Original Article

Assessment of Severity of Methaemoglobinemia Following Fibreoptic Bronchoscopy with Lidocaine

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ABSTRACT

Background. Lidocaine is commonly used for topical anaesthesia during fibreoptic bronchoscopy (FOB) and it can cause methaemoglobinemia. The present study was undertaken to evaluate the severity of post-bronchoscopy methaemoglobinemia while using lidocaine as a topical anaesthetic agent.

Methods. We prospectively studied consecutive adult patients who underwent diagnostic FOB in our institution. Blood methaemoglobin levels were estimated by co-oximetry before bronchoscopy and one hour after first instillation of lidocaine. Occurrence of symptoms suggestive of mild methaemoglobinemia (*i.e.*, fatigue, palpitation, dizziness, nausea and headache) were recorded in a severity scale before collection of post-bronchoscopy blood samples.

Results. A total of 48 adult patients were enrolled in this study. The mean amount of lidocaine used for bronchoscopy during this study was 7.4±1.4mg/kg body weight. The mean pre- and post-bronchoscopy methaemoglobin levels were 0.44mg/mL and 0.80mg/mL, respectively. After bronchoscopy, severe and very severe symptoms were reported by 2.1% to 10.4% patients. However, severities of the symptoms were unrelated to post-bronchoscopy methaemoglobin level or the amount of lidocaine used during the FOB.

Conclusions. Blood methaemoglobin levels following FOB remained within the physiological limits when British Thoracic Society recommended dose of lidocaine was used. However, few patients had symptoms similar to mild methaemoglobinemia after FOB. **[Indian J Chest Dis Allied Sci 2011;53:211-214]**

Key words: Methemoglobin, Lidocaine, Bronchoscopy.

INTRODUCTION

Local anaesthetic agents are used during fiberoptic bronchoscopy (FOB) for topical anaesthesia of the upper and lower respiratory tracts. These agents increase the comfort of patient and decrease cough during the procedure. Benzocaine is a potent oxidising agent and its use for FOB was associated with infrequent but fatal complications of methaemoglobinemia. Hence, lidocaine has replaced benzocaine as the local anaesthetic agent of choice for FOB.[1] Lidocaine is administered as gel and 1% to 4% solution. It is rapidly absorbed following intra-tracheal and endobronchial administration and can cause methaemoglobinemia during FOB.[2] Lidocaine-induced methaemoglobinemia especially when used with benzocaine have been documented earlier.[1,3-5]

Therefore, we planned a study to evaluate the severity of methaemoglobinemia after FOB when lidocaine is used as a topical anaesthetic agent.

MATERIAL AND METHODS

We prospectively studied consecutive adult patients who underwent diagnostic FOB without sedation in our institution from July 2009 to February 2010. Patients taking medications known to cause methaemoglobinemia were excluded from the study. A written informed consent was taken from all the patients.

The patients were instructed to remain in the fasting state for at least six hours prior to the procedure. No pre-medication or sedation were administered during FOB. Before instillation of lidocaine, venous blood samples were collected and co-oximetry was performed with Avoximeter 4000® (A-Vox Systems Inc, Texas USA).

During FOB, oropharynx and hypo-pharynx were sprayed with 15% lidocaine and 4% lidocaine was instilled inside the nostril. The tip of bronchoscope was lubricated by 2% lidocaine jelly and vocal cords

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were anesthetised by 4% lidocaine. Carina and tracheobronchial tree were anesthetised by spraying 2% lidocaine through the working channel. If required, additional 2% lidocaine was instilled in the peripheral airways during the procedure. Supplemental oxygen was administered during the bronchoscopy as and when required basis. After bronchoscopy, blood samples were collected one hour after the first instillation of lidocaine spray and co-oximetry was performed. The percentages of methaemoglobin levels were expressed in absolute values to calculate the absolute increase in methaemoglobin levels.

Demographic profiles of the patients, indication for FOB and amount of lidocaine used during FOB were recorded. Occurrence of symptoms suggestive of mild methaemoglobinemia (*i.e.*, fatigue, palpitation, dizziness, nausea and headache) were recorded before collection of post-bronchoscopy blood samples. The bronchoscopy technician recorded the severity of these symptoms using a severity scale (none, mild, moderate, severe and very severe). Hindi translations of this questionnaire were used during this study.

Statistical Analysis

Normally distributed data were presented as mean±standard deviation and non-normally distributed data were presented with mean and standard error of mean (SEM). Chi-square test was used to compare methaemoglobin level and severity of symptom score. Pearson's rank correlation coefficient was used to assess the univariate relationship between blood methaemo-globin level and lidocaine. A value of $p<0.05$ was considered significant. The statistical analysis was done using Statistical Package for the Social Sciences (SPSS)-version 9.0 (USA).

RESULTS

Forty-eight consecutive adult patients were enrolled in this study. Their mean age was 52.3±12.5 years; there were 39 males (81%). The average haemoglobin level of study population was 11.2±1.7g/dL%. The mean±SEM methaemoglobin level in the blood before FOB was 0.44±0.05mg/mL (range 0 to 1.32). Corresponding value for post-bronchoscopy was 0.80±0.07mg/mL (range 0.135 to 1.97). The increase of methaemoglobin level in blood one hour after instillation of first dose of lidocaine was 0.36±0.04mg/mL. The mean time interval between the collections of two blood sample was 59.3±3.8 minutes.

The mean amount of lidocaine used for FOB during this study was 7.4±1.4mg/kg of body weight. No statistically significant positive correlation was found between post-bronchoscopy increase in blood methaemoglobin and the amount of lidocaine used (Figure 1). One hour after first instillation of lidocaine, 45.8% to 72.9% subjects reported no symptoms (fatigue 54.2%, palpitation 45.8%, dizziness 79.2%, nausea 45.8% and headache 72.9%). The incidences of mild and moderate symptoms were varied from 16.7% to 50% (fatigue 37.5%, palpitation 43.8%, dizziness 16.7%, nausea 50% and headache 25%). Severe and very severe symptoms were reported by 2.1% to 10.4% (fatigue 8.3%, palpitation 10.4%, dizziness 4.2%, nausea 4.2% and headache 2.1%) subjects. Symptom severity scores for fatigue, palpitation, dizziness, nausea and headache are shown in figure 2. No additional treatment was required for any of these post-bronchoscopy symptoms.

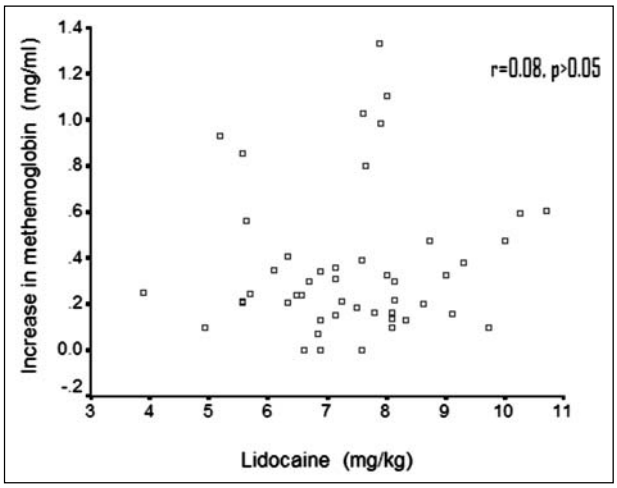

Figure 1. Scatter plot of lidocaine used during bronchoscopy and absolute rise of methaemoglobin level.

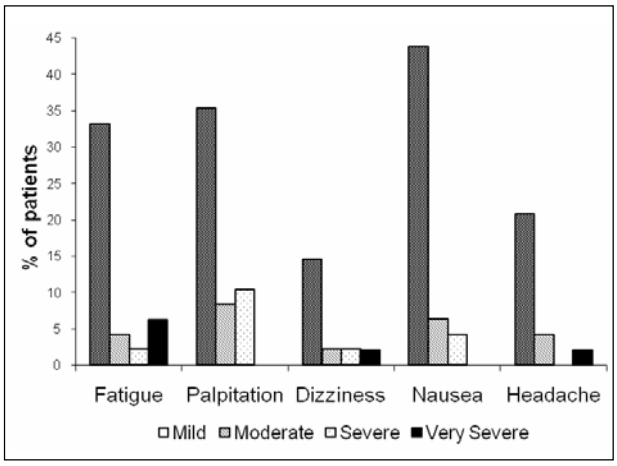

Figure 2. Symptoms severity scores one hour after the first dose of lidocaine instillation.

There was no significant difference in symptom severity scores between the amounts of lidocaine used or post bronchoscopy methaemoglobin to normal haemoglobin ratio was observed. Gender of the subjects also had no relationship with the severity of symptom scores.

DISCUSSION

In this study, we evaluated the severity of post-bronchoscopy methaemoglobinemia with lidocaine as a topical anaesthetic agent. Methaemoglobinemia is an uncommon, but potentially fatal haemo-globinopathy. It results from oxidation of haeme iron moieties of the haemoglobin tetramer from ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state. This auto-oxidation of haemoglobin occurs in normal physiological process. But reductive metabolic pathways, *i.e.* nicotinamide adenine dinucleotide (NAD)-dependent cytochrome b5 reductase enzyme system, methaemoglobin reductase and nicotinamide adenine dinucleotide phosphate (NADPH) directly reduce the ferric haemoglobin to ferrous haemoglobin. The causes of methaemoglobinemia are either hereditary or acquired. Hereditary methaemoglobinemia is rare and is caused by either a homozygous deficiency of NADH-methaemoglobin reductase or the presence of haemoglobin variant, such as haemoglobin M. The acquired forms of methaemoglobinemia are due to exposure to oxidising agents in a quantity that overwhelms the reductive metabolic processes. A wide variety of agents including drugs, *i.e.* acetaminophen, sulfonamide, chloroquine, phenytoin, nitrate etc induce methaemoglobinemia.[1] Lidocaine occasionally causes methaemoglobinemia in unusually susceptible individuals. But, the mechanism of increased individual susceptibility to lidocaine is not clear and probably most common cause is heterozygous form of NADH-methaemo-globin reductase deficiency.[6]

The methaemoglobin can not bind with oxygen and in addition it shifts the oxygen dissociation curve towards left and further decrease tissue oxygen delivery by the remaining normal haemoglobin. Normal methaemoglobin in blood is less than 1.5% of the total haemoglobin (<2.4mg/mL).[7] Depending upon reductase activity, excessive nitrate concentration in drinking water can cause severe methaemoglobinemia (7%-27%) in healthy individuals.[8] Methaemoglobin level in Indian population may be variable due to variable nitrate content of drinking water and adaption of cytochrome b5 reductase activity. Smoking can cause methaemoglobinemia, but the effects of smoking on blood methaemoglobin levels are variable across the studies.[9,10]

Clinical symptoms and signs of methaemo-globinemia depend on the ratio of methaemoglobin to total haemoglobin. Central cyanosis usually occurs with methaemoglobin concentrations greater than 15%, though it can occur with level as low as 2.5% in anaemic individuals.[1] When methaemoglobin level reaches to 20% to 30%, patients develop fatigue, anxiety, light headache, dizziness, nausea, vomiting and tachycardia.[11] These symptoms are due to decreased tissue oxygenation. Higher blood methaemoglobin level may cause generalised seizures, coma, arrhythmias, haemodynamic instability and the level of 70% is usually fatal. In the absence of serious underlying illness, when the offending agent is removed and oxygen is administered, methaemoglobinemia less than 30% usually resolve spontaneously over 15 to 20 hours. The treatment of acute methaemoglobinemia is determined by the level of methaemoglobin and the presence or absence of symptoms.

Lidocaine is a tertiary amide derivative of diethylaminoacetic acid. Plasma level of lidocaine reaches peak within 15 minutes of application to larynx and trachea and within five minutes when instilled in distal airways.[11] Plasma half-life of lidocaine varies from 70 to 110 minutes in healthy adults. During the bronchoscopy, variable amount of lidocaine is either aspirated or cough out by the patients, and thus, all the administered lidocaine does not reaches into systemic circulation. Absorption of lidocaine gel is limited, and thus, lidocaine gel used during bronchoscopy have little influence on peak serum concentration.[12] Systemic adverse effects of lidocaine are due to involvement of central nervous system (CNS), cardiovascular system and gastrointestinal (GI) tract. Except for GI system, the adverse effects are dosing related.[11] At low serum concentration, CNS toxicity symptoms, *i.e.* nervousness, tingling sensation, tremor, dizziness, nausea appear and these symptoms may mimic the symptoms of mild methaemoglobinemia.

British Thoracic Society (BTS) guidelines[13] recommend that total dose of lidocaine during bronchoscopy in adults should be limited to 8.2 mg/kg. However, Frey *et al*[14] reported that use of lidocaine at a dosage higher than the BTS recommended dose (>12mg/kg) during FOB does not cause toxic serum lidocaine level or toxicity symptoms and methaemoglobinemia. Ameer *et al*[15] failed to observe any serious lidocaine toxicity symptoms during bronchoscopy with toxic serum levels of lidocaine (>5µg/mL). The amount of lidocaine used in our study was 7.4±1.4mg/kg and this was within the BTS recommended dose for bronchoscopy. Post-bronchoscopy symptoms scores in our study were not related to the amount of lidocaine used during the procedure. In a retrospective cohort study, post-operative methaemoglobinemia (2.2%-18%) was observed with subcutaneous administration of lidocaine (13±3.1mg/kg) in 20% infants.[16] Whereas, in a study where intravenous lidocaine was used in 40 patients with arrhythmias failed to show clinically significant elevated level of methaemoglobin.[17] *To the best of our knowledge*, no study has evaluated the severity of methaemoglobinemia after FOB while

using lidocaine in BTS recommended dose. In the present study, pre-bronchoscopy methaemoglobin was undetectable in five cases (10.4%) and post-bronchoscopy methaemoglobinemia varied from 0.1% to 1.5%, except in one case. We failed to observe any significant correlation with the amount of lidocaine used for bronchoscopy and increment of methaemoglobin level after FOB. This is possibly due to variable absorption of lidocaine from mucous membrane and individual susceptibility to lidocaine induced methaemo-globinemia.

In the present study, 2.1% to 10.4% patients reported severe and very severe symptoms after FOB with palpitations being the most common symptom. However, symptoms severity scores were unrelated to post-bronchoscopy methaemoglobin level or the amount of lidocaine used during the bronchoscopy. If FOB is performed under sedation, 35 to 60 minutes wake up time is necessary to make the patient alert enough to assess their discomfort and these discomforts are often masked by the sedatives used.[17] Frey *et al*[14] administered questionnaire two hours after bronchoscopy with conscious sedation and observed mild dizziness and headache in 11.8% and 1% cases, respectively. We performed FOB without any pre-medication or sedation and apparently high incidence of severe post-bronchoscopy symptoms were possibly due to the absence of amnestic effects of sedatives and early administration of questionnaire.

The BTS guidelines recommend[15] that all patients should have pulse oximetry during bronchoscopy and supplemental oxygen should be administered to maintain the arterial oxygen saturation at or above 90%. Pulse oximeter uses only two different wavelengths of light and it cannot distinguish deoxyhaemoglobin from methaemoglobin. In presence of methaemoglobin, pulse oximeter gives erroneous result, and thus, pulse oximeter is not useful to detect methaemoglobinemia during bronchoscopy. The co-oximeter measure the relative absorbance at four different wavelengths of light and thus able to differentiate methaemoglobin from carboxyhemoglobin, oxyhaemoglobin, and deoxy-haemoglobin. Methaemoglobinemia during FOB can be suspected in presence of cyanosis with low oxygen saturation on pulse oximetry and a normal partial pressure of oxygen and saturation in arterial blood gas analysis. However, before initiating the treatment, diagnosis of methaemoglobinemia must be confirmed by co-oximetry.

In conclusion, our study showed that post-bronchoscopy methaemoglobin level remained within the normal level while using lidocaine in BTS recommended dose. If no sedatives are used during the bronchoscopy, patient may have complaints similar to mild methaemoglobinemia after the procedure. These symptoms are unlikely due to methaemoglobinemia or lidocaine toxicity unless the patient was receiving any oxidising medicines or the use of lidocaine exceeded the recommended dose.

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