



## A COMPARATIVE REVIEW OF ROLE OF LOW DOSES OF MIDAZOLAM AND FENTANYL IN BLUNTING THE HEMODYNAMIC STRESS RESPONSE DURING LARYNGOSCOPY AND INTUBATION

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| Article Info   | ABSTRACT   |
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| <p>Received 15/02/2015<br/>Revised 27/03/2015<br/>Accepted 29/04/2015</p>                            | <p>Stress during direct laryngoscopy and tracheal intubation and means of ameliorating it has been a topic of constant research and study. The mechanical stimulus of laryngoscopy induces autonomic stimulation leading to tachycardia, hypertension, and alteration in bronchomotor tone. These can be detrimental in patients with critically balanced cardio-respiratory system. An attempt was made to evaluate the effects of pre-treatment with low dose Fentanyl Citrate and Midazolam Hydrochloride in blunting the stress response. Ninety patients requiring orotracheal general anesthesia were studied. Premedication, induction agent and anesthesiologist were constant in all patients. In Group F: Fentanyl 1.5 microgram / kg body weight was given intravenously five minutes before induction of anesthesia. Group M: Midazolam 0.04 mg/kg body weight was given intravenously five minutes before induction of anesthesia. In Group C: control group: None of the above mentioned methods were used to suppress the intubation stress response. Rise in heart rate from operation theatre baseline value during laryngoscopy and intubation was 6.7 % in group F, 16.1% in group M, 17.6% in group C. One minute after, a rise of 11.1%, 22.6%, 24.17% was noted in the three groups respectively (<math>p &lt; 0.001</math>). Rise in systolic blood pressure of 3.3%, 7.5 %, 8.2 % was observed during laryngoscopy in the three groups respectively. One minute after, a rise of 6.6 %, 10.8 %, 13.1 % respectively was recorded (<math>p &lt; 0.001</math>). Diastolic blood pressure also rose in the same manner. The response to laryngoscopy and intubation was observed more, one minute after wards than during actual laryngoscopy. Fentanyl was more effective than Midazolam in suppressing the stress response.</p> |
| <p><b>Key words:</b><br/>Laryngoscopy,<br/>Tachycardia,<br/>Hypertension,<br/>Bronchomotor tone.</p> |  |

### INTRODUCTION

The pressor response to laryngoscopy and tracheal intubation is a sympathetic reflex provoked by stimulation of the epipharynx and laryngopharynx [1]. Transitory hypertension and tachycardia are probably inconsequential in healthy individuals but may be hazardous to those with hypertension, myocardial insufficiency or cerebrovascular disease[2-3]. Thus it was felt that an attempt to suppress the responses would be worthwhile. Many drugs such as Phentolamine, Sodium Nitroprusside, Clonidine, Fentanyl, Esmolol, Lignocaine, Midazolam in various dosages have

been advocated to blunt the response with varying success rate. This study was done to analyze the role of low doses of intravenous Fentanyl and intravenous Midazolam in overcoming the stress response.

### MATERIAL AND METHODS

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients



After obtaining the required departmental ethical committee approval, this clinical study was conducted on ninety adult patients belonging to ASA class I or II of either sex in the age group 25-65 years and weighing between 45-70 kilograms. These patients were scheduled for elective surgery of one to three hours duration from various specialties like general surgery, urology, orthopedics, oto-rhino-laryngology and gynecology. Patients with cardiovascular disease, systemic hypertension, endocrine disorders, allergic diathesis and those on long term steroid therapy or beta- blockers were excluded from the study.

Each patient was examined thoroughly by the Anesthesiologist during the Pre-anaesthetic check up. Weight, heart rate, blood pressure, electrocardiogram and chest x-ray were obtained for each patient in addition to other required investigations. Informed consent was obtained from all patients. They were premedicated uniformly with intramuscular injection of Morphine 0.2mg/kg body weight, Promethazine 0.5mg/kg body weight and a uniform dose of Atropine 0.6mg together one hour before the proposed induction of anesthesia. All patients were divided into three groups of thirty each according to the method attempted to suppress the intubation stress as follows:

Group F Fentanyl group : Fentanyl 1.5 microgram / kg body weight was given intravenously five minutes before induction of anesthesia

Group M Midazolam group : Midazolam 0.04 mg/kg body weight was given intravenously five minutes before induction of anesthesia.

.Group C Control group : None of the above mentioned methods were used to suppress the intubation stress response.

All anaesthetic and monitoring equipment were checked for satisfactory functioning. The patient was received into the operation theatre fifteen minutes before commencement of surgery . Multiparameter monitor (Hewlett Packard M3 Viridia M3046A , Source – St. Stephens` hospital) and blood pressure cuff were attached. Electrocardiogram leads were fixed and connected to the cardiac monitor (Lifepak 20 Medtronics , Source – St. Stephens` hospital). Basal recordings of heart rate and blood pressure were noted after patient had calmed down and before intravenous infusion was started. These readings were regarded as the reference readings to measure the stress-response .Then an intravenous line was started using eighteen gauge cannula. Group F patients were administered injection Fentanyl 1.5mg/kg bodyweight intravenously and time noted. Group M patients were administered injection Midazolam 0.04mg/kg body weight intravenously. In Group C patients no pre-treatment was given. After two minutes preoxygenation of the patient for three minutes, at a flow of six liters/minute, via a non-rebreathing circuit was done. All patients were induced with slow intravenous injection of Thiopentone

sodium four mg/kg body weight. Lungs were inflated gently adding Nitrous oxide six liters to three liters Oxygen flow, while observing the vital parameters. After the eyelash reflex of the patient disappeared, check ventilation was done and then Suxamethonium 1.5 mg/kg was administered intravenously. One minute after Suxamethonium injection the head was gently tilted back and laryngoscopy and intubation performed with a proper size of endotracheal tube. Pulse rate, systolic and diastolic blood pressure readings were recorded before, during and at one minute, three minute, five minute and fifteen minutes following laryngoscopy and intubation.

The breathing circuit was connected and 1% Isoflurane added to the breathing mixture of Oxygen and Nitrous Oxide. Injection Vecuronium bromide 0.08 mg/kg intravenously was administered to ensure adequate skeletal muscle relaxation. Subsequently, all patients were mechanically ventilated by Datex Ohmeda 7000 ventilator (Source – St. Stephens` hospital) at tidal volume of ten ml/kg and respiratory rate of fourteen per minute. At the end of surgery, relaxant effect was reversed by Atropine 1.2 mg and Neostigmine 2.5 mg given intravenously as a single injection. Extubation was carried out when ventilation and muscle tone were clinically adequate. The results were compiled and analyzed statistically using appropriate tests.

### Statistical methods applied

Chi square test was applied for the cross tabulations between the groups for age, sex, weight and ASA class Paired sample test was applied to compare the baseline value with all subsequent values Student t test was done to compare the data in each group with respect to other groups for all the parameters .

### RESULTS

The age, sex, body weight and ASA Class distribution is comparable among the three groups. The demographic data is presented for all the three groups in Table 1.

Rise in heart rate from operation theatre baseline value during laryngoscopy and intubation was 6.7 % in group F, 16.1% in group M, 17.6% in group C .One minute after, a rise of 11.1%, 22.6%, 24.17% was noted in the three groups respectively (p<0.001). The response to laryngoscopy and intubation was observed more, one minute after wards than during actual laryngoscopy. The mean heart rate returned to baseline at 5 minutes in Fentanyl group and at 15 minutes in both other groups. Rise in heart rate both absolute and percentage at various intervals from OT baseline value is presented in Table 2. Rise in systolic blood pressure of 3.3%, 7.5 %, 8.2 % was observed during laryngoscopy in the three groups respectively. One minute after, a rise of 6.6 %, 10.8 %, 13.1 % respectively was recorded (p<0.001). Diastolic



blood pressure also rose in the same manner. The systolic and diastolic blood pressure returned to baseline value in three minutes in Fentanyl group and at five minutes in both the other groups. Rise in systolic blood pressure both absolute and percentage at various intervals from OT

baseline value is presented in Table 3. Thus Fentanyl caused maximum attenuation of heart rate, systolic and diastolic blood pressure response as compared to Midazolam and control group.

**Table 1. Demographic data**

| Parameters Recorded           | Fentanyl Group | Midazolam Group | Control Group |
|-------------------------------|----------------|-----------------|---------------|
| Mean Age in Years             | 40             | 42              | 44            |
| Mean Body Weight in Kilograms | 55             | 54              | 55            |
| Sex M:F                       | 11:19          | 15:15           | 13:17         |
| As a Class I:II               | 23:7           | 22:8            | 21:9          |

**Table 2. Rise in heart rate both absolute and percentage at various intervals from OT baseline value**

| Parameters Recorded (Heart Rate) | OT Baseline | Rise During Laryngoscopy | 1 min after Laryngoscopy | 3 min after Laryngoscopy | 5 min after Laryngoscopy | 15 min after Laryngoscopy |
|----------------------------------|-------------|--------------------------|--------------------------|--------------------------|--------------------------|---------------------------|
| Fentanyl Group                   | 90          | 6<br>(6.6%)              | 10<br>(11.1%)            | 4<br>(4.4%)              | 1<br>(1.1%)              | -6<br>(-6.6%)             |
| Midazolam Group                  | 93          | 15<br>(16.1%)            | 21<br>(22.6%)            | 13<br>(13.9%)            | 5<br>(5.3%)              | -3<br>(-3.2%)             |
| Control Group                    | 91          | 16<br>(17.6%)            | 22<br>(24.1%)            | 14<br>(15.3%)            | 6<br>(6.59%)             | -3<br>(-3.3%)             |

**Table 3. Rise in systolic blood pressure both absolute and percentage at various intervals from OT baseline value**

| Parameters Recorded (Systolic Blood Pressure) | OT Baseline | Rise During Laryngoscopy | 1 min after Laryngoscopy | 3 min after Laryngoscopy | 5 min after Laryngoscopy | 15 min after Laryngoscopy |
|---|-------------|--------------------------|--------------------------|--------------------------|--------------------------|---------------------------|
| Fentanyl Group                                | 121         | 4<br>(3.3%)              | 8<br>(6.6%)              | 2<br>(1.6%)              | -6<br>(-4.9%)            | -11<br>(-9.0%)            |
| Midazolam Group                               | 120         | 9<br>(7.5%)              | 13<br>(10.8%)            | 4<br>(3.3%)              | -5<br>(-4.1%)            | -11<br>(-9.1%)            |
| Control Group                                 | 122         | 10<br>(8.2%)             | 16<br>(13.1%)            | 7<br>(5.7%)              | -6<br>(-4.9%)            | -16<br>(-13.1%)           |

**Table 4. Rise in diastolic blood pressure both absolute and percentage at various intervals from OT baseline value**

| Parameters Recorded (Diastolic Blood Pressure) | OT Baseline | Rise During Laryngoscopy | 1 min after Laryngoscopy | 3 min after Laryngoscopy | 5 min after Laryngoscopy | 15 min after Laryngoscopy |
|--|-------------|--------------------------|--------------------------|--------------------------|--------------------------|---------------------------|
| Fentanyl Group                                 | 81          | 2<br>(2.4%)              | 5<br>(6.1%)              | -1<br>(-1.2%)            | -5<br>(-6.1%)            | -11<br>(-13.5%)           |
| Midazolam Group                                | 83          | 3<br>(3.6%)              | 5<br>(6.0%)              | 1<br>(1.2%)              | -7<br>(-8.4%)            | -11<br>(-13.2%)           |
| Control Group                                  | 82          | 5<br>(6.0%)              | 10<br>(12.2%)            | 2<br>(2.4%)              | -3<br>(-3.6%)            | -9<br>(-10.9%)            |

**Table 5. Lists the various publications with different doses of Fentanyl**

| Authors                   | Dose of Fentanyl used (micrograms/kg) |
|---------------------------|---------------------------------------|
| Martin[4]                 | 8                                     |
| Kautto [5]                | 2 groups—6 and 2                      |
| Dahlgren and Messeter [6] | 5                                     |
| Chung [7]                 | 2 groups-5 and 2                      |
| Benett and Stanley [8]    | 4                                     |
| Feng [9]                  | 3                                     |
| Sparr [10]                | 2.5                                   |



**Table 6. Lists the various publications with different doses of Midazolam**

| Authors           | Dose of Midazolam used (mg/kg body weight) |
|-------------------|--|
| Samuelson [11] PN | 0.2  |
| Baber [12] R      | 0.15                                       |
| Boralessa [13] H  | 0.3  |
| Kawar [14] P et   | 0.3  |

## DISCUSSION

Airway management and tracheal intubation are the quintessential skills associated with the practice of anaesthesia. Laryngoscopy and endotracheal intubation is a procedure that requires training and experience to make it safe, effective and atraumatic. Laryngoscopy and tracheal intubation can cause sympathoadrenal stimulation and cause fluctuations in heart rate, rhythm and arterial pressure. These may not be of serious consequence in healthy adults but can be disastrous in patients with coronary artery disease, intra-cranial vascular anomalies, hypertensives and in patients with hypersensitive airway. To alleviate such responses, various methods have been adopted in the past. Use of pharmacological agents both intravenous and topical, limiting duration of laryngoscopy, choice of laryngoscopic blades, deepening plane of anaesthesia are measures adopted to meet that end. In the present clinical study, an attempt was made to compare the efficacy of intravenous injection of Fentanyl citrate and Midazolam hydrochloride in attenuation of stress response to laryngoscopy and intubation. The study tried to focus on circulatory changes at various time intervals starting from basic levels when patient was well settled in the operation theatre, through induction, laryngoscopy and intubation. Values obtained at each stage were compared with the baseline value.

Fentanyl caused maximum attenuation of heart rate, systolic and diastolic response as compared to Midazolam and control group. Fentanyl has been used in varying doses in many studies to blunt the stress response. The various studies are listed in Table 5. Fentanyl was administered 5 minutes before induction in our study similar to Ko [15] et al. They indicate it as the optimal injection time.

Similarly midazolam has also been used in various doses. The various studies regarding Midazolam are listed in Table 6. Midazolam has been primarily used for induction in these articles and not as pre-treatment 5 minutes before induction. The efficacy of low doses of both drugs Fentanyl citrate and Midazolam hydrochloride in attenuating the stress response was evaluated in this study. Low dose has the advantage of minimal side effects and cost effectiveness. Fentanyl even at dosage of 1.5

microgram/kg was able to blunt the stress response unlike Midazolam 0.04mg/kg.

## CONCLUSION

A clinical study was undertaken to analyze the efficacy of low doses of both injection Fentanyl and Midazolam given as Pre-treatment five minutes before induction, for attenuation of the hemodynamic stress response to laryngoscopy and intubation. Heart rate, Systolic and Diastolic blood pressure were recorded at laryngoscopy and intubation and at 1, 3, 5, 15 minutes thereafter. They were compared with the baseline values in the operation theatre. A rise in all parameters was noted in the three groups which was more one minute after laryngoscopy than at time of laryngoscopy and intubation. Fentanyl caused maximum attenuation of heart rate, systolic and diastolic blood pressure responses as compared to Midazolam and control group and so was more effective. Even a low dose of 1.5 microgram/kg was able to blunt the stress response.

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## Declarations of interest

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