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ARAŞTIRMA/RESEARCH

Effect of propofol and dexmedetomidine on pulmonary mechanics in intensive care unit patients

Yoğun bakım hastalarında propofol ve deksmedetomidinin akciğer mekanikleri üzerine etkisi

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Abstract

Purpose: Propofol and dexmedetomidine are most preferred sedative agent for mechanically ventilated ICUs patients. The aim of this study is to compare the early effects of propofol and dexmedetomidine on pulmonary mechanics in these patients.

Material and Methods: Between the ages of 18-65 years, requiring sedation, mechanically ventilated 70 patients were included in this study. Patients were divided into two groups and received dexmedetomidine infusion (dexmedetomidine group, Group D) and propofol infusion (propofol group, Group P) for sedation. Ventilation modes, blood gas analysis, pulmonary mechanics (airway resistance, positive end-expiratory pressure, frequency, tidal volume, minute volume, peak airway pressure, compliance, endtidal CO_2, S_{vO2}) and ventilator-patient conflict were evaluated and recorded at baseline, 5,15,30,45 and 60 minutes.

Results: Demographic data and ventilation modes were similar between the groups. Pulmonary compliance gradually increased during 60 minutes in Group D but this difference was not statistically significant. Other pulmonary mechanics were similar between the groups. Arterial blood gase analysis remained within the normal range in both groups. Ventilator-patient conflict was significantly better in Group P than Group D. The number of patients with respiratory depression was higher in Group P than Group D at 45th and 60th minutes.

Conclusions: Dexmedetomidine causes minimal respiratory depression altough propofol has better ventilator-patient conflict. Therefore dexmedetomidine may preferred during weaning period in ICUs patients. Further studies with larger simple size are warranted to reveal a significant difference in terms of pulmonary compliance between propofol and dexmedetomidine.

Key words: Intensive care, peak airway pressure, airway resistance, pulmonary compliance

Öz

Amaç: Propofol ve deksmedetomidin mekanik olarak ventile edilen yoğun bakım hastalarında en sık tercih edilen sedatif ajanlardır. Bu çalışmanın amacı; propofol ve deksmedetomidinin akciğer mekanikleri üzerine erken etkilerini karşılaştırmaktır.

Gereç ve Yöntem: Sedasyon ihtiyacı olan, mekanik olarak ventile edilen, 18-65 yaş arası 70 hasta çalışmaya dahil edildi. İki gruba ayrılan hastalara sedasyon amacıyla deksmedetomidin grubuna (Grup D) deksmedetomidin infüzyonu, propofol grubuna (Grup P) propofol infüzyonu uygulandı. Uygulanan ventilasyon modları, kan gazı analizi, akciğer mekanik değerleri (havayolu direnci, pozitif soluk sonu basıncı, solunum sıklığı, tidal volüm, dakika volümü, tepe havayolu basıncı, kompliyans, soluk sonu CO_2, S_{vO2} değerleri) ve ventilatör-hasta uyumu başlangıç, 5,15,30,45 ve 60 dakikalarda değerlendirilerek kaydedildi.

Bulgular: Demografik veriler ve ventilasyon modları gruplar arasında benzerdi. Akciğer kompliyansı Grup D'de 60 dakika boyunca artmış olmasına rağmen istatistiksel olarak anlamlı değildi. Diğer akciğer mekanikleri değerleri gruplar arasında benzerdi. Arter kan gazı değerleri her iki grupta da normal aralıkta seyretti. Ventilatör-hasta uyumunun Grup P'de Grup D'ye göre daha iyi olduğu saptandı. Solunum depresyonu olan hasta sayısı Grup P'de Grup D'ye göre 45. ve 60. dakikalarda daha yüksekti.

Sonuç: Propofol ile daha iyi ventilatör-hasta uyumu sağlanmasına rağmen, deksmedetomidin daha az solunum depresyonu yapar. Bu nedenle weaning dönemindeki yoğun bakım hastalarında deksmedetomidin tercih sebebi olabilir. Daha geniş örneklem büyüklüğü ile yapılacak çalışmalar propofol ve deksmedetomidinin akciğer mekanikleri üzerine etkilerini netleştirecektir.

Anahtar kelimeler: Yoğun bakım, tepe havayolu basıncı, havayolu direnci, akciğer kompliyansı

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INTRODUCTION

Sedation are needed to tolerate the endotracheal tube or tracheostomy canulla, mechanically lung ventilation and invasive procedures in ICUs patients[1]. Effective sedation helps to decreased anxiety and depression, improved sleeping, reduced ventilator-patient conflict, increased patient comfort and facilitates the processes of critical illness of patients[2-4]. On the other hand, excessive sedation can lead to prolonged the length of ICU stay and weaning from mechanical ventilation, weakness, inability of the neurological status assessment[5]. Therefore, the choice of sedative agent is extremely important in ICUs patients.

Propofol and dexmedetomidine are the most commonly used agents for this purpose. Propofol has a short duration of action but substantial respiratory depression can occur with its higher doses[6]. Dexmedetomidine, a selective α_2-adrenergic receptor agonist, has various considerable effects (analgesia, sedation, minimal respiratory depression etc.) but the use of this drug is not recommended for long-term period of time (>24 hours)[7]. The aim of this study is to compare the effects of propofol and dexmedetomidine on early period pulmonary mechanics in mechanically ventilated ICUs patients. We hypothesized that dexmedetomidine would be better in terms of pulmonary mechanics compared to propofol during intensive care therapy. The primary outcome measures were airway resistance and peak airway pressure and secondary outcome measure was ventilator-patient conflict in this study.

MATERIALS AND METHODS

This prospective, single center, randomized study was conducted in 9-bed medical ICU at Cukurova University between January 2011 and August 2015. This study is registered at Clinical Trials gov (ClinicalTrials.gov Identifier: NCT02330120). Following faculty ethics committee approval (No: 7/3; Date: 07.01.2010) and written informed consent from patients or patients' relatives, between the ages of 18-65 years, requiring sedation, mandatory artery and central cateterization, mechanically ventilated 70 patients were included in this study. Exclusion criteria were the history of hepatorenal disease, primary pulmonary disease, sensitivity or contraindication to propofol and dexmedetomidine, drug or alcohol abuse, hemodynamic instability (vasopressor use or systolic blood pressure<95 mmHg), bradycardia (heart rate<60 bpm), second or third degree heart block, morbid obesity (body mass index of greater than 40 kg/m^2 or body mass index of greater than 35 kg/m^2 and experiencing obesity related health conditions), pregnancy and neurological disease. The subjects requiring sedative or analgesic therapy for nonroutine sedation (severe pain, seizure, substance withdrawal, increased intracranial pressure, aggressive ventilatory treatment) were excluded from this study.

Patients were divided into two groups with computer randomization method. Dexmedetomidine group (Group D, n=35) received dexmedetomidine loading dose (1μg/kg) over 10 min followed by maintenance infusion (0.2-0.7 μg/kg/h) and propofol group (Group P, n=35) received propofol loading dose (1 mg/kg) over 10 min followed by maintenance infusion 0.5-2 mg/kg/h for sedation. Blood gas analysis, airway resistance (cm H_2O/L/sec), PEEP (cm H_20), frequency (breath/min), tidal volume (mL/kg), minute volume (mL), peak airway pressure (cm H_20), pulmonary compliance (mL/cm H_20), endtidal CO_2 (mm Hg), SvO_2 (%) values were obtained by Drager Evita 4 ventilator and recorded at baseline, 5, 15, 30, 45 and 60 minutes. Sedation was assessed using 6-points Ramsey Sedation-Agitation Scale (1= anxious or restless or both, 2= cooperative, orientated and tranquil, 3= responding to commands, 4= brisk response to stimulus, 5= sluggish response to stimulus, 6= no response to stimulus). Drugs infusion rates were titrated according to Ramsey Sedation Scale to be 2-3. Ventilator-patients conflict was evaluated as adaptation to mechanical ventilation (poor=0, moderate=1, excellent=2). A fraction of inspired oxygen (FiO_2) of 30-50% was administered to the all patients. Ventilation modes and the presence of respiratory depression were recorded. Respiratory depression was defined as 30% reduction of initial respiratory rate.

Statistics

SPSS 18.0 package program was used for statistical analysis for data. While categorical measurements (gender, diagnosis, ventilation mode, etc.) were summarized as number or percentage, continuous measurements (age, weight, etc.) were summarized

as mean and standard deviation. Student-t test was used to evaluate the changing of continuous measurements of patients at different times (compliance, airway resistance, peak airway pressure, etc.) during the follow-up. Independent samples t-test or as an alternative Mann-Whitney U test was used to detect instant differences between the groups. Chi-Square test was used to evaluate the patient comfort and respiratuar depression. For all statistical analysis, a p value of less than 0.05 was considered significant.

RESULTS

Seventy patients were eligible for this study but six patients were excluded; four patients were because of not meeting inclusion criteria and two patients were because of declined to participate. Demographic data (age, weight, gender) and ventilation modes were similar between the two groups (Table 1) ($p>0.05$). There was no significantly difference between the values of pulmonary mechanics including airway resistance, PEEP, frequency, tidal volume, minute volume, peak airway pressure, pulmonary compliance, endtidal CO_2 and SvO_2 values (Table 2 and 3) ($p>0.05$). In dexmedetomidine group, pulmonary compliance value gradually increased during 60 min (54.89±22.84 and 64.22±50.37, respectively), but this difference was not statistically significant (Table 2). In propofol group, pulmonary compliance values were similar at all the time intervals. Arterial pH, PaO_2 and $PaCO_2$ measurements remained within the normal range in both groups (Table 4).

Ventilator-patient conflict scores were significantly better in Group P than Group D at the all time intervals (Table 5). The number of patients with respiratory depression was higher in Group P than Group D at 45th and 60th minute ($p=0.041$, $p=0.041$, respectively) (Table 6).

Table 1. Demographic values and ventilation modes of the groups.

	Group P (n=31)	**Group D** (n=33)	**p**
Gender (male/female)	24/7	27/6	0.76
Age (year)	46.6±19.1	54.1±21.0	0.14
Weight (kg)	66.4±14.9	68.7±12.0	0.61
Mechanic ventilation modes (SIMV/ASB/BIPAP)	15/15/1	17/16/0	0.58

Data are presented mean±SD or number of patients. Statistical analysis included Chi-Square and Student-t test.

Table 2. Pulmonary mechanics and pressures of the groups.

	Group P (n=31) (mean±SD)	**Group D (n=33) (mean±SD)**	**p**
Compliance			
Baseline	57.43±28.49	54.89±22.84	0.11
5th minute	52.25±22.42	57.49±28.97	0.20
10th minute	54.49±24.22	61.40±30.79	0.32
30th minute	55.12±28.13	65.93±50.65	0.34
45th minute	53.73±26.86	61.70±33.54	0.79
60th minute	55.10±22.31	64.22±50.37	0.11
Airway resistance			
Baseline	13.79±9.62	16.64±11.94	0.35
5th minute	13.78±9.97	18.07±16.84	0.26
10th minute	13.92±7.54	17.33±10.77	0.18
30th minute	15.00±8.42	17.28±11.01	0.75
45th minute	15.22±9.71	16.95±8.67	0.70
60th minute	14.90±8.38	17.63±11.65	0.44
Peak airway pressure			
Baseline	23.45±6.34	22.12±4.94	0.17
5th minute	23.68±6.79	23.42±5.29	0.28
10th minute	23.77±6.94	23.18±6.02	0.53
30th minute	24.06±6.63	22.67±5.77	0.45
45th minute	24.51±6.42	23.51±5.73	0.85
60th minute	24.25±7.11	23.30±5.60	0.46

PEEP			
Baseline	6.06±1.87	5.21±1.02	0.05
5th minute	5.93±1.89	5.09±1.04	0.05
10th minute	5.87±1.74	5.15±1.06	0.06
30th minute	5.83±2.05	5.21±1.02	0.05
45th minute	5.64±1.66	5.11±1.18	0.16
60th minute	5.93±1.89	5.27±1.23	0.05

Data are presented mean±SD and statistical analysis included Student-t test.

Table 3. Mechanical ventilator settings of the groups

	Group P (n=31) (mean±SD)	**Group D (n=33) (mean±SD)**	**p**
Tidal volume			
Baseline	559.29±128.38	543.63±107.13	0.15
5th minute	568.83±117.78	545.93±97.99	0.20
10th minute	573.25±123.00	549.63±107.09	0.37
30th minute	570.35±119.69	539.57±92.67	0.14
45th minute	558.90±120.03	542.69±88.36	0.25
60th minute	558.93±124.31	528.30±86.38	0.99
Minute volume			
Baseline	11.52±5.13	11.94±4.86	0.99
5th minute	11.56±4.07	11.79±4.32	0.45
10th minute	11.03±4.37	11.57±4.45	0.36
30th minute	11.12±4.60	10.99±4.03	0.90
45th minute	11.17±4.31	10.86±4.31	0.63
60th minute	11.22±4.14	10.84±4.10	0.65
Frequency			
Baseline	23.93±10.12	23.30±10.23	0.75
5th minute	23.22±8.92	22.54±8.80	0.70
10th minute	22.22±7.74	23.09±8.53	0.42
30th minute	21.29±8.17	22.57±8.01	0.97
45th minute	21.25±7.89	21.63±7.33	0.95
60th minute	22.19±9.12	22.12±7.73	0.63

Data are presented mean±SD and statistical analysis included Student-t test.

Table 4. Artery blood gase analysis of the groups

	Group P (n=31) (mean±SD)	**Group D** (n=33) (mean±SD)	**p**
pH			
Baseline	7.40±0.88	7.38±0.88	0.92
5th minute	7.40±0.87	7.38±0.74	0.67
10th minute	7.40±0.84	7.39±0.73	0.87
30th minute	7.40±0.88	7.39±0.71	0.42
45th minute	7.40±0.83	7.39±0.69	0.68
60th minute	7.40±0.83	7.39±0.64	0.26
PaO_2			
Baseline	99.41±61.94	94.57±29.29	0.30
5th minute	98.89±45.00	89.50±25.68	0.15
10th minute	92.02±23.00	89.21±29.18	0.47
30th minute	93.50±23.11	92.57±28.15	0.70
45th minute	91.49±22.30	93.02±30.53	0.44
60th minute	91.80±20.93	92.22±30.91	0.11
$PaCO_2$			
Baseline	39.05±12.18	37.61±9.30	0.81
5th minute	39.80±11.90	36.87±7.70	0.25
10th minute	40.03±12.07	36.47±7.06	0.36
30th minute	40.09±10.29	36.54±7.41	0.37
45th minute	40.07±8.63	36.65±8.45	0.96
60th minute	39.42±7.48	36.69±9.27	0.28

Data are presented mean±SD and statistical analysis included Student-t test.

Table 5. Ventilator-patient confict of the groups (0=poor, 1=moderate, 2=excellent)

	Group P (n=31) (0/1/2)	**Group D** (n=33) (0/1/2)	**p**
Baseline	1/4/26*	12/5/16	0.000*
5th minute	1/5/25*	12/3/18	0.004*
10th minute	0/4/27*	12/3/18	0.001*
30th minute	0/3/28*	11/3/19	0.002*
45th minute	0/2/29*	11/3/19	0.001*
60th minute	0/3/28*	11/3/19	0.002*

Data are presented the number of patients. *p<0.05, compared with Group D. Statistical analysis included Chi-Square test.

Table 6. The respiratory depression incidance of the groups

	Group P (n=31)	**Group D** (n=33)	**p**
5th minute	6 (19.4%)	2 (6.1%)	0.142
10th minute	8 (25.8%)	3 (9.1%)	0.103
30th minute	8 (25.8%)	3 (9.1%)	0.103
45th minute	8 (25.8%)	2 (6.1%)	0.041*
60th minute	8 (25.8%)	2 (6.1%)	0.041*

Data are presented the number of patients. *p<0.05, compared with Group D. Statistical analysis included Chi-Square test.

DISCUSSION

We found that dexmedetomidine and propofol provide effective sedation without clinically important effect on lung mechanics. Propofol produces improved ventilator-patient conflict but higher respiratory depression rate compared to dexmedetomidine in mechanically ventilated ICUs patients.

In recent years, the definition of "conscious sedation" has been used more frequently in ICUs patients. The primary goal of sedation in ICUs is to provide a minimal sedative exposure, maximum comfort and unchanging or minimal effect on respiratory and hemodynamic variables. In this context, the quest for the ideal sedative agent is still ongoing. In our study we used dexmedetomidine and propofol for sedation in ICUs patients.

Dexmedetomidine is often preferred for ventilated or non-ventilated patients who require sedation[7]. It has rapid distribution (6 min) and elimination (2 h) half time (8,9). In animal and human studies demostrated that α_2 agonists did not increase the respiratory depression[10-11]. However, expecially in higher doses, α_2 agonists found in one of the part of the brain, locus ceruleus. This area plays a role in respiratory control as well as sleep modulation[12]. Therefore, it can be proposed that dexmedetomidine has sedative, analgesic and respiratory effects[13]. The effect of dexmedetomidine on respiratory mechanics were shown in the several animal and human studies[14-17]. Intravenous administration of dexmedetomidine in clinically relevant doses significantly attenuates histamine-induced reflex bronchoconstriction and leads to reduce airway resistance via presynaptic neural mechanism in canine airways[16]. Hsu et al compared the respiratory effects of dexmedetomidine with remifentanil in healthy volunteers and they reported an increase in respiratory rate with dexmedetomidine infusion but sample size (n=8) of this study is very small.[14] In contrast, Belleville et al reported dexmedetomidine decreased respiratory rate and caused apnea periods in human volunteers[17]. However in this study, they used 1-2 μg/kg/h dexmedetomidine infusion and this is very higher than recommended infusion dosage (0.2-0.7 μg/kg/h) of dexmedetomidine for sedation[4]. In addition, the authors demostrated that dexmedetomidine infusion increased $PaCO_2$ values, decreased minute volume expecially 10 min following administration. Fernandes et al reported that dexmedetomidine did not affect respiratory mechanism but irregular breating and apnea episodes occured after infusion in rats[18]. In our study, we did not observe any apne episodes in both groups but respiratory depression rate was lower in dexmedetomidine group.

Propofol is one of the most widely used sedative and anesthetic agent, however it can cause respiratory depression particularly in higher doses[6].

In induction dose of propofol leads to decreased tidal volume, respiratory rate and minute volume[19]. In addition, propofol produces a reduction in ventilatory response to hypoxia and CO_2, consequently CO_2 values are increased, pH is decreased[20,21]. In sedative doses, it has minimal negative effect on minute ventilation and tidal volume and it dose not change arterial blood gase values[22]. Some studies demostrated that propofol decreased airway resistance in humans and rats due to its direct relaxant effect on smooth muscle[23-26]. Yamakage et al showed that this effect of propofol may be associated with a reduction of the calcium entry into the porcine tracheal smooth muscle cells[23]. Heil and his colleagues compared the short-time effects of dexmedetomidine and propofol in a model of diet-induced obese rats[27]. They found that a 1-hour propofol infusion increased airway resistance, bronchoconstriction index, atelectasis and inflammatory cytokines and decreased antioxidative enzymes. Morever, they determined short-term dexmedetomidine infusion did not affect biologic and morphofunctional structure of the lung. In another study, dexmedetomidine was shown to improve oxygenation and lung mechanics in patients with chronic obstructive pulmonary disease[28]. On the other hand, our study supported that dexmedetomidine and propofol did not cause to any changing on patients' pulmonary mechanics. We observed that airway compliance value was higher than initial value in dexmedetomidine group at 60th minute but this difference was not statistically significant.

In the literature, several studies were reported comparing the effects of propofol with dexmedetomidine on sedation, their side effects and recovery characteristics in mechanically ventilated subjects[29,30]. In our study, we used propofol (0.5-2 mg/kg/h) or dexmedetomidine (0.2-0.7 μg/kg/h) for sedation in ICUs patients and obtained an appropriate sedation levels with both drugs. However we determined the higher ventilator-patient conflict in propofol group than dexmedetomidine group.

There are some limitations in our study. First, we did not investigate the blood concentrations of dexmedetomidine and propofol. Second, we evaluated patients' pulmonary mechanics during first 60 min following sedative drug administration because we aimed the effect of these drugs on early period pulmoner mechanics.

Dexmedetomidine has minimal respiratuar depression properties altough propofol has better ventilator-patient conflict than dexmedetomidine. Therefore dexmedetomidine may be useful during weaning period in ICUs patients. Further studies with larger simple size are warranted to reveal a significant difference in terms of pulmonary mechanics between propofol and dexmedetomidine.

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