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Retrospective evaluation of two different thrombolytic agents in the treatment of patients with massive pulmonary embolism: Alteplase vs reteplase

Masif pulmoner emboli hastalarında trombolitik ajan olarak kullanılan alteplaz ve reteplazın klinik etkinliğinin retrospektif değerlendirilmesi

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ABSTRACT

Aim: To compare clinical effectiveness of reteplase and alteplase in patients with massive pulmonary embolism.

Material and Methods: Between 2010 and 2016 all patients treated with one of the thrombolytic agents, alteplase or reteplase, for massive pulmonary embolism were eligible for the study. We compared demographic data, hemodynamic parameters at baseline and at 2th, 4th, 6th, 12th, 24th hours after thrombolysis, the early and 1 year mortality rates and bleeding complications between two groups.

Results: Seventy five patients (32 alteplase and 43 reteplase) were included study. Mean age was 64.2±13.6 years. Compared to the baseline values, hemodynamic parameters improved significantly at 2th, 4th, 6th, 12th and 24th hours after thrombolysis in both groups. In alteplase group, systolic blood pressure between baseline and at 6th and 12th hours altered significantly when compared with reteplase group. No significant difference was found in mortality rates and major bleeding events between groups. Minor bleeding events were higher in alteplase group than reteplase group, 28.1% vs 2.3%, respectively and the difference was significant.

Conclusion: Reteplase seems as safe and effective as alteplase in the thrombolytic treatment of patients with massive pulmonary embolism.

Keywords: Alteplase, pulmonary embolism, reteplase, tissue plasminogen activator, thrombolysis

ÖZ

Amaç: Masif pulmoner emboli hastalarında alteplaz ve reteplazın klinik etkinliğinin karşılaştırılması.

Gereç ve Yöntemler: 2010-2016 yılları arasında masif pulmoner emboli nedeniyle trombolitik tedavi olarak alteplaz ya da reteplaz verilen tüm hastalar çalışmaya alındı. Demografik veriler, bazal, 2., 4., 6., 12., ve 24. saatteki hemodinamik parametreler, erken ve geç mortalite ile kanama komplikasyonları karşılaştırıldı.

Bulgular: Yaş ortalaması 64.2±13.6 yıl olan toplam 75 hasta, (32 alteplaz, 43 reteplaz) çalışmaya alındı. Her iki grupta da hemodinamik parametrelerde anlamlı düzelme saptandı. Sistolik kan basıncında bazal değerlere göre 6. ve 12. saatlerdeki artış alteplaz grubunda reteplaz grubundan anlamlı olarak daha yüksek bulundu. Mortalite ve majör kanama her iki grupta da benzer bulundu. Minör kanama ise alteplaz grubunda reteplaz grubuna göre anlamlı olarak daha yüksek saptandı, sırasıyla %28,1 vs %2,3.

Sonuç: Masif pulmoner emboli hastalarında trombolitik tedavide reteplaz, alteplaz kadar etkin ve güvenli görünmektedir.

Anahtar Kelimeler: Alteplaz, doku plazminojen aktivatörü, pulmoner emboli, reteplaz trombolizis

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Highlights

- Systemic thrombolysis provides more rapid clot lysis and faster restoration of pulmonary perfusion.
- Minor bleeding events were significantly higher in the alteplase group.
- Mortality and major bleeding events were similar.
- Improvement in hemodynamic parameters was similar.
- Reteplase seems as safe and effective as alteplase.

INTRODUCTION

Acute pulmonary embolism (PE) is the most serious clinical presentation of venous thromboembolism and is one of the most important cause of mortality, morbidity and hospitalization (1). PE is associated with more than 300000 deaths per year in Europe and United States (2,3). Right-sided heart failure is the primary cause of death in fatal PE whether it is potentially reversible if emergency management is effective (4-6). In all patients with high clinical suspicion of PE, anticoagulation therapy with unfractionated heparin or low-molecular-weight heparins, should be initiated as soon as possible (5). Systemic thrombolytic therapy is recommended in patients with acute PE who develop hypotension and are not at risk of bleeding (6). Systemic thrombolysis provides more rapid clot lysis and faster restoration of pulmonary perfusion, reduction of pulmonary vascular bed obstruction and improvement in right ventricle (RV) functions more rapidly than anticoagulation alone (1,4,7). These effects are faster than heparin at 24 hours but by 7 days, blood flow improves similarly and mortality rates did not differ significantly (8).

At the present, first generation thrombolytic agents, streptokinase, urokinase and second generation thrombolytic, tissue plasminogen activator (tPA), alteplase, have been approved by U.S. Food and Drug Administration for the treatment of acute PE whereas, reteplase and tenecteplase have not been yet (9).

In our clinical practice we use alteplase or reteplase for the treatment of PE due to availability of them in hospital pharmacy. In this retrospective study, we aimed to compare the effect of two different thrombolytic agents, alteplase and reteplase, on the hemodynamic parameters, bleeding complications and mortality rates in patients with massive PE.

MATERIAL and METHODS

Hospital automation system was used to detect the patients who were discharged with a diagnosis of International Statistical Classification of Diseases, I26.0–I26.9, (PE). Patients diagnosed as PE with a high probability ventilation perfusion scintigraphy or computed tomography pulmonary angiography (CTPA) and given thrombolytic therapy were eligible for the study. Demographic data including age, gender, presence of comorbidity, arterial blood gases, echocardiography and laboratory findings (complete blood count, serum d-dimer, troponin I or T, brain natriuretic peptide (BNP), N terminal pro-BNP if available) were recorded. RV dysfunction described as the presence of at least one of the following criteria: 1. Dilatation or systolic dysfunction of RV on echocardiography, 2. RV dilatation on CTPA, 3. Elevation of BNP or N-terminal pro-BNP, 4. Electrocardiographic changes (10). Baseline shock index (heart rate divided systolic blood pressure) and simplified PE Severity Index (sPESI) scores were calculated in all patients. The sPESI includes the variables of age, presence of cancer or chronic cardiopulmonary disease, heart rate (>110 beats/min), systolic blood pressure (<100 mm Hg), and oxyhemoglobin saturation level (<90%) (11). A shock index ≥1 or sPESI score of 1 or more have been showed to be independent predictors of 30-day mortality in patients with acute PE (6,11,12).

Hemodynamic parameters (heart rate, systolic and diastolic blood pressures, arterial saturation of oxygen, respiratory rate) at baseline (before thrombolysis) and at the 2nd, 4th, 6th, 12th and 24th hours after thrombolysis were retrieved from patient charts. Decision of thrombolysis had given individually by clinicians who followed the patients, according to the extent of thrombus in CTPA, hemodynamic parameters (systolic blood pressure, heart rate, arterial oxygen saturation) and RV dysfunction (elevated BNP or N terminal pro-BNP, echocardiography). Alteplase is given in a standard dose of 100 mg over 2 hours intravenous infusion without an accelerated infusion whereas reteplase is given a 10U bolus doses administered 30 minutes apart (10U +10U). Early (in-hospital or 30 days mortality) and 1 year mortality rates were assessed by using hospital records and national death reporting system. Study population divided into two groups as reteplase and alteplase. Mortality and complication rates, improvement in clinical parameters were compared between two groups. Intracranial or retroperitoneal hemorrhage, or the bleeding that requiring surgical control, blood transfusion, or death due to bleeding considered as major hemorrhage (13). Patients with an estimated survival less than 1 year, the patients did not receive full dose of

thrombolytic (100 mg for alteplase and 20 U for reteplase) were excluded. Written informed consents were obtained from all patients before thrombolytic therapy. The study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 19.0 software (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk test was used to assess the distribution of the data. Continuous variables are presented as mean ± standard deviations whereas categorical variables as frequencies and percentages. The Pearson Chi-squared or Fisher's exact chi-square tests were used to determine for difference between groups for categorical variables. Continuous variables were compared between two groups using by the independent sample t test or the Mann–Whitney U-test. Repeated measures were compared with paired t-test or Wilcoxon signed ranks test if the data were not normally distributed. Binary logistic regression analyse was performed to determine the independent predictors of bleeding events. A p-value < 0.05 was considered to indicate significance for all tests.

RESULTS

Seventy-eight patients received thrombolytic therapy during the study period. One patient (terminal stage lung cancer) and 2 patients who were not given full dose thrombolytic (in one patient 50 mg alteplase and the other 10 IU reteplase) were excluded. Finally a total of 75 patients, 40 (53.4%) female, 35 (46.6%) male, mean age 64.2±13.6 (ranged between 35-88) years, were included the study. Twenty-two patients (42.7%) received alteplase, 43 patients (57.3%) received reteplase. Mean age, gender, presence of comorbidity, shock index, sPESI scores, hematological parameters and vital signs were similar between groups (Table 1). Only the respiratory rate at admission was significantly higher in reteplase group than alteplase. Serum D-dimer levels were positive in all patients whereas cardiac biomarkers were found positive in 75% of the patients. All patients had RV dysfunction that was assessed by echocardiography and elevated BNP or N terminal pro BNP. Mortality rates were similar between groups (Table 2). Two patients developed fever ≥38°C after the administration of thrombolytic agent (one patient in reteplase and one patient in alteplase group). In a patient received reteplase (2.3%), hemoglobin values dropped to 4.5 g/dL after thrombolysis and required blood transfusion thus considered as major bleeding event. Minor bleeding events were significantly higher in alteplase group when compared reteplase group (Table 2). Overall proportion of patients experiencing at least one bleeding event was 14.6%. Binary logistic regression analysis was performed to determine the independent predictors of bleeding complication in both groups. When age, gender, platelet count, thrombolytic agent, sPESI scores were included to regression model, only the cofactor, thrombolytic agent (alteplase), remained significant with an odds ratio of 6.9 for the bleeding event (Table 3). Systolic blood pressure, heart rate, respiratory rate and arterial oxygen saturation improved significantly when compared to baseline values. The mean absolute difference in systolic blood pressure between baseline and 6th and 12th hours were significantly higher in alteplase group than reteplase group (Table 4).

Table 1: Demographic data of patients with pulmonary embolism

Variables	Alteplase (n=32)	Reteplase (n=43)	p
Age, years	61.7±12	66.1±13	0.089
Gender, male, n (%)	12 (37.5)	23 (53.4)	0.127
Shock index*	0.95±0.2	0.87±0.2	0.106
Hemoglobin, g/dL	12.7±1.9	12.5±1.7	0.739
Hematocrit, %	37.8±6	37.6±4.9	0.903
Platelet count $10^3/\mu L$	249±105	245±88	0.849
sPESI ≥1, n (%)	27 (84.3)	34 (75)	0.392
Arterial blood gases (missing: 3)			
pH	7.47±0.05	7.45±0.04	0.367
pO_2, mmHg	56.4±14.1	53.4±13.1	0.087
pCO_2, mmHg	29.9±12.6	37±22.3	0.084
Sat O_2, %	89.3±8.1	90±6.2	0.651
Vital signs			
SBP, mmHg	112.1±17.9	120.8±18.3	0.098
DBP, mmHg	69.7±12.1	74.2±13.3	0.133
Heart rate, bpm	105±20	103.2±18.5	0.692
SO_2	90.7±5.1	92.1±3.9	0.172
RR, per minute	26.4±6.6	23.4±5.6	0.044
Comorbidities			
CVD, n (%)	5 (15.6)	10 (23.2)	0.454
CPD, n(%)	3 (9.3)	2 (4.5)	0.426
DM, n (%)	11 (34.4)	15 (34.9)	0.518
Cancer, n (%)	3 (9.4)	2 (4.7)	0.364

Data are expressed as mean ± standard deviation, ***:** heart rate divided systolic blood pressure, **sPESI:** Simplified Pulmonary Embolism Severity Index, **CVD:** Cardiovascular disease (coronary artery diseases and/or congestive heart failure), **CPD:** Chronic pulmonary diseases (chronic obstructive pulmonary disease, interstitial lung-diseases, asthma) **DM:** Diabetes Mellitus

Table 2: Baseline laboratory and echocardiographic features and outcomes of study groups

Parameters	Alteplase	Reteplase	p
Cardiac biomarker* n (%)			
Positive	18 (75)	33 (76)	0.371
Negative	6 (25)	4 (24)	0.251
D-dimer n (%)			
Positive	27 (84.4)	39 (91.7)	0.145
Echocardiography			
Right-sided failure** n (%)	32 (100)	43 (100)	0.153
EF %	59.1±4.2	58.1±3.7	0.294
sPAB mmHg	60.8±17	64.3±15.2	0.358
Mortality n (%)			
Early***	2 (6.25)	6 (9.3)	0.316
1 year	5 (15.6)	2 (4.6)	0.252
Bleeding event**** n (%)			
Minor	9 (28.1)	1 (2.3)	0.002
Major	0	1 (2.3)	0.573

EF: ejection fraction, **sPAB:** systolic pulmonary arterial pressure, p value belongs to the relevant row.
*: positivity of at least one of following biomarkers, troponin I or T, brain natriuretic peptid (BNP) or N terminal pro BNP.
**: Dilatation of right ventricule and/or paradoxal movement of interatrial septum and/or tricuspide regurgitation.
***: in hospital or 30 days mortality.
****: Intracranial bleeding, or bleeding that needs surgical intervention or blood transfusion or an event resulted with death.
Minor bleeding events include: Hematuria 2 patients, hemoptysis 2 patients, hematoma in triceps muscle in 3 patients, leak from injection sites and incision site in 2 patients that had a recent operation history.

Table 3: Logistic regression analyse to show independent predictors of bleeding events in patients with pulmonary embolism

Covariate	OR	95% Confidence Interval	
		Lower	Upper
Age	0.980	0.930	1.033
Gender	0.648	0.955	2.901
sPESI	0.962	0.923	2.147
Trombolytic agent (alteplase)	6.971	1.263	37.964
Platelet count	0.997	0.987	1.007

sPESI: simplified Pulmonary Embolism Severity Index.Binary logistic regression analyse: Only the cofactor, thrombolytic agent (alteplase), remained significant with an odds ratio of 6.9 for the bleeding event.

DISCUSSION

This retrospective study showed that, reteplase seems as effective and safe compared to alteplase in the thrombolytic treatment of patients with PE. Improvement in the hemodynamic parameters, mortality rates and major hemorrhagic complications were similar between two groups whereas minor bleeding events were significantly higher in alteplase group.

Thrombolytic agents convert circulating inactive proenzyme plasminogen to plasmin which hydrolyzes and degrades the fibrin matrix and results with clot lysis (1,14,15). Activity of thrombolytic agents is highly dependent on binding to fibrin which results with larger rates of clot-bound plasmin production and more targeted clot-specific fibrinolysis. Therefore, these drugs are less effective on circulating plasminogen and do not significantly alter unbound plasmin production or affect systemic thrombolysis in the absence of fibrin (16). The most common used fibrinolytics are unmodified form of human tPA, alteplase, and modified form of human tPA, reteplase and tenecteplase. Reteplase, penetrates into the clot and preferentially activates fibrin-bound plasminogen rather than fluid-phase plasminogen whereas alteplase accumulates on the surface of clot. Thus the thrombolysis produced by reteplase was found more rapid, complete and stable compared to alteplase infusion in acute myocardial infarction (MI) (17). Reteplase has been shown to be more effective than alteplase in experimental studies with a rabbit model of jugular vein thrombosis and a canine model of coronary artery thrombosis (18). The recommended dose of reteplase in acute MI is 10 U bolus given twice, 30 minutes apart. Reteplase is approved as a thrombolytic agent in patients with acute MI (19).

In English literature we were able to found only one randomised controlled trial (RCT) that compared reteplase and alteplase in the treatment of PE (20). Also there were a few case reports which reteplase was used successfully for thrombolysis in patients with PE (21-23).

In the present study, the improvement in the hemodynamic parameters in patients with PE received thrombolytic therapy, alteplase or reteplase, were assessed and compared. In both groups, except diastolic blood pressure, hemodynamic parameters improved significantly according to baseline values. Only the mean difference between baseline systolic and diastolic blood pressures and the values at 6th and 12th hours were singinificantly higher in alteplase group than reteplase group. This may be appeared because of the shorter plasma half life of alteplase than reteplase, 3–4 minutes versus 14–18 minutes, respectively (18). In a RCT (20) which included a total of 36 patients (23 reteplase and 13 alteplase), reteplase was given 10 IU two apart in 30 min (total 20 IU) and alteplase a total of 100 mg doses in 90 min infusion. In both groups total pulmonary resistance and mean pulmonary arterial pressure decreased significantly but were not significantly different between groups. In both of the groups, significant improvement in hemodynamic paremeters, decrease in heart rate and increase in arterial

Table 4: Clinical parameters of patients with pulmonary embolism before and after thrombolytic therapy

Variable		Absolute change			% of change		
		Alteplase	Reteplase	p	Alteplase	Reteplase	p
SBP mmHg	Δ_2	6.1±15.3	6.7±14.2	0.215	3.8±11.8	3.8±9.6	0.242
	Δ_4	9.1±16.2	9.9±16.5	0.533	5.3±15.9	4.9±14	0.331
	Δ_6	14.1±16.3	14.4±16.9	0.001	1.9±12.1	2.5±10.4	0.061
	Δ_{12}	13.2±21.8	14.6±22.9	0.011	1.1±15.4	0.5±13.2	0.082
	Δ_{24}	6.8±22.6	9.1±23.2	0.208	0.7±21.9	1.6±17.2	0.546
DBP mmHg	Δ_2	2.3±13.5	4.8±19.9	0.379	0.34±9.4	0.44±13.3	0.841
	Δ_4	1.6±11.4	4.7±19.1	0.827	1.1±11.2	3.1±16.1	0135
	Δ_6	6.1±14.8	11.6±25.1	0.039	0.3±11.8	1.3±16.3	0.171
	Δ_{12}	3.6±12.8	7.7±21.8	0.046	2.6±11.8	1.2±20.4	0.168
	Δ_{24}	3.2±17.7	8.6±29.1	0.158	2.4±15.3	1.3±20.5	0.365
Heart rate bpm	Δ_2	11.1±16.5	9.1±13.7	0.881	9.7±12.7	8.9±12.1	0.256
	Δ_4	12.8±17.1	10.4±14.8	0.731	10.1±12.6	9.2±12.2	0.741
	Δ_6	12.1±16.9	9.9±13.9	0.312	14.2±13.6	12.7±11.6	0.236
	Δ_{12}	13.3±15.4	11.2±13.6	0.743	13.8±14.3	12.7±12.2	0.452
	Δ_{24}	12.3±14.5	10.4±12.2	0.244	16.7±18.3	15.1±17.3	0.632
Respiratory Rate per minute	Δ_2	0.7±6.5	0.2±4.3	0.600	0.4±21.1	1.4±18.6	0.147
	Δ_4	1.6±5.5	1.1±4.2	0.882	4.9±19.7	2.9±19.4	0.476
	Δ_6	2.9±5.8	1.5±4.1	0.307	8.3±19.3	4.5±17.3	0.398
	Δ_{12}	2.9±6.4	2.1±4.5	0.747	8.1±20.1	6.2±18.8	0.875
	Δ_{24}	3.3±5.3	2.1±3.9	0.520	9.9±15.5	6.8±14.6	0.159
SO_2 %	Δ_2	4.1±4.9	1.9±2.9	0.069	4.8±5.7	2.1±3.2	0.125
	Δ_4	4.2±4.4	2.2±3.3	0.091	4.9±5.2	2.5±3.7	0.105
	Δ_6	4.3±5.1	2.4±3.7	0.218	5.1±6.1	2.7±10.4	0.368
	Δ_{12}	4.8±4.6	2.8±3.1	0.072	5.6±5.5	3.2±3.4	0.589
	Δ_{24}	4.6±5.6	2.3±3.4	0.129	5.4±6.6	2.4±3.8	0.098

SBP: systolic blood pressures, **DBP:** diastolic blood pressures. Values were given as mean of absolute difference between two variables and % of change. Δ_2, Δ_4, Δ_6, Δ_{12}, Δ_{24} mean differences between baseline and the after thrombolytic therapy at 2nd, 4th, 6th, 12th and 24th hours, respectively. p values belong to the relevant row.

oxygen saturation were observed whereas no consistent change in respiratory rate, systolic or diastolic blood pressure was observed (20).

In the present study, early all cause mortality and 1 year mortality rates were 10.6% and 20%, respectively. Mortality rates were similar between groups. Similarly, Tebbe et al. (20) did not found significant difference in patients with PE treated with alteplase or reteplase in terms of early mortality rate. In the literature a wide range of mortality rates has been reported in patients with PE received thrombolytic therapy. Several studies and meta-analysis, reported different mortality rates ranging between 2.2%-30%, in patients with PE (7,20,24,25). In a recent study, İpek et al. assessed the effectiveness of thrombolytic therapy in elderly patients (age ≥ 65 years) and reported that 1 year mortality rate was 10.2% in patients received alteplase (26).

The most common complication of thrombolytic therapy is hemorrhage. The most common site of hemorrhage is catheter insertion site especially in patients who were used invasive imaging methods such as pulmonary angiography for diagnostic work-up (1,27). Advanced age and the presence of comorbidities have been found to be associated with a higher risk of bleeding. The most serious complication is intracranial hemorrhage, reported to be between 0.2 and 3% in large trials of recipients (1,28,29). The incidence of major life threatening bleeding has been found 7.8%-12.9% (10,24). Meta analyses showed major bleeding risk is nearly three-fold higher in thrombolytic therapy than heparin with no reduction in all-cause mortality (7,29).

In the present study, one patient who received reteplase treatment experienced major bleeding event. Hemoglobin concentration dropped 4.5 g/dL and required blood tranfusion. Intracranial hemorrhage was not occurred neither in reteplase group nor in alteplase group. Minor bleeding events (hemoptysis, hematuria, bleeding from injection site) were significantly higher in alteplase group than reteplase group. The fact that reteplase is less effective on aged clots and preserves hemostatic plaques may explain its fewer bleeding complications (17).

In a study, Grunwald and Hofmann (30) compared catheter directed thrombolysis with, alteplase, reteplase and urokinase in VTE and found that major and minor bleeding events rates were not statistically different among groups, 5.3%, 3.1% and 8.3%, respectively, and 5.3%, 9.4%, and 8.3 respectively. In a recent review major bleeding was found 0%-20.6% and intracranial bleeding was found 0%-7.4% in patient received alteplase (31).

The number of patients treated with reteplase for acute MI who experienced at least one bleeding episode was similar to that of patients receiving other thrombolytic agents. In large trials, complications such as intracranial hemorrhage and hemorrhagic stroke were found to be similar in patients receiving reteplase and alteplase (17). In a review by Simpson et al. (14) demonstrated that in patients with acute MI received reteplase or alteplase, the proportion of the patients experienced at least one bleeding event was found 30.5%-47.4% for reteplase and 30.8%-47.9 for alteplase.

Our study had some limitations. First, the retrospective design of the study resulted with missing values in a few patients. Small study population was another limitation. Ideally the study should be designed prospectively in a larger cohort. Also the lack of control echocardiographic evalution of patients after thrombolytic therapy was another limitation. Effect of thrombolytic therapy was assessed only improvement of vital signs within first 24 hours and mortality rates. Also recurrence of PE, echocardiographic evaluation and arterial blood gases should be assessed. Despite all of the these limitations the present study carries an importance because of reflecting the real life experience.

Conclusion

Reteplase seems as effective and safe compared to alteplase in the thrombolytic treatment of patients with PE. But randomised controlled trials with more patient population are needed.

Author Contributions

Study conception and design: **Hakan Tanrıverdi, Bülent Altınsoy, Ayşegül Tomruk Erdem, Meltem Tor,** data collection: **Hakan Tanrıverdi, Bülent Altınsoy, Ayşegül Tomruk Erdem,** analysis or interpretation of results: **Hakan Tanrıverdi, Meltem Tor, Bülent Altınsoy,** draft manuscript preparation **Hakan Tanrıverdi, Bülent Altınsoy, Ayşegül Tomruk Erdem, Meltem Tor.** The authors reviewed the results and approved the final version of the article.

Conflicts of Interest

The authors have no confict of interest to declare.

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Ethical Approval

The study protocol was approved by the Non-Interventional Clinical Researches Ethics Committee of Zonguldak Bülent Ecevit University Faculty of Medicine. (Approval no: 2024/08 and Approval date: April 24th, 2024)

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