Turk Toraks Derg 2015; 16: 53-8 DOI: 10.5152/ttd.2015.4323

ORIGINAL INVESTIGATION / ÖZGÜN ARAŞTIRMA

Does Total Parenteral Nutrition Increase the Mortality of Patients with Severe Sepsis in the ICU?

Total Parenteral Beslenme, Yoğun Bakımda Ağır Sepsisli Hastaların Mortalitesini Arttırır mı?

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Abstract

OBJECTIVES: We aimed to evaluate the independent association between total parenteral nutrition (TPN) and nosocomial infection and intensive care unit (ICU) mortality in patients with severe pulmonary sepsis.

MATERIAL AND METHODS: The present study was designed as a retrospective observational cohort study. We enrolled all patients with severe sepsis due to pulmonary infections who stayed more than 24 h in the respiratory ICU between January 2009 and December 2010. We recorded demographic characteristics, ICU severity scores, Acute Physiologic and Chronic Health Evaluation II (APACHE II) and first day Sequential Organ Failure Assessment (SOFA) score in the ICU, TPN because of intolerance to enteral feeding, ICU data, and mortality. To evaluate the risk factors for mortality, we performed adjusted logistic regression test for TPN, nosocomial infection, and SOFA in the model.

RESULTS: Five hundred and fifty patients (males=375, females=175) with severe sepsis were involved in the study during the study period. The median and interquartile range (IQR) of age, APACHE II, and SOFA score at the time of admission to the ICU were 65 years (53-73), 20 (16-25), and 4 (3-6), respectively. Mortality rate was 18% (n=99). Adjusted odds ratio (OR), confidence intervals (CI) 95%, and p values of TPN, nosocomial infection, and first day SOFA score for mortality were as follows: OR:3.8, CI:2.3-6.1, p<0.001; OR:2.4, CI: 1.4-3.9, p<0.001; and OR: 1.3, CI:1.2-1.4, p<0.001, respectively.

CONCLUSION: Nosocomial infection and the need for TPN because of intolerance of enteral nutrition (EN) is associated with a higher mortality rate in patients with severe sepsis in the ICU. Rational use of antibiotics and application of hospital acquired infection control program will further reduce mortality.

KEY WORDS: Severe sepsis, total parenteral nutrition, intensive care unit, nosocomial infection

Özet

AMAÇ: Ağır pulmoner sepsisi olan hastalarda total parenteral beslenme (TPB), nozokomiyal enfeksiyon ve yoğun bakım ünitesindeki (YBÜ) mortalite arasındaki bağımsız ilişkiyi araştırmayı amaçladık.

GEREÇ VE YÖNTEMLER: Çalışma retrospektif, gözlemsel kohort çalışma olarak tasarlandı. Ocak 2009-Ekim 2010 tarihleri arasında YBÜ'de 24 saatten fazla yatan solunumsal kaynaklı tüm ağır sepsis hastaları çalışmaya dahil edildi. Hastaların demografik bilgileri, yoğun bakım ciddiyet skorları APACHE II (Acute Physiologic and Chronic Health Evaluation) ve YBÜ'deki ilk gün SOFA (Sequential Organ Failure Assessment) skoru, beslenme şekli (enteral beslenme, TPB), YBÜ bilgileri ve mortalite durumu kayıt edildi. Mortalite risk faktörlerini değerlendirmek amacıyla TPB, nozokomiyal enfeksiyon ve SOFA skorunu içeren düzeltilmiş lojistik regresyon testi uygulandı.

BULGULAR: Belirtilen zaman içerisinde kriterlere uyan 550 hasta (375 erkek) çalışmaya dahil edildi. Yaş (yıl), APACHE II ve başvuru anındaki SOFA skoru için medyan ve çeyrekler arası oran (ÇAO) sırasıyla 65 (53-73), 20 (16-25), 4 (3-6) idi. Mortalite oranı 18% (n=99) idi. TPB, nozokomiyal enfeksiyon ve ilk gün SOFA değerlerinin mortalite için düzeltilmiş odds oranı (OR), %95 güven aralığı (CI) ve p değeri sırasıyla OR: 3,8, CI: 2,3-6,1, p<0,001, OR: 2,4, CI: 1,4-3,9 p<0,001, OR: 1,3, CI: 1,2-1,4, p<0,001 idi.

SONUÇ: Ağır sepsisi olan yoğun bakım hastalarında TPB ve nozokomiyal enfeksiyon yüksek mortalite oranı ile ilişkilidir. Akılcı antibiyotik kullanımı ve hastane enfeksiyon kontrol programları mortalite oranlarını düşürecektir.

ANAHTAR SÖZCÜKLER: Ağır sepsis, total parenteral beslenme, yoğun bakım ünitesi, nozokomiyal enfeksiyon

Received/Geliş Tarihi: *30.05.2014* ***Accepted/Kabul Tarihi:*** *09.02.2015*

This study was accepted as an oral presentation at the 10th Congress of the Turkish Medical and Surgical Intensive Care Medicine Society (November 27-30, 2013, İstanbul, Turkey).
Bu araştırma, 10. Türk Dahili ve Cerrahi Bilimler Yoğun Bakım Derneği Kongresi'nde (27-30 Kasım 2013, İstanbul) sözlü bildiri olarak sunulmuştur.

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INTRODUCTION

Mortality rates due to severe sepsis in the intensive care unit (ICU) remain high (19%-30%), although Surviving Sepsis Campaign guidelines was implemented worldwide in 2004 for sepsis treatment and management [1-6]. Diagnosis of severe sepsis and implication of sepsis protocols since 2006 led to promising results in reduction of mortality of patients with severe sepsis/septic shock [7,8]. Therefore, current research focused on determining modifiable factors associated with sepsis mortality in addition to the well-known parameters. Various factors should be considered in the management of severe sepsis. Antibiotic resistance of the infectious agents may particularly contribute to the outcomes in severe sepsis; however, identification of other modifiable factors is necessary to reduce mortality [9].

In the previous study that was conducted in our respiratory ICU, presence of multi-organ failure (MOF), TPN, and higher APACHE II scores were found to be risk factors for mortality in patients with severe sepsis who were treated according to the modified sepsis protocol [10]. The present study was conducted 3 years after the first study because our experience in sepsis protocols improved. We aimed to investigate the association between potential modifiable factors (TPN and nosocomial infection) and mortality due to severe sepsis in the ICU.

MATERIAL AND METHODS

This observational cohort study was performed in a 22-bed respiratory ICU in a tertiary training and research hospital. All patients were followed up by the same pulmonary specialist team (n=6) between January 2009 and December 2010.

Patients: All patients who were admitted to the ICU because of severe sepsis due to pulmonary infections (pneumonia, infective bronchitis, bronchiectasis, etc.) and stayed more than 24 h were enrolled in the study.

Study Design: Retrospective observational cohort study.

Data Collection: Data was obtained from the hospital electronic database.

Definitions

Sepsis: Sepsis was defined as Systemic Inflammatory Response Syndrome (SIRS) with a proven or suspected source of infection. SIRS was defined as the presence of two or more of the following variables [11].

- Core body temperature of >38°C or <36°C
- Heart rate of ≥90 bpm
- Respiratory rate of ≥20 breaths/min (or $PaCO_2$ of <32 mmHg)
- White blood cell count of ≥12,000/μL or ≤4000/μL or >10% immature

Severe Sepsis

Severe sepsis is defined as sepsis and sepsis-induced organ dysfunction or tissue hypoperfusion characterized by any of the following conditions [12].

1) Sepsis-induced hypotension,
2) Lactate above normal upper limits laboratory,
3) Urine output <0.5 mL/kg/h for more than 2 h despite adequate fluid resuscitation,
4) Acute lung injury with PaO_2/FiO_2 <250 in the absence of pneumonia as an infection source,
5) Acute lung injury with PaO_2/FiO_2 <200 in the presence of pneumonia as an infection source,
6) Creatinine >2.0 mg/dL (176.8 μmol/L),
7) Bilirubin >2 mg/dL (34.2 μmol/L),
8) Platelet count <100 000 μL,
9) Coagulopathy (international normalized ratio >1.5).

Pre-intensive care unit locations and date of ICU admission were recorded for all patients. Patients' demographics, comorbid diseases (i.e., diabetes, cardiovascular diseases, chronic renal diseases, chronic respiratory diseases), arterial blood gases analysis and blood biochemistry values, SIRS criteria at the time of ICU admission, APACHE II score both at the time of admission and discharge from the ICU, and SOFA score on the first and third day of the admission to the ICU were evaluated. ICU outcomes (implication and durations of invasive and non-invasive mechanical ventilation, administration of sedation and nutrition style) were recorded from patients' ICU files [1,13,14]. Presence of nosocomial infection on admission to ICU and resistant pathogens were recorded, and all patients were treated according to the guidelines [9,15,16].

We followed the Modified Protocol for surviving sepsis [3], Early Directed Goal Therapy protocol (EGDT) [1], moderate tidal volume on invasive mechanical ventilation (IMV) [17] if the patient was unresponsive to or had any contraindications for non-invasive mechanical ventilation (NIMV) [18], and moderate steroid dose [16,19] was used (20 mg tid for 7 days [14,16]) in patients without contraindication [1,3,17-19]. Glucose control protocol was followed to maintain blood glucose level between 110 and 140 mg/dL (<150 mg/dL). During mechanical ventilation, the sedation protocol was applied. The Richmond agitation-sedation (RAS) scale was used for the assessment of daily need for sedation [20,21].

Feeding protocols: All patients were nourished primarily by the enteral route (oral feeding or via oro-gastric tubes in intubated patients or nasogastric tubes or percutaneous endoscopic gastrostomy-PEG), unless there was a presence of intolerance to or any contraindications for enteral feeding [22]. Contraindications for enteral feeding were defined as follows:

1) Hemodynamic instability requiring high dose inotropic agents such as adrenaline/noradrenaline/dopamine/dobutamine infusion,
2) First 24 h after cardiopulmonary resuscitation,
3) Probability of intubation in 4-6 h,
4) Intestinal obstruction,
5) Surgical abdominal pathology,
6) Intestinal ischemia,
7) Active upper gastrointestinal bleeding,
8) Pancreatitis, and
9) After bone marrow transplantation.

Total parenteral nutrition was initiated if enteral feeding was unsuccessful. Methods of feeding were recorded. H2-receptor antagonists or proton pump inhibitors were given for gastrointestinal bleeding prophylaxis [3].

Enteral nutrition: All patients who are not expected to be on a full oral diet within 3 days were nourished within 24-48 h in the absence of any contraindications according to guidelines via nasogastric or oro-gastric tubes or PEG (Percutaneous endoscopic gastrostomy) [23]. Daily caloric demand was calculated as 25-30 kcal/kg (ideal weight). Before feeding, elevation of the head to 30-45° was performed routinely. After inserting the enteral tube, placement of the tube into the gastric antrum was controlled by the stethoscope. Patients were fed by either bolus or infusion. Enteral feeding was initiated with the amount of 30 mL/h and after 3 h of feeding period, it was interrupted for 1 hour to control gastric residual volume (GRV) to determine the presence of gastric intolerance. If there was no evidence of intolerance, the amount of feeding was gradually increased up to 100 mL/h to reach the daily caloric demand. Gastric intolerance was defined as the presence of one or more of the following conditions:

1) Abdominal distention that disturbs patient,
2) Increased abdominal diameter,
3) Aspiration,
4) Vomiting (Once a day or more),
5) Diarrhea (More than four defecation a day without another explanation), and
6) Gastric residual volume (GRV) ≥150 mL, or

GRV>5 mL/kg, or

GRV >previous feeding volume during bolus feeding, or

GRV >2 h feeding volume during drip infusion volume.

Total Parenteral Nutrition

The major indication for TPN is gastrointestinal dysfunction of processing and absorbing food from either oral or enteral feeding. TPN was started when gastric intolerance occurred and is administered via central venous catheters because of its high osmolality. TPN was started initially at 50 mL/h for 24 h, and the infusion dose was progressively increased in the following days. Daily assessment was performed to decide the duration of TPN and whether the patient became suitable for enteral nutrition.

Microbiology: Bronchial secretions of patients were collected via deep tracheal aspiration in intubated patients, whereas sputum was collected into a sputum Petri dish for other patients. In case of hyper- or hypothermia (<36°C or >38°C), blood culture was obtained and incubated into aerobe culture media.

Statistical Analysis

Data were analyzed by using the Statistical Package for the Social Sciences (SPSS version 20.0 Ibm, Chicago, IL, USA) statistical software. Descriptive statistics were used to define the characteristics of the study population. We divided patients with severe sepsis into two groups according to their mortality. The demographics and the clinical features, ABG values, SIRS criteria, SOFA score on the first and third day, and co-morbidities of survivors and non-survivors were compared by using the Mann-Whitney U test and Student's t-test for non-parametric and parametric variables, respectively. All non-parametric values were defined as median; IQR is 25%-75%. We used Chi-square test to compare categorical variables (sex, comorbidity, status of IMV, and NIMV) between survivors and non-survivors.

We used logistic regression analysis to evaluate univariate and multivariate associations between risk factors and mortality. To assess for the risk of nosocomial infections and TPN on our primary outcome (mortality), we stratified the factors that affect the mortality as confounders or mediators. The significant parameters that were determined by comparison between survivors and non-survivors were stratified and after effect modifications such as septic shock, sedation, mechanical ventilation, and insulin demand were accepted as mediators of mortality. SOFA score was accepted as a confounder, and SOFA was included in our model in addition to TPN and nosocomial infection. The multivariate model was adjusted for baseline severity (SOFA score on admission to the ICU). Odds ratios, 95% confidence intervals, and p values are reported. All analysis was performed using SPSS (15.0 versions). P values <0.05 were considered statistically significant.

RESULTS

During the study period, 1469 patients were admitted to the respiratory ICU, and 550 patients with severe sepsis were enrolled into the study. Pre-ICU locations were the emergency department (n=207, 37.6%), ward (n=286, 52.0%), and other ICUs (n=57, 10.4%). Patients' demographics and ICU data were described in Table 1.

Among the 336 patients (61.1%) in whom microbiological diagnostic testing was conducted, 196 (58.3%) patients had positive cultures for resistant pathogens. The identified pathogens were as follows: *Pseudomonas aeruginosa* (n=55, 28%), *Candida spp.* (n=31, 16%), *Acinetobacter baumanni* (n=21, 11%), *Methicillin resistant Staphylococcus. aureus* (n=15, 8%), *Enterococcus spp.* (n=7, 4%), extended spectrum beta lactamase (ESBL) (+) *Escherichia coli* (n=12, 6%), ESBL (+) *Klebsiella spp.* (n=16, 8%), *Stenotrophomonas maltophilia* (n=3, 2%), *Serratia spp.* (n=3, 2%), *Influenza A* (H1N1) virus (n=2, 1%), *Legionella spp.* (n=1, 0.5%), and more than one resistant pathogen (n=30, 15%). Among all enrolled patients, 143 of them (26.0%) had nosocomial infection upon admission to the ICU and a resistant pathogen was identified in 56 (10%) cases.

Demographic characteristics [age, gender, body mass index (BMI)] and SIRS criteria were not significantly different between survivor and non-survivor groups. The survivor status was compared across ICU data, ICU severity scores, and infectious agents in Table 2.

Mechanical ventilation (NIMV, IMV), need of sedation, insulin infusion, TPN because of intolerance of enteral nutrition, presence of MOF during the entire study period, and length of ICU stay were compared between survivor and non-survivor groups (Table 3).

Total parenteral nutrition and nosocomial infections were independently associated with mortality after adjusting for SOFA scores at the day of admission to the ICU (Table 4).

Table 1. Demographics clinical characteristics of the study population

Variables*	Total n=550	
Age, year	550	65 (53-73)
Gender, Male/Female, n	550	375/175
Body mass index	531	24 (22-28)
Nosocomial infection	143	26.0%
Co-morbid diseases	507	92%
Chronic pulmonary diseases	412	74.9%
Cardiac diseases	264	48.0%
Neurologic diseases	66	12.0%
Cancer	56	10.2%
Chronic renal diseases	23	4.2%
Rheumatological diseases	10	1.8%
Pre-ICU length of stay in hospital		
Ward, day	286	3 (3-7)
Other ICU, day	57	7 (4-13)
SIRS criteria		
Leucocyte count	550	13725 (9800-17440)
Hearth rate per minute	550	112 (99-127)
Breath per minute	550	27 (23-33)
Fever, ºC	550	36.5 (36.0-37.0)
ICU data		
Serum Albumin mg/dL	437	2.9 (2.4-3.3)
C- reactive protein, mg/dL	515	75.5 (31.9-157.0)
PaO_2/FiO_2	550	157 (110-224)
$PaCO_2$ mmHg	550	63.4 (41.0-79.6)
pH	550	7.33 (7.25-7.43)
SOFA score	550	4 (3-6)
APACHE II score	550	20 (16-25)
Mortality, n (%)	550	99 (18.0)

*Continues variables median Interquartile range (25%-75%). ICU: intensive care unit; SIRS: systemic inflammatory response syndrome; PaO_2/FiO_2:arterial partial oxygen pressure over fractionated inspired oxygen; $PaCO_2$: arterial partial carbon dioxide pressure; SOFA score: sequential organ failure assessment score; APACHE II: acute physiological and chronic health evaluation score

Table 2. ICU data and severity of survivor and non-survivor patients with severe sepsis

Variables*	Survivors, n=451	Non-survivors, n=99	p
Pre-ICU day	3 (2-7)	6 (2-10)	0.023
pH	7.33 (7.26-7.43)	7.30 (7.22-7.45)	0.09
$PaCO_2$, mmHg	64.0 (40.7-79.0)	59.7 (43.5-84.0)	0.93
PaO_2/FiO_2	161 (115-225)	130 (90-207)	0.006
APACHE II on admission to ICU	19 (15-24)	23 (19-28)	0.001
SOFA score on admission to ICU	4 (3-6)	6 (4-9)	0.001
Nosocomial infection on admission to ICU, n (%)	103 (22.8)	40 (40.4)	0.001
Bacteriological culture study, n (%)	255 (56.5)	81 (81.8)	0.001
Resistant pathogen, n (%)	96/ 255 (37.6)	45/81 (55.6)	0.004

*Continues variables median, Interquartile range (25%-75%). p<0.05 is accepted as statistically significant. ICU: intensive care unit; $PaCO_2$: arterial partial carbon dioxide pressure; PaO_2/FiO_2: arterial partial oxygen pressure over fractionated inspired oxygen; SOFA score: sequential organ failure assessment score; APACHE II: acute physiological and chronic health evaluation score

Table 3. ICU data and outcomes of survivor and non-survivor patients with severe sepsis

Variables*	Survivors, n=451	Non-survivors, n=99	p
IMV days	5 (3-9)	5 (3-11)	0.38
IMV, n (%)	167 (37.0)	68 (68.7)	0.001
NIMV days	6 (4-10)	5 (3-8)	0.037
NIMV, n (%)	373 (85.4)	62 (63.5)	0.001
Insulin infusion, n (%)	78 (17.3)	40 (40.4)	0.001
Sedation infusion, n (%)	53 (11.8)	28 (28.3)	0.001
Central catheter, n (%)	46 (10.2)	32 (32.3)	0.001
Total parenteral nutrition, n (%)	98 (21.7)	56 (56.6)	0.001
Septic shock on admission to ICU, n (%)	48 (10.7)	50 (50.5)	0.001
Multi organ failure, n (%)	54 (12.0)	55 (55.6)	0.001
Length of ICU stay, days	8 (5–12)	8 (4-13)	0.63

*Continues variables median, Interquartile range (25%-75%). p<0.05 is accepted as statistically significant. ICU: intensive care unit; IMV: invasive mechanical ventilation; NIMV: noninvasive mechanical ventilation

DISCUSSION

This study shows that nosocomial infection and need of TPN because of intolerance of enteral nutrition are independent risk factors for ICU mortality in patients with pulmonary originated severe sepsis. To date, there are a few studies that have evaluated the role of TPN and nosocomial infection as a risk factor of mortality in patients with severe sepsis.

In a previous study, we had found that implication of TPN because of intolerance of enteral nutrition was a risk factor of mortality, and in the present study, we designed a model to evaluate if both TPN and nosocomial infection were a predictor of mortality as good as the SOFA score in patients with severe sepsis in the ICU [10].

As the experience with the use of sepsis protocols increases in course of time, the mortality is expected to decrease in each year, and in our center, sepsis-related mortality decreased from 26% in 2006 to 18% in the present study [3,5-8,10]. Despite the application of sepsis protocols, mortality rate is still high in septic ICU patients, particularly in the septic shock and multi-organ failure patients [16,24,25]. In addition to classical sepsis protocols, there are many

Table 4. Predictors of mortality on admission of ICU in patients with severe sepsis

Variables	Odds ratio	Confidence interval, 95%	p
Total parenteral nutrition	3.8	(2.3-6.1)	0.001
Nosocomial infection	2.4	(1.4-3.9)	0.001
SOFA score on 1st day of ICU	1.3	(1.2-1.4)	0.001

Multivariate logistic regression analysis, p<0.05 is accepted as statistically significant
SOFA score: sequential organ failure assessment score; ICU: intensive care unit

adjunctive therapies in severe sepsis to reduce the mortality further [3]. A strategy of glycemic control in patients with severe sepsis should include a nutrition protocol with the preferential use of the enteral route [26]. This recommendation was supported by the demonstration of a greater harm than benefit ratio with routine parenteral nutrition in postoperative patients because of higher blood glucose levels [27].

Total parenteral nutrition causes the translocation of bacteria into the gastrointestinal tract and increases the resistant pathogen population by decreasing obligate anaerobes, particularly in elderly patients with SIRS/sepsis [28-30]. In the present study, resistant pathogens were higher in the non-survivor group. This result provides further evidence for the abovementioned mechanism. TPN worsens the outcome of patients with sepsis by increasing the resistant pathogens. Gastrointestinal motility is crucial for the physiological balance between pathogens and normal flora within the gut. This not only leads to bacterial translocation but also aspiration pneumonia and sepsis [31]. Enteral feeding is mainly recommended to continue the process of intestinal motility, to protect immune and barrier functions of intestine, and to decrease cost. Unfortunately, gastrointestinal blood supply is decreased in a majority of critically ill patients, particularly in patients with sepsis and septic shock because of hypotension, need for an inotropic agent, and adrenergic discharge, which leads to impaired gastrointestinal absorption. Therefore, patients with sepsis and septic shock frequently encounter gastrointestinal intolerance. On the other hand, there are studies that show suboptimal offer-demand nutrition in critically ill patients, which is characterized by deterioration of nutritional status, higher rates of multiple organ dysfunction, complications, cachexia, loss of muscle strength, prolonged length of stay, and mortality [32,33].

Therefore, intensivists tend to feed the patient at any cost and they are prone to start TPN earlier than recommended. The American Society for Parenteral and Enteral Nutrition (ASPEN) guideline recommends "If early enteral nutrition is not available in the first 7 days following admission to the ICU, no nutrition support therapy should be provided in the patient who was previously healthy prior to critical illness with no evidence of protein malnutrition; use of parenteral nutrition should be reserved and initiated only after the first 7 days of hospitalization (when enteral nutrition is not available)" [34].

All other nutrition guidelines for critically ill patients including ESPEN, ASPEN, SCCM, and CCCPG agree with the benefits of early enteral feeding, and enteral feeding is superior to parenteral feeding [35].

The limitations of our study include the retrospective study design with involvement of a single center with a unique patient population. Moreover, microbiological samples were lacking in 39% of the patients because of the unavailability of the microbiology laboratory at nights and weekends. Lastly, a bacteriological agent was not detected in 41% of the patients in whom samples were obtained despite clinical characteristics suggestive of severe infection and this may be attributed to the receipt of broad spectrum antibiotics. The patient population in respiratory ICU is expected to be older, majority with respiratory acidosis, hypoxemia, and hypercapnia. APACHE II scores of half of our patients were 20; therefore, our mortality rate of 18% may be considered a good outcome. Sevransky et al. [36] recently published their data that evaluated the mortality differences in patients with pulmonary versus non-pulmonary sepsis and they found the mortality similar in both groups. In the same study, interquartile range of APACHE II scores of pulmonary sepsis patients were reported as 19-33 with a mortality rate of 42%.

In conclusion, the results of our study indicate an independent association of total parenteral nutrition and nosocomial infection with ICU mortality in patients with severe sepsis. Therefore, rational use of antibiotics and application of hospital acquired infection control program may help to reduce mortality. Moreover, TPN may contribute to infections with resistant microorganisms in patients with severe sepsis in the ICU.

Ethics Committee Approval: Ethics committee approval was not received for this study, since it was designed retrospectively.

Informed Consent: Due to the retrospective design of the study, the informed consent forms were not able to be taken.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - H.B.T., Z.K.; Design - H.B.T., Z.K.; Supervision - Z.K.; Materials - H.B.T.; Analysis and/or Interpretation - H.B.T., C.S., M.B., F.K., Ö.Y.M., E.Ç., Ö.D., M.Y., İ.Ö.; Literature Review - H.B.T., C.S., M.B., F.K., Ö.Y.M., G.G., E.Ç., Ö.D., M.Y., İ.Ö.; Writer - H.B.T., Z.K., G.G.; Critical Review - N.A., G.G.

Acknowledgements: This was a 2011 MECOR level IV ATS-Turkish Thoracic Society Course project of author Dr. Zuhal Karakurt has awarded by ATS-MECOR-tutorial MECOR Level IV Global Course Award. We are grateful to William Vollmer, Cecilia M Patini, Sonia Buist and Özge Yılmaz for improving our manuscript in MECOR level IV Global Course held by ATS in 2011 Nairobi-Kenya.

Conflict of Interest: No conflict of interest was declared by the authors.

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

Etik Komite Onayı: Çalışmamız retrospektif olduğundan etik kurul onamı alınamadı.

Hasta Onamı: Çalışmamız retrospektif olduğundan hasta onamı alınamadı.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - H.B.T., Z.K.; Tasarım - H.B.T., Z.K.; Denetleme - Z.K.; Malzemeler - H.B.T.; Analiz ve/veya yorum - H.B.T., C.S., M.B., F.K., Ö.Y.M., E.Ç., Ö.D., M.Y., İ.Ö.; Literatür taraması - H.B.T.,

C.S., M.B., F.K., Ö.Y.M., G.G., E.Ç., Ö.D., M.Y., İ.Ö.; Yazıyı yazan - H.B.T., Z.K., G.G.; Eleştirel İnceleme - N.A., G.G.

Teşekkür: Bu Çalışma ile 2011 yılında Nairobi-Kenya'da yürütülen MECOR Level IV Global Course projesi olarak Dr. Zuhal Karakurt ATS-MECOR- MECOR Level IV Global Course ödülüne layık görülmüştür. William Vollmer, Cecilia M Patini, Sonia Buist ve Özge Yılmaz'a projeyi geliştirdikleri için teşekkür ederiz.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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