DISCUSSION

Laryngoscopy and intubation are associated with cardiovascular changes such as hypertension, tachycardia, dysrhythmias and even myocardial ischemia, as well as increased circulating catecholamines and may lead to cerebral hemorrhage. [1- 3]

This haemodynamic response, known as the intubation response, may be associated with detrimental effects and should be blunted, especially in the presence of cardiovascular and cerebrovascular diseases, as these pressor responses increase peri-operative morbidity and mortality. [79, 80]

Transient cardiovascular changes are well tolerated in healthy individuals but are of great concern in susceptible individuals particularly those with systemic hypertension, coronary artery disease, leaking abdominal aneurysm, intracranial aneurysm and recent myocardial infarction. In such patients these transient changes can result in potentially deleterious effects such as myocardial ischemia and cerebral hemorrhage. [81]

To minimize these potentially harmful responses, various methods include laryngoscopy and intubation in a deeper plane of anesthesia, topical anaesthesia of upper respiratory tract prior to laryngoscopy with lignocaine, transient cardiovascular vasodilators like nitoprusside, hydralazine and nitroglycerine have been used to attenuate these responses, Calcium channel blockers, beta blockers and opioids such as alfentanil, fentanyl and remifentanil have also been used in different dosage regimens to control or attenuate haemodynamic responses to laryngoscopy and intubation. Each method and drug has variable effectiveness and contradictory results. Moreover, no technique is free of side effects and thus no single method has achieved universal acceptance. [81]

Arterial blood pressure and heart rate responses have been shown to be greater when the duration of laryngoscopy exceeds 30 seconds .It appears that the maximum increase in arterial pressure occurs with laryngoscopy and the maximum increase in heart rate occurs with endotracheal intubation. [7] Moreover stoelting demonstrated that the time required for performing endotracheal intubation directly correlates with an increase in MAP. [82]

Pregablin was introduced in 2004 as a second generation anticonvulsant drug for the treatment of peripheral neuropathic pain and as an adjunctive therapy for partial seizures in patients with epilepsy. [82] The introduction of pregablin was based on results from 10 trials studying more than 9000 patients. [82] In December 2004, the Food and Drug Administration approved pregabalin, for the treatment of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia. In June 2005, pregabalin was approved as an adjunctive treatment of partial onset epilepsy in adults. More recently, in March 2006, the European Commission approved pregabalin for the treatment of generalized anxiety disorder. [82]

It is interesting that a single drug may have multi modal effects; it was not, until recently, thought to be useful in acute peri-operative conditions.

A growing body of evidence suggests that peri-operative administration of pregablin is effective for postoperative analgesia, preoperative anxiolysis, prevention of chronic post-surgical pain and in attenuation of the hemodynamic response to laryngoscopy and intubation. [69]

The current study aimed at studying the additive effect of oral pregabalin premedication to intravenous fentanyl as regards the effectiveness and safety to attenuate the haemodynamic stress response to laryngoscopy and endotracheal intubation. It was carried out in Alexandria university hospital, on 60 patients with ASA physical status I-II.

The patients were divided into three groups 20 patients each, scheduled for elective, minor lower abdominal surgeries under general anaesthesia with endotracheal intubation. They randomly allocated into three equal groups using the closed envelope technique.

These three groups were:

Group I: Each patient received a placebo tablet given orally with sips of water 1 hour before induction of general anaesthesia and intravenous fentanyl at a dose of 1 µg/kg three minutes before induction.

Group II: Each patient received a pregabalin 75 mg tablet given orally with sips of water 1 hour before induction of general anaesthesia and intravenous fentanyl at a dose of 1µg/kg three minutes before induction.

Group III: Each patient received a pregabalin 150 mg tablet given orally with sips of water 1 hour before induction of general anaesthesia and intravenous fentanyl at a dose of 1µg/kg three minutes before induction.

In the present study there were no significant demographic differences between the three studied groups regarding age, sex, body weight.

Heart rate, systolic arterial blood pressure, diastolic arterial blood pressure, means arterial blood pressures were monitored continuously and recorded at the following times before starting the surgery:

- Pre-induction.
- Immediately before endotracheal intubation.
- Immediately after endotracheal intubation.
- At 1, 3, 5 and 10 minutes after intubation.

In this study, as regard heart rate there was no statistically significant differences between the three studied groups before induction, immediately before, immediately after intubation and at 1, 3, 5 and 10 minutes after intubation. The maximal increase in heart rate from base line occurred at 1 minute after intubation with the least increase in group III but still statistically insignificant in comparison to Group I and Group II. Similar results were reported by others. [83, 84]

Gupta et al [83] studied pregabalin premedication as a new treatment option for haemodynamic stability during general anaesthesia. The 80 adult consented patients of ASA I and II of either gender aged 24-54 were randomized into two treatment groups of 40 patients each. Oral pregabalin 150 mg or placebo capsule were given 60-75 min before surgery. Patients were premedicated with 10 mg metoclopramide, 0.2 mg glycopyrrolate and 1 µg/kg fentanyl. Anaesthesia was induced with propofol and rocuronium and maintained with isoflurane and oxygen.

They found that there was no statistically significant difference in heart rate between the two studied groups and no statistically significant attenuation of heart rate in pregabalin

premedicated groups with a maximal increase in heart rate at 1 minute after intubation with least increase in group II but still statistically insignificant in relation to group I.

Similarly Rastogi et al [84] who studied oral pegabalin premedication for attenuation of haemodynamic pressor response of airway instrumentation during general anaesthesia. Patients were randomized into three treatment groups of 30 patients each. Group I received oral placebo, group II oral pregabalin 75 mg and group III oral pregabalin 150 mg 1 h prior to induction and anaesthetic technique was standardized in all groups. Again they found that there was no statistically significant difference regarding heart rate between the three studied groups and no statistically significant attenuation of heart rate in pregabalin premedicated groups.

In our study, the mean systolic arterial blood pressure increased significantly immediately after intubation and at 1, 3, 5 and 10 minutes after intubation in comparison to immediately before intubation in in group I and group II but in group III it was significantly higher immediately after intubation, at 1 and 3 min after intubation in comparison to immediately before intubation but was significantly lower at 5 and 10 min after intubation in comparison to immediately before intubation.

The mean diastolic arterial blood pressure increased significantly immediately after intubation and at 1, 3, 5 and 10 minutes after intubation in comparison to immediately before intubation in group I and group II but in group III it was significantly higher immediately after intubation, at 1, 3 and 5 min after intubation while it was insignificantly lower at 10 min after intubation in comparison to immediately before intubation.

The mean value of mean arterial blood pressure increased significantly immediately after intubation and at 1, 3, 5 and 10 minutes after intubation in comparison to immediately before intubation in group I and group II butIn group III it increased significantly immediately after intubation , at 1 and 3 min after intubation in comparison to immediately before intubation and was insignificantly higher at 5 min after intubation in comparison to immediately before intubation while it was significantly lower at 10 min after intubation in comparison to immediately before intubation.

In our study regarding the systolic, diastolic and mean arterial blood pressures there was no statistically significant difference between the three studied groups at pre-induction and immediately before endotracheal intubation, while they were significantly higher in group I and in group II compared to group III Immediately after endotracheal intubation and at 1, 3, 5 and 10 minutes after intubation. On comparing group I to group II the relationship was statistically insignificant.

This result was in agreement with Gupta et al [83] who studied pregabalin premedication (150 mg) as a new treatment option for haemodynamic stability during general anaesthesia and found that there was no statistically significant difference between the two studied groups regarding the systolic, diastolic, mean arterial blood pressures before and after pregabalin premedication but immediately after laryngoscopy and intubation the attenuation of blood pressure in pregabalin premedicated (150 mg) group was statistically significant in comparison to the control group.

Similarly with Rastogi et al [84] who studied oral pregabalin premedication for attenuation of haemodynamic pressor response of airway instrumentation during general

anaesthesia and found that there was no significant difference in blood pressure before and after premedication in the three studied groups but immediately after laryngoscopy and intubation the attenuation of blood pressure in pregabalin premedicated group (150mg) was statistically significant in comparison to the control group and pregabalin premedicated group (75mg)

Similar results were reported by Salman et al. [85] and Eren at al. [86] They observed the significant increase in heart rate and blood pressure in group I (control group) and the attenuation of blood pressure in group II premedicated with 150 mg pregabalin after laryngoscopy and intubation.

Our study evaluated the safe and clinically effective dose of oral pregabalin premedication for attenuation of haemodynamic pressor response of airway instrumentation of direct laryngoscopy and intubation and for its sedative effect.

The increase in haemodynamic values in the control group may be due to inadequate sedation and analgesia and the significant attenuation of haemodynamic pressor response was observed by oral pregabalin premedication in a dose related manner, with minimal effect on heart rate.

A possible effect of pregabalin on heart rate may have been covered by propofol and fentanyl; propofol producing bradycardia and hypotension may partially compensate the haemodynamic changes (hypertension and tachycardia) related to laryngoscopy and intubation.

Regarding the level of sedation which was assessed before induction (before fentanyl administration) by Ramsy sedation scale we found that sedation was significantly higher in group III as compared to group II and group I.

Similarly White et al [87] studied the effect of pregabalin on preoperative anxiety and sedation levels in 108 ASA I–III outpatients undergoing elective surgery were randomly assigned to one of four pregabalin premedication treatment groups (placebo, 75, 150, 300 mg).

The effects of the study drug on the patients' level of anxiety, sedation, and pain were assessed immediately before study drug administration, at 30 and 60 min after drug administration, and immediately before induction of anesthesia, as well as at 30-min intervals in the (PACU).

They found that preoperative pregabalin administration increased perioperative sedation in a dose-related fashion where the highest dose of pregabalin produced deeper levels of sedation both before and after ambulatory surgery.

Similarly with Gupta et al [88] who studied oral premedication with pregabalin (150 mg) or clonidine (200 μg) for haemodynamic stability during laryngoscopy and laparoscopic cholecystectomy. All groups were compared for preoperative sedation and anxiety level along with changes of heart rate and mean arterial pressure. They found a clear increase in sedation levels in pregabalin and clonidine premedicated groups as compared with control groups. Preoperative sedation was higher in oral pregabalin premdicated group as compared with clonidine premedicated group. Similar results were reported by others. [83]

Pregabalin is alleged to modulate the release of excitatory neurotransmitters, leading to a reduction in levels of anxiety and pain. [89]

There is a growing body of evidence suggests that perioperative administration of pregabalin is efficacious for preoperative anxiolysis, preventing chronic postsurgical pain, postoperative nausea and vomiting, and delirium. [87, 90]

With the use of up to 150 mg of pregabalin in this study, no postoperative complications were observed. Paul et al used up to 300 mg of pregablin, they didn't find any side effects. However when the attempted to use higher doses (e.g. 600mg) in a pilot study, the occurance of profound Somnolence leading to prolonged PACU stays and delayed discharge. [87]

SUMMARY

Laryngoscopy and intubation are associated with cardiovascular changes such as hypertension, tachycardia, dysrhythmias and even myocardial ischemia, as well as increased circulating catecholamines and may lead to cerebral hemorrhage.

This haemodynamic response, known as the intubation response, may be associated with detrimental effects and should be blunted, especially in the presence of cardiovascular and cerebrovascular diseases, as these pressor responses increase peri-operative morbidity and mortality.

To minimize these potentially harmful responses, various methods include laryngoscopy and intubation in a deeper plane of anesthesia, topical anaesthesia of upper respiratory tract prior to laryngoscopy with lignocaine, transient cardiovascular vasodilators like nitoprusside, hydralazine and nitroglycerine have been used to attenuate these responses, Calcium channel blockers, beta blockers and opioids such as alfentanil, fentanyl and remifentanil have also been used in different dosage regimens to control or attenuate haemodynamic responses to laryngoscopy and intubation. Each method and drug has variable effectiveness and contradictory results. Moreover, no technique is free of side effects and thus no single method has achieved universal acceptance.

Pregablin was introduced in 2004 as a second generation anticonvulsant drug for the treatment of peripheral neuropathic pain and as an adjunctive therapy for partial seizures in patients with epilepsy.Its main site of action appears to be on the α_2-δ subunit of presynaptic, voltage-dependent calcium channels that are widely distributed throughout the peripheral and central nervous system. Pregabalin appears to produce an inhibitory modulation of neuronal excitability, particularly in areas of the central nervous system dense in synaptic connections.

The present study aimed to evaluate the additive effect of oral pregabalin premedication to intravenous fentanyl as regards the effectiveness and safety to attenuate the haemodynamic stress response to laryngoscopy and endotracheal intubation.

After approval of the local ethics committee and taking an informed written consent from each patient, the present study was carried out on 60 adult patients of either sex (three groups each of tweanty patients). All patients were of ASA physical status class I-II and fulfilled the exclusion criteria and scheduled for elective, minor lower abdominal surgeries under general anaesthesia with endotracheal intubation.

Group I: Each patient received a placebo tablet given orally with sips of water 1 hour before induction of general anaesthesia and intravenous fentanyl at a dose of 1 µg/kg three minutes before induction.

Group II: Each patient received a pregabalin 75 mg tablet given orally with sips of water 1 hour before induction of general anaesthesia and intravenous fentanyl at a dose of 1µg/kg three minutes before induction.

Group III: Each patient received a pregabalin 150 mg tablet given orally with sips of water 1 hour before induction of general anaesthesia and intravenous fentanyl at a dose of 1µg/kg three minutes before induction.

The following parameters were measured:

A. **Demographic Data:** Age, Sex and Body weight.

B. Haemodynamic measurements:

- Heart rate, systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP) and mean arterial blood pressure (MAP).
- Arterial oxygen saturation (S_aO_2).
- Dysrhythmias.

They were monitored continuously and recorded at the following times before starting the surgery:

- Pre-induction.
- Immediately before endotracheal intubation.
- Immediately after endotracheal intubation.
- At 1, 3, 5 and 10 minutes after intubation.

C. The level of sedation:

It was assessed before induction (before fentanyl administration) by Ramsy sedation scale.

D. Side effects.

The main results of the present study revealed that, regarding the heart rate there was no statistically significant differences between the three studied groups.

Regarding the systolic, diastolic and mean arterial blood pressures there was no statistically significant difference between the three studied groups at pre-induction and immediately before endotracheal intubation, while they were significantly higher in group I and in group II compared to group III Immediately after endotracheal intubation and at 1, 3, 5 and 10 minutes after intubation. On comparing group I to group II the relationship was statistically insignificant.

Regarding the level of sedation, we found that sedation was significantly higher in group III as compared to group II and group I.

From the previous data it was concluded that oral Pregabaline premedication has an additive effect to intravenous fentanyl to attenuate the increase in systolic, diastolic and mean arterial blood pressures resulting from laryngoscopy and intubation in a dose of 150 mg with a sedative effect.

It is recommended to use pregabalin 150 mg as an oral prmedication to attenuate the pressor respose to laryngoscopy and intubation and to promote further studies to evaluate the efficacy and safety of different higher doses used for premedication with pregabalin.

CONCLUSIONS

1. Oral Pregabalin premedication has no additive effect to intravenous fentanyl to attenuate the increase in heart rate resulting from laryngoscopy and intubation in the doses used in this study.

2. Oral Pregabalin premedication has an additive effect to intravenous fentanyl to attenuate the increase in systolic, diastolic and mean arterial blood pressures resulting from laryngoscopy and intubation in the higher dose used (150 mg).

3. Oral pregabalin premedication increases perioperative sedation in a dose-related fashion where the higher dose of pregabalin produces deeper levels of sedation.

4. Oral Pregabalin premedication in a dose of 150 mg is highly safe.