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Contribution of fibrinolysis to the physical component summary of the SF-36 after acute submassive pulmonary embolism

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Abstract

Acute pulmonary embolism (PE) can diminish patient quality of life (QoL). The objective was to test whether treatment with tenecteplase has an independent effect on a measurement that reflects QoL in patients with submassive PE. This was a secondary analysis of an 8-center, prospective randomized controlled trial, utilizing multivariate regression to control for predefined predictors of worsened QoL including: age, active malignancy, history of PE or deep venous thrombosis (DVT), recurrent PE or DVT, chronic obstructive pulmonary disease and heart failure. QoL was measured with the physical component summary (PCS) of the SF-36. Analysis included 76 patients (37 randomized to tenecteplase, 39 to placebo). Multivariate regression yielded an equation $f(8, 67)$, $P<0.001$, with $R^2 = 0.303$. Obesity had the largest effect on PCS ($\beta = -8.6$, $P<0.001$), with tenecteplase second ($\beta = 4.73$, $P = 0.056$). After controlling for all interactions, tenecteplase increased the PCS by +5.37 points ($P = 0.027$). In patients without any of the defined comorbidities, the coefficient on the tenecteplase variable was not significant (−0.835, $P = 0.777$). In patients with submassive PE, obesity had the greatest influence on QoL, followed by use of fibrinolysis. Fibrinolysis had a marginal independent effect on patient QoL after controlling for comorbidities, but was not significant in patients without comorbid conditions.

Keywords

Pulmonary embolism; Submassive; Fibrinolysis; Quality of life

Introduction

The effect of acute pulmonary embolism (PE) on patient quality of life (QoL) has been previously studied using both the generic Short Form 36 (SF-36) instrument as well as the more disease-specific pulmonary embolism quality of life (PEmb-QoL) instrument [1, 2]. Klok et al. found that survivors of acute PE have significantly lower QoL scores than age- and sex-adjusted population norms [2]. They also found that age, obesity (BMI>30 kg/m^2), active malignancy and cardiopulmonary comorbidities were associated with worsened QoL after acute PE [2]. However, patient QoL after acute PE remains significantly understudied. Despite the existing knowledge of the negative impact of acute PE on patient QoL outcomes, much debate still remains concerning the treatment of PE, specifically in the use of fibrinolytics in acute submassive PE.

The recent TOPCOAT study demonstrated an increased probability of a good functional composite outcome in patients with submassive PE randomized to treatment with tenecteplase. TOPCOAT used the normalized score on the SF-36 physical component summary (PCS) score as one measurement of the composite functional outcome and identified a score less than two standard deviations below the mean as a poor outcome [3]. However, this trial was terminated early with the resultant possibility for imbalanced randomization and associated bias [4]. The objective of this work was to investigate the effect of fibrinolysis on the PCS score measured in patients with acute submassive PE, using a multivariate linear regression analysis to control for other predictors of poor QoL.

Materials and methods

Overall design

This was a secondary analysis of a multicenter, prospective trial with enrollment occurring at eight academic emergency departments [3]. Inclusion criteria for the original study were as follows: (i) age>17 years; (ii) PE diagnosed on CTPA performed within 24 h; and (iii) normal arterial systolic blood pressure with evidence of RV strain. Exclusion criteria included systolic hypotension (SBP<90 mmHg), inability to walk, contraindications to fibrinolysis, and end-stage conditions. A more detailed methodology of this study has been previously illustrated in a separate publication [5]. This study was approved at each of the Institutional Review boards of participating hospitals and all patients gave written informed consent. This trial was registered NCT00680628.

Quality of life

Patient QoL was measured at follow-up at 90 days using a normalized PCS score, which incorporates scores from the physical function, role physical, bodily pain and general health subscales of the SF-36 [6]. This method of measuring QoL was chosen during the initial planning phase of the original study in 2008. At that time, disease-specific instruments for assessing QoL, such as the PEmb-QoL, had not yet been developed and validated. Therefore, the more generic SF-36 instrument was selected, as it is a tool that has been extensively utilized in clinical research. This survey was administered by trained researchers to patients at a follow-up appointment 90 days from diagnosis of PE.

Statistical analysis

Using methods similar to those described previously, we constructed a multivariate linear regression to test the independent predictive value of treatment with tenecteplase on the outcome variable of PCS score [7]. Predefined independent predictor variables, derived from Klok et al., included in the regression equation were: age (transformed by $\log_e$), obesity (defined as BMI>30 kg/m^2), active malignancy (defined as ongoing care by an oncologist, palliative treatment or metastatic disease), history of PE or DVT, recurrent PE or DVT, chronic obstructive pulmonary disease and congestive heart failure. These predictor variables, identified through patient report, represented specific demographics and comorbid conditions that we expected to influence patient QoL measures based on previously published studies [2]. The primary study question was the marginal contribution of tenecteplase to the PCS score after controlling for all other variables in an average marginal effects model. As a secondary analysis to document magnitude of independent contribution of tenecteplase, we did not set an a priori P value to reject the null hypothesis. Heteroskedasticity-consistent standard errors were calculated to account for non-normality due to small sample size. Statistical analyses were performed using StataSE 13 (College Station, TX).

Results

The original study included 40 patients in the tenecteplase group and 43 in the placebo group. Of these 83 patients, a total of seven patients (three from tenecteplase and four from

placebo) were omitted from this analysis as they either died during initial hospitalization (n = 1 treated with placebo and n = 1 treated with tenecteplase) or were lost to follow-up (n = 2 tenecteplase and n = 3 placebo) and were therefore unavailable to complete the SF-36. The clinical characteristics of study participants are shown in Table 1. This table contains demographic data as well as the specific comorbid conditions included in the multivariate regression equation. Patients in the group randomized to tenecteplase had an average age of 56 (SD of 13, median age = 57). This group had an average BMI of 32.5 kg/m^2 (median = 30.4 kg/m^2) with 54 % defined as obese with a BMI>30 kg/m^2. The placebo group contained patients with an average age of 54 (SD of 15, median age = 52) and mean BMI of 34.2 kg/m^2 (median = 33.6 kg/m^2) with 64 % with a BMI over 30 kg/m^2. The comorbid conditions listed in Table 1 include active malignancy, chronic obstructive pulmonary disease and systolic heart failure. Five patients (14 %) randomized to tenecteplase were reported to have an active malignancy by the explicit definition, compared to zero randomized to placebo. Three placebo patients had COPD (8 %) compared to zero tenecteplase patients. One patient (3 %) in each treatment group had systolic heart failure. Table 1 also includes data on prior history of PE or DVT [five (14 %) of tenecteplase and eight (21 %) of placebo] and recurrent PE or DVT [one (3 %) of tenecteplase and four (10 %) of placebo].

The main outcome investigated in this secondary analysis was the PCS score from the SF-36. The mean PCS score reported from patients randomized to the tenecteplase group was 46.8 (SD 10) compared to 41.6 (SD 13) in the placebo group (between group difference of 5.2 points). Table 2 shows the results from the regression analysis. Multivariate regression with PCS score as the dependent variable yielded an equation $F(8,67)$, $P<0.001$ with an estimated R^2 value of 0.3026, indicating that ~30 % of the variance in the PCS score was explained by the eight predictors. Obesity was found to have the largest effect on PCS score (coefficient of −8.6, $P \leq 0.001$), indicating that obese patients with a BMI over 30 kg/m^2 scored an average of 8.6 points lower on the PCS than their non-obese counterparts. Fibrinolysis had the second most important effect on PCS score. The tenecteplase variable had a coefficient of 4.73 with borderline statistical significance ($P = 0.056$), thus suggesting that the use of tenecteplase versus placebo in patients with acute submassive PE was associated with increased patient QoL at 90 days as measured by the PCS score on the SF-36. After transformation with the natural logarithm, the coefficient for age was 7.61 ($P = 0.083$), indicating that for approximately every 10 % increase in patient age, the PCS score decreased by 7.6 points.

Data were collected for all possible interactions to investigate the effect of tenecteplase when under the influence of each potential combination of comorbid conditions. Table 3 lists the results of the interaction between tenecteplase and the independent predictor variables included in the regression. We could not test for interaction between tenecteplase and malignancy as all patients with active malignancy were randomized to tenecteplase. Similarly, the interaction between tenecteplase and COPD was not assessed as all patients with COPD were randomized to placebo. The interaction with recurrent PE or DVT was found to be significant (coefficient of 16.06, $P = 0.018$). This indicates that the increase in PCS score associated with tenecteplase was 16.06 points greater in patients with recurrent PE or DVT than in patients without recurrent thromboembolism. The interaction with heart

failure was also significant (coefficient of 33.31, P =<0.001), although this result may be unreliable as there was only one heart failure patient in each group. Utilizing an average marginal effects model based on the data gathered from the regression including interaction terms, we were able to determine the effect of tenecteplase after controlling for the effect of all other predictor variables on the tenecteplase coefficient. The coefficient for tenecteplase after controlling for interactions was determined to be 5.37 with P = 0.027, providing further indication of the independent effect of tenecteplase on the PCS score. Because the standard deviation of the normalized PCS score is about ten points, this suggests that a +5.37 point increase equates to approximately a 33 % improvement in patient perception of physical wellness afforded by tenecteplase relative to those receiving placebo [6]. An additional notable finding from the regression plus interactions was the effect of tenecteplase in patients without comorbidities. The coefficient of the tenecteplase variable in patients with no comorbidities was not significant (−0.835, P = 0.777), suggesting no effect of fibrinolysis on QoL in otherwise healthy patients with PE.

Table 4 shows the enrollment features of the patients excluded from analysis because of death in the initial hospitalization period or loss to follow-up. This table was included to investigate whether there existed any imbalance in the predictors utilized in the regression analysis. Seven patients (three in tenecteplase group and four in placebo group) were omitted from this analysis. One patient in each treatment group died. The average age of those omitted from the tenecteplase group was 71 (SD 16) and in the placebo group was 54 (SD 7). The average BMI from those omitted from tenecteplase was 34.1 kg/m^2 (SD 12.6) compared to 31.7 kg/m^2 (SD 5.5) for placebo. One patient in the tenecteplase group had a history of PE/DVT. One patient in the placebo group had a history of systolic heart failure. No patients were omitted from either group with an active malignancy or history of COPD.

Discussion

This study evaluated the relative quantitative contribution of treatment with tenecteplase (fibrinolysis) to a measurement of QoL after acute submassive PE. Obesity had the largest negative independent effect on QoL, reducing the PCS by 8.6 points, when assessed 90 days later. Fibrinolysis was associated with a 5.4-point increase in normalized PCS score and had its greatest positive effect in patients with prior VTE or heart failure. Our findings support previous reports that survivors of acute PE have diminished QoL, and their QoL is further decreased by comorbid conditions. Specifically, work conducted by Klok et al. on a population of 392 patients with a history of acute PE found that these patients had significantly lower QoL on seven subscales of the SF-36 as compared to sex- and age-adjusted Dutch population norms [2]. These differences were most pronounced in the subscales associated with physical role limitation and functioning. A more recent study by J. van Es et al. also demonstrated decreased QoL in survivors of PE, utilizing both the SF-36 as well as the more disease specific PEmb-QOL instrument [1]. To our knowledge, ours is the first study to measure the independent effect of fibrinolytics on patient QoL measures after adjusting for comorbid conditions. Although no data on QoL or long- term follow up were provided in the recently published PEITHO study, the largest randomized controlled trial of thrombolytics in submassive PE to ever be conducted, analysis of functional status and severity of dyspnea after 180 days is planned [8, 9]. These data should provide

additional information on the effect of thrombolytics on QoL and may provide insight on which patients are most likely to benefit from thrombolytic therapy.

The independent predictor variables we chose to include in our regression analysis were based on previously published data identifying specific clinical characteristics including obesity, active malignancy, prior PE and cardiopulmonary comorbid conditions, to be significant predictors of impaired QoL [2]. Results from the multivariate regression equation shown in Table 2 provide additional support for this hypothesis, demonstrating obesity to be a significant independent predictor of reduced PCS scores, having the overall greatest effect of all regression variables on the SF-36, even more so than the use of fibrinolysis. The significant negative effect of obesity on PCS score was not a particularly surprising finding, as obesity has been extensively studied and shown to result in diminished patient QoL across all conditions [10]. However, we were surprised to find the impact of obesity on PCS score to be greater than the impact of treatment with fibrinolysis. Another somewhat surprising finding in the data obtained from our regression plus interactions analysis was that in otherwise healthy patients with none of the comorbid conditions included as our potential confounders, fibrinolysis showed no benefit on patient QoL. However, this finding can be interpreted as consistent with findings from Klok et al., who found comorbid conditions to cause a major decrement in SF-36 scores in patients with PE [2]. Taken together, these findings generally suggest that fibrinolysis in submassive PE has its greatest effect on preventing deterioration in patients likely to have their QoL decreased by PE in association with comorbid conditions, such as recurrent VTE or coexisting heart failure.

This study reports an important novel finding with patient-oriented treatment implications, as it is the first to demonstrate an independent effect on fibrinolysis on a QoL measure in patients with submassive PE. PE has been associated with reduced right ventricular function, persistent dyspnea and lower exercise tolerance [11, 12]. Patients desire to avoid these outcomes. Using the standard gamble technique, Hogg et al. studied perceptions of patients with prior DVT or PE to scripted negative consequences of DVT, PE, gastrointestinal or intracranial hemorrhage [13]. The PE script included a description of persistent dyspnea. These patients rated the PE script worse than the DVT script and similar to gastrointestinal hemorrhage or minor intracranial hemorrhage script, but less severe than the major intracranial hemorrhage script [13]. Treatment of acute submassive PE with fibrinolysis is a controversial topic in current clinical practice, as clinicians seek to balance the potential benefit of adjunctive fibrinolysis on short-term hemodynamic stability versus risk of major hemorrhage with the long-term health outcomes of severe PE treated with anticoagulation only [14]. The results of this study could be employed by practicing clinicians as an additional piece of evidence when advising patients as to the risks and benefits of therapy.

It is important to note additional limitations of this study. The results do not show a robust effect of tenecteplase, with $P = 0.056$ in the base equation, suggesting more than 5 % probability that tenecteplase did not have a significant, independent effect on PCS score. Further, seven patients from the original TOPCOAT trial had to be omitted from this secondary analysis. One patient randomized to each group died during the initial hospitalization, thus balancing their exclusion to some degree. However, an additional five patients were lost to follow-up and unable to fill out SF-36 surveys. The clinical

characteristics of these patients were investigated to determine whether a significant imbalance existed between those initially randomized to separate treatment groups. These enrollment features are shown in Table 4. Another possible limitation of this study was the relatively small sample size. The small number of patients in each group resulted in low numbers of patients with comorbid conditions. This limited our overall data analysis, specifically the examination of interaction effects, as we were unable to interact tenecteplase with malignancy and COPD. The smaller sample size may also explain why clinical characteristics described in previous publications to be significant determinants of decreased QoL, such as malignancy, prior history of PE or DVT, and cardiopulmonary comorbidities, were not reported to be significant in our results, as this study may have been underpowered to detect such effects. It should also be mentioned that no consensus exists currently as to the most accurate instrument for measuring patient QoL after PE. The SF-36 was chosen in the initial study based on its extensive history of use and the lack of a disease-specific instrument at that time.

Conclusion

In patients with acute submassive PE, obesity had the greatest effect on PCS score of the SF-36. Fibrinolysis had the second largest contribution, as a single bolus of tenecteplase was found to independently increase the PCS score at 90-day follow-up after adjusting for eight comorbid conditions. Examination of interactions revealed that tenecteplase did not increase the PCS score in patients who lacked the pre-specified comorbid conditions.

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Table 1

Clinical characteristics of patients with submassive pulmonary embolism

Clinical finding	Placebo		Tenecteplase		P
	N = 39		N = 37		
Obesity (BMI>30 kg/m^2)	25	64 %	20	54 %	0.37
Active malignancy	0	0 %	5	14 %	0.02
Prior history of PE or DVT	8	21 %	5	14 %	0.42
Recurrent PE or DVT	4	10 %	1	3 %	0.18
Chronic obstructive pulmonary disease	3	8 %	0	0 %	0.09
Heart failure	1	3 %	1	3 %	0.99
Age (years, mean and SD)	54 (15)		56 (13)		0.54
Body mass index (kg/m^2)	34.2 (10)		32.5 (9)		0.44

PE pulmonary embolism, *DVT* deep venous thrombosis, *BMI* body mass index, *SD* standard deviation

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Table 2

Multivariate regression analysis results

Variables	Estimated coefficients for physical component summary score	P
Tenecteplase	4.73	0.056
Age (natural logarithm)	−7.60	0.083
Obesity (BMI>30 kg/m^2)	−8.59	<0.001
Active malignancy	−8.26	0.178
History of PE or DVT	−0.30	0.924
Recurrent PE or DVT	−8.95	0.072
Chronic obstructive pulmonary disease	−5.32	0.329
Heart Failure	−12.61	0.143

PE pulmonary embolism, *DVT* deep venous thrombosis, *BMI* body mass index

Table 3

Interaction results

Interaction term with tenecteplase	Estimated coefficients	P
Age (natural logarithm)	−11.29	0.185
Obesity (BMI>30 kg/m^2)	5.43	0.238
History PE or DVT	6.20	0.276
Recurrent PE or DVT	16.06	0.018
Heart failure	33.31	<0.001

PE pulmonary embolism, *DVT* deep venous thrombosis, *BMI* body mass index

Table 4

Clinical characteristics of patients omitted from original trial

Clinical finding	Placebo		Tenecteplase	
	N =4		N= 3	
Obese (BMI>30 kg/m^2)	3	75 %	1	33 %
Active malignancy	0	0 %	0	0 %
Prior history of PE or DVT	0	0 %	1	33 %
Chronic obstructive pulmonary disease	0	0 %	0	0 %
Heart failure	1	25 %	0	0 %
Age (years, mean and SD)	54 (7)		71 (16)	
Body mass index (kg/m^2)	32 (6)		34 (13)	

PE pulmonary embolism, *DVT* deep venous thrombosis, *BMI* body mass index, *SD* standard deviation