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ORIGINAL ARTICLE

Pain, fentanyl consumption, and delirium in adolescents after scoliosis surgery: dexmedetomidine vs midazolam

Mustafa S. Aydogan[1], Mehmet F. Korkmaz[2], Ulkü Ozgül[1], Mehmet A. Erdogan[1], Aytac Yucel[1], Abdurrahman Karaman[3], Turkan Togal[1], Mahmut Durmus[1] & Cemil Colak[4]

1 Department of Anesthesiology and Reanimation, Faculty of Medicine, Inonu University, Malatya, Turkey
2 Department of Orthopedic Surgery, Faculty of Medicine, Inonu University, Malatya, Turkey
3 Department of Pediatric Surgery, Faculty of Medicine, Inonu University, Malatya, Turkey
4 Department of Biostatistics and Medical Informatics, Faculty of Medicine, Inonu University, Malatya, Turkey

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Correspondence
Mustafa Said Aydogan, MD, Assistant Professor of Anesthesiology and Reanimation, Department of Anesthesiology and Reanimation, Inonu University School of Medicine, Malatya, Turkey
Email: dr_mustafasaid@hotmail.com

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Summary

Background: The study aim was to compare the efficacy of dexmedetomidine vs midazolam for sedation during the early postoperative period in adolescents who underwent scoliosis surgery.

Methods: We performed a prospective, randomized trial in an intensive care unit (ICU) in a tertiary care center. In this study, 42 patients (American Society of Anesthesiology physical status I and II) who underwent scoliosis surgery were divided into two groups according to sedation protocols: group dexmedetomidine (DEX) (n = 22) and group midazolam (MDZ) (n = 20). Adolescents (12–18 years) requiring mechanical ventilation underwent a continuous infusion of either dexmedetomidine (group DEX; starting dose, 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$) or midazolam (group MDZ; starting dose, 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$) with intermittent fentanyl, as needed. The efficacy of sedation was assessed using the Richmond Agitation Sedation Scale (RASS). Quality of pain relief was measured using the Numeric Visual Analog Scale (NVAS). Delirium was determined in patients in the RASS range of −2 to +1 using the Confusion Assessment Method for the ICU (CAM-ICU). Fentanyl consumption, incidence of delirium, NVAS scores, and hemodynamics were recorded postoperatively at 2, 4, 6, and 24 h in the ICU.

Results: The NVAS pain scores and fentanyl consumption at all the evaluation time points were significantly higher in group MDZ than those in group DEX ($P < 0.05$). Further, total fentanyl consumption in group MDZ was significantly higher than that in group DEX ($P < 0.05$). Delirium was significantly higher in the group MDZ than that in group DEX (31.3% vs 12.5%) when analyzed as the endpoint of CAM-ICU ($P < 0.05$). The heart rate was significantly lower in group DEX compared with that in group MDZ at all the evaluation time points ($P < 0.05$).

Conclusion: Dexmedetomidine was associated with the decreased postoperative fentanyl consumption, NVAS scores, and a decreased incidence of delirium. These findings may be beneficial for managing sedation protocols in adolescents who have undergone scoliosis surgery.

Introduction

Surgical correction of scoliosis deformities in children results in challenging postoperative pain control, and a multimodal approach to pain management is often necessary (1). In pediatric patients, sedative and analgesic agents (benzodiazepines and opioids) are an important aspect of adequate postoperative patient care, and

ample evidence has shown that effective postoperative pain management reduces patient morbidity and improves patient care (2).

As a potent and highly selective α-2 adrenoreceptor agonist, dexmedetomidine possesses analgesic, anxiolytic, sedative, attributes of sympatholytic and does not cause respiratory depression (3,4). Dexmedetomidine-sedated patients have been reported to experience significantly more delirium-free days in the intensive care unit (ICU) than those receiving benzodiazepines (5). Because of these properties, dexmedetomidine is used postoperatively in children following major spine surgery associated with significant pain (6).

We hypothesized that a sedation strategy using dexmedetomidine would improve in adolescents following scoliosis surgery compared with a strategy using midazolam. The aim of this study was to compare the effects of dexmedetomidine and midazolam on pain, opioid use, delirium, and side effect profiles during the early postoperative period in adolescents following scoliosis surgery.

Materials and methods

This study used a randomized, prospective, double-blinded design. Prior to the undertaking of the study, ethical approval for the study was provided by the Ethics Committee of the Inonu University in Malatya (acceptance number: 2011/198), and written informed consent was obtained from the parents. This prospective study consisted of 42 consecutive adolescents (12–18 years) with scoliosis who had fulfilled the following inclusion criteria: admittance to the ICU and a requirement of mechanical ventilation with an endotracheal tube. Patients who had a history of allergies to midazolam and/or dexmedetomidine; delirium, developmental delay, or mental retardation, as reported by parents; an American Society of Anesthesiologists classification greater than III; known previous reactions to anesthesia; a history of asthma or an anticipated difficult airway; a history of hypertension, chronic opioid, sedative, analgesic, antihypertensive agents or digoxin use prior to the procedure, and concomitant disease (neuromuscular scoliosis or neurodegenerative disease) were excluded from the study.

Anesthetic management

The anesthetic technique was standardized, with no analgesics or sedatives used preoperatively. Upon patient arrival in the operating room, noninvasive arterial pressure (BP), electrocardiography, capnography, and peripheral oxygen saturation (SpO_2) were monitored. Two intravenous catheters were placed in the patient, and Ringer's lactate solution was infused at a rate of 5 $ml \cdot kg^{-1} \cdot h^{-1}$. A bispectral index (BIS) A-2000XP monitor (host version 3.3; Aspect Medical Systems, Newton, MA, USA) was used to evaluate the depth of the anesthesia. Anesthesia was administered to all patients using a standardized technique: 30 s after remifentanil administration (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$), a 0.5 $mg \cdot kg^{-1}$ bolus dose of propofol was administered. A propofol infusion was then started at a dose of 75 $mg \cdot kg^{-1} \cdot min^{-1}$. Atracurium (0.6 $mg \cdot kg^{-1}$) was administered for neuromuscular blockage. The trachea was intubated when the BIS value was between 45 and 60. After intubation, mechanical ventilation was continued with a 40% O_2-air mixture and 35–40 mm Hg end-tidal CO_2 ($ETCO_2$). Patients were monitored with somatosensory-evoked potentials and motor-evoked potentials by a neurologist during the perioperative period. At the end of the surgical procedure, propofol and remifentanil infusions were discontinued without tapering after the closure of the skin incision. All patients were weaned off mechanical ventilation.

Sedation management

An independent person who was not involved in the study performed the computerized randomization procedure. Each patient was randomly assigned a specific study number and group; these assignments were then enclosed in envelopes and sealed. After surgery, the patients were assigned to one of two groups according to the results of the randomization procedure: The dexmedetomidine group (DEX) received 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ intravenous (i.v.) dexmedetomidine, and the midazolam group (MDZ) received 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$ of i.v. midazolam (7). The quality of sedation was assessed hourly throughout the treatment period using the Richmond Agitation Sedation Scale (RASS) by a single anesthesiologist who was not involved study (8). During each arousal assessment, patients within the RASS range of −2 to +1 were asked to perform four tasks (open eyes to voice command, track investigator with eyes, squeeze hand, and stick out tongue). Patients were considered awake when they could perform three of the four tasks. If the patient's RASS score was greater than +1 at the time of a scheduled assessment, study medication was titrated until a RASS score of −2 to +1 was achieved, and then an arousal assessment was performed. If oversedation (RASS range, −3 to −5), the study drug was interrupted until a RASS score of −2 to 0 was achieved, and an arousal assessment was subsequently performed. The targeted levels of sedation ranged from −2 to +1. After randomization, if the patient in either group was judged

to be inadequately sedated, a bolus of either midazolam (0.1 $mg \cdot kg^{-1}$) or dexmedetomidine (0.25 $\mu g \cdot kg^{-1}$) was given before the initiation of the infusion or the midazolam infusion was increased by 0.05–0.1 $mg \cdot kg^{-1} \cdot h^{-1}$, and the dexmedetomidine infusion was increased by 0.15–0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ at 10–15-min intervals until adequate sedation (RASS range, −2 to +1) was achieved with a maximum dose of 4 mg in 8 h. These bolus doses were included in the total daily dose of the medication.

Pain management

Quality of pain relief was assessed using the Numeric Visual Analog Scale (NVAS; 0 = no pain to 10 = worst imaginable pain) (9). The targeted levels of analgesia ranged from 0 to 4. If the pain score was 0, the situation was accepted as oversedation, and then the study drug infusion was stopped. After the initiation of the infusions, supplemental analgesia was provided through intermittent doses of fentanyl (0.5–1.0 $\mu g \cdot kg^{-1}$) every 15 min, as required. This bolus dose was included in the total daily dose of the medication. Intravenous bolus doses of fentanyl could also be given prior to an anticipated noxious stimulation, such as chest physiotherapy or suctioning. Patients generally slept between these assessments, but were easy to arouse or awaken.

Delirium management

During the arousal assessment, delirium was assessed twice daily in the patients in the RASS range of −2 to +1 using the Confusion Assessment Method for the ICU (CAM-ICU) (9). According to the CAM-ICU, patients had a diagnosis of delirium when an acute onset of mental status change or a fluctuating course of delirium symptoms and inattention were accompanied by either disorganized thinking or an altered level of consciousness. Patients were monitored for delirium by a neurologist who not involved in the study. When patients whose scores were positive for delirium by the CAM-ICU, delirium was categorized as 'Present'; otherwise, all the others were categorized as 'Absent' while patients were in the ICU. Intravenous haloperidol was permitted for the treatment of agitation or delirium in increments of 1–5 mg, with the treatment repeated every 10–20 min as needed.

Other effect measures

The decision for extubation readiness was based on several observations, including hemodynamic stability, an alert and awake patient, $ETCO_2$, SpO_2, and stable ventilation. Patients identified for extubation typically had normal lung function and hemodynamics, and a trial of 8 $ml \cdot kg^{-1}$ tidal volume usually led to successful extubation. In both groups, the drug infusion was stopped at the time of extubation for ending the mechanical ventilation. After 24 h on either the midazolam or the dexmedetomidine infusions, if ongoing mechanical ventilation was still necessary, the patient was switched to the alternative agent and the study stopped.

Pain, opioid use, incidence of delirium, heart rate (HR), and mean arterial pressure (MAP) were assessed in the patients on the sedation protocol every 2 h. Hemodynamic changes, including hypotension, hypertension, bradycardia, and tachycardia, were defined as a $\geq 20\%$ change from respective baseline preoperative values. Interventions for bradycardia, tachycardia, and hypertension included titration or interruption of the study drug or administration of medication. The initial treatment of hypotension included fluid bolus (5 $ml \cdot kg^{-1}$ %0,9 NaCl) followed by ephedrine 3 mg at 3 min intervals until the mean arterial pressure was returned to within 20% of baseline. If required, the infusion of study drugs was stopped. Atropine was administered as a second-line drug, for hypotension with bradycardia, depending on the clinical judgement of physician.

Statistical analyses

The sample size was based on a power analysis. At least 13 patients were required in each group to detect a fentanyl consumption difference of 30% between the groups with a type I error of 0.05 and a type II error of 0.20. Within the groups, the normality of variables was measured using the Shapiro–Wilk test. Differences between groups were evaluated using an independent samples *t*-test and the Mann–Whitney *U*-test. Categorical variables were compared by Yates corrected chi-square test as appropriate. Data are expressed as mean values (standard deviation [SD]), median (min–max), or numbers (*n*). A *P* value of less than 0.05 was considered statistically significant.

Results

A total of 42 pediatric patients were considered for inclusion in the study. However, 10 patients were excluded for the following reasons: (i) not meeting inclusion criteria (four patients); (ii) declining to participate in the study (three patients); and (iii) other reasons (three patients) (Figure 1). Data from the remaining 32 children enrolled in this study (group DEX, $n = 16$; group MDZ, $n = 16$) were analyzed. Table 1 shows that the patient characteristics did not differ between the two groups of patients.

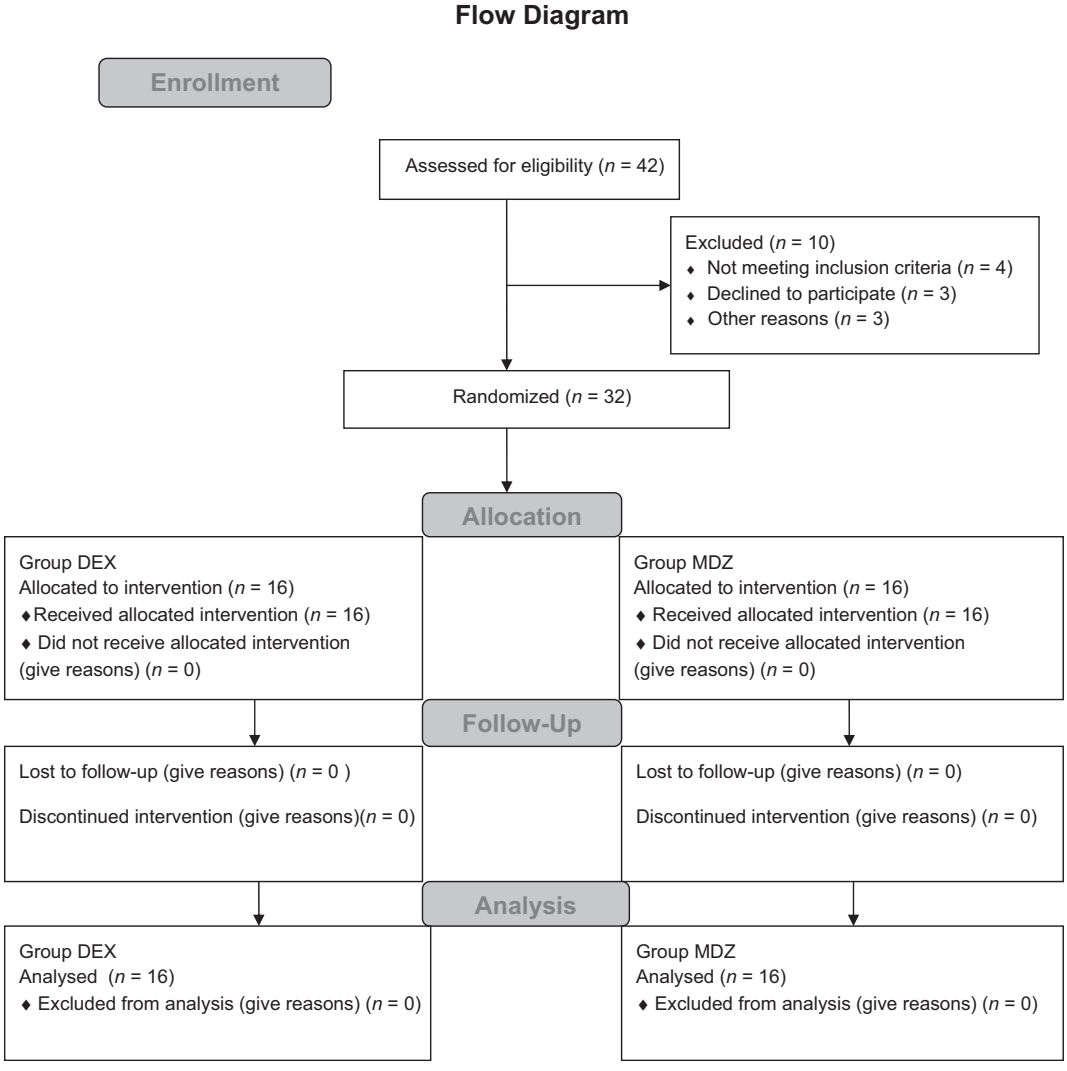

Figure 1 Study enrollment flow diagram.

Table 2 presents the comparison of the NVAS scores and the cumulative fentanyl consumption between the two groups. The NVAS pain scores and fentanyl consumption at all the evaluation time points were significantly higher in group MDZ than those in group DEX ($P < 0.05$). Further, total fentanyl consumption in group MDZ was significantly higher than that in group DEX ($P < 0.05$).

The overall level of sedation was significantly greater in the MDZ group, with a median RASS level of −1.84 (−2 to +2) compared with 1.12 (−1 to +1) in the DEX group ($P < 0.05$). The total amount of study drug required per group consisted of a mean dose of 125 $\mu g \cdot kg^{-1} \cdot h^{-1}$ in the DEX patients and 21.3 $mg \cdot kg^{-1} \cdot h^{-1}$ in the MDZ patients. Delirium was significantly higher in the MDZ group (31.3% vs 12.5%) when analyzed as the endpoint of CAM-ICU ($P < 0.05$). Haloperidol was used to treat delirium in 4% (1/16) of the patients in group DEX and in 25% (4/16) of those in group MDZ ($P < 0.05$). Duration of mechanical ventilation (MV) in group MDZ was significantly higher than that in group DEX ($P < 0.05$). There was no clinically significant change between the two groups in terms of ICU stay day.

The HR was significantly lower in group DEX relative to that in group MDZ at all the evaluation time points (Table 3, $P < 0.05$). Although the MAP values were lower at all measurement points in group DEX than in group MDZ, no significant differences were observed between the two groups in terms of this parameter during the measurement period. More patients in the DEX group developed adverse events related to treatment (37.5% [6/16] vs 18.7% [3/16]), primarily

Table 1 Patient characteristics

Variable	Group MDZ (n = 16)	Group DEX (n = 16)	P
Age (year)	14,8 (12–17)	13,6 (12–16)	0.458
Male/Female	9/7	8/8	0.565
Height (cm)	156 (140–168)	153 (135–162)	0.347
Weight (kg)	37 (30–41)	38 (33–43)	0.654
ASA II/III (n)	10/6	11/5	0.474
APACHE II (score)	17,1(14–19)	17,3 (14–20)	0.547
Duration of MV (min)	225 (104–520)*	107 (65–280)	0.035
Length of ICU stay (day)	2 (2–2)	2 (1–2)	0.421

MDZ, midazolam; DEX, dexmedetomidine; ASA, American Society of Anesthesiologists; APACHE II, acute physiology and chronic health evaluation MV, mechanical ventilation; ICU, intensive care unit.
The data are presented as median (min–max) or number a.
*Significantly different compared with Group DEX ($P < 0.05$).

Table 2 Comparison of the results of the variables with respect to groups

Variable	Group MDZ (n = 16)	Group DEX (n = 16)	P
VAS			
1 h	4.56 ± 0.5	4.24 ± 0.4*	0.012
2 h	4.21 ± 0.7	3.14 ± 0.6*	0.003
4 h	3.20 ± 1.1	2.15 ± 0.5*	0.001
6 h	2.58 ± 1.1	2.04 ± 0.8*	0.003
24 h	1.51 ± 0.5	1.18 ± 0.5*	0.004
Fentanyl consumption (μg)			
1 h	54.3 ± 11.5	43.9 ± 5.0*	0.006
2 h	95.0 ± 17.0	72.2 ± 8.7*	0.002
4 h	122.5 ± 15.0	96.0 ± 14.1 *	0.023
6 h	136.3 ± 19.9	102.7 ± 24.2*	0.001
24 h	165.8 ± 32.8	124.1 ± 28.0*	0.002

MDZ, midazolam; DEX, dexmedetomidine; VAS, visual analog scale.
Values are mean± standard deviation (SD).
*Significantly different compared with Group DEX ($P < 0.05$).

because of a greater incidence of bradycardia (25% [4/16] vs 6.25% [1/16]).

Discussion

The primary finding of this study was that dexmedetomidine-sedated pediatric patients had reduced fentanyl consumption, lower VAS scores, and a decreased incidence of delirium than those patients sedated with midazolam in the early postoperative period following scoliosis surgery.

Children with scoliosis undergo more invasive procedures than many patients with other types of conditions. For this reason, these children require postoperative ICU care and pain medication, including opioids. Multimodal pain management is used for children who

Table 3 Hemodynamics variables

Variable	Group MDZ (n = 16)	Group DEX (n = 16)	P
HR (bpm)			
1 h	73 (68–79)*	60 (42–76)	0.014
2 h	88 (70–95)*	64 (53–98)	0.001
4 h	76 (68–98)*	66 (51–88)	0.025
6 h	78 (72–92)*	64 (50–81)	0.004
24 h	82 (75–91)*	62 (50–80)	0.001
MAP (mmHg)			
1 h	99 (68–119)	91 (67–118)	0.097
2 h	89 (77–108)	78 (63–105)	0.061
4 h	92 (69–114)	88 (67–110)	0.132
6 h	90 (65–121)	86 (67–98)	0.101
24 h	74 (62–110)	72 (60–107)	0.202

MDZ, midazolam; DEX, dexmedetomidine; MAP, mean arterial pressure; HR, heart rate.
*Significantly different compared with Group MDZ ($P < 0.05$). The data are presented as median (min–max).

experience greater pain and require more opioids than normal to limit the side effects. The central inhibition of the sympathetic outflow from the locus ceruleus in the brainstem (10) and the binding of the spinal cord α2-adrenergic receptors mediate dexmedetomidine's primary physiologic effects, including sedation, anxiolysis, analgesia, blunting of the sympathetic nervous system, and lowering of HR and BP (11,12). Arain *et al.* (4) showed that the administration of dexmedetomidine before the completion of major inpatient surgical procedures significantly reduced the early postoperative need for morphine by 66%, and was associated with a slower HR in the postanesthesia care unit. Moreover, in healthy subjects (13), DEX patients were more easily arousable, more cooperative and could better communicate pain than patients receiving midazolam. Thus, the study showed that the use of dexmedetomidine led to a significant morphine sparing effect. In this study, we showed that group MDZ required a greater amount of fentanyl during the first 24 h after scoliosis surgery than group DEX. Although several noteworthy methodological differences (e.g., the type of subject) are present between these previous studies and our study, our findings are consistent with these previous ones and support the use of dexmedetomidine over midazolam for pain management.

Delirium is a recognized brain dysfunction that complicates critical illness and constitutes a major challenge to ICU practitioners worldwide (14). Moreover, several studies have shown that ICU patients experience higher rates and longer durations of delirium than non-ICU patients (15). Some studies have reported that the incidence of delirium in children after surgery ranges from 20% to 30% (3,14). Children have a great risk of

injuring themselves by dislodging intravenous tubing or drains, losing a skin graft, bleeding from the operative site, increasing their pain, and injuring their caregivers (3). Several factors influence the severity and occurrence of delirium, such as pain and perioperative medications. Furthermore, ICU delirium has been found to be a significant factor in prolonged ventilation and hospital stays (16). The ICU-CAM is a rapidly administered instrument that can be performed reliably by nurses and physicians. Dexmedetomidine, which provides sedation as well as analgesia, has been shown to reduce delirium when given intravenously during the intraoperative period (17). Additionally, alpha receptor agonists have been used to treat delirium (18). The SEDCOM study (5) concluded that dexmedetomidine reduced the prevalence of delirium. Contrary to other studies, our study design included the 'sedation stops' if the patients were oversedated. Despite important differences current study design, the findings of this study support that dexmedetomidine can provide decreased incidence of delirium.

Hypotension and bradycardia have been reported with the use of dexmedetomidine in adult patients, especially in those with comorbid cardiac disease, or following a large or rapid bolus dose of dexmedetomidine (11). In a pediatric study, during general anesthesia with children aged 1–12 years old, no clinical significant hypotension or bradycardia was observed with the intraoperative administration of dexmedetomidine ($0.5\ \mu g \cdot kg^{-1}$) (19). A recent study of dexmedetomidine in children following congenital cardiac and thoracic surgery concluded that dexmedetomidine is a well-tolerated and effective agent for both spontaneously breathing and mechanically ventilated children (20). Further, dexmedetomidine has been used in combination with remifentanil to provide controlled hypotension during posterior spinal fusion (21). As with any sedative agent, dexmedetomidine has the potential for adverse end-organ effects. Although Tobias and *et al.* (3) suggested that these events are relatively uncommon with dexmedetomidine, the hemodynamic effects have the potential for significant morbidity or even mortality in critically ill children. Potential cardiovascular effects include bradycardia, with rare reports of cardiac arrest (22). Hypotension and bradycardia occur more commonly with the initial loading dose. Only one patient (6.25%) required an intervention for bradycardia with atropine; use of atropine was not associated with severe hypertension.

This study has several limitations. First, difficulties in communication and pain assessment may have contributed to oversedation and suboptimal analgesia. Thus, dexmedetomidine should be further assessed for mild-to-moderate sedation rather than as a sedative solely for deep sedation. Second, this study showed that delirium and positive CAM-ICU (but not the proportion of positive CAM-ICU for those assessed) were more frequent in MDZ and that reducing the incidence of delirium should improve the findings. Dexmedetomidine was shown to reduce the rate of delirium in some studies (23); other reports were uncertain on this matter (19). Finally, this study included a small sample size. Therefore, additional large randomized clinical trials to test the effects of dexmedetomidine on relevant clinical findings should be performed.

In conclusion, dexmedetomidine may be beneficial for managing sedation protocols in adolescents who have undergone scoliosis surgery.

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Ethical approval

This study used a randomized, prospective, double-blinded design. Prior to the undertaking of the study, ethical approval for the study was provided by the Ethics Committee of the Inonu University in Malatya (acceptance number: 2011/198).

Conflict of interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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