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Dexmedetomidine versus Midazolam as an Anesthetic Adjuvant in Pediatric Cardiac Surgery: An Entropy Evaluation Study

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Received Date: 02th October 2019
Accepted Date: 01st November 2019
Published Date: 04th November 2019

Citation: Taman HI, Eldereym AA. Dexmedetomidine versus Midazolam as an Anesthetic Adjuvant in Pediatric Cardiac Surgery: An Entropy Evaluation Study. Enliven: J Anesthesiol Crit Care Med. 2019; 6(2): 009-016.

Abstract

Introduction

Volatile anesthetics have dose-dependent myocardial depressant properties. Thus anesthetists should balance between myocardial stability and adequate depth of anesthesia. Certain adjuvant drugs like dexmedetomedine and midazolam can be used to obtain adequate depth of anesthesia with lower inhalational anesthetic requirement. Thus, avoiding of inhalational anesthetic drugs associated myocardial suppressing affect in such patients with already diseased heart.

Patients and Methods

Seventy children patients with corrective congenital open heart surgery were divided into two groups. One received dexmedetomedine (0.5 µg/Kg/hour) and the other received midazolam infusion (0.05 mg/Kg/hour) as adjuvant to sevoflurane based anesthesia monitored by entropy. End-tidal concentration of sevoflurane, heart rate, MAP, additional fentanyl boluses, extubation time, vomiting and emergence agitation were all recorded.

Results and Conclusion

Sevoflurane end tidal concentration, entropy readings, additional doses of fentanyl, heart rate, MAP, were higher in midazolam group when compared to dexmedetomedine group. Similarly extubation time was longer in midazolam group in comparison to dexmetetomedine group. Emergence agitation score was of no significant value between dexmedetomedine and midazolam group.

Conclusion

with continuous infusion of 0.5 µg/Kg/hour dexmedetomedine during sevoflurane based anesthesia, lower end tidal sevoflurane concentration and entropy readings were noticed in comparison to midazolam infusion. In addition, lowers intraoperative additional opioid requirements and shorter extubation time with more hypotension and bradycardia were observed with dexmedetomedine infusion when compared to midazolam infusion in pediatric congenital corrective cardiac surgery.

Keywords: End Tidal Concentration; Opioid Sparing; Adjuvant; Emergence Agitation; Hemodynamic Stability; Pain Assessment.

Introduction

Patient safety during anesthetic management of pediatric cardiac surgery is fundamental. Almost all of anesthetic medications have dose-dependent myocardial depressant properties hence; there is no single universally-accepted agent for anesthetic management during cardiac surgery (1).

Generally, volatile anesthetics reduce systemic vascular resistance, slow the sinoatrial node discharge rate, increase conduction time and suppress myocardial contractility by changing of calcium ion flux (2,3). Sevoflurane is frequently used in pediatric cardiac surgery because of its non-pungency odor and rapid increases in alveolar concentration (4). However, with this agent cardiac output is not maintained with higher incidence of emergence agitation (5).

In order to reduce the required doses of anesthetic agents, adjuvant drugs can be used to obtain sufficient depth of anesthesia. Dexmedetomedine and midazolam are two commonly used

adjuvants. Dexmedetomedine is an alpha 2 adrenergic receptor agonists with sedative, analgesic, sympatholytic, and hemodynamic stabilizing properties (6,7). Midazolam is another sedative adjuvant, which promotes effective sedation, anxiolysis, and anterograde amnesia. Unfortunately, postoperative altered behavior and paradoxical hyperactive reactions may occur after its use (8).

To ensure adequate depth of anesthesia, entropy monitor is now used to assess the depth of anesthesia (9). Entropy indices is less interfered with electrocautery unit than BIS during intraoperative period (10).

We hypothesized that the addition of dexmetedomedine as an adjuvant to sevoflurane based anesthesia in pediatric congenital cardiac surgery decreases Sevoflurane requirement to obtain adequate depth of anesthesia with more hemodynamic stability and low emergence agitation and side effects when compared to midazolam.

This study aimed mainly at comparing the efficacy of Dexmedetomidine versus Midazolam as an adjuvant to inhalational anesthetics in pediatric cardiac surgery using entropy as a monitor of anesthesia depth. The second aim was to evaluate the effect of both drugs on hemodynamic stability, emergence agitation after sevoflurane use as well as any prominent associated side effects.

Patients and Methods

Seventy patients aged between 3 and 5 years old, who were planned for elective corrective congenital open heart surgery using cardiopulmonary bypass under general anesthesia, were enrolled in this comparative study.

An informed written consent from all participants' guardians and acceptance of institutional review board were obtained. Patients with active respiratory tract infections, hepatic and renal insufficiency, previous or redo heart surgery, neurological dysfunction and endocarditis were excluded from the study.

Anesthesia was induced using sevoflurane 2%-3%., with loss of consciousness, intravenous line was inserted followed by injection of 5 μg/Kg fentanyl and rocuronium 1 mg/Kg to facilitate endotracheal intubation. After securing ETT, all patients were connected to a closed anesthetic breathing circuit and the fresh gas flow was set at 1 L/min. lungs were artificially ventilated using pressure controlled ventilation mode aiming at tidal volume 6–8ml/kg, inspiratory and expiratory ratio 1: 2 and end-tidal carbon dioxide concentrations at 35–40 mmHg.

Five leads electrocardiogram (ECG), pulse oximetry, side stream capnography, nasopharyngeal temperature, response entropy (RE) and state entropy (SE) were attached to each patient. A radial artery catheter (22 G) was inserted after doing modified Allen's test to monitor the arterial blood pressure and blood sampling during the entire procedure. Latter all patients were randomly allocated into two equal groups using closed envelop method:

A) Dexmedetomidine group: Patients received continuous infusion dexmedetomidine of 0.5 μg/Kg/hour throughout the operation (11).
B) Midazolam group : Patients received continuous infusion of midazolam at 0.05 mg/Kg/hour throughout the operation (12).

Anesthesia was maintained in both groups with sevoflurane using Vapor 19.3 vaporizers (Drager, Lubeck, Germany). Vaporizer setting was increased slowly to obtain state and response entropy score values around 45-60 during surgery.

The commercially available Datex-Ohmeda module calculates entropy was used to monitor the depth of anesthesia. Two separate numerical values on a scale between 0 and 100 were recorded. The maximum value of the response entropy (RE) is 100, and the maximum value of the state entropy (SE) is 91. Numbers close to 100 mean that the patient is conscious, and numbers close to zero denote very 'deep' anesthesia. A clinically practical level of anesthesia is achieved when the value is between 45 and 60. Adequate level of anesthesia is obtained when the RE and SE values differs by (0-3). The increase in the difference between the RE and SE is an early sign of inadequate anesthesia (10, 13).

Intraoperatively, end-tidal concentration of sevoflurane, heart rate, MAP were recorded before starting the infusion of the tested drug, 10 minutes after drug infusion, skin incision, sternotomy, pericardiotomy, beginning and termination of CPB, closure of sternum and skin.

Additional fentanyl boluses, which were required to attenuate sympathetic stimulation throughout the surgery (when MAP or HR increased more than 25% of basal values), extubation time (elapsed time between cessation of anesthesia and tracheal extubation) and the incidence of postoperative vomiting were all recorded. Atropine and metraminol were used to treat any life threatening bradycardia or hypotension.

Emergence agitation was assessed at arrival to ITU and every 15 min for up to 2 hours. Emergence agitation was rated using a four-point scale modified by Watcha, et al (1=calm, 2=crying, but can be consoled, 3=crying and cannot be consoled, 4=agitated and thrashing around). Children with scores of 3 or 4 were considered to have an emergence agitation epi¬sode (14).

Sample size Calculation

We were planning a study of a continuous response variable from independent control and experimental subjects with 1:1 ratio of two groups. In a previous study the response within each subject group was normally distributed with standard deviation 3.48. If the true difference in the experimental and control means is 3, we would need to study 29 experimental subjects and 29 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.85. We had increased the number in each group up to 35 patients. The Type I error probability associated with this test of this null hypothesis was 0.05 (15).

Statistical Analysis

Klomogorov-Smirnov test was used to test the data normality of distribution. t-test and Mann-Whitey U test were used for

analysis of normally and non-normally distributed continuous data. Chi-square or Fisher's exact tests were used for analysis of categorical data. The results were expressed as mean (SD), median and range or number and % of patients as appropriate. A P value < 0.05 was considered statistically significant. Statistical analysis was performed using statistical package for social sciences (SPSS) software (SPSS Inc., Chicago, USA), version 18.0.

Tables and Results

No significant differences were found as regard age, gender weight, primary congenital defect, duration of surgery, CPB time and Cross clamp time when both groups were compared together (Table 1).

End tidal of sevoflurane concentrations required to obtain adequate depth of anesthesia were higher in midazolam group when compared to dexmetetomedine group after skin incision, sternotomy, pericardiotomy, start of CPB. The main reduction in end tidal sevoflurane concentration was 22.68 in dexmedetomedine group and 25.46 in midazolam group when compared to their basal values (Figure 1).

Both response and state entropy values were higher in midazolam group when compared to dexmetetomedine group after skin incision, sternotomy and pericardiotomy (Figure 2).

Additional doses of Fentanyl were higher in midazolam group when compared to dexmetetomedine group (Figure 3).

Only 7 cases were extubated after 1 hour in dexmedetomedine group and 5 cases in midazolam group. There was no significant difference between extubated cases in both groups as regard emergence agitation incidence (Table 2).

Time of extubation was longer in midazolam group 4.4 ± 0.59 in comparison to dexmetetomedine group 3.2 ±0.47 (figure 4). Meanwhile the incidence of vomiting was insignificant between two groups 6 versus 7 cases respectively (Figure 5).

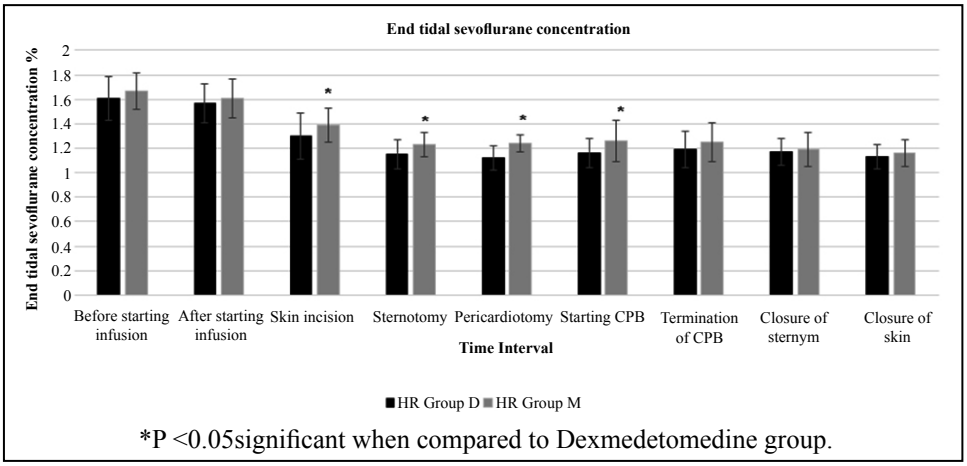
Both heart rate and mean arterial blood pressure were significantly higher in midazolam group when compared to dexmedetomedine group at skin incision, sternotomy and pericardiotomy time interval (Figure 6).

Table 1. Demographic data of the studied groups. Data are expressed as number, %, mean ± SD.

	Group D (n=35)	Group M (n=35)
Age (months)	44.1 ±7.5	46.2 ± 8.9
Weight (kg)	21.5 ±3.7	22.1 ± 4.1
Gender (n, %.)		
Male	19 (54.29%)	15 (42.56%)
Female	16 (45.71%)	20 (57.14%)
Surgery (n, %.)		
ASD	10 (28.57%)	12 (34.28%)
VSD	11 (31.43%)	10 (25.57%)
SAM	9 (25.71%)	8 (22.59%)
CAVC	5 (16.67%)	5 (16.67%)
Duration of surgery (hrs)	4.3 ± 0.9	4.15 ± 1.11
CPB time (min)	56.1 ± 16.3	58.2 ± 15.6
Cross clamp time (min)	38.12 ± 11.5	41.2 ± 13.6

ASD: atrial septal defect, VSD: ventricular septal defect, SAM: sub aortic membrane, CAVC: Common atrio-ventricular canal, CPB: cardiopulmonary bypass.

Figure 1. Average end tidal sevoflursne concentration in the studied groups Data are expressed in mean ± SD.



*P <0.05significant when compared to Dexmedetomedine group.

Figure 2. Response and state entropy values in the studied groups Data are expressed in mean ± SD.

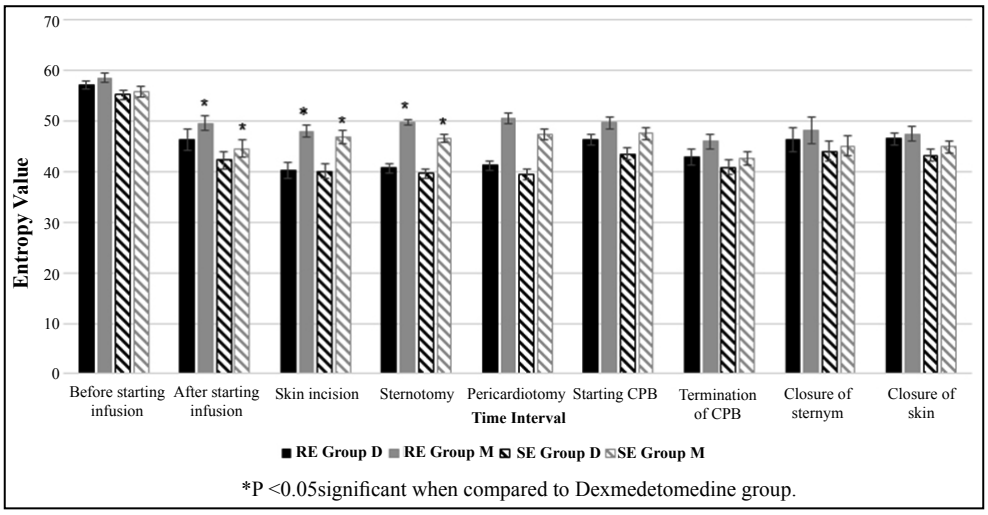


Figure 3. Additional doses of fentanyl the studied groups Data are expressed in mean ± SD.

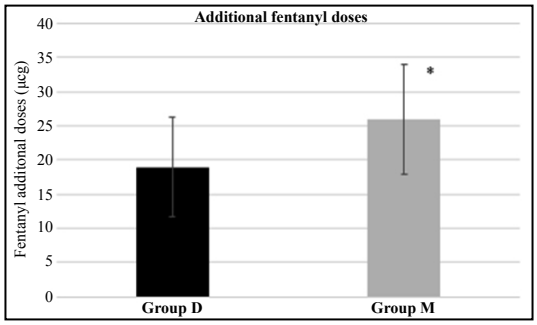


Table 2. Emergence agitation incidence in the studied groups. Data are expressed as median and range.

	Group D (*n*=7)	Group M (*n*=5)
After 60 minutes in ITU	1 (1 - 2)	1 (1 - 2)
After 75 minutes in ITU	1 (1 - 2)	2 (1 - 2)
After 90 minutes in ITU	2 (2 - 3)	2 (2 - 3)
After 105 minutes in ITU	2 (2 - 3)	2 (2 - 3)
After 120 minutes in ITU	2 (2 - 3)	2 (2 - 3)

ITU: Intensive Therapy Unit.

Figure 4. Time of extubation in the studied groups Data are expressed in mean ± SD.

Figure 5. Incidence of vomiting in the studied groups Data are expressed in mean ± SD.

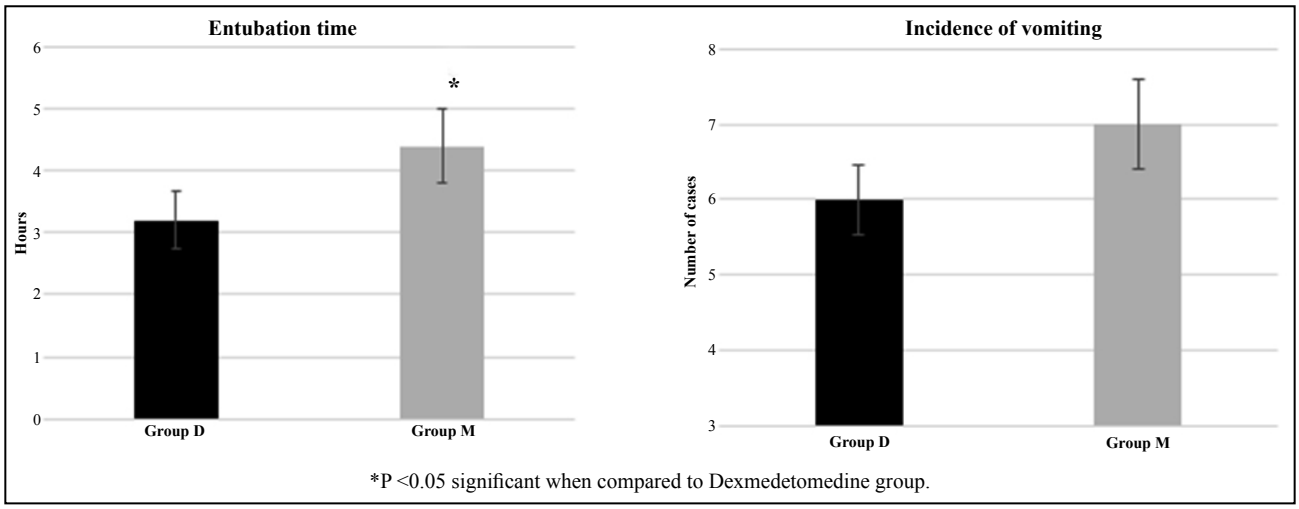
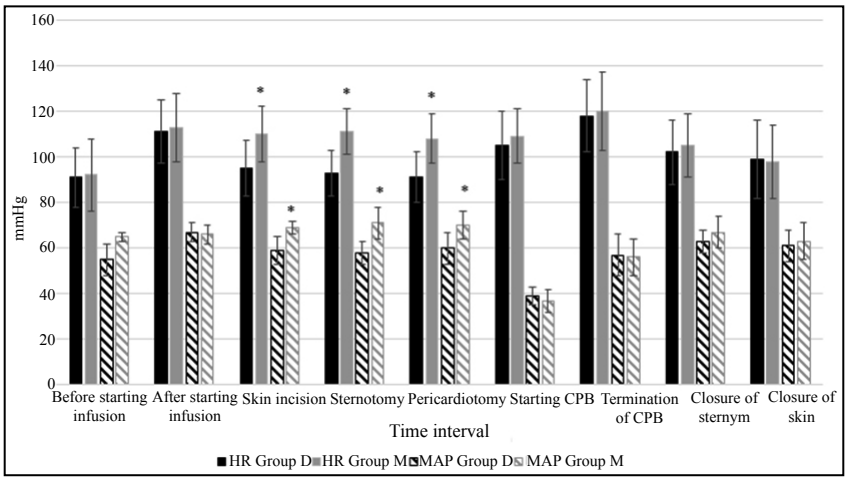


Figure 6. Intraoperative heart rate (beat/ minute) and mean arterial blood pressure of the studied groups Data are expressed in mean ± SD.



Discussion

The main finding in the current study, was that sevoflurane anesthetic requirements are decreased with dexmedetomidine infusion compared to midazolam infusion. In addition, lower intraoperative opioid requirement, and shorter extubation time were noticed to be associated with dexmedetomedine when compared to midazolam infusion.

In the current study, low end tidal sevoflurane concentrations with lower entropy readings were recorded during anesthesia with dexmedetomedine infusion when compared to midazolam. The main reduction in end tidal sevoflurane concentration was 22.68% in dexmedetomedine group and 25.46% in midazolam group when compared to their basal values.

Dexmedetomidine activates presynaptic α2-adrenoceptors located in the locus ceruleus which represents the main brain noradrenergic nucleus. Locus ceruleus gives origin of different medullo-spinal noradrenergic tracts which are known as an important modulator of nociceptive neurotransmission where α2-adrenergic and opioidergic systems have common effector mechanisms (16).

Generally, activation of presynaptic α2adrenoceptor can reduce norepinephrine secretion with interruption of pain impulse progression. Postsynaptic central α2 adrenoceptors activation suppresses the sympathetic activity. α2-adrenoceptor activation suppresses the neuronal firing, resulting in lowering blood pressure, heart rate, sedation, analgesia as well as decreasing gut motility, vascular and smooth muscle contraction according to its location in the CNS (16,17). Dexmedetomedine disinhibit the ventrolateral preoptic nucleus that releases inhibitory neurotransmitters as a part of the regulatory system of the circuitry natural sleep. Electroencephalogram studies concluded that dexmedetomidine sedative effects resemble stage 2 NERM sleep pattern (17). Based on the above facts, dexmedetomidine is an effective additive drug in general anesthesia by reducing the requirements of anesthetics and pain reliving medications to obtain an adequate anesthetic depth (18).

Regarding midazolam (an imidazobenzdiazepine derivative), its activation of GABAA receptor can produce sedation, convulsions termination, central muscle relaxation and anti-grade amnesia, although it has query systemic analgesic effect (19).

In pediatric anesthesia, dexmedetomidine use was associated with reduction of other anesthetic requirements, inhibition of the sympathetic response to nociceptive stimuli and achievement of intraoperative hemodynamic stability as sedation during mechanical ventilation (20,21).

In previous studies, end-tidal sevoflurane was reduced by 27.3-33% with the use of dexmedetomidine 1 μg/kg bolus followed by infusion of 0.6 μg/kg/h (22). Similarly, in pediatric tonsillectomy patients, end-tidal sevoflurane decreased to 41.6% when dexmedetomidine 2 μg/kg bolus was given followed by infusion of 0.7 μg/kg/h when compared with fentanyl bolus (23). This reduction percentage in those studies are higher than in our study, this can be explained by low dose used in our study 0.5 compared to 0.6 μg/kg/h and 0.7 μg/kg/h used in previous researches.In a different study, when dexmedetomi¬dine was infused at 0.1 μg/kg/h in children undergoing minor surgery, surgical stimulation was attenuated and anesthetic requirements was reduced significantly (5,24).

Emergence agitation is a common phenomenon with sevoflurane anesthesia especially in young children. In spite of spontaneously terminated, it causes anxious recovery with possible patient harm, surgical site affection and patients dissatisfaction. This phenomenon is a multifactorial depending on patients' age and behavior, anes¬thetic medications and surgical complexity (25). Sevoflurane may irritate the central nervous system at certain points resulting in higher incidence of emergence agitation up to 70% (26).

In this study, we tried to evaluate the impact of using dexmedetomedine and midazolam on emergence agitation with sevoflurane anesthesia. In cardiac aesthesia, it is a routine to keep patient sedated and ventilated until ensuring postoperative hemodynamic, ventilation and hemostatic stability before extubation. This causes difficulty in assessing the impact of both drugs on emergence agitation as its peak incidence usually occurs within the early period after stoppage of sevoflurane anesthesia (14).

However it was reasonable to mention that some recent studies reported low possibility of emergence agitation after sevoflurane in children premedicated with dexme¬detomidine either

as a bolus or continuous infusion (7,23). Also, Shukry et al noticed decreased symptoms of postoperative agitation in young patients premedicated with dexmedetomidine after sevoflurane without prolonged extubation or discharge time (27). In the same way, Jooste EH et al tried to find the optimal method for administration and dosing of dexmedetomidine for emergence agitation. He concluded that in contrast to our study, a rapid dexmedetomedine administration may be better than prolonged bolus infusion over 10 min (28).

For midazolam, Kulka et al., reported insignificant administration of 0.1 mg/kg of midazolam near the end of surgery for decreasing emergence agitation in children (29). Similarly, Kim et al., and Cohen et al., reported inefficacy of small midazolam dose given by end of procedures on emergence agitation phenomenon (30,31). In contrast, low dose of midazolam (0.03 mg/kg) was found to produce accepted suppression of emergence agitation with elongation according to Cho et al., (32).

In addition, intraoperative fentanyl doses required to achieve adequate analgesia and attenuation of sympathetic response to painful stimulations were lower in dexmedetomedine group when compared to midazolam group.

Dexmedetomidine produces its analgesic action through stimulation of Presynaptic α2-adrenoceptors in the locus ceruleus. These special types of receptors are responsible for regulation of sedation and pain relief in vivo (16,33).

Midazolam has also some analgesic properties. This is achieved by activating central benzodiazepine receptors (γ-amino butyric acid (GABA) receptor) in the central nervous system (34).

Despite intraoperative dexmedetomedine is known to decrease opioid requirements in children, the exact mechanism of dexmedetomedine opioid-sparing effects are still under investigations. Recently, a meta-analysis study reported that intraoperative dexmedetomedine can reduce postoperative pain scores and morphine consumption in adult (35). Dexmedetomedine could provide equivalent postoperative analgesic effect to intraoperative opioid use with superior postoperative analgesia in comparison to placebo group according to a new meta-analysis which has compared the effects of intraoperative dexmedetomedine, propofol and placebo on postoperative pain, analgesic doses, and untoward event (36).

In another study, administration of dexmedetomedine (2 and 4 μg kg−1 I.V.) just after tube insertion decreases the post-operative required amount of opioid and increasing the intervals between opioid doses in comparison to administration of 1 or 2 μg kg−1 fentanyl (37). Also dexmedetomidine was reported to lower intraoperative opioid use, has morphine-sparing effects and shorten hospital stay after tonsillectomy and adenoidectomy (38,39). Similar to our study, administration of dexmedetomedine (0.5 μgkg−1 bolus and 0.5 μgkg−1 h−1 infusion) for children (less than 6 years old) undergoing cardiac surgery, is associated with attenuation of hemodynamic and neuroendocrine responses at incision, sternotomy, and post-bypass with reduction of opioid requirements (40).

According to Reves et al., study, which has investigated the antinociceptive effect of midazolam administration systemically on induced acute thermal and inflammatory pain in animal. Midazolam appears to have a dual action, midazolam has analgesic effect by acting at spinal level and hyperalgesic effects by acting at supraspinal level (41).

Extubation time was shorter in dexmedetomidine group when compared to the midazolam group. This may be explained by either the shorter half-life of dexmedetomedine (2.1–3.1 hours) than that of midazolam (2.6 to 17.7 hours) or the lower additional fentanyl doses used in dexmedetomidine group in comparison to midazolam group (42,43).

Riker et al. compared the extubation time between dexmedetomidine and midazolam. He reported shorter extubation time in patients premedicated with dexmedetomidine compared with those receiving midazolam, which is in the same way with our finding (44). In the same way Dutta S, has compared the extubation times between dexmedetomidine, propofol and midazolam. He revealed equivalent extubation time of dexmedetomidine and propofol, besides both were shorter when compared with midazolam (45). Also, dexmedetomidine has been proposed to reduce the duration of mechanical ventilation with earlier extubation in comparison to midazolam (44).

According to the current study, dexmedetomedine has decreased both the heart rate and mean arterial pressure more significantly than during midazolam infusion at skin incision, sternotomy, pericardiotomy. The reduction in heart rate with dexmedetomidine could be attributed to triggering vagal neural activity, suppression of the sinus and atrioventricular node and reduction of catecholamines release (46,47).

Dexmedetomidine' induced mean arterial pressure reduction can be explained by the decline in heart rate, decrease of catecholamines release (43), inhibition of renin-angiotensin system, diuretic effect (48) and both its sedative and analgesic effects (49). Similar to this study, Vilo and his colleagues proved that dexmedetomidine can cause critical hypotension and bradycardia through blunting the sympathetic responses to stressful events (42).

In contrast, midazolam causes a remarkable increase in heart rate and minimal change in MAP, suggesting decreased parasympathetic activity and unchanged sympathetic activity or delayed recovery of parasympathetic activity after cessation of midazolam infusion (50). Galletly et al., discovered a vagolytic effect of midazolam (0.1 mg/kg) that increased the heart rate and mean arterial pressure (51).

Klamt et al. and Tokuhira et al investigated the antihypertensive effects of dexmedetomidine at two different infusion doses (1 μg/kg/h and 0.4 μg/kg/h) and they found that the degree of systolic blood pressure reduction is remarkably dose dependent (52,53).

In contrary to the current study, Friesen et al. reported an elevation of the mean arterial blood pressure and systemic vascular resistance index after dexmedetomidine loading dose (1 μg/kg, 0.75 μg/kg, or 0.5 μg/kg) (54).

No significant difference was found between two groups as regard vomiting attacks. Postoperative nausea and vomiting (PONV) are common after sevoflurane. Although the exact mechanism is not well recognized, this may be explained by the

degradation of sevoflurane to formaldehyde or exposure to low levels of carbon monoxide (55). Both, dexmedetomidine and midazolam have antiemetic effect. Dexmedetomidine exerts its antiemetic effect through direct antiemetic of α2 agonists, suppression of sympathetic tone. Meanwhile midazolam has direct action at the chemoreceptor trigger zone reducing dopamine synthesis and release (56,57).

This study has some limitations, it is known that the higher incidence of emergence agitation usually in the early postoperative period. With lower number of extubated cases within first hour in ITU, we were unable to assess the preventive effect of both drugs on the incidence of emergence agitation after sevoflurane anesthesia.

Conclusion

With continuous infusion of 0.5 μg/Kg/hour dexmedetomedine during sevoflurane based anesthesia, lower end tidal sevoflurane concentration and entropy readings were noticed in comparison to midazolam infusion. In addition, lowers intraoperative additional opioid requirements and shorter extubation time with more hypotension and bradycardia were observed with dexmedetomedine infusion when compared to midazolam infusion in pediatric congenital corrective cardiac surgery.

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