success				30-day mortality	
	Univariate analysis		*Multivariate analysis*		*Univariate analysis*	
	OR (95%CI)	*p*	*OR (95%CI)*	*p*	*OR (95%CI)*	*p*
Gender	-	0.141	2.49 (0.78-7.98)	0.125	2.04 (0.78-5.29)	0.144
Underlying malignancy	0.76 (0.27-2.10)	0.596	-	-	1.66 (0.59-4.69)	0.339
Cardiovascular comorbidities	1.00 (0.35-2.87)	0.996	-	-	0.65 (0.20-2.13)	0.472
Prior promoting bleeding treatment	0.69 (0.27-1.79)	0.448	-	-	2.53 (0.85-7.52)	0.095
Systolic blood pressure < 90mmHg	3.24 (1.27-8.27)	0.014	-	-	0.26 (0.09-0.70)	0.008
RBC units transfused ≥ 3	0.14 (0.04-0.51)	0.003	0.20 (0.05-0.80)	0.025	5.74 (1.58-20.92)	0.008
Coagulopathy	0.52 (0.21-1.32)	0.169	-	-	4.14 (1.39-12.27)	0.011
Bleeding site						
Muscle vs digestive	1.65 (0.57-4.79)	0.366	1.04 (0.32-3.40)	0.337	2.72 (0.83-8.97)	0.006
Visceral vs digestive	6.70 (1.86-24.20)	0.005	3.12 (0.78-7.99)	0.081	0.45 (0.11-1.86)	0.033
Positive angiography	1.97 (0.76-5.07)	0.162	-	-	0.84 (0.30-2.31)	0.729
Other agent used	0.93 (0.32-2.69)	0.900	-	-	0.46 (0.12-1.71)	0.245
Cancer related bleeding	0.39 (0.08-1.88)	0.241	-	-	1.54 (0.28-8.53)	0.621
Clinical success	-	-	-	-	0.09 (0.03-0.26)	<0.0001

Footnote:

OR, odds ratio; CI, confidence interval; vs, versus

Figure 1 : Study Flowchart

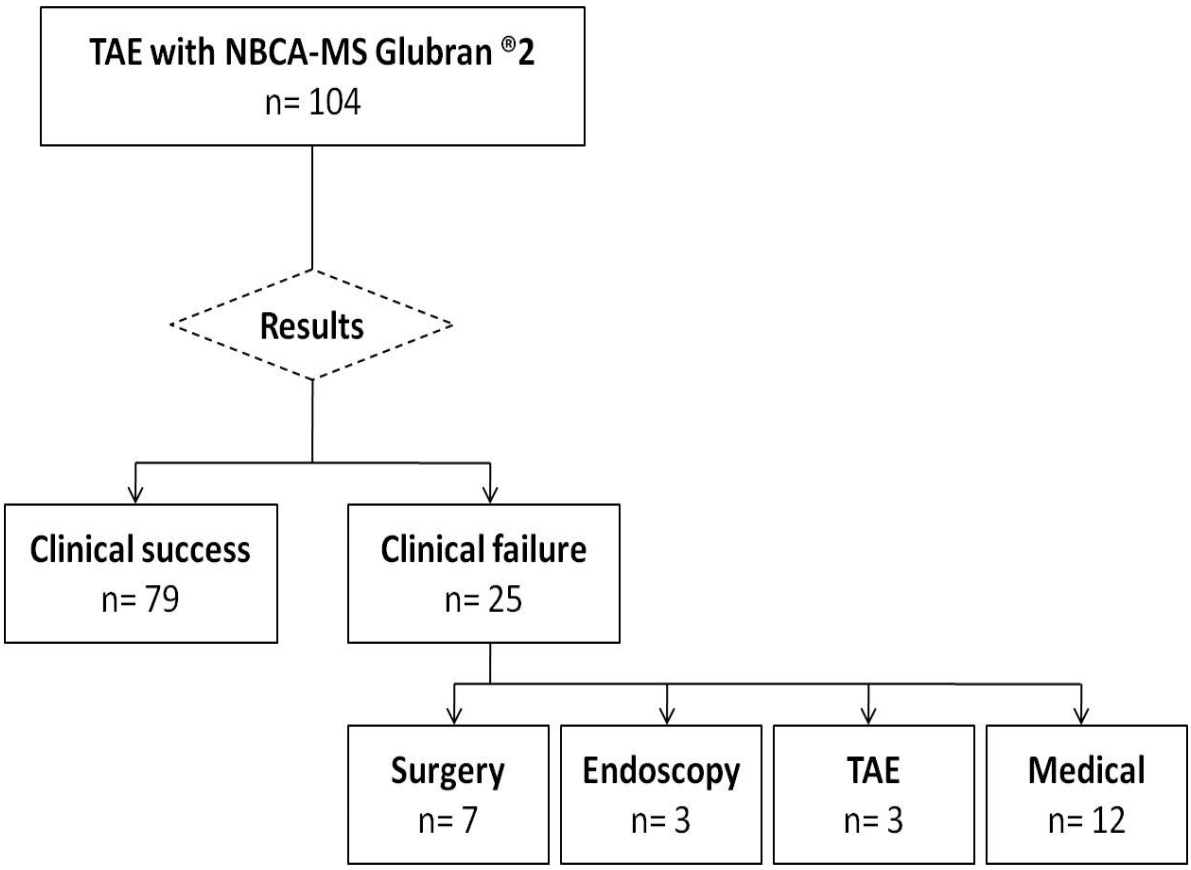
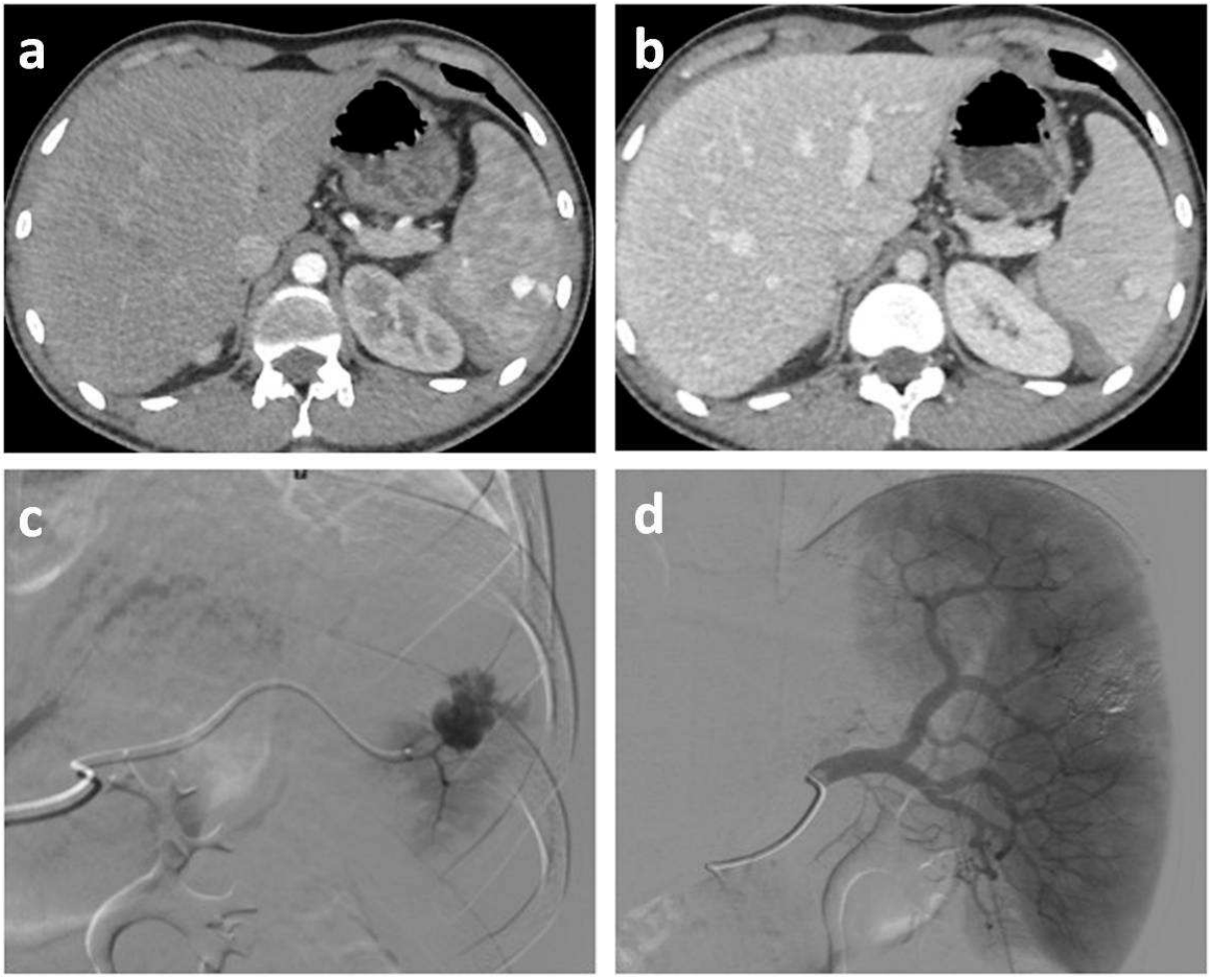
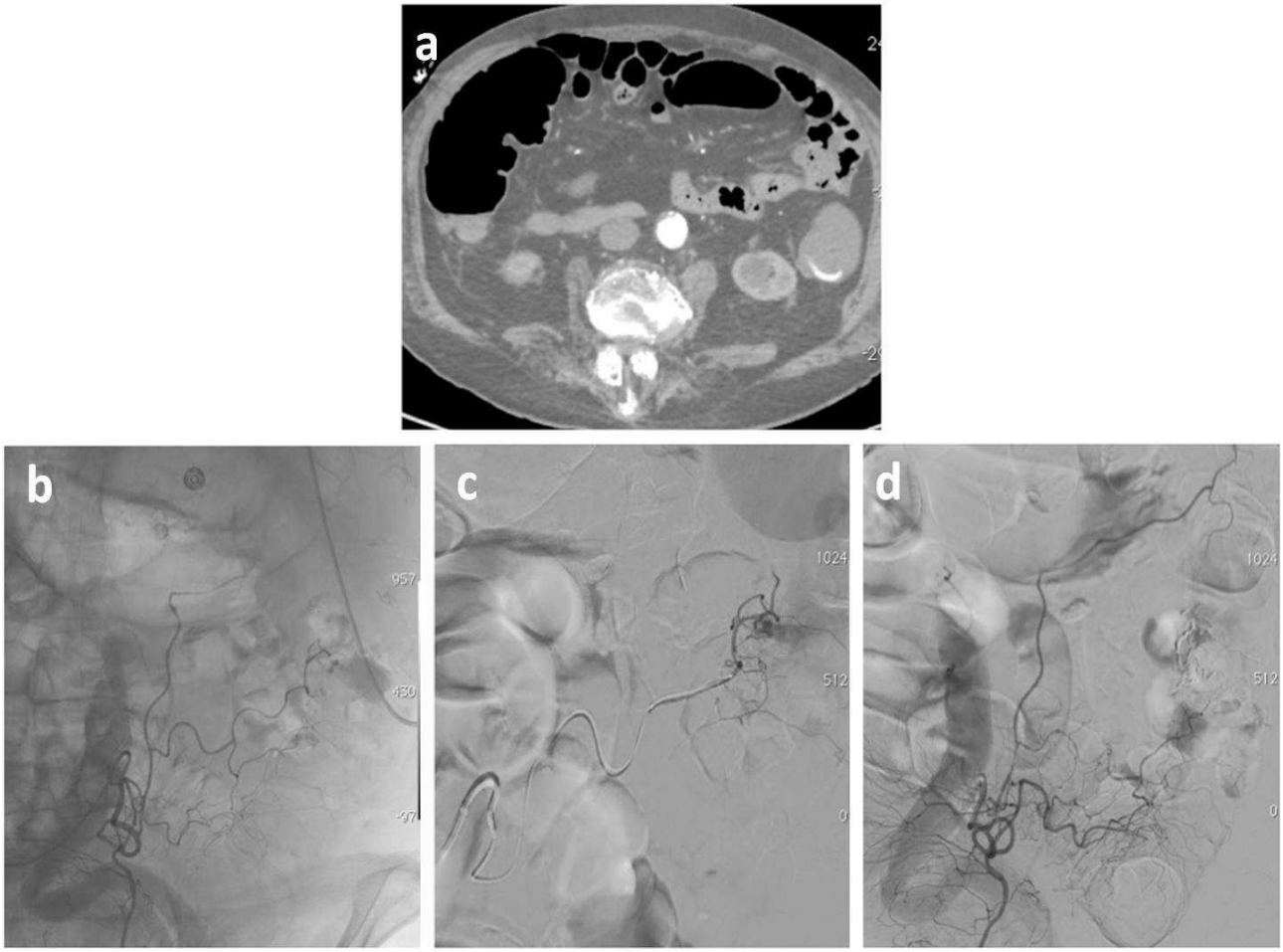


Figure 2 : Pseudoaneurysm within the spleen after trauma in a 22-year-old man treated with NBCA-MS Glubran®2 TAE.



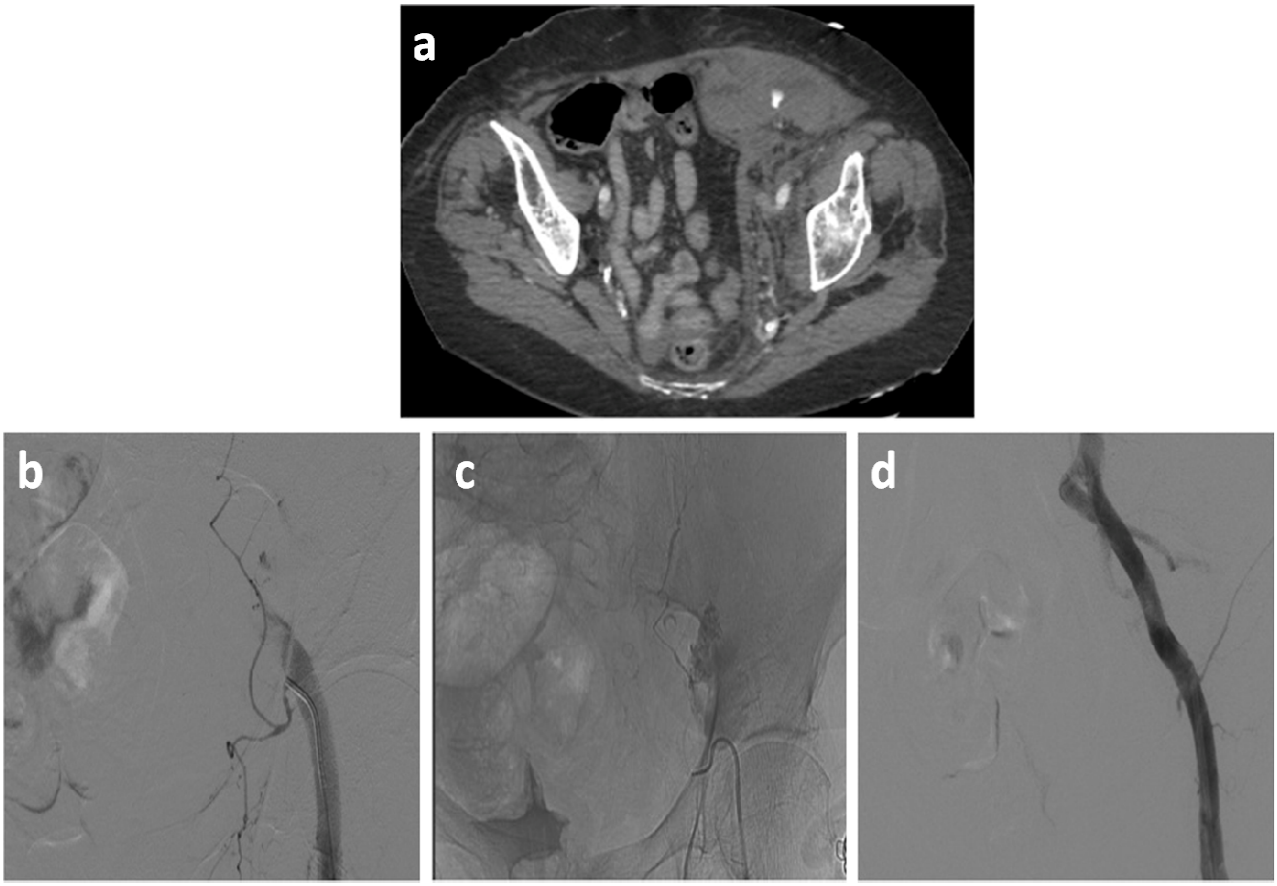
(a) CT scan of the abdomen at the arterial phase: false aneurysm within the spleen. **(b)** CT scan at the portal phase: perisplenic posterior hematoma. **(c)** Splenic artery angiogram showing bleeding intraparenchymal pseudoaneurysm arising from a distal branch **(d)** Angiographic control after superselective glue embolization confirming complete and successful occlusion of the feeding artery with small infarction area.

Figure 3 : : Lower GI bleeding from the left colon in a 60-year-old man treated with NBCAMS Glubran®2 TAE.



(a) CT scan of the abdomen showing extravasation of contrast medium within left colon lumen. **(b)** Angiogram of the inferior mesenteric artery showing active bleeding from a straight artery of the left colon. **(c)** Selective angiography of the marginal artery confirming active bleeding from one vasa recta. **(d)** Control after sandwich glue embolization of the bleeding vessel confirming superselective occlusion of the bleeding vasa recta and the ones on both sides from the marginal artery.

Figure4 : Left rectus sheath hematoma in a 74-year-old woman treated with NBCA-MS Glubran®2 TAE.



(a) CT scan of the abdomen showing left rectus sheath hematoma with extravasation of contrast medium. **(b)** Selective arteriogram of the left inferior epigastric artery confirming active bleeding with extravasation of contrast medium. **(c)** Abdomen X-ray showing arterial distribution of the glue/lipiodol mixture. **(d)** Final angiography after glue embolization demonstrating cessation of bleeding

Université de Bourgogne

UFR des Sciences de Santé

Circonscription Médecine

TITRE DE LA THESE :

EFFICACITE ET SURETE DE L'EMBOLISATION D'HEMOSTASE AU CYANOACRYLATE GLUBRAN®2 : UNE ETUDE MONOCENTRIQUE DE 104 PATIENTS.

AUTEUR : ABDUL MALAK Gilles

RESUME :

Objectif : Etudier l'efficacité et la sureté du Glubran®2 n-butyl cyanoacrylate metacryloxysulfolane (NBCA-MS) pour les embolisations artérielles d'hémostase sur plusieurs sites de saignements. Evaluer les facteurs pronostiques de l'efficacité clinique et de la mortalité à 30 jours.
Matériels et Méthodes : Etude rétrospective incluant des patients successifs ayant été traités par une embolisation artérielle d'hémostase au NBCA-MS Glubran®2 entre juillet 2014 et aout 2016. L'âge, le sexe, les antécédents néoplasiques et cardiovasculaires, les données du bilan de coagulation, la tension artérielle systolique et le nombre de culot globulaires transfusés avant embolisation ont été collectés. L'efficacité clinique, la mortalité à 30 jours, et la prévalence des complications ont été étudiés. Les facteurs pronostiques ont été évalués en analyse uni- et multivariée concernant l'efficacité clinique, et en analyse uni-et bivariée après ajustement sur le site de saignement pour la mortalité à 30 jours.
Résultats : 104 patients inclus avec des saignements musculaires (n=34,32.7%), digestifs (n=28, 26.9%) ou viscéraux (n=42, 40.4%). L'efficacité clinique était de 76% (n=79), la mortalité à 30 jours de 21.2% (n=22). L'échec clinique était significativement associé à la mortalité ($p<0.0001$). Un nombre de culots globulaires transfusés supérieur ou égal à 3 diminuait significativement l'efficacité clinique ($p=0.025$) et augmentait la mortalité ($p=0.03$). Les complications majeures (n=4, 3.8%) nécessitant un traitement chirurgical étaient locales au point de ponction. Aucune complication ischémique n'a été constatée. La durée moyenne d'embolisation était de 4.55 minutes.
Conclusions : Les embolisations artérielles d'hémostase au NBCA-MS Glubran®2 sont efficaces et sures.

Mots-clés :

Embolisation artérielle, hémorragie digestive, hématome musculaire, embolisation, résultats, cyanoacrylate