Use of EKOS® Catheter in the management of Venous Thromboembolism

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Introduction

Georgia Thrombosis Forum (GTF, [www.gtfonline.net](http://www.gtfonline.net)) is an affiliate of North American Thrombosis Forum (NATF, [www.natfonline.org](http://www.natfonline.org)). GTF is dedicated to the advocacy of thrombosis in the community and conducting research in the area of various aspects of management of thrombosis. GTF is also focused on training the next generation of leaders, and encourages youth volunteers as a medium for action in the community.

This latest research project is on the EKOS® Catheter, an innovative technique for the management of thrombosis. In this report, GTF will be discussing some general facts about the EKOS® Catheter, and delving into some specifics on what it is, how it is used, what are the results (both efficacy and safety).

1. What is EKOS® Catheter?

EKOS® Catheter uses ultrasound pressure and acoustic streaming along with physician specified fluids, including thrombolytic agents to dissolve the thrombus.
EKOS® Catheter set up
A. Ultrasound core

B. EKOS® Catheter

A schematic representation of EKOS® Catheter. This demonstrates the guide wire crossing the occlusion prior to the placement of the EKOS® Catheter.
2. Who developed the EKOS® Catheter?

The EKOS® Catheter was created in 2005 as part of an acoustic movement to treat thrombotic conditions. It is made by the EKOS® Corporation, and is used by many endovascular physicians, including cardiologists, radiologists and surgeons.

3. How does EKOS® Catheter work?

The EKOS EkoSonic® Endovascular System generates ultrasonic energy waves which emit high frequency, low power ultrasound at the treatment zone. The ultrasound emanates radially into and through blood, thrombus, or tissue surrounding the treatment zone, within the patient’s vasculature. The EKOS® system is available for the treatment of pulmonary embolism (PE), deep vein thrombosis (DVT), and peripheral arterial occlusions.

EKOS® makes the clot become permeable. Ultrasound pressure drives the physician specified thrombolytic agent through the permeated thrombus.

EKOS® Catheter is different from other catheters because it is able to deliver drugs effectively to the source of the clot. The acoustic pressure generated thus allows the physician recommended thrombolytic agent to remain embedded at the local site of the thrombus for a longer period of time, increasing the efficiency.

4. Insertion of the EKOS® Catheter / technology

The EKOS® Catheter is inserted through the thrombus. The ultrasonic wire is advanced through the Catheter and secured in place. Infusion of the physician specified thrombolytic agent is then started. The ultrasound component of the EKOS® technology is then engaged, thus allowing for the generation of the acoustic streaming which allows the clot to be more effectively dissolved.

5. Risks of the EKOS® Catheter / technology

As with any endovascular procedure, there is a risk of infection or allergic reaction during skin penetration. Damage to the blood vessel, bruising or bleeding at the puncture site, and infection: none of these is unique to the EKOS® catheter.

Whenever any thrombolytic agent is used, there is an inherent risk that bleeding could occur.
There is also a risk of damage to the kidneys, especially with those have pre-existing kidney disease due to the contrast medium used during the procedure.

6. Role played by EKOS® Catheter in the management of VTE

Compared to many other treatments, EKOS® is relatively new. Many endovascular physicians use EKOS® Catheter exclusively as the first line of treatment. Some physicians use EKOS® Catheter after traditional therapy has been used.

GTF is a volunteer group dedicated to the advocacy of thrombosis in the community and doing research in the area of the treatment and prevention of thrombosis. This latest research project conducted by GTF is on the EKOS® Catheter, an innovative treatment for patients with thrombosis.
The authors selected a series of three articles which give a detailed description of the application of EKOS® Catheter in multi-center trials for the treatment of venous thromboembolism (VTE). Through these articles, we hope to assess the role of the EKOS® Catheter in its management of VTE, as well as the pros and cons of its usage.

End point: Reduction in RV Strain in all 3 trials

The ULTIMA Trial
This multicenter randomized, controlled trial investigated whether UltraSound-Assisted catheter-directed Thrombolysis (USAT) is superior to anticoagulation alone in the reversal of RV dilatation in intermediate-risk patients.

Fifty-nine patients (63±14 years) with acute main or lower lobe pulmonary embolism were randomized in 2 groups

Group 1: Received unfractionated heparin alone (n=29).

Group 2: Ultrasound-Assisted catheter-directed thrombolysis (USAT) group. This consisted of infusion of 10 to 20 mg recombinant tissue plasminogen activator over 15 hours (n=30)

**Primary outcomes**

Efficacy outcome: The difference in the RV/LV ratio from baseline to 24 hours.

Safety outcome: Death, major and minor bleeding, and recurrent venous thromboembolism at 90 days.

**Results**

1. The USAT group:

1.1. The mean RV/LV ratio improved significantly from 1.28±0.19 at baseline to 0.99±0.17 at 24 hours (P<0.001).

1.2. The reduction in RV / LV ratio was significantly greater (than that in the control group) at 24 h and improved at 90 days

2. The heparin group

2.1. Mean RV/LV ratios were 1.20±0.14 and 1.17±0.20, respectively (P=0.31).

3. At 90 days, there were no deaths in the USAT group, and 1 death in the heparin group

4. There was no major bleeding in either of the 2 groups
5. There were 3 minor bleeding events in the USAT group and 1 in the heparin group ($P=0.61$).

6. There was no recurrent venous thromboembolism in any of the 2 groups.

**Conclusion**

In patients with pulmonary embolism, a standardized USAT regimen was superior to anticoagulation with heparin alone in reversing RV dilatation at 24 hours, without an increase in bleeding complications.
The SEATTLE II Trial

A prospective, single-arm, multicenter trial to evaluate the safety and efficacy of ultrasound-facilitated, Catheter-directed, low-dose fibrinolysis, using the EkoSonic Endovascular System

Hypothesis

Systemic fibrinolysis for acute pulmonary embolism (PE) reduces cardiovascular collapse but causes hemorrhagic stroke at a rate exceeding 2%.

Eligible patients had a proximal PE and a right ventricular (RV)-to-left ventricular (LV) diameter ratio ≥0.9 on chest computed tomography (CT).

The authors included the following 2 groups of patients:

1. Patients with acute massive PE (n = 31)
2. Patients with submassive PE (n = 119)

Dosing

<table>
<thead>
<tr>
<th>Clinical outcomes at 90 days</th>
<th>EkoSonic with tPA + Heparin N = 30</th>
<th>Heparin N = 29</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>1*</td>
<td>0.49</td>
</tr>
<tr>
<td>Recurrent venous thromboembolism</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>3**</td>
<td>1</td>
<td>3%</td>
</tr>
</tbody>
</table>

* Rehospitalization and death from advanced pancreatic cancer
** Two patients with transient mild hemoptysis without medical intervention, one patient with groin hematoma requiring manual compression
† One patient with transient anorectal bleeding following endoscopic removal of colon polyp
Tissue-plasminogen activator (t-PA) was administered at a dose of 24 mg either as 1 mg/h for 24 h with a unilateral Catheter, or 1 mg/h/Catheter for 12 h with bilateral Catheters.

**Primary efficacy outcome**

The change in the chest CT-measured RV/LV diameter ratio within 48 h of procedure initiation.

**Primary safety outcome**

Major bleeding within 72 h of procedure initiation.

**Results**

The mean RV/LV diameter ratio decreased from baseline to 48 h post-procedure (1.55 vs. 1.13; mean difference, -0.42; p < 0.0001).

Mean pulmonary artery systolic pressure (51.4 mm Hg vs. 36.9 mm Hg; p < 0.0001) decreased post-procedure.

One GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries)-defined severe bleed (groin hematoma with transient hypotension) and 16 GUSTO-defined moderate bleeding events occurred in 15 patients (10%).

No patient exhibited intracranial hemorrhage.

When results from the following 3 major trials were compared, there appears to be a reduction of the risk of intracranial bleeding:

ICOPER (Goldhaber et al, 1999): 9 / 304 (3 %)

PEITHO (Meyer et al, 2014): 10 / 506 (2%)

SEATTLE II ((Piazza et al, 2014): 0 / 150 (0%)

**Conclusion**
Ultrasound-facilitated, Catheter-directed, low-dose fibrinolysis decreased RV dilation, reduced pulmonary hypertension, decreased anatomic thrombus burden, and minimized intracranial hemorrhage in patients with acute massive and submassive PE. Over the period of time, there appears to be a reduced risk of intracranial bleeding from the 3 studies.

**25% decrease in RV/LV ratio over 48 hours**

![Graph showing 25% decrease in RV/LV ratio over 48 hours](chart)

**Minimized risk of intracranial hemorrhage**

<table>
<thead>
<tr>
<th>Study</th>
<th>Intracranial Hemorrhage (Fibrinolysis Group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICOPE</td>
<td>9/304 (3%)</td>
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<tr>
<td>(Goldhaber SZ, et al. 1999)</td>
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<td></td>
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<tr>
<td>SEATTLE II</td>
<td>0/150 (0%)</td>
</tr>
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</table>
The Nykamp et al Trial

This was a retrospective review of a single-center, acute massive and submassive PE cases with case matching for controls was conducted.

The objective of the review was to evaluate the safety and effectiveness of ultrasound accelerated thrombolysis in patients with acute PE.

The patients were divided into 2 groups:

1. Control Group, N=45 with systemic anticoagulation alone

2. Treatment Group, N=45 with Ultrasound-accelerated
EKOS® catheter access was obtained through a common femoral vein under ultrasound guidance. A 0.035” guidewire and angiographic Catheter was introduced to cross occlusion. With a guidewire tip within the large lower-lobe segmental branch, the angiographic Catheter was exchanged for EKOS® Infusion Catheter. Subsequently, infusions were started, and ultrasound was turned on.

**Infusion Protocol**

1. An average of 30.5 mg rtPA was infused at the rate of 1 mg / h. At the same time, saline coolant 35 ml / h was used during the infusion.

2. rtPA was reduced to 0.5 mg / h after four hours.

3. The average thrombolytic time was 14.2 hours.

4. At the end, EKOS® devices were removed. Standardized anticoagulation was administered.

**Key results**

1. Complete resolution of cardiac dysfunction was observed in 64% of patients immediately following the procedure

2. Pulmonary artery pressure showed an average reduction of 40.2%

3. The average length of stay was reduced from 6.7 days in the control group to 3.2 days in the treatment group.

4. When followed for a period of 24 months, the EKOS® treated patients showed a significantly higher survival rate.

5. No deaths through 90 days of follow-up and no major periprocedural bleeding events.
**Conclusion**

EKOS® therapy is an effective PE treatment for reducing pulmonary artery pressures and resolving hemodynamic abnormalities, with excellent mortality and complication rates.
Summary and Conclusion

The data from these studies shows that the EKOS® Catheter, with regard to its applications in localized drug delivery, is a viable treatment option for patients with venous thromboembolism. Since the thrombolytics can be delivered directly to the site of the thrombus, significant improvement in cardiac function is observed rapidly, and the incidence of bleeding is greatly minimized.

Acknowledgements

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References


4. Figures courtesy from John Bandera, EKOS® Corporation, and from literature for EKOS® Catheter

@ This data was presented at the NATF Annual Summit, Boston, September 2017