CLINICAL STUDY

Safety of Therapeutic Anticoagulation with Low-Molecular-Weight Heparin or Unfractionated Heparin Infusion during Catheter-Directed Thrombolysis for Acute Pulmonary Embolism

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ABSTRACT

Purpose: To examine the safety of therapeutic-dose anticoagulation during catheter-directed thrombolysis (CDT) for acute pulmonary embolism (PE).

Materials and Methods: A retrospective review of 156 consecutive cases (age, 56.6 ± 15.4 years; 85 males) of CDT with alteplase for acute PE (symptoms, <14 days) between 2009 and 2019 was performed. All patients received full-dose anticoagulation before, during, and after thrombolysis with low-molecular-weight heparin (LMWH) (n = 45) or unfractionated heparin (n = 111) infusion. Massive PE was diagnosed in 21 of 156 patients at presentation; submassive PE was diagnosed in 135 of 156 patients at presentation. The Simplified Pulmonary Embolism Severity Index was ≥1 in 69 of 156 patients.

Results: There were 4 mild (2.6%), 3 moderate (1.9%), and 3 severe (1.9%) hemorrhagic complications (Global Use of Strategies to Open Occluded Arteries), 1 of which (0.6%) was intracranial. No significant differences in hemorrhagic complication rates ($P = .3$, $P = 1.0$, and $P = .6$, respectively) or general complication rates (Society of Interventional Radiology [SIR] minor, $P = .2$; SIR major, $P = .7$) were noted between the LMWH and heparin groups. Mean pulmonary arterial pressure for the entire cohort improved from 28.9 ± 7.6 mmHg to 20.4 ± 6.5 mmHg ($P < .001$), whereas the Miller score improved from 19.3 ± 4.6 to 7.3 ± 3.9 ($P < .001$). The average infusion duration was 26 ± 11.9 hours over 2.3 ± 0.6 total visits to the angiography lab, during which a mean of 27.85 ± 14.2 mg of tissue plasminogen activator were infused.

Conclusions: Therapeutic anticoagulation during CDT for PE appears to be safe. The current study did not find a significant difference between LMWH and heparin infusion with respect to hemorrhagic and general complication rates.

ABBREVIATIONS

CDT = catheter-directed thrombolysis, GUSTO = Global Use of Strategies to Open Occluded Arteries, PAP = pulmonary arterial pressure, PE = pulmonary embolism, PEA = pulseless electrical activity, LMWH = low-molecular-weight heparin, tPA = tissue plasminogen activator

A multidisciplinary approach to the treatment of acute submassive and massive pulmonary embolism (PE) is leading to an increase in the use of catheter-directed thrombolysis (CDT) (1). Despite the increased interest in CDT (1), consensus opinion has not been reached regarding the safety of therapeutic-dose anticoagulation

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EDITORS' RESEARCH HIGHLIGHTS

- In this single-institution review of 156 pulmonary embolism patients, full anticoagulation during local thrombolysis did not result in higher bleeding rates than those reported in studies published to date, suggesting that this practice may not increase risk of hemorrhage.
- There is no accepted standard regarding anticoagulation during pulmonary embolism thrombolysis, although prompt initiation of anticoagulation at diagnosis of a pulmonary embolism is important. Additional studies can further help establish optimal dosing of anticoagulation during pulmonary embolism thrombolysis.

versus subtherapeutic anticoagulation during CDT (2). Moreover, differences in outcome between treatment with low-molecular-weight heparin (LMWH) and unfractionated heparin infusion have also not been established (2). Such differences have been described in fibrinolysis for myocardial infarction, where use of adjunctive therapeutic-dose anticoagulation (3) and LMWH in particular (4) resulted in superior efficacy (3,4) at the cost of increased hemorrhagic complications, compared to adjunctive subtherapeutic anticoagulation (3) and unfractionated heparin infusion (4). The goal of this study was to evaluate the safety of therapeutic-dose anticoagulation during CDT for acute PE, as it manifests in hemorrhagic complications.

MATERIALS AND METHODS

This Health Insurance Portability and Accountability Act-compliant retrospective cohort study was approved by the institutional review board, and informed consent was waived.

Patient Selection

Consecutive patients who underwent CDT for acute massive or submassive PE between December 2009 and July 2019 were identified by searching the electronic medical records of a single community hospital system with shared physician and ancillary personnel. Included were patients who presented with acute submassive or massive PE within 14 days of symptom onset and underwent pulmonary artery CDT (unilateral or bilateral) with recombinant tissue plasminogen activator (tPA; alteplase; Genentech Inc, San Francisco, California). Acute massive PE was defined as acute PE in the setting of sustained hypotension, profound bradycardia, or pulselessness (5). Acute submassive PE was defined as acute PE in the setting of right ventricular to left ventricular ratio greater than 0.9 or biochemical marker evidence of myocardial necrosis (5). Excluded were patients with onset of symptoms more than 14 days before presentation or evidence of chronic PE as diagnosed on computed tomography (CT) pulmonary angiography (6), as well as patients in whom CDT for massive PE was planned but who did not survive the initiation of CDT.

A total of 171 patient charts were reviewed. Of these, 16 patients were excluded (14 owing to chronic PE and 2 who suffered cardiac arrest before and during the catheter placement procedure but did not survive to undergo infusion of tPA). The final cohort of 155 patients underwent 156 CDT treatments, as a single male patient had 2 separate treatments 5 months apart with an interim CT pulmonary angiography demonstrating complete resolution of PE before the second CDT procedure. Patient demographics and PE-related clinical metrics, including the Simplified Pulmonary Embolism Severity Index (7), are presented in **Table 1**.

Procedures

All procedures were performed by 1 of 9 fellowship-trained interventional radiologists, with experience ranging from 1 to 19 years. All patients received full-dose anticoagulation with either a weight-based continuous intravenous unfractionated heparin infusion or a weight-based (1 mg/kg) twice-a-day regimen of LMWH (Lovenox; Sanofi, Paris, France). Both were initiated at the time of diagnosis of PE on the basis of physician preference and continued throughout the course of treatment. For the patients who received heparin, partial thromboplastin time was monitored every 6 hours for a target of 50–80 seconds. The CDT procedure was performed as previously described (8) using several types of infusion catheters either exclusively or in combination, including 5-Fr AP2 infusion angled pigtail catheters (Cook Medical, Bloomington, Indiana), EkoSonic Endovascular System catheters (EKOS Corp, Bothell, Washington), and Uni-Fuse multi-side-hole infusion catheters (Angiodynamics, Queensbury, New York). The infusion catheters were deployed either unilaterally or bilaterally, as determined by the operating physician, along with the choice of catheter (**Table 2**). Clot fragmentation, angioplasty, and/or thrombectomy (**Table 2**) were performed at the operating physician's discretion before the initial catheter placement or during the follow-up visits to the angiography suite, using pigtail catheters, balloons, the Indigo System CAT 8 (Penumbra Inc, Alameda, California), or the FlowTriever system (Inari Medical, Irvine, California). All patients were monitored in the intensive care unit for the duration of the infusion period, with measurement of serum fibrinogen levels every 6 hours. Follow-up visits to the angiography suite included pulmonary arterial pressure (PAP) measurements and pulmonary angiography followed by a decision to continue or conclude CDT.

Endpoints

Primary endpoints for the study included hemorrhagic complications according to the Global Use of Strategies to

Table 1. Patient Demographics and Baseline Clinical Data

Variable	Entire Cohort	LMWH	Heparin Infusion	Significance, *P* Value
Number of treatments	156	45 (28.8%)	111 (71.2%)	N/A
Age (years)	56.6 ± 15.4	57.2 ± 14.3	56.3 ± 15.8	.7
Males	85/156 (54.5%)	24/45 (53.3%)	61/111 (55%)	.9
BMI (kg/m^2)	35.3 ± 9.1	33.5 ± 7.9	36.1 ± 9.5	.1
Diabetes mellitus	37/156 (37%)	8/45 (17.8%)	29/111 (26.1%)	.3
Hyperlipidemia	55/156 (35.3%)	15/45 (33.3%)	40/111 (36%)	.9
Risk factors for VTE				
Chronic heart disease	8/156 (5.1%)	0/45 (0%)	8/111 (7.2%)	.1
Active smoking	14/156 (9%)	4/45 (8.9%)	10/111 (9.0%)	1.0
Fracture of long bone	8/156 (5.1%)	1/45 (2.2%)	7/111 (6.3%)	.4
Hypercoagulable state	6/156 (3.8%)	2/45 (4.4%)	4/111 (3.6%)	1.0
Hypertension	88/156 (56.4%)	25/45 (55.6%)	63/111 (56.8%)	1.0
Immobilization	68/156 (43.6%)	21/45 (46.7%)	47/111 (42.3%)	.7
Indwelling venous catheters	3/156 (1.9%)	0/45 (0%)	3/111 (2.7%)	.6
Malignancy	13/156 (8.3%)	2/45 (4.4%)	11/111 (9.9%)	.4
Obesity (BMI ≥30 kg/m^2)	103/156 (66%)	26/45 (57.8%)	77/111 (69.4%)	.2
Oral contraceptive use	6/156 (3.8%)	2/45 (4.4%)	4/111 (3.6%)	1.0
Preexisting respiratory disease	12/156 (7.7%)	6/45 (13.3%)	6/111 (5.4%)	.1
Pregnancy and postpartum state	2/156 (1.3%)	0/45 (0%)	2/111 (1.8%)	1.0
History of cerebrovascular accident	0/156 (0%)	0/45 (0%)	0/111 (0%)	N/A
Surgery within last 30 days	24/156 (15.4%)	6/45 (13.3%)	18/111 (16.2%)	.8
Lower extremity DVT	135/154 (87.7%)	36/45 (80%)	99/109 (90.8%)	.1
Autoimmune etiology	3/156 (1.9%)	0/45 (0%)	3/111 (1.9%)	.6
PE severity				
Massive	21/156 (13.5%)	2/45 (4.4%)	19/111 (17.1%)	.04
Submassive	135/156 (85.5%)	43/45 (95.6%)	92/111 (82.9%)	.04
RV:LV ratio*	1.7 ± 0.4	1.6 ± 0.3	1.7 ± 0.4	.09
Dyspnea	144/156 (92.3%)	41/45 (91.1%)	103/111 (92.8%)	.8
Syncope	40/156 (25.6%)	9/45 (20%)	31/111 (27.9%)	.4
Tachycardia >100 beats/minute	126/156 (80.8%)	30/45 (66.7%)	96/111 (86.5%)	.007
Systolic blood pressure <90 mmHg for more than 15 minutes	21/156 (13.5%)	2/45 (4.4%)	19/111 (17.1%)	.04
sPESI score at PE presentation ≥1	69/156 (44.2%)	17/45 (37.8%)	52/111 (46.8%)	.4
Positive troponin (≥0.04 ng/ml)	80/150 (53.3%)	22/44 (50%)	58/106 (54.7%)	.7
BNP level at presentation (pg/ml)†	3452.9 ± 4549.1	2221.1 ± 2728.7	3960 ± 5040.9	.07
Positive BNP level at presentation (>500 pg/ml)†	87/120 (72.5%)	23/35 (65.7%)	64/85 (75.3%)	.4

Note–Values presented as means ± standard deviation where applicable.
BMI = body mass index; BNP = brain natriuretic peptide; DVT = deep vein thrombosis; LMWH = low-molecular-weight heparin; LV = left ventricle; N/A = not applicable; PE = pulmonary embolism; RV= right ventricle; sPESI = simplified Pulmonary Embolism Severity Index; VTE = venous thromboembolism.
*RV:LV ratio was calculated on axial computed tomography views.
†Data exist for 120 patients.

Open Occluded Arteries (GUSTO) (3) classification and all complications according to the Society of Interventional Radiology reporting standards (9).

Secondary endpoints included change in invasive PAP as measured during the CDT procedures and change in the Miller Pulmonary Embolism Severity Index (10). Also recorded were the tPA infusion rates (mg/hour), tPA infusion duration (hours), and total tPA dose infused (mg). A subgroup analysis comparing LMWH and heparin infusion was also performed for all of the aforementioned parameters.

Statistical Analysis

Study data were collected and managed using REDCap electronic data capture tools hosted at the study institution (11). Comparison of continuous variables between the LMWH and heparin infusion groups was performed using the Mann–Whitney U test for unpaired nonparametric variables. Binomial variables, pertaining mostly to complications and patient demographics, were compared using Fisher's exact test. The significance of change in continuous variables between the initial and subsequent visits to the

Table 2. Treatment and Procedure Details

	Entire Cohort	LMWH	Heparin Infusion	Significance, *P* Value
Systemic tPA was administered before initial CDT procedure	8/156 (5.1%)	0/45 (0%)	8/111 (7.2%)	.1
Time between imaging diagnosis and initiation of CDT (days)	0.65±0.82	0.64±0.77	0.65±0.84	.9
Maceration, angioplasty, or thrombectomy performed during treatment	20/156 (12.8%)	3/45 (6.7%)	17/111 (15.3%)	.2
Bilateral catheters placed	145/156 (92.9%)	42/45 (93.3%)	103/111 (92.8%)	1.0
Total number of visits to the angiography suite	2.3±0.6	2.4±0.6	2.2±0.6	.1
Average infusion time (hours)	26±11.9	27.1±12.6	25.5±11.6	.5
Average rate of tPA infusion via each catheter (mg/hour)	0.59±0.2	0.59±0.2	0.59±0.2	.8
Total tPA infused (mg)	27.9±14.2	28.6±13.3	27.5±14.5	.5
tPA infusion prematurely terminated	6/156 (3.8%)	0/45 (0%)	6/111 (5.4%)	.2

CDT = catheter-directed thrombolysis; LMWH = low-molecular-weight heparin; N/A = not applicable; tPA = tissue plasminogen activator.

angiography suite within each study group was evaluated using the Wilcoxon signed-rank test for paired nonparametric variables. All statistical analyses were performed using SPSS version 25 (IBM Corp, Armonk, New York), with two-tailed P values $\leq$ .05 indicating statistical significance.

RESULTS

Complication rates are presented in Table 3, including the subgroup analysis that did not demonstrate a significant difference in any complication category between the LMWH and heparin groups. The thrombocytopenia occurrences included cases of heparin-induced thrombocytopenia, which are also presented separately. There were 10 (6.4%) hemorrhagic complications, including 4 (2.6%) GUSTO minor, 3 (1.9%) GUSTO moderate, and 3 (1.9%) GUSTO major. A comparison of the hemorrhagic complication rates between the massive and submassive patients is presented in Table 4.

The minor GUSTO hemorrhagic complications included parenchymal pulmonary wire trauma; hepatic hematoma that did not require intervention in a patient with history of a motor vehicle crash 2 weeks before the CDT procedure (computed tomography [CT] on admission did not demonstrate gross hepatic injury); and epistaxis in a patient who also received 100 mg of systemic tPA before CDT and had a small access site groin hematoma. Moderate GUSTO complications included a rectus sheath hematoma 3 days after conclusion of CDT, which required transfusion; a thigh hematoma (non-accessed leg) 11 hours after initiation of CDT, which required transfusion; and an access site groin hematoma that appeared approximately 15 minutes after initiation of CDT and required a transfusion. Major GUSTO complications included a case of disseminated intravascular coagulation and hemoglobin decrease without a clear hemorrhagic source 5 hours after initiation of CDT resulting in vasopressor support and a transfusion in a massive PE patient who underwent 3 pulseless electrical activity (PEA) arrests and received 100 mg of systemic tPA before initiation of CDT. This patient was successfully weaned off vasopressor support yet died several days after termination of CDT. A second major GUSTO complication involved a massive PE patient who arrived on vasopressor support after PEA arrest in the field. Six hours after initiation of CDT, the patient developed a thigh hematoma (non-accessed leg), required a transfusion, and then had 2 more PEA arrests and hematemesis. Care was withdrawn by the family during active resuscitation attempts. The third major GUSTO complication was an asymptomatic subarachnoid hemorrhage that was found during prescheduled brain magnetic resonance imaging (MRI) that was performed several hours after termination of CDT. MRI was performed to evaluate a chronic infarct seen on CT of the head before initiation of CDT. The hemorrhage noted on MRI was not at the same location as the chronic infarct noted on CT. The patient was never symptomatic from the intracranial hemorrhage and was discharged home on full anticoagulation 4 days after conclusion of CDT.

The all-cause 30-day mortality rate for the cohort was 5.1% (n = 8). Two mortalities occurred in the submassive cohort (2/135, 1.5%) and 6 in the massive cohort (6/21, 28.6%) ($P < .001$). Procedure-related mortality was 1.3% (2/156) for the entire cohort, both in patients who received heparin infusion. No procedure-related mortalities were recorded in the submassive cohort, whereas 2 (9.5% of 21) procedure-related mortalities were recorded in the massive cohort ($P = .02$).

Initial and final systolic, diastolic, and mean PAP, as well as the initial and final Miller PE Severity Index scores are presented in Table 5. No significant difference was found between the LMWH and heparin groups in these parameters (Table 5). There was a significant mean improvement in systolic PAP, diastolic PAP, mean PAP, and Miller score for the entire cohort as well as in the LMWH and heparin groups ($P \leq 001$ for all variables). The LMWH and heparin groups demonstrated similar reduction in PAP and Miller score, as noted in Table 5.

Table 3. Complications

	Entire Cohort	LMWH	Heparin Infusion	Significance, *P* Value
Minor bleeding complication (GUSTO)	4/156 (2.6%)	0/45 (0%)	4/111 (3.6%)	.3
Moderate bleeding complication (GUSTO)	3/156 (1.9%)	1/45 (2.2%)	2/111 (1.8%)	1.0
Major bleeding complication (GUSTO)	3/156 (1.9%)	0/45 (0%)	3/111 (2.7%)	.6
Cardiac arrest after initial procedure	4/156 (2.6%)	0/45 (0%)	4/111 (3.6%)	.3
Thrombocytopenia	10/156 (6.4%)	2/45 (4.4%)	8/111 (7.2%)	.7
Heparin-induced thrombocytopenia	3/156 (1.9%)	1/45 (2.2%)	2/111 (1.8%)	1.0
Acute kidney injury	0/156 (0%)	0/45 (0%)	0/111 (0%)	N/A
SIR minor complication	7/156 (4.5%)	0/45 (0%)	7/111 (6.3%)	.2
SIR major complication	6/156 (3.8%)	1/45 (2.2%)	5/111 (4.5%)	.7
All-cause 30-day mortality	8/156 (5.1%)	1/45 (2.2%)	7/111 (6.3%)	.4
CDT procedure-related mortality	2/156 (1.3%)	0/45 (0%)	2/111 (1.8%)	1.0

CDT = catheter-directed thrombolysis; GUSTO = Global Use of Strategies to Open Occluded Arteries; LMWH = low-molecular-weight heparin; N/A = not applicable; SIR = Society of Interventional Radiology.

Table 4. Hemorrhagic Complications by Pulmonary Embolism Severity

	Submassive PE ($n = 135$)	Massive PE ($n = 21$)	Significance, *P* Value
Minor bleeding complication (GUSTO)	2/135 (1.5%)	2/21 (9.5%)	.09
Moderate bleeding complication (GUSTO)	2/135 (1.5%)	1/21 (4.8%)	.4
Major bleeding complication (GUSTO)	1/135 (0.7%)	2/21 (9.5%)	.048

GUSTO = Global Use of Strategies to Open Occluded Arteries.

Table 5. Clinical Effectiveness Parameters

	Entire Cohort	LMWH	Heparin Infusion	Significance, *P* Value
Initial systolic PAP (mmHg)	55.9 ± 13.8	56.1 ± 13.1	55.8 ± 14.1	.7
Final systolic PAP (mmHg)	42.5 ± 11.6	42.5 ± 11.9	42.5 ± 11.5	.9
Change in systolic PAP (mmHg)	-13.4 ± 11.7	-13.7 ± 8.3	-13.3 ± 13	.9
Initial diastolic PAP (mmHg)	15.3 ± 6.7	15.7 ± 6.2	15.1 ± 7.0	.5
Final diastolic PAP (mmHg)	9.3 ± 5.6	9.2 ± 5.6	9.4 ± 5.6	.9
Change in diastolic PAP (mmHg)	-5.9 ± 7.2	-6.5 ± 5.7	-5.7 ± 7.8	.4
Initial mean PAP (mmHg)	28.9 ± 7.6	29.2 ± 6.9	28.7 ± 7.9	.4
Final mean PAP (mmHg)	20.4 ± 6.5	20.3 ± 6.5	20.4 ± 6.6	.8
Change in mean PAP (mmHg)	-8.5 ± 7.1	-8.9 ± 4.9	-8.3 ± 7.9	.4
Initial Miller PE Severity Index	19.3 ± 4.6	19.2 ± 4.7	19.3 ± 4.5	.8
Final Miller PE Severity Index	7.3 ± 3.9	7.3 ± 3.8	7.4 ± 3.9	.9
Change in Miller PE Severity Index	-11.9 ± 4.3	-11.9 ± 4.5	-11.9 ± 4.3	.9

LMWH = low-molecular-weight heparin; PAP = pulmonary arterial pressure; PE = pulmonary embolism.

DISCUSSION

A recent survey of multiple specialties involved in the Pulmonary Embolism Response Team Consortium revealed that 14% of physicians discontinue heparin completely during CDT, 60% continue heparin at a subtherapeutic level, and 13% continue heparin at a full-dose therapeutic level (2). One of the goals of this study was to report the general complication rates and, more specifically, the hemorrhagic complication rates of CDT, while administering therapeutic-dose anticoagulation, in a method that is more standardized across the multiple specialties that treat PE (12) (ie, GUSTO (3) classification), thus attempting to clarify the question of anticoagulation during CDT while facilitating future comparisons and meta-analyses (13). The current study reports GUSTO-major (1.9%, including a single intracranial hemorrhage), GUSTO-moderate (1.9%), and GUSTO-minor (2.6%) complication rates that are similar (13,14) or lower (15,16) than those reported in studies using full therapeutic-dose anticoagulation (14,15), the GUSTO (16) classification, and in a meta-analysis (13). The SEATTLE II trial (16), the largest CDT trial to use GUSTO criteria, reported 0.7% GUSTO-major complications (1 groin

hematoma and no intracranial hemorrhages) and 10.7% GUSTO-moderate complications in 150 patients treated with CDT and heparin infusion. GUSTO-minor complications were not reported in the SEATTLE II trial. Bloomer et al (15) reported 9.4% major hemorrhagic complications (that were approximate to a combination of GUSTO-major and GUSTO-moderate complications), including 1.4% intracranial hemorrhages in 137 patients treated with CDT and heparin infusion. Kennedy et al (14) reported 1.7% major hemorrhagic complications (0 intracranial hemorrhages) and 1.7% minor hemorrhagic complications in 60 patients treated with CDT and heparin infusion. Again, major complications reported by Kennedy et al (14) appear to be a composite of GUSTO-major and GUSTO-moderate complications. A meta-analysis performed by Giri et al (13) as part of the American Heart Association scientific statement on interventional therapies for acute PE analyzed 6 studies (which included the SEATTLE II trial (16) and the study by Bloomer et al (15)) with a total of 556 patients and found a major hemorrhage rate of 4.3% (composite of GUSTO major and GUSTO moderate) and an intracranial hemorrhage rate of 0.7%. In comparison, the current study found a combined GUSTO-major and GUSTO-moderate hemorrhagic rate of 3.8% and an intracranial hemorrhage rate of 0.6%. When comparing the subgroup of patients treated with full-dose therapeutic heparin ($n = 111$), the GUSTO-major (2.7%), GUSTO-moderate (1.8%), and GUSTO-minor (3.6%) complication rates were lower than previously reported by Bloomer et al (15). The current study also reports a subgroup of patients ($n = 45$) who were treated with full-dose therapeutic LMWH, which demonstrated very low GUSTO-major (0%), GUSTO-moderate (2.2%), and GUSTO-minor (0%) complication rates. These rates, although not significantly lower than the heparin group ($P = .3$, $P = 1.0$, and $P = .6$, respectively, possibly due to the comparison being underpowered), are similar to those reported in the PERFECT (17) registry (0% major and 12.9% minor) that used subtherapeutic anticoagulation. These findings raise a question regarding the potentially better safety profile of LMWH compared to full-dose or subtherapeutic-dose heparin as also reported by Robertson and Jones (18) in an analysis that did not include endovascular treatment. This needs to be further investigated in larger studies, as the LMWH subgroup reported here might have been too small to detect rare complications. In a study evaluating the ability to reach therapeutic partial thromboplastin time with unfractionated heparin infusion in 505 patients with acute PE, 60.6% of patients were subtherapeutic 48 hours after initiation of therapy, 11% were supratherapeutic, and only 28.4% were within therapeutic range (60–80 seconds) (19). Prucnal et al (19) also postulate that treatment with heparin infusion is often justified by the potential need for advanced treatment (ie, endovascular intervention). Overall, LMWH and heparin at a full therapeutic dose appear to be safe during CDT, although it is not currently endorsed by the Society of Interventional Radiology (20). The current study reasserts the need for further research evaluating this recommendation by comparing therapeutic and subtherapeutic anticoagulation during CDT for PE. At a minimum, practitioners may feel safe performing CDT even if treatment with full-dose therapeutic LMWH or unfractionated heparin has already been initiated.

Limitations of the current study include its retrospective nature and the size of the LMWH and heparin subgroups, which resulted in the comparison between the 2 groups being underpowered. Moreover, LMWH was used later in the study period than heparin, which also corresponds to higher yearly volume of treatments later in the study period. This represents a confounding factor because a higher volume of procedures likely results in more technically experienced operators and possibly fewer procedure-related complications. A caveat to this is that, whereas procedure-related complications might decrease with more experienced operators, the proportion of hemorrhagic complications related directly to the choice of anticoagulation might not be affected by operator experience. Information regarding the duration needed to achieve the target partial thromboplastin time for the heparin group, or regarding missed doses in the LMWH group, could not be verified for the current cohort. This might confound the complication and effectiveness results as patients might have been over- or under-coagulated during the course of their treatment (19). Regression analysis evaluating variables that might contribute to higher risk of hemorrhagic complications was not performed owing to the overall low number of complications. Two patients were excluded because they did not survive the initial catheter placement procedure due to repeated cardiac arrests, which occurred before and during the procedure. These were not hemorrhagic complications but rather mortalities attributed to moribund presentation and clinical deterioration secondary to massive PE.

In conclusion, therapeutic-dose anticoagulation with LMWH and heparin infusion during CDT for PE appears to be safe and similar to CDT with subtherapeutic anticoagulation. The current study did not find a significant difference between LMWH and heparin infusion with respect to these parameters, although further exploration of this subject is warranted as the current study was underpowered for this purpose.

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CME TEST QUESTIONS: APRIL 2020

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The CME questions in this issue are derived from the article "Safety of Therapeutic Anticoagulation with Low-Molecular-Weight Heparin or Unfractionated Heparin Infusion during Catheter-Directed Thrombolysis for Acute Pulmonary Embolism" by Graif et al.

This is a retrospective review of 155 patients undergoing catheter directed thrombolysis (CDT) in the setting of pulmonary embolus (PE) and the observed hemorrhagic complications. All patients were therapeutically anticoagulated concurrently with low molecular weight or unfractionated heparin.

1. What clinical presentations were included in the authors' review?
   a. Acute submassive PE
   b. Acute massive PE
   c. Chronic PE
   d. A and B

2. Of the following, which was observed most commonly in the study population?
   a. Syncope
   b. Positive troponin
   c. Simplified pulmonary embolism severity index (sPESI) ≥ 1
   d. Tachycardia > 100 beats/min

3. True or False: Patients treated with low molecular weight heparin during CDT experienced a statistically significant higher hemorrhagic complication rate than those treated with unfractionated heparin.
   a. True
   b. False

4. What was the observed major hemorrhagic complication rate in the study population as defined by the Global Use of Strategies to Open Occluded Arteries (GUSTO) classification?
   a. 2.6%
   b. 1.9%
   c. 3.8%
   d. 1.3%