Magnesium is More Efficient than Dexmedetomidine or Ketamine as a Prophylaxis against Bronchospasm during Emergence of Asthmatic Patients

AHMED M. EL-SHAARAWY, M.D.
The Department of Anesthesia, Faculty of Medicine, Beni-Suef University

Abstract

Background: Anesthesiologists face multiple problems during management of asthmatic patients especially when endotracheal intubation is required. Bronchospasm is a risk due to the hypersensitive airway. A reliable technique for improving ETT tolerance while facilitating rapid and full emergence from general anesthesia would be desirable especially in patients with bronchial hyper-reactivity.

Patients and Methods: This study was designed to compare the effect of magnesium, dexmedetomidine and ketamine in attenuating the response to the endotracheal tube during emergence From GA. Forty-five asthmatic patients were included in the study. Patients were randomly assigned to receive either MgSO4 20mg/kg, dexmedetomidine 0.5 µg/kg or ketamine 0.5mg/kg during recovery from general anesthesia. The incidence of bronchospasm was recorded before administration of the study drugs, after administration of the study drugs and after extubation. Hemodynamics, the incidence of coughing and gagging and the time required for recovery were recorded.

Results: Bronchospasm during emergence from general anesthesia was significantly lower in the magnesium group as compared to the other two groups. In the dexmedetomidine group, the time to recovery from GA was significantly shorter compared to the magnesium and ketamine groups. No significant difference between the studied groups as regard the incidence of coughing or gagging at extubation.

Conclusion: Magnesium is more effective than dexmedetomidine and ketamine in reducing the incidence of bronchospasm in response to the endotracheal tube during recovery from general anesthesia in asthmatic patients although it is associated with some delay in the recovery time. The three drugs were comparable regarding the incidence of coughing and gagging.

Key Words: Magnesium – Ketamine – Dexmedetomidine – Asthma – General anesthesia – Bronchospasm.

Introduction

ASTHMA is a significant source of morbidity and mortality in both adult and pediatric populations [1]. Asthma presents anesthesiologists with a unique set of challenges, especially in those patients requiring endotracheal intubation. Bronchial asthma carries the risk of perioperative bronchospasm. During emergence from general anesthesia, responses that result from the airway reflex such as coughing are frequent (cough risk is about 76-80%) [2,3]. Coughing during emergence from general anesthesia can result in hypertension, tachycardia or other arrhythmias, myocardial ischemia, surgical bleeding or bronchospasm [4].

Magnesium can relax airway smooth muscles, [5] dilate the airways, [6] inhibit cholinergic neuromuscular transmission, stabilize mast cells, and stimulate the production of nitric oxide and prostacyclin [7]. Further bronchodilator mechanisms of magnesium are inhibition of calcium channels of the airway smooth muscles and inhibition of calcium release from the sarcoplasmic reticulum, thus interfering with calcium-mediated smooth muscle contraction [5]. Intravenously administered magnesium sulfate has been reported to be a useful adjunctive therapy for patients with acute asthma refractory to treatment with inhaled ß-agonists [8].

The alpha two selective agonist dexmedetomidine has been shown to be effective in suppressing the coughing and bronchoconstriction induced by airway manipulation. Intravenous dexmedetomidine in doses of 1mcg/kg significantly reduced bronchospasm in asthmatic volunteers [9].

Ketamine is associated with bronchodilation and is considered safe for use in patients with bronchial hyperreactivity. The suppression of the
cough reflex achieved after the use of ketamine is beneficial in patients with asthma [9].

We conducted a prospective randomized study to compare the efficiency of dexmedetomidine, ketamine and magnesium sulphate in attenuating the coughing and bronchoconstriction reflexes in response to the endotracheal tube during emergence from general anesthesia in asthmatic patients.

**Material and Methods**

This study was conducted in Beni Suef University Hospital after approval of the local ethical committee and written informed consent was obtained from all patients.

The study included 45 adult patients with a diagnosis of asthma for at least one year scheduled for elective surgery requiring general anesthesia and endotracheal intubation in the period from January 2013 to March 2015. Exclusion criteria were active wheezes in the preoperative period, recent upper respiratory tract infection in the previous two weeks before surgery, difficult intubation requiring awake or fiberoptic intubation and ASA status III or IV. A detailed history for asthma symptoms, smoking exposure, and asthma medication were collected to detect a possible bias of differences in asthma severity. Patients were randomly allocated into one of three equal groups using computer-generated random numbers table:

- **Group M:** Received magnesium sulphate 20mg/kg during emergence from general anesthesia.
- **Group D:** Received dexmedetomidine 0.5 µg/kg during emergence.
- **Group K:** Received ketamine 0.5mg/kg during emergence.

Patients were instructed not to take any of their regular asthma medicines on the day of surgery.

On arrival to the operating theatre, a peripheral intravenous 20G cannula was inserted. All patients were premedicated with midazolam (1-2mg administered intravenously), and after standard noninvasive monitors (ECG, pulse oximetry, and non-invasive blood pressure monitoring) were applied, patients were pre-oxygenated with 100% oxygen for three minutes. Induction of anesthesia was standardized using propofol (2mg/kg), fentanyl (2 µg/kg), and endotracheal intubation was facilitated by the administration of cisatracurium (0.15mg/kg). Laryngoscopy and tracheal intubation were performed 4min. after the administration of the muscle relaxant to ensure adequate muscle relaxation using a 7.5-mm endotracheal tube for men and 7.0mm for women. Anesthesia was maintained with isoflurane 1-1.5% as guided by the hemodynamic response. Auscultation for wheezing was performed at 2 and 5min. after tracheal intubation by an assessor blinded to the study. The development of bronchospasm after intubation was treated by deepening of the level of anesthesia or selective B2 adrenergic agonist bronchodilator aerosol and auscultation repeated after 2min. to confirm the absence of wheezing. All patients were mechanically ventilated with 100% oxygen at a respiratory rate of 10 breaths/min with a tidal volume of 10 ml/kg body weight.

At the conclusion of surgery and skin closure, isoflurane was shut off and the study drugs administered. All drugs were diluted in 25ml of isotonic saline and administered slowly over a period of 3 minutes by an anesthesiologist blinded to the study. The patients were allowed to recover to assess bronchoconstriction in response to the endotracheal spontaneously and when the patient shows adequate spontaneous breathing attempts, a combination of atropine 0.01mg/kg i.v. And neostigmine 0.05mg/kg was given to reverse the neuromuscular block. The trachea was extubated when the patient showed spontaneous eye opening and adequate motor power. Heart rate and blood pressure were recorded immediately after discontinuation of anesthesia and before administration of the study drugs, after administration of study drug and before extubation and then at 3min after extubation. The chest was auscultated for the occurrence of bronchospasm at the same time intervals. Tube auscultation was performed on both sides of the chest at the fourth Intercostal Space (ICS) in the midaxillary line, the fifth ICS in the midclavicular line, and the second ICS in the parasternal line. The presence of wheezing was determined by a simple yes or no, and no grading was made. Patients who developed bronchospasm after administration of the study drugs were treated with inhaled B2 agonist before removal of the endotracheal tube. Persistent wheezing after extubation was treated with aminophylline 5mg/kg by intravenous infusion over a period of 30 minutes and hydrocortisone 100mg intravenously. The incidence of coughing or gagging in response to the endotracheal tube was recorded. Time to recovery defined as the time interval between the end of surgery and tracheal extubation was also recorded. All the data were collected by a physician not involved in the study and blinded to the protocol.

**Statistical analysis:**

Power analysis showed that for 80% power, a sample size of 39 patients allocated into three
groups would be needed to detect a large effect size (W) of 0.5 in the incidence of wheezing at emergence, using a Chi-Square test of independence in a 3-by-2 contingency table with degrees of freedom = 2 and a significance level (alpha) of 0.05. Estimation of sample size was performed using computer program PASS 11 (NCSS, LLC. Kaysville, Utah, USA. www.ncss.com).

Collected data were presented as mean ± SD, numbers and percentages as appropriate. Categorical variables were analyzed using Chi-square (χ²) test. Continuous variables were tested using One-way Analysis of Variance (ANOVA) with post hoc Tukey test, or mixed-design ANOVA for repeated measures. Statistical analysis was performed using SPSS (Version 20, 2011). p-value <0.05 was considered statistically significant.

Results

The three groups were comparable with regard demographic data including age, sex, duration of asthma and smoking history. There was no statistically significant difference between the three groups concerning operative data including length of surgery, the incidence of wheezing after intubation or the requirement for B₂ agonist for the treatment of bronchospasm after intubation. The heart rate was significantly lower at three minutes after extubation as compared to baseline value before administration of the study drug in the magnesium group, the time to recovery after extubation was significantly shorter in the magnesium group compared to the other two groups. In the dexmedetomidine group, the MAP values were comparable to baseline values immediately before extubation while the values were significantly higher compared to baseline values at three minutes after extubation. In the ketamine group, the heart rate increased significantly immediately before extubation while the values were comparable to baseline values at three minutes after extubation. In the Dexmedetomidine group, there was no significant change in the heart rate values immediately before extubation or at three minutes after extubation. As regard mean arterial blood pressure, the MAP was significantly higher than baseline values immediately before extubation and at three minutes after extubation in both the magnesium and ketamine groups. In the dexmedetomidine group, the MAP values were comparable to baseline values both immediately before extubation and at three minutes after extubation. There was no statistically significant difference between the three groups as regard the incidence of coughing or gagging at extubation. The incidence of bronchospasm during emergence from general anesthesia was significantly lower in the magnesium group as compared to the other two groups. In the dexmedetomidine group, the time to recovery from general anesthesia was significantly shorter compared to the magnesium and ketamine groups.

### Table (1): Demographic data.

<table>
<thead>
<tr>
<th></th>
<th>Magnesium (N=13)</th>
<th>Dexmedetomidine (N=15)</th>
<th>Ketamine (N=12)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>38.2±1.72</td>
<td>38.1±8.78</td>
<td>45.0±13.72</td>
<td>0.115</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>5:8 (38.5%)</td>
<td>5:10 (33.3%)</td>
<td>8:4 (66.7%)</td>
<td>0.165</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>5:8 (38.5%)</td>
<td>5:10 (33.3%)</td>
<td>8:4 (66.7%)</td>
<td>0.165</td>
</tr>
<tr>
<td>Duration of asthma (years)</td>
<td>3.1±0.86</td>
<td>3.2±1.16</td>
<td>4.0±0.85</td>
<td>0.059</td>
</tr>
<tr>
<td>Smoking</td>
<td>3 (23.1%)</td>
<td>2 (13.3%)</td>
<td>4 (33.3%)</td>
<td>0.465</td>
</tr>
</tbody>
</table>

### Table (2): Operative data.

<table>
<thead>
<tr>
<th></th>
<th>Magnesium (N=13)</th>
<th>Dexmedetomidine (N=15)</th>
<th>Ketamine (N=12)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (min)</td>
<td>72.3±13:01</td>
<td>78.7±40:06</td>
<td>76.7±32:28</td>
<td>0.862</td>
</tr>
<tr>
<td>Wheezing after intubation.</td>
<td>4 (30.8%)</td>
<td>2 (13.3%)</td>
<td>2 (16.7%)</td>
<td>0.486</td>
</tr>
<tr>
<td>B₂ agonist</td>
<td>3 (23.1%)</td>
<td>3 (13.3%)</td>
<td>4 (8.3%)</td>
<td>0.572</td>
</tr>
</tbody>
</table>

### Table (3): Changes in heart rate during emergence from anesthesia and extubation in the three treatment groups. Data are presented as mean ± SD.

<table>
<thead>
<tr>
<th></th>
<th>Magnesium (N=13)</th>
<th>Dexmedetomidine (N=15)</th>
<th>Ketamine (N=12)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before study drug</td>
<td>93.3±28.24</td>
<td>98.9±8.56</td>
<td>83.6±22.88</td>
<td></td>
</tr>
<tr>
<td>Before extubation</td>
<td>98.1±26.17</td>
<td>95.8±5.87</td>
<td>108.6±17.42</td>
<td></td>
</tr>
<tr>
<td>3min after extubation</td>
<td>81.6±14.05</td>
<td>96.8±14.48</td>
<td>88.3±13.70</td>
<td></td>
</tr>
</tbody>
</table>

†: Significant difference versus baseline values (p<0.05; repeated measures ANOVA).

### Table (4): Changes in mean arterial blood pressure during emergence from anesthesia and extubation in the three treatment groups. Data are presented as mean ± SD.

<table>
<thead>
<tr>
<th></th>
<th>Magnesium (N=13)</th>
<th>Dexmedetomidine (N=15)</th>
<th>Ketamine (N=12)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before study drug</td>
<td>93.8±11.57</td>
<td>98.3±5.36</td>
<td>81.0±5.58</td>
<td></td>
</tr>
<tr>
<td>Before extubation</td>
<td>121.2±14.4†</td>
<td>98.8±5.92</td>
<td>96.1±8.86†</td>
<td></td>
</tr>
<tr>
<td>3min after extubation</td>
<td>103.1±18.11</td>
<td>98.1±5.18</td>
<td>89.0±7.29†</td>
<td></td>
</tr>
</tbody>
</table>

†: Significant difference versus baseline values (p<0.05; repeated measures ANOVA).

### Table (5): Incidence of coughing and gagging at extubation.

<table>
<thead>
<tr>
<th></th>
<th>Magnesium (N=13)</th>
<th>Dexmedetomidine (N=15)</th>
<th>Ketamine (N=12)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coughing</td>
<td>4 (30.8%)</td>
<td>3 (20%)</td>
<td>3 (25%)</td>
<td>0.806</td>
</tr>
<tr>
<td>Gagging</td>
<td>2 (15.4%)</td>
<td>2 (13.3%)</td>
<td>3 (25%)</td>
<td>0.709</td>
</tr>
</tbody>
</table>

### Table (6): Incidence of bronchospasm during emergence from anesthesia.

<table>
<thead>
<tr>
<th></th>
<th>Magnesium (N=13)</th>
<th>Dexmedetomidine (N=15)</th>
<th>Ketamine (N=12)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheezing before study drug</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Wheezing before extubation</td>
<td>1 (7.7%)*</td>
<td>7 (46.7%)</td>
<td>6 (50%)</td>
<td>0.042</td>
</tr>
<tr>
<td>Wheezing 3min after extubation</td>
<td>0 (0%)*</td>
<td>5 (33.3%)</td>
<td>5 (41.7%)</td>
<td>0.036</td>
</tr>
</tbody>
</table>

*: Significant difference versus other groups (p<0.05; Chi-square test).
Table (7): Time to recovery from general anesthesia.

<table>
<thead>
<tr>
<th></th>
<th>Magnesium (N=13)</th>
<th>Dexmedetomidine (N=15)</th>
<th>Ketamine (N=12)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to recovery (min)</td>
<td>11.8±2.09</td>
<td>8.5±0.92*</td>
<td>12.2±2.04</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*: Significant difference versus other groups (p<0.05; Chi-square test).

Fig. (1): Time to recovery from GA.

*: Significant difference versus other groups p-value <0.05; post hoc Tukey test.

Discussion

Our study showed that IV magnesium sulfate during recovery from general anesthesia significantly reduced the incidence of reflex bronchospasm in response to the endotracheal tube as compared to dexmedetomidine and ketamine while it was less effective than dexmedetomidine in abolishing the increase in blood pressure associated with recovery. The three drugs were equally effective in abolishing the cough and gag reflexes during recovery.

Physiologic responses to the emergence and tracheal extubation include unwanted airway and circulatory reflexes, which result in coughing, laryngospasm, bronchospasm, tachycardia, and hypertension.

The process of contraction and relaxation of the myofibrillar proteins in bronchial smooth muscle cells are the results of phosphorylation and dephosphorylation reactions regulated by specific enzymes and by the intracellular content of calcium [5]. Because bronchial smooth muscle cells possess only one membrane system and a scarce sarcoplasmic reticulum, calcium transport across the cellular membrane is the most important regulator of intracellular calcium content, which is mainly attained by the action of a calcium magnesium-dependent membrane ATPase and by voltage and receptor-operated channels [10]. The enzymes that regulate phosphorylation and dephosphorylation reactions are protein kinases and phosphoprotein phosphatases. Because magnesium is involved in calcium transport across the cellular membrane, which determines intracellular calcium content, magnesium directly or indirectly influences both types of enzymes [10]. Indeed, magnesium sulfate has been shown to relax bronchial smooth muscle by a decrease in intracellular free calcium [12].

Several reports confirmed positive results of magnesium administration in acute airway constriction [13-17] although some studies reported negative results [18-23]. To our knowledge, no previous studies have addressed the effect of magnesium in abolishing the broncho-constrictive and hemodynamic response to the endotracheal tube during emergence from general anesthesia especially in asthmatic patients who are at a higher risk for bronchospasm during recovery due to bronchial hyperreactivity.

Although the precise mechanism responsible for the cardiovascular changes during tracheal extubation remains to be elucidated, multifactorial stimuli during tracheal extubation, including wound pain, emergence from anesthesia, and tracheal irritation, are involved in the events. The beneficial effect of dexmedetomidine on the hemodynamic sequences may be due, in part, to direct cardiac depression and peripheral vasodilation. Extubation irritates airways and causes a cough, which is known to produce hypertension and tachycardia. IV dexmedetomidine suppresses the cough reflex [24]. Dexmedetomidine has been extensively studied in preventing the stress response to laryngoscopy and tracheal intubation [25-28]. However, few studies have addressed its efficacy in preventing emergence hypertension, tachycardia, cough and bronchospasm.

The effectiveness of dexmedetomidine in suppressing the hemodynamic response to the endotracheal tube during emergence from anesthesia has been demonstrated in a number of studies. Seo et al., [29] showed that a single dose of dexmedetomidine at the termination of anesthesia resulted in lower heart rate and blood pressure on emergence as compared to controls. A similar finding was observed in another study by Turan et al., in which a bolus dose of dexmedetomidine 0.5 µg/kg provided more stable hemodynamics and better recovery profile following intracranial surgery [30].

The influence of dexmedetomidine on the cough reflex is less clear. In a recent study by Lee et al., [31] administration of a single bolus dose of dexme-
dotemididine was effective in suppressing the cough reflex and hemodynamic response during recovery from general anesthesia. In contrast, Park et al., found that dexmedotomididine was less effective than remifentanil infusion in attenuating the cough reflex during emergence [32].

Ketamine is an intravenous anesthetic that has long been used as an induction agent in asthmatic patients. Ketamine possesses bronchodilating effect and was found to be effective in both prevention and treatment of wheezing in patients with bronchial hyperreactivity subjected to anesthesia and endotracheal intubation [33]. Ketamine relaxes the smooth muscles of the bronchi and attenuates histamine induced bronchospasm. However, the usefulness of ketamine in preventing bronchospasm during emergence from anesthesia has not been tested before in randomized trials.

Recently, ketamine has been evaluated for suppressing the cough reflex induced by fentanyl. In a study by Guler et al., [34] ketamine 0.5 mg/kg was more effective than lidocaine in suppressing the cough reflex during fentanyl anesthesia. A similar finding was observed in a more recent study which demonstrated that a combination of ketamine and dexmedotomididine was more effective than either drug alone for abolishing fentanyl induced cough [35].

In our study, recovery time was significantly prolonged in patients receiving MgSO4 and those receiving ketamine in comparison to the dexmedotomididine group. The delay in recovery may be due to CNS depressant effect of MgSO4 and ketamine. A narcotic state in human beings undergoing surgical operations was achieved in a study by Peck and Meltzer, [36] who attempted anesthesia by MgSO4 infusion in three patients of hemiophragy. However, Aldrete and Vazeery [37] suggested this was actually a sleep-like state caused by cerebral hypoxia from progressive respiratory and cardiac depression. When ventilation was maintained, even very high level of serum Mg produced no CNS depression.

Conclusion:

In conclusion, our study demonstrates that magnesium sulphate is more effective than dexametomididine and ketamine in attenuating reflex bronchospasm in response to the endotracheal tube during emergence from general anesthesia in asthmatic patients while dexmedotomididine provides a better hemodynamic profile. The three drugs were comparable regarding the incidence of coughing and gagging. Magnesium can be used safely to prevent reflex bronchospasm during recovery from general anesthesia in asthmatic patients although it is associated with some delay in recovery. Magnesium is a cheap and safe drug without known serious side effects that may serve as an adjunct to standard treatment in bronchial hyperreactivity.

Conflict of interest:

No conflict of interest declared.

References


12- KUMASAKA D., LINDEMAN K.S., CLANCY J., LANDE B., CROXTON T.L. and HIRSHMAN C.A.
Magnesium is More Efficient than Dexmedetomidine or Ketamine as a Prophylaxis


الملخص العربي

الخلاصة: يواجه أطباء التخدير مشاكل متعددة أثناء التعامل مع مرضى الربو وخاصة عندما تكون هناك حاجة للتنبيث الرغامي حيث يشكل التشنج القصبي خطراً وذلك لزيادة حساسية الممرات الهوائية. وتتوفر تقنيات يمكن الاعتماد عليها لتحسين تحمل الأنثوبية الحنجورية مع تسهيل الإفراقة السريعه والكاملة من التخدير العام يكون من المرغوب فيه وخاصة في المرضى الذين يعانون من فرط تفاعل الشعوب الهوائية.

الطريقة: تم تصميم هذه الدراسة لمقارنة تأثير المغنيسيوم مع كل من الديكسيدوميدين والكيتامين في تخفيض تأثير الأنثوب الرغامي أثناء الإفراقة من التخدير العام. تم إعطاء خمسة وأربعين مريضاً يعانون من الربو في الدراسة. تم تقسيم المرضى عشوائياً لتلقى إما كبريتات المغنيسيوم 20 ملغ/كغ أو الديكسيدوميدين 5 ملغم/كغ أو الكيتامين 5 ملغ/كغم خلال التخدير العام. تم تسجيل حدوث التشنج القصبي قبل اعطاء أنثوية الدراسة، بعد إعطاء أنثوية الدراسة بعد نزع الأنثوب. كما تم تسجيل ديناميكا الدم، حالات السعال والإسكات والوقت اللازم لتحقيق الإفراقة.

النتائج: كان التشنج القصبي خلال الإفراقة من التخدير العام أقل بكثير في مجموعة المغنيسيوم بالمقارنة مع المجموعتين الأخريتين. في مجموعة الديكسيدوميدين، كان وقت التعليفات من التخدير العام أقصر بكثير بالمقارنة بكل من مجموعة المغنيسيوم ومجموعة الكيتامين. لم يوجد فرق كبير بين المجموعات المدروسة من حيث حدوث السعال أو الإسكات عند نزع الأنثوب.

الاستنتاج: المغنيسيوم هو أكثر فعالية من كل من الديكسيدوميدين والكيتامين في الحد من حدوث التشنج القصبي ردًا على الأنثوب الرغامي خلال التخدير العام في مرضى الربو على الرغم من أنه يصاحبه بعض التأخير في وقت الإفراقة. وكانت العقاقير الثلاثة مماثلة بشأن حدوث حالات السعال والإسكات.