Archives of Anesthesiology and Critical Care (Autumn 2024); 10(Supplement 1): 468-473.

Available online at http://aacc.tums.ac.ir

Research Article

Clinical Outcomes of Using Dexmedetomidine, ProDex and Popfol for Sedation during Mechanical Ventilation in Patients Hospitalized in the Intensive Care Unit: A Triple Blinded Clinical Trial

Saied Morteza Heidari[1], Mohammadreza Habibzadeh[1], Azim Honarmand[1], Behzad Nazemroaya[1]*, Sayed Abolfazl Mousavi[2]

[1]*Department of Anesthesiology and Critical Care, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.*

[2]*School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.*

ARTICLE INFO

Article history:
Received 25 December 2023
Revised 16 January 2024
Accepted 01 February 2024

Keywords:
Dexmedetomidine;
Propofol;
Mechanical ventilation;
Ramsey score

ABSTRACT

Background: Sedation plays a crucial role in the care of intensive care unit (ICU) patients, addressing the challenges presented by factors such as agitation, anxiety, and delirium, particularly during mechanical ventilation (MV). Dexmedetomidine and propofol are commonly used sedatives, each with its unique characteristics and side effects. Combining these agents has been proposed to optimize effectiveness and minimize adverse effects. This study aims to compare the efficacy of the dexmedetomidine-propofol combination with dexmedetomidine alone and propofol alone for sedation during mechanical ventilation in ICU patients.

Methods: A triple-blinded clinical trial was conducted in Isfahan, Iran, involving patients eligible for spinal fusion surgery and mechanical ventilation. Patients were randomized into three groups: dexmedetomidine alone (DO), propofol alone (PO), and a combination of both drugs (DP) dexmedetomidine-propofol (ProDex). Various dosages and infusion protocols were carefully administered, and patients were assessed for demographic and clinical variables. Hemodynamic parameters and sedation levels were monitored, and statistical analysis was performed.

Results: The study involved 87 patients, with the ProDex group demonstrating the shortest mechanical ventilation duration. Hemodynamic stability was observed in the ProDex group, with significantly lower systolic blood pressure and heart rate compared to other groups. Sedation scores did not differ significantly among groups, suggesting similar sedative effects. The ProDex group exhibited favorable outcomes despite differences in hemodynamic variables.

Conclusion: The dexmedetomidine-propofol combination appears effective in minimizing side effects associated with monotherapy sedation, leading to favorable clinical outcomes. This study contributes valuable insights into optimizing sedation strategies for mechanically ventilated ICU patients.

The authors declare no conflicts of interest.

*Corresponding author.
E-mail address: behzadnazemroaya797@gmail.com

Introduction

Sedation is an important part of the intensive care unit (ICU) and, given the many challenges that often affect specific patients, should be appropriately considered to minimize any adverse effects that may occur. dead. In general, symptoms of anxiety, depression, and negative emotions are rare and associated with negative outcomes. Additionally, ICU patients may experience discomfort with specific medical care, especially mechanical ventilation (MV), which reduces MV tolerance, leaves equipment invisible, and metabolic demands increase during heart disease and respiratory failure. Therefore, the administration of sedative and analgesic drugs in mechanical ventilation may be important in reducing MV-related pain and anxiety [1-3]. Current sedatives show different side effects and continue to cause problems in the long term [4]. Dexmedetomidine is the most frequently used sedative in clinical practice [5]. This compound, which is a specific agonist of α2-adrenergic receptors, effectively blocks thyroxine release by activating α2-adrenergic receptors, thus reducing the activity of the nervous system [6]. Respiratory depression was not observed in patients receiving dexmedetomidine anesthesia, which was good for patients struggling with ventilator failure [7]. Propofol is a long-acting alkylphenol sedative and sobering agent that does not affect GABA receptors outside the brain. However, individuals may experience loss of consciousness and allergic reactions after taking propofol [8-9]. Previous studies have shown that dexmedetomidine and propofol are effective in sedating patients. Both drugs have been shown to be effective in reducing pain, reducing delirium, and shortening hospital stay. However, a recent meta-analysis published inconclusive results showing no significant difference in clinical outcomes between the two drugs [10]. Although the advantages of dexmedetomidine include respiratory problems, it should not be forgotten that the good effects of dexmedetomidine include reducing blood pressure and heart rate [11-12]. Because no reaction occurs. Since it is an excellent sedative, there is interest in combining various drugs to improve and reduce side effects. Some studies have shown that these combinations are more effective than single drugs [13-14]. Additionally, a recent study examined the effectiveness of the combination of dexmedetomidine and propofol in maintaining anesthesia. The results of the study show that the combined use of propofol and dexmedetomidine reduces side effects while increasing the stability of the cardiovascular system. It also leads to a comparison between the order of propofol and a higher score [15]. Therefore, the aim of this study is to compare the sedative effects of the dexmedetomidine-propofol combination with dexmedetomidine alone and propofol alone during mechanical ventilation in critically ill patients.

Methods

A triple-blinded clinical trial was conducted to assess the comparative efficacy of the dexmedetomidine-propofol combination against dexmedetomidine alone and propofol alone for sedation during mechanical ventilation among patients admitted to the intensive care unit (ICU). The study was carried out in Isfahan city in 2023, specifically in Isfahan hospitals. Ethical considerations were scrutinized and approved by the Isfahan University of Medical Science Committee for Ethics in Research, with approval granted under the code IR.MUI.MED.REC.1402.261. The clinical trial protocol received approval under the code IRCT20160307026950N54.

The study population consisted of patients eligible for spinal fusion surgery admitted to Alzahra Hospital between 2022 and 2023. Inclusion criteria encompassed the requirement for mechanical ventilation, age between 18 and 70 years, and a Glasgow Coma Scale score higher than 9. Exclusion criteria included serious psychological disorders, dementia, contraindications for dexmedetomidine and propofol, allergy to either drug, serious infectious diseases, and significant chronic conditions such as liver dysfunction, cardiac blocks, heart rate less than 60, cardiac failure with ejection fraction less than 30%, diabetes, and uncontrolled severe hypertension (blood pressure more than 180/120). Patients who succumbed within 24 hours of ICU admission were also excluded.

The enrolled patients were randomized into three groups with a 1:1:1 allocation ratio. The first group received intravenous dexmedetomidine (DO), the second group received intravenous propofol (PO), and the third group received a combination of both drugs (DP). Dosages and infusion protocols varied for each group, with careful attention to loading and maintenance doses.

- In the first group (DO), patients were initially injected with an intravenous loading dose of dexmedetomidine at a dosage of 1 μg kg^{-1} over 10 minutes, followed by a maintenance dose of dexmedetomidine at 0.1 μg $kg^{-1}h^{-1}$ via infusion.
- In the second group (PO), patients received an initial intravenous loading dose of 1% propofol at 1 mg kg^{-1} over 10 minutes, followed by a maintenance dose of propofol at 1 mg $kg^{-1}h^{-1}$ via infusion.
- In the third group (DP), patients were initially injected with a loading dose of dexmedetomidine at 0.5 μg $kg^{-1}h^{-1}$ and propofol at 0.5 mg kg^{-1} intravenously. For maintenance, infusion of dexmedetomidine at 0.05 μg $kg^{-1}h^{-1}$ and propofol at 0.5 mg $kg^{-1}h^{-1}$ were administered.

Patients were assessed for demographic variables such as age and sex, as well as clinical variables including blood pressure (BP), mean arterial pressure (MAP), heart rate (HR), peripheral oxygen saturation (SPO2), and the need for extra sedative dosages. The duration of

mechanical ventilation was also recorded. Hemodynamic variables were measured every 6 hours during the first two days of ICU admission.

Sedation levels were evaluated using the Ramsay scale, a six-grade scale ranging from restless or agitated (Grade 1) to no response to stimuli (Grade 6). The Ramsay scale was translated into Persian, and its validity and reliability were assessed.

The sample size for the study was calculated as 90 in total and 30 per group, assuming a 5% alpha level, 80% power, and a 10% attrition rate. Randomization was achieved using the envelope method, ensuring triple blinding of the study. The intervention type for each patient remained concealed from patients, researchers, and statisticians.

Statistical Analysis

Statistical analysis was performed using SPSSv26. Descriptive statistics included frequency and percentage for qualitative variables and mean with standard deviation for quantitative variables. Chi-square tests were employed for qualitative variable comparisons, and normal distribution of quantitative variables was assessed using the Kolmogorov-Smirnov test. Between-group comparisons were conducted using repeated measurement ANOVA tests. A 95% confidence interval was applied for all analyses.

Results

A total of 28 patients were allocated to the Propofol group, 30 to the Dexmedetomidine group, and 29 to the Propofol-Dexmedetomidine group. Unfortunately, one patient in the ProDex group and two patients in other groups succumbed within the initial 24 hours of mechanical ventilation. The Dexmedetomidine group exhibited a higher average age of patients, and a predominance of male patients was observed across all groups. Detailed baseline characteristics of the patients are presented in (Table 1).

Hemodynamic Characteristics

The hemodynamic characteristics of the patients were systematically examined. Overtime comparison of systolic blood pressure (SBP) revealed higher values in the ProDex group, with statistical significance (P<0.001). Diastolic blood pressure (DBP) values were higher in the mixed group, although repeated measurement ANOVA showed no statistical significance (P=0.239). Mean arterial pressure (MAP) was also elevated in the mixed group, but no significant difference was observed between the groups (P=0.152). Heart rate was higher in the Propofol group with statistical significance (P<0.001). Saturation of peripheral oxygen (SPO2) showed no significant difference between the groups (P=0.928). Comparative analysis of variable values over different time points is summarized in the subsequent tables (Table 2).

Sedation Scores

Sedation scores of patients in the three groups were assessed, revealing higher endpoint sedation in the Propofol group. However, no significant difference was noted in the sedation scale among the three groups (P=0.473). As previously mentioned, values over time for hemodynamic variables were compared. ANOVA testing for sedation scores supported the results obtained from repeated measurement ANOVA.

Duration of Mechanical Ventilation and Sedative Dose Requirement:

Examination of the duration of mechanical ventilation indicated that the ProDex group had the shortest duration, showing statistical significance. Additionally, patients in the Propofol group exhibited a higher requirement for extra sedative doses, although statistical analysis did not reveal significance (Table 3).

Table 1- The Characteristics of patients

Variable		Dex [30]	Pofol [28]	ProDex [29]	P value
Age		56.77±13.99	55±10.87	56.41±11.25	0.2
Height		175±7.2	178±7.9	174±6.2	0.4
Weight		72.7±7.7	70.8±12.1	71.8±7.1	0.2
BMI		23.7±2.4	23.3±2.7	24.7±3.2	0.7
Sex	Male	16	15	16	
	Female	14	13	13	

Table 2- The vital signs of patients in three group

Variable	Time	Dex	ProDex	Pofol	P value
MAP	T_0	97.67±6.49	97.47±7.28	96.46±6.77	0.777
	T_1	81.98±5.30	96.42±7.58	92±6.64	0.000
	T_2	80.47±5.29	95.88±7.70	89.75±6.61	0.000
	T_3	80.41±5.20	95.45±7.15	90.15±6.29	0.000
	T_4	80.07±5.19	94.63±7.11	99.58±77.30	0.219
	T_5	80.11±5.78	95.28±7.69	85.34±5.96	0.000
	T_6	80.1±6.17	95.27±7.60	85.04±6.25	0.000
	T_7	80.41±5.89	94.67±8.01	90.08±7.07	0.000

	T_8	79.97±5.78	94.70±7.67	85.01±6.31	0.000
	T_0	146.94±13.12	146.68±13.92	146.17±13.47	0.977
	T_1	123.87±9.76	143.06±13.35	137.07±13.64	0.000
	T_2	121.37±9.74	141.31±13.35	134.32±13.55	0.000
	T_3	121.3±10.22	141.27±13.57	135.32±12.99	0.000
SBP	T_4	121.37±9.74	141.27±13.33	120.89±9.91	0.000
	T_5	120.4±10.41	141.37±13.23	120. ±10.10	0.000
	T_6	120.37±10.91	141.27±12.93	119.92±10.03	0.000
	T_7	121.3±10.22	141.24±13.54	135. ±12.99	0.000
	T_8	121.37±9.74	141.27±13.33	120.89±9.91	0.000
	T_0	73.03±3.2	72.86±4.02	71.60±3.46	0.000
	T_1	61.03±3.2	73.10±5.30	69.46±3.24	0.000
	T_2	60.033±3.20	73.17±5.73	67.46±3.24	0.000
	T_3	59.97±3.65	72.55±5.07	67.57±4.04	0.224
DBP	T_4	59.43±3.90	71.31±5.10	88.92±113.78	0.000
	T_5	59.97±3.65	72.24±5.25	67.53±4.02	0.000
	T_6	59.97±4.29	72.27±5.64	67.60±4.85	0.000
	T_7	59.97±5.42	71.37±5.96	67.46±5.43	0.000
	T_8	59.27±4.82	71.41±5.81	67.07±5.63	0.000
	T_0	89.6±14.11	94.48±13.30	91.89±14.20	0.405
	T_1	85.8±13.83	94.72±12.98	96.78±13.68	0.006
	T_2	84.97±13.47	94.58±12.81	96.85±13.55	0.002
	T_3	85.2±13.08	95.10±13.61	97±13.64	0.002
HR	T_4	85.2±13.19	95±13.51	96.82±13.68	0.003
	T_5	85±12.83	94.86±13.49	97±13.64	0.002
	T_6	85.2±13.08	95±13.56	96.85±13.55	0.003
	T_7	89.6±14.54	93.89±13.32	92.10±14.81	0.510
	T_8	89.63±14.15	94.44±13.69	91.78±14.60	0.429
	T_0	99.13±0.77	99.31±0.60	99.25±0.70	0.614
	T_1	99.5±0.50	99.51±0.50	99.46±0.50	0.923
	T_2	99.4±0.49	99.41±0.50	99.42±0.50	0.977
	T_3	99.4±0.49	99.41±0.50	99.42±0.50	0.977
SPO_2	T_4	99.4±0.49	99.41±0.50	99.42±0.50	0.977
	T_5	99.4±0.49	99.41±0.50	99.42±0.50	0.977
	T_6	99.4±0.49	99.41±0.50	99.42±0.50	0.977
	T_7	99.4±0.49	99.41±0.50	99.42±0.50	0.977
	T_8	99.4±0.49	99.41±0.50	99.42±0.50	0.977

Table 3- Sedation Scores (Ramsay) in three group

Variable	**Time**	**Dex**	**ProDex**	**Pofol**	**P value**
	T0	1.233±0.43	1.27±0.45	1.25±0.44	0.933
	T1	5.3±0.75	5.20±0.81	5.42±0.79	0.568
	T2	5.2±0.84	5.24±0.78	5.17±0.81	0.957
	T3	5.1±0.75	5.17±0.84	5.35±0.82	0.468
Ramsay	T4	5.24±0.72	5±0.75	5.35±0.73	0.184
	T5	5.13±0.77	5.20±0.81	5.28±0.85	0.777
	T6	5.13±0.81	5.13±0.87	5.32±0.77	0.618
	T7	5.14±0.77	5.06±0.84	5.17±0.81	0.877
	T8	5.17±0.79	5.10±0.85	5.32±0.77	0.581
Mechanical Ventilation	hour	95.63±28.61	85.24±27.19	136.82+±53.52	0.000
	Yes	5	3	7	
Need for sedative					0.340
	No	25	26	21	

Discussion

The intensive care unit (ICU) is dedicated to the care of a diverse group of critically unwell individuals [16]. Due to their severe condition, many ICU patients encounter respiratory challenges. Mechanical ventilation in the clinical setting aids respiration by supporting airways, improving ventilation, and preventing hypoxia [17]. However, patients often struggle to tolerate mechanical ventilation, necessitating the administration of sedatives to facilitate assisted ventilation [18].

In various clinical settings, intravenous sedatives are frequently employed for medical procedures and critical care interventions [19-23]. Dexmedetomidine (DEX), with potent α2 agonistic properties, is utilized for mild sedation in the ICU [24]. Propofol, a rapid and short-acting intravenous anesthetic, is widely employed in clinical settings for anesthesia and sedation of critically ill patients in the ICU [25]. Combining these drugs is hypothesized to improve sedative outcomes and reduce individual side effects [26-27].

Our investigation demonstrated lower hemodynamic alterations in the ProDex group, with no difference in sedative effects among the groups. The ProDex group also exhibited a significantly shorter duration of mechanical ventilation, suggesting favorable clinical outcomes.

Regarding hemodynamic effects, our study indicated a lower probability of bradycardia in the ProDex group, consistent with a previous study by Wanat [27]. This study compared length of stay in ICU, mechanical ventilation, and incidence of delirium in three groups, showing a significant difference in the combination group. Another study in monitored anesthesia care reported a higher frequency of bradycardia in the Dexmedetomidine group, along with the lowest decrease in MAP [15]. Our study further revealed the shortest mechanical ventilation duration in the ProDex group, contrary to some literature. A study by Buckley showed the shortest duration of mechanical ventilation in the Dexmedetomidine group [28]. Our result, indicating no significant difference between groups in sedation scale, aligns with previous studies showing no significant difference between Propofol and Dexmedetomidine in sedative effect [29-30]. While our study had limitations, such as a short follow-up duration and lack of respiratory examination, it also had strengths. Notably, the trial's randomized nature reduced the risk of bias in patient selection, and blinding procedures further minimized bias.

Conclusion

The combination of Propofol and Dexmedetomidine proves effective in mitigating side effects associated with monotherapy sedation. However, this combination does not impact the overall sedation scale in patients.

References

[1] Sessler CN, Wilhelm W. Analgesia and sedation in the intensive care unit: an overview of the issues. Critical Care. 2008; 12:1-4.

[2] Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJ, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med. 2018; 46(9):e825-73.

[3] Pearson SD, Patel BK. Evolving targets for sedation during mechanical ventilation. Curr Opin Crit Care. 2020; 26(1):47-52.

[4] Gommers D, Bakker J. Medications for analgesia and sedation in the intensive care unit: an overview. Crit Care. 2008; 12(3):1-5.

[5] Aouad MT, Zeeni C, Al Nawwar R, Siddik-Sayyid SM, Barakat HB, Elias S, et al. Dexmedetomidine for improved quality of emergence from general anesthesia: a dose-finding study. Anesth Analg. 2019; 129(6):1504-11.

[6] Weerink MA, Struys MM, Hannivoort LN, Barends CR, Absalom AR, Colin P. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. Clin Pharmacokinet. 2017; 56(8):893-913.

[7] Su X, Meng ZT, Wu XH, Cui F, Li HL, Wang DX, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet. 2016; 388(10054):1893–902.

[8] Qiu Q, Choi SW, Wong SSC, Irwin MG, Cheung CW. Effects of intra-operative maintenance of general anaesthesia with propofol on postoperative pain outcomes - a systematic review and meta-analysis. Anaesthesia. 2016; 71(10):1222–33.

[9] Kreienbühl L, Elia N, Pfeil-Beun E, Walder B, Tramèr MR. Patient-Controlled Versus Clinician-Controlled Sedation With Propofol. Anesth Analg. 2018; 127(4):873–80.

[10] Heybati K, Zhou F, Ali S, Deng J, Mohananey D, Villablanca P, et al. Outcomes of dexmedetomidine versus propofol sedation in critically ill adults requiring mechanical ventilation: a systematic review and meta-analysis of randomised controlled trials. Br J Anaesth. 2022; 129(4):515–26.

[11] Arain SR, Ebert and TJ. The Efficacy, Side Effects, and Recovery Characteristics of Dexmedetomidine Versus Propofol When Used for Intraoperative Sedation. Anesth Analg. 2002; 95(2):461–6.

[12] Bloor Byron C, Ward Denham S, Belleville Jon P, Maze M. Effects of Intravenous Dexmedetomidine in Humans. Anesthesiology. 1992; 77(6):1134–42.

[13] Cohen LB, Hightower CD, Wood DA, Miller KM, Aisenberg J. Moderate level sedation during

endoscopy: a prospective study using low-dose propofol, meperidine/fentanyl, and midazolam. Gastrointest Endosc. 2004; 59(7):795–803.

[14] Yan JW, McLeod SL, Iansavitchene A. Ketamine-Propofol Versus Propofol Alone for Procedural Sedation in the Emergency Department: A Systematic Review and Meta-analysis. Acad Emerg Med. 2015; 22(9):1003-13.

[15] Kim KN, Lee HJ, Kim SY, Kim JY. Combined use of dexmedetomidine and propofol in monitored anesthesia care: a randomized controlled study. BMC Anesthesiol. 2017; 17:34.

[16] Krinsley JS, Maurer P, Holewinski S, Hayes R, McComsey D, Umpierrez GE, et al. Glucose control, diabetes status, and mortality in critically ill patients: the continuum from intensive care unit admission to hospital discharge. Mayo Clin Proc. 2017; 92(7):1019-1029.

[17] Dres M, Dubé BP, Mayaux J, Delemazure J, Reuter D, Brochard L, et al. Coexistence and impact of limb muscle and diaphragm weakness at time of liberation from mechanical ventilation in medical intensive care unit patients. Am J Respir Crit Care Med. 2017; 195(1):57-66.

[18] Venn RM, Grounds RM. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions. Br J Anaesth. 2001; 87(5):684-90.

[19] Mizrak A, Koruk S, Ganidagli S, Bulut M, Oner U. Premedication with dexmedetomidine and midazolam attenuates agitation after electroconvulsive therapy. J Anesth. 2009; 23:6-10.

[20] Ruokonen E, Parviainen I, Jakob SM, Nunes S, Kaukonen M, Shepherd ST, et al. "Dexmedetomidine for Continuous Sedationq Investigators. Dexmedetomidine versus propofol/midazolam for long-term sedation during mechanical ventilation. Intensive Care Med 2009; 35:282-90.

[21] Munro HM, Tirotta CF, Felix DE, et al. Initial experience with dexmedetomidine for diagnostic and interventional cardiac catheterization in children. Paediatr Anaesth. 2007; 17:109-12.

[22] O'Daniel TG, Shanahan PT. Dexmedetomidine: a new alpha-agonist anesthetic agent for facial rejuvenation surgery. Aesthet Surg J. 2006; 26: 35-40.

[23] Bekker AY, Basile J, Gold M, et al. Dexmedetomidine for awake carotid endarterectomy: efficacy, hemodynamic profile, and side effects. J Neurosurg Anesthesiol. 2004; 16:126-35.

[24] Flieller LA, Alaniz C, Pleva MR, Miller JT. Incidence of rebound hypertension after discontinuation of dexmedetomidine. Pharmacotherapy: Pharmacotherapy. 2019; 39(10):970-4.

[25] Doi M, Morita K, Takeda J, Sakamoto A, Yamakage M, Suzuki T. Efficacy and safety of remimazolam versus propofol for general anesthesia: a multicenter, single-blind, randomized, parallel-group, phase IIb/III trial. J Anesth. 2020; 34:543-53.

[26] Li Y, Wang Y, Chang H, Cheng B, Miao J, Li S, et al. Inhibitory Effects of dexmedetomidine and propofol on gastrointestinal tract motility involving impaired enteric glia Ca 2+ response in mice. Neurochem Res. 2021; 46:1410-22.

[27] Wanat M, Fitousis K, Boston F, Masud F. Comparison of dexmedetomidine versus propofol for sedation in mechanically ventilated patients after cardiovascular surgery. Methodist Debakey Cardiovasc J. 2014; 10(2):111-7.

[28] Buckley MS, Agarwal SK, MacLaren R, Kane-Gill SL. Adverse hemodynamic events associated with concomitant dexmedetomidine and propofol for sedation in mechanically ventilated ICU patients. J Intensive Care Med. 2020; 35(12):1536-45.

[29] Venn RM, Grounds RM. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions. Br J Anaesth. 2001; 87(5):684-90.

[30] Yektaş A, Gümüş F, Alagol A. Dexmedetomidine and propofol infusion on sedation characteristics in patients undergoing sciatic nerve block in combination with femoral nerve block via anterior approach. Braz J Anesthesiol. 2015; 65:371-8.