ORIGINAL INVESTIGATION

J Crit Intensive Care 2020;11(2):31–36
https://doi.org/10.37678/dcybd.2020.2317

The Comparative Changes in Inflammatory Markers Between Fiber Optic Bronchoscopy Guided and Classical Percutaneous Dilatational Tracheostomy

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Cite this article as: Mungan I, Sarı S, Bayındır Dicle C, Altınkaya Cavus M, Bektas S, Turan S. The Comparative Changes in Inflammatory Markers Between Fiber Optic Bronchoscopy Guided and Classical Percutaneous Dilatational Tracheostomy. J Crit Intensive Care 2020; 11(2):31–36

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Received: Jun 08, 2020
Accepted: Jun 20, 2020
Available online: Aug 10, 2020

ABSTRACT

Aim: Approximately ¼ of mechanically ventilated patients undergo tracheostomy in the intensive care units and percutaneous dilatational tracheostomy (PDT) replaces traditional open surgical tracheostomy. Various studies compare tracheostomy techniques according to safety, efficacy and cost affectivity. The biomarkers are used to reflect systemic acute-phase reaction (APR) which is in accordance with the severity of the tissue trauma. In the present study, we aimed to describe APR in patients undergoing PDT with or without bronchoscopy guidance, by analyzing changes in chosen inflammatory biomarkers.

Study design: This single-center, retrospective descriptive study of 231 patients who underwent PDT was conducted between July 2016 and December 2018, in our tertiary ICU.

Materials and Methods: The demographic data, the clinical outcomes and inflammatory biomarkers before and after PDT were derived from the hospital's database. All statistical analyses were performed with SPSS version 24 and for all analyses, a p-value ≤0.05 was regarded as statistically significant.

Results: In this study, we compared the acute phase reaction caused by Fiber Optic Bronchoscopy Guided PDT and Classical PDT using inflammatory markers. Although the length of hospital and intensive care unit stay was longer with the guidance of bronchoscopy, the difference was not statistically significant between groups. In terms of inflammatory markers, the difference between the groups was found statistically significant.

Conclusion: PDT was compared to open surgical tracheostomy (OST) largely in the literature and it was found less inflammation-related while we found that FOB guidance related less inflammatory response and the relative changes in APR were less.

Keywords: Percutaneous Dilatational Tracheostomy, Fiber Optic Bronchoscopy, Inflammatory Markers, Acute-Phase Reaction

Introduction

Prolonged mechanical ventilator dependency is the major indication for the tracheostomy procedure and approximately ¼ of mechanically ventilated patients undergo tracheostomy in the intensive care unit (ICU). Percutaneous dilatational tracheostomy (PDT) which replaces traditional open surgical tracheostomy (OST) in most ICUs with its cost-effectivity, safety, and feasibility at the bedside, is still evolving with various alternative techniques (1, 2). It is mainly composed of serial dilatation technique that was done blindly until 1990 when Marelli et al. (3) used bronchoscopy to increase safety. The usage of fiber optic bronchoscopy (FOB) not only facilitates direct visualization of the trachea and verification of needle entry but also eliminates the risk of blind insertion (4).

In the literature, various studies compare OST and PDT with or without bronchoscopy or radiologic assistance according to safety, efficacy, and cost-effectivity (5, 6, 7). Even though PDT is claimed to be superior to OST it also induces an acute inflammatory response, and many complications like bleeding, pneumothorax or posterior tracheal wall perforation may occur in the early period (6, 8). New techniques and devices like augmented reality-assisted percutaneous dilatational tracheostomy are utilized to overcome oversight problems and to decrease the potential risks with advances in technology (9, 10).

A systemic acute-phase reaction (APR) which is following systemic inflammatory response is induced after all types of tissue traumas including surgical procedures and tracheostomy (8, 11). In

the literature, numerous biomarkers like C-reactive protein (CRP), total leucocyte count (TLC) and neutrophil-lymphocyte ratio (NLR) are used to reflect the APR which is in accordance with the severity of the tissue trauma. They have been used to compare the extent of tissue injury, APR and inflammatory response of different procedures (11, 12). CRP and TLC are also utilized as a prognostic indicator in various types of tumor whereas NLR indicates the equilibrium between inflammation and regulatory factors (13, 14).

In the present study, we aimed to describe APR in patients undergoing PDT with or without FOB guidance, by analyzing changes in chosen inflammatory biomarkers: CRP concentrations, TLC and NLR after PDT and to find out any relation with clinical outcomes. To the best of authors' knowledge, no previous studies have compared classical PDT and FOB guided PDT regarding their inflammatory response. We chose these three laboratory markers (CRP, TLC, and NLR) to investigate as APR indicators because they are valid, cheap and easy to obtain from patients' medical files.

Methods

This single-center, retrospective descriptive study of 231 patients who underwent PDT, with or without FOB guidance, was conducted between July 2016 and December 2018, in a tertiary ICU. Exclusion criteria from the study were incomplete or missed data and laboratory values in the medical records, patients age less than 18, patients with known or suspected infections and PDT in emergent cases. Ethics Committee of Türkiye Yüksek Ihtisas Hastanesi approved our study (№; 2019//929) and the need for written informed consent was waived by the ethics committee due to its retrospective nature.

The clinical data, patients' outcomes and laboratory values were collected or retrieved from the institutional database and ICU spreadsheet and recorded into a Microsoft Excel *sheet* (Microsoft Excel 2013, Microsoft Corporation) by three authors of this study. The aforementioned authors did not participate in the literature search, data analysis or manuscript writing to avoid acquisition information bias and this precaution also prevents the variability in the data collection. In the classical PDT group, no assistance was used before or after the needle entry while in the FOB guided PDT group bronchoscopic visualization was maintained. In both groups standard Griggs' guide wire dilating forceps technique was used for PDT procedure.

The gathered data were as following: age, gender, Charlson comorbidity index score, and duration of ventilation-mechanical ventilator support (MVS) period- (days) before and after PDT, indication for PDT, length of duration of PDT procedure (minutes), complications related to PDT, length of stay (LOS) in the hospital and ICU, mortality and laboratory values before and after PDT. The length of duration of PDT procedure (minutes) was considered as the duration between sterile drape placement till to the insertion of the tracheostomy cannula. Early complications and late complications related to PDT were bleeding, malposition of the cannula, pneumothorax, and posterior esophageal injury, tracheal stenosis and tracheoesophageal fistula respectively. The complications that occurred during the first week after PDT were defined as early complication, while the complications were defined as late if they were diagnosed after the first week until death or hospital discharge. The Charlson Comorbidity Index, which evaluates the medical comorbidities presence was used to decrease the influence of comorbidities like malignancies and congestive heart failure on laboratory values (15).

Laboratory values

All laboratory values, preferably day before PDT and within 24 hours after the PDT procedure, were either collected or derived from the hospital's database. In our ICU, complete blood count and CRP values were requested on a daily base as a routine manner and no other laboratory test was required for the study. The nephelometry method had been used to measure serum CRP values while TLC and absolute neutrophil count were collected from the medical database. NLR was computed as absolute neutrophil count/ absolute lymphocyte count.

After completing all data we also calculated the difference of the laboratory values; X (TLC, CRP, and NLR) and the calculation method was as follows:

$$\frac{deltaX = XvaluebeforePDT - XvalueafterPDT}{XvaluebeforePDT} * 100$$

Statistical Analysis

In the first part of the statistical analyses, the Kolmogorov-Smirnov test was utilized as a normality test to decide either parametric or non-parametric tests would be appropriate. As the normal distribution of the variables was not achieved, the non-parametric tests were used. Categorical data like demographic and clinical variables were expressed as frequency and percentage whereas continuous variables were expressed as median and interquartile range (IQR). For the comparison of continuous variables between groups, either the Mann Whitney U test or Kruskal Wallis test was used. The correlations between categorical variables were evaluated by the Spearman Rho correlation test. All statistical analyses were performed with SPSS version 24 (SPSS 24, Chicago, IL, USA) and for all analyses, a p-value ≤ 0.05 was regarded as statistically significant.

Results

Between July 2016, and December 2018, 231 patients who met the inclusion criteria were included and 32 of the PDT cases excluded from the study. 24 of them had missing data, 2 of them were emergent cases and 6 patients were younger than 18 years old. 47.2 % of the study population (n=109) was FOB guided PDT group and 52.8 % of the included cases (n=122) was classical PDT group. Of the 231 patients, 157 (68%) were men; the median value of age (with interquartile range) was 68 (56-77) years old.

The descriptive variables like age, gender, and indication for PDT were compared in Table 1 and the difference was not statistically significant. Also, the median value of Charlson comorbidity index score [7 (5-9) versus 7 (5-10)] and the duration of MVS before

Table 1. Demographic variables and details about PDT procedure

Variable	Total (n=231)	FOB guidance (+) in PDT (n=109)	FOB guidance (-) in PDT (n=122)	p*
Male gender, n (%)	157 (68%)	75 (68.8%)	82 (67.2%)	0.797
Age (years), median (IQR)	68 (56-77)	67 (55.5-75.5)	69.5 (56-77)	0.316
Charlson comorbidity index score, median (IQR)	7 (5-10)	7 (5-9)	7 (5-10)	0.265
Indications for MVS				
Pneumonia, n (%)	33 (14.3%)	16 (14.7%)	17 (13.9%)	0.872
Sepsis, n (%)	35 (15.2%)	16 (14.7%)	19 (15.6%)	0.851
COPD, n (%)	8 (3.5%)	2 (1.8%)	6 (4.9%)	0.202
CHF, n (%)	59 (25.5%)	32 (29.4%)	27 (22.1%)	0.210
Poor Neurological status, n (%)	47 (20.3%)	16 (14.7%)	31 (25.4%)	0.053
Other causes of respiratory failure, n (%)	49 (21.2%)	27 (24.8%)	22 (18%)	0.213
Duration of the procedure (minutes), median (IQR)	10 (9-12)	12 (10-14)	9 (8-10)	<0.001
Early complications				
None, n (%)	217 (93.9%)	103 (94.5%)	114 (93.4%)	
Bleeding, n (%)	10 (4.3%)	4 (3.7%)	6 (4.9%)	0.743
Aborted, n (%)	3 (1.3%)	2 (1.8%)	1 (0.8%)	
Pneumothorax, n (%)	1 (0.4%)	1 (0.8%)	0	
Late complications, n (%)	0	0	0	NA

Subgroups according to the FOB guidance in PDT
p*-values calculated for comparison of FOB guidance (+) versus FOB guidance (-) by statistical analysis.
Data expressed as median and interquartile range or n (%)
*Determined by Mann-Whitney U test.
Abbreviations: PDT: Percutaneous dilatational tracheostomy; MVS: mechanical ventilation support; FOB: fiber optic bronchoscopy; COPD: Chronic obstructive pulmonary disease; CHF: Congestive heart failure; IQR: interquartile range

PDT (days) [15 (9-17) versus 14 (7-17)] did not differ between groups (p>0.05).

The rate of early complications related to PDT was 6.6% in the classical PDT group and 5.5% in the FOB guided PDT group (p=0.743). The major complication was bleeding in both groups and occurred in 10 cases after PDT. The most serious early complication was pneumothorax in the classical PDT group and the patient received closed drainage of the thoracic cavity.

The duration of the procedure (minutes) in the classical PDT group was shorter than FOB guided PDT group (p<0.001) as expected [9 (8-10) minutes versus 12 (10-14) minutes] probably due to bronchoscopy preparation. As it was summarized in Table 2, the clinical outcomes also did not statistically different (p>0.05). The decannulation rate and in-hospital mortality rate were similar between groups. Even though the length of stay in hospital and ICU, and MVS post-PDT (days) were longer in the FOB guided PDT group, the difference was not statistically significant.

After the PDT procedure -both in classical and FOB guided group- the inflammatory markers were elevated as expected while the increment was remarkable with respect to CRP level. The values of inflammatory markers along with the changes after

Table 2. The relation between clinical outcomes and FOB guidance in PDT procedure

Variable	Total (n=231)	FOB guidance (+) in PDT (n=109)	FOB guidance (-) in PDT (n=122)	p*
MVS pre-PDT (days), median (IQR)	15 (8-17)	15 (9-17)	14 (7-17)	0.07
MVS post-PDT (days), median (IQR)	30 (20-50)	32 (19-57.5)	30 (20-45.5)	0.550
Decannulation rate, n (%)	34 (14.7%)	17 (15.6%)	17 (13.9%)	0.723
In-hospital mortality (+), n (%)	172 (74.5%)	84 (77.1%)	88 (72.1%)	0.393
LOS in hospital (days), median (IQR)	46 (28- 71)	48 (29.5-73)	44 (27.8-70)	0.347
LOS in ICU(days), median (IQR)	35 (22-58)	35 (22-62.5)	35.5 (23.5-52.8)	0.647

Subgroups according to the FOB guidance in PDT
p*-values calculated for comparison of FOB guidance (+) versus FOB guidance (-) by statistical analysis.
Data expressed as median and interquartile range or n (%)
*Determined by Mann-Whitney U test.
Abbreviations: PDT: Percutaneous dilatational tracheostomy; FOB: fiber optic bronchoscopy; MVS: mechanical ventilator support; LOS: length of stay; ICU: intensive care unit; IQR: interquartile range

Table 3. The relation between inflammatory markers' levels and FOB guidance

Variable	Total (n=231)	FOB guidance (+) in PDT (n=109)	FOB guidance (-) in PDT (n=122)	p*
TLC pre-PDT(mg/dl), median (IQR)	10.3 (8.2-13.4)	10.5 (8.4-13.4)	10.2 (8-13.4)	0.644
TLC post-PDT(mg/dl), median (IQR)	11.2 (8.8-14.4)	11.3 (8.6-13.8)	11.2 (9.2-14.6)	0.485
Delta TLC, median (IQR)	5.2 (-3.2-18.2)	3.2 (-5-12.7)	9.2 (-1.2-21.8)	0.010
CRP pre-PDT(mg/dl), median (IQR)	103 (60-160)	98.8 (55-158)	108.5(65-160)	0.170
CRP post-PDT(mg/dl), median (IQR)	110 (64-167)	97 (54.5-147.5)	121.2 (71.9-172)	0.009
Delta CRP, median (IQR)	10 (-36-67)	2 (-13-12.5)	12 (-12.3-31.3)	0.015
NLR pre-PDT, median (IQR)	12.7 (7.5-20.5)	13.4 (8-21.7)	11.3 (7.5-18.5)	0.277
NLR post-PDT, median (IQR)	13.9 (8-22)	13.8 (8.5-21.5)	14.3 (7.1-22.3)	0.464
Delta NLR, median (IQR)	2.8 (-28-34)	-1.7 (-32.2-31.8)	7 (-24.9-38.6)	0.251
Delta neutrophil, median (IQR)	0.3 (-2.2-2.9)	0.1 (-2.5-3)	0.6 (-1.8-2.9)	0.391
Delta lymphocyte, median (IQR)	-2.6 (-25-35)	0.1 (-23-40.9)	-5.3 (-25.8-28.6)	0.256

Subgroups according to the FOB guidance in PDT
p*-values calculated for comparison of FOB guidance (+) versus FOB guidance (-) by statistical analysis.
Data expressed as median and interquartile range or n (%)
*Determined by Mann-Whitney U test.
Abbreviations: PDT: Percutaneous dilatational tracheostomy; FOB: fiber optic bronchoscopy; CRP: C-reactive protein; TLC: total leucocyte count; NLR: neutrophil-lymphocyte ratio; IQR: interquartile range

the PDT procedure were summarized in table 3. There was no difference between groups related to pre-procedural and post-procedural inflammatory markers' (CRP, TLC, and NLR) levels. The only exception was the serum CRP value after the PDT which was higher in the classical PDT group and the difference was statistically significant (p=0.009).

The calculated values of delta TLC, delta NLR, and delta CRP were also displayed in Table 3. The difference between groups regarding delta CRP and delta TLC was significant (p=0.015 and p=0.010) while delta NLR did not display significant difference statistically (p=0.251). To find out whether the components of the NLR was statistically different between groups, we further calculated delta neutrophil count and delta lymphocyte count. There was no difference between groups according to these variables as well.

Discussion

In non-urgent prolonged MVS cases, PDT was suggested as the first choice in major guidelines while subjective factors, experience, economic issues, and availability determine the usage of auxiliary techniques like bronchoscopy, ultrasonography and video assistance (9, 10, 16). All interventions, particularly surgical procedures including minimally invasive ones and PDT, induce stress response related to tissue damage which can be qualified by a rise in inflammatory markers. Although this increment in inflammatory markers and APR are not diagnostic for any specific illness, they guided the researchers to less invasive and less deleterious techniques of the same intervention (11, 16, 17). Our retrospective descriptive study compared Fiber Optic Bronchoscopy Guided PDT and Classical PDT by using inflammatory markers in aspect to APR.

The laboratory values (CRP, TLC, and NLR) that we utilized are accepted as simple, cheap and easily available markers and used to reflect inflammation response by various studies (18, 19). Both CRP and NLR are utilized in various malignancies as a prognostic marker as well (14). Jager et al. (20) claimed that NLR had better prognostic value than TLC and CRP while other studies favored CRP and claimed to be better than NLR (18, 21).

To overcome selection bias, the patients who had high serum inflammation biomarkers related to the indication of PDT or admission diagnosis like pneumonia or sepsis were not excluded. As a result in both groups CRP, NLR and TLC values before and after the procedure were higher than the normal values. We calculated the delta value of these variables as mentioned in the material method section to overcome this issue. It was claimed that serum CRP levels reflect the APR earlier than the other non-specific biomarkers like NLR (19) and in our study, we collected the laboratory values before PDT and one day later. This might explain why the difference between groups was statistically significant with respect to CRP and TLC while it was not significant according to NLR.

In the present study, the median value (with interquartile range) of the duration of the PDT procedure (including all cases) was 10 (9-12) minutes while in other studies it was ranged between 9.8 to 20 minutes (5, 7). Shen et al. (7) claimed that FOB shortened the procedure while the difference between FOB guided and classical PDT favored the traditional method in our study [12 (10-14) minutes versus 9 (8-10) minutes]. We considered this period as the duration between sterile drape placement till to the insertion of the tracheostomy cannula and bronchoscopy guidance time might cause the difference.

The rate of complications after PDT is reported between 0.38% and 12% in the literature (3, 5) and our study finding (6.1%) was consistent with this rate while no late complications like laryngotracheal stenosis was recorded in our study. Early complications and FOB guidance were not related and this finding was parallel to previous studies that did not find any difference in

the no-bronchoscope cohort statistically (7). The mortality rate and the decannulation rate among survivors were similar in both groups.

We found that FOB guidance related less inflammatory response and the relative changes in CRP and TLC were less. Although the duration of the procedure was longer in the FOB guidance group, direct visualization of the needle, guide-wire, and the cannula might decrease the inflammatory response and the APR. The clinical outcomes like the decannulation rate and the mortality rate did not differ between groups while LOS in hospital and ICU were longer in the FOB guided group. But this difference is not statistically significant.

Limitations

We had to admit that the retrospective nature of this study was constituting the major limitations. First of all, the relations between high inflammatory markers' level before PDT procedure and indications of PDT, comorbidities, and complications were not clear enough to claim the PDT procedure as the only variable affecting APR. However, we utilized the Charlson comorbidity index and delta values to standardize the patients' profile and the change in inflammatory markers.

As a second limitation, the mortality rate in our study group was high (74.5%) and this might prevent us to make an assumption about clinical outcomes. The third limitation of this study was being single-center research and depending mainly on the database of our institution and ICU sheets. We believed that the benefit of FOB guidance with respect to inflammatory changes should be studied via a randomized, prospective study.

Conclusion

PDT was compared to OST largely in the literature and it was found less inflammation-related while as far as we know the present study was the only one which compared classical and FOB guided PDT procedure with respect to inflammation. FOB guidance in the PDT procedure might decrease the inflammatory response but does not affect the clinical outcomes statistically probably due to the high mortality rate among the study population.

AUTHOR CONTRIBUTIONS:

Concept: IM, ST; **Design:** IM, SB; **Supervision**: ST, SB, IM; **Fundings:** SS, MAC, CBD; **Materials:** IM, SS, MAC; **Data Collection and/or Processing:** CBD, MAC, IM, SB; **Analysis and/or Interpretation**: IM, ST, SB; **Literature Search:** IM, SS, CBD, MAC; **Writing Manuscript**: IM; **Critical Review:** ST, SB, IM.

Ethics Committee Approval: Ethics Committee of Türkiye Yüksek Ihtisas Hastanesi approved our study (no: 2019//929)

Peer-review: Externally peer-reviewed.

Conflict of Interest: Authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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