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Research Article

Comparative study between prophylactic single dose of fentanyl and dexmedetomidine in the management of agitation after sevoflurane anesthesia in children

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KEYWORDS

Agitation;
Sevoflurane;
Fentanyl;
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Abstract *Objective:* The higher incidence of post sevoflurane agitation presents a great dilemma. This controlled study was performed to test the hypothesis that the prophylactic single dose of either dexmedetomidine or fentanyl reduces the incidence of emergence agitation post sevoflurane anesthesia in children.

Patients and methods: Ninety pediatric patients were scheduled for elective surgical procedures under general anesthesia and caudal block. They were randomized to one of three groups (each one is 30 patients); fentanyl group (1 μg/kg), dexmedetomidine (DEX) group (0.15 μg/kg), and control group. Recovery was assessed by time until eye opening on command, pain was evaluated by the children's and infants' postoperative pain scale (CHIPPS) and adequacy of recovery was assessed using a Modified Aldert score. Both were recorded every 15 min. Behavior score was recorded in the pre- and postoperative periods.

Main results: Patients in control group obtained higher values (9.65 ± 0.34) in the modified Aldert score than patients who received fentanyl (9.58 ± 0.30) and dexmedetomidine (9.37 ± 0.37). There was significant difference between dexmedetomidine and fentanyl groups For pain assessment, patients in control group suffered from pain when measured by CHIPPS (0.93 ± 0.56) more than patients in dexmedetomidine group (0.48 ± 0.45) and fentanyl group (0.13 ± 0.35), with more significant pain in dexmedetomidine group when compared to fentanyl group ($p < 0.05$). As regard

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behavior during emergence, there were significant differences between the placebo with 40% agitation and both fentanyl group with 21.4% agitation ($p = 0.002$) and dexmedetomidine group with 16.7% agitation ($p = 0.001$), while there were no significant differences between fentanyl and dexmedetomidine group.

Conclusions: Incidence of postoperative agitation in pediatric patients receiving sevoflurane was decreased from 40% with placebo to 16.7% with dexmedetomidine and 21.4% with fentanyl with no significant differences between dexmedetomidine and fentanyl groups.

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1. Introduction

Sevoflurane is used frequently in pediatric patients, when inhalational induction of anesthesia is required, because of its fast and non-irritating effects on the airway. The speed of emergence from sevoflurane anesthesia, however, sometimes presents a dilemma to both patient and anesthetist. Sevoflurane in particular has been associated with an increased amount of agitation on emergence from anesthesia in children when compared with a more soluble anesthetic (halothane) even in the absence of any surgical intervention [1,2]. However, the exact etiology of restlessness after sevoflurane anesthesia is still not known [3]. Postoperative pain is regarded as a contributing factor, but the phenomenon is also present when there is adequate pain control [4]. Concern about pain, the presence of strangers or rapid return to consciousness in an unfamiliar environment might provoke post anesthetic agitation in children [5].

The use of analgesics or sedatives has been proposed for the management of these restless post anesthetic states. However, the side effects of these drugs, including respiratory depression, are potentially harmful and lead to an increased length of stay in the postanesthesia care unit (PACU), resulting in patient discomfort and increased perioperative costs [6].

In children, emergence delirium may mimic pain, separation anxiety and/or hunger. The lack of consistent definition and difficulty with reproducing results may make comparisons of different studies difficult [1].

Dexmedetomidine has a relatively high ratio of α_2/α_1 activity (1620:1 as compared with 220/1 for clonidine), and therefore, is considered a full agonist of the α_2 receptor. This may result in more potent effects of sedation without unwanted cardiovascular effects from α_1 receptor activation. The 2-h half-life of dexmedetomidine is nearly fourfold shorter than that of clonidine, which increases the likelihood that a continuous infusion of dexmedetomidine might be useful for sedation [7].

This controlled study was performed to test the hypothesis that the prophylactic use of either dexmedetomidine or fentanyl reduces the incidence of emergence agitation after sevoflurane based anesthesia in children.

2. Patients and methods

2.1. Patient population

This controlled randomized study was done after approval of institutional ethics committee and obtaining an informed written consent from parents. The study was conducted at Abu El Rish Pediatric Hospital from October 2007 to November 2008. It was designed to include ninety pediatric patients, aged 5–10 years, with physical status ASA I. All surgical procedures were elective of an expected duration of 30–60 min, e.g. inguinal hernia repair, hydrocele, or circumcision under general anesthesia and caudal block to relief pain. All operations were performed in supine position. Exclusion criteria include chronic or acute intake of any sedative and analgesic drug, any known adverse effect to the study drugs, and failure of the caudal block.

2.2. Methods

2.2.1. Anesthesia technique and study design

After history tacking and clinical examination, the following laboratory tests were ordered and reviewed preoperatively; complete blood picture, kidney function tests (urea and creatinine), liver function tests (SGOT, SGPT, albumin and bilirubin) and bleeding profile (PT, PTT and INR). Solid food was not allowed 6 h before surgery but clear fluids were given for up to 4 h preoperatively. No premedication was given to the patients. Before induction of anesthesia routine monitoring was applied which include pre-cordial stethoscope, noninvasive automatic blood pressure, pulse oximeter and electrocardiograph. Body core temperature was measured by oropharyngeal temperature probe and maintained between 36 and 37 °C using heated mattress and warmed intravenous fluids.

Induction of anesthesia was with 50% nitrous oxide and sevoflurane up to 8% in oxygen with total gas flow $\geqslant 5$ L/min. After loss of consciousness, a peripheral arm vein was cannulated for drug and fluid administration. The trachea was intubated using an appropriately-sized uncuffed endotracheal tube when patients were in a sufficiently deep level of anesthesia. Intubation was performed without the use of muscle relaxants. A gas module (Drager/Vamos) for measurement of end-expiratory concentration of sevoflurane and end-tidal carbon dioxide tension was applied after intubation.

At this point, patients were randomly assigned by a concealed envelope method into one of three groups (each group is 30 patients); fentanyl group, received 1 μg/kg fentanyl, dexmedetomidine (DEX) group (Precedex®, Abbott Laboratories Inc., Abbott Park, IL) (supplied in 2-ml ampoules at a concentration of 100 mg/ml) received 0.15 μg/kg. The calculated dose of fentanyl and dexmedetomidine for each patient was prepared in a total volume of 10 ml normal saline and was infused over a period of 10 min. The 3rd group is control group, received saline 10 ml over 10 min. All syringes with dexmedetomidine, fentanyl or placebo were prepared by the same investigator. Administration of anesthesia and the study drugs and perioperative data collection were done by two investigators blinded to the study drugs.

After endotracheal intubation, patients were breathing spontaneously via a Jackson-Rees modification of the Ayre's

T-piece circuit to allow the assessment of the effects of the studied drugs on respiratory function (respiratory rate and end-tidal CO_2). No muscle relaxants were used throughout the operative procedure. Sevoflurane then reduced to 3% in 50% nitrous oxide, and caudal block with (0.25% bupivacaine) 0.5 ml/kg was been performed in all patients. Then the concentration of sevoflurane set at 1% end-tidal in 50% nitrous oxide until the end of surgery. Failure of caudal block was been defined as any increase in heart rate (HR) and/or mean arterial blood pressure (MAP) >10% than the preincision value. Patients received an infusion of Ringer's solution in 5% dextrose, given a rate of 6 ml/kg/h. At the end of surgery, sevoflurane was discontinued and the trachea was extubated, and time to eye opening was calculated (defined as time from the end of anesthesia to eye opening on command).

2.2.2. Postoperative recovery and assessment

Patients were transferred to the recovery room for further observation. Pain was evaluated by the *children's and infants' postoperative pain scale* (*CHIPPS*) (Table 1) and adequacy of recovery was assessed using a *Modified Aldert score* (Table 2). Behavior during both pre- and postoperative periods was rated on a *four-point scale*: 1 = calm; 2 = not calm but could be easily calmed; 3 = not easily calmed, moderately agitated or restless; 4 = combative, excited or disoriented. For purposes of analysis, grades 1and 2 in the scale of behavior were considered no agitation and grades 3 and 4 were considered presence of agitation.

2.2.3. Data collection

HR and *MAP* were recorded at the following periods: Before induction of anesthesia (baseline), after administration of study drugs (every 5 min intraoperatively) and = every 15 min in the PACU. *Respiratory rate* (*RR*) *and end-tidal* CO_2 ($EtCO_2$) were recorded after induction and just prior to administration of study drugs and every 5 min intraoperatively.

- Recovery was assessed by time until eye opening on command.
- Modified Aldert score and CHIPPS score were recorded every 15 min.
- Behavior score was recorded in the pre- and postoperative periods.

2.2.4. Statistical analysis

Data were statistically described in terms of range, mean ± standard deviation (±SD), frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables between the study groups was done using one way AVOVA for independent samples in comparing three groups when normally distributed and Kruskal Wallis for independent samples when not normally distributed. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows. Sample size calculation was done using Behavior score as it was considered to be the principal study outcome. According to previous studies, the expected responses of agitation in control was set at 47 – 60% while that of fentanyl was 13 – 15 % and for dexmetomidine was 10 – 17 %. If the true difference in the experimental and control proportions is 30 – 45, we will need to study around 20 to 36 subjects per group to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with 80% power. Type

Table 2 Modified Aldert score.

	Score	
Activity	2	Able to move four extremities
	1	Able to move two extremities
	0	Not able to move any extremities
Respiration	2	Able to breathe deeply and cough
	1	Limited respiratory effort (dyspnea)
	0	No spontaneous respiratory effort
Circulation	2	Systolic ABP ±20% of preanesthetic level
	1	Systolic ABP ±20% to 50% of preanesthetic level
	0	Systolic ABP ±51% or more of preanesthetic level
Consciousness	2	Full alertness seen in patient's ability to answer questions
	1	Aroused when called by name
	0	Failure to elicit a response upon auditory stimulation
SPO_2 (% on room air)	2	>94%
	1	90–94%
	0	<90%

Table 1 Children's and infants' postoperative pain scale [8].

Categories	0	1	2
Facial expression	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, quivering chin, clenched jaw
Position of the legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Position of the trunk	Lying quietly or normal position moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Crying	No cry	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaint

Table 3 Demographic data of patients in all groups (mean ± SD and ratio for sex).

	Control group (n = 30)	DEX group (n = 30)	Fentanyl group (n = 30)
Age (years)	6.6 ± 1.32	6.07 ± 1.4	6.84 ± 1.7
Gender (M/F)	28/2	27/3	27/3
Body weight (kg)	21.3 ± 2.7	19.9 ± 3.5	21.67 ± 3.7
Duration of anesthesia (min)	60.14 ± 4.29	62.45 ± 4.13	60.25 ± 4.22
Duration of surgery (min)	47.3 ± 4.96	42.61 ± 5.30	45.05 ± 4.22

Table 4 Hemodynamic data of patients in all groups (means ± SD).

		Control group (n = 30)	DEX group (n = 30)	Fentanyl group (n = 28)
Pre-operative	HR	105.3 ± 13.27	109.03 ± 15.87	102.73 ± 10.96
	MAP	72.8 ± 5.32	73.43 ± 5.2	72.1 ± 5.7
Intra-operative	HR	97.66 ± 8.24	89.69 ± 6.4[#, *]	94.5 ± 8.1[+]
	MAP	68.64 ± 3.1	68.26 ± 4.4	64.86 ± 4.7[#, +]
	RR	26.9 ± 4.1	26.02 ± 4.29	23.98 ± 3.46
	$ETCO_2$	36.7 ± 3.04	36.93 ± 2.8	35.66 ± 2.18
Post-operative	HR	101.48 ± 6.5	98.04 ± 12.04	99.7 ± 6.74
	MAP	75.5 ± 4.44	74.82 ± 5.57	72.05 ± 5.28

[*] $p < 0.05$ control vs. dexmedetomidine groups.
[+] $p < 0.05$ control vs. fentanyl groups.
[#] $p < 0.05$ fentanyl vs. dexmedetomidine groups.

Table 5 Time (min) to eyes opening and to discharge from post-anesthesia care unit.

	Control group (n = 30)	DEX group (n = 30)	Fentanyl group (n = 28)
Time to eye opening	8.27 ± 1.41	9.20 ± 1.6[*]	8.79 ± 2.149
Time to shift to ward	17.6 ± 2.37	19.53 ± 6.569	18.07 ± 6.104

[*] $p < 0.05$ control vs. dexmedetomidine groups.

I error probability associated with this test of this null hypothesis is 0.05. The case: control ratio was set at 1. Calculations were done using PS Power and Sample Size Calculations software, version 2.1.30 for MS Windows (William D. Dupont and Walton D. Vanderbilt, USA).

3. Results

Ninety patients were recruited for this study (thirty in each of the study group). Two patients were excluded in the fentanyl group because of failure of caudal block (as there was increase in HR and MAP >10% than the pre-incision value). All groups were comparable as regards demographic criteria (age, gender and body weight) as well as duration of anesthesia and duration of surgery (Table 3). Also, the results of all laboratory tests were within normal and comparable in all groups.

HR decreased significantly, intraoperatively, in both dexmedetomidine and fentanyl groups in comparison to control group ($p < 0.05$), and it showed more significant decrease in dexmedetomidine when compared to fentanyl group ($p < 0.05$). In the postoperative period HR increased in all groups in comparison to intraoperative values but there were no significant differences between them ($p > 0.05$). Also, MAP decreased in all groups during the procedures but its decrease was more in fentanyl group than dexmedetomidine and control groups ($p < 0.05$) and no significant differences between dexmedetomidine and control group. In the postoperative period the MAP increased in all groups, the differences between the three groups were insignificant. Respiratory rate (RR) and end-tidal carbon dioxide ($ETCO_2$) were comparable in all groups of the study intraoperatively ($p > 0.05$) (Table 4).

Time to eye opening was greater in the dexmedetomidine group compared to the fentanyl and control groups, with significant differences between dexmedetomidine and control groups ($p < 0.05$). The difference between fentanyl group and the other two groups were statistically insignificant ($p > 0.05$) (Table 5). Time to discharge from post-anesthesia care unit (PACU) in the dexmedetomidine group was slightly greater than that in the fentanyl and control groups but the differences between the three groups were statistically insignificant ($p > 0.05$) (Table 5).

Adequacy of recovery was assessed using a modified Aldert score, and pain was assessed with the children's and infants' postoperative pain scale (CHIPPS). Both were evaluated by the anesthetist in the recovery room. Patients in control group recovered from anesthesia faster and obtained higher values (9.65 ± 0.34) in the modified Aldert score than patients who received fentanyl (9.58 ± 0.30) and dexmedetomidine (9.37 ± 0.37). There were significant differences between con-

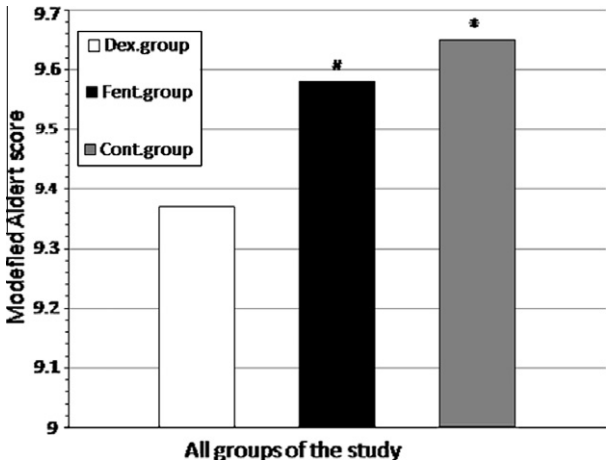

Figure 1 Modified Aldert score in all groups of the study. $^{*}p < 0.05$ control vs. dexmedetomidine groups. $^{+}p < 0.05$ control vs. fentanyl groups. $^{\#}p < 0.05$ fentanyl vs. dexmedetomidine groups.

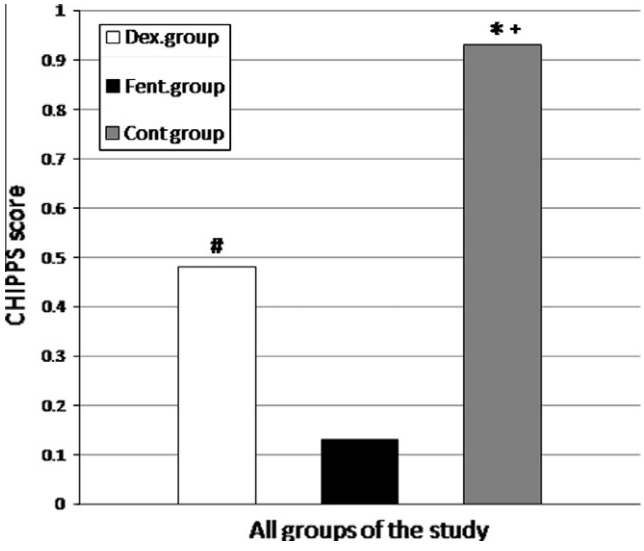

Figure 2 CHIPPS score in all groups of the study. $^{*}p < 0.05$ control vs. dexmedetomidine groups. $^{+}p < 0.05$ control vs. fentanyl groups. $^{\#}p < 0.05$ fentanyl vs. dexmedetomidine groups.

trol and dexmedetomidine groups, and between dexmedetomidine and fentanyl groups, with no significant differences between fentanyl and control groups (Fig. 1).

As regard pain assessment in postoperative period, patients in control group suffered from pain when measured by CHIPPS (0.93 ± 0.56) more than patients in dexmedetomidine group (0.48 ± 0.45) and fentanyl group (0.13 ± 0.35) ($p < 0.05$). The number of patients who suffered from pain or discomfort was higher in dexmedetomidine group when compared to fentanyl group ($p < 0.05$) (Fig. 2).

Regarding behavior during emergence, there were significant differences between the placebo with 40% agitation and both fentanyl group with 21.4% agitation ($p = 0.002$) and dexmedetomidine group with 16.7% agitation ($p = 0.001$), while there were no significant differences between fentanyl and dexmedetomidine groups ($p > 0.05$). For purposes of analysis, grades 1 and 2 in the scale of behavior were considered no agitation and grades 3 and 4 were considered presence of agitation (Table 6).

Table 6 Behavior score-postoperative.

		Control ($n = 30$)	Fentanyl ($n = 28$)	DEX ($n = 30$)
Behavior-post				
Score 1	Count	9	21	25
	% Within group	30.0	75.0	83.3
Score 2	Count	9	1	0
	% Within group	30.0	3.6	0.0
Score 3	Count	7	6	5
	% Within group	23.3	21.4	16.7
Score 4	Count	5	0	0
	% Within group	16.7	0.0	0.0

4. Discussion

The results of the current study showed that 40% of pediatric patients developed emergence agitation after sevoflurane anesthesia. As all patients in this study were healthy, no oxygen desaturation occurred, and fluid and pain therapy were adequate, so we can exclude hypoxia, pain and metabolic disturbance as causes of the agitation. In our study which had been applied to children between 5 and 10 years old, using fentanyl 1 μg/kg or dexmedetomidine 0.15 μg/kg after induction of anesthesia with sevoflurane showed reduced incidence of emergence agitation (21.4% and 16.7%, respectively) if compared with placebo (40%), but the incidence of agitation was slightly higher with fentanyl (21.4%) compared with dexmedetomidine (16.7%).

Emergence agitation is a common side effect of sevoflurane in pediatric anesthesia, yet there is no clinical evidence that agitation affects long term outcome. As mechanism of agitation after sevoflurane anesthesia is not clear, there is no well-known prophylaxis or treatment, although the incidence of this excitatory behavior seems to be reduced by the perioperative use of sedative and analgesic drugs [9].

Similar to our findings, Cravero et al. [6] demonstrated that addition of fentanyl 1 μg/kg to inhaled sevoflurane anesthesia decreased incidence of postoperative agitation in children scheduled for magnetic resonance imaging scans without any surgical intervention. The first study to describe postoperative agitation done by Eckenhoff et al. [10] found that patients who received an opioid-based anesthesia has less frequent incidence of postoperative disturbance behavior when compared with those who received cyclopropane anesthesia (0.4% *vs.* 8%). With respect to the use of opioids and their effect on agitation, Galinkin et al. [11] observed that the use of intranasal fentanyl 2 μg/kg administered after induction of anesthesia reduced the incidence of agitation after sevoflurane anesthesia from 23% to 2% without increasing the discharge times. In contrary to our study, Aono et al. [12] stated that agitation after sevoflurane anesthesia in children is present even if adequate analgesia given intraoperatively or even if regional block was used.

In the study by Lapin et al. [9] he compared placebo with oral midazolam 0.5 mg/kg administered before surgery and

found that midazolam reduced the incidence of agitation after sevoflurane anesthesia from 67% to 39% after myringotomy surgery. While in another study, Viitanen et al. [13] investigated children 1–3 years of age undergoing adenoidectomy and found that midazolam did not significantly influence the incidence of agitation but delayed recovery from anesthesia. Davis et al. [14] observed that incidence of excitement and agitation was less in patients receiving halothane or sevoflurane when ketorolac was given IV after induction of anesthesia (14% *vs.* 38%) ($p < 0.05$). Also Johannesson et al. [15] found that acetaminophen given after induction of anesthesia decreased agitation after sevoflurane anesthesia. Murray et al. [16] evaluated the effect of 0.1 mg/kg oxycodone (premedication) on emergence in children undergoing otolaryngology surgery using halothane or sevoflurane anesthesia. Emergence agitation was decreased in patients who received halothane anesthesia and oxycodone premedication (15% *vs.* 45%) but not for patients receiving sevoflurane.

In our study, Time to discharge from postanesthesia care unit (PACU) was not affected with administration of fentanyl and dexmedetomidine and the differences between them and the placebo group were not significant. Similar findings were observed in the study of Joseph et al. [6] which documented that time to reach discharge criteria was unchanged by the addition of small dose of fentanyl to an anesthetic using sevoflurane when compared with placebo.

Kulka et al. [17] documented a significant decrease in agitation (10% *vs.* 72%) in a clonidine-treated group undergoing circumcision. Also, Bock et al. [18] have shown that clonidine 3 μg/kg intravenously or caudal is effective in preventing agitation after sevoflurane anesthesia. In our study, we used dexmedetomidine which is more specific than clonidine as α_2 agonist. This was in agreement with the results of Ibacache et al. [19] who observed that dexmedetomidine decreased the incidence of agitation after sevoflurane anesthesia.

In our study, it was noticed that dexmedetomidine in a dose of 0.15 μg/kg intravenously appear to be safe for intraoperative use in children as regard hemodynamics. This finding are supported by a more recent work of Tobias et al. [20] who used dexmedetomidine for controlled hypotensive anesthesia in children with scoliosis for posterior spinal fusion by giving initial bolus of dexmedetomidine 0.5 μg/kg then infusion dose of 0.25 μg/kg/h. Kamibayashi and Maze [21] found that the sympatholytic actions of dexmedetomidine resulted in reduction of blood pressure and heart rate due to both sympatholytic as well as vagomimetic effect. However, Bloor et al. [22] found that dexmedetomidine had competing vasodilator (central sympatholytic α_2-a) and vasoconstrictive (peripheral vascular α_2-b) effects resulted in initial transient hypertension as a result of initial high peak plasma levels of the drug. Following the rapid redistribution of the loading dose, the centrally mediated sympatholytic effect of dexmedetomidine became dominant and attenuation of sympathetic tone ensues. In our study, it was noticed that with low dose of dexmedetomidine (0.15 μg/kg) there was mild decrease in the MAP and HR intra-operatively but it returned back to baseline values postoperatively.

Maxwell [23] was the first to report the lack of respiratory depression in patients receiving α_2 agonists. However, more recent data suggested that clonidine may cause mild respiratory depression [24]. Ebert et al. [25] demonstrated that respiratory rates increased with increased dexmedetomidine plasma concentration in healthy volunteers. In another study comparing dexmedetomidine to placebo in 33 patients, extubated after major surgery, no difference in respiratory rates and arterial oxygen saturation were found [26]. In addition, another study data demonstrated that the slope of the CO_2 response curve remains unchanged in patients receiving dexmedetomidine [27]. In our study, it was found that administration of dexmedetomidine in a dose of 0.15 μg/kg over 10 min did not affect the respiratory rate and end tidal CO_2 as there were no significant differences between dexmedetomidine and placebo.

Manaa et al. [28] observed that the time for first postoperative analgesic dose was significantly lower with dexmedetomidine when compared with placebo. Judith et al. [29] studied the sedative, amnestic, and analgesic properties of small dose dexmedetomidine infusion, in healthy volunteers, and discovered that dexmedetomidine infusion resulted in reversible sedation and mild analgesia due to its effect on the central α_2 adrenoreceptors in the locus ceruleus and receptors in the dorsal horn of the spinal cord. In another study done by Ebert et al. [25] on the effect of increasing plasma concentration of dexmedetomidine in humans, they found that there is progressive increase in sedation and analgesia with increasing concentration of dexmedetomidine. In our study, it was noticed that in postoperative period patients in control group suffered from pain more than patients in the other two groups, and number of patients who suffered from pain or discomfort were higher in dexmedetomidine group compared to fentanyl group.

In conclusion, dexmedetomidine was found to be a safe drug for use in spontaneously breathing pediatric patients under general anesthesia and the incidence of postoperative agitation in pediatric patients receiving sevoflurane was decreased from 40% with placebo to 16.7% with intravenous 0.15 μg/kg dexmedetomidine and from 40% with placebo to 21.4% with intravenous 1 μg/kg fentanyl with no significant differences between dexmedetomidine group and fentanyl group. However, further studies for the effects of different doses of dexmedetomidine and fentanyl on emergence agitation after sevoflurane anesthesia may be required.

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