CAFFEINE IN CHILDREN WITH OBSTRUCTIVE SLEEP APNEA

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Summary

Background: Children with obstructive sleep apnea (OSA) have a higher rate of adverse post-extubation respiratory events, such as laryngospasm, upper airway obstruction, apnea, desaturation and/or need for re-intubation. They are overly sensitive to sedatives and narcotics. Although the etiology of OSA is primarily obstruction (mechanical or neuromuscular), a central element may contribute to OSA. Caffeine citrate has been shown to be effective in treating apnea of prematurity. This study evaluated whether the administration of caffeine benzoate to children with OSA decreases the number of children who experience adverse post-extubation respiratory events.

Methods: In a randomized, double-blind and placebo-controlled study, children with OSA scheduled for adenotonsillectomy (T&A) received either caffeine benzoate, 20 mg/kg IV, (caffeine group, n = 36) or saline (placebo group, n = 36). The primary outcome evaluated the

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number of children who developed adverse post-extubation respiratory events, and the secondary outcome was the incidence of those events.

Results: The results demonstrated the two groups differed in the number of children who developed adverse post-extubation respiratory events (p = 0.032). The overall incidence of adverse postoperative respiratory events was less in the caffeine group than the placebo group (p = 0.0196).

Conclusion: In children with OSA scheduled for T&A, administration of caffeine benzoate, 20 mg/kg IV, decreased the number of children who developed adverse post-extubation respiratory events and decreased the overall incidence of adverse post-extubation respiratory events. PACU duration, hospital discharge time and postoperative delirium did not differ between groups.

Keywords: Children, obstructive sleep apnea; anesthesia; adverse post-extubation respiratory events; caffeine.

Introduction

Obstructive sleep apnea (OSA) is one of the most common respiratory disorders of childhood, affecting an estimated 1-2% of normal children[1]. Children with OSA usually present with snoring, restless sleep, and apnea[2]. OSA is thought to peak in preschool children due to adenotonsillar hypertrophy[1-4].

The etiology of OSA is multifactorial, with anatomical and neuromuscular abnormalities playing a major role[5]. OSA occurs cyclically during sleep, due to airway obstruction causing hypoxia and hypercarbia. This, in tum, stimulates the peripheral baroreceptors and chemoreceptors, causing cortical and sub-cortical arousal with return of pharyngeal tone and respiration[6].

Children may manifest problems with learning, hyperactivity, attention deficit, aggression and other behavior disorders, which may improve after adenotonsillectomy for OSA[7-8]. Patients with OSA reportedly have a higher rate of severe respiratory complications

associated with upper airway obstruction during anesthesia and sedation or immediately after anesthesia[9-10]. The children's opioids requirement for analgesia is reduced[11].

Although the etiology of OSA is mainly obstruction, we postulated that a central element contributes to OSA; because children with OSA are sensitive to sedatives and narcotics[11]. Caffeine proved to be effective in central apnea of prematurity. We hypothesized that administration of caffeine a central respiratory stimulant, to children with OSA may decrease the number of children who develop adverse post-extubation respiratory events.

The aim of the study was to evaluate whether the administration of caffeine, to children with OSA, decreases the number of children who develop adverse post-extubation respiratory events and whether caffeine administration decreases the incidence of those adverse events.

Methods and Materials

Institutional approval and written informed consent from parents or guardians of 75 healthy children, with OSA, who were scheduled for elective outpatient or inpatient adenotonsillectomy at our hospital, were obtained. Written child assent was obtained from children 7 years and older. The research assistants invited parents or guardians, in DSU area, to allow their children to be part of the study. The study was randomized, double blinded and placebo controlled. A computer generated randomization list was used, and the study was registered with clinical.trials.gov.

Children with OSA, 2.5-12 years of age, both genders were eligible to be part of the study. OSA was diagnosed by history alone or by history and polysomnography. The clinical diagnosis for OSA was based on three criteria: the patient should have: (a) Snoring, irregular breathing, and apnea during sleep. (b) Periodic snorting and evidence of arousal, and. (c) Daytime fatigue, somnolence or hyperactivity. Children with compromised cardiovascular, pulmonary or renal function, those with

congenital syndromes, and those with history of seizures were excluded. Research assistants asked parents or guardians about symptoms and examined children for signs of upper airway obstruction.

Children were randomized into two groups. The caffeine group received caffeine benzoate, 20 mg/kg IV, which is equivalent to 10 mg/kg of caffeine base. The placebo group received a similar volume of saline. Study medication was prepared by the hospital research pharmacy. The same concentration of caffeine solution was used for all patients with no upper limit for the dose. The research pharmacy assigned participants to their group according to the computer generated randomization list. The only person who knew what the child received was the research pharmacist who prepared the study drug. The principal investigator, co-investigators, patients, nurses, and research assistants were all blinded. The research pharmacist assured the blinding was successful.

The primary outcome of the study was the number of children who developed adverse post-extubation respiratory events, including laryngospasm, upper airway obstruction, apnea, desaturation (defined as decrease in oxygen saturation <95% while breathing oxygen via mask for any length of time) and need for reintubation, both in the OR and in the PACU. The secondary outcome of the study was the incidence of adverse post-extubation respiratory events.

Preoperative oxygen saturation while the child breathing room air was recorded, after which children were premedicated with midazolam, 0.25 mg/kg p.o., mixed with syrpalta syrup and were continuously monitored with pulse oximetry. In the operating room after applying routine monitors and recording post-sedation pulse oximetry, anesthesia was induced with a mask using sevoflurane and oxygen. Rocuronium, 0.5 mg/kg IV, Fentanyl, 2 μg/kg IV, and glycopyrrolate, 5 μg/kg IV were administered. Study medication was then administered intravenously by the anesthesiologist over one minute and before intubation. Anesthesia was maintained with isoflurane and 60% nitrous oxide in oxygen. The level of isoflurane concentration was adjusted to keep systolic blood pressure within 20% of preoperative value.

To prevent postoperative nausea and vomiting, a combination of dexamethasone, 100 μg/kg IV was given on anesthesia induction, and ondansetron 100 μg/kg IV at anesthesia end.

At the end of surgery, residual muscle weakness was antagonized using neostigmine, 50 μg/kg IV and glycopyrrolate, 10 μg/kg IV. Patients were placed in the lateral position before extubation and during transport to the PACU. The endotracheal tube was removed in the OR when the child was awake, regained upper airway reflexes and motor power, breathed regularly and responded to verbal commands.

An independent observer evaluated the number of children who developed adverse post-extubation respiratory events, in the OR an PACU. The independent observer also evaluated the incidence of the events. The independent observer stayed with each patient in the OR and PACU until the patient was discharged from the PACU to go home or to a hospital room.

Extubation time from end of anesthesia until extubation; awakening time from end of anesthesia until the child reached a score of 6 on the Steward recovery score[12]; PACU duration; length of hospital stay; and unplanned hospital admission or discharge, were evaluated. The incidence of possible side effects, such as postoperative delirium, was also evaluated.

In the PACU, morphine sulfate, 0.05 mg/kg IV was titrated and repeated if needed. PACU nurses assessed pain using the Standard Pain Scale, when possible, to obtain the patient self-report of pain or the Behavior Pain Assessment Scale. Morphine was administered if a child had a pain score of 3 or higher using either scale.

Children were discharged from the hospital when they had fulfilled the hospital discharge criteria: they were awake, had stable vital signs, were breathing adequately, had O_2 saturation >95% while breathing room air, were able to swallow fluids, had no or minimal pain, and were able to ambulate without excessive nausea, vomiting, or dizziness. The independent observer contacted parents the following day to evaluate possible postoperative complications after hospital discharge, such as

respiratory problems, bleeding, inability to swallow, fever, repeated vomiting or hospital readmission.

Sample Size and Statistical Analysis

Based on our clinical experience, we estimated that 50% of children with OSA receiving placebo and 20% receiving caffeine may develop post-extubation respiratory complication events. A sample size of 36 in each group may allow us to detect a reduction in the proportion of children developing post-extubation respiratory complication events in a caffeine group, using two sample proportions test at 5% significance level and 80% power.

Data were summarized and reported as mean ± standard deviation for the continuous variables and as frequency (%) for the categorical variables. Between treatment group differences in continuous variables were evaluated using two sample t-tests. The Fisher exact test evaluated the significance of differences between groups in categorical variables. Additionally, the Poisson regression analysis was used to compare the secondary outcome variable, incidence of post-extubation respiratory complication events between groups. All statistical tests were 2 tailed and significance level (alpha) was 0.05. Statistical analyses were conducted using SAS 9.1 (SAS Institute, Cary, NC). A p value <0.05 was considered significant.

Results

Seventy-two children, 36 in each group were randomly assigned, received intended treatment, completed the study protocol, and were analyzed for the primary outcome. Three other children whose parents consented to the study were dropped from the study, because the study medication was not prepared by the research pharmacist timely, and they did not receive the study medication. All children received the same anesthesia technique. The majority of the cases were performed by the same surgeon. No local anesthetic was injected at the surgical site. There

were no other protocol deviations.

There was no substantial difference in demographic data between the two groups (Table 1) of the participating 72 children (36 females, 36 males). Age, height, and weight were 5.3 ± 2.5 yr (mean ± SD), 112.8 ± 15.5 cm, and 27.2 ± 15.8 kg respectively. Twenty-three children were overweight (BMI ≥ 95 percentile), and two children were underweight (BMI ≤ 5th percentile).

Table 1
Demographic Data

Group	n	Age, yr	Weight, kg	Height, cm	Gender F/M, n
Caffeine	36	5.3 ± 2.2	29.5 ± 18.2	115.1 ± 15.3	19/17
Placebo	36	5.3 ± 2.9	24.9 ± 12.9	110.4 ± 15.5	17/19

Age, height, and weight values are presented as mean ± SD; n = number of patients All values are statistically similar between the two groups.

Preoperatively, children presented with a variety of symptoms and signs due to upper airway obstruction. These did not differ between the two groups (Table 2). Thirteen children (18%) did not perform well in school.

The number of the children who had sleep studies preoperatively was not different between the two groups. Of the 72 children, 38 (53%) had preoperative sleep studies – 17 children of 36 (47%) in the caffeine group, and 21 children of 36 (58%) in the placebo group. Mean and SD of apnea index, apnea/hypopnea index and the saturation indices did not differ between the two groups (Table 3). In our practice, a small fraction of our patients undergo sleep studies preoperatively due to cost and time commitment; and the sleep study is ordered by the surgeon.

Table 2

Preoperative Symptoms and Signs

Symptoms and Signs	Study Group n = 72 Frequency, (%)	Caffeine Group n = 36 Frequency, (%)	Placebo Group n = 36 Frequency, (%)
Snoring	72 (100%)	36 (100%)	36 (100%)
Mouth Breathing	64 (88.9%)	30 (83.3)	34 (94.4%)
Hypo-Nasal Speech	32 (45.7%)	13 (37.1%)	19 (54.3)
Supra Sternal Retraction	7 (9.7%)	4 (11.1%)	3 (8.3%)
Pectus Excavatum	6 (8.3%)	1 (2.8%)	5 (13.9%)
Allergy	9 (12.5%)	5 (13.9%)	4 (11.1%)
Daytime Hyperativity	34 (49.3%)	16 (45.7%)	18 (52.9)
Attention Deficit	12 (17.4%)	5 (14.3%)	7 (20.6)
Aggressiveness	15 (21.7%)	6 (17.1%)	9 (26.5%)
Enuresis	21 (30.4%)	12 (34.3%)	9 (25%)
Hypersomnolence	18 (25.7%)	9 (25.7%)	9 (25.7%)
Parasomnia	14 (20.3%)	7 (20.0%)	7 (20.6%)
Daytime Naps	37 (52.9%)	15 (42.9%)	22 (62.9%)
Excessive Night Sleep	21 (30.0%)	8 (22.9%)	13 (37.1%)
Headache	10 (13.9%)	6 (16.6%)	4 (11.1%)
Daytime Fatigue	31 (43.7%)	13 (36.1%)	18 (51.4%)
Abnormal Position During Sleep	19 (27.5%)	10 (28.6%)	9 (26.5%)
Obesity	14 (19.7%)	8 (22.2%)	6 (18.4%)
Failure To Thrive	6 (8.3%)	2 (5.6%)	4 (11.1%)

The preoperative symptoms and signs are not statistically different between the two groups.

Table 3

Apnea Index, Apnea/Hypopnea Index and Oxygen Saturation Indices

Group	Apnea Index		Apnea/Hypopnea Index		O_2 Saturation Baseline		O_2 Sat During Sleep Average		O_2 Sat During Lowest Sleep	
	N	Mean±SD	N	Mean±SD	N	Mean±SD	N	Mean±SD	N	Mean±SD
Caffeine	14	6.65±6.7	11	9.71±9.58	17	98.2±1.6	17	97.4±2.1	17	83.9±11.5
Placebo	17	5.65±4.8	10	12.54±13.0	20	98.5±1.3	20	97.5±2.4	20	84.7±11.3

Data are presented as mean ± SD; N = number of patients.

Number of Children who Developed Post-Extubation Respiratory Complication Events

In the combined OR and PACU periods, the two groups differed significantly in the number of children who developed adverse post-extubation respiratory events, i.e. 11 of 36 in the caffeine group and 21 of 36 in the placebo group (p = 0.032) (Table 4). In the OR, the number of children who developed adverse post-extubation respiratory events was 3 out of 36 (8.3%) and 9 out of 36 in the placebo group (25%), (p = 0.056), a weak evidence of significance.

Table 4
Number of Children who Developed Adverse Post-Extubation Respiratory Events

OR		**PACU**		**Combined OR & PACU***	
Caffeine Group (n = 36)	Placebo Group (n = 36)	Caffeine Group (n = 36)	Placebo Group (n = 36)	Caffeine Group (n = 36)	Placebo Group (n = 36)
3	9	9	17	11	21

* The number of children who developed adverse post-extubation respiratory events, in the combined OR & PACU, was significantly less in the caffeine group compared to placebo group (p = 0.032). In the OR, there was weak evidence of significance (p = 0.056).

The Incidence of Adverse Post-Extubation Respiratory Events

In the OR, the caffeine group developed less adverse post-extubation respiratory events than the placebo (p = 0.048). Two children in the caffeine group and 6 in the placebo group developed laryngospasm; 1 child in the caffeine group and 3 in the placebo group developed apnea; 2 children in the caffeine group and 4 in the placebo group desaturated; and 1 child in the placebo group was reintubated (Table 5).

In the PACU, the incidence of adverse post-extubation respiratory

events did not differ between the two groups. Nine children in the caffeine group and 13 in the placebo group desaturated; 2 children in each group developed apnea and 1 child in the caffeine and 5 in the placebo group developed upper airway obstruction (Table 5).

The overall incidence of adverse post-extubation respiratory events in the combined OR and PACU periods was significantly less in the caffeine group, i.e. 17 vs. 34 in the placebo group (p = 0.0196) (Table 5).

Table 5

Incidence of Adverse Post-Extubation Respiratory Events

Incidence of Postoperative Respiratory Complications	**OR***		**PACU**		**Combined OR+PACU****	
	Caffeine Group (n = 36)	Placebo Group (n = 36)	Caffeine Group (n = 36)	Placebo Group (n = 36)	Caffeine Group (n = 36)	Placebo Group (n = 36)
Laryngospasm	2	6			2	6
Reintubation	0	1			0	1
O_2 Saturation <95%	2	4	9	13	11	17
Apnea	1	3	2	2	3	5
Upper Airway Obstruction			1	5	1	5
Total	5	14	12	20	17	34

* The caffeine group developed less adverse post-extubation respiratory events, in the OR, compared to the placebo group (p = 0.048).

** The caffeine group developed less adverse post-extubation respiratory events, in the combined OR and PACU, than the placebo group (p = 0.0196).

Snoring was less in the caffeine group, 9 of 36 (25%), than in the placebo group, 19 of 36 (53%); ($p < 0.0287$).

The baseline, pre-sedation oxygen saturation was 99.06 ± 1.3% for the caffeine and 99.06 ± 0.99% for the placebo group. The post-sedation O_2 saturation for the caffeine group was 99.2 ± 1.6%, and 99.05 ± 1.3% for the placebo group. The change in O_2 saturation from baseline was

insignificant in both groups. One child required oxygen after sedation due to a decrease in O_2 saturation to 94% while breathing room air.

All the children were extubated in the OR. One child in the placebo group, desaturated after extubation in the OR where he was re-intubated, moved to the PACU while intubated, and subsequently extubated in the PACU.

In the PACU, 31 children in the caffeine group and 33 children in the placebo group received morphine. Mean ± SD of the morphine dose in the caffeine group was 0.072 ± 0.06 mg/kg, and 0.080 ± 0.058 mg/kg in the placebo group. There were no differences in the morphine doses received by the two groups. Eleven of 36 children in the caffeine group desaturated. Of those, 7 desaturated before and 2 after receiving morphine. Two children of the 11 received no morphine in the postoperative period. In the placebo group 13 of 36 children desaturated, 11 before and 1 after receiving morphine. One child received no morphine.

Anesthesia duration for all participants (N = 72) was 40.3 ± 13.6 min (mean ± SD). Surgery duration was 25.2 ± 12.8 min, extubation time was 9.9 ± 7.6 min, awakening time was 26.4 ± 23.2 min. PACU duration was 102.7 ± 55.0 min, and hospital discharge time was 195.5 ± 83.4 min. Anesthesia duration, surgery duration, extubation time, awakening time, PACU duration, and hospital discharge time did not differ between the two groups (Table 6).

Table 6
OR, PACU, and Hospital Durations of the Two Groups

	Caffeine Group	**Placebo Group**
Anesthesia Duration (min)	41.5 ± 12.3	39.1 ± 14.8
Surgery Duration (min)	25.6 ± 11.5	24.8 ± 14.1
Extubation Time (min)	8.6 ± 4.9	11.3 ± 9.4
Awakening Time (min)	26.1 ± 28.8	26.6 ± 16.0
PACU Duration (min)	74.4 ± 43.7	84.8 ± 44.1

Hospital Discharge Time (min)	98.2 ± 55.9	107.0 ± 54.5

Thirty-three of 36 children in the caffeine group and 31 of 36 children in the placebo group were scheduled to have outpatient surgery. Preoperatively, the surgeon schedules patients to have surgery as outpatient or inpatient; depending on severity of symptoms and or age of the child. The number of children scheduled for outpatient surgery did not differ between the two groups. Three children in the placebo group and 1 child in the caffeine group were originally scheduled to have outpatient surgery; however, they were drowsy and had to be admitted to the hospital for overnight observation. One child in the caffeine group originally scheduled to be admitted to the hospital, did well and was discharged home on the day of surgery. Eighty-eight percent of children in the caffeine group and 80% of the placebo group were discharged home on the day of surgery once they met the hospital discharge criteria. Two children in the placebo group were admitted to the hospital – one developed skin rash and the other facial swelling.

In the PACU, 16 children were agitated, 6 of 36 (16.7%) in the caffeine group and 10 of 36 (27.8%) in the placebo group. There was no difference between the two groups. None of the children who were discharged home on the day of the surgery had to be readmitted to the hospital due to surgical or anesthesia complication.

Discussion

The results of this study demonstrated that the administration of caffeine benzoate, 20 mg/kg IV to children with OSA decreased the number of children who developed adverse post-extubation respiratory events. Caffeine also decreased the incidence of adverse post-extubation respiratory events. The mechanisms by which caffeine decreases the adverse post-extubation respiratory events could be multiple. It has been reported that caffeine is an inhibitor of adenosine, a cardiac and central nervous system activity suppressant. Its effects include increased central respiratory drive, increased chemoreceptor sensitivity to carbon dioxide,

improved skeletal muscle contraction, potentiation of catecholamine response, improved oxygenation, increased ventilation and decreased episodes of hypoxia[13]. Caffeine may also enhance inspiratory muscle endurance[14]. Children with OSA are sensitive to sedatives and narcotics; this may be due the recurrent episodes of hypoxia and or hypercarbia to which their respiratory center are cyclically exposed to during sleep. Caffeine, may have improved children's ventilation, oxygenation and muscle tone.

Normal children have a relatively narrow upper airway, but maintain airway patency during sleep because of increased upper airway neuromotor tone and an increased ventilatory drive. However, children with OSA lack the compensatory upper airway neuromotor responses[6]. Although snoring is not a complication, it is a manifestation of partial upper airway obstruction. In this study, the incidence of snoring in PACU was significantly less in the caffeine group than the placebo group. Children who received caffeine may have increased upper airway neuromotor tone and an increased central ventilatory drive.

In this study we administered 20 mg/kg of caffeine benzoate which provided 10 mg of caffeine base, similar to the dose of caffeine citrate that Welborn administered to premature babies[15]. In this study, caffeine benzoate, 20 mg/kg IV, decreased the number of children who developed adverse post-extubation respiratory events from 58% to 31%. It is possible that using a higher dose may further decrease the number of children who develop the adverse post-extubation respiratory events. Using 20 mg/kg of caffeine benzoate was not associated with apparent side effects.

A shortcoming of this study is the fact that not all children had a preoperative sleep study, due to logistic reasons. The Practice Guidelines for perioperative management of patients with obstructive sleep apnea: published by the American Society of Anesthesiologists discuss the diagnosis of OSA on clinical grounds[16].

In this study, similar to a previous study[17], children tolerated a small dose of midazolam, 0.25 mg/kg p.o. for premedication. Admission of a child with OSA to the hospital after adenotonsillectomy or discharge on day of surgery varies from institution to institution. Some hospitals admit

all children with OSA overnight; due to concern for upper airway obstruction, plus or minus the potential for apnea. Other institutions discharge a high percentage of these children on the day of surgery once they meet discharge criteria[18]. We are not recommending administering caffeine to children and sending them home without careful assessment and close observation in the postoperative period, nor do we recommend caffeine to facilitate discharge from the hospital when other criteria have not been met.

In summary, this study demonstrated that administration of caffeine to children with OSA, scheduled for adenotonsillectomy, decreases the number of children who develop adverse post-extubation respiratory events and decreased the overall incidence of adverse postextubation respiratory events without apparent side effects. This information could be useful for anesthesiologists managing patients, children or adults, with OSA and having general anesthetic.

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