Rev Bras Anestesiol. 2019;69(5):469–476

Sociedade Brasileira de Anestesiologia

REVISTA BRASILEIRA DE ANESTESIOLOGIA

Publicação Oficial da Sociedade Brasileira de Anestesiologia
www.sba.com.br

SCIENTIFIC ARTICLE

Oral trans-mucosal dexmedetomidine for controlling of emergence agitation in children undergoing tonsillectomy: a randomized controlled trial

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Received 26 April 2019; accepted 29 June 2019
Available online 6 September 2019

KEYWORDS
Children;
Tonsillectomy;
Emergence agitation;
Oral transmucosal buccal dexmedetomidine

Abstract
Objectives: Emergence agitation is a negative behavior commonly recorded after pediatric tonsillectomy. We investigated the efficacy of preoperative premedication with oral transmucosal buccal dexmedetomidine on the incidence and severity of emergence agitation in preschool children undergoing tonsillectomy under sevoflurane anesthesia.
Methods: Ninety patients aged (3–6 years), ASA I–II were enrolled into three groups (n = 30) to receive oral transmucosal dexmedetomidine 0.5 $\mu g.kg^{-1}$ (Group DEX I), 1 $\mu g.kg^{-1}$ (Group DEX II) or saline placebo (Group C). Our primary endpoint was the Watcha agitation score at emergence in PACU. Secondary outcomes were preoperative sedation score, intraoperative hemodynamics, postoperative Objective Pain Scale (OPS) and adverse effects.
Results: The patients' demographics, preoperative sedation scores and extubation time showed no difference between groups. Significant differences between groups in incidence and frequency distribution of each grade of Watcha score were evident at 5 minutes ($p = 0.007$), 10 minutes ($p = 0.034$), 30 minutes ($p = 0.022$), 45 minutes ($p = 0.034$) and 60 minutes ($p = 0.026$), postoperatively with significant differences between DEX I and II groups. DEX groups showed lower OPS scores at 5 minutes ($p = 0.011$), 10 minutes ($p = 0.037$) and 30 minutes ($p = 0.044$) after arrival at PACU, with no difference between DEX I and II groups. Patients in DEX II group exhibited lower intraoperative mean heart rate at 15 minutes ($p = 0.020$), and lower mean arterial pressure at 30 minutes, ($p = 0.040$), 45 minutes ($p = 0.002$) and 60 minutes ($p = 0.006$) with no significant differences between groups in other time points.

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https://doi.org/10.1016/j.bjane.2019.07.001

Conclusion: This study demonstrates the clinical advantage and the simple technique of oral transmucosal DEX premedication for emergence agitation in preschool children undergoing tonsillectomy under sevoflurane anesthesia compared with saline placebo.
Trial registration: Clinical Trials.gov trial registry: NCT02720705.

PALAVRAS-CHAVE
Crianças;
Amigdalectomia;
Agitação ao despertar;
Dexmedetomidina transmucosa oral

Dexmedetomidina transmucosa oral para controle da agitação ao despertar em crianças submetidas a amigdalectomia: ensaio clínico randomizado

Resumo
Objetivos: A agitação ao despertar da anestesia é um comportamento negativo comumente registrado após amigdalectomia pediátrica. Avaliamos a eficácia da pré-medicação com dexmedetomidina via transmucosa oral no pré-operatório sobre a incidência e gravidade da agitação ao despertar em crianças pré-escolares submetidas à amigdalectomia sob anestesia com sevoflurano.
Métodos: Noventa pacientes entre três e seis anos e estado físico ASA I–II foram incluídos em três grupos (n = 30) para receber 0,5 μg.kg^{-1} ou 1 μg. kg^{-1} de dexmedetomidina via transmucosa oral (Grupo DEX I e Grupo DEX II, respectivamente) ou solução salina (Grupo C). O desfecho primário foi o escore de agitação ao despertar medido com a escala de Watcha na SRPA. Os desfechos secundários foram escore de sedação pré-operatória, hemodinâmica intraoperatória, escore OPS *(Objective Pain Scale)* e efeitos adversos no pós-operatório.
Resultados: A demografia dos pacientes, os escores de sedação pré-operatória e o tempo de extubação não apresentaram diferença entre os grupos. Diferenças significativas entre os grupos na distribuição da incidência e frequência de cada grau do escore de Watcha foram evidentes aos 5 minutos ($p = 0,007$), 10 minutos ($p = 0,034$), 30 minutos($p = 0,022$), 45 minutos ($p = 0,034$) e 60 minutos ($p = 0,026$) no pós-operatório, com diferenças significativas entre os grupos DEX I e II. Os grupos DEX apresentaram escores OPS mais baixos aos 5 minutos ($p = 0,011$), 10 minutos ($p = 0,037$) e 30 minutos ($p = 0,044$) após a chegada à SRPA, sem diferença entre os grupos DEX I e II. Os pacientes do grupo DEX II apresentaram menor frequência cardíaca média aos 15 minutos de intraoperatório ($p = 0,020$) e menor pressão arterial média aos 30 minutos, ($p = 0,040$), 45 minutos ($p = 0,002$) e 60 minutos ($p = 0,006$), sem diferenças significativas entre os grupos em outros momentos.
Conclusão: Este estudo demonstra a vantagem clínica e a técnica simples da pré-medicação com DEX por via transmucosa oral para agitação ao despertar em crianças pré-escolares submetidas à amigdalectomia sob anestesia com sevoflurano, comparado à solução salina.
Registro do estudo: Clinical Trials.gov trial registry: NCT02720705.

Introduction

Since their first description in 1960, emergence agitation (EA) and emergence delirium (ED) continue to remain a significant problem when anesthetizing children.[1,2] Upon arrival to the Post Anesthesia recovery room, 10% and up to 80% of preschool children (3–6 years) may be presented with anxiety, restlessness with non-purposeful movements, inconsolability and thrashing around.[3] This negative attitude adds a burden on nursing care, causes self-harm to the child and delays discharge from the recovery room.[2] Major contributors to this phenomenon were the use of low-solubility inhalational anesthetics, type of surgery, age, the child and parents' preoperative level of anxiety and early postoperative pain.[4]

Pharmacological treatment for EA has been accomplished in 52% of such cases.[5] Based on efficacy, the used drugs for the treatment of ED and EA are listed as dexmedetomidine,[6] opioids such as remifentanil,[7] ketamine,[8] clonidine[9] and propofol bolus at end of surgery.[10] As a highly selective α2 agonist, dexmedetomidine has been frequently used for treating such conditions owing to its dual effect as a sedative and analgesic agent,[11] either preoperative or intraoperative and at different dose regimens.[6] It has been administered oral,[12] intranasal,[13] intravenous bolus,[14] or infusion.[15]

Oral transmucosal (OTM) route is a novel needle-free approach with rapid absorption of drugs through oral mucosa

with buccal bioavailability for dexmedetomidine of 82% in adults and with an adequate correlation between the plasma levels and sedative effects.[16] Being odorless, tasteless and painless, dexmedetomidine can be a suitable drug for the preoperative medication in small children through the OTM route.[7,16]

We aimed to investigate the efficacy of preoperative premedication with OTM dexmedetomidine in two doses of (0.5 and 1 $\mu g.kg^{-1}$) on the severity and incidence of emergence agitation in preschool children following tonsillectomy under sevoflurane anesthesia.

Patients and methods

Ethical considerations

This randomized controlled clinical trial was conducted in anesthesia and Ear-Nose and Throat departments in Assiut University main hospital after being approved from the Medical Ethics Committee, faculty of medicine, Assiut University, Assiut, Egypt (IRB: 00008718). The study protocol was registered before the enrollment of the first patient in clinical trial.gov [ID: NCT02720705]. Informed written consent was obtained from the patients' legal guardian before randomization. Children aged from 3 to 6 years, ASA I–II who were scheduled for elective tonsillectomy with and without adenoidectomy were enrolled in this study. Excluded from the study patients with significant cardiac, respiratory, renal, neurological, or neuromuscular diseases.

Randomization and blinding

Randomization was accomplished using a computer-generated table of random numbers, with group allocation hidden in closed opaque covers. Children were allocated in three groups (of 30 children each) to receive: saline placebo (Control Group or Group C), buccal trans-mucosal dexmedetomidine 0.5 $\mu g.kg^{-1}$ (Group DEX I) or 1 $\mu g.kg^{-1}$ (Group DEX II). Study medications were prepared in color-coded syringes by a blinded physician. Patients in DEX groups received the

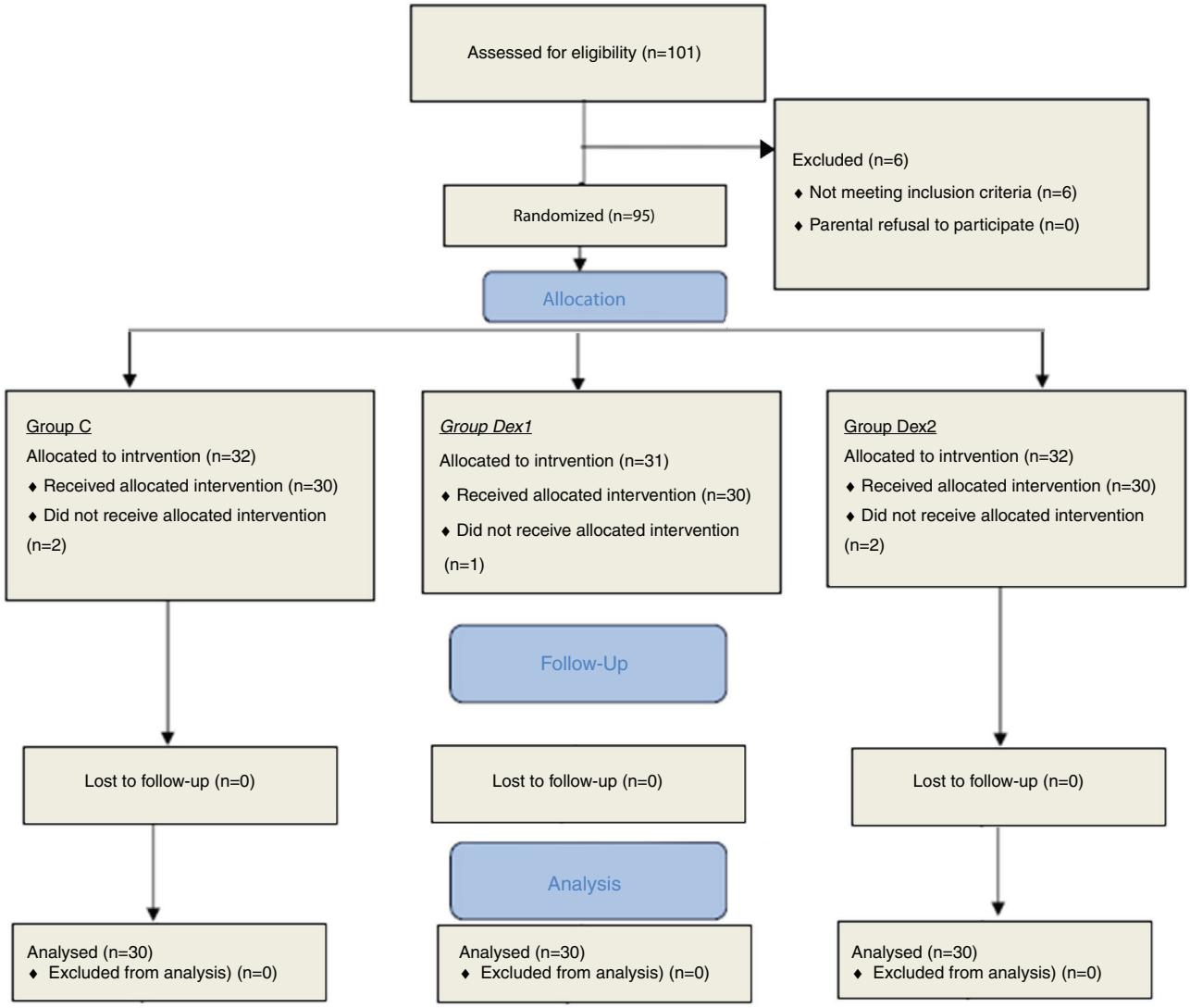

Figure 1 Participant flow diagram (Group C, Placebo Control; Group DEX I, 0.5 $\mu g.kg^{-1}$; Group DEX II, 1 $\mu g.kg^{-1}$).

drug undiluted and patients in the control group received a matched volume of normal saline. The attending surgeons, anesthesiologists, data collecting researchers, and the patients' parents were blinded to the group assignment.

Study protocol

Thirty minutes before anesthesia induction, all patients received the tested drugs according to group assignment. While gently closing the patient's nose, the study drug was administered by an insulin syringe (1 mL) and dropped in the buccal mucosa. The child's head and neck were gently stabilized for 5–10 s to prevent swallowing of the study drug. Routine monitoring was attached and children were observed for any adverse effects (e.g. respiratory depression, hypotension, bradycardia or arterial desaturation SPO_2 <92%).

In the operative theatre, the preoperative sedation level was evaluated before anesthesia induction by the sedation score.[17] The scale is composed of 5 points; 1 = agitated, 2 = alert, 3 = calm, 4 = drowsy and 5 = asleep. A score ≥3 was the accepted sedation level. Then anesthesia induction was accomplished with sevoflurane inhalation 8% in 70% oxygen/air mixture. A venous line was established and all patients received 1 $\mu g.kg^{-1}$ fentanyl, 0.5–1 $mg.kg^{-1}$ lidocaine and 1–2 $mg.kg^{-1}$ propofol before endotracheal intubation. Patients were left spontaneously breathing without the aid of muscle relaxants. Sevoflurane in 50% oxygen/air mixture was used for maintenance of anesthesia and the concentration of sevoflurane was adjusted to maintain ±20% of baseline non-invasive mean arterial blood pressure. All patients received intravenous 0.2 $mg.kg^{-1}$ dexamethasone and 15 $mg.kg^{-1}$ paracetamol. At the end of the surgery, sevoflurane was discontinued and patients were extubated fully awake. The extubation time (time in minutes from discontinuation of sevoflurane anesthesia to awake extubation) was recorded. Then, patients were transported to the Post Anesthesia Care Unit (PACU).

In the PACU, the incidence and severity of emergence agitation were assessed by Watcha scale.[18] This 5 point scale consisted of; 0 = child is asleep, 1 = awake/calm, 2 = irritable with a consolable cry, 3 = inconsolable cry, 4 = the child is agitating, thrashing around and restlessness. Agitation was recorded at 5, 10, 15, 30, 45 and 60 min after coming to the PACU. The child was considered to have Emergence agitation if agitation score was ≥3. Objective Pain Scale (OPS) was used for simultaneously assessing the patients' level of pain at the same time points mentioned above.[19] Emergence agitation was differentiated from postoperative pain by the presence of 'no eye contact' and 'no awareness of the surroundings'.[4] Patients with an agitation score ≥3 and/or OPS score ≥3 received intravenous nalbuphine 0.2 $mg.kg^{-1}$ diluted in saline 0.9% to 5 mL volume. One hour after admission into the PACU, patients were discharged to the ward if they were calm, pain-free and attained a modified Aldrete score >9.[20] In the ward, Patients were observed for 24 h postoperative for the occurrence of any adverse effects.

Any perioperative adverse effect was treated and recorded such as bradycardia (heart rate ≤60 $beats.min^{-1}$), hypotension (≥20% decrease in mean arterial pressure compared to baseline value), respiratory depression (respiratory rate ≤12 min) or oxygen desaturation (SPO_2 ≤92%).

Statistics

Sample size calculation

Our primary endpoint was the agitation score at emergence in the PACU. Secondary outcomes were preoperative sedation score, intraoperative hemodynamics and postoperative OPS and perioperative adverse effects. Based on previous studies,[16,21] power analysis suggested that 26 patients in each group would be sufficient to yield a significant difference between groups in the postoperative agitation score with an alpha error of 0.05 and a power of 80%. To overcome patients' dropout, we enrolled 30 patients in each group.

Statistical testing

The SPSS program version 22 was used for data analysis (Statistical Package for Social Science). Data presented as numbers, frequency and median (range). Normality of continuous data was analyzed with the Kolmogorov–Smirnov test. Student's *t*-test, Paired samples *t*-test, and ANOVA test were used for normally distributed continuous data. For not normally distributed continuous data, Kruskal–Wallis and Mann–Whitney tests were used to analyze variables among the three groups and between every two groups, respectively. Chi-squared or Fisher's exact test was used to analyze frequency variables as appropriate. A p-value of <0.05 was our cutoff value for statistical significance.

Results

From May 2016 till November 2018, 101 children were eligible and recruited for this study. Six children were excluded and 5 did not receive the allocated intervention after being randomized. Finally, 90 patients (30 for each group) completed the study and were subjected to statistical analysis (Fig. 1). The patients' demographics and surgical data were matched between groups ($p > 0.05$). No significant differences were recorded between groups in the preoperative sedation score or in the median extubation time either (Table 1).

Patients in DEX II Group exhibited lower mean heart rate at 15 min intraoperatively ($p = 0.020$), with no significant differences between groups in other time points (Fig. 2). The mean intraoperative arterial blood pressure showed the highest decrease in DEX II Group at 30 min, ($p = 0.040$), 45 min ($p = 0.002$) and 60 min ($p = 0.006$) with no significant differences between groups in other time points (Fig. 3).

Investigating the severity of EA by assessing the median agitation scores at each respective time showed no significant differences between groups. However, we recorded significant differences between groups regarding the incidence and frequency distribution of each grade of Watcha score at 5 min ($p = 0.007$), 10 min ($p = 0.034$), 15 min ($p = 0.028$), 30 min ($p = 0.022$), 45 min ($p = 0.034$) and 60 min ($p = 0.026$), postoperatively with significant differences between DEX I and DEX II Groups (Table 2).

Compared to the control group, patients in DEX groups had significantly lower OPS scores at 5 min ($p = 0.011$), 10 min ($p = 0.037$) and 30 min ($p = 0.044$) after arrival at the PACU,

Table 1 Demographic data and operative details in study groups.

	Group C (n = 30)	Group DEX I (n = 30)	Group DEX II (n = 30)	*p*-Value
Age	5 (2.5–6)	5 (3–6)	5 (3–6)	0.581
Sex: male/female	19/11	23/7	20/10	0.510
ASA Class: I/II	27/3	30/0	29/1	0.160
Weight	15 (12–22)	15 (10–25)	18 (10–25)	0.095
Operative time (min)	35 (13–61)	35 (15–60)	33.5 (15–60)	0.740
Pre-operative sedation score				
Agitated/alert/calm/drowsy/sleep	15/15/0/0/0	18/12/0/0/0	16/10/4/0/0	0.054
Median (range)	1.5 (1–2)	1 (1–2)	1 (1–3)	0.612
Extubation time (min)	8 (5–15)	10 (5–12)	9 (5–12)	0.413

Data presented as median (range), frequency and number.
ASA, American society of anesthesiologists.
$p < 0.05$ significant difference between groups.

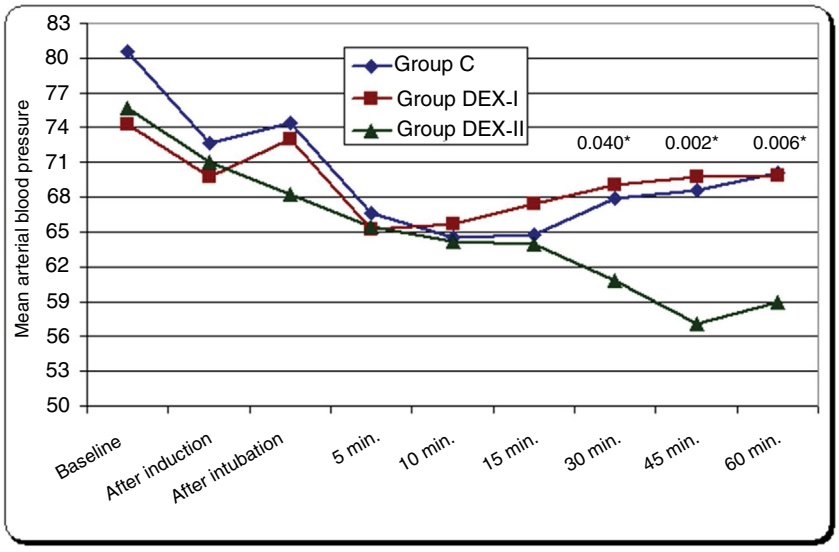

Figure 2 Mean arterial blood pressure (Group C, Placebo Gontrol; Group DEX I, 0.5 μg.kg^{-1}; Group DEX II, 1 μg.kg^{-1}).

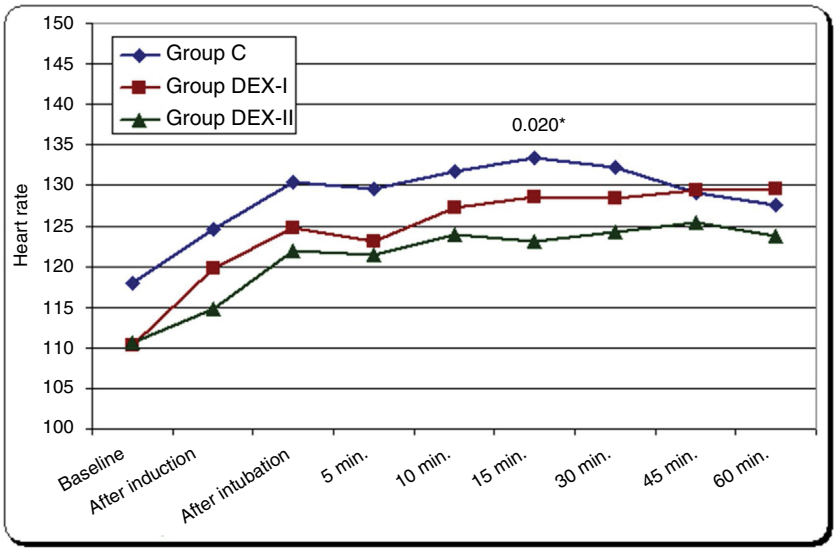

Figure 3 Heart rate (Group C, Placebo Gontrol; Group DEX I, 0.5 μg.kg^{-1}; Group DEX II, 1 μg.kg^{-1}).

Table 2 Watcha agitation scale in study groups.

Item	Group C (n = 30)	Group DEX I (n = 30)	Group DEX II (n = 30)	*p*-Value
Ag. score 5 min				
Median (range)	2 (1–3)	2 (0–3)	2 (0–3)	$p = 0.076$
Number: 0/1/2/3/4	0/2/21/7/0	3/9/11/7/0	5/2/20/3/0	$p = 0.007$[a]
(Ag. score ≥3)	7	7	3	$p1 = 0.027$[a]
Ag score 10 min				
Median (range)	2 (0–3)	2 (0–3)	2 (0–3)	$p = 0.109$
Number: 0/1/2/3/4	1/3/21/5/0	3/9/15/3/0	6/1/20/3/0	$p = 0.034$[a]
(Ag. score ≥3)	5	3	3	$p1 = 0.044$[a]
Ag score 15 min				
Median (range)	2 (0–3)	1 (0–2)	1 (0–3)	$p = 0.487$
Number: 0/1/2/3/4	2/12/13/3/0	2/15/13/0/0	8/8/11/3/0	$p = 0.079$
(Ag. score ≥3)	3	0	3	$p = 0.031$[a]
Ag score 30 min				
Median (range)	1 (0–3)	1 (0–2)	1 (0–2)	$p = 0.168$
Number: 0/1/2/3/4	5/16/7/2/0	3/24/3/0/0	11/13/6/0/0	$p = 0.022$[a]
(Ag. score ≥3)	2	0	0	$p1 = 0.012$[a]
Ag score 45 min				
Median (range)	1 (0–3)	1 (0–1)	1 (0–1)	$p = 0.122$
Number: 0/1/2/3/4	8/17/4/1/0	6/24/0/0/0	12/18/0/0/0	$p = 0.034$[a]
(Ag. score ≥3)	1	0	0	$p1 = 0.091$
Ag score 60 min				
Median (range)	1 (0–2)	1 (0–1)	1 (0–1)	$p = 0.055$
Number: 0/1/2/3/4	10/18/2/0/0	4/26/0/0/0	13/17/0/0/0	$p = 0.026$[a]
(Ag. score ≥3)	0	0	0	$p2 = 0.010$[a]

Data presented as median (range) and number.
[a] $p < 0.05$ significant difference between groups. $p1 < 0.05$ significant difference between DEX I and II Groups in the frequency distribution of Watcha scale.

Table 3 Objective Pain Scale (OPS) in study groups.

Item	Group C (n = 30)	Group DEX I (n = 30)	Group DEX II (n = 30)	*p*-Value
OPS 5 min	2 (1–6)	1.5 (0–6)	2 (0–6)	$p = 0.011$[a]
Children with OPS ≥ 3	14	13	8	$p1 = 0.982$
OPS 10 min	2 (0–6)	1 (0–4)	2 (0–5)	$p = 0.037$[a]
Children with OPS ≥ 3	12	10	8	$p1 = 0.348$
OPS 15 min	2 (0–6)	1 (0–3)	0 (0–5)	$p = 0.133$
Children with OPS ≥ 3	6	1	3	$p1 = 0.874$
OPS 30 min	0 (0–6)	0 (0–1)	0 (0–2)	$p = 0.044$[a]
Children with OPS ≥ 3	2	0	0	$p1 = 0.348$
OPS 45 min	0 (0–6)	0 (0–1)	0 (0–1)	$p = 0.432$
Children with OPS ≥ 3	2	0	0	$p1 = 0.690$
OPS 60 min	0 (0–2)	0 (0–1)	0 (0–1)	$p = 0.947$
Children with OPS ≥ 3	0	0	0	$p1 = 0.390$
Children received analgesia in PACU (n)	10	9	5	$p = 0.303$

Data presented as median (range) and number.
[a] $p < 0.05$ significant difference between groups. $p1 < 0.05$ significant difference between DEX I and II groups.

with no difference between DEX I and II Groups. Ten, versus 9 and 5 showed OPS ≥3 and received nalbuphine analgesia in Group C, DEX I and DEX II, respectively ($p = 0.303$) (Table 3).

There were no detected adverse events during the study period neither in the pre-operative room, operative theatre, nor in the PACU.

Discussion

In this clinical investigation, we studied the efficacy of OTM dexmedetomidine in reducing the incidence and severity of emergence agitation after pediatric tonsillectomy. Compared to placebo controls, dexmedetomidine 0.5 and 1 $\mu g.kg^{-1}$

reduced the incidence of EA with an added analgesic effect and without delaying recovery from anesthesia.

In accordance with our results, Tsiotou et al. found that 1 $\mu g.kg^{-1}$ DEX iv bolus after induction of anesthesia reduced incidence of EA at 20 min and 30 min postoperatively in pediatric tonsillectomy.[21] Dexmedetomidine 0.3 $\mu g\,kg^{-1}$ iv bolus administered before end of sevoflurane anesthesia similarly reduced the incidence of EA at 0, 5 and 15 min from PACU admission.[22] El-Hamid and Yassin reported that intraoperative intranasal 1 $\mu g.kg^{-1}$ dexmedetomidine controlled of EA in pediatric tonsillectomy.[23]

Despite that the OTM route for drug administration is easy needle-free and avoids the first-pass metabolism, it is under-utilized in human researches. Cimen et al. compared the OTM buccal versus the nasal administration of 1 $\mu g.kg^{-1}$ dexmedetomidine for sedative premedication in children.[16] Children received nasal dexmedetomidine showed less separation anxiety, satisfactory sedation, and higher mask and drug acceptance scores. They recommended the nasal route for sedative premedication in children and suggested the use of higher doses for OTM buccal dexmedetomidine in order to be effective. Sakurai et al. compared between buccal dexmedetomidine 3–4 $\mu g.kg^{-1}$ and rectal diazepam 0.7 $mg.kg^{-1}$ for sedative premedication in children. They found that buccal dexmedetomidine was superior over rectal diazepam, with no significant difference between the two groups in hemodynamic variables.[24] However, these two studies were powered to investigate buccal dexmedetomidine for sedative premedication not for the control of early postoperative EA. Our results come to an agreement with Cimen et al. in that 1 $\mu g.kg^{-1}$ buccal dexmedetomidine was not effective for sedative premedication. However, we disagree with the authors in that we recorded that 1 $\mu g.kg^{-1}$ buccal dexmedetomidine reduced the incidence of EA. We also disagree with Sakurai et al. in that we recorded lower mean heart rate and mean arterial pressure in children received 1 $\mu g.kg^{-1}$ buccal dexmedetomidine. Indeed, the dose they investigated (3–4 $\mu g.kg^{-1}$) is high to be devoid of hemodynamic derangements. Oral swallowing is a significant problem that complicates dosage adjustments for OTM buccal drug delivery in children. Further dose-finding studies for OTM dexmedetomidine powered to investigate early postoperative EA in children are needed.

In the PACU, the clinical presentations of early postoperative pain and the early negative behaviors of EA are closely related.[2,4,25] Acute pain is also associated with excitement, abnormal facial expression, and inconsolability, thereby, making the early identification of EA difficult.[19] In this study, we evaluated EA simultaneously with the assessment of pain score. The lake of awareness to the surrounding environment and failure to make eye contact were our key tools to differentiate EA from acute pain.[4] The combination of these two features had been shown to have a high sensitivity to detect EA in the PACU.[18] In this study, we observed that all patients who showed EA with agitation score $\geq$3 simultaneously had OPS score $\geq$3, while not all patients with OPS score $\geq$3 had agitation score $\geq$3 and that intravenous nalbuphine 0.2 $mg.kg^{-1}$ was effective in controlling both pain and EA. These results are in accordance with many studies who concluded that pain and EA are closely linked and that early postoperative pain is an important risk factor for EA.[1–4,21–25]

The administration of dexmedetomidine has been linked to prolonged emergence and PACU discharge times.[6] While some clinical investigations recorded a significant prolongation of extubation time in DEX Groups,[11] others found that there were no significant differences in recovery parameters or PACU stay between DEX and Control Groups.[21] In accordance, in this study, the extubation time was comparable between the two DEX groups and the placebo controls.

In this study, lower intraoperative heart rates at 15 min and lower arterial blood pressure mean values at 30, 45 and 60 min were recorded in children received the high dose of OTM dexmedetomidine (1 $\mu g.kg^{-1}$) compared to control and DEX 0.5 $\mu g.kg^{-1}$ groups ($p < 0.05$). However, this statistical significance was not evident clinically and either hypotension or bradycardia were recorded in any patient in this study. As shown in similar studies, these hemodynamic effects were within the normal clinical limits and required no pharmacological interventions.[16,21–24]

This study was limited by its small sample size. Another limitation is the recording of agitation and pain scores at 15 min intervals. A 5 min interval would have been more precise for diagnosing such negative behaviors. Third, the period of strict postoperative follow up for EA was limited to one-hour, indeed a longer follow-up period was recommended for further understanding of EA, its late effects, sequel and response to pharmacological treatment. We also agree with Mason, who suggested that EA should be considered as a vital sign and it should be assessed and documented in every patient's PACU record.[4]

In conclusion, this study demonstrates the clinical advantage and the simple technique of OTM DEX premedication for EA in preschool children undergoing tonsillectomy under sevoflurane anesthesia compared with saline placebo.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgment

The authors are thankful to the PACU staff who helped in data collection in this study.

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