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Orgınal Article

Comparison of the effects of Propofol. Dexmedetomidine and Midazolam on Sedation and Oxidative-Antioxidant System in Critically ill Patients

Yoğun Bakım Hastalarında Propofol, Deksmedetomidin ve Midazolam'ın Sedasyon. Oksidan – Antioksidan Sistem Üzerine Etkilerinin Karşılaştırılması

Mehmet Kenan Erol[1], Saban Yalcin[1], Harun Aydogan[1], Evren Buyukfirat[1], Mahmut Alp Karahan[1], Cengiz Mordeniz[2], Nurten Aksoy[3]

[1] Harran University Faculty of Medicine Hospital. Department of Anesthesiology and Reanimation Sanliurfa / TURKİYE

[2] Namik Kemal University Faculty of Medicine Hospital. Department of Anesthesiology and Reanimation Tekirdag / TURKİYE

[3] Harran University. Faculty of Medicine. Department of Biochemistry. Sanliurfa / TURKİYE

Corresponding author:
Dr. Mehmet Kenan Erol (MD)
Adress:
Harran University, Faculty of Medicine, Department of Anesthesiology and Reanimation Sanliurfa / TURKİYE
E-mail: kenanerol970@gmail.com
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Highlights

- Among sedative drugs, dexmedetomidine has better results in terms of oxidative stress parameters.

Abstract

Background: This study aimed to compare the impact of midazolam, propofol, dexmedetomidine infusions for 24th hour on total antioxidant status (TAS), total oxidant status (TOS), oxidative stres index (OSI) and prolidase levels.

Material and Method: 75 patient ICU patient who were mechanically ventilated enrolled to the study. Patients randomised to three groups. Group I (n=25, midazolam): 0.02 mg/ kg/h midazolam, Group II (n = 25, propofol): 1mg/kg/h propofol, Group III (n=25, dexmedetomidine): 0.2 µg/ kg/h dexmedetomidine infusions was started. Dosage were arrange to achieve Ramsay sedation score 3. Blood samples were collected in basal, 6.,12.,18., 24. hour, and hemodynamic parameters were also recorded in the same time intervals. **Results**: In midazolam group 24. hour TAS levels were significantly decreased and TOS, prolidase and OSI levels were significantly increased compared to the basal level ($p<0.05$). 24. hour TAS levels were significantly decreased and TOS, prolidase and OSI levels were significantly increased compared to basal level in propofol group ($p<0,05$). In dexmedotimidine groups 24.hour TAS and prolidase levels were significantly decreased, OSI levels were increased compared to the basal levels ($p<0.05$). Increase in TOS levels were not statistically significant ($p>0.05$). Basal TAS, TOS, prolidase, OSI levels were not statistically significantly between the different groups ($p>0.05$).**Conclusion:** Dexmedetomidine was found to be having statistically significant favorable results in comparison to others. However there results should be clinically and molecularity verified with large scale further studies. **Keywords**: Intensive care unit, sedation, oxidative stress, midazolam, propofol, dexmedetomidine

ÖZ

Amaç: Bu çalışmada yoğun bakımda sık kullanılan sedasyon ajanlarındanmidazolam, propofol ve deksmedetomidinin sedasyon amacıyla 24 saatlik infüzyonlarınıntotal antioksidan seviye (TAS), total oksidan seviye (TOS), oksidatif stres indeksi (OSI), ve prolidaz değerleri üzerine olan etkilerini karşılaştırmak amaçlandı.**Materyal ve Metod:** Çalışmaya yoğun bakımda yatmakta olan 75 erişkin hasta dahil edildi. Çalışmaya dahil edilen olgular üç gruba randomize edildi. Grup I'e (n=25, midazolam): 0,02 mg/kg/saatmidazolam, Grup II'ye (n = 25, propofol): 1mg/kg/saat propofol, Grup III'e (n=25, deksmedetomidin): 0,2 µg/kg/saat deksmedetomidin infüzyonuna başlandı. Hastaların bazal 6.,12.,18., ve 24. saatteki hemodinamik parametreleri kaydedilerek kan örnekleri alındı. **Bulgular:** Grup içi incelemelerde midazolam grubunda 24. saatte TAS değerleri bazale göre istatistiki olarak azalırken, TOS, prolidaz ve OSI değerleri istatistiki olarak artmıştır ($p<0,05$). Propofol grubunda 24. saat TAS değerleri bazale göre istatistiki olarak azalırken, TOS, prolidaz ve OSI artış tespit edilmiştir ($p<0,05$). Deksmedetomidin grubunda TAS ve prolidaz değerlerinde istatistiksel olarak anlamlı azalma görülürken ($p<0,05$), OSI değerlerinde istatistiksel olarak anlamlı artış görülmüştür ($p<0,05$). TOS değerlerindeki artış ise istatistiksel olarak anlamlı bulunmamıştır ($p>0,05$). **Sonuç:** Grup içi ve gruplar arası incelemelerde deksmedetomidin ile ilgiliistatistiksel olarak anlamlı olumlu sonuçlar elde edilmiştir. Sonuçların daha geniş çalışmalarlahem moleküler hem de klinik açıdan desteklenmesi gerektiğini düşünmekteyiz. **Anahtar kelimeler:** Yoğun bakım, sedasyon, oksidatif stres, midazolam, propofol, deksmedetomidin

Introduction

Patients who undergo mechanical ventilation (MV) in the Intensive Care Unit often need sedation. even if they are unconscious. There are still debates about which drug should be given in what dose. among the various agents routinely used for sedation. and their superiority over each other (1).

Providing sedation in intensive care patients receiving MV support is one of the important components of treatment. Being on a mechanical ventilator in the intensive care unit is a cause of anxiety in itself. In addition. pain and agitation may lead to increased myocardial oxygen consumption, immunosuppression, and hypercoagulopathy (1,2).

Disrupted sleep pattern/abnormal sleep rhythm in intensive care patients is also an important cause of orientation and psychological disorders. It is accepted that the fatigue caused by the deterioration in sleep rhythm in the critically ill is an important reason for the termination of MV and the prolongation of the time of discharge from the intensive care unit (3).

Hearing is the last sense to deteriorate in humans. and unusual sounds such as medical comments and monitor alarms heard by the intensive care patient are other serious causes of anxiety (2).

One of the scariest situations a person can find themselves in is being therapeutically paralyzed and fully aware of it. For this reason. sedation is strictly indicated in all paralyzed intensive care patients (4).

Another picture that can occur frequently in intensive care patients is agitation. This is probably a clinical condition of anxiety. disorientation and pain. However. the important thing here is to eliminate organic causes such as hypoxia, hypercarbia, hypoglycemia, drug or alcohol withdrawal and encephalopathy that cause agitation. Therefore. differential diagnosis is extremely important before intervening in agitation (5).

By providing sedation. these negative factors can be prevented and the length of stay of the patient in the mechanical ventilator and the length of stay in the intensive care unit can be shortened. For this purpose. various drugs are used today. Despite their clinically significant beneficial effects. drugs used for sedation have significant side effects. making it difficult for clinicians to choose appropriate drugs and doses. In this study. to compare the effects of the sedation agents of midazolam. propofol and dexmedetomidine. which are frequently used in intensive care units. on hemodynamics and total antioxidant level (TAS), total oxidant level (TOS), oxidative stress index (OSI) and prolidase values was intended.

Propofol, midazolam and dexmedetomidine are some of the commonly used intravenous agents for the induction and maintenance of general anesthesia. procedural and intensive care sedation. Dexmedetomidine. which is a candidate to be an alternative to frequently used midazolam-propofol or midazolam-opioid combinations; It is a sedo-analgesic with analgesic, sedative, anxiolytic properties. Although it was originally produced for the sedation of intensive care patients. It is increasingly used in non-operating room sedoanalgesia. Sedation without respiratory depression Its analgesic property is superior to other agents (6-10).

Methods

Patient Selection

Ethical approval was taken 03.12.2008/9 Ethics Committee of Harran University Faculty of Medicine Clinical Research Ethics Committee. Written consent was obtained from the parents or guardians of the unconscious patients, who were informed about the procedures to be done. Afterwards, 75 adult patients (18-70 years old) who were treated with MV between January 2009 and January 2010 in the General Intensive Care Unit of the Department of Anesthesiology and Reanimation were included. On the day they started to receive treatment, their physical examinations were performed and their hemograms and biochemical parameters were recorded.

Exclusion Criteria:

Those who are allergic to the drug, the patient or his family does not accept it, there is a drug interaction between the other drugs he uses and the drugs we will use.

The patients were randomly randomized and divided into 3 groups of 25 patients.

Group I (n=25. midazolam): The subjects were given 0.02 mg/kg/hour midazolam as an infusion.

Group II (n=25. propofol): The subjects were given 1mg/kg/hour of propofol as an infusion.

Group III (n=25. dexmedetomidine): The subjects were given 0.2 microgram/kg/hour of dexmedetomidine as an infusion.

Demographic Data

The day when the patients included in the study started to receive mechanical ventilator therapy. their name. surname. Age, weight, height, gender, smoking, diagnosis, whether there was any additional pathology other than the current diagnosis, and nutritional status were recorded. Basal 6.. 12.. 18. and 24. Hours at heart rate. mean arterial pressure values. arterial oxygen saturation. TAS. TOS. prolidase values were recorded.

Blood samples were sent to the biochemistry laboratory in a 5 cc biochemistry tube. The obtained samples were centrifuged at 3000 rpm for 5 minutes and stored in a deep freezer at -80ºC until the working time. On the study day, prolidase enzyme activity was thawed to evaluate TAS and TOS status. The newly developed optimized

modified Chinard Method (11. 12). a colorimetric measurement method for prolidase enzyme activity. and a fully automatic colorimetric method developed by Erel (Rel-Assay commercial kits) were used to measure TAS and TOS states (13-16).

Statistical Analysys

SPSS (Statistical Package for Social Sciences) for Windows 11.5 (SPSS Inc. Chicago USA) program was used for Statistical analysis.The normal distribution of the data was based on skewness and cortisis values. The data were distributed normally. Analysis of Variance in Repeated Measurements test was used to evaluate recurrent hemodynamic data within the group. One Way ANOVA test was used for quantitative comparisons between and within groups. and Chi-Square test was used for categorical data. Results were expressed as mean ± standard deviation. and $p<0.05$ was considered statistically significant.

RESULTS

Demographic Data

To this study; Seventy-five adult patients who were treated with mechanical ventilators between January 2009 and January 2010 in the Department of Anesthesiology and Reanimation, Department of Anesthesiology and Reanimation, Harran University were included. 51 of the patients (68%) were male and 24 were female (32%). The demographic data of the groups are given in **Table 1**.

Table.1 Cross-group demographic data

	Midazolam	Propofol	Deksmedetomidin
Age (years)	65.52 ± 17.26	58.96 ± 19.1	60.6 ± 23.59
Weight (kg)	73.76 ± 10.68	69.64 ± 11.30	68.52 ±12.46
Height (cm)	165.8 ± 8.42	166.32 ± 9.68	165.48 ± 7.01

Aberrations: cm:centimeter kg: kilogram Data are given as standard deviation from mean ±.SD

TAS. TOS. OSI. Prolidase basal. 6th. 12th and 24th hour values of the midazolam group are shown in Table 2. When the TAS values of the Midazolam Group patients were compared, a statistically significant decrease was found in the 6th. 12th and 24th hour values compared to the baseline value ($P<0.05$). When the TOS values of Midazolam Group Patients were compared. they were 6..12. Statistically significant increase was detected at 24th and 24th hours ($p<0.05$). When the Midazolam Group Prolidase values were compared, a statistically significant increase was found compared to the basal value at the 6th. 12th and 24th hours ($p<0.05$). When the OSI values of the patients in the Midazolam Group were compared. a statistically significant increase was found compared to the baseline value ($p<0.05$) **(Table 2).**

Table.2 Midazolam group TAS. TOS. OSI and Prolidase values

Parametres	BaSal	6.hours	12.hours	24.hours
TAS (mmol TroloksEqv./L**)**	1.3252±0.28475	1.2773±0.2853*	1.0245±0.23321*	0.9067±0.12984*
TOS(µmol H_2O_2 Eqv./L)	14.990±3.891	17.248±3.756*	23.408±4.924*	26.9464±5.1552*
OSI (AU)	1.2396±0.4081	1.4248±0.4575*	2.441±0.957*	3.0445±0.756*
Prolidaz (U/L)	686.649±12.559	690.0358±12.544*	693.174±18.226*	702.872±10.674*

Aberrations:* Statistically significant ($p<0.05$) when compared with baseline value. Data are given as mean ± standard deviation.TAS: Total Antioxidant Level TOS: Total Oxidant Level OSI: Oxidative Stress Index

Propofol group TAS, TOS, OSI, Prolidase basal, 6^{th}, 12th and 24th hour values are shown in Table 3. When the TAS values of the Propofol Group patients were compared, the decrease determined at the 6th hour value compared to the baseline value was not statistically significant ($p>0.05$). While the 12th and 24th hour values decreased statistically significantly compared to the baseline value ($p<0.05$). When the TOS values of the Propofol Group patients were compared, a statistically significant increase was found compared to the baseline value ($p<0.05$). When the Propofol Group Prolidase values were compared, a statistically significant increase was found compared to the basal value at the 6th. 12th and 24th hours ($p<0.05$). When the OSI values of the Propofol Group patients were compared. a statistically significant increase was found compared to the baseline value ($p<0.05$) **(Table 3).**

Table.3. Propofol group TAS. TOS. OSI and Prolidase values

Parametres	BaSal	6.hours	12.hours	24.hours
TAS (mmolTroloksEqv./L)	1.3196±0.28475	1.2283±0.2119	1.055±0.240*	0.9258±0.1694*
TOS (μmol H_2O_2 Eqv./L)	15.404±3.704	26.681±6.188*	28.010±6.466*	31.196±3.431*
OSI (AU)	1.2784±0.420	2.2118±0.611*	2.819±1.021*	3.49±0.79*
Prolidaz(U/L)	694.08±26.48	696.91±26.56*	698.42±14.51*	707.64±11.40*

Aberraions:* Statistically significant (p<0.05) when compared with baseline value. Data are given as mean ± standard deviation. TAS: Total Antioxidant Level TOS: Total Oxidant Level OSI: Oxidative Stress Index

Dexmedetomidine group TAS. TOS. OSI. Prolidase basal 6th 12th and 24th hour values are shown in Table 4. When the TAS values of the Dexmedetomidine Group patients were compared. a statistically significant decrease was found at the 6th hour value compared to the baseline value (p<0.05). Although there were lower levels compared to the baseline value at the 12th and 24th hour values. it was not statistically significant. A statistically significant increase was observed in the 12th hour value compared to the 6th hour p(<0.05). When the TOS values of the Dexmedetomidine Group patients were compared. there was a statistically significant increase in the 6th and 12th hour values compared to the baseline value (p<0.05). while no statistically significant difference was found between the baseline value and the 24th hour (p>0.05). When the Dexmedetomidine Group Prolidase values were compared. a statistically significant decrease was found between the baseline value and the 24th hour (p<0.05). When the OSI values of the Dexmedetomidine Group patients were compared. a statistically significant increase was found in the 6th. 12th and 24th hour values compared to the baseline value (p<0.05) **(Table 4).**

Table.4. Dexmedetomidine group TAS. TOS. OSI and Prolidase values

Parameters	BaSal	6.hours	12.hours	24.hours
TAS (mmolTroloksEqv./L	1.276±0.2824	0.89±0.20*	1.1857±0.344	1.067±0.34
TOS (μmol H_2O_2 Eqv./L)	16.81±5.81	23.15±6.13*	27.75±6.66*	20.34±5.96
OSI (AU)	1.40±0.64	2.76±1.04*	2.49±0.85*	2.14±0.95*
Prolidaz (U/L)	690.51±14.8	693.30±14.85	675.34±32.91	671.11±20.87*

Aberrations:* Statistically significant (p<0.05) when compared with baseline value. Data are given as mean ± standard deviation. TAS: Total Antioxidant Level TOS: Total Oxidant Level OSI: Oxidative Stress Index.There was no statistically significant difference between the groups in terms of demographic data (p>0.05).

Discussion

Approximately 1/3 of the patients hospitalized in the intensive care unit need MV and often require analgesia and sedation. Despite their clinically significant beneficial effects, drugs used for sedation have significant side effects, making it difficult for clinicians to choose drugs and doses (17). In patients undergoing MV, pain also has important side effects such as increased endogenous catecholamine activity,anxiety and delirium (18).

In the study conducted by Wunsch et al. (19) in the United States. 51.5% of 109.671 patients who underwent MV received one or more sedative infusions. sedative use increased from 39.7% in 2001 to 66% in 2007. They reported that it increased to 0.7. that 81% of those who received sedatives took propofol, 31% took benzodiazepine, 34% took dexmedetomidine. Nowadays. intensive care sedations are increasingly performed within the framework of protocols. However. Ethier et al. (20) found in their study that more than 50% of patients discharged from the intensive care unit, despite sedation protocols. recalled the pain. fear and anxiety they experienced, and severe or moderate events. Midazolam, propofol and dexmedetomidine used in this study are widely used for intensive care sedation.

In this study, it was aimed to investigate the effects of propofol, midazolam and dexmedetomidine on TAS, TOS, OSI and prolidase after 24 hours when used for sedation in the intensive care unit.

It is known that propofol has positive effects on oxidative stress and inflammation due to its chemical structure. Balyasnikova et al. (21) showed that propofol prevents oxidative damage in the lung. Tsuchiya et al. (22) examined the effects of propofol on oxidative damage on human erythrocytes and showed that propofol increases the resistance to hemodynamic and physical stress by increasing membrane flow in erythrocytes, protects against repetitive oxidative and physical stresses, and has an effective and safe antioxidant potential.

Tsuchiya et al. (23) compared the antioxidant activities of propofol and midazolam and showed that propofol has a greater potential to reduce oxidative stress compared to midazolam.

In one of the limited studies examining the effects of dexmedetomidine on inflammation, it was shown that subhypnotic doses of dexmedetomidine decreased IL-12 release from macrophages and decreased the Th1/Th2 ratio (24). Tasdogan et al. (25) compared the effects of propofol and dexmedetomidine infusions on the inflammatory response. intra-abdominal pressure values. and IL-1. IL-6. TNF-α levels in 40 adult patients hospitalized in the intensive care unit after abdominal surgery and dependent on mechanical ventilator. They showed that IL-1. IL-6 TNF-α and intra-abdominal pressure were lowered more. Qioa H. et al. (26) showed that dexmedetomidine and midazolam can reduce early mortality in severely septic rats. and the decrease in mortality indicates the low TNF-α levels in both groups. Venn et al. (27) in their study in which they compared the effects of dexmedetomidine and propofol on the endocrine, metabolic, inflammatory and cardiovascular systems of patients hospitalized in the intensive care unit after a major surgery (28). They randomly divided 20 patients in need of postoperative sedation into two groups and divided them into one group with dexmedetomidine 0.2-2.5 μg/kg. They gave 1-3 mg/kg/hour propofol to the other group/hour. Blood pressures. heart rate. and cortisol. ACTH, growth hormone. prolactin. insulin, glucose, and IL-6 levels were measured respectively. While the heart rate was lower in the dexmedetomidine group. while there was no difference between the two groups in arterial pressures, cortisol, ACTH, prolactin, and glucose concentrations. It was shown that IL-6 level was lower in the dexmedetomidine group. Aslan et al. (29) investigated the effect of dexmedetomidine after traumatic spinal cord injury, traumatic spinal cord injury was found to be associated with lipid peroxidase elevation and a decrease in enzymatic, non-enzymatic endogenous antioxidative defense system. It has been shown that dexmedetomidine inhibits lipid peroxidation and causes an increase in the endogenous antioxidant defense system in CSF and spinal cord tissue samples. Yagmur et al. (30) showed that dexmedetomidine significantly reduced hypoxanthine production in ischemia and malondiaaldehyde production in reperfusion period on ischemia-reperfusion injury due to tourniquet applied during upper extremity surgery on 40 patients.

In this study, in-group studies it was shown that TAS decreased within 24 hours in the propofol and midazolam group but did not change in the dexmedetomidine group. It was determined that OSI increased at the end of 24 hours in all three drugs, while prolidase increased after 24 hours in other groups and decreased in the dexmedetomidine group. In the examinations between the groups, it was determined that there was no difference in TAS at the end of 24 hours, and there was a significant decrease in TOS and OSI and prolidase values in the dexmedetomidine group.

The high OSI values in all three drug groups at the end of 24 hours indicate the severe oxidative stress that intensive care patients are exposed to. In particular. the decrease in TAS values and the increase in TOS values confirm this. In the comparison between groups, the fact that TAS and TOS values did not statistically change in the dexmedetomidine group and showed a change in the direction of increasing OSI in the other groups shows that dexmedetomidine is more preferable for sedation in intensive care patients.

In our study, we also examined prolidase enzyme activities in all three groups for 24 hours and examined whether collagen metabolism was changed. Collagen, one of the most common proteins in our body. can undergo metabolic changes in case of severe oxidative stress (6).

It was determined by the increased prolidase enzyme activity that the metabolism of this protein, which is likely to be mechanically damaged as well as oxidative damage in intensive care patients due to MV, accelerates in general. From this point of view, we demonstrated that the dexmedetomidine group did not accelerate the metabolism of collagen proteins, and therefore catabolism did not increase, with the decreased prolidase enzyme activity detected at the end of 24 hours. According to the results of this study; a statistically significant positive result was obtained with dexmedetomidine both in and between groups. The biochemical results obtained in this study at the end of 24 hours can be considered in terms of choosing between drugs for intensive care sedation. However, we think that the results should be supported by larger studies, both molecularly and clinically. Confirmation of our results by evaluating both oxidant-antioxidant and prolidase enzyme activity levels. especially in larger patient population and patients under longer follow-up. will make a great contribution to the medical literature.

Study Limitation

The biggest limitation of this study is the absence of a control group.

Conclusion

According to the results of this study. no significant difference was found between the groups in terms of hemodynamics. Statistically significant positive results were obtained with dexmedetomidine in the in-group and between-group examinations. We think that the results should be supported by larger studies. both molecularly and clinically.

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Ethical Approval: *Ethical approval was taken 03.12.2008/9 Ethics Committee of Harran University Faculty of Medicine Clinical Research Ethics Committee. We conducted this study according to the principles of the Declaration of Helsinki. Informed consent was obtained from all the participants.*

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