The comparability of Second dose Thiopental with Lidocaine in The attenuation of Cardiovascular response to Endotracheal intubation

A Honarmand, MR Safavi

Department of Anesthesiology and Intensive Care, Isfahan University of Medical Sciences, Isfahan, Iran

Background: This study was carried out to appraise the usefulness of second dose thiopental for hemodynamic response to laryngoscopy and intubation.

Patients and Methods: The present study comprised 120 patients aged 15 to 65 years who were divided into four groups each of 30 patients. Patients in each group were given 2 µg/kg fentanyl iv, 4 mg/kg thiopental for induction of anesthesia, followed by 0.5 mg/kg atracurium for muscle relaxation and a second dose of thiopental (1mg/kg in group I, 2mg/kg in group II) immediately prior to laryngoscopy and intubation, lidocaine 1.5 mg/kg (group III) or normal saline 5 ml (group IV) 2 minutes prior to laryngoscopy and intubation. The heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), and rate pressure product (RPP) were determined before induction of anaesthesia and laryngoscopy (baseline), and at 1min (T1), 3min(T3), 5min(T5), and 10min (T10) after laryngoscopy and intubation.

Results: Our findings demonstrated similar effects of lidocaine and second dose thiopental 2mg/kg on attenuation of DAP, MAP, RPP, and HR changes at 1, 3, and 5 min after endotracheal intubation (EI).

Conclusions: Second dose thiopental can be employed as a substitute for lidocaine in attenuation of cardiovascular response to intubation in patients devoid of ischemic heart disease.

Key words: Thiopental, Lidocaine, Intubation, Cardiovascular Response.

Introduction

Intubation with direct laryngoscopy, in the majority of practiced hands and under standard circumstances, is still coupled with a number of impending stresses. The pressor response to laryngoscopy and intubation produced by impulse augmented in both sympathetic and sympathoadrenal activity poses possible threats of myocardial ischemia, myocardial failure and cerebral hemorrhage in critically ill patients. A large array of pharmacological agents was employed to attenuate the hemodynamic responses similar to opioids. Whether endotracheal intubation is actually painful, is not recognized, but the reality is that basic physiological measurements appear to be positively impacted by premedication and indicate that careful use of an analgesic/anaesthetic agent throughout endotracheal...
intubation is of possible benefit. Thiopental is one such agent and its pharmacological effects impede the pain pathways. It almost certainly operates throughout the gamma aminobutyric acid (GABA) receptor complex type A,\(^\text{11}\) the most important inhibitor neurotransmitter of the mammalian central nervous system. Ebegue et al. showed that the second dose thiopental method significantly attenuated the post-intubation increase in heart rate (HR), systolic arterial pressure (SAP) and rate pressure product (RPP).\(^\text{12}\) Lidocaine hydrochloride, an aminoethylamide local anesthetic and class ΙΒ antidysrhythmic agent, is a satisfactory agent for attenuation of cardiovascular response to intubation.\(^\text{13}\) Kyokong et al, demonstrated that 1.5 mg/kg lidocaine administered intravenously 2 min prior to intubation may perhaps attenuate the cardiovascular response to laryngoscopy and intubation.\(^\text{14}\) Conversely there was no study comparing the effects of intravenous lidocaine and second dose thiopental in attenuating the noxious stimuli by laryngoscopic intubation. In the current study, we assessed the efficacy of second dose thiopental with intravenous lidocaine for attenuating cardiovascular responses to laryngoscopy and intubation.

**Patients and Methods**

This randomized, double-blind study consisted of 120 patients, ASA status I–II, aged 15–65 years, planned for elective surgeries in the departments of abdominal surgery, gynecology or otolaryngology. The study was supported by the Institutional Review Board and written informed consent was obtained from every patient prior to participation in the study. Exclusion criteria comprised patients with a heart rate<70 beats/min, cardiac disease, pulmonary disease, diabetes, hypertension (systolic blood pressure of>160 mmHg and/or diastolic blood pressure of>95 mmHg as described by the World Health Organization, hepatic, gastrointestinal or renal disease, morbid obesity, history of drug or alcohol abuse, difficult airway, coagulation disorder and patients on α or β blockers. Morbid obesity was identified as a body mass index (BMI)>35 kg.m² and difficult airway was limitation of mouth opening less than two fingers, thyromental distance less than 6 cm, and modified Mallampati test grade III or more . No premedication was prescribed. On entrance in the operating room an iv infusion of 7 ml/kg of Lactated Ringer's solution was initiated. Usual monitoring was done consisted of arterial blood pressure (AP), an electrocardiogram (ECG) and oxygen saturation (SpO2). The AP was determined automatically and recorded with an automated non-invasive AP monitor. Heart rate (HR) was monitored by ECG. Patients were arbitrarily allocated to one of four groups each of 30 patients by computer-generated randomization. The baseline blood pressure and heart rate (B) were documented subsequent to a resting period of 5 min, and preoxygenation was then provided. One minute after taking baseline blood pressure, patients in each group were prescribed 2 µg/kg fentanyl iv, 4 mg/kg thiopental for induction of anaesthesia, followed by 0.5 mg/kg atracurium for muscle relaxation and a second dose of thiopental (1mg/kg in group I, 2mg/kg in group II) immediately prior to laryngoscopy and intubation. The group III and IV received thiopental 4 mg/kg
for induction of anaesthesia, fentanyl 2µg/kg, atracurium 0.5 mg/kg for muscle relaxation, lidocaine 1.5 mg/kg (group III) or normal saline 5 ml (group IV) 2 minutes before performing laryngoscopy and intubation. The study drugs encoded and enclosed in a similar wrapping were ordered by a physician who was blinded to their identities. The endotracheal tube cuff was inflated gradually. Systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), heart rate (HR), and rate pressure product (RPP), ECG in lead II, SpO2 and EtCO2 were recorded after induction and immediately prior to laryngoscopy (BL), at 1 min (T1), 3 min (T3), 5 min (T5), and 10 min (T10) after endotracheal intubation (EI) by another independent anesthesiologist. Every intubation was performed by an MD anesthesiologist and was completed in 20s. None of the patients were given topical lidocaine before placement of tracheal tube. Subsequent to tracheal intubation, ventilation was controlled with 50% nitrous oxide in oxygen and 1.2 % isoflurane. EtCO2 was kept at 33–40 mmHg throughout surgery. Following termination of surgery, the remaining neuromuscular blockade was reversed with neostigmine 0.05 mg/kg and atropine 0.02 mg/kg. The incidence of any arrhythmias, hypertension (diastolic blood pressure>110 mmHg), and RPP>20000 mmHg/min was also recorded. The rate-pressure product was computed by multiplying the systolic blood pressure by the heart rate. Rate-pressure product was monitored as values larger than 20000 mmHg has been demonstrated to associate with angina and myocardial ischemia. According to earlier study, a sample-size approximation pointed out that 30 patients per group would provide a power of 80% at a level of 0.05 for identifying 30% attenuation in the post-intubation increase in heart rate. Data are stated as mean ± standard deviation (SD). The pre-induction values, the values of the hemodynamic variables throughout and subsequent to intubation and the changes in the hemodynamic variables produced by EI were analyzed with one-way factorial ANOVA with Scheffe’s F post hoc test. Chi-squared test or Fisher’s exact test, when proper, was utilized for categorical data. P<0.05 was deemed as statistically significant.

Results

Demographic variables of patients and the length of surgery were comparable between the four groups (Table 1). The blood pressure (SAP, DAP, MAP), RPP, and HR are expressed as mean ± SD and the baseline values of SAP, DAP, MAP, RPP, and HR were comparable in four groups (Fig. 1a-e). SAP, DAP, MAP, RPP, and HR were not significantly different among the four groups after each of the prescribed drugs and immediately prior to laryngoscopy (Fig. 1a-e). Induction time (time from administration of induction drugs till initiation of laryngoscopy), apnea duration (from removal of mask ventilation to the institution of mechanical ventilation), and duration of laryngoscopy were comparable between the groups (Table 1). There was no significant difference among the four groups in ratio of minimum SPO2 to maximum heart rate (MinSPO2/MaxHR) during laryngoscopy (Table 1). As figure 1a and figure 1c shows, compared with group IV, rising values in SAP or MAP were significantly attenuated till 3 min after EI in group II and 5 min in
Table 1. Demographic characteristics, operation time and minSPO2/maxHR of patient

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>16/14</td>
<td>13/17</td>
<td>12/18</td>
<td>17/13</td>
</tr>
<tr>
<td>ASA (I/II)</td>
<td>Mean(SD)</td>
<td>28.5 (10.3)</td>
<td>28.5 (7.0)</td>
<td>28.9 (7.6)</td>
</tr>
<tr>
<td>Age (ys)</td>
<td>Mean(SD)</td>
<td>69.6 (5.3)</td>
<td>68.0 (7.8)</td>
<td>69.3 (8.7)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Mean(SD)</td>
<td>168.2 (5.2)</td>
<td>170.1 (3.8)</td>
<td>168.2 (3.9)</td>
</tr>
<tr>
<td>Surgical time (min±SD)</td>
<td>74.2 (7.0)</td>
<td>75.5 (7.5)</td>
<td>73.8 (7.7)</td>
<td>75.2 (7.1)</td>
</tr>
<tr>
<td>MinSPO2/MaxHR</td>
<td>0.91(0.13)</td>
<td>0.92 (0.11)</td>
<td>0.93 (0.15)</td>
<td>0.91 (0.14)</td>
</tr>
<tr>
<td>Induction time (sec)</td>
<td>113.3 (3.3)</td>
<td>115.1 (2.9)</td>
<td>113.7 (3.1)</td>
<td>113.9 (3.2)</td>
</tr>
<tr>
<td>Apnea duration (sec)</td>
<td>11.7 (2.2)</td>
<td>12.0 (1.7)</td>
<td>11.8 (1.1)</td>
<td>12.4 (1.6)</td>
</tr>
<tr>
<td>DOL (sec)</td>
<td>9.5 (1.2)</td>
<td>9.1 (1.0)</td>
<td>9.2 (0.9)</td>
<td>9.1 (1.4)</td>
</tr>
</tbody>
</table>

MinSPO2/MaxHR = Ratio of minimum spo2 to maximum heart rate during laryngoscopy; DOL= Duration of laryngoscopy.
No significant difference among groups.

After EI from the baseline value is shown in Figure 2a-e. At T1 and T3, SAP, MAP, and RPP changes were significantly less in group II and III compared with group IV (P<0.05). There was no significant difference between group II and III in SAP or RPP changes after EI compared with baseline. At all times after EI, SAP changes were less, but not statistically significant, in group of patients receiving thiopental 1 mg/kg compared with placebo. DAP changes after EI was significantly less in group III compared with the other groups at T1 (P<0.05). HR changes was significantly less in group I, II, and III compared with group IV at T1, T3, and T5 (P<0.05). HR changes in group I was significantly less (P<0.05) than that of group IV at T1, T3, and T5 (Fig. 2e).
Premature ventricular contraction (PVC) during laryngoscopy and intubation in groups I and IV respectively ($P<0.0001$). Arrhythmia was spontaneously vanished within few minutes. There was no case of PVC in group II or III. There were four cases of hypertension in group I, two in group II, three in group III, and seven in group IV ($P<0.0001$). Hypotension, bradycardia, RPP > 20000 mmHg/min and ST depression were not found in any of the groups.
Discussion
Our study compared the efficacy of second dose of thiopental 2 mg/kg iv immediately before laryngoscopy and lidocaine 1.5 mg/kg iv 2 minutes prior to laryngoscopy and intubation for managing hemodynamic responses. We noticed the comparable lidocaine and second dose thiopental effects in attenuation of DAP, SAP, MAP, RPP, and HR changes at 1, 3, and 5 min subsequent to EI. Direct laryngoscopy and tracheal intubation lead to increasing blood pressure and heart rate. Mechanism of cardiovascular response to intubation is presumed to be a reflex sympathetic response to the mechanical stimulation of larynx and trachea. Reflex changes in the cardiovascular system subsequent to laryngoscopy and intubation result in increase in blood pressure.
by 40-50% and rise in heart rate by 20%. Significant rises in serum levels of norepinephrine and epinephrine following laryngoscopy with and without tracheal intubation have been reported. A variety of anesthetic methods and drugs are accessible for controlling the hemodynamic response to the laryngoscopy and intubation. The technique or drug of choice rests on the necessity and duration of operation, choice of anesthetic technique, route of administration, medical circumstance of the patient. Ever since 1960, lidocaine has been centered on reducing cardiovascular response to intubation. Abou-Madi et al. advocated lidocaine 1.5 mg/kg iv for prophylaxis prior to intubation. The consequence of lidocaine administration on attenuation of cardiovascular response to laryngoscopy and intubation was also demonstrated by Kyokong and colleagues. In a meta-analysis was performed by Zed et al. on possible advantages of lidocaine in attenuating the noxious stimuli made by laryngoscopic intubation. 25 studies were included with eight showing successful attenuation of both BP and HR, seven demonstrating advantage to BP but not HR, and ten did not show any advantage of lidocaine over either BP or HR. Four studies indicated reduced post-intubation dysrhythmias in patients premedicated with intravenous or aerosol lidocaine prior to intubation. Our study, demonstrated the efficacy of lidocaine in blunting the pressor response to intubation.

The mechanism underlying the attenuation of hemodynamic response to laryngoscopic intubation by thiopental is due to its sedative-hypnotic effect on GABA receptor. The standard effect of thiopental on central nervous system (CNS) neurophysiologic system is augmentation of the synaptic actions of inhibitory neurotransmitters and blocking of the synaptic actions of excitatory neurotransmitters. Whether or not the hemodynamic response to the laryngoscopy is due to pain has not been established. Nevertheless the alleviation by analgesic drugs could explain its possible relationship. Thiopental has effect hyperalgesic on pain that is explicated by such comparable mechanism. One more probable justification of the therapeutic result of thiopental is elimination by the drug of the anti-vagal reflex and sympathetic responses to handling of the oropharynx during intubation. Intubation triggers vagal parasympathetic reflexes by means of stimulation of vagal afferent fibers in the pharynx, esophagus, and the respiratory tract, which, in turn, may cause reflex sinus bradycardia. Increased sympathoadrenal activity has been hypothesized as the cause of hypertension during laryngoscopy and intubation. This may well be ascribed to mechanical reflexes provoked by pressure on the root of the tongue and epiglottis, most likely by means of stimulation of the epipharyngeal and laryngopharyngeal area. Stimulation of this region is known activate cervical sympathetic efferent fibers. Bhutada et al. demonstrated that the heart rate and blood pressure of infants premedicated with thiopental are kept closer to baseline values than those without premedication. A study performed by Ebegue et al. demonstrated the effect of the second dose thiopental on cardiovascular response to intubation. They compared the second dose thiop-
with placebo immediately prior to the laryngoscopy and intubation and showed significant attenuation of the post-intubation increase in HR, SAP, and RPP. Our study showed that second dose thiopental 2 mg/kg significantly inhibited not only a rise in HR, SAP, and RPP after EI, but also an increase in MAP and DAP. This demonstrates the advantage of lower dosage of second dose thiopental over higher dosing in attenuating the cardiovascular response to EI. The effect of lidocaine on attenuation of rising SAP, MAP, RPP, and HR lasted for 5 min after intubation. Lidocaine’s effect on blunting DAP elevation continued for 3 minutes after laryngoscopy. Compared with second dose thiopental 2 mg/kg, the effect of lidocaine on these pressor responses, except for RPP and HR, was prolonged, which is most likely due to their pharmacokinetic properties. The effect of thiopental, an ultrashort acting barbiturate, appears after 10-30 s and persisted for about 5-8 min. The onset of action of intravenous doses of lidocaine is instant and duration of effect is about 10-20 min. Blood pressure starts to rise after 15s of laryngoscopy and becomes maximal 30-45 s after direct laryngoscopy. This demonstrates that the peak effect of the second dose of thiopental or iv lidocaine is at maximal pressor response to laryngoscopy. A more prolonged action of iv lidocaine persisted until 5 min after EI. Our study was demonstrated that comparable with lidocaine, the second dose thiopental 2 mg/kg significantly reduced SAP, MAP, and RPP changes for 3 min after EI. Compared with placebo, HR changes were significantly decreased after the second dose thiopental 2 mg/kg until 5 min after EI. The decreasing effects of thiopental on HR were longer than lidocaine by 3 min after EI. Additionally, the second dose thiopental 1 mg/kg iv immediately prior to laryngoscopy significantly reduced HR changes after EI compared with the placebo for 5 min after EI. This explains why in comparison with placebo, the second dose thiopental 1 or 2 mg/kg is effective in blunting HR response to laryngoscopy and intubation. This elucidated the inhibitory effect of thiopental on sympathetic response to the laryngoscopy. On the other hand, some patients in thiopental and lidocaine groups developed hypertension subsequent to EI which was not statistically significant. More prominently, there was significant difference between the numbers of patients in placebo group who developed hypertension and those of the other three groups. This confirms that lidocaine or second dose thiopental inhibits hypertension which probably takes place subsequent to EI. The serum concentrations of norepinephrine or epinephrine during laryngoscopy and intubation were not determined in our patients.

The data obtained in this prospective randomized placebo controlled trial support the assumption that patients treated with lidocaine or second dose of thiopental (2mg/kg) before laryngoscopy kept the hemodynamic indices close to baseline values. The effect of thiopental on cardiovascular response to laryngoscopy in patients with ischemic heart disease is an attractive issue for future studies. In addition, it is worth to compare the second dose thiopental with such agents as opioids.
Acknowledgements

This work was financially supported by Vice Chancellor for Research of Isfahan University

References

16. Stoelting RK. Circulatory changes during direct laryngoscopy and tracheal intubation: influence of duration of laryngoscopy with or without prior lidocaine. Anesthesiology 1997;47:381-4. [900548]