Intravenous Caffeine for Adult Patients with Obstructive Sleep Apnea Undergoing Uvulopalatopharyngoplasty: Effects on Postoperative Respiratory Complications and Recovery Profile

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Abstract

Background: This randomized double blind placebo controlled study, aimed at investigating the effects of intravenous caffeine benzoate on post extubation adverse respiratory events and recovery from sevoflurane anesthesia in patients with obstructive sleep apnea (OSA) undergoing uvulopalatopharyngoplasty (UPPP).

Methods: 60 patients ASA I and II scheduled for UPPP for OSA were blindly grouped to receive either 500mg caffeine benzoate or 0.9% normal saline as placebo control following completion of surgery and discontinuation of sevoflurane. Premedication was omitted. Anesthesia was induced with propofol 2mg/kg, fentanyl 1 µg/kg and atracurium 0.05mg/kg. Anesthesia was maintained with sevoflurane 2.5-3% in 100% oxygen, atracurium 0.1mg/kg was used for further muscle relaxation and no other narcotics were used intraoperatively. After injection of the study drug the following were recorded: BIS values and heart rate for 15 minutes, in addition time to eye opening, extubation, response to verbal commands and duration of recovery as well as duration of PACU stay and compared in both groups. The number of patients who developed post extubation respiratory complications is recorded during the recovery period and in the PACU and compared in both groups.

Results: Recovery times (Time to eye opening, extubation, response to verbal commands and duration of recovery as well as duration of PACU stay) were significantly shorter in the caffeine group \( P<0.05 \). The BIS values were significantly higher in the caffeine group from minute 3 to minute 11 compared to the placebo. \( P<0.05 \). The mean heart rate increased in the caffeine group from minute 4 to 9 \( P<0.05 \), but this finding was clinically insignificant. The number of patients who developed adverse post extubation events during the recovery period and in the PACU was significantly less in the caffeine group compared to the placebo \( P<0.05 \).

Conclusion: The current study demonstrated that administration of caffeine benzoate to patient with OSA scheduled for UPPP decreases the number of patients who developed adverse post extubation respiratory events and hastens recovery from sevoflurane anesthesia.

Key Words: Obstructive sleep apnea – Caffeine benzoate – Uvulopalatopharyngoplasty – Recovery profile and post extubation complications.

Introduction

Obstructive sleep apnea is a common sleep disorder caused by repetitive partial or complete obstruction of the upper airway and is characterized by episodes of cessation of breathing during sleep lasting more than 10 seconds, causing hypoxia and hypercarbia. This is in turn, stimulates the peripheral baroreceptors and chemoreceptors, causing cortical and subcortical arousal with return of pharyngeal tone and respiration [1]. Population-based epidemiologic studies have shown a frequent prevalence of undiagnosed OSA, and even mild obstructive sleep apnea is associated with significant morbidity and mortality [2].

Uvulopalatopharyngoplasty (UPPP) has been used as a surgical procedure to treat obstructive sleep apnea. Despite the frequency of this procedure, appropriate monitoring of postoperative respiratory complications is of great concern [3].

Although the etiology of obstructive sleep apnea is mainly obstruction, we postulated that a central element contributes to OSA; because patients with OSA are sensitive to sedatives and narcotics [4].

Caffeine proved to be effective in central apnea of prematurity being as effective as theophylline, having a longer half life and is associated with fewer adverse events. Caffeine stimulates the respiratory and central nervous system more effectively and penetrates into the cerebrospinal fluid [5]. Caffeine is also able to partially antagonize the hypnotic effects of ethanol [6].
We hypothesized that administration of caffeine to patients with OSA undergoing UPPP would decrease the post extubation respiratory adverse events. The aim of the study was to evaluate whether the administration of caffeine to patients with OSA undergoing UPPP decreased the post extubation respiratory events or not and to assess the effects of caffeine on the speed of recovery of these patients.

**Material and Methods**

Following institutional ethical committee approval, 60 consenting adult patients undergoing UPPP were enrolled in the study. Patients were all ASA class I and II and were all ≤ 3 based on modified Mallampati classification [7].

**Exclusion criteria:**

Patients with severe cardiopulmonary comorbidity, apnea associated cardiac events, patients with history of peptic ulcers, gastroesophageal reflux, impaired renal or hepatic function, seizures disorders, also patients with agitation, anxiety or tremors and finally those with body mass index ≥32 are all excluded. Premedication was omitted, upon arrival to the OR usual monitors were applied to all patients (ECG, pulse oximetry, non invasive blood pressure and capnography added after intubation). Additionally, after cleaning the skin with alcohol, disposable BIS electrodes were placed on the patients forehead and attached to the BIS monitor (Aspect Medical Systems, Inc., USA) for monitoring of BIS values.

After preoxygenation, anesthesia was induced with intravenous propofol 2mg/kg, fentanyl 1 µg/kg and endotracheal intubation is facilitated with atracurium 0.5mg/kg. Anesthesia was maintained with 2.5-3% sevoflurane in 100% oxygen maintaining the BIS in the range of 50±5. No additional opioids were used intraoperatively, while muscle relaxation is maintained with 0.1mg/kg atracurium when muscle relaxation was needed according to nerve stimulator. At 5 minutes before completion of surgery the anesthetic gas was turned off and patients were blindly grouped to receive either 500mg caffeine benzoate equivalent to 250mg caffeine base (American Regent Laboratories Inc.) intravenously or 0.9% normal saline as placebo control in identical appearing syringes administered by an assistant who was blind to the identity of the study drugs, then residual muscle relaxation was antagonized with neostigmine 0.05mg/kg and atropine 0.01 mg/kg. Patients were extubated when they were breathing regularly, regained motor power and upper airway reflexes, were fully awake and responding to verbal commands. A nasopharyngeal airway is inserted and patients were then transferred to the PACU when fully awake. Recovery was assessed by a second anesthetist who was unaware of the group to which the patient had been allocated, and the following were recorded: Time to eye opening, time to extubation, time to response to command (hand squeezing) and post operative recovery time (from the time the patient left the OR until discharge from the recovery room). BIS index values and heart rate were determined in all patients just before and after injection of the test drug for 15 minutes. in the PACU where pain was controlled with ketorolac 30mg/kg and patients remained until they were discharged when reaching an Aldrete score of 9 or more [8]. During the recovery period and in the PACU all patients were observed for adverse post extubation respiratory events and the number of patients developing desaturation, supraglottic obstruction, breath holding, need for reintubation and laryngospasm is recorded and compared in both groups.

**Statistical analysis:**

Data was analyzed using SPSS win statistical package version 16. Numerical data were expressed as mean ± SD. Qualitative data were expressed as frequency and percentage. Chi-square test was used to examine difference between qualitative variables. For quantitative data, comparison between the two groups was done using student t-test or the corresponding non-parametric one (Mann-Whitney test) for variables not normally distributed. p-value less than 0.05 was considered significant.

**Results**

Sixty patients completed the study, 30 in each group. All patients received the same anesthetic technique. There were no differences between the two groups with respects to age, ratio of male to female, ASA class, Malampatti score and BMI (Table 1). No patient received any medication during the course of anesthesia which was not specified by the study protocol.

The mean time to eye opening, time to extubation, time to response to commands, post operative recovery time and duration of PACU stay were all

<table>
<thead>
<tr>
<th>Table (1): Patients characteristics.</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Caffeine group (n=30)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
</tr>
<tr>
<td>ASA (I/II)</td>
</tr>
<tr>
<td>Malampatti score (1/2/3)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
</tr>
</tbody>
</table>
significantly shorter in the caffeine group compared to the placebo group (Table 2).

Prior to injection of the study drug, BIS was comparable between the 2 groups, however after injection of the drug the BIS values were significantly higher in the caffeine group from 3 to 11 minutes after injection (Fig. 1).

The mean heart rate showed slight increase in the caffeine group compared to the placebo that was clinically insignificant. Statistically, the difference between the two groups was significant from 3rd to 9th minute after injection (Fig. 2).

We recorded adverse post extubation respiratory complications during the recovery period and in the PACU in 7 patients of the caffeine group (23.3%) compared to 16 patients in the placebo group (53.3%) \( (p=0.034) \). Complications are detailed in table (3).

### Discussion

Table (3): Post-extubation respiratory complications in the studied groups.

<table>
<thead>
<tr>
<th></th>
<th>Caffeine group (n=30)</th>
<th>Placebo group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery Period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laryngospasm</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Supraglottic obstr</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Need for reintubation</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Breath holding</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Desaturation &lt; 95%</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

One patient may suffer more than one complication.

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Table (2): Recovery time variables in both groups.

<table>
<thead>
<tr>
<th></th>
<th>Caffeine group (n=30)</th>
<th>Placebo group (n=30)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to eye opening (min.)</td>
<td>6.2±2.3</td>
<td>8.1±2.4</td>
<td>0.003</td>
</tr>
<tr>
<td>Time to extubation (min.)</td>
<td>7.8±2.6</td>
<td>9.5±3.6</td>
<td>0.040</td>
</tr>
<tr>
<td>Time to response to command (min.)</td>
<td>10.2±2.4</td>
<td>12.7±1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postoperative recovery time (min.)</td>
<td>20.3±2.3</td>
<td>24.4±3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PACU stay (min)</td>
<td>65.8±26.6</td>
<td>78.6±19.1</td>
<td>0.036</td>
</tr>
</tbody>
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Fig. (1): Changes of BIS in the 15 minutes following injection of the drug in the two groups.

Fig. (2): Changes of the Heart Rate in the 15 minutes following injection of the drug in the two groups.
The results of this study demonstrated that the intravenous administration of 500mg caffeine benzoate to patients with OSA undergoing UPPP decreased the number of patients who developed post extubation respiratory complications during the recovery period and in the PACU and improved the recovery from sevoflurane anesthesia thus correlating with the BIS values.

The mechanism by which caffeine decreases the 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 decreased central respiratory drive, increased chemoreceptor sensitivity to carbon dioxide, improved skeletal muscle contracture potentiation of catecholamine response, improved oxygenation, increased ventilation and decreased episodes of hypoxia [9]. Caffeine also enhances inspiratory muscle inutance [10].

Similar results have been demonstrated by Khalil, et al. [11] who administered caffeine benzoate 20mg/kg to children with OSA undergoing tonsillectomy and proved that the caffeine group showed less post operative respiratory complications in both the OR and PACU, in his study caffeine decreased significantly the number of patients with post extubation respiratory complications.

The current study also demonstrated that administration of caffeine benzoat just prior to discontinuation of sevoflurane speeds recovery, an effect that correlates with BIS values. In the current study, the caffeine group showed shorter time to eye opening, to extubation, to response to commands with shorter post operative recovery time and less duration of PACU stay. In the current study the administration of caffeine benzoate slightly increased the heart rate, an effect which was insignificant clinically.

Similarly, in a study done by Wu, et al. [12], doxapram: A respiratory stimulants with effects on both peripheral and central chemoreceptors and a CNS stimulant was found to hastens early recovery from sevoflurane anesthesia when given in a dose of 1mg/kg without appreciable side effects. In another study by Sakurai, et al. [13], aminophylline proved to be effective in reversing prolonged propofol induced sedation and anesthesia in the post operative period. Another study done by Hupfl, et al. [14] demonstrated that 3mg/kg aminophylline has the ability to partially antagonize the sedative effects of general anesthetics. In another study by Turan, et al. [15], recovery from sevoflurane was improved in early period when aminophylline was given at emerging from anesthesia. It is also important to correlate the effects of caffeine on recovery from anesthetics to its widely known and widely used effects on alcohol induced sedation [6]. In the current study the administration of caffeine increased the heart rate from minutes 4 to minute 9 after injection in the caffeine group. Although statistically significant, this tachycardia was clinically insignificant and resolved after 10 minutes from injection without interference. This observation was similar to that of Hupfl, et al. [14] who administered 3mg/kg aminophylline intravenously after discontinuation of anesthetics and found an increase in heart rate after both sevoflurane and total intravenous anesthesia.

In conclusion, the current study demonstrated that administration of caffeine benzoate to patient with OSA scheduled for UPPP decreases the number of patients who developed adverse post extubation respiratory events and hastens recovery from sevoflurane anesthesia and this effects correlate well with BIS values. This information could be useful for anesthesiologists in managing patients with OSA having general anesthesia.

References

apnea in former premature infants. Anesthesiology, 68:


