EkoSonic Thrombolysis as a Therapeutic Adjunct in Venous Occlusive Disease

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Abstract

The use of ultrasound waves in conjunction with local thrombolysis may accelerate clot resolution and serve as an important therapeutic adjunct in the treatment of venous occlusive disease. Our goal was to provide a larger sample population over a 5-year period to evaluate our experience with the EkoSonic endovascular system (EKOS, EKOS Corporation, Bothell, WA). We suspected that ultrasound-accelerated thrombolysis (UAT) using EKOS would provide excellent thrombolysis and midterm patency rates with minimal thrombolytic complications.

A retrospective study was conducted to provide a case series with UAT using EKOS. Data were collected over a 5-year period. Primary end points included degree of thrombolysis. Secondly, we analyzed thrombolytic usage, complication rates, and midterm patency, over a 1-year period.

A total of 48 limbs were treated with UAT. Forty cases were diagnosed as acute, whereas the remaining 8 were chronic. Complete thrombolysis was successful in 38/48 (79%) of patients, and partial thrombolysis was accomplished in 10/48 (21%) of patients. Overall mean infusion time was 22.4 hours $\pm$ 3.6. There were a total of three complications (6%), all of which were minor bleeding. One-year patency was shown to be 87% with no signs of valvular reflux.

UAT using EKOS demonstrated effective rates of thrombolysis with very few complications. In addition, our 1-year patency rates were comparable to published data using conventional catheter-directed thrombolysis. UAT provides lytic therapy by utilizing the benefits of ultrasonic waves to help augment the fibrinolytic process. Our institution currently favors the use of EKOS as the treatment of choice in patients that are appropriate thrombolytic candidates.

Keywords

- catheter-directed thrombolysis
- deep vein thrombosis
- DVT
- endovascular procedure
- iliofemoral occlusive disease
- percutaneous
- thrombolytic

Pharmacologic thrombolysis has been used as an accepted modality of treatment for conditions such as deep venous thrombosis (DVT) and pulmonary embolus. Catheter-directed thrombolysis (CDT) offers the advantage of local lytic therapy, thereby reducing the potential systemic adverse effects of thrombolytics. Also, this modality allows the opportunity to treat underlying lesions simultaneously. In multiple series, CDT has been shown to be successful in the treatment of DVT without concern for significant major bleeding.^{1–3}

The decision to use thrombolysis in the treatment of DVT has been controversial. Long-term DVT or significant clot

burden has been proposed in the development of post-thrombotic syndrome (PTS). It has been postulated that the thrombus produces an adjacent inflammatory reaction with subsequent fibrosis of the involved valves.⁴ The continued venous insufficiency later produces venous stasis, leg swelling, and ulcerations.⁵ About 20 to 50% of patients with symptomatic DVT develop PTS within 1 to 2 years. Retrospective analysis using local CDT has suggested improved quality of life and reduced incidence of PTS.^{2,6,7} Therefore, some vascular surgeons have advocated the use of thrombolysis in select patients who are high risk

for developing PTS and those who may not be candidates for long-term oral anticoagulation.

The rapid evolution of endovascular equipment and techniques have provided more appealing alternative and effective minimally invasive treatment options in peripheral vascular diseases. The EkoSonic endovascular system (EKOS, EKOS Corporation, Bothell, WA) maintains the basic principle of local thrombolytics via a catheter infusion system. The difference is the utility of a core wire that combines high-frequency, low-intensity ultrasound waves to assist in clot fragmentation. The EKOS endovascular system consists of a 5.2F, 106-cm-long infusion catheter, an ultrasound core wire, and a control unit. The saline solution is infused via a coolant port to diffuse heat energy generated by the ultrasound transducer. The treatment segment varies from 6 to 50 cm in length with a series of microinfusion pores that provides the delivery of drugs into the thrombus.

The theory behind ultrasound is its ability to drive the thrombolytic agent into the formed clot ultimately leading to the disaggregation of the fibrin mesh.^{8,9} Numerous invitro studies using ultrasound have demonstrated increased effectiveness in delivering thrombolytic agents allowing improved and accelerated fibrinolysis.^{10–19}

We suspected our experience with ultrasound-accelerated thrombolysis (UAT) using EKOS provides safe and effective thrombolysis with decreased quantity of thrombolytics. We also postulated comparable midterm patency rates, as seen in patients treated with CDT noted in the literature.

Methods

This was a retrospective study at a single level-1 tertiary center. Patients were selected from 2008 through 2013. Occlusive symptoms were divided into acute (≤ 14 days) and chronic (>14 days) based on reporting standards for lower extremity DVT.²⁰ Patients must have undergone UAT with EKOS. The diagnosis was initially made using a venous duplex ultrasonography (DUS) and further confirmed with a diagnostic venogram at the time of catheter placement. One patient had a pulmonary embolus that was included and diagnosed also by a pulmonary arteriogram. Tissue plasminogen activator (TPA) was used as the thrombolytic agent. Thrombolysis rates were analyzed and recorded based on a grading scale. Data were collected over 5 years. Degree of thrombolysis, TPA dosage, duration of lytic therapy, and bleeding complications were recorded.

Patient Selection

Before data collection and chart review, the protocol was approved by the institutional review board. Those included in the study must have presented with a DVT, either acute or chronic, be at least 18 years of age, and have no contraindications to venography or thrombolytic therapy. Exclusion criteria included those who were not acceptable candidates for thrombolytic therapy such as active bleeding, recent cerebrovascular accident, surgery or trauma, contrast allergy, contraindications to full anticoagulation, pregnancy, or coagulopathy. Those with superficial or infrapopliteal thromboses were also excluded.

Treatment and Follow-Up

Procedures were performed by three board-certified vascular surgeons trained in endovascular techniques. Our institution contains two dedicated hybrid vascular operative suites with a designated on-call operating room team consisting of a scrub tech, circulating nurse, and radiology technologist that are available during all hours of the day. All patients with confirmed DVT received access from the ipsilateral popliteal vein using a micropuncture technique. A 6F sheath was inserted. The infusion catheter was placed across the occlusion. TPA was initiated through the side-hole delivery infusion. The dosages used did vary based on the patient's weight. Normal saline solution was infused as coolant through the central lumen. Patients also received a continuous infusion of heparin set at 500 units/hour through the introducer sheath. The ultrasound energy was delivered through a microsonic core wire containing a series of ultrasound transducer elements (2 MHz, 0.45 W). The duration of thrombolysis also varied based on the patient's clinical symptoms and clot burden noted on their initial venogram. Those who appeared to improve clinically, based on decreased swelling and level of pain, were taken back within 24 hours. Thrombolysis was prolonged in those who had persistent symptoms. Postoperatively these patients were strictly monitored in a vascular intermediate unit.

Percutaneous transluminal venoplasty and stenting were performed for underlying stenotic lesions after thrombolysis. The duration of thrombolysis was recorded from the initial placement of the EKOS catheter with thrombolytic infusion until the time of its removal where thrombolysis was stopped. The total amount of TPA administered and bleeding complications were among the other variables that were used. One-year patency rates were determined from a DUS.

Venous Patency

Site involvement and degree of thrombolysis as described by Porter et al²¹ were used to interpret the degree of clot formation within the limb during venography to minimize any user subjectivity. Diagnostic evaluation was via ultrasound and ultimately confirmed by an initial venogram during the insertion of the thrombolysis catheter. The inferior vena cava, common iliac veins, external iliac veins, common and superficial femoral veins and popliteal veins were graded with a score of 0 when the vein was patent, 1 when there was a subsegmental nonocclusive clot, 2 when there was a subsegmental occlusive thrombus, and 3 if the entire segment was occluded. The tibial and superficial veins of the leg were not included in the scoring process. A score was then calculated from the different vein segments. The difference between the prelysis score and the postlysis score divided by the prelysis score provided the percentage of thrombolysis. This method was initially used by Mewissen et al²² in their multicenter venous registry using standard CDT and is being used in this study to minimize interpretation bias. Grade III thrombolysis was defined as 100% or complete thrombolysis. Grade II ranged from 50 to 99% and grade I equated to less than 50%.

A review of the literature was conducted to facilitate a comparison among other case studies using EKOS or UAT. We also wanted to correlate our results with historical published data from those using CDT. A Medline literature review was performed with medical subject headings that included “catheter directed thrombolysis,” “local thrombolysis,” “ultrasound accelerated thrombolysis,” “deep venous thrombosis or thrombus.” We included randomized controlled trials, clinical trials, and case series over a 15-year period.

Statistical Analysis

Descriptive statistics were produced, using means, medians, ranges, and standard deviations for continuous variables, and percentages for categorical variables. Independent variables included age, gender, surgical complications, duration, and total dosage of thrombolytic therapy. Inferential statistics included Pearson chi-square tests for categorical variables and independent sample *t*-tests for continuous variables. Primary outcome variables included degree of thrombolysis and 1-year patency on follow-up. Statistical significance was evaluated at the 5% ($\alpha = 0.05$) level. All statistical analyses were performed using IBM SPSS version 21.0 statistical software (Chicago, IL).

Results

There were a total of 48 limbs included in the study. Demographic characteristics are reported in ► **Table 1**. The majority of our patients had iliofemoral and popliteal disease DVTs. Overall, 83% of the patients were diagnosed with acute symptoms. Details regarding the degree of thrombolysis in relation to duration of symptoms and thrombolytic dosage and duration are summarized in ► **Table 2**. Overall lysis, which included both complete and partial, occurred in 100% of the patient sample. Grade III or complete thrombolysis was successful in 38/48 (79%) and 10/48 (21%) of patients had achieved partial thrombolysis (50–99%) using EKOS.

Mean infusion time was 22.4 hours ± 3.6 with an average TPA dosage of 15.7 ± 4.6 mg. Three (6%) patients had minor bleeding at the catheter insertion site that did not require a transfusion or interruption of thrombolytic therapy. No major hemorrhagic complications were present.

No statistically significant difference in degree of thrombolysis was observed between patients with acute or chronic symptoms. Additionally, no correlations were noted with respect to the location of the thrombus and the efficacy of therapy. Patients who had a history of DVT's responded less favorably with EKOS thrombolysis than those without a recurrent DVT ($p = 0.001$). Out of the eight patients with chronic DVT, six were treated successfully.

Recurrent DVT was diagnosed with a DUS. Within a 12-month follow-up period, only six (13%) patients developed a recurrence that required repeat thrombolysis. One patient was lost to follow-up. The remaining 41 patients demonstrated patency on follow-up DUS without signs of valvular reflux. Of the six patients with recurrences, four displayed venous reflux on ultrasound. The overall 1-year patency rate was shown to be 87% (► **Table 3**). All patients diagnosed with a

Table 1 Demographics

Demographics	Value
Number of patients (N)	40
Number of limbs	48
Gender	
Male	14 (35%)
Female	26 (65%)
Mean age (y)	47
Vein location	
IVC	8
Ileofemoral	44
Popliteal	16
Acute (≤ 14 d)	40
Chronic (>14 d)	8
Comorbidities (%)	
Hypertension	14 (35%)
Hyperlipidemia	3 (7%)
Diabetes mellitus	8 (18%)
CAD	5 (11%)
Renal disease	0 (0%)
Hypercoagulability	1 (2%)
Atrial fibrillation	2 (4%)
May–Thurner syndrome	1 (2%)
History of DVT	21 (48%)
Tobacco use	21 (53%)

Abbreviations: CAD, coronary artery disease; DVT, deep venous thrombosis; IVC, inferior vena cava.

Table 2 Grades of thrombolysis in relation to multiple variables

	Grade III	Grade II	Grade I	<i>p</i> Value
History of DVT	15	6	0	0.001
Duration of symptoms				
Acute	32 (67%)	8 (17%)	0	0.75
Chronic	6 (12%)	2 (4%)	0	
Average infusion time (h)	22.2	23.3	NA	0.35
Total average TPA (mg)	15.7	16.8	NA	0.47
Average LOS (d)	3.5	2.9	NA	0.62
DVT location				
IVC	8	1	0	0.91
Ileofemoral	43	9	0	
Popliteal	15	2	0	

Abbreviations: DVT, deep venous thrombosis; IVC, inferior vena cava; LOS, length of stay; TPA, tissue plasminogen activator.

Table 3 One-year follow-up data

	Total limbs	Grade III	Grade II	Grade I
Patent after 1 y	41 (87%)	32 (86%)	8 (80%)	0
Required repeat thrombolysis	6 (13%)	5 (14%)	2 (20%)	0
Total	47	37	10	

Note: One patient was lost to follow-up. Patency was determined by venous duplex.

DVT were educated and maintained their use of anticoagulation postprocedure until further notice by their physician.

Discussion

With the advent and rapid evolvement of endovascular techniques, it has become more appealing to provide alternative and minimally invasive treatment options that have equal or more efficacious outcomes. Endovascular thrombolytic methods have evolved considerably in recent years. The use of delivery systems for thrombolysis offers several benefits relative to systemic therapy. Placement of a catheter system within the thrombus can reduce the treatment time, reduce the thrombolytic load, and minimize adverse side-effects associated with systemic thrombolysis.

Data on the use of conventional CDT for the treatment of DVT are currently available through numerous case series. The National Venous Thrombosis Registry conducted by Mewissen et al is the largest prospective multicenter study using conventional CDT on patients with venous occlusions.²² There were a total of 287 patients with iliofemoral and popliteal DVTs treated with urokinase demonstrating complete lysis in only 96 (31%) patients, partial lysis in 162 (52%), and minimal response in the remaining 54 (17%) with an average lysis time of 53.4 hours. There were a total of 131 complications, including major and minor bleeding. Primary patency rates at 6 and 12 months were 65 and 60%, respectively. More recent case studies implementing CDT have shown complete thrombolysis rates ranging from 0 to 92% with shorter infusion times using other thrombolytic agents (►Table 4).^{23–35} Complication rates remain higher than what is reported for UAT averaging above 20% and possibly related to the longer infusion times noted within these studies.

The purpose of the EKOS is to allow improved efficiency of CDT by accelerating the fibrinolytic process with the application of ultrasound. The first reports using UAT for venous occlusive disease came from Raabe and Motarjeme. Raabe reported the treatment of 45 venous occlusions (25 lower extremity, 17 upper extremity, 2 hepatic vein, 1 arterial venous fistula) using the EKOS.³⁶ Complete lysis was achieved in 71% of the patients and partial lysis in an additional 20%. The average time to achieve complete lysis was 24.7 hours with only two (4.4%) complications. Motarjeme demonstrated complete clot resolution in 83% of venous occlusions with an average thrombolysis time of 21.2 hours.³⁷

Our results compared favorably in relation to other published works using EKOS for acceptable thrombolysis candidates (►Table 5).^{36–40} Our study contained a larger patient population than most reporting the use of UAT and additionally looked at midterm patency over 1 year. Complete thrombolysis was achieved in 79% of patients with the remaining having achieved partial thrombolysis. Our infusion time average of 22.4 hours compared similarly to other case studies utilizing UAT. Also, the infusion times for those using CDT were noticeably longer. We also encountered minimal bleeding complications where only 6% of our study had some minor bleeding at the venipuncture site that was self-limiting. This may be explained by the reduced drug dosages and duration of treatment that we experienced in our study in addition to what others have reported using EKOS compared with standard CDT.

At 12 months, our patients received a DUS for surveillance to identify continued patency of the vein. Resolution of the thrombus with continued patency was documented in 41 (87%) cases. This is an improvement from what was reported in the National Venous Thrombosis Registry at 60%. Other studies using CDT witnessed 1-year patency ranging from 40 to 93% (►Table 4). The degree of thrombolysis also correlated with continued patency seen over 1 year. A total of 14% of patients with grade III thrombolysis required additional lytic intervention compared with 20% of patients who received partial thrombolysis.

Our objective was to specifically investigate the use of EKOS thrombolysis, however, there are other modalities that utilize pharmacomechanical devices such as the use of trellis for iliofemoral DVTs. A comparison between the two devices was not conducted in this study. In addition, we did not perform a cost analysis, comparison between UAT and standard CDT. Whether EKOS thrombolysis is cost effective compared with alternative treatment options remains unanswered. An estimated control unit could cost as much as \$14,000 with each infusion catheter approaching nearly \$2,300.⁴¹ Although the initial costs may be high, it still is unclear whether UAT may indirectly decrease the overall expense of the hospitalization by minimizing that total thrombolytic drugs used and the duration of infusion. Shorter monitoring in an intensive care unit may also drastically decrease hospital costs. Future studies would be necessary to investigate whether this approach would be ideal from a cost-to-benefit ratio.

The current investigation was limited in that it was a retrospective and nonrandomized study. The sample size was also limited. In light of this being a retrospective study, not all patients who met criteria for thrombolysis ultimately underwent UAT and, instead, were offered medical treatment with anticoagulation creating a subjective bias. Follow-up patency of the vein was confirmed with a DUS, which is limited in its ability to detect thrombus more proximal in the iliac veins and the inferior vena cava. In addition, the reliability and duration of continued outpatient anticoagulation could not be controlled may have affected the midterm patency rates.

Additional randomized prospective studies that objectively assess the degree of thrombolysis, infusion duration, complications, and costs between CDT and UAT should greatly

Table 4 Studies using CDT for venous occlusive disease

Study	Year	N (limbs)	Intervention	Complete lysis	Partial lysis	Minimal lysis	Complications	1-y patency	Infusion time (h)
AbuRahma et al ²³	2001	18	CDT with UK or r-tPA	15 (83)	NR	NR	5 (28)	83%	NR
Bjarnason et al ²⁴	1997	77 (87)	CDT with UK	69 (79)	0 (0)	18 (21)	16 (20)	40–63%	NR
Castaneda et al ²⁵	2002	15	CDT with r-PA	23 (92)	NR	2 (8)	1 (4)	NR	0.3–84
Comerota and Kagan ²⁶	2001	54	CDT with UK or rt-PA	14 (26)	28 (52)	NR	12 (22)	NR	NR
Elsharawy and Elzayet ²⁷	2002	18	CDT	13 (72)	5 (28)	0 (0)	0 (0)	NR	NR
Grunwald and Hofmann ²⁸	2004	74 (82)	CDT with UK, t-PA, or r-PA	54 (73)	26 (32)	NR	10 (13)	NR	31.9
Jackson et al ²⁹	2005	28	CDT with UK, r-PA	5 (18)	20 (72)	NR	2 (7)	80%	NR
Kim et al ³⁰	2006	23 (26)	CDT with UK	21 (81)	3 (11)	2 (8)	3 (11)	NR	56
Laiho et al ³¹	2004	16	CDT with rt-PA	8 (50)	5 (31)	NR	6 (38)	NR	NR
Mewissen et al ²²	1999	287 (312)	CDT with UK	96 (31)	162 (52)	54 (17)	131 (27)	60%	53.4
Ogawa et al ³²	2005	10	CDT with UK	0 (0)	10 (100)	None	None	NR	NR
Semba and Dake ³³	1996	32	CDT with UK	21 (32)	9 (28)	2 (6)	None	None	NR
Sillesen et al ³⁴	2005	45	CDT with rt-PA	42 (93)	NR	NR	7 (16)	93% ^a	71
Verhaeghe et al ³⁵	1997	24	CDT with alteplase	19 (79)	5 (21)	0 (0)	6 (25)	NR	NR

Abbreviations: CDT, catheter-directed thrombolysis; NR, not reported; r-PA, recombinant plasminogen activator; rt-PA, recombinant tissue plasminogen activator; t-PA, tissue plasminogen activator; UK, urokinase.

^aValues are expressed as *n* (%).

Table 5 Studies using ultrasound-accelerated thrombolysis in peripheral venous occlusive disease

Study	Year	N (limbs)	Intervention	Complete lysis ^a	Partial lysis ^a	Minimal lysis ^a	Complications ^a	1 y patency	Infusion time (h)
Current study	2015	48	UAT with TPA	38 (79)	10 (21)	0	3 (6)	87%	22.4
Dumantepe et al ³⁸	2013	26	UAT with alteplase	14 (54)	10 (38)	2 (8)	3 (12)	NR	25.3
Grommes et al ³⁹	2011	13	UAT with rtPA, UK	11 (85)	1 (7.5)	1 (7.5)	1 (7.6)	NR	NR
Motarjeme ³⁷	2007	12	UAT with UK	10 (83.1)	1 (8)	1 (8)	0 (0)	92%	21.2
Parikh et al ⁴⁰	2008	53	UAT with UK, tPA, rtPA	37 (69.8)	11 (20.8)	5 (9.4)	2 (4)	NR	22
Raabe ³⁶	2006	45	UAT	32 (71.1)	9 (20)	4 (9)	2 (4.4)	NR	24.7

Abbreviations: NR, not reported; rt-PA, recombinant tissue plasminogen activator; t-PA, tissue plasminogen activator; UAT, ultrasound-accelerated thrombolysis; UK, urokinase.

^aValues are expressed as *n* (%).

assist the physician in deciding the most optimal modality for thrombolysis for patients with clinically significant DVTs who are acceptable candidates. Most recently, Engelberger et al⁴² challenged the notion that the use of ultrasound actually provided any thrombolytic benefit. Their randomized prospective clinical trial compared patients with iliofemoral DVTs treated with and without the ultrasound component using the EKOS. The use of ultrasound energy did not affect patency rates, the incidence of PTS or reduce the use of additional endovascular procedures, such as venoplasty and stenting. They concluded that no statistically significant differences were present between those that used intravascular ultrasound energy and those that did not.

Conclusion

Advantages of the CDT are its minimally invasive nature, the ability to simultaneously diagnose and treat vascular lesions, and local clot removal. Potential drawbacks include the extended time and intensive monitoring of treatment, cost, bleeding complications, and repeat venography that could further lead to renal dysfunction. The incidence of complications appears to be related to the duration of treatment as prolonged infusions can lead to depleted fibrinogen levels and increased bleeding. For this reason, multiple studies have investigated the use of UAT in hopes that ultrasound can alleviate some of the shortcomings of CDT. The data using EKOS has shown effective rates of thrombolysis. Multiple case studies using UAT have shown a significant reduction in thrombolysis infusion times. Until a more universal approach is adopted regarding the choice and dosage of the thrombolytic agent being used in these devices, the verdict remains inconclusive that EKOS can definitely decrease thrombolysis times or the quantity of drug. UAT is becoming more prevalent as more vascular surgeons are becoming exposed and eventually trained in the technique. Although the EKOS system may serve as an adjunct to the vascular surgeon's armamentarium, it remains inconclusive whether UAT offers any benefit at all compared with conventional CDT in the treatment of DVT.

Conflict of Interest

None.

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