Original Article

Long-Term Dexmedetomidine versus Midazolam in Patients Under Mechanical Ventilation: A Double-blinded Randomized Clinical Trial

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Abstract

Background: Dexmedetomidine has been approved for short-term analgesia and sedation of patients in the intensive care unit (ICU). Longer duration of sedation with Dexmedetomidine is off-label, and its safety has not yet been tested. This study aims to examine the safety profile for long-term use of Dexmedetomidine and compare it to midazolam (MID) based sedation in the ICU.

Materials and Methods: One hundred and one patients on mechanical ventilation were randomized to receive either Dexmedetomidine 0.2-1.0 µg/kg/h or MID 20- 40 µg/kg/h in a double-blinded fashion to reach the target of -2 to 1 on the Richmond Agitation-Sedation Scale (RASS). Duration of mechanical ventilation was the primary endpoint; secondary endpoints included the occurrences of composite cardiac adverse event (CCAE), bradycardia, hypotension, significant dysrhythmias, heart failure myocardial infarction or death within 28 days, ICU length of stay, need for additive analgesic, time spent at target sedation, and delirium.

Results: The duration of mechanical ventilation and ICU stay were almost two days shorter in the Dexmedetomidine group (P= 0.002 and 0.001, respectively), but regarding CCAE, sinus bradycardia occurred more frequently (P= 0.399), and mortality was similar in both groups (P=0.378).

Conclusion: Our results confirmed the results of previous trials showing that long-term Dexmedetomidine was comparable to benzodiazepines for the frequency of major complications in critically ill patients. Physicians should weigh these benefits against the occurrence of significant bradycardia and hypotension.

Keywords: Dexmedetomidine, Long-term Sedation, Critical Care, Mechanical ventilation

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Introduction

Sedation is continuously used in critically ill patients to decrease agitation, asynchrony, hemodynamic instability, and better toleration of mechanical ventilation (1). High doses of sedative drugs for a long time may increase the duration of mechanical ventilation, ICU stays, and incidence of delirium or neurocognitive dysfunction that may contribute to increased inflammation, oxidation stress, mortality, and/or prolonged hospitalization among critically ill patients (2,3). The advantages of applying sedation vacations and using more sophisticated sedation protocols to decrease morbidity or mortality rates are controversial (2,4). Propofol, lorazepam, and midazolam are commonly used sedative drugs in critically ill patients. Each class of medications may lead to clinical complications secondary to the accumulation of the drug after their continuous infusion (5,6).

Dexmedetomidine is a relatively newer agent available for sedating critically ill patients who require endotracheal intubation and mechanical ventilation (7). It belongs to a class of adrenergic drugs that selectively stimulates α2 receptors and differs from the other sedative agents acting through gamma-aminobutyric acid receptors (8). Dexmedetomidine produces an ideal level of sedation with a rapid onset and short half-life, making it an ideal drug to be used as an adjuvant to anesthesia in suppressing the stress response and the release of proinflammatory cytokines after an external noxious stimulus (9, 10). This drug decreases sympathetic excitation and agitation and has a minimal depressive effect on respiration (11). There are many reports regarding the protective effects of Dexmedetomidine on kidneys, lungs, and the myocardium (12). In a study of mechanically ventilated patients, sedation with Dexmedetomidine decreased the mortality rates compared to those sedated with either midazolam or propofol (13). A multicenter study (DEXCOM) compared Dexmedetomidine with morphine sulfate in critically ill patients and showed that reaching the target sedation is similar between the two groups, while the time to extubation was longer in patients receiving morphine sedation (14). Inflammation, immune response, and resultant organ dysfunction are the most important causes of morbidity and mortality in critically ill patients (15, 16). Previous studies showed that Dexmedetomidine could decrease inflammation via changes in the modulation of inflammatory signaling pathways (by decreasing IL1, IL6, IL8, and TNF) and α2 adrenoreceptors, modulate the immune response, improve different organ dysfunctions, and exert neuroprotection, cardioprotection, and renoprotection (17-19).

On the other hand, there are conflicting results about the long-term use of Dexmedetomidine in patients on mechanical ventilation for a prolonged period (20,21). The main concern following prolonged use of Dexmedetomidine is cardiovascular adverse events in the form of bradycardia and hypotension. Herein, we designed a double-blinded clinical trial to examine the beneficial effects of Dexmedetomidine on respiration by the duration of mechanical ventilation as the primary endpoint; and examined the safety profile of Dexmedetomidine in causing major adverse events in patients who received this drug for periods longer than 48 hours. We hypothesized that using Dexmedetomidine was superior to the other sedation alternatives in reducing the duration of mechanical ventilation without any increase in the frequency of composite cardiac adverse events (CCAE).

Methods

Study Design: The institutional review board and committee for research ethics reviewed and approved the research design, study protocol, and the informed consent form for its scientific merit. This double-blinded clinical trial was registered with a governmental registry of the clinical trial (www.irct.gov.ir). (number: IRCT201608192582N16, 2016.11.08). A partial waiver of the Health Insurance Portability and Accountability Act allowed the investigating team to screen the patient records and determine their enrollment eligibility. Our study adheres to CONSORT guidelines and includes a completed CONSORT checklist as an additional file.

Patients and Inclusion Criteria: All subjects were adult patients (18 to 80 years old), who were admitted

to the surgical intensive care units (sICU) of two major university-affiliated medical centers in the northwest of Iran (Tabriz) and required endotracheal intubation with mechanical ventilation for greater than 48 hours (from Jan 2017 to Oct 2019). Exclusion criteria were the history of hypersensitivity reaction to Dexmedetomidine or midazolam, pregnancy, previous history of addiction, organic brain disease with existent neurocognitive dysfunction, refractory hypotension with systolic blood pressure < 90 mmHg, systolic heart failure with a left ventricular ejection fraction <30%, heart rate less than 60/min, current liver dysfunction and need for renal replacement therapy. We further excluded patients who were prescribed both study drugs, midazolam and Dexmedetomidine, at the treating intensive care practitioner (Figure 1). During the study period, 167 patients were assessed for eligibility, of whom 119 were randomized. The main reasons for follow-up loss were kidney injury requiring RRT, mortality in the first 48 hours, and consent withdrawal, which did not significantly differ between the two groups.

Randomization and Intervention: After determining the eligibility and obtaining informed consent from either patient's next-of-kin or healthcare proxy, using random sequence generated balanced block randomization by the research pharmacy team, patients were randomly assigned into two intervention groups. Group (DEX) received dexmedetomidine infusion at 0.2–1.0 µg/kg/h and group (MID) received midazolam infusion at 20–40 µg/kg/h to attain a sedation target of -2 to 1 on the Richmond Agitation-Sedation Scale (RASS) (22). The study drugs were prepared by the research pharmacy and were delivered to the main investigator (AM). Then he labeled similar packages with A and B and delivered them to ICU for infusion, so neither the patient's family nor the care team was aware of the nature of the treatment. The sedation infusion was ceased from 7 AM to 9 AM to evaluate four scores (eyes opening, eye contact with the physician, handgrip, and tongue extrusion). Considering the nature of critically ill patients, each patient received the exact treatment planned to receive based on the allocation protocol.

Primary and Secondary Outcomes: The study's primary outcome was the duration of mechanical ventilation, and the secondary outcome was ICU length of stay. The outcome assessment was conducted during the patient's stay in the ICU, which could be different for each patient. The secondary outcome variables also included death within 28-days and the occurrence of delirium in addition to the occurrence of a CCAE, which included the occurrences of systolic blood pressures < 90 mmHg requiring vasopressors, heart rates < 40 beats per min, significant and sustained ventricular dysrhythmias, myocardial injury with or without ST-segment elevation documented with serum troponin I levels > 0.2 ng/L, systolic heart failure associated with cardiogenic shock, and a need for insertion of a temporary pacemaker.

The patients' demographic characteristics, including acute physiology and chronic health evaluation (APACHE-II) scores at the time of admission, were recorded. All patients received enteral feeding via nasogastric feeding tube with standard formula (Ensure, Abbott laboratories, Holland, 1 kcal/mL) with the aim of 25 kcal/kg. All patients received standard treatment for mechanical ventilation (low tidal volume strategy: 6 mL /Kg of ideal body weight), prophylaxis for deep vein thrombosis and stress ulcer, head elevation, and bundle criteria for prevention of ventilator-associated pneumonia (VAP). VAP occurrence was suspected with the development of clinical signs of pneumonia, radiographic evidence of a new consolidation in the lungs verified with the presence of > 10,000 colony-forming units in one milliliter of mini-bronchial-alveolar wash fluid (BAL). RASS scores were obtained every 4 hours, and the time to reach the target RASS score was recorded for every patient along with the time spent at targeted RASS. The need to adjust the infusion rate or to add an adjuvant sedative/analgesic drug was noted and decided at the discretion of the treating intensive care specialist. If the patient was overly sedated, the infusion rate was decreased by 50% until the RASS score reached the preset target. Additional rescue sedation/analgesia was provided with fentanyl citrate boluses of 0.5–1.0µg/kg if needed. Patients also received fentanyl citrate boluses before painful procedures like tracheal suctioning and physiotherapy. Delirium was assessed

by the confusion assessment method for ICU (CAM-ICU) and treated with 1-5 mg intravenous boluses of haloperidol and the repeated doses every 10-20 min until the desired response was acquired. The weaning process was based on decreasing pressure support (PS) levels (based on clinical symptoms, ABG results, and rapid shallow breathing index (RSBI) levels of <105) in pressure support ventilation mode until reaching to PS level of 5-6 cmH_2O. Also, during this time, all patients underwent a spontaneous awakening trial and a spontaneous breathing trial (SBT) for 30-120 min if they tolerated it. If the patient was awake and tolerated the SBT, he/she was extubated.

Statistical Analyses: Sample size determination was performed using an online power calculator provided by the University of British Columbia (www.ubc.edu.ca/stat) and was calculated based on the published duration of the primary endpoint in critically ill patients. In a recent publication, the median duration for mechanical ventilation was six days (3-10), accounting for a mean of 144 hours and a standard deviation of 60 hours (23). Assuming the incidence of a 30% reduction of the duration to 104 hours in the intervention group to 104 hours of mechanical ventilation, a minimum of 36 patients in each arm was needed to obtain $\alpha = 0.05$ and $\beta = 80\%$. In addition, considering a historical 20% drop out of cases, the sample size was adjusted to 50 patients for each group.

Kolmogorov-Smirnov goodness of fit test was used for the assessment of the normal distribution of numerical variables. For normally distributed continuous variables, independent t-test, and for those variables lacking a normal distribution, the non-parametric Mann-Whitney U test was used. Normally distributed variables were presented through mean ± standard deviation. The frequency and percentage of the categorical data were assessed using Fisher's Exact test if the number of the occurrence was less than 5 and for the remaining the Chi-square test was utilized. Statistical analysis was achieved using SPSS statistical package 24.0 (IBMTM, Chicago, IL).

Ethical Aspects: The study protocol and the informed consent were reviewed and approved by the institutional review committee on health research ethics at Tabriz University of Medical Sciences for its merit (Study protocol approval date: 2016.07.25. Ethics committee reference number: IR.TBZMED.REC.1395.406). Written consent was obtained from the study participants.

Results

One hundred and sixty-seven critically ill patients on mechanical ventilation were screened, and after excluding the patients who did not meet the criteria for enrollment, a total of 119 patients were randomized to either study arm (Figure 1). A total of 18 patients (11 in the Dexmedetomidine group and 7 in the MID group) were lost to follow-up by missing critical information and major deviation to the study protocol. Six patients died within 48 hours of enrollment and were therefore excluded from the analysis. Five patients in the Dexmedetomidine group and four in the MID group were further excluded due to the development of acute kidney injury requiring renal replacement therapy.

Table 1: Demographic characteristics of patients in study groups.

	DEX Group (N = 51)	MID Group (N = 50)	P-Values
Male / Female	30 / 21	28 / 22	0.774
Age (years)	60 [48 – 69]	63 [49 – 70]	0.999
APACHE-II	21.4 ± 7.4	20.1 ± 8.7	0.767
Parenteral Nutrition	2 (3.9%)	2 (4.0%)	0.881

APACHE: Acute Physiologic and Chronic Health Evaluation

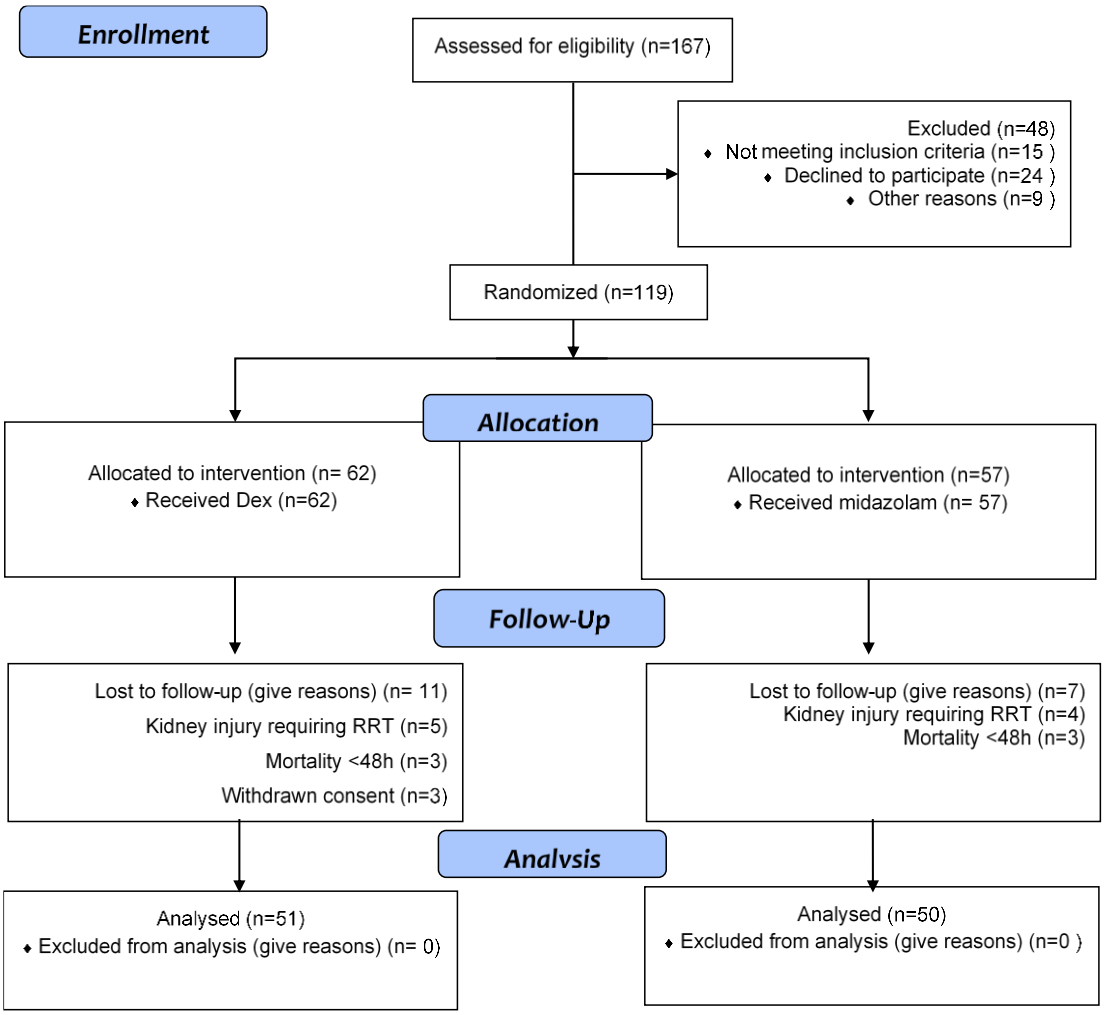

Figure 1. CONSORT Diagram of the Study

58 men and 43 women with an average age of 63 (52–74) years old were enrolled in the study. There was no difference in age and gender distribution of patients between the two study arms (Table 1). Parenteral nutrition was started in 4 patients, and the remaining 97 patients received enteral feeding. The average APACHE-II score was 20.7 (13.0 –28.0) in all patients, with no difference between the treatment groups (Table 1).

The duration of mechanical ventilation was 112.0 ± 73.2 hours in the Dexmedetomidine group, significantly shorter than 176.6 ± 94.1 hours in the MID controls (P = 0.001). Forty-nine percent of patients in the Dexmedetomidine group and 36% of patients in the MID group had an ICU length of stay of fewer than seven days. Similarly, ICU length of stay was shorter in the dexmedetomidine group compared to the MID group (P = 0.002). On the other hand, the patients' time in target sedation was 8 hours longer in the dexmedetomidine group than those in the MID group (P=0.001). Forty-three out of 51 patients in the Dexmedetomidine group (84.3%) regained their consciousness, while 64% of the patients in the MID group became conscious following the washout period (P = 0.024). The need for a rescue dose of fentanyl for analgesia and sedation was significantly less frequent in the dexmedetomidine group (7.8% vs 30%, P = 0.004). (Table 2)

The most common complications in the dexmedetomidine group were bradycardia (the heart rate < 40 beats/min) and hypotension (systolic blood

Table 2: Clinical outcome and associated complications the patients in sedation groups.

	DEX (N= 51)	MID (N= 50)	P value
ICU length of stay (days)	8.3 ± 3.8	11.6 ± 5.1	0.002
Duration of mechanical ventilation (hours)	112.0 ± 73.2	176.6 ± 94.1	0.001
Ventilator associated pneumonia	7 (13.7%)	10 (20%)	0.399
Time spent on target sedation (hours)	75.8 ± 10.3	67.1 ± 11.9	0.001
Need for rescue drug for further sedation	4 (7.8%)	15 (30%)	0.004
Regained consciousness after washout	43 (84.3%)	32 (64.0%)	0.024
Pao2/Fio2	212.24±24.11	187.16±19.10	0.035
GFR	85.46±6.12	78.26±6.25	0.092
Delirium	7 (17.6%)	17(34%)	0.040
Bradycardia	17 (33.3%)	0 (0.0%)	<0.001
Hypotension	14 (27.5%)	0 (0.0%)	<0.001
Vasopressor/chronotrope	3((5.8%)	0(0%)	0.085
Bradycardia or hypotension	22 (43.2%)	0 (0.0%)	<0.001
Composite cardiac adverse events	14 (27.5%)	9 (18.0%)	0.343
Mortality	6 (11.8%)	9 (18.0%)	0.378

GFR: Glomerular Filtration Rate

pressure < 90 mmHg), which occurred in 33% and 27% of patients, respectively. Either bradycardia or hypotension occurred in 22 out of 51 patients in the dexmedetomidine group, while neither complication was seen in the MID group (P<0.001). However, the need for vasopressor or chronotropic support was not significantly different between the two groups, so the mentioned complications were not serious and improved with stopping or decreasing the dose of the medication. In 21% of patients, both complications occurred simultaneously. We did not have any case of significant ventricular tachycardia or need to insert a pacemaker in either group. The frequency of CCAE was not significantly different in the two study arms (P=0.343).

Similarly, VAP prevalence and mortality were not significantly different between the two groups (P-value: 0.399 and 0.378, respectively) (Table2). There was a significant difference in the incidence of delirium in the Dexmedetomidine group with a P-value of 0.040. Also, we did not significantly differ regarding organ dysfunction (kidney and pulmonary) in this study.

Discussion

Our results showed that long-term infusion of Dexmedetomidine as a sedative agent in critically ill patients was significantly associated with a shorter

ICU length of stay and a shorter duration of mechanical ventilation, but the patients spent on target sedation were longer. Bradycardia and hypotension only occurred in patients who received Dexmedetomidine even though the frequency of requiring the medications that augment the heart rate or blood pressure did not differ between the two study arms. We further failed to demonstrate any difference between Dexmedetomidine-based and MID-based sedation in the prevalence of VAP, delirium, 28-day death, or CCAE.

Midazolam was recommended as a sedative in addition to propofol in the previous guidelines published by the Society of Critical Care Medicine, but recent guidelines emphasize more on Dexmedetomidine (7, 24). Although Dexmedetomidine exhibits have beneficial properties and may have some advantages over the other sedatives, reports of treatment failure in long-term use of Dexmedetomidine are concerning (20, 25, 26). Pasin et al., in a meta-analysis of 28 trials (3,648 patients) showed that Dexmedetomidine was not inferior to the other sedatives from a mortality perspective while it shortened the ICU length of stay by 0.79 days reduced time to extubation by almost 3 hours (27). Although there are heterogeneity and risk of bias in trials analyzed by this meta-analysis, its main results agree with our findings herein. However, in a meta-analysis of 242 critically ill patients diagnosed with sepsis, Zamani et al. demonstrated a close to 50% decrease in ICU mortality (28), a finding that we cannot reproduce in this study. In line with the findings in the current study, a recent trial of 201 patients with sepsis showed that the use of Dexmedetomidine was not associated with any decreases in mortality rates (23).

In the literature reviewed by Kunisawa, Dexmedetomidine was reintroduced as a long-term sedative (2 to 30 days), which could reduce time to extubation and the ICU length of stay among critically ill patients. However, this review also calls for further studies to verify its efficacy and safety as a long-term sedative drug in this population (20). Abuhasna et al. retrospectively examined the medical records of 73 critically ill patients who were sedated with an infusion of Dexmedetomidine (23 patients for ≤24 hours and 50 patients for > 24 hours) (29). These investigators reported no difference in the incidence of hypotension or bradycardia between the two cohorts. Ozaki et al. prospectively examined the safety of Dexmedetomidine as a sedative agent beyond 24 hours in critically ill patients (30). They enrolled 75 patients in their trial and confirmed that Dexmedetomidine was useful for maintaining target levels of sedation in both surgical and medical patients. This trial reported no clinically significant adverse events related to the long-term use of Dexmedetomidine or noticeable withdrawal effects after cessation of its infusion compared to its short-term use (30).

Interestingly, both the trial by Ozaki et al. and the retrospective study by Abuhasna et al. only compared the long-term use (> 24 hours) to the short-term use (≤ 24 hours) of Dexmedetomidine, which showed practically no difference in the prevalence of hypertension, hypotension or bradycardia between the two groups. However, when we compared the long-term use of Dexmedetomidine to midazolam in the current trial, we found a significant increase in the incidence of hypotension (> 20% of the baseline) and bradycardia with the use of DEX, while they were absent when midazolam was used as the sedative. Both negative chronotropic and vasodilatory effects of Dexmedetomidine are expected, as Dexmedetomidine suppresses both endogenic norepinephrine and epinephrine in healthy individuals. However, the clinical significance of these adverse events was unknown, as there was no significant difference in the need to treat either bradycardia or hypotension between the two study arms. Consequently, the difference between the two groups was not clinically important. As Dexmedetomidine can lead to hypotension, one of the most important problems can be kidney dysfunction; we did not see any significant acute kidney injury (urine output, blood urea creatinine) in this report. These findings support the cardioprotective and renoprotective properties of Dexmedetomidine in critically ill patients. It seems that Dexmedetomidine can improve pulmonary function (immunomodulation and bronchodilation) as it increases the Pao2/Fio2 and decreases the duration of mechanical ventilation. Considering delirium and CNS dysfunction, Dexmedetomidine decreases delirium to improve

neurologic function in critically ill patients (19). Our findings also demonstrated the neuroprotective effects of Dexmedetomidine regarding delirium prevention in critically ill patients.

Another meta-analysis showed that Dexmedetomidine had potential benefits in reducing time to extubation and lowering the risk of delirium. However, the adverse events of hypotension and bradycardia should be closely monitored when this drug is used for critically ill patients under mechanical ventilation (31). Shah et al. showed that Dexmedetomidine appears to have an acceptable safety profile compared to propofol in the ICU settings (32). Compared to propofol sedation validated by bispectral index (BIS) monitoring, Dexmedetomidine was more effective in reducing the heart rate while propofol possessed more vasodilatory effects (33).

Another group of investigators found that Dexmedetomidine might is suitable for light to medium sedation in critically ill patients under mechanical ventilation while expressing some concerns regarding its safety, so they asked for more trials (34). Kawazoe et al., in a clinical trial of 201 mechanically ventilated patients with sepsis, showed that Dexmedetomidine was superior in reaching the target level of sedation compared to midazolam. At the same time, they failed to demonstrate any reduction in mortality or ventilator-free days with prolonged infusion of Dexmedetomidine (23). All of these findings are similar to our study results regarding improving organ function and especially lungs. A recently published Cochrane systematic review confirmed that prolonged infusion of Dexmedetomidine reduces the duration of mechanical ventilation without any significant effect on delirium and mortality (35). These investigators were nevertheless concerned about the lower quality and the higher risk of bias of the trials included in their review and called for future well-conducted large-scale trials to make firmer recommendations.

In summary, most studies that reported a lower complication rate with the long-term use of Dexmedetomidine considered only respiratory advantages such as duration of mechanical ventilation and time to remove the endotracheal tube (36-38). Inter-patient variability that affects the pharmacokinetics of Dexmedetomidine in critically ill patients includes patient age, co-morbid and anthropometric characteristics, and relevant genetic polymorphism or the trait of these patients (25). A study regarding cost analysis showed that Dexmedetomidine appears to be a preferable option compared with standard sedatives for providing light to moderate sedation for more than 24 hours (39). Our study had some limitations. This study was a clinical trial with an almost small sample size in surgical ICU patients, limiting its generalizability. We also could not perform therapeutic drug monitoring for our medications in the study. However, we assessed the cardiac adverse effects and long-term use of Dexmedetomidine which are the strength of our study.

Further mechanistic, translational, and clinical studies are warranted to define the exact mechanism and properties of Dexmedetomidine on organ function. One of the most interesting and valuable future directions of Dexmedetomidine research involves its potential for neuroprotection and long-term neuroprotective cognition. Also, the effect of Dexmedetomidine on pulmonary function and inflammatory biomarkers is very important, especially in critically ill patients with COVID-19. The pharmacological properties and possible adverse effects of Dexmedetomidine should be well understood by all physicians who use the drug (40).

Conclusion

Our study confirms Dexmedetomidine as an appropriate agent for rapid-onset and stable sedation in critically ill patients. Dexmedetomidine, however, failed to demonstrate any survival benefit and had some hemodynamic complications in the form of bradycardia and hypotension though not clinically significant. Regardless, physicians who use Dexmedetomidine as a sedative drug should consider preexisting low blood pressure, history of coronary artery disease, and higher acuity as risk factors to avoid hemodynamic instability of these patients (41). Furthermore, our study was limited since it only included surgical patients and used subjective clinical tools (RASS) to assess the level of sedation.

Acknowledgment

None.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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