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Research Article

Pharmaco-Mechanical Catheter-Directed Deep Venous Thrombolysis in Phlegmasia Cerulea Dolens: A Monocentric Retrospective Study of 32 Patients between 2013 and 2020

John Philippe[1*], Nirvan Issur[2]

[1]Department of Cardiology and Vascular Disease, Colmar Hospital, Colmar, France; [2]Department of Emergency Medicine, Strasbourg Regional University Hospital, Strasbourg, France

ABSTRACT

Background: Phlegmasia Cerulea Dolens (PCD) is a rare form of deep venous thrombosis leading to a massive edema creating an obstruction of the arterial flow resulting in varying degree of arterial ischemic damage. In addition to the acute risks, there are important long-term complications. Recently some studies have shown that systemic anticoagulation accompanied by Pharmaco-Mechanical Catheter-Directed (P-CDT) deep venous thrombolysis has to be the first-line treatment for patients with PCD.

Methods: We report a series of 32 patients in our regional hospital presenting a phlegmasia cerulea dolens and treated by pharmaco-mechanical catheter-directed deep venous thrombolysis using Recombinant Tissue Type Plasminogen Activator (r-TPA; Actilyse) accompanied with systemic anticoagulation, between 2013 and 2020.

Results: 32 patients including 20 males and 12 females were enrolled in our study. There were 7 patients with underlying malignancy and 12 patients with a simultaneous pulmonary embolism. 10 patients had thrombophilia acquired or inherited and 9 patients had a previous VTE. Limb salvage was achieved in all patients. 10 patients had adjunctive treatment of iliac lesions with self-expandable metallic stents.

No periprocedural deaths occurred, there were no systemic bleeding complications. Major bleeding occurred in 4 patients. 7 patients presented an Autoimmune Heparin-Induced Thrombocytopenia (aHIT). 3 post-procedural acute renal failure occurred. There was a statistical trend of an increased bleeding risk with using big size catheter. No other risk factor of complication was found. The middle-term results of our study appear to be as least as good as those of other trials involving continuous infusion catheter directed thrombolysis with no PTS in 62% of the patients at 1 year.

Conclusion: These results confirm malignancy and previous DVT as a main risk factor of PCD. The treatment of PCD with pharmaco-mechanical catheter directed thrombolysis using Recombinant Tissue Type Plasminogen Activator (r-TPA; Actilyse), is safe and effective. It shows a good mid-term clinical outcome for patients with a diminution of post thrombotic syndromes.

Keywords: Plagemia cerulea dolens; Pharmaco- mechanical catheter- directed deep vein thrombolysis; Complications; Post thrombotic syndrome; Deep venous

INTRODUCTION

Phlegmasia Cerulea Dolens (PCD) is a rare syndrome defined clinically as a classical triad of acute limb swelling, pain and cyanosis. It is a particular type of deep venous thrombosis, in which a massive proximal venous thrombus is causing a total or near total venous occlusion. This leads to a massive edema creating an obstruction of the arterial flow resulting in varying degree of arterial ischemic damage (Figure 1).

In the most cases, PCD results from a Deep Venous Thrombosis (DVT) with proximal localization, most frequently the iliofemoral area. Diagnosis is based on clinical examination findings and on doppler ultrasound echography. Actually, no therapeutic algorithms or guidelines exist. PCD continues to have mortality rates of 25% to 40% and amputation rates from 20% to 50% respectively [1,2]. To prevent the progression to limb gangrene, fast diagnosis and treatment are a key factor.

Correspondence to: John Philippe, Department of Cardiology and Vascular Disease, Colmar Hospital, Starsbourg, France, E-mail: john.philippe@etu.unistra.fr

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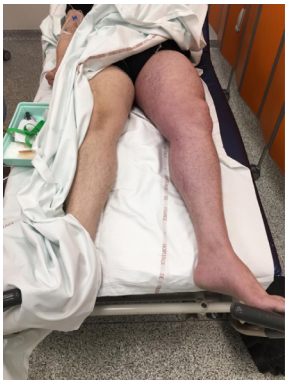

Figure 1: Phlegmasia coerulea dolens in a patient in the emergency room.

In addition to the acute risks, there are important long-term complications. Thrombus can cause valvular incompetence and luminal obstruction, which can ultimately lead to Post Thrombotic Syndrome (PTS) and chronic venous disease, such as varicosities, hyperpigmentation, non-healing ulcers, pain, and edema, all of which represent a significant socioeconomic burden [3]. The goals to treatment are a fast restoration of a venous outflow by reducing the established thrombus load, the prevention of further thrombus formation, and the preservation of collateral circulation, in order to restore the arterial flow.

The management of PCD has evolved in recent years to encompass the use of systemic anticoagulation as well as pharmacological thrombolysis and mechanical thrombectomy. More recently, some studies have shown that systemic anticoagulation accompanied by Pharmaco-Mechanical Catheter-Directed (P-CDT) deep venous thrombolysis has to be the first-line treatment for patients with PCD [1,2].

We report a series of 32 patients in our regional hospital presenting a phlegmasia cerulea dolens and treated by pharmaco-mechanical catheter-directed deep venous thrombolysis accompanied with systemic anticoagulation, between 2013 and 2020 [4,5].

METHODOLOGY

Selection of patients

This study was reviewed and approved by the Ethics Committee of Strasbourg (CE-2020-131). This retrospective study was performed on 32 patients who underwent a PCD and treated by pharmaco-mechanical catheter-directed deep venous thrombolysis accompanied by systemic anticoagulation between December 2013 and Mai 2020 in Colmar regional hospital. Patient's characteristics are listed in Table 1.

Procedures

The ipsilateral vein was punctured with a venous catheter under ultrasound guidance. The puncture sites varied according to the accessibility of the veins and extension of the thrombus. Patients were kept in supine position on the angiographic table. To confirm the degree of extension of DVT, a digital subtraction angiography was performed by injecting contrast material. In all cases, thrombolysis was carried out using Recombinant Tissue Type Plasminogen Activator (r-TPA, Actylise). Infusion was performed through the coaxial catheter of Mc Namara at a rate of 1.2 mg/h between 2013 and 2015, and then from 2016 at a rate of 1.5 mg/h over a maximum period of 72 hours. The protocol was modified in 2016, secondary to medical formation.

Continuous intravenous infusion was simultaneously conducted to administer Unfractionated Heparin (UFH); the dose was modified to increase the activated partial thromboplastin time by 1.8 to 2.2 times. During thrombolytic therapy, the patient was rested in bed in intensive care unit since a close monitoring is essential to detect any evidence of hemorrhagic complication.

Lysis progression was monitored with twice a day doppler ultrasound echography, and venography was performed when signs of recanalization were found of doppler ultrasound. Pharmaco-mechanical desobstruction was then performed and the thrombolysis was terminated if the flow was restored and no additional lysis was needed (Figure 2).

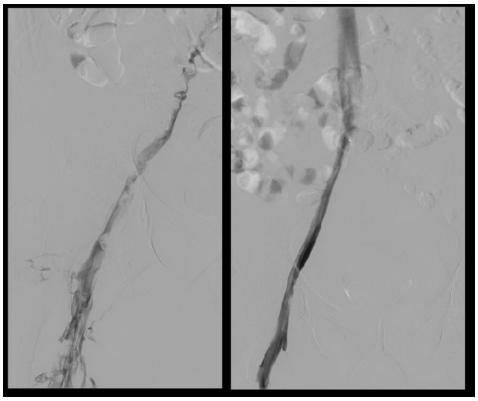

Figure 2: (A) Digital substraction angiography of the left iliac vein before and (B) 48 hours after pharmaco-mechanical catether directed thrombolysis.

Self-expandable metallic stents were used to treat stenosis or short occlusion at the level of the iliac veins, mostly represented by cases of May-Turner-Cockett syndrome, in which the left iliac vein is compressed by the right iliac artery (Figure 3)[6,7]. At discharge anticoagulation was prescribed for at least 6 months. In addition, the patients were recommended to wear elastic stockings.

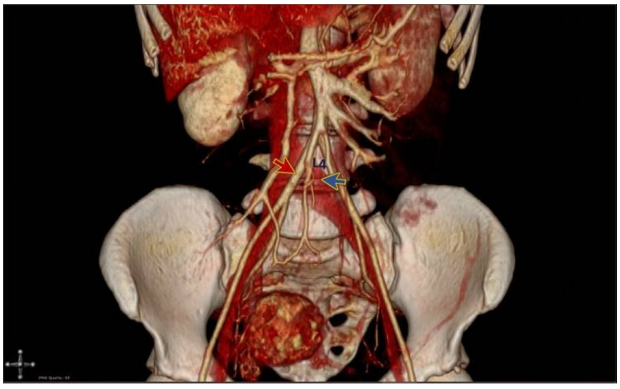

Figure 3: L4 May-Thurner-Cockett syndrome.

Follow-up assessments

A control visit was performed between 12 months and 18 months, the patients received a clinical evaluation according to the Villalta

scale which includes five symptoms (pain, cramps, heaviness, pruritus, and paresthesia) and six objective signs (edema, skin induration, hyperpigmentation, venous ectasia, redness, and pain during calf compression) [8]. Each sign or symptom was rated as 0 (absent), 1 (mild), 2 (moderate), or 3 (severe).

Absence of PTS is indicated by a total score <5, mild or moderate PTS is indicated by a score of 5 to 14, and severe PTS is indicated by a score of ≥ 15 (or the presence of venous ulcer).

Complication definitions

Complications were classified by the outcome with using the SIR (Society of Interventional Radiology) classification system for complication.

Major bleeding is defined as an intracranial bleed, bleeding resulting in death, or bleeding requiring transfusion, surgery, or cessation of treatment. Minor bleeding is defined as less severe bleeding managed by local compression, increases in vascular sheath size, or decreases in dose of the lytic, anticoagulant, or antiplatelet drug. Non bleeding complications include puncture-related injury, local arterial injury (perforation, dissection, occlusion), embolization requiring intervention, re-thrombosis, peri catheter thrombosis requiring unexpected additional intervention, reperfusion injury, compartment syndrome, renal failure, acute myocardial infarction, etc [9,10].

Acute kidney injury was defined as an absolute increase in serum creatinine concentration of ≥ 26.4 micromoles/L (0.3 mg/dL) within 48 hours or an increase >50% from baseline within the prior 7 days [11].

Statistical analysis

Statistics analysis have been conducted with R studio version 1.2.5033 under "Lesser General Public License". Quantitative values were described with frequency per category and relative frequencies. Quantitative values have been described with measures of central tendencies (mean, median, minimum, first quartile, third quartile, and maximum) and measures of dispersion (standard deviation, range, variance). Student paired t test was used for comparisons between normally distributed continuous variables. Measures of central tendencies and dispersion have been first reported, followed by the t test outcome represented by p-value. A P-value <0.05 was considered significant.

To study the relationship between the "hemoglobin loss" quantitative value and several qualitative explanatory variables, an Analysis of Variance Test (ANOVA) was used. Parameters were first described with measures of central tendencies and dispersion, before giving the result of the test represented by p-value. A P-value <0.05 was considered significant. The measures of central position and dispersion of qualitative variables were displayed on box plots.

RESULTS

32 patients including 20 males (62.5%) and 12 females (37.5%) were enrolled in our study. There were 7 patients with underlying malignancy and 12 patients with a simultaneous pulmonary embolism. 10 patients had thrombophilia acquired or inherited and 9 patients had a previous VTE. Clinical characteristics of patients were listed in Table 1.

Table 1: Univariate analysis of Clinical characteristics.

Characteristics	Number (percentage)
Demographic characteristics	
Male	20 (62.5)
Female	12 (37.5)
Age (Mean ± SD) in years	51 ± 20
PE associated	12 (37.5)
Biological characteristics	
Creatinine (micromole/L) (Mean ± SD)	76.9 ± 24.0
Prothrombin time (%) (Mean ± SD)	84.5 ± 17.8
Activated partial-thromboplastin ratio (Mean ±SD)	1.2 ± 0.4
High-sensitivity C-reactive protein (mg/L) (Mean ± SD)	107.2 ± 90.8
Blood platelet (x109/L) (Mean ± SD)	230 ± 97
Hemoglobin (g/dL) (Mean ± SD)	13.1 ± 1.7
TVE risk factors	
Major general or orthopedic surgery	1 (3.1)
Traumatology: Fracture of hip or legs <3 months	3 (9.4)
Prolonged immobility (>3 days)	0 (0.0)
Long travel (>5 hours)	1 (3.1)
Family history of VTE	8 (25.0)
Previous VTE	9 (28.1)
Oral contraceptives or estrogen treatment for menopause symptoms	1 (3.1)
Pregnancy/post-partum	0 (0.0)
Malignancy	7 (21.9)
Inflammatory disease	1 (3.1)
Thrombophilia acquired or inherited (Antiphospholipid antibody syndrome, Antithrombin deficiency, Heterozygote mutation of factor II or V gene)	10 (31.2)
Hemorrhagic risk	
HTA	5 (15.6)
Personal history of major bleeding	0 (0.0)
Personal history of minor bleeding	0 (0.0)
RIETE score	
0	13 (40.6)
1	10 (31.2)
2	4 (12.5)
3	1 (3.1)
4	4 (12.5)

Procedure

- The mean amount of rTPA was of 41.91 mg.
- The median CDT time was of 24 (with an interquartile range of 36 hours).

- Limb salvage was achieved in all patients.
- 10 patients had adjunctive treatment of iliac lesions with self-expandable metallic stents.
- Procedure characteristics are listed in Table 2.

Table 2: Univariate analysis of Procedure characteristics.

Procedure characteristics	
Total amount of rTPA (mg)	41.9 (± 28.55)
Infusion dose/kg (mg/kg)	0.51 (± 0.37)
Infusion rate/kg (mg/kg/h)	0.03 (± 0.03)
CDT time (hours)	24 (IQR 36)
Catheter size	
5F	16 (50)
6F	2 (6.25)
7F	2 (6.25)
9F	1 (3.125)
11F	11 (34)

Complications

No periprocedural deaths occurred, there were no systemic bleeding complications. Major bleeding occurred in 4 patients (12.5%). The bleeding was caused by an access hematoma in 2 patient (6%) who required blood transfusion and by diffuse subcutaneous hematoma in 2 patients (6%) who equally required blood transfusion. Compartment syndrome occurred in 2 patients (6%) requiring additional surgery. No catheter infection occurred. Minor bleeding at the access site occurred in 7 patients (22%). 4 patients (12%) presented an Autoimmune Heparin-Induced Thrombocytopenia (aHIT). 3 post-procedural acute renal failure occurred. The complications are listed in Table 3. The univariate analysis of procedure factors of bleeding didn't show any statistical difference but a statistical trend regarding the size of the catheter in millimeters as a risk of bleeding (p=0.062) (Table 4). There was no statistical difference between the group bleeding and no bleeding, regarding the RIETE hemorrhagic risk score in the analysis of variance (p-value at 0.0613) (Figure 4).

Table 3: Peri and post procedural complications.

Complications	
Catheter infection documented	
Major bleeding in the 7 days post procedure	4 (12.5)
Minor bleeding in the 7 days post procedure	7 (21.9)
Transfusion	2 (6.2)
Autoimmune Heparin-Induced Thrombocytopenia (aHIT)	7 (21.9)
Compartment syndrome	2 (6.2)
Acute renal failure	3 (9.3)

Table 4: Univariate analysis of procedure factors of bleeding.

	No bleeding	Bleeding (major and minor bleeding)	p-value
Catheter size (mm)	2.16 (0.76)	2.70 (0.71)	0.062
Total amount of rTPA (mg)	46.57 (31.54)	33.44 (20.81)	0.226
Infusion dose/kg (mg/kg)	0.57 (0.41)	0.40 (0.25)	0.222
Infusion rate/kg (mg/kg/h)	0.03 (0.03)	0.03 (0.03)	0.934
CDT time (hours)	29.95 (22.27)	21.86 (14.05)	0.284

Effect on post thrombotic symptoms

Between 12 and 18 months, the average Villalta score as measure of PTS was 4 (range from 0-11). Based on the Villalta score, no PTS was observed in 18/29 patients (62%) and mild PTS was observed in 11/29 patients (38%). None presented a severe PTS. 3 patients died before the control visit. The patients with aHIT presented a greater risk of developing a mild PTS (p=0.036). There were no statistical differences between the two groups (mild PTS and no PTS) regarding clinical or procedure characteristics. The univariate analysis of risk factor of developing a mild PTS are listed in Table 5.

Table 5: Univariate analysis of risk factor of developing mild PTS.

	Mild PTS	No PTS	p-value
Age (mean (SD))	45.64 (23.14)	52.11 (18.66)	0.415
Weight (mean (SD))	82.45 (22.82)	77.56 (17.55)	0.521
Previous VTE (%)	4 (36.4)	4 (22.2)	0.69
Catheter size (%)			0.701
10F	3 (27.3)	5 (27.8)	
5F	5 (45.5)	11 (61.1)	
6F	1 (9.1)	1 (5.6)	
7F	1 (9.1)	1 (5.6)	
9F	1 (9.1)	0 (0.0)	
Total amount of rTPA (mg) (mean (SD)	36.91	0.284	0.284
(26.35)	48.31 (27.53)	0.287	0.284
Infusion dose/kg (mg/kg) (mean (SD)	0.42 (0.26)	0.60 (0.40)	0.2
Infusion rate/kg (mg/kg/h) (mean (SD)	0.05 (0.05)	0.02 (0.01)	0.03
CDT time (hours) (mean (SD)	23.50	0.284	0.284
(18.70)	31.28 (19.57)	0.3	0.284
Adjuctive treatment of iliac lesions with self-expandable metallic stents (%)	1 (9.1)	8 (44.4)	0.113
Autoimmune heparin-induced thrombocytopenia (aHIT) (%)	5 (45.5)	1 (5.6)	0.036

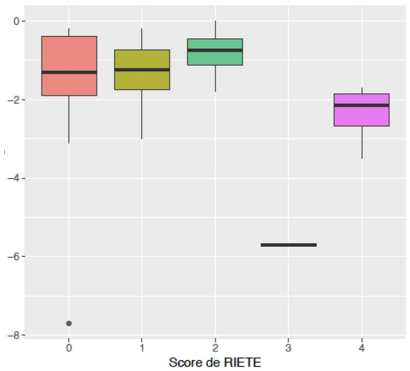

Figure 4: Analysis of variance of the RIETE hemorrhagic risk score based on the hemoglobin loss. **Note:** Score de RIETE (■) 0; (■) 1; (■) 2; (■) 3; (■) 4.

DISCUSSION

Population

In our study, complete lysis and limb salvage was achieved in 100% of patients, showing better results that the study of Verhaeghe and et al. (79%) and Chang and et al [12,13]. (80%) but similar results of the metanalysis of Protack and al [14]. (94%) the results of our study confirm malignancy and previous DVT as a main risk factor of PCD. 22% of our patients had an underlying malignancy. These rates are the same than in Mühlberger and et al. study (29%) but higher rates of malignancy (33%) have been reported by Chinsakchai and et al [15,16].

28.1% of our patients had a previous history of DVT. These rates are similar to the case series of Mühlberger and et al. with 29% of previous DVT. 37.5% of our patients had a complementary pulmonary embolism. The prevalence of PE was nearly similar in the case series of Kutsukata and et al. of Mühlberger and et al. with 47% of PE and in the meta-analysis of Chinsakchai and et al. with 29% of PE [15-17].

In comparison with the other series, we had a lower amount of additional stenting 31% versus 58% in Mühlberger and et al. series, but a higher rate of thrombophilia with 30% of the patients in our series, compared to 6% in Mühlberger and et al. These differences are difficult to explain and may be due to the small simple size included in our study.

Complications

We encountered a low amount of complication mainly bleeding complications. 4 major bleedings caused by an access hematoma in 2 patient (6%) and by diffuse subcutaneous hematoma in 2 patients (6%). It represents 12.5% less than the percentage of bleeding found by Verhaeghe and et al. who reported 25% of bleeding requiring transfusion at puncture site [12]. This can probably be explained by the use of low dose of rtPA in comparison to Verhaeghe and et al. who used a high dose of 3 mg/h. There was a statistical trend of an increased bleeding risk with using big size catheter. This should be confirmed by a prospective study. No other risk factor of complication was found.

Concerning the periprocedural PE risk, we did not use IVC filter since 37.5% of the patients had already a PE, and a metanalysis of Protack and et al. in 2006 showed that CDT without universal IVC filter placement was safe and effective in treating acute DVT [14].

Middle-term results

Regarding the post thrombotic syndrome, the middle-term results of our study appear to be as least as good as those of other trials involving continuous infusion catheter directed thrombolysis with no PTS in 62% of the patients at 1 year, thought the other trials were treating DVT and not PCD.

The patients with aHIT presented a greater risk of developing a mild PTS (p=0.036), probably explained by the re-thrombosis secondary to the aHIT, requiring a delayed re-intervention. A long-term follow-up would be necessary to evaluate the frequency of chronic venous insufficiency in the PCD patients treated by P-CDT.

Strengths and limitations

Our study analyzed a total of 32 patients in 7 years, which is, to our knowledge one of the highest numbers of PCD cases. 2 recent studies published results of 17 patients and of 15 patients [15,18]. A limiting factor of this study is the retrospective analysis, nevertheless, prospective study are difficult to realize due to the rare incidence of this disease (4 patients a year).

CONCLUSION

These results confirm malignancy and previous DVT as a main risk factor of PCD. The treatment of PCD with pharmaco-mechanical catheter directed thrombolysis using Recombinant Tissue Type Plasminogen Activator (r-TPA; Actilyse), is safe and effective. It shows a good mid-term clinical outcome for patients with a diminution of post thrombotic syndromes.

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