ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

# Comparison of Dexmedetomidine and Morphine for Postoperative Pain and Sedation Management in Pediatric Patients Undergoing Congenital Cardiac Surgery: A Retrospective Study

Konjenital Kalp Cerrahisi Geçiren Pediatrik Hastalarda Postoperatif Ağrı ve Sedasyon Yönetimi İçin Deksmedetomidin ve Morfinin Karşılaştırılması: Retrospektif Çalışma

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ABSTRACT Objective: In this retrospective study, it was aimed to compare the effects of dexmedetomidine and morphine on postoperative pain, sedation, extubation time and hemodynamics in patients who underwent congenital cardiac surgery. Material and Methods: From December 2012 to December 2013, 46 patients between 1 to 5 years of age, who underwent congenital cardiac surgery were included and divided into two groups based on the sedative regimen used in the postoperative period. Twenty-three patients (Group Morp) received morphine at an infusion dose of 0.01 to 0.04 mg/kg/h; 23 patients (Group Dex) received dexmedetomidine at an infusion dose of 0.05 to 0.5 mcg/kg/h. Pain scores were measured using Children's Hospital Eastern Ontario Pain Scale (CHEOPS); sedation scores with the Ramsay Sedation Scale (RSS); and hemodynamic parameters were recorded with these measured values. Sedation debth was monitored by using the Bispectral Index (BIS). In this retrospective study, postoperative pain, sedation and hemodynamic effects of intravenous dexmedetomidine in pediatric patients undergoing congenital cardiac surgery, and the effects of mechanical ventilation duration and length of intensive care unit (ICU) stay were compared with morphine. Results: Mean doses of morphine and dexmedetomidine infused were 7.04±3.94 mg/24 h and 94.33±48.38 mcg/24 h, respectively. BIS values were higher in Group Dex than Group Morp (p<0.01). Mechanical ventilation duration was shorter in Group Dex compared to Group Morp 5.74±1.98 hours vs 7.83±3.08 hours) (p<0.05). The length of ICU stay and other outcome measurements between the two groups were similar. Heart rate was lower in the group Dex only in the first two hours (p<0.01). CHEOPS pain scores were similar in two groups (p>0.05). RSS scores at 1st, 2nd, 3rd, 4th hours were higher in Group Dex than Group Morp (p <0.01); however, there was no difference between the groups in terms of RSS scores at the 12th, 16th, 20th and 24th hours (p> 0.05). There was no difference between the groups in terms of the frequency of side effects (p> 0.05). Conclusion: With regard to our study findings, dexmedetomidine can provide effective analgesia and sedation with shorter mechanical ventilation duration without adverse reaction compared to morphine in pediatric patients undergoing congenital cardiac surgery.

Keywords: Dexmedetomidine; morphine; postoperative pain; cardiac surgical procedures; pediatrics

ÖZET Amaç: Bu retrospektif çalışmada konjenital kalp cerrahisi uygulanan hastalarda deksmedetomidin ve morfinin postoperatif ağrı, sedasyon, ekstübasyon süresi ve hemodinami üzerine etkilerinin karşılaştırılması hedeflenmiştir. Gereç ve Yöntemler: Çalışmaya Aralık 2012 ve Aralık 2013 tarihleri arasında konjenital kalp ameliyatı geçirmiş 1-5 yaş arası 46 hasta dahil edildi ve hastalar ameliyat sonrası dönemde kullanılan sedasyon rejimine göre iki gruba avrıldı. Yirmi üc hasta (Morp grubu) 0.01-0.04 mg/kg/saat infüzyon dozunda morfin alırken; 23 hasta (Dex grubu) 0,05-0,5 mcg/kg/saat intravenöz infüzvon dozunda deksmedetomidin almıştır. Ağrı skorları, Çocuk Hastanesi Doğu Ontario Ağrı Ölçeği (Children's Hospital Eastern Ontario Pain Scale: CHE-OPS) kullanılarak; sedasyon skorları Ramsay Sedasyon Ölçeği (Ramsay Sedation Scale : RSS) ile ölçülmüştür; ve bu ölçülen değerler ile hemodinamik parametreler kaydedilmiştir. Sedasyon derinliği Bispektral İndeks (BİS) kullanılarak izlenmiştir. Bu retrospektif çalışmada konjenital kalp cerrahisi geçiren pediyatrik hastalarda intravenöz deksmedetomidinin postoperatif ağrı, sedasyon ve hemodinamik etkileri ile mekanik ventilasvon süresi ile voğun bakım ünitesi (YBÜ)'nde kalıs süresine olan etkileri morfin ile karşılaştırılmıştır. Bulgular: İnfüze edilen ortalama morfin ve deksmedetomidin dozları sırasıyla 7,04±3,94 mg/24 saat ve 94,33±48,38 mcgug/24 saat idi. BIS değerleri Dex grubunda Morp grubundan daha yüksekti (p<0,01). Dex grubunda mekanik ventilasyon süresi Morp grubuna göre daha kısaydı (morfin: 7,83±3,08 saat; deksmedetomidin: 5 74±1 98 saat) (p<0 05) İki grup arasında YBÜ'de kalış süresi ve diğer sonuç ölçümleri benzerdi. Kalp hızı deksmedetomidin grubunda sadece ilk iki saatte düşüktü (p<0,01). CHEOPS ağrı skorları iki grupta benzerdi (p>0,05). RSS skorları 1., 2., 3., 4. saatlerde Dex grubunda Morp grubundan daha yüksekti (p<0,01); bununla birlikte 12., 16., 20. ve 24. saatlerde RSS skorları bakımından gruplar arasında fark yoktu (p>0,05). Yan etki görülme sıklığı bakımından da gruplar arasında fark yoktu (p>0,05). Sonuç: Çalışma bulgularımıza göre, deksmedetomidin, konjenital kalp ameliyatı geçiren pedivatrik hastalarda morfine kıvasla van etki olmadan daha kısa mekanik ventilasyon süresi ile etkili analjezi ve sedasyon sağlayabilmiştir.

Anahtar Kelimeler: Deksmedetomidin; morfin; postoperatif ağrı; kardiyak cerrahi işlemler; pediatri

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2146-894X / Copyright © 2020 by Türkiye Klinikleri. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). Adequate sedation and analgesia is very important to prevent unexpected surgery-related events after congenital heart surgery. The most commonly used analgesic and sedative agents are opioids, especially morphine. Although the use of morphine can provide excellent analgesia, it may lead to undesirable side effects, such as respiratory depression, prolonged duration of mechanical ventilation (MV), hemodynamic instability, tolerance and significant withdrawal symptoms, and gastrointestinal dysfunction which delays patient's recovery and rehabilitation.<sup>1,2</sup>

Although morphine and other opioids such as fentanyl have been the drug of choice for many years, they have been recently replaced by dexmedetomidine in many settings because of the potential benefits of dexmedetomidine.<sup>3,4</sup>

Dexmedetomidine is a highly selective  $\alpha$ 2adrenoceptor agonist that produces dose-dependent sedation, anxiolysis, and analgesia without respiratory depression, unlike other sedatives and opioids.<sup>5-7</sup> Its cardiovascular depressant effects are minimal, because of this it has been increasingly used following congenital heart surgeries, due to its combined sedative-analgesic, and anti-sympathetic effects.<sup>8-10</sup>

Effective postoperative pain management is very important in congenital heart surgery for the maintenance of early and safe extubation and may decrease complication rates and therefore costs.<sup>3-5</sup> Recent studies have shown that Dex reduces the length of MV and so cardiovascular intensive care unit (CICU) stay, compared to traditional sedative-analgesic agents, such as propofol, midazolam, fentanyl, and morphine.<sup>5,6</sup>

In this retrospective study, we aimed to investigate the sedative and analgesic effects and hemodynamic effects of intravenous dexmedetomidine administration on postoperative pain management compared to morphine consumption in children who underwent congenital cardiac surgery.

### MATERIAL AND METHODS

After approval of the University Ethics Committee (KA13/88), we searched our institutional database

and medical records for pediatric patients who underwent an operation due to the congenital heart disease between December 2012 and December 2013. The study was conducted in accordance with the 2008 Helsinki Decleration.

We retrospectively reviewed medical data of children between the ages of 1 and 5 years who underwent congenital heart surgery and received a continuous infusion of dexmedetomidine (Precedex<sup>®</sup>, Abbott Laboratories) or morphine during the first 24 hours of the postoperative period. Patients who underwent elective congenital heart operations of the first category of the STS-EACTS Congenital Heart Surgery Mortality Score were included who were expected to have a shorter length of CICU stay and so to gain relatively homogenous cohort of patients.<sup>11</sup> Operations were performed under deep hypothermia, patients who underwent complex congenital heart surgery and who need extracorporeal membrane oxygenation (ECMO) support were excluded.

During this period, 23 patients who met the inclusion criteria were receiving Dex and 86 patients were receiving morphine postoperatively who have met the inclusion criteria. As the number of patients received Dex was lower than those received morphine, the morphine group was randomly selected to match the dexmedetomidine group based on the age and the type of operation applied. Depending on the drug used, the patients were divided into two groups: Of a total of 46 patients, 23 patients were assigned to the morphine group (Group Morp), 23 patients to the Dex group (Group Dex) (Figure 1).



FIGURE 1: Study flow chart.

All operations were performed by a single surgical team using the same standardized technique. Anesthesia was induced in all patients with thiopental (4-6 mg/kg), fentanyl (8-10 mcg/kg), and vecuronium (0.08 mg/kg) and maintained with a fentanyl infusion (8 mcg/kg/h), %0.5 to %0.7 isoflurane in an oxygenair mixture, and intra-venous injection of vecuronium (0.02 mg/kg every 30 minutes). Before sternal closure, fentanyl 1 mcg/kg and midazolam 0.05 mc/kg were administered to all patients.

After the operation, all patients were taken to the CICU. In the CICU, all monitorization that done in the operating room were continued (invasive arterial pressure, HR, SPO<sub>2</sub>, BIS, santral venous pressure) hourly over 24 h and the patients weaned when they were fully awake, hemodynamically stable with full recovery of muscular forces, and met the weaning and extubation criteria according to our protocols of the CICU.

According to the clinical practice in the CICU of our institution, the decision to administer a bolus and exact initial infusion dose is based on the physician's discretion and level of sedation-analgesia that the patient experienced, before the initiation of infusion (i.e., the degree of residual intraoperative anesthesia). Postoperatively Dex had been administered at a dose of 0.05 to 0.5 mcg/kg/h infusion (n=23); while morphine had been administered at a dose of 0.01 to 0.04 mg/kg/h.

Hemodynamic parameters including heart rate (HR), mean arterial pressure (MAP), oxygen saturation measured via pulse oximetry, duration of MV, length of CICU stay, requirements for additional sedative/analgesic drugs, adverse effects (arrhythmia, hypotension, bradycardia episodes, hypertension, pruritus, vomiting, atelectasis, constipation) were recorded.

Sedation levels were measured by using the Ramsay Sedation Scale (RSS); the pain was assessed by Children's Hospital Eastern Ontario Pain Scale (CHEOPS) which we used routinely in our CICU to maintain proper sedation-analgesia. If sedation/ analgesia were considered inadequate by the bedside nurse and by the physician on duty, rescue analgesia of morphine of 0.03 mg/kg was given to all patients whose RSS<2 and CHEOPS score>7 which are the adequate sedation levels.<sup>12,13</sup>

The CHEOPS is a behavioral scale for evaluating postoperative pain in young children, which incorporates six categories of behavior, each is scored individually (range: 0-2 or 1-3) and then totaled for a pain score ranging from 4 to 13.<sup>13</sup>

Bispectral Index (BIS) (Aspect A-1050, Aspect Medical Systems, Natick, Massachusetts) was used to monitor the depth of sedation, as we routinely use in our CICU, using electroencephalography data via a set of electrodes (BIS Sensor, Aspect Medical Systems) attached to the patient's forehead according to the manufacturer's instructions. While the BIS values ranged from 0 to 100 (from no cerebral activity to fully awake patient) target BIS value was 65-85.<sup>14</sup> A BIS value of 100 indicates the patient is fully awake, a BIS value of 0 indicates the absence of brain activity.

Vital signs, clinical parameters, sedation and pain scores documentations were recorded at the time of CICU arrival and 30<sup>th</sup> minutes, 1<sup>st</sup>, 2<sup>nd</sup>, 4<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 16<sup>th</sup>, 20<sup>th</sup>, 24<sup>th</sup> hours of the postoperative period from the medical charts.

#### STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS for Windows version 15.0 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed in mean, standard deviation, and frequency. The Student t-test was used to analyze normally distributed variables, while the Mann-Whitney U test was used to analyze non-normally distributed variables. Nominal data between the groups were compared using Fisher's exact and chi-square tests. Pearson's correlation analysis was used to investigate any correlation among variables. A p-value of <0.05 was considered statistically significant.

As a result of the power analysis, when we took the difference (D) 12 for the morphine consumption, the number of samples determined for power:0.80, b:0.20 and a:0.05 was determined as minimum 12 patients for each group.

		Gr	oup Morp (Morphine)	Group Dex (Dexmedetomidine)	p value
Age (months), median (range) <sup>1</sup>			20.29±21.91 (8)	26.31±24.18 (12)	0,373*
Weight (kg), median (range)1			8.48±4.70 (6)	9.84±5.39 (9.2)	0,575*
			n (%)	n (%)	p value <sup>3</sup>
	Sex	Female	11 (%47.8)	11 (%47.8)	1,000*
		Male	12 (%52.2)	12 (%52.2)	
Diagnosis	Surgical Procedures		n (%)	n (%)	
ASD	ASD closure		4(%23)	3(%13)	
VSD	VSD closure		9(%39)	8(%34)	
ASD+PS	ASD closure, PS repair		2(%8.6)	3(%13)	
VSD+PS	VSD closure, PS repair		4(%17)	3(%13)	
CAVSD	CAVSD repair		2(%8)	2(%8.6)	
PAVSD	PAVSD repair		2(%8.6)	4(%17.3)	

<sup>1</sup>Mann-Whitney U test <sup>3</sup>Chi-square test p>0.05.

ASD: Atrial septal defect; VSD: Ventricular septal defect; PS: Pulmonary stenosis; CAVSD: Complet atrioventricular septal defect; PAVSD: Parsial atrioventricular septal defect.

## RESULTS

The study protocol was conducted at CICU of Baskent University Istanbul Hospital. There were no significant differences in baseline demographics between the groups (Table 1).

The mean doses of morphine and dexmedetomidine infused were  $7.04\pm3.94$  mg/24 h and  $94.33\pm48.38$  mcg/24 h, respectively. The HR was lower at the first and second hours in Group Dex, compared

to Group Morp (p<0.01). MAP, SPO<sub>2</sub>, and blood gas analysis were within the normal ranges, and there were no differences in hemodynamic parameters between the groups (p>0.05).

In all measurement time intervals, BIS values were significantly higher in the Dex group, (p=0.001) (Figure 2). However, there was no significant difference in the CHEOPS scores between the groups in all measurement time points (p>0.05) (Figure 3).



FIGURE 2: BIS (Bispectral Index) scores of the groups.



FIGURE 3: CHEOPS (Children's Hospital Eastern Pain Scale) scores of the groups.



FIGURE 4: Ramsay Sedation Scale (RSS) of the groups.

Ramsay Sedation Scale 1 Patient is anxious and agitated or restless, or both, 2 Patient is co-operative, oriented, and tranquil, 3 Patient responds to commands only, 4 Patient exhibits brisk response to light glabellar tap or loud auditory stimulus, 5 Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus, 6 Patient exhibits no response.

There was no statistically significant difference in RSS scores between the groups within the initial times of ICU stay and at the 12, 16, 20 and 24<sup>th</sup> hours (p>0.05); but in the time points of 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup> and 4<sup>th</sup> hours the RSS scores were higher in the Group Morp compared to the Group Dex (p<0.01) (Figure 4).

The mean MV duration of the Group Dex  $(5.74\pm1.98 \text{ hours})$  was significantly lower than the Group Morp  $(7.83\pm3.08 \text{ hours})$  (p:0,02). However, the length of CICU stay was similar between the groups (p>0.05) (Table 2). Also, there was no difference in the surgical procedures applied to the groups (p>0.05); in the aortic cross-clamping

<b>TABLE 2:</b> Mechanical ventilation (MV) and intensive care unit (ICU) duration.							
	Group Morp	Group Dex	р				
MV time (hour) <sup>1</sup>	7.83 ± 3 (9)	5.74 ± 1.2 (5)	0.022*				
Stay in ICU <sup>2</sup>	$30.7 \pm 6.4$	28.8 ± 7.7	0.363				

<sup>1</sup>Mann-Whitney U test, <sup>2</sup>Student test, \*p<0.05.

time and cardiopulmonary bypass time (p>0.05) (Table 1).

There was no statistically significant difference concerning the need for rescue analgesia between the groups. The amount of morphine used

TABLE 3: Rescue analgesia and adverse events.							
	Group Morp	Group Dex	р				
Adverse Events <sup>1</sup>							
Yes (n, %)	3 (13 %)	4 (17.4 %)	1.000				
No (n, %)	20 (87 %)	19 (83 %)					
Rescue analgesia (mg), <sup>2</sup>	1.02 ± 0.6 (1)	0.91 ± 0.47 (0.8)	0.703				
median (range)							

<sup>1</sup>Fisher's Exact Test. <sup>2</sup>Mann Whitney U test.

as rescue analgesia in Group Morp was  $1.02\pm0.59$  mg while in Group Dex  $0.91\pm0.47$  mg (p>0.05) (Table 3).

There was no significant difference in the adverse events including arrhythmia, hypotension, hypertension, pruritus, vomiting, atelectasis, and constipation between the groups (p>0.05) (Table 3). Bradycardia occurred in four patients (%17.4) in Group Dex, while hypotension developed in three patients (%13) and bradycardia in one patient (%4) in Group Morp that spontaneously recovered within one hour.

### DISCUSSION

In this retrospective study, we investigated whether dexmedetomidine can provide adequate analgesiasedation compared with morphine during the early postoperative period after elective congenital heart surgery.

One of the primary outcomes of this study was the duration of MV which is shorter in Dex group compared to Morp group. However, there was no significant difference in the length of the CICU stay between the groups. Dexmedetomidine showed statistically significant higher values of BIS when compared with morphine (BIS value was within the range of 65-70 in Group Dex as opposed to 50-55 in Group Morp).

Although morphine, like other opioids, provides effective analgesia, respiratory depressant effect of it may prolong the duration of MV and so intensive care unit stay.<sup>9,10,15-17</sup> On the other hand, dexmedotimidine with its minimal respiratory depressant effects, may provide shorter MV

duration providing early extubation. The use of dexmedotimidine in the postoperative period after congenital heart surgery can decrease opioid consumption and provide adequate analgesia with fewer side effects. <sup>18-23</sup>

Pan et al. have demonstrated a meta-analysis that presented the effects of dexmedetomidine on the duration of MV.<sup>18-22</sup> According to the results of this meta-analysis, perioperative use of dexmedetomidine is associated with better outcomes in pediatric patients undergoing congenital heart surgery, including more stable intraoperative hemodynamics, shorter MV duration with earlier extubation.

Similar to our findings, in many studies, it has been demonstrated that continuous infusion of dexmedetomidine was as effective as usual sedatives for maintaining proper sedation at a RSS score of 2 or 4 levels before and after extubation in CICUs. At arrival to the CICU and the 12, 16, 20, 24th hours there was no statistically difference between the groups concerning RSS scores (p>0.05); but at the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, and 4<sup>th</sup> hours the RSS scores were higher in the Group Morp compared to the Group Dex (p<0.05). But in both groups, especially after the first hours at arrival to the CICU, the RSS scores were within the 2-4 ranges which is a reflection of adequate sedation, in all measurement time points. The RSS scores were ranged between 3-6 in the first hours after the operation with the effect of anesthetic drugs used during the operation. Similarly, average CHEOPS values were below 7 which is considered an effective analgesia level. Also, there was no difference in the CHEOPS scores between the groups in all measurement times (p>0.05).

Chrysostomou et al. performed a retrospective study including patients who underwent cardiothoracic surgery and received dexmedotimidine in doses of 0.3 mcg/kg/hr.<sup>16</sup> According to this study, Dex provided adequate sedation 93% of the time and adequate analgesia 83% of the time. N. Abd. Aziz et al. have studied the efficacy and safety of dexmedotimidine versus morphine in postoperative cardiac surgery patients;<sup>17</sup> he also demonstrated that dexmedotimidine can be used safely with its effective sedation-analgesia compared to morphine. In this study, the rescue analgesic requirement was similar in the groups.

In our study, the cumulative morphine requirement in Group Morp was  $7.04\pm3.94$  mg/24 h as an infusion and  $1,02\pm0,59$  mg as rescue analgesia. The total amount of morphine used as rescue analgesia in Group Dex was  $0,91\pm0,47$  mg which is lower than the morphine group. There was a tendency to use less rescue analgesia in Group Dex as compared to Group Morp, but the difference did not reach statistical significance.

Bispectral Index is an objective method for the measurement of the depth of sedation and analgesia which is used frequently in intensive care units 8,20,21 In our study, the administration of dexmedotimidine provided higher BIS levels compared to morphine. In both groups infusions titrated to maintain BIS values in the 65-85 range intervals. In early hours BIS values ranged 40-65, but after BIS values increased to the target level of 65-85. Similar to our study, Chen et al. <sup>21</sup> found higher BIS values in the Dex group compared to the propofol group in their study and compared the effects of Dex and propofol on the accuracy of BIS in predicting the loss of consciousness (LOC). Furthermore, LOC occurred at higher BIS values in the presence of Dex compared to propofol.

In a study performed by Tobias et al., dexmedotimidine with doses of 0.5 mcg/kg/h provided more effective sedation and reduced the rescue doses of morphine.<sup>24</sup> In our study, sedation levels in the Group Dex were adequate and comparable with Group Morp (p>0.05); the required rescue doses of morphine were comparable in both groups while BIS values were higher in the Group Dex which means more awakeness.

The main reasons for dexmedotimidine preference for sedation and analgesia in the intensive care unit after congenital heart surgery are rapid redistribution, short elimination half-life, minimal risk of respiratory depression, and relative low cardiovascular effect. The most common cardiovascular side effects are bradycardia and hypotension, but generally, these side effects seen after bolus doses.<sup>18-25</sup> То provide more stable hemodynamics, according to our clinic's sedativeanalgesic protocol, we use only infusion doses without a loading dose. Although we haven't used high doses of dexmedetomidine, we could maintain adequate sedation without any side effects.

The HR was lower at the first and second hours in Group Dex, compared to Group Morp (p<0.01). However, this decline didn't require any treatment and spontaneous recovery was seen within one hour. Since it was early times of the postoperative period, low heart rates in the first and second hour can be related to the anesthetic drugs used in the operation. Nevertheless, bradycardia developed in four patients (%17.4) in Group Dex and one patient (%4) in Group Morp. Hypotension developed in three patients (%13) in Group Morp, while none of the patients experienced hypotension in Group Dex. But these findings didn't require any treatment.

Nausea and vomiting can be seen related to opioids and benzodiazepines, especially in higher doses. Unlike opioids, dexmedotimidine does not reduce enteral motility significantly and in this way the incidence of ileus seen fewer with the usage of DEX. It provides a significant advantage, especially in the neonatal and infant population. This provides major advantages to the patients for early nutrition in the postoperative period.<sup>15,21</sup> All patients in the dexmedotimidine and morphine groups started enteral nutrition in the early post-extubation period. As we monitored all patients within 24 hours, we observed no gastrointestinal side effects. But with long-term usage opioids may compromise the gastrointestinal side effects such as nutritional deficiencies.

The limitation of our study is first, the study design was retrospective. Secondly, due to retrospective data collection, we didn't use Dex for the patients who underwent complex congenital heart surgery. Compared to complex cardiac surgery, our patients have a lower risk of adverse cardiovascular effects due to dexmedetomidine.

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To our knowledge, this was one of the first studies performed in Turkish pediatric cardiac surgery patients using dexmedetomidine undergoing congenital heart surgery.

In this retrospective study, we found that dexmedetomidine could provide adequate sedation and analgesia compared to morphine without any side effects while shortening the duration of MV which will decrease complications due to the long duration of MV and CICU stay.

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#### **Conflict of Interest**

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

#### Authorship Contributions

Idea/Concept: Dilek Altun; Design: Dilek Altun, Ayda Türköz; Control/Supervision: Dilek Altun, Ayda Türköz; Data Collection and/or Processing: Dilek Altun, Ayda Türköz; Analysis and/or Interpretation: Dilek Altun, Abdullah Doğan, Ayda Türköz; Literature Review: Dilek Altun, Abdullah Doğan, Ahmet Arnaz; Writing the Article: Dilek Altun, Abdullah Doğan, Ayda Türköz; Critical Review: Dilek Altun, Abdullah Doğan, Ayda Türköz, Ahmet Arnaz; References and Fundings: Dilek Altun, Ayda Türköz; Materials: Dilek Altun, Ayda Türköz.

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