Université de Bourgogne
UFR des Sciences de Santé
Circonscription Médecine

ANNÉE 2017

N°

OUTCOMES OF TRANSCATHETER ARTERIAL EMBOLIZATION WITH GLUBRAN®2 CYANOACRYLATE GLUE FOR SPONTANEOUS ILIOPSOAS AND RECTUS SHEATH HEMATOMAS.

LE RESULTAT DU TRAITEMENT PAR EMBOLISATION ARTERIELLE AU GLUBRAN®2 CYANOACRYLATE DES HEMATOMES SPONTANES DES MUSCLES GRAND-DROIT ET ILIO-PSOAS CHEZ LES PATIENTS SOUS ANTI-COAGULANT.

THÈSE

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 **RANY JAWHARI**

Né le 21/10/1986

à Aramoun (Liban)

Université de Bourgogne
UFR des Sciences de Santé
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Monsieur le Professeur Romaric LOFFROY (Directeur de thèse)

Monsieur le Professeur Pierre-Emmanuel CHARLES

REMERCIEMENTS

À mon jury de thèse :

Mon Président du Jury, Monsieur le Professeur Denis KRAUSE,
Je vous remercie sincèrement d'avoir accepté de présider cette thèse, c'est un honneur pour moi de vous présenter ce travail. Votre implication, votre disponibilité et votre bienveillance sont exemplaires pour tous. Ce jour est d'autant plus symbolique, qu'il s'agit de votre dernière journée de jury de thèse.

Monsieur le Professeur Romaric LOFFROY,
Je te remercie de m'avoir confié ce travail. J'ai apprécié ton implication et ton encadrement pour ma thèse. Je reste admiratif de ton travail en radiologie interventionnelle.

Monsieur le Professeur Frédéric RICOLFI,
Je vous remercie d'avoir accepté de faire partie de mon jury. Je suis fier d'avoir effectué un semestre en IRM à vos côtés et d'avoir ainsi pu bénéficier de vos incroyables connaissances en radiologie diagnostic et interventionnelle.

Monsieur le Professeur Pierre-Emmanuel CHARLES,
Je vous remercie d'avoir accepté avec enthousiasme de juger mon travail. Veuillez trouver ici l'expression de mes remerciements respectueux.

À mes maîtres :

CHU François Mitterand (Dijon)

Docteur Pierre THOUANT,
Ta manière de travailler concise et rigoureuse est un modèle pour moi. Merci pour tout.

Docteur Pierre-Yves GENSON,
Je suis heureux de partager nos derniers instants au CHU de Dijon ensemble. Tous mes voeux de bonheur pour la belle aventure qui t'attend.

Docteur Adrien CHAVENT,
Ta gentillesse et ta patience sont exemplaires.

Docteur Sylvain FAVELIER,
Un plaisir d'avoir travaillé avec toi et partagé ta passion de la radiologie interventionnelle. Encore toutes mes félicitations pour l'heureux événement.

Docteur Pierre POTTECHER,
Merci de m'avoir fait découvrir l'imagerie ostéo-articulaire. Je te souhaite beaucoup de bonheur avec la prochaine naissance et ton installation à Annecy.

Docteur Brivael LEMOGNE,
Merci pour ton calme, ta disponibilité et ton implication. Félicitations pour ton mariage cet été.

CGFL (Dijon)

Docteurs Sylvaine FEUTRAY, France GUY, Nathalie MEJEAN, Olivier VARBEDIAN, merci pour ce semestre d'été 2016 que j'ai adoré. Je garde un très bon souvenir de mon passage dans votre service.

Polyclinique Val de Saône (Mâcon)

Docteurs Thomas EUVRARD, Anne GRANIER, Jacques VICENTE, Marie-Clémence GIGNIER, Thierry GUILLEMAIN, merci de m'avoir intégré dans votre équipe avec une si bonne ambiance.

CH de Mâcon

Docteurs Pierre MARX, Adnan FATTOUCH, Damien SAUTIER, Hélène BENHAMICHE, Matthieu PAPILLARD, merci pour votre accompagnement et le partage vos connaissances lors de mon premier semestre d'interne en radiologie.

Je remercie par ailleurs l'ensemble **des manips et secrétaires** que j'ai côtoyés au cours de ces cinq dernières années. Merci pour votre travail indispensable et votre compréhension de mon accent.

<u>À mes co-internes :</u>

Gilles,
Un demi-internat avec de très bon souvenirs, une amitié solide est née. J'espère qu'on se retrouvera, au soleil, dans le sud.

Benjamin,
Le plus fou de tous. En soirée ou à l'hôpital, tu m'as beaucoup fait rire avec ton humour et ton cynisme. Bon courage pour ta vie à Paris et ton clinicat en radiologie interventionelle.

Luce,
Quelle gentillesse ma chère amie ! Heureusement que tu étais là pour me faire rire et papoter. Je te souhaite beaucoup de bonheur dans ta vie professionnelle et personnelle.

Romaric,
Content d'avoir partagé quelques semestres avec toi. Je te souhaite une belle vie dijonnaise. Félicitations pour ton mariage l'an prochain.

Sophie,
Heureusement que tu as changé de vocation, nous avons ainsi pu nous connaitre. Je te souhaite une belle vie à Mâcon avec Xavier et toutes tes commandes vente-privée.

PE,
Le plus calme de nous tous. Dommage que nous n'ayons pas effectué de stage ensemble pour mieux se connaitre. Je te souhaite réussite pour ton assistanat au CHU de Dijon.

Olivier, Loïc et Floriane, Florian, Sophie, Marie-Tiphaine, Violaine, Maxime, Julien, Pauline, Marc, Anne-Solène, Grégoire, Léa, Alan, Céline, Jeremy, Lucy, … et les plus jeunes que je connais moins. Merci à vous tous.

<u>À ma famille, mes amis :</u>

Ma mère,
Merci pour tout ce que tu as fait pour moi, je te dois beaucoup, notamment d'avoir pu venir étudier en France. Ta confiance en moi et ton investissement ont été très importants pour moi.

Mon père,
Merci de tout ce que tu as fait pour notre famille. J'aurais tant aimé que tu sois encore parmi nous aujourd'hui.

Dany,
Merci pour tout. De m'avoir chaleureusement accueilli lors de ma première année de médecine. Et surtout, d'avoir toujours été à mes côtés avec ton soutien tout au long de mes études.

Chadi,
Merci pour tout. Ta bonne humeur et ton optimisme sont un pilier dans notre famille. Je me réjouis de t'avoir à nos côtés, ici, à Dijon.

Amandine,
Merci d'être à mes côtés, et de m'avoir aidé à accomplir ce travail (clinical success). Je suis heureux de partager ma vie avec toi. De très belles choses nous attendent.

Corinne,
Merci pour vos petits plats, bien que parfois ratés, vous êtes sur le bon chemin.

Geoffrey,
Un de mes premiers amis en France, nous partageons de très bons souvenirs, du week-end d'intégration à aujourd'hui.

Thomas,
De beaux moments de révision nous lient. Tu as témoigné de notre amitié en me demandant d'être ton témoin de mariage. Je te souhaite une belle vie avec Justine et Maëlia.

Roy,
On s'est connu au Liban au lycée et aujourd'hui on se retrouve en France. Quelle joie de te compter parmi mes amis.

Batou,
Les six mois de Mâcon restent mémorables et ont scellé notre amitié. J'ai hâte de refaire un voyage avec toi et Adrien.

Vianney,
Tu as toujours été à mes côtés durant nos études et encore aujourd'hui. Merci d'avoir convier le « petit libanais » à découvrir la campagne nivernaise.

Nicolas Maillot, Olivier Maillot, Victor Harly, Pierre Faglin,
De beaux souvenirs d'étudiants. J'espère qu'on se reverra vite, je vous attends dans le sud.

<u>À mes amis du Liban et aux oubliés</u> (et il y en a peut-être), merci pour tout et à très vite.

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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."

TABLE DES MATIÈRES

ABBREVIATIONS

TAE = transcatheter arterial embolization

NBCA-MS = n-butyl cyanoacrylate metacryloxysolpholane

IPHs = iliopsoas hematomas

RSH = rectus sheath hematomas

CT = computed tomography

INR = international normalized ratio

PTT = partial thromboplastin time

MBP = mean blood pressure

RBC = red blood cells

OUTCOMES OF TRANSCATHETER ARTERIAL EMBOLIZATION WITH GLUBRAN®2 CYANOACRYLATE GLUE FOR SPONTANEOUS ILIOPSOAS AND RECTUS SHEATH HEMATOMAS.

Rany Jawhari, Olivier Chevallier, Nicolas Falvo, Philippe d'Athis, Sophie Gehin, Pierre-Emmanuel Charles, Marco Midulla, Romaric Loffroy.

ABSTRACT

Purpose: To assess the efficacy and safety of Glubran®2 n-butyl cyanoacrylate metacryloxysulfolane (NBCA-MS) transcatheter arterial embolization (TAE) for anticoagulation-related soft-tissue bleeding and to evaluate predictive factors of clinical success and 30-day mortality.

Materials and Methods: Retrospective review of anticoagulated patients who underwent emergent Glubran®2 NBCA-MS TAE for spontaneous iliopsoas (IPHs) and/or rectus sheath (RSHs) hematomas with extravasation of contrast medium on computed tomography (CT) scan between August 2011 and November 2016. Variables including age, sex, coagulation parameters, volume of hematoma, mean blood pressure and number of red blood cells (RBC) units transfused were collected. Clinical success, 30-day mortality and complication rates were evaluated. Uni- and multivariate logistic regression analyses were used to assess predictive factors of clinical success and 30-day mortality.

Results: Active bleeding was present on all CT scans (100%). Angiograms revealed extravasation in 44 (88%) of 50 patients. Technical success was achieved in 50/50 (100%) patients. Clinical success was achieved in 33/50 (66%) patients. Mortality within 30 days of TAE was 44% (22/50). No complications related to embolization procedure occurred. Lower mean blood pressure (p=0.003), greater number of RBC units transfused (p=0.003), greater volume of hematoma (p=0.04), and IPH location (p=0.02) were associated with lower clinical success. Clinical failure (p=0.00002), lower mean blood pressure (p=0.004), greater number of RBC units transfused (p=0.002), and IPH location (p=0.01) were significantly associated with higher 30-day mortality.

Conclusion: TAE with Glubran®2 NBCA-MS is safe and efficient to treat refractory soft-tissue bleeding in anticoagulated patients despite the high mortality of this severe condition.

Keywords: Iliopsoas hematoma, rectus sheath hematoma, soft-tissue bleeding, transcatheter embolization, cyanoacrylate glue.

INTRODUCTION

Les hématomes musculaires spontanés sont généralement une complication peu fréquente et non critique. En effet, dans la majorité des cas, ils sont traités par une prise en charge conservatrice incluant la correction des troubles de l'hémostase, le remplissage vasculaire et la transfusion sanguine (1). En raison de l'utilisation croissante des traitements anti-coagulants, notamment chez les patients âgés, l'incidence du saignement des tissus mous lié à un traitement anti-coagulant est de plus en plus courante (1-11). Les principaux sites concernés par les hématomes spontanés sont les muscles grand-droit et ilio-psoas (9). La prise en charge conservatrice des hématomes spontanés menaçant la vie des patients est controversée et demande une intervention plus invasive pour éviter de sérieuses complications et la mortalité (12-14). La chirurgie perturbe l'effet tampon des compartiments musculaires et est indiquée en dernier recours (12). Cependant, la chirurgie permet difficilement d'identifier le pédicule vasculaire à l'origine du saignement et de contrôler le site de saignement. L'embolisation transartérielle de l'artère responsable du saignement est devenue une option largement utilisée pour le traitement des patients souffrant d'un saignement artériel aigu. Cependant, seuls quelques cas et petites séries traitant de cela existent dans la littérature (15-22). En outre, l'embolisation transartérielle avec des microcoils et / ou le gelfoam a été la technique endovasculaire la plus fréquemment utilisée (23-27).

L'utilisation de la colle n-butyl cyanoacrylate (NBCA) est une autre option, qui a pour avantage d'être administrée rapidement par rapport aux micro-coils, ce qui est important dans un contexte d'instabilité hémodynamique. Cependant, la colle n'est pas populaire et est sous-utilisée dans le domaine de la radiologie interventionnelle, car elle est considérée comme un produit difficile à manipuler.

La colle acrylique Glubran®2 a été préférée comme premier agent embolique dans notre établissement pour le traitement endovasculaire des hématomes réfractaires au traitement conservateur. Glubran®2 est une colle chirurgicale dans laquelle la NBCA est combinée avec un autre comonomère, le métacryloxysulpholane (MS), pour produire un polymère plus souple et stable que les cyanoacrylates classiques, comme Histoacryl®, dont la réaction exothermique plus basse (45 ° C) entraîne moins d'inflammation et de toxicité cellulaire (28). À notre connaissance, il n'existe pas de larges études sur la prise en charge au Glubran®2 NBCA-MS des hématomes spontanés des muscles grand-droit et ilio-psoas menaçant la vie des patients. L'objectif principal de cette étude rétrospective est de rendre compte de notre expérience d'embolisation transartérielle au Glubran®2 NBCA-MS des hématomes spontanés de l'ilio-psoas et grand-droit dans une grande population de patients sous anticoagulants et de déterminer les facteurs prédictifs de succès clinique et de la mortalité à 30 jours.

INTRODUCTION

Spontaneous intramuscular hematomas are usually a rare and noncritical condition because majority of the cases are self-limiting by conservative management including rectification of coagulation parameters, fluid resuscitation and blood transfusion (1). Due to the increasing use of anticoagulant therapy, especially in elderly patients, the incidence of anticoagulation-related soft-tissue bleeding has recently become a very common condition (1-11). Iliopsoas and rectus sheath muscular compartments are the main sites of soft-tissue hemorrhage (9). Management of life-threatening bleeding refractory to conservative medical treatment remains controversial and should indicate more aggressive intervention to avoid serious complications and mortality (12-14). Open surgery has been thought to disturb the tamponade effects of the muscular compartments and is indicated as a last resort (12). However, surgery is difficult with regard to identification of the bleeding source and bleeding site control. Transcatheter arterial embolization (TAE) of the bleeding artery has become a widely used option for the treatment of patients with acute arterial bleeding. However, only few reports and small case series exist in the literature in such a setting (15-22). Furthermore, TAE with microcoils and/or gelfoam has been the most frequently used endovascular technique (23-27).

The use of n-butyl cyanoacrylate (NBCA) glue is another option, which has therefore the benefit of being quickly administered in comparison with microcoils, what is important in a setting of hemodynamic instability. However, glue is not popular and underutilized in interventional radiology field, because it is considered as a hard product to handle.

Glubran®2 acrylic glue has been preferred as first embolic agent in our institution for endovascular treatment of hematomas refractory to conservative therapy. Glubran®2 is a surgical glue in which NBCA is combined with another comonomer, metacryloxysulpholane (MS), to produce a more pliable and stable polymer than classic cyanoacrylates as Histoacryl® whose milder exothermic reaction (45°C) results in less inflammation and histotoxicity (28). No large studies exist to our knowledge concerning the management of life-threatening anticoagulation-related iliopsoas (IPHs) and rectus sheath hematomas (RSHs) with Glubran®2 NBCA-MS. The primary goal of this retrospective study was to report our focused experience in endovascular treatment of spontaneous IPHs and RSHs with Glubran®2 NBCA-MS TAE in a large population of anticoagulated patients, and to determine the predictive factors of clinical success and 30-day mortality.

MATERIALS AND METHODS

Patients Selection

We retrospectively reviewed the medical records of patients who underwent emergent TAE with Glubran®2 NBCA-MS for spontaneous IPHs and/or RSHs from August 2011 to November 2016 at our institution. Patients were identified using the database maintained prospectively by our Interventional Radiology Department. Exclusion criteria were as follows: patients with recent trauma, patients treated with other embolic agents, hematoma concerning a recent operation site, patients without extravasation of contrast medium on computed tomography (CT) scan, patients with other sites of soft-tissue bleeding. All radiological and electronic medical records were reviewed to collect data on patients. The following variables were collected: patients demographics, treatments, laboratory data on coagulation parameters as international normalized ratio (INR), partial thromboplastin time (PTT) and platelet count, hemoglobin level, mean blood pressure (MBP) and number of red blood cells (RBC) units transfused before TAE, bleeding sites, CT scan and angiographic findings, vessel(s) embolized, embolic material used, technical and clinical outcomes, complications and 30 day-mortality. This retrospective study was performed in compliance with the requirements of our institutional review board. Informed consent was not required.

Computed Tomography Imaging Evaluation

Contrast-enhanced CT images were reviewed for the location of the hematoma and extravasation on the arterial and the late venous images. The bleeding artery was defined in case of apparent arterial extravasation. Hematoma size was measured to calculate approximative volume (cm^3) defined by the pragmatic following formula: volume (V) = (a x b x c) x 0.52, where a and b were the maximum anteroposterior and transversal diameters of the hematoma in the axial plane (cm), and where c was the height of the hematoma in the sagittal plane (cm) (24).

Embolization Technique

All angiographic procedures were performed by 1 of 3 experienced interventional radiologists with standard percutaneous transfemoral catheterization using a 5-French or 6-French sheath. Selective opacification of the suspected bleeding artery was performed using standard 4-French or 5-French catheters after global angiogram, followed by superselective arteriography using a 2.7-French co-axial microcatheter (Progreat; Terumo, Leuven, Belgium). All pathologic arteries were embolized

using Glubran®2 NBCA-MS (GEM Srl, Viareggio, Italy). When no vascular abnormality on angiography, the feeding artery was empirically embolized based on CT findings. Highly selective angiograms of the other arteries supplying the region were obtained in case of no extravasation on the angiogram. 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, Villepinte, France) at a ratio ranging from 1:4 to 1:6 (Glubran®2/Lipiodol) 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 2 mL 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 RSH, the targeted vessel for embolization was the homolateral inferior epigastric artery (*Figure 1*). For IPH, the homolateral bleeding lumbar artery was embolized based on angiographic findings (*Figure 2*). Furthermore, lumbar arteries above or below the bleeding one were empirically or angiographically guided embolized to avoid revascularization, at the discretion of the interventional radiologist. Glubran®2 was released near the bleeding site until cessation of angiographic extravasation and/or occlusion of the targeted vessel as shown by fluoroscopic monitoring. Hemostasis of the access site was obtained with 5-French or 6-French vascular closure devices.

Definitions and Analytic Items

Mean blood pressure in mmHg was calculated according to the following formula commonly used in intensive care medicine: mean blood pressure (MBP) = (SBP + 2 x DBP) x 1/3, where SBP (mmHg) was systolic blood pressure and DBP (mmHg) was diastolic blood pressure (29). Hemorrhagic shock was defined as MBP $\leq$ 65 mmHg. Patients who met one of the following criteria were classified in the coagulopathy group: INR greater than 1.5, PTT longer than 45 seconds, or platelet count less than 80,000/mm^3. Arteriography was considered positive in case of extravasation of contrast medium. Technical success was defined as complete occlusion of the target vessel or cessation of extravasation on the postembolization arteriography. 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.

Statistical Analysis

Qualitative variables were described as frequencies (percentages) and compared with Fisher's exact test or Chi-square test. Quantitative variables were described as means or medians with standard deviation (SD) or difference between 1st (Q1) and 3rd (Q3) quartile, and were compared with the nonparametric test of Mann-Whitney. All *p* values less than 0.05 were considered statistically significant. Statistical analysis was performed using Triomphe software. Logistic regression analyses were performed using Stata version 8 software (2003).

RESULTS

Patient Characteristics

A total of 50 patients with active bleeding on CT scan underwent technically successful emergent Glubran®2 NBCA-MS TAE for spontaneous anticoagulation-related IPHs and/or RSHs during the study period and were included for statistical analysis as shown in the study flow shart (*Figure 3*). At baseline, all patients were in critical status, and required vascular filling and RBC transfusion in 47 cases (94%). There were 25 males (50%) and 25 females (50%) with a mean age of 71.7±14.2 years (range, 19-87 years) (*Table 1*). All patients were treated with anticoagulant therapy. Additional antiplatelet therapy was taken in 26% of patients (*n*=13). Furthermore, 22 (44%) patients had a coagulopathy as previously described. Indications for anticoagulant therapy were as follows: rhythmic cardiopathy (*n*=23), venous thromboembolic disease (*n*=14), prosthetic valve (*n*=5), prophylaxis (*n*=5), arteriopathy (*n*=3). Thirty-seven patients had at least one comorbidity and 31 patients had at least 2 comorbidities among the following ones: chronic cardiovascular or disease, chronic renal disease, chronic liver disease. Regarding parameters that reflected the severity of initial hemorrhage, the mean number of RBC units transfused before TAE was 4.8±3.2 (range, 0-14). Moreover, median level of hemoglobin before TAE was 9.7 g/dL (range, 6.2-18 g/dL) and median MBP was 62.5 mmHg (range, 58.3-75 mmHg). Bleeding sites with active bleeding were

identified on CT scans in all patients as inclusion criteria. Location of the hematoma was iliopsoas muscle in 38 (76%) patients, rectus sheath in 11 (22%) patients and a combination of both in 1 (2%) patient. The mean volume of hematoma was 1119.2±863.5 cm^3 (range, 134.0-3589.0 cm^3). Arteriography showed active bleeding in 44 (88%) of the 50 patients. Contrast extravasation was present on angiogram in 35/38 patients with an IPH, in 8/11 patients with a RSH, and in 1/1 patient with both IPH and RSH. Bleeding arose from the lumbar arteries (*n*=37), inferior epigastric arteries (*n*=11), iliolumbar arteries (*n*=5), or deep circumflex iliac arteries (*n*=5). Empiric embolization of the inferior epigastric artery or the lumbar artery was performed in 3 RSHs and 3 IPHs, respectively, in order to prevent rebleeding after the loss of the tamponade effect. Furthermore, at least one more lumbar artery immediately above or below the bleeding one was systematically embolized either empirically to avoid revascularization or angiographically guided because of revascularization, at the discretion of the interventional radiologist. In case of bleeding from the iliolumbar artery, only the lumbar artery above was potentially additionally embolized. Hematoma locations and embolized arteries are summarized in *Table 2*.

Clinical Outcomes

Clinical Success

The overall clinical success rate was 66% (*n*=33) (*Table 3*). Clinical failure (*n*=17, 34%) was related to persistent bleeding (*n*=10) or rebleeding (*n*=7) (*Figure 1*). Among the 17 patients with clinical failure, the 10 patients with persistent bleeding died within 48 hours from multiorgan failure due to hemorrhagic shock despite TAE and 7 rebled after 48 hours but within 30 days of TAE. Among these 7 patients, 2 were successfully managed with glue reembolization (*n*=1) or conservative medical treatment (*n*=1), 2 underwent surgery for iliopsoas hematoma decompression but continued to bleed and died, and 3 more patients died from multiorgan failure before further intervention.

30-Day Mortality

The 30-day mortality rate was 44% (*n*=22) (*Table 4*). Among deaths, 15 were due to multiorgan failure secondary to hemorrhagic shock within 48 hours (*n*=10) or after 48 hours (*n*=5) (*Figure 1*). Other etiologies of death after 48 hours were sepsis secondary to pulmonary infection in 4 patients and heart attack in 3 patients. The 30-day mortality rate directly related to persistent bleeding (*n*=10) or rebleeding (*n*=5) was 30% (*n*=15).

Complications

Overall complication rate was 10% (*n*=5). No technical complications as catheter adherence or mistarget embolization occurred. Minor complications were noted in 4% of the study population (*n*=2), consisting in hematoma at the puncture site, managed conservatively with medical treatment. Major complications were observed in 3 patients (6%): a hematoma at puncture site which required surgical treatment in 1 patient and an abscess of retroperitoneal hematoma after one week in 2 patients, successfully treated by percutaneous drainage.

Predictors of Outcomes

Lower MBP (*p*=0.003), greater number of RBC units transfused before TAE (*p*=0.003), and greater volume of hematoma (*p*=0.04) were significantly associated with lower clinical success rate in the univariate analysis. Additionnally, clinical success was statistically lower in the IPH group (*n*=24, 61.5%) than in the RSH group (*n*=11, 100%) (*p*=0.02). Clinical failure (*p*=0.00002), lower MBP (*p*=0.004), and greater number of RBC units transfused before TAE (*p*=0.02) were significantly associated with higher 30-day mortality rate in the univariate analysis. Additionnally, 30-day mortality was statistically higher in the IPH group (*n*=22, 56.4%) than in the RSH group (*n*=0, 0%) (*p*=0.01). Age, hemoglobin level, platelets level, and INR value did not impact neither the clinical success rate nor the 30-day mortality rate in the univariate analysis. Data are summarized in *Tables 3 and 4*. In the logistic regression analysis, a volume of hematoma greater than or equal to 813.6 cm^3 was associated with lower clinical success (*p*=0.027). In other words, patients with a volume of hematoma greater than or equal to 813.6 cm^3 were 5.5 times more likely to rebleed (OR=5.5, 95% CI, 1.2-24.8).

DISCUSSION

The current study, presently the largest series focused on anticoagulated patients with iliopsoas muscle and/or rectus sheath hematomas treated with Glubran®2 NBCA-MS TAE, demonstrated the safety and feasibility of TAE with glue and confirmed that anticoagulation in elderly patients is especially dangerous. Increased rate of life-threatening spontaneous soft-tissue bleeding due to the use of anticoagulants has been reported, especially in the elderly population because of microangiopathy and vascular fragility, which are major contributors to hemorrhage (24, 25). Arterial embolization has been favored over surgery when conservative therapy fails because comorbidities make patients poor candidates for surgery and ability of surgery has been limited in

bleeding control (13, 14). However, the role of the endovascular therapy in the patient management remains unclear. There are no validated guidelines so far regarding the use of TAE. Endovascular management of anticoagulation-related soft-tissue bleeding by embolization has been reported previously (23-27). In our study, the technical success rate was 100% and the overall clinical success rate was 66%. Approximately 34% of the patients experienced either continued bleeding or rebleeding after embolization. However, and despite agressive treatment, 44% of the patients died within 30 days after TAE. The major complications were minimal and not related to the procedure. Clinical failure was associated with higher mortality. No previous NBCA TAE studies assessed predictive factors of clinical failure and mortality.

Poorer outcomes in our study differed from the existing literature despite the use of NBCA. Indeed, Farrelly et *al* (23), Maleux et *al* (24), Dohan et *al* (25) and Popov et *al* (27) reported clinical success rates of 91%, 98%, 69% and 88%, respectively, and mortality rates of 29%, 14%, 31% and 30%, respectively, with the use of gelfoam, coils or particles, whereas Ozyer et *al* (26) reported clinical success and mortality rates of 92% and 16%, respectively, with the use of Histoacryl® NBCA with none of the patients who died due to a progression of the hematoma in this series. This discrepancy may be explained by several factors. First, the definition of clinical success was slightly different and in favor of previous series. Second, patients in our study were older than those in some series, with severe comorbidities, which may contribute to poorer general condition. Third and more importantly, our study included very selected bleeding patients who were all under anticoagulant therapy and had all extravasation of contrast medium on CT scans. It may have led to specific poorer outcomes, considering that patients with active bleeding are more likely to be hemodynamically unstable. On the other hand, great volume of hematoma was strongly associated with clinical failure in our study. This suggests that IPHs and RSHs are life-threatening condition with poor prognosis 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. Lastly, lower MBP and greater number of RBC units transfused before TAE were 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.

Our study also showed that CT can aid in accurate empiric embolization and should be obtained whenever possible because it was a useful tool for diagnosing the hematoma and planning the endovascular treatment (30, 31). It could provide faster and more accurate endovascular intervention. One of the important clinical points open to discussion is whether embolization should always be performed and, more specifically, which clinical or imaging points should trigger

emergent embolization. Unfortunately, there are no specific guidelines to suggest when to intervene with endovascular embolization or even open surgery to stop the bleeding. In patients with severe ongoing bleeding, we presume that delaying the adequate treatment could be responsible for significant mortality. Popov et *al* (27) proposed an algorithm integrating not only the hemodynamic condition of the patient but also CT features that might predict the outcome with conservative measures. Even more, our data supports the fact to skip conservative management in case of active bleeding on CT scan and suggest that TAE should be considered as soon as possible in such a setting, whatever the hemodynamic status of the patient, before hematoma becomes large and leads to poorer outcomes.

Numerous embolic materials are commercially available and each possesses its advantages and disadvantages (23-27, 32-34). The choice of embolic material is still a matter of debate and 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 interventions, and no series reported the use of Glubran®2 NBCA-MS for anticoagulation-related soft-tissue bleeding. In our institution, selective TAE using NBCA glue as the only embolic agent has become the salvage treatment of choice for acute arterial bleeding, whenever parent vessel may be compromised, especially for the management of soft-tissue hematomas in which fast, distal and complete embolization is mandatory. Liquid adhesive embolic agents offer the advantages of low viscosity for easy injection through small or tortuous catheters (34). Cyanoacrylates are glues with a high adhesive strength. 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 (28). Trufill® is has Food and Drug Administration 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 European Conformity 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 (34). Glubran®2 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® (32, 34). 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 (35, 36). The final polymer is

more flexible and, unlike conventional cyanoacrylate, does not fragment. Glubran®2 has a European Conformity 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. This allows the operator to control the degree of distal vessel penetration, allowing for occlusion at or significantly beyond the catheter tip (37). 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 (34, 35). The presence of a coagulopathy did not affect clinical outcomes in the present study whereas 44% 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 (34). Although strong recommendations cannot be drawn from our retrospective study, clinical outcomes could have been even worst with the use of other embolic agents. 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. These results correlate well with the experience of Ozyer et *al* (26), who similarly had no such complications despite the use of Histoacryl®. Other reported complications of NBCA embolization include abscess formation after end-soft-tissue ischemia (24). We experienced this complication in 2 of 50 patients, managed with percutaneous drainage. However, abscess formation was probably more related to spontaneous evolution of large hematomas into septic collections than to embolic material itself. Furthermore, surgical decompression of large rectus sheath hematomas is sometimes necessary despite TAE as reported in our series in2 patients and by Maleux et *al* (24), and may lead to poorer outcomes. Lastly, the presence of a radiculomedullary artery must be checked during angiography of lumbar arteries in order to avoid serious ischemic complications.

Our study had some limitations. First, this is a retrospective study from a single center only focused on IPHs and RSHs, with a small number of patients involved, although to our knowledge this series is the largest thus far reported. Second, there was a major bias of selection since all bleeding patients included in the study were under anticoagulant therapy and had extravasation of contrast medium on CT scan. It may have led to specific poorer outcomes, considering that patients with active bleeding are more likely to be hemodynamically unstable. Third, the absence of a control group treated with other embolic agents to compare the efficacy of NBCA embolization

should be noted. Fourth, although our study suggests that late embolization may have poorer outcomes and should be avoided, no accurate data was available on time between bleeding onset and endovascular intervention. Another minor shortness of the study is that the volume of hematoma may have been underestimated by the formula used for this purpose. Lastly, the goal of this study was to assess the efficacy of emergent hemostatic procedures, then no long-term follow-up was available. Therefore, further studies with larger groups are required to better establish the role of TAE in such a setting.

CONCLUSION

In conclusion, our study shows that TAE with Glubran®2 NBCA-MS is a safe and feasible endovascular treatment for life-threatening anticoagulation-related soft-tissue bleeding with acceptable success rate despite the high mortality of this severe condition. This intervention should be considered as soon as possible in case of active bleeding on CT scan, whatever the hemodynamic status of the patient, before hematoma becomes large and leads to poorer outcomes. However, further investigations are warranted to define the ideal strategy and the best embolic agent.

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THESE SOUTENUE PAR M. RANY JAWHARI

CONCLUSIONS

L'hématome spontané des muscles grand-droit et / ou ilio-psoas représente une complication courante et grave des patients sous traitement anti-coagulant (TAC). Les hématomes de grande taille mettent en danger la vie du patient, et leur prise en charge est controversée. La chirurgie permet difficilement d'identifier le pédicule vasculaire à l'origine du saignement et perturbe l'effet tampon. L'embolisation transartérielle est donc préconisée, permettant ainsi un acte moins invasif et plus ciblé. Il n'existe que peu d'étude sur l'embolisation des hématomes spontanés.

L'embolisation transartérielle au N-Butyl Cyanoacrylate-Metacryloxyl Sulfolane (Glubran®2) est une technique sûre et efficace dans le traitement des hématomes spontanés des muscles grand-droit et / ou ilio-psoas chez des patients sous TAC.

Le succès clinique est élevé malgré un fort taux de mortalité pour cette pathologie grave. Cette intervention est à pratiquer en urgence s'il existe un saignement actif au scanner, peu importe l'état hémodynamique du patient, avant que l'hématome ne grossisse et s'auto-développe.

Le Président du jury,

Pr D. Ghrani

Vu et permis d'imprimer

Dijon, le 14 Juin 2017

Le Doyen

Pr. F.HUET

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Table 1. Characteristics of 50 patients.

Characteristics	Number or value (%)
Age (years)	
Mean±SD (range)	71.7±14.2 (19-87)
Median (Q1-Q3)	77 (67-82)
Gender	
Male	25 (50)
Female	25 (50)
Anticoagulant therapy	50 (100)
Heparin therapy	22 (44)
Enoxaparin	14
Calciparin	3
Tinzaparin	3
Fondaparinux	2
Vitamin K antagonist therapy	21 (42)
Fluindione	13
Warfarin	8
Heparin and vitamin K antagonist	7 (14)
Enoxaparin and fluindione	4
Calciparin and fluindione	3
Antiplatelet therapy	13 (26)
Aspirin	9
Clopidogrel	4
Coagulopathy*	22 (44)
Hemoglobin (g/dL)	22 (44)
Mean±SD	10.2±2.4
Median (range)	9.7 (6.2-18.0)
INR	
Mean±SD (range)	2.5±1.5 (1.0-6.9)
Median (Q1-Q3)	1.7 (1.3-3.2)

Characteristics	Number or value (%)
RBC units transfused	
Mean±SD (range)	4.8±3.2 (0-14)
Median (Q1-Q3)	4 (3-7)
MBP before TAE (mmHg)	
Mean±SD (range)	68.7±15.9 (48.3-113.7)
Median (Q1-Q3)	62.5 (58.3-75.0)
Platelets level (x10^3/mm^3)	
Mean±SD (range)	178.3±80.3 (41-407)
Median (Q1-Q3)	158 (115-223)
Volume of hematoma (cm^3)	
Mean SD (range)	1119.2±863.5 (134.0-3589.0)
Median (Q1-Q3)	813.6 (432.3-1518.5)
Site of bleeding	
Iliopsoas muscle	38 (76)
Rectus sheath	11 (22)
Iliopsoas and rectus sheath	1 (2)

Footnote:
** Partial thromboplastin time > 45 seconds and/or platelet count < 80,000/mm^3 and/or international normalized ratio > 1.5; SD, standard deviation; INR, international normalized ratio; RBC, red blood cell; MBP, mean blood pressure; TAE, transcatheter arterial embolization; Q1, first quartile; Q3, third quartile.*

Table 2. Hematoma locations and embolized arteries.

Muscle compartment involved	Type of artery	Number of patients	Number of embolized arteries
Iliopsoas (*n*=38)	LA	37	82
	ILA	4	4
Rectus sheath (*n*=11)	IEA	11	11
	DCIA	4	4
Iliopsoas + Rectus sheath (*n*=1)	ILA	1	1
	DCIA	1	1

Footnote:
LA, lumbar artery; ILA, iliolumbar artery; IEA, inferior epigastric artery; DCIA, deep circumflex iliac artery. Overall, 103 arteries were embolized in 50 patients.

Table 3. Factors associated with clinical success within 30 days of embolization.

Variables	Clinical success *n*=33	Clinical failure *n*=17	*p-value*
Age (years)	70.1±15.8	75.8±8.2	0.386
Hb (g/dL)	7.4±1.9	6.8±1.4	0.442
Platelets level (x10^3/mm^3)	178.2±71.2	178.6±103.4	0.523
INR	2.2±1.4	3.1±1.7	0.051
MBP before TAE (mmHg)	72.8±16.7	58.1±6.0	0.003
RBC units transfused	3.9±2.8	6.9±3.3	0.003
Volume of hematoma (cm^3)	951.0±752.5	1551.6±1003.4	0.04

Footnote:
Hb, hemoglobin; INR, international normalized ratio; MBP, mean blood pressure; TAE, transcatheter arterial embolization; RBC, red blood cell.
$p<0.05$ was considered as statistically significant.

Table 4. Factors associated with mortality within 30 days of embolization.

Variables	Alive *n*=28	Dead *n*=22	*p-value*
Age (years)	69.2±14.2	74.9±13.9	0.193
Hb (g/dL)	7.6±2.1	6.8±1.1	0.273
Platelets level (x10^3/mm^3)	174.2±75.4	183.5±87.8	0.945
INR	2.3±1.6	2.6±1.5	0.134
MBP before TAE (mmHg)	74.9±18.0	60.7±7.5	0.004
RBC units transfused	3.8±2.6	6.0±3.5	0.02
Volume of hematoma (cm^3)	973.8±805.6	1304.2±917.3	0.132
Clinical success	26	7	0.00002

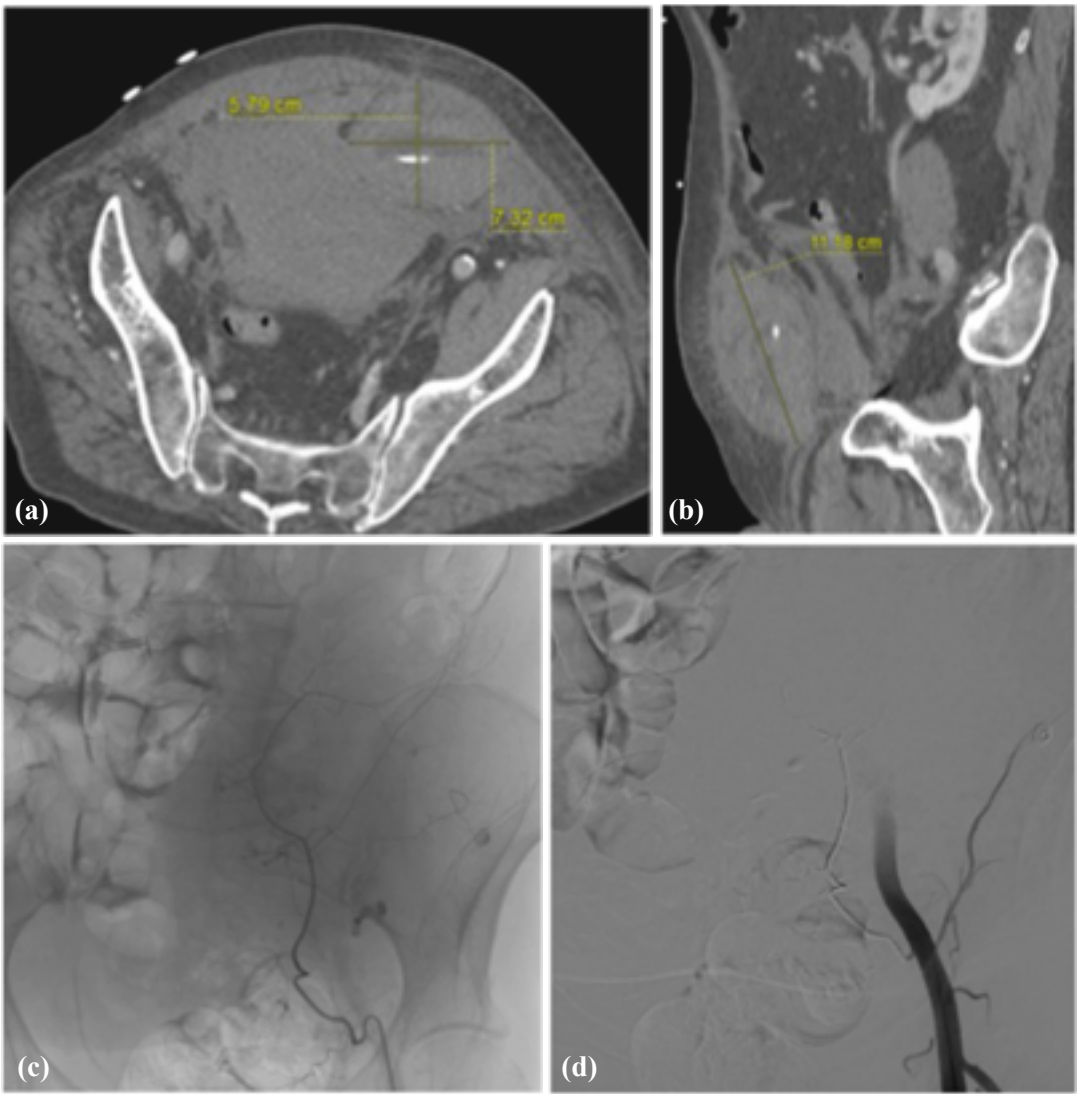
Footnote:
Hb, hemoglobin; INR, international normalized ratio; MBP, mean blood pressure; TAE, transcatheter arterial embolization; RBC, red blood cell.
$p<0.05$ was considered as statistically significant.

Table 5. Published series of transcatheter arterial embolization for spontaneous soft-tissue bleeding that included >10 patients during a 10-year period.

Characteristics	Farrelly et *al* (23)	Maleux et *al* (24)	Dohan et *al* (25)	Ozyer et *al* (26)	Popov et a*l* (27)	Our study
Year of publication	2011	2012	2015	2016	2017	2017 ?
Period of inclusion*	11	7	7	12	8	5
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
Number of patients	25	42	36	38	27	50
Gender						
Male	13 (52%)	24 (57%)	12 (33%)	19 (50%)	6 (22%)	25 (50%)
Female	12 (48%)	18 (43%)	24 (67%)	19 (50%)	21 (78%)	25 (50%)
Age (years)						
Mean	64	71	74	58	73	72
Range	30-82	22-87	39-91	19-93	52-91	19-87
Anticoagulant therapy	20 (71%)	42 (100%)	36 (100%)	21 (55%)	24 (89%)	50 (100%)
Antiplatelet therapy	NA	NA	7 (19%)	3 (8%)	NA	13 (26%)
Coagulopathy			12 (33%)	23 (60%)	NA	22 (44%)
Active bleeding						
At CT scan	20 (80%)	35 (83%)	22 (73%)	34 (89%)	22 (81%)	50 (100%)
At arteriography	22 (88%)	36 (86%)	27 (75%)	29 (76%)	19 (70%)	44 (88%)
Embolic agent	Gelfoam, coils	Coils, particles	Gelfoam, coils, particles	NBCA Histoacryl®	Gelfoam, coils, particles	NBCA-MS Glubran®2
Technical success	22 (100%)	42 (100%)	36 (100%)	37 (98%)	26 (96%)	50 (100%)
Clinical success	20 (91%)	41 (98%)	25 (69%)	35 (92%)	23 (88%)	33 (66%)
Further TAE						
Second TAE	2 (9%)	0 (0%)	6 (16%)	2 (5%)	5 (19%)	1 (2%)
Third TAE	0 (0%)	0 (0%)	0 (0%)	1 (2%)	2 (8%)	0 (0%)
Major complications	0 (0%)	9 (22%)	0 (0%)	0 (0%)	1 (4%)	3 (6%)
30-day mortality	6 (29%)	6 (14%)	11 (31%)	6 (16%)	8 (30%)	22 (44%)

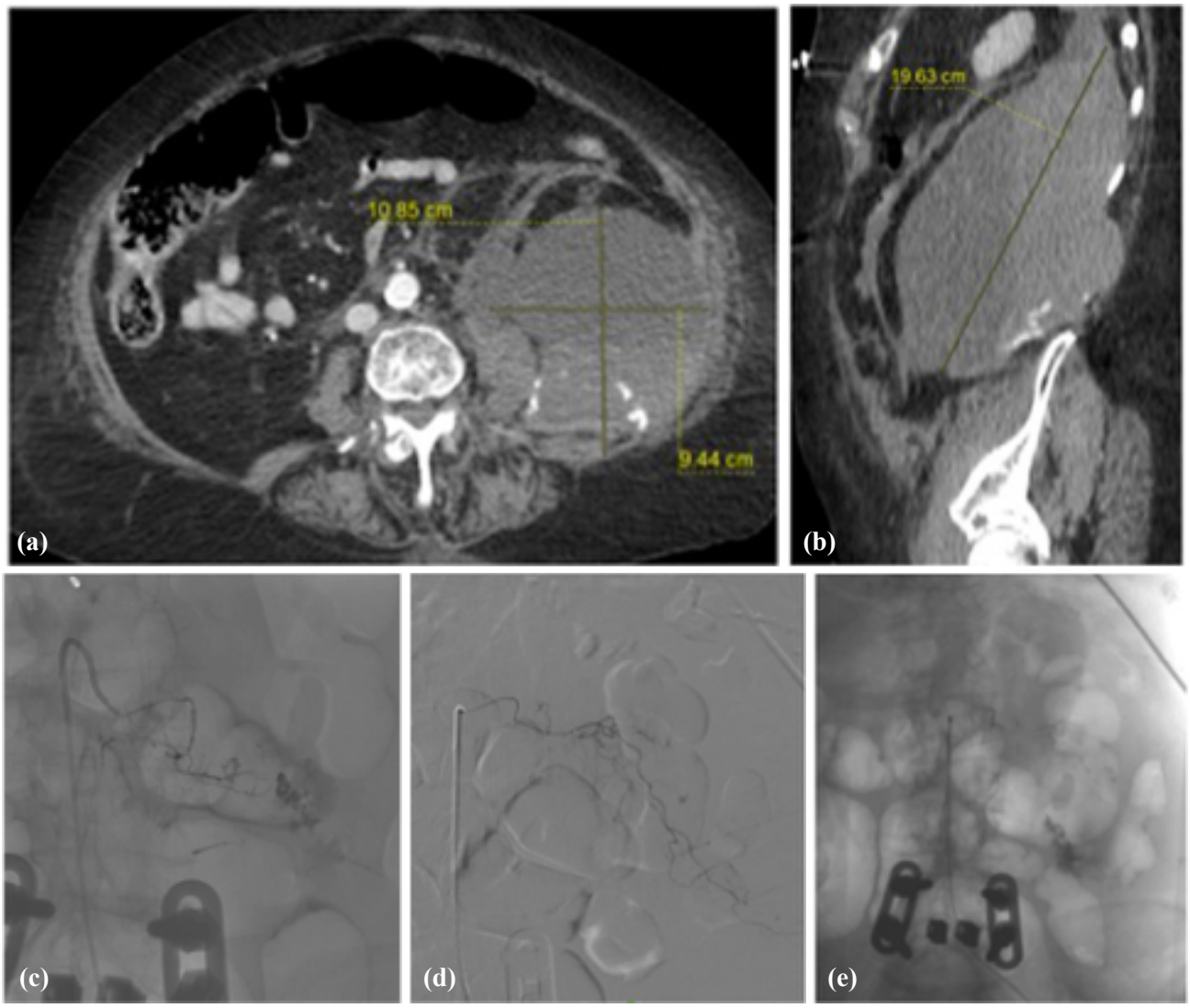
Footnote:
** in years; ** if they required surgery and/or prolonged hospitalization; CT, computed tomography; TAE, transcatheter arterial embolization; NBCA, n-butyl cyanoacrylate; NBCA-MS, n-butyl cyanoacrylate metacryloxysulfolane; NA, not available.*

Figure 1. Spontaneous left rectus sheath hematoma responsible for pain and hemodynamic shock in an 88-year-old man treated with enoxaparin for atrial fibrillation.



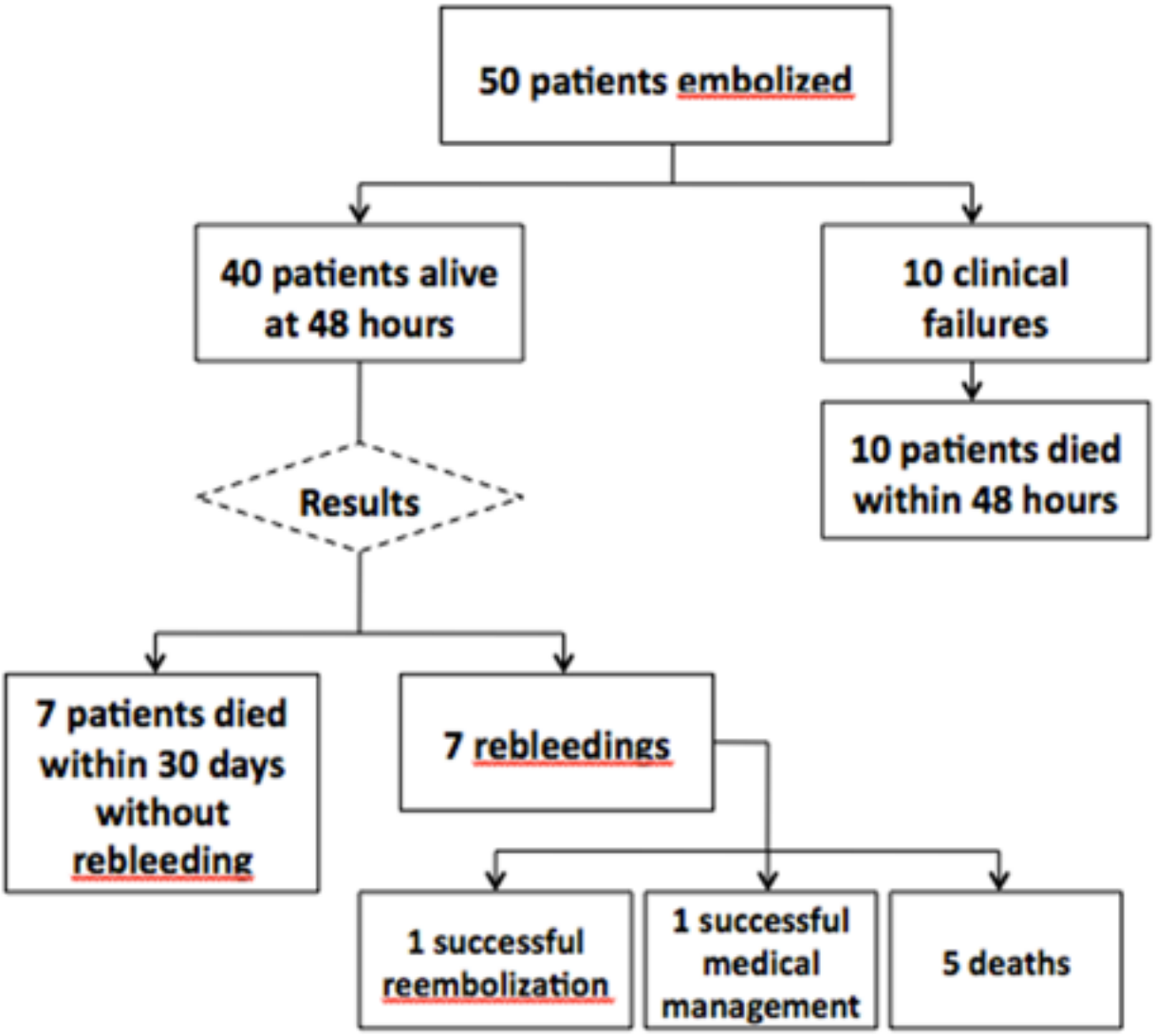
(a) *Axial contrast-enhanced CT scan of the abdomen shows extravasation of contrast medium within left rectus sheath hematoma associated with pelvic peritoneal diffusion.* ***(b)*** *Sagittal reformatted CT image demonstrates the great volume of the hematoma with extravasation.* ***(c)*** *Selective angiogram via ipsilateral common femoral artery approach shows multiple active bleedings from the left inferior epigastric artery.* ***(d)*** *Angiographic control after superselective microcatheterization and embolization with a Glubran®2/Lipiodol mixture (1:4) confirms complete and successful occlusion of the feeding artery. The patient was alive at 30 days after the procedure.*

Figure 2. Spontaneous left iliopsoas hematoma with hemodynamic unstability shock in an 79-year-old woman under anticoagulation treatment for deep vein thrombosis.



(a) *Axial contrast-enhanced CT scan of the abdomen shows large left retroperitoneal hematoma with multiple sites of active bleeding.* ***(b)*** *Sagittal reformatted CT image confirms the height of the hematoma and extravasation.* ***(c)*** *Selective left lumbar arteriogram at the L4 level shows multiple foci of extravasation.* ***(b)*** *Selective left lumbar angiography at the upper L3 level also shows multiple sites of active bleeding.* ***(e)*** *Abdomen X-ray shows arterial distribution of the mixture of Glubran®2/Lipiodol mixture (1:5) after successful embolization of the two bleeding lumbar arteries. Despite technically and clinically successful embolization, the patient died 17 days after the procedure, never having recovered from hematoma.*

Figure 3. Study flow shart.



Université de Bourgogne
UFR des Sciences de Santé
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TITRE DE LA THÈSE :

Le résultat du traitement par embolisation artérielle au glubran®2 cyanoacrylate des hématomes spontanés des muscles grand-droit et ilio-psoas chez les patients sous anti-coagulant.

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RÉSUMÉ :

Objectifs : Evaluer efficacité et sûreté de l'embolisation transartérielle (TAE) au Glubran®2 n-butyl cyanoacrylate metacryloxysulfolane (NBCA-MS) des hématomes spontanés dus à un traitement anti-coagulant (TAC) et évaluer les facteurs prédictifs de succès clinique et de mortalité à 30 jours.
Matériel et Méthodes : Etude rétrospective de août 2011 à novembre 2016 chez les patients sous TAC traités par TAE au Glubran®2 NBCA-MS pour un hématome spontané des muscles grand-droit (GD) ou ilio-psoas (IP) avec saignement actif au scanner. Les variables collectées sont : âge, sexe, paramètres de la coagulation, volume de l'hématome, pression artérielle moyenne et nombre de culots globulaires transfusés. Succès clinique, mortalité à 30 jours et taux de complications sont évalués. L'évaluation des facteurs prédictifs de succès clinique et de mortalité à 30 jours est fait par une analyse uni- et multivariée avec régression logistique.
Résultats : Saignement actif présent sur tous les scanners (100%). Saignement actif à l'artériographie pour 44 (88%) sur 50 patients. Succès technique est de 100%. Succès clinique est de 66% (33/50 patients). Le taux de mortalité dans les 30 jours suivant l'embolisation est de 44% (22/50). Aucune complication liée à la procédure d'embolisation. Pression artérielle moyenne basse (p=0.003), grand nombre de culots globulaires transfusés (p=0.003), volume d'hématome important (p=0.04), et localisation dans IP (p=0.02) sont associés à un faible taux de succès clinique. Echec clinique (p=0.00002), pression artérielle moyenne basse (p=0.004), grand nombre de culots globulaires transfusés (p=0.002), et localisation dans IP (p=0.01) sont significativement associés à un fort taux de mortalité à 30 jours.
Conclusion: TAE au Glubran®2 NBCA-MS est une technique efficace et sûre pour traiter les hématomes spontanés musculaires chez les patients sous TAC malgré un fort de taux de mortalité de cette grave pathologie.

MOTS-CLÉS : Hématome ilio-psoas, hématome grand-droit, saignement des tissus mous, embolisation transartérielle, cyanoacrylate