INTRODUCTION

Various narcotic drugs like morphine, fentanyl, alfentanil, sufentanil and ramifentanil have been tried for attenuation of pressor response associated with laryngoscopy and tracheal intubation. A linear relationship exists between increasing the opioid dose and cardiovascular response reduction. Tramadol is a novel central acting analgesic and has been used both for intraoperative and postoperative pain relief. In cats, it reduces the MAC of sevoflurane when compared with saline solution. However, its effect on the haemodynamic response following laryngoscopy and tracheal intubation is less explored. Pang et al. showed that 3 mg/kg tramadol showed lesser attenuation of haemodynamic parameters compared to 3 μg/kg fentanyl following tracheal intubation after thiopentone induction. A variable concentration of sevoflurane is also used to supplement induction and offers haemodynamic advantages of depression of baroreflex function to a greater extent than other inhalational agents like isoflurane. This effect is additive to suppression of haemodynamic response and has generally not been measured in studies. Inhalational anaesthetics have been previously used as a pharmacological method for attenuating the intubation response. End tidal concentration of inhalational anaesthetics was not monitored in these studies and current monitors can now reliably measure the end tidal concentration of delivered agents.

The objective of this study was to compare the effects of a single tramadol bolus 2 mg/kg on the haemodynamic response to intubation compared to a placebo following standardized induction with thiopentone, atracurium and one MAC (2%) sevoflurane.

METHODOLOGY

Institutional ethical committee approval was taken for this prospective randomized controlled trial. Thirty four ASA grade I, II and stable III patients of either gender, aged between 18 to 65 years, scheduled for surgery under general anaesthesia with tracheal intubation were enrolled between January 2009 to April 2009. Written informed consent was taken from all patients. Patients
with expected difficult intubation, obesity (BMI > 28 kg/m²) or those suffering from hypertension, ischaemic heart disease, or increased intracranial pressure were excluded. Patients on drugs which were known to alter minimum alveolar concentration (MAC) of sevoflurane or affect the heart rate, were also excluded. A sample size of 17 patients in each group was calculated based on standard deviations of maximum systolic blood pressure in peri intubation period (26 mmHg in tramadol and 20 mmHg in placebo group) and keeping 20 mmHg as a significant difference between two groups. The calculation was made at 5% significance level and power of 80%.

Patients were randomly allocated to one of two groups of 17 patients each, sevoflurane alone group-S or sevoflurane and tramadol combination (group ST). We used computer generated random number table for making sealed opaque envelopes containing slips with group name written on each. After identifying patients enrollment, an anaesthetist unrelated to the study pulled out one envelope. All the slips along with medical record numbers of patients were kept safe by an assigned research medical officer.

Midazolam 7.5 mg tablet was given to all the patients approximately 30 minutes before induction as pre-medication. Placebo (normal saline only) and tramadol were prepared in identical 5 cc syringes and were labeled as study drug by a recovery room nurse unconnected with the study. Baseline readings were taken in the operating room after a rest period of 5 minutes. The drug was administered by the primary anaesthesit blind to the study groups. All the measurements including heart rate (HR), systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP) and oxygen saturation were recorded before induction. ECG was monitored continuously by Lead II of Datex Ohmeda S / 5 monitor (Helsinki, Finland).

Group-S patients had anaesthetic induction with intravenous placebo 5 mls, thiopentone 5 mg/kg and atracurium 0.6 mg/kg. Sevoflurane was administrated along with N₂O and oxygen (60:40 ratio) through the face-mask till end tidal minimum alveolar concentration (MAC) of one (2%) was achieved. Group-ST patients received intravenous tramadol 2 mg/kg in a blinded fashion followed by thiopentone and atracurium in identical doses and sevoflurane in the same manner. Tracheal intubation was performed by a single investigator who was unaware of the study groups by using Macintosh laryngoscope size three for females and size four for males, and trachea was intubated with poly-vinyl-chloride tracheal tube size 7 for females and size 8 for males. HR, SBP, DBP and MAP (primary outcomes) were recorded every minute after induction and upto 7 minutes after intubation by a research medical officer who was blinded to group allocation.

Systolic blood pressure (SBP) more than 25% of pre-operative value was to be treated with intravenous metoprolol 2 mg boluses. SBP less than 25% of pre-operative value was to be treated with either intravenous (IV) ephedrine 5 mg or phenylephrine 50 micrograms boluses depending on heart rate. Tachycardia was defined as heart rate more than 100 beats per minute and was to be treated with IV metoprolol 2 mg boluses. Bradycardia was defined as heart rate less than 60 beats per minute and was to be treated with IV atropine 0.5 mg boluses. We recorded the number of haemodynamic events (SBP more than 25% of baseline, SBP less than 25%, bradycardia, tachycardia any new arrhythmias or ST segment changes) and also administration of vasoactive drugs during the study period. These were the secondary outcomes.

All data was entered, double checked and analysed by version 16 (copyright © SPSS Inc, 1989-2007, Chicago, USA). Summary statistics of patient age, weight, induction time, and laryngoscopy time for both groups were reported as mean ± standard deviation and analyzed using independent t-test. Intra- and inter-group analysis for heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were statistically evaluated using repeated measure ANOVA and paired T-tests. Qualitative variables like gender, number of haemodynamic events, requirement of vasoactive drugs and numbers of adverse events including arrhythmias and myocardial ischaemia were analysed by Chi-square test. P-value of less than 0.05 was considered significant.

RESULTS

All patients who entered the study completed it and there were no dropouts. The baseline characteristics of age, weight, gender, baseline heart rate, systolic, diastolic, and mean pressure and duration of laryngoscopy were similar in both groups (Table I).

In group-S the heart rate was significantly different from baseline at two and three minutes post-induction and 1, 2 and 3 minutes post-intubation (p < 0.05 ). In group-ST the HR was significantly different from baseline at one and six minutes post-intubation (p < 0.05). The maximum increase of 18% from baseline was observed at one minute post-intubation in group-S compared to 11% in group-ST.

Intragroup comparison showed significant difference at 2 and 3 minutes post-induction and 1, 2 and 3 minutes post-intubation with values being lower in group-ST (p < 0.05, Figure 1).

Systolic blood pressure (SBP) was significantly different from baseline at 2 minutes post-induction and at 1, 5, 6 and 7 minutes post-intubation in group-S and at 1, 4, 5, 6 and 7 minutes post-intubation in group-ST (p < 0.05). In both groups, maximum increase from baseline was
Effect of addition of tramadol to one MAC sevoflurane on the haemodynamic response to laryngoscopy and tracheal intubation

Table I: Baseline and demographic characteristics of patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups</th>
<th>p-value</th>
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<tbody>
<tr>
<td></td>
<td>Sevoflurane (n = 17)</td>
<td></td>
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<tr>
<td></td>
<td>Sevoflurane and tramadol (n = 17)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>39.8 (13.3)</td>
<td>0.56</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.6 (14.5)</td>
<td>0.10</td>
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<tr>
<td>Gender: M:F ratio</td>
<td>56.42</td>
<td>0.49</td>
</tr>
<tr>
<td>Duration of laryngoscopy (seconds)</td>
<td>13 (3.6)</td>
<td>0.68</td>
</tr>
<tr>
<td>Baseline heart rate (beats min⁻¹)</td>
<td>90.5 (12.7)</td>
<td>0.69</td>
</tr>
<tr>
<td>Baseline systolic blood pressure (mmHg)</td>
<td>127.2 (17.7)</td>
<td>0.14</td>
</tr>
<tr>
<td>Baseline diastolic blood pressure</td>
<td>75.9 (10.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>Baseline mean blood pressure (mmHg)</td>
<td>92.5 (11.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>Baseline pulse pressure (mmHg)</td>
<td>49.4 (11)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

The values are mean (SD). There was no significant difference in baseline characteristics between two groups.

Figure 1: Comparison of heart rate between control (●) and tramadol group (■). The symbol ● indicates significant difference from baseline while symbol ▼ indicates significant difference in heart rate between two groups.

Figure 2: Comparison of systolic blood pressure between sevoflurane alone (●) and sevoflurane/tramadol group (■). The symbol ● indicates significant difference from baseline while # indicates significant difference in systolic blood pressure between two groups.

Figure 3: Comparison of diastolic blood pressure between sevoflurane alone (●) and sevoflurane/tramadol group (■). The symbol ● indicates significant difference in absolute values between groups while # indicates significant difference in percentage change from baseline between two groups.

Figure 4: Comparison of mean blood pressure between sevoflurane alone (●) and sevoflurane/tramadol group (■). The symbol ● indicates significant difference in absolute values between groups while # indicates significant difference in percentage change from baseline between two groups.

observed at one minute post-intubation (13.7% in group-S and 12.7% in group-ST). Intergroup comparison did not show any significant difference at any time point during study period (Figure 2).

Diastolic blood pressure (DBP) was significantly different from baseline at 1, 6 and 7 minutes post-induction in group-S and at 1 and 2 minutes post-induction and 1, 3 and 5 minutes post-intubation in group-ST (p < 0.05). Maximum increase in DBP was observed in group-S (22%) and group-ST (17%) at 1 minute post-intubation. While intergroup comparison did not show a significant difference at any time (Figure 3).

Mean arterial pressure (MAP) was significantly different from baseline at 1, 5, 6 and 7 minutes post-induction in group-S and at 1, 2, 5, 6 and 7 minutes post-induction in group-ST (p < 0.05). Maximum increase in MAP was observed in group-S (18%) and group-ST (14.7%) at one minute following laryngoscopy and tracheal intubation.
intergroup comparison did not show any significant difference between two groups any time during study period with higher values in ST-group (Figure 4).

Ten haemodynamic events including six episodes of hypertension (rise of BP more than 25% of baseline) and two episodes of tachycardia were noted in the group-S, compared to seven events in group-ST (three episodes of hypertension and two episodes of hypotension). Hypotension required injection ephedrine and phenylephrine and episode of hypertension required injection metoprolol in all cases. No significant difference was observed in occurrence of haemodynamic events between the two groups (p = 0.2).

**DISCUSSION**

Opiates like fentanyl, remifentanil, sufentanil, and alfentanil have been successfully used in completely attenuating the haemodynamic responses but in the recommended doses they can cause hypotension, bradycardia and respiratory muscle rigidity. Fentanyl has been shown to suppress the response with both thiopentone and etomidate induction. Adachi and colleagues found that pre-treatment with 2 μg/kg of fentanyl could blunt the haemodynamic effects of tracheal tube passage, but not the haemodynamic effects of laryngoscopy.

In contrast with fentanyl, tramadol is a non-selective opioid receptor agonist, with an effect on norepinephrine neuronal reuptake and 5-HT release. Pang et al. compared the effect of 3 mg/kg tramadol with 3 microgram/kg fentanyl and reported that after intubation, heart rate and systolic, mean and diastolic arterial pressure (SAP, MAP, DAP) increased significantly above baseline in both groups, except for DAP in fentanyl group. At 6 and 9 minutes, the heart rate, MAP and DAP were significantly higher and lasted longer with tramadol than fentanyl. Bigat et al reported that post-intubation, heart rate increased above the baseline level with both tramadol (2 mg/kg) and fentanyl (2 micrograms/kg) while blood pressures were higher at 3, 5, 10 minutes after intubation with tramadol group compared to fentanyl.

Currently, tramadol is used for the relief of mild to moderate pain including postoperative situations. Unlike other opioids, tramadol causes minimal respiratory depression, shows more stable haemodynamics with no postoperative nausea and vomiting and pruritis and low addiction liability and tolerance. Because of these reasons, tramadol can be used to substitute fentanyl at the time of induction especially in countries where fentanyl or other short acting narcotic availability is a problem. In Pakistan, the availability of fentanyl is limited but tramadol is freely available.

The effect of inhalational agents alone on haemodynamic response to tracheal intubation is variable. Lin et al. reported that the end-tidal 1.5 MAC sevoflurane following 4.5 minutes of tidal-volume ventilation did not suppress intubation induced haemodynamic responses. Pre-treatment with fentanyl provided better haemodynamic control for tracheal intubation. The depth of anaesthesia after 9 minutes of ventilation with 3.5% sevoflurane was not found sufficient to suppress the intubation induced haemodynamic response. Nakayama et al. showed that anaesthesia with 2 MAC of isoflurane and sevoflurane was also not sufficient to prevent changes in haemodynamic responses. Munoz et al. reported that vital capacity rapid inhalation induction with sevoflurane 3 – 6% following fentanyl 3 micrograms/kg can be considered for blunting the haemodynamic response to tracheal intubation in healthy patients. On this study, sevoflurane 2% endtidal concentration alone kept the SBP and heart rate values to less than 20% of baseline at all times in the sevoflurane alone group.

The present results are similar to those reported by Van den Berg et al. who used 3 mg/kg tramadol. In the present study, the HR returned to baseline by the third minute post-intubation in the tramadol group as compared to 5th minutes reported in Van den Berg's study while SAP returned to baseline by 3 minutes post-intubation in both studies. Compared to Van den Berg, thiopentone was used as induction agent here which might have altered the haemodynamic responses in this study. The addition of 2 mg/kg tramadol is a useful additive to one MAC sevoflurane anaesthesia in ASA-1 and 2 patients in situations where short acting narcotics like fentanyl are not available to attenuate the haemodynamic response to tracheal intubation.

One limitation of this study was that no pre-emptive analgesia was used in the sevoflurane group during the study period, but the rationale was that sevoflurane was a pharmacological agent that also provided protection to this response because of its effects on peripheral vascular resistance and heart rate. We recommend further studies to assess the different concentration of sevoflurane anaesthesia and their combination with varying dosage of tramadol for obtaining an optimum response.

**CONCLUSION**

Heart rate and SBP values following laryngoscopy and tracheal intubation in both groups was less than 20% of baseline. Addition of 2 mg/kg tramadol to one MAC (2%) sevoflurane displayed further suppression of chronotropic response to laryngoscopy and intubation as compared to one MAC sevoflurane alone following thiopentone and atracurium induction.
REFERENCES