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Original Article / Özgün Makale

Analysis of pulmonary embolism patients treated with EkoSonic™ endovascular system

EkoSonic™ endovasküler sistem ile tedavi edilen pulmoner embolili hastaların analizi

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ABSTRACT

Background: The aim of this study was to evaluate the efficacy and the safety of the EkoSonic™ endovascular system applications in patients hospitalized with the diagnosis of intermediate-high-risk pulmonary embolism.

Methods: Between January 2018 and March 2019, a total of 15 patients (7 males, 8 females; mean age 64.7±17.8 years, range, 35 to 90 years) who underwent ultrasound-accelerated thrombolysis using the EkoSonic™ endovascular system for pulmonary embolism were retrospectively analyzed. The diagnosis of pulmonary embolism was made based on pulmonary computed tomography angiography. All patients were evaluated by echocardiography for right ventricular dysfunction and serum levels of troponin I and brain natriuretic peptide were recorded.

Results: The mean arterial blood gas oxygen saturation values of the patients before and after the procedure were 86.3±3.5% and 94.2±2.5%, respectively, indicating a statistically significant difference (p=0.001). The mean partial oxygen pressure values before and after the procedure were 73.3±7.7 mmHg and 90.7±5.0 mmHg, respectively, indicating a statistically significant difference (p=0.001). There was also a statistically significant difference in the mean right ventricular diameter before and after the procedure (p=0.001). The mean pre- and post-procedural pulmonary arterial pressure was 44±7.1 mmHg and 36.3±4.5 mmHg, respectively, indicating a statistically significant difference (p=0.001). Of the patients, 93.7% were free from post-procedural complications.

Conclusion: The EkoSonic™ endovascular system improved right ventricular dysfunction, decreased pulmonary arterial pressure, and improved oxygenation in patients with intermediate-high-risk pulmonary embolism without increasing the risk for bleeding.

Keywords: EkoSonic™ endovascular system, pulmonary embolism, ultrasound-accelerated thrombolysis.

ÖZ

Amaç: Bu çalışmada, orta-yüksek riskli pulmoner emboli tanısıyla hastaneye yatırılan hastalardaki EkoSonic™ endovasküler sistem uygulamalarının etkinliği ve güvenliliği değerlendirildi.

Çalışma planı: Ocak 2018 - Mart 2019 tarihleri arasında, pulmoner emboli nedeniyle EkoSonic™ endovasküler sistemi kullanılarak ultrasonografi ile hızlandırılmış tromboliz yapılan toplam 15 hasta (7 erkek, 8 kadın; ort. yaş 64.7±17.8 yıl; dağılım, 35-90 yıl) retrospektif olarak incelendi. Pulmoner emboli tanısı, pulmoner bilgisayarlı tomografi anjiyografi ile konuldu. Hastaların tümü sağ ventrikül disfonksiyonu açısından ekokardiyografi ile değerlendirildi ve serum troponin I ve beyin natriüretik peptid düzeyleri kaydedildi.

Bulgular: Hastaların işlem öncesinde ve sonrasında ortalama arteriyel kan gazı oksijen satürasyon değerleri sırasıyla %86.3±3.5 ve %94.2±2.5 olup, istatistiksel olarak anlamlı fark saptandı (p=0.001). İşlem öncesinde ve sonrasında ortalama parsiyel oksijen basıncı değerleri 73.3±7.7 mmHg ve 90.7±5.0 mmHg olup, istatistiksel olarak anlamlı fark saptandı (p=0.001). İşlem öncesinde ve sonrasında ortalama sağ ventrikül çapı açısından da istatistiksel olarak anlamlı bir fark vardı (p=0.001). İşlem öncesinde ve sonrasında ortalama pulmoner arter basıncı sırasıyla 44±7.1 mmHg ve 36.3±4.5 mmHg olup, istatistiksel olarak anlamlı fark saptandı (p=0.001). Hastaların %93.7'sinde işlem sonrasında komplikasyon gözlenmedi.

Sonuç: EkoSonic™ endovasküler system orta-yüksek riskli pulmoner emboli hastalarında kanama riskinde bir artışa neden olmaksızın sağ ventrikül disfonksiyonunu iyileştirdi; pulmoner arter basıncını azalttı ve oksijenasyonu düzeltti.

Anahtar sözcükler: EkoSonic™ endovasküler sistem, pulmoner emboli, ultrasonografi ile hızlandırılmış tromboliz.

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Venous thromboembolism (VTE) is the third most common acute cardiovascular syndrome after ischemic heart disease and ischemic stroke.[1] As a result of increase in the world population and prolonged life expectancy, VTE prevalence tends to increase.[1] In 2010, one of four deaths worldwide were due to thromboembolic diseases.[2] Although the incidence of VTE ranges between 79 and 269 per 100,000, the incidence increases significantly with increasing age.[2] In a study conducted with hospitalized patients in the United States, the incidence of VTE between age of 18-39 years and 80 years and older was 60 and 1,134 per 100,000, respectively.[3]

Pulmonary arterial pressure (PAP) increases as a result of 30 to 50% occlusion of the pulmonary vascular bed due to thromboembolism. The primary cause of death in high-risk pulmonary embolism (PE) is right ventricular (RV) failure due to acute pressure increase. In patients with PE, high-risk markers include increased troponin and brain natriuretic peptide (BNP), RV dysfunction (RVD), and hemodynamic instability.[4] The prognosis of high-risk PE patients is poor and mortality rates reach up to 65%.[4]These patients should be treated appropriately with thrombolytic therapy or emergency interventional therapies. However, the treatment of intermediate-high-risk PE patients still remains controversial.[5] Although thrombolytic therapy has been shown to reduce mortality in these patients, it increases the risk for major bleeding and intracranial hemorrhage.[6] In the Pulmonary Embolism Thrombolysis (PEITHO) trial, tenecteplase and unfractionated heparin (UFH) were compared with UFH alone in intermediate-high-risk PE patients, and the long-term results of this study showed no effect of thrombolytic therapy over long-term mortality, and no advantage over UFH alone in reducing RVD and residual dyspnea.[7] In their study, Kline et al.[8] compared patients with intermediate-high-risk PE who were treated with anticoagulants alone and anticoagulants plus thrombolytic therapy. In the follow-up after six months, only the anticoagulant group had a statistically increased risk for pulmonary hypertension compared to the other group. In the Moderate Pulmonary Embolism Treated with Thrombolysis (MOPETT) study, 121 patients with intermediate-high-risk PE were included and one group received half-dose alteplase (50 mg for 1 h) and UFH, while the other group received only UFH.[9] At 28 months of follow-up, the number of patients with chronic thromboembolic pulmonary hypertension (CTEPH) was lower in the thrombolytic group, mortality was similar, but no bleeding was observed. On the other hand, no change in the mortality rates between the groups, elevation of troponin or BNP levels in 68% of patients, 21% RV enlargement and 57% CTEPH in the control group were subjects of criticism in this study.[10]

Mechanical disintegration, aspiration of thrombus, and administration of thrombolytic drugs directly to the thrombus are the percutaneous catheter-guided methods used to eliminate pulmonary thrombus. Catheter-directed thrombolytic administration requires a much lower dose of thrombolytic agent than systemic thrombolytic administration. In ultrasound-accelerated thrombolysis (USAT), sound waves are used with the ultrasonic transducer in the structure of the catheter which increase the penetration of a thrombolytic agent into the thrombus.[11] The EkoSonic™ endovascular system (EKOS) provides the efficacy of systemic lithics by reducing the RV afterload rapidly and improving RV size and function, but with a lower risk profile comparable to anticoagulants alone.

In this study, we aimed to evaluate the efficacy and the safety of the EKOS applications in patients hospitalized with intermediate-high-risk PE.

PATIENTS AND METHODS

Between January 2018 and March 2019, a total of 15 patients (7 males, 8 females; mean age 64.7±17.8 years, range, 35 to 90 years) admitted to the Department of Pulmonology of Sultan 2. Abdülhamid Han Training and Research Hospital with the diagnosis of intermediate-high-risk PE were retrospectively analyzed. The diagnosis of PE was made based on pulmonary computed tomography (CT) angiography in all patients. All patients were evaluated by echocardiography for RVD and serum levels of troponin I and (BNP) were recorded. Risk stratification of the patients with acute PE was done according to the 2019 European Society of Cardiology (ESC) Guidelines on Acute PE.[4] Only patients with intermediate-high-risk PE were included in the study. All patients included in the study had RVD on echocardiography and elevated cardiac biomarker levels (particularly a positive cardiac troponin test). Those with low or high-risk PE were excluded from the study. A written informed consent was obtained from each patient. The study protocol was approved by the Ümraniye Training and Research Hospital Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The RV diameters, PAPs and tricuspid regurgitation, arterial blood gas oxygen saturation (SaO_2) and partial oxygen pressure (PaO_2) values were recorded before and

after the procedure. In addition, complete blood count (CBC), hemoglobin, hematocrit, platelet count, urea, and creatinine values of the patients were evaluated. At the first month of follow-up, these measurements were also recorded. Pulmonary embolism and deep venous thrombosis (DVT) localization were examined. Complications related to the procedure were evaluated. The additional procedures were also recorded after the EKOS application.

Patients with intermediate-high-risk PE were transferred from the pulmonology department where they were hospitalized to the cardiovascular surgery department. They were treated using the EKOS (EKOS Corp., Bothell, WA, USA). The EKOS consists of three components: an intelligent drug delivery catheter (IDDC), a removable Micro Sonic Device containing multiple small ultrasound transducers distributed over the treatment zone, and the EKOS control unit. The patients were processed in the hybrid operating room of Sultan 2. Abdulhamid Han Training and Research Hospital Cardiovascular Surgery Department. Lower extremity venous system mapping was performed with ultrasound before the procedure. The patients were monitored for invasive arterial blood pressure, cardiac rhythm, pulse rate, and oxygen saturation. Pulmonary artery angiography was performed by placing the 6F sheath to the main femoral vein by the Seldinger method from non-DVT extremity with venous system mapping and advancement of the pigtail catheter to the RV. The localization of PE and pulmonary artery structure were confirmed. The USAT catheter was advanced to the PE site over 0.035 guidewire. 2 mg bolus alteplase was administered to patients with a low bleeding risk and 1 mg bolus alteplase to patients with a high bleeding risk. The patients were, then, transferred to the cardiovascular surgery third level intensive care unit (ICU). Ultrasound waves at a frequency of 2 MHz and alteplase infusion at a rate of 1 mg/h for 24 h for patients with a low bleeding risk and 0.5 mg/h for 24 h for patients with a high bleeding risk were applied to the embolism by the USAT catheter in ICU. Saline coolant infusion of 35 mL/h for 24 h was also used during the procedure. At the end of the procedure, the catheter was removed. Patients who did not develop an early complication were kept under observation for one or two days in the pulmonology department of the hospital. Patients who were treated with anticoagulants during this period were discharged.

Statistical analysis

Statistical analysis was performed using the PSPP Free version 3 (GNU General Public License) and Microsoft Excel computer programs (Microsoft Inc., Redmond, WA, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency. The normality distribution was analyzed using the Kolmogorov-Smirnov test. Since the data were suitable for normal distribution, t-test was used in dependent groups. A p value of <0.05 was considered statistically significant with 95 confidence interval (CI).

RESULTS

Of the patients, 80% had no malignancy and 20% had malignancy. One patient (6.67%) had a history of coronary artery bypass grafting and four patients (26.67%) had a history of trauma. All patients (100%) were suffering from dyspnea. Three patients (20%) reported palpitations and one patient (6.67%) reported syncope. Pulmonary CT angiography showed bilateral PE localization in 73.3% of the patients, 13.3% on the right, and 13.3% on the left. Deep venous thrombosis was detected in 53.3% of the patients. Bilateral peroneal vein was found in 6.67% of the patients, 13.33% were in the right common femoral vein (CFV), 13.33% were

Table 1. Pulmonary embolism and deep venous thrombosis localizations

Localization	n	%
Pulmonary embolism		
Bilateral	11	73.33
Right	2	13.33
Left	2	13.33
Deep venous thrombosis		
Bilateral peroneal vein	1	6.67
Right common femoral vein	2	13.33
Right superficial femoral vein	2	13.33
Left common femoral vein	1	6.67
Left superficial femoral vein	2	13.33
No	7	46.67

Table 2. Complications and additional procedures

	n	%
Complication		
Yes	1	6.67
No	14	93.33
Additional procedure		
Inferior vena cava filter	1	6.67
No	14	93.33

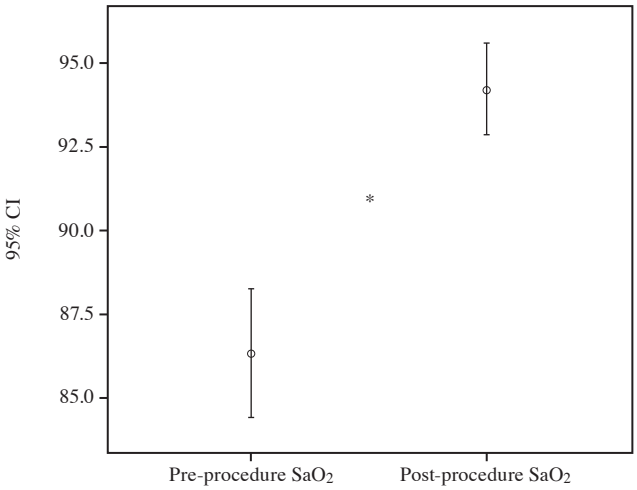

Figure 1. Mean values of arterial blood gas oxygen saturation (SaO2) before and after the procedure.

* Statistically significant (p<0.05; paired samples t-test).

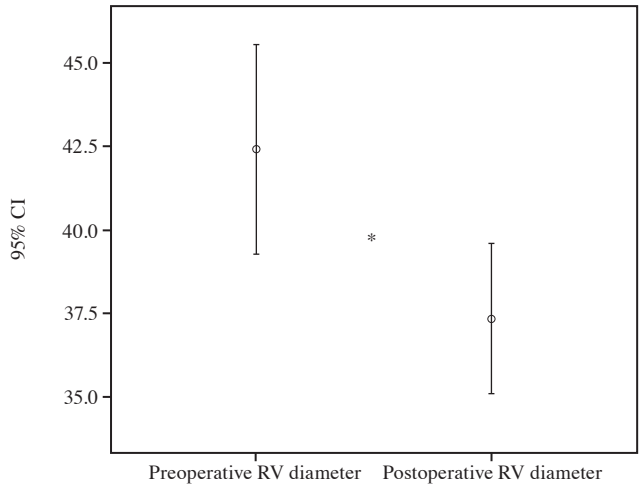

Figure 2. Mean diameters of right ventricle before and after the procedure.

* Statistically significant (p<0.05; paired samples t-test).

in the right superficial femoral vein (SFV), CFV was present in 6.67% of the patients, and 13.33% were in the left SFV (Table 1). Complications were not observed in 93.75% of the patients after the procedure. A pulmonary hematoma was found in one patient (6.6%). After USAT, one patient (6.6%) underwent a vena cava filter as an additional procedure. No patient had bradycardia during the procedure (Table 2).

The mean SaO_2 values of the patients before and after the procedure were 86.3±3.5% and 94.2±2.5%, respectively. The change before and after the procedure was statistically significant (p=0.001) (Figure 1). The mean PaO_2 values before and after USAT were 73.3±7.7 mmHg and 90.7±5.0 mmHg, respectively. The change before and after the procedure was statistically significant (p=0.001). There was no statistically significant difference in the number of white blood cells, hemoglobin, platelet, urea, and creatinine levels measured before and after the procedure (p>0.05). The mean hematocrit value of the patients before and after USAT was 34.5±5.5% and 31.1±4.7%, respectively. The change before and after the procedure was statistically significant (p=0.017). The mean preoperative RV diameter was 42.4±5.7 mm and the postoperative RV diameter was 37.3±4.1 mm, indicating a statistically significant difference (p=0.001) (Figure 2). The mean

Table 3. Evaluation of laboratory variables before and after the procedure

	Before	After	
	Mean±SD	Mean±SD	*p*
SaO_2 (%)	86.3±3.5	94.2±2.5	0.0001
PaO_2 (mmHg)	73.3±7.7	90.7±5.0	0.0001
Right ventricle diameter (mm)	42.4±5.7	37.3±4.06	0.0001
Pulmonary arterial pressure (mmHg)	44±7.1	36.3±4.5	0.0001
White blood cell ($10^3/\mu L$)	9.1±3.8	9.3±2.9	0.8200
Hemoglobin (g/dL)	11.2±1.7	10.2±1.8	0.0590
Hematocrit (%)	34.5±5.5	31.1±4.7	0.0170
Platelet ($10^3/\mu L$)	216.7±72.0	237.9±74.8	0.3650
Urea (mg/dL)	42.4±5.7	40.6±20.1	0.0550
Creatinine (mg/dL)	1.1±0.3	1±0.3	0.0650

SaO_2: Arterial blood oxygen saturation; PaO_2: Arterial blood oxygen partial pressure.

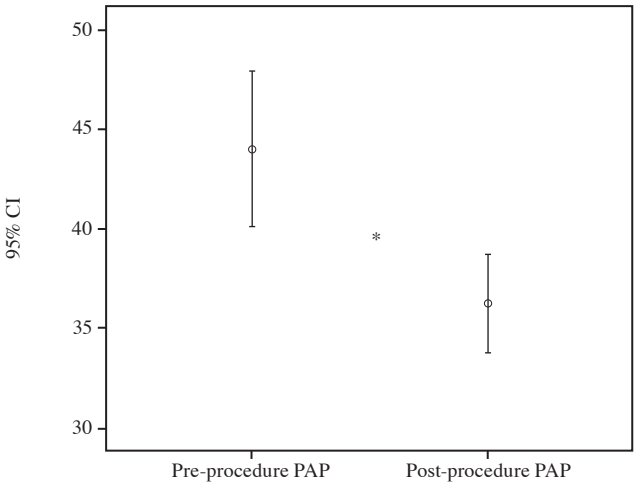

Figure 3. Mean pressure of pulmonary artery before and after the procedure.

PAP: Pulmonary arterial pressure; * Statistically significant ($p<0.05$; paired samples t-test).

preoperative PAP was 44±7.1 mmHg and the mean postoperative PAP was 36.3±4.5 mmHg, indicating a statistically significant difference (p=0.001) (Table 3, Figure 3).

DISCUSSION

The main goals of reperfusion therapy are to improve right heart hemodynamics by eliminating thrombi in the major pulmonary arteries, to achieve RV recovery, to improve oxygenation by eliminating ventilation/perfusion (V/P) mismatch, to improve symptoms, and to reduce mortality.[12] In our study, we observed a decrease in the RV size, improvement in function, decrease in PAP, and increase in oxygenation in the early period after USAT application.

In the Ultrasound Accelerated Thrombolysis of Pulmonary Embolism (ULTIMA) study, 59 patients were treated with either USAT or UFH. The decrease in the RV/left ventricle (RV/LV) ratio in the USAT group was significantly higher than in the UFH group. At the same time, no major hemorrhage was detected, transient hemoptysis was detected in two patients who underwent USAT and one patient had a groin hematoma.[13] Similarly, in our study, decreases in the RV size and in PAP, an increase in oxygenation were observed. In the Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism (OPTALYSE PE) study, 101 patients underwent thrombolytic therapy with USAT at different doses and durations, and four major hemorrhages were reported.[14] It is not possible to conclude that USAT is effective and safe from our study due to small sample size; however, a lung hematoma was developed only in one patient.

In the Submassive and Massive Pulmonary Embolism Treatment with Ultrasound Accelerated Thrombolysis Therapy (SEATTLE II) study, 119 patients with an intermediate-high-risk PE and 31 patients with high-risk PE underwent USAT.[15] There was a statistically significant decrease in the RV/LV ratio and PAP within 48 h. One patient Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) -defined severe bleeding (transient hypotension-associated groin hematoma) and 15 patients had GUSTO-defined moderate bleeding. No intracranial hemorrhage was detected.[15] In the SEATTLE II sub-analysis study, it was emphasized that elderly patients had higher PE-related mortality and less systemic thrombolytic therapy, compared to younger patients.[16] When patients over 65 years and below 65 years were compared, there was no significant difference between the decrease in the RV/LV ratios after the procedure and in major bleeding rates after 72 h.[16] Although this study did not compare USAT with the systemic thrombolytic group, the results that support the safety and efficacy of USAT were observed.

McCabe et al.[17] found that the rates of PAP and RV/LV were significantly lower after the procedure in the study of 53 patients who underwent USAT. Bleeding developed in five patients (9.4%) and, in one patient (1.8%), the USAT procedure was stopped early and no blood transfusion or interventional procedure was required. Similarly, in a retrospective study of 45 patients with intermediate-high-risk PE, a decrease in PAP and improvement in RVD were statistically significant in 30-day follow-up after USAT.[18] Complications revealed minor bleeding in four patients and major bleeding in two patients at the sites of entry.[18] In these two studies, PAP reduction and correction of RVD were similar to the results of our study.

In a study, there was no significant difference in thrombus resolution between the USAT and standard catheter-directed thrombolysis (CDT) performed in acute DVT.[19] In a recent retrospective study of PE, USAT and CDT were compared and PAP reduction, RV/LV ratio, ICU stay, and bleeding rates were similar.[20] In the Paced Electrocardiogram Requiring Fast Emergent Coronary Therapy (PERFECT) study, PAP changes were similar in patients who underwent USAT and CDT for massive and submassive PE, but there was no significant comparison in the improvement of RVD.[21]

In a retrospective study of 63 patients, no significant difference was found between USAT and CDT in terms of all clinical and hemodynamic parameters, mortality, and procedural complications at three-month and one-year follow-up.[22] Prospective studies on the differences between standard CDT and USAT, such as Standard versus Ultrasound-assisted Catheter Thrombolysis for Submassive Pulmonary Embolism (UltraStar sPE) and Standard versus ultrasound-assisted catheter thrombolysis for submassive pulmonary embolism (SUNSET sPE) are ongoing.[23,24]

In a retrospective study by Sharifi et al.,[25] USAT was compared with half-dose thrombolytic therapy in intermediate-high-risk PE patients. There was no superiority between the two groups in terms of decreased PAP and RV/LV ratios, although hospitalization time and cost of hospitalization were significantly lower in the half-dose thrombolytic group. In addition, there were no statistically significant differences in the bleeding rates. There were two deaths and three patients required transfusion in the USAT group, while there was neither death nor bleeding in the half-dose thrombolytic group. However, this study should be supported by prospective studies to eliminate the current confusion in the choice of treatment in patients with intermediate-high-risk PE. The limitations of the study were that there was no control group as in the SEATTLE II study. Therefore, no comparison was able to be made with conventional catheter-guided techniques and systemic thrombolytic therapies. Secondly, patients were not evaluated for RVD, CTEPH, and residual dyspnea during long-term follow-up due to the lack of long-term follow-up data. Thirdly, the sample size was relatively small and the study was retrospective in nature. The results of EKOS in patients with high-risk and intermediate-high-risk PE were analyzed retrospectively in another study including Turkish patients.[26] The authors found that USAT achieved thrombus resolution and hemodynamic healing in both high-risk and intermediate-high-risk PE patients. The complications related to the procedure were acceptable.

Pulmonary embolectomy and EKOS are treatment alternatives for selected patients with intermediate-high-risk PE who are not suitable for medical therapy.[27] A multidisciplinary approach is needed to tailor the most appropriate treatment option. Surgical pulmonary embolectomy is recommended for patients with high-risk PE in whom thrombolysis is contraindicated or has failed according to the ESC guidelines.[4] The patients with high-risk (17.8%) or intermediate-high-risk (82.2%) PE who underwent surgical embolectomy were evaluated retrospectively.[28] The mortality rate in the hospital was between 11.7% and 32.1% for the patients experiencing preoperative cardiac arrest.

The main limitations of the study are its retrospective nature, relatively small sample size, relatively short follow-up period, and lack of a comparative arm. Therefore, the findings of our study should be confirmed with larger and longer comparative, prospective studies.

In conclusion, ultrasound-accelerated thrombolysis improved right ventricular dysfunction, decreased pulmonary arterial pressure, and improved oxygenation in intermediate-high-risk pulmonary embolism patients in our study. One patient developed a lung hematoma as a side effect, and one patient received an inferior vena cava filter. None of the patients required transfusion. Based on these results, we can speculate that ultrasound-accelerated thrombolysis may be an effective treatment in correcting right ventricular dysfunction in patients with intermediate-high-risk pulmonary embolism without increasing the risk for bleeding. Nevertheless, further large-scale, prospective, randomized-controlled studies are needed to confirm these findings.

Declaration of conflicting interests

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